

**IN THE MATTER OF:  
THE PATENTS ACT 1970 (as amended in 2005),  
THE PATENTS RULES 2005**

IN THE MATTER of a representation  
under Section 25(1) read with Rule 55



IN THE MATTER OF:

Indian Application No. 6087/DELNP/2005 dated 27.12.2005

Filed by GILEAD PHARMASSET LLC, USA;

..... APPLICANT


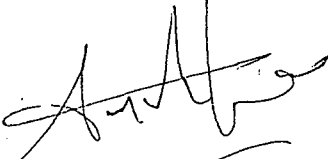
OPTIMUS PHARMA LTD.

... OPPONENT

**REPLY TO PRE-GRANT REPRESENTATION**

Paper Book Of Reply to representation under section 25(1) On behalf of Applicant

Dated this August 07, 2015.

  
  
SANJEEV K. TIWARI & AMRISH TIWARI  
[K&S PARTNERS]  
ATTORNEYS FOR THE APPLICANT

The Controller of Patents  
The Patent Office, New Delhi.

IPO DELHI 07-08-2015 17:37

August 07, 2015



Intellectual Property Attorneys



To  
The Controller of Patents  
The Patent Office,  
Intellectual Property Building,  
Plot No. 32, Sector 14  
Dwarka  
New Delhi - 110 075

**Asst. Controller: Mr. Hardev Karar**

Re: Reply to Representation u/s 25(1) read with Rule 55  
in respect of Indian Application No.: 6087/DELNP/2005  
Filed on: 27.12.2005  
Applicant: GILEAD PHARMASSET LLC  
Opponent: Optimus Pharma Ltd.  
Title: "A (2'R)-2'-DEOXY-2'-FLUORO-2'-C-METHYL NUCLEOSIDE"  
Our ref: IP 31149/AMT/md

Dear Sir,

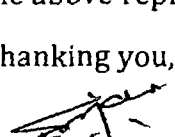
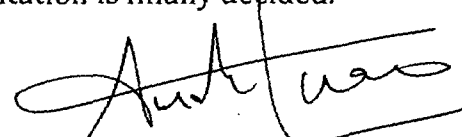
We submit herewith reply to the representation filed by Optimus Pharma Ltd. We state that the notice of the Pre-Grant Opposition along with copies of Opposition Petition and documents were received by us on May 08, 2015. Accordingly, the present reply with accompanying documents is within limitation period.

We crave leave of the Controller to provide additional documents as evidence as called for by the Controller or if necessary to support any of the averments in the reply.

The Controller is requested to take the documents on record and proceed further in the matter and keep the Applicant advised of each and every step taken in the matter.

Lastly, we request the Controller to grant us an opportunity of being heard before the above representation is finally decided.

Thanking you,

  
  
SANJEEV K. TIWARI & AMRISH TIWARI  
[K&S PARTNERS]  
ATTORNEYS FOR THE APPLICANT

Encls: As above

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DELHI 07-08-2015 17:37



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**IN THE MATTER OF:  
THE PATENTS ACT 1970 (as amended in 2005),  
THE PATENTS RULES 2005**

IN THE MATTER of a representation  
under Section 25(1) read with Rule 55

IN THE MATTER OF:

Indian Application No. 6087/DELNP/2005 dated 27.12.2005

Filed by GILEAD PHARMASSET LLC, USA;

..... APPLICANT

OPTIMUS PHARMA LTD.

... OPPONENT

**REPLY TO PRE-GRANT REPRESENTATION**

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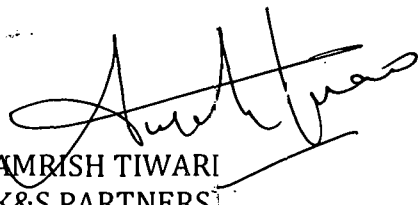
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Dated this August 07, 2015.

  
  
 SANJEEV K. TIWARI & AMRISH TIWARI  
 [K&S PARTNERS]  
 ATTORNEYS FOR THE APPLICANT

The Controller of Patents  
 The Patent Office, New Delhi.

IPO DELHI 07-08-2015 17:37<sup>3</sup>

**BEFORE THE CONTROLLER OF THE PATENTS  
PATENT OFFICE, DELHI**

**IN THE MATTER OF THE PATENTS (AMENDMENT) ACT, 2005**

AND

IN THE MATTER OF  
an application for the grant of a patent  
No. Patent Application No. 6087/DELNP/2005  
of 27.12.2005 filed in the name of  
GILEAD PHARMASSET LLC  
having a principal place of business at  
Gilead Sciences, Inc., 333 Lakeside Drive,  
Foster City, California 94404,  
USA

... Applicant

AND

IN THE MATTER OF pre-grant representation filed  
to the grant of patent on subject application  
under Section 25(1) of said Act by  
OPTIMUS PHARMA LTD.  
Corporate office: #1-2-11/1,  
Above SBI bank,  
Street No. 2, Kakatiya Nagar,  
Habsiguda, Hyderabad - 500007  
India.

... Opponent

**REPLY STATEMENT ON BEHALF OF THE APPLICANT**

We, Gilead Pharmasset LLC, (hereinafter referred to as "Applicant"), submit our  
reply to the pre-grant representation as under.

At the outset, we submit that the opposition of Optimus Pharma Ltd. ("Opponent") is baseless, misconceived and frivolous, and should be dismissed *in limine*. All the allegations and averments made in the opposition petition under reply are denied unless specifically admitted herein.

The Applicant's response and submissions, in detail, are herein under:

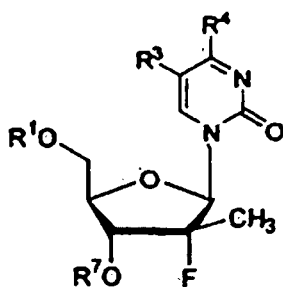
1. That the averments at **paragraph 1** are facts on record. The contents of this paragraph relating to Application Number, Title, Indian Filing Date, PCT Publication Number, PCT Filing Date, Priority, etc. are matters of record and need no specific reply. As such the Applicant has no comments as they are mere narration of matters on record.
2. In **paragraph 2**, the Opponent purports to recite the claims of the present patent application. The Opponent's purported recitation is denied and disputed as the same is inaccurate. In this regard, the Applicant relies on **Exhibit A** submitted herewith.
3. In **paragraph 3**, the Opponent contends that Patent Application No. 6087/DELNP/2005 (hereinafter "'6087'")'s specification discloses and admits items listed in sub-paragraphs a) through d). The Opponent's analysis of the specification is denied and disputed as the same is inaccurate. In this regard, the Applicant relies on the averments made in '6087. The averments made in the present reply may be read as part reply to the present paragraph.
4. The averments made in **paragraph 4** are baseless and should be rejected. The Opponent contends that the stereochemistry of the claimed compounds at the 2' position "has been achieved by inversion configuration" and that "this mechanism is known and is obvious to a person skilled in the art." Applicant explains below how, as of the present application's effective filing date, methods for making the claimed compounds were neither taught by the

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prior art nor obvious. To the contrary, it would have been extraordinarily difficult for an artisan to synthesize nucleosides with a 2'-fluoro (down)-2'-C-methyl (up) configuration (see Section 10.3 below).

5. In reply to **paragraphs 5 and 6** of the opposition petition, it is submitted that none of the cited references discloses or suggests the compounds of the present patent application. The present application discloses and claims an invention pertaining to New Chemical Entities (NCEs). The disclosed and claimed compounds are novel, inventive and patentable within the meaning of Patents Act, 1970. Accordingly, the grounds alleged in the opposition should be rejected and the application granted.
6. Additionally, the following may also be in reply to these paragraphs of the opposition:

The present application is directed to (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides and their corresponding monophosphate, diphosphate, and triphosphate forms. In particular, the present application claims a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside of the following formula:



wherein

R<sup>1</sup> and R<sup>7</sup> are independently H, a monophosphate, a diphosphate, or a triphosphate; and

R<sup>3</sup> is H and R<sup>4</sup> is NH<sub>2</sub> or OH.

(4)

T

The Applicant has demonstrated that compounds of this formula have high levels of activity against hepatitis C virus ("HCV"),<sup>1</sup> low toxicities and other favorable characteristics.

Without prejudice to the above and solely to expedite the grant, the Applicant presently amends the claims. A copy of marked-up claims along with its clean copy is enclosed herewith as **Exhibit A**. The averments made elsewhere in the present reply may be read as part reply to the present paragraph.

7. As explained in more detail below, Opponent's opposition is completely baseless and frivolous and without any merit and ought to be dismissed *in limine*.

#### **REPLY ON MERITS**

In view of the above, all the averments made in the pre-grant opposition are false and hereby denied. No averment may be deemed to be admitted for want of traverse. For purposes of brevity the Applicant herein addresses the main issues in the opposition without going into specific denials. However, it is clarified that none of the averments made in the opposition are admitted. We now proceed to analyze and reply to the pre-grant opposition:

#### **8. The Present Invention**

The present invention is directed towards compounds useful for the treatment of HCV infection. HCV infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, and ultimately death in a substantial number of infected individuals, estimated to be about 170 million worldwide and about 18 million in India.

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<sup>1</sup> HCV is a member of the *Flaviviridae* virus family.

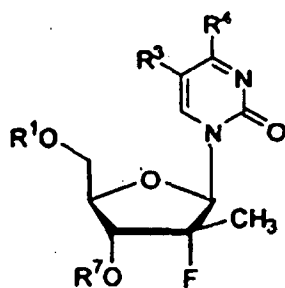


As of the present application's effective filing date, interferons (IFNs) had been commercially available for the treatment of chronic HCV infection for approximately a decade. Unfortunately, the effect of IFNs is temporary, and a sustained virologic response (a cure of HCV) occurs in only 8% - 9% of patients chronically infected with HCV (Gary L. Davis. Gastroenterology 18: S104-S114, 2000). Further, most patients have difficulty tolerating IFN treatment, which causes severe flu-like symptoms, weight loss, and lack of energy and stamina. Another drug, ribavirin (1-(3-D-ribofuranosyl-1- $\beta$ -D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a synthetic, non-interferon-inducing, broad spectrum antiviral nucleoside analog sold under the trade name Viriazole (The Merck Index, 11th edition, Editor: Budavari, S., Merck & Co., Inc., Rahway, NJ, p. 304, 1989). Ribavirin reduces serum amino transferase levels to normal in 40% of patients, but it does not lower serum levels of HCV-RNA (Gary L. Davis, 2000). Additionally, ribavirin has significant toxicity and is known to induce anemia. Ribavirin is not approved for monotherapy against HCV. It has been approved in combination with IFN alpha-2a or IFN alpha-2b for the treatment of HCV infection. Therapies using ribavirin and IFN require 48 weeks of treatment—nearly a whole year. The cure rate of patients completing a course of treatment with the most advanced IFN + ribavirin therapies is about 55%. However, because of the severe side effects and long duration of therapy, many patients are non-compliant and, thus, do not receive the complete course of therapy to cure the disease. Moreover, given the low success rate of interferon and ribavirin combination treatment, many patients endured the severe side effects in vain.

In light of the fact that HCV infection had reached epidemic levels worldwide and has tragic effects on the infected patient, at the time the present application was filed, there was a strong need to provide new effective pharmaceutical agents to treat HCV that have low toxicity to the host and that can shorten the duration of treatment.

The present application specifically claims (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides of the following formula:





wherein

R<sup>1</sup> and R<sup>7</sup> are independently H, a monophosphate, a diphosphate, or a triphosphate; and

R<sup>3</sup> is H and R<sup>4</sup> is NH<sub>2</sub> or OH.

The Applicant has demonstrated that compounds of this formula have high levels of activity against HCV, low toxicities and other favorable characteristics.

Contrary to Opponent's arguments, the present invention is novel and involves inventive step for at least the following reasons:

- A. The Opponent's cited references do not disclose or suggest the compounds claimed in the present application;
- B. Neither the Opponent's cited references, nor any other teachings in the prior art, enabled the synthesis of the claimed (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides; and
- C. Neither Opponent's cited references, nor any other teachings in the prior art, demonstrated or suggested that the claimed (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides would be useful, e.g., as anti-HCV therapeutics.

It is submitted that none of the prior art documents impeach the novelty or inventiveness or patentability of the invention as contained in the present application. The submissions of Applicant herein below may be read in this regard and be treated as a reply on merits.

In addition, the Applicant has also invented novel and inventive prodrugs of the compounds claimed in the present application. The Applicant claimed the invention relating to such prodrugs, including sofosbuvir, the active ingredient in Sovaldi®, in a separate application being Indian Patent Application No. 3658/KOLNP/2009.

Sovaldi® offers a cure rate of about 90% when taken as prescribed, and has shortened treatment duration and reduced debilitating side effects, enabling more people to complete treatment. This revolutionary product was approved by the Central Drug Standard Control Organization (CDSCO) on January 13, 2015. To date, the applicant has signed a licensing and technology transfer agreement with the following 11 Indian pharmaceutical companies: Biocon, Cadila Healthcare, Cipla, Hetero Labs, Mylan Laboratories, Ranbaxy Laboratories, Sequent Scientific, Strides Arcolab, Natco Pharma Ltd., Aurobindo Pharma Ltd., and Laurus Labs Pvt. Ltd. The agreement allows these companies to manufacture and distribute generic sofosbuvir in 91 developing countries, including India. Eight licensees have launched or are in the process of launching generic sofosbuvir and other companies are expected to follow soon. The drug has thus been made readily available for the patient population at reasonably affordable prices.

Consistent with the overwhelming success of this product, patents with claims corresponding to the claims of this application have been granted in the following 18 countries and regions:

Country	Patent Nos.
Australia	2004253860
Canada	2527657

China	200480019148.4
Colombia	1214
Indonesia	P0028288
Israel	172259 and 210367
Japan	4958158 and 5266357
Korea	200883703
Mexico	275935
Malaysia	138477
Norway	0333700
New Zealand	543867
Philippines	1-2005-502136
Russia	2358979
Singapore	117252
South Africa	2005-09521
Taiwan	I333956
United States	7429572 and 8415322;

None of the prior art documents cited by the Opponent discloses or suggests the compounds of the present invention and, as such, these documents cannot impeach the novelty or inventiveness of the invention as contained in the instant application.

The submissions of the Applicant herein below may be read in this regard and be treated as reply on merits.

## **GROUND:**

### **9. Lack of Novelty**

The averments made in paragraph 5 sub-paragraphs 3-15 regarding anticipation are factually and legally incorrect, and are furthermore misleading, and hence denied. Regarding novelty, for an invention to be anticipated by a single reference, the invention must be fully and identically described in that reference. The structural and functional differences between the claimed invention and the prior art cannot be ignored. In order for an invention to be held to be anticipated all the same elements of the invention must be found in the same situation and united in the same way to perform an identical function. Furthermore, the reference must enable those skilled in the art to practice the claimed invention without undue experimentation or undue burden.

#### **I. WO 02/057287 (WO'287)**

As per the Opponent, claims 1-10 of present application are anticipated by WO 02/057287 ("WO'287") (Annexure 1 to Opponent's submission). As per the Opponent, WO'287 discloses a Markush structure that is drawn to several nucleoside compounds and the compounds as claimed in claims 1 to 5 and in claim 6 and 7 are known and encompassed within the basic chemical structure of the WO'287 application.

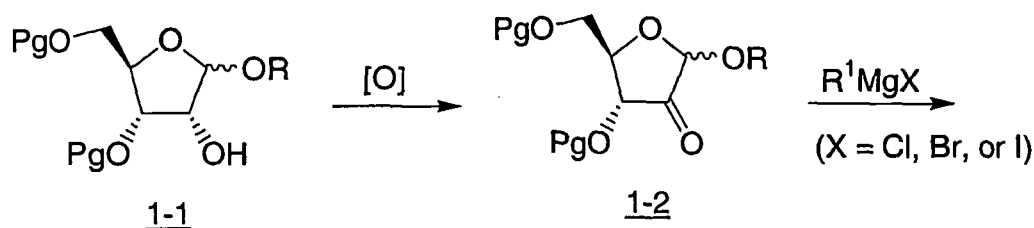
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### Applicant's Response

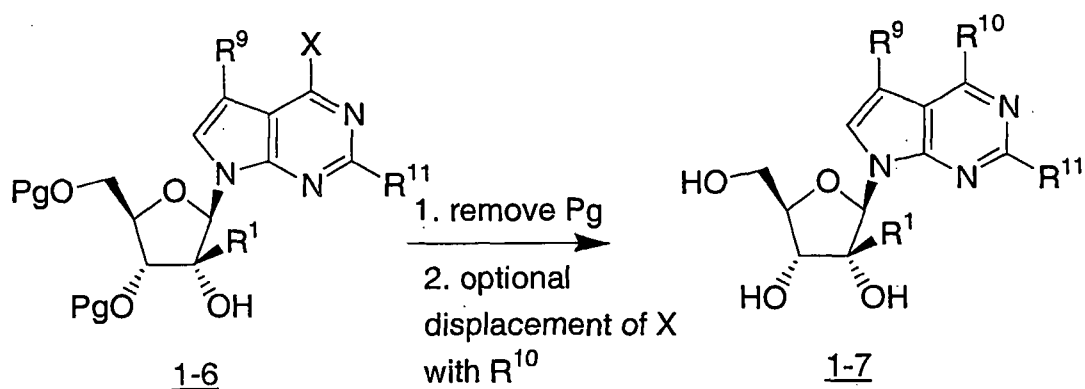
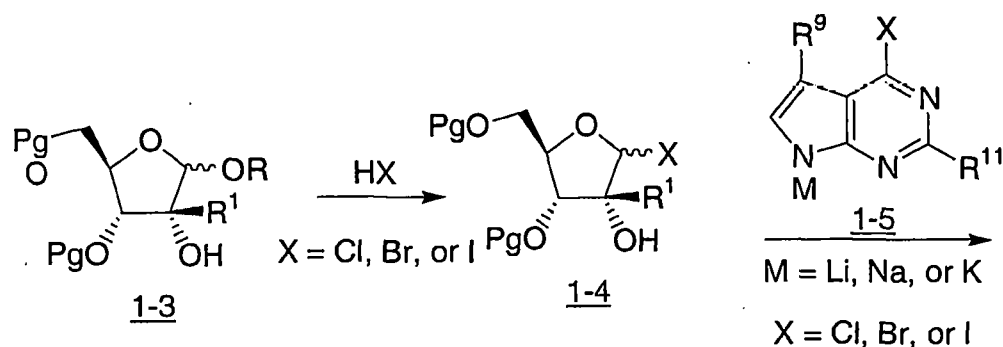
In response, Applicant respectfully disagrees with Opponents assertions. The compounds of WO'287 are structurally very different compounds than the nucleoside compounds of present application. Applicant submits that a careful analysis of WO'287 reveals that the compounds of the present application are not at all anticipated by the cited reference.

Firstly, it is to be noted that the compounds disclosed and taught by WO'287 are purine analogue compounds, particularly, pyrrolo[2,3-d]pyrimidine compounds unlike the compounds of the present application.

Secondly, all the exemplified or promising compounds of WO'287 either have a 2'-hydroxy (down) - 2'-methyl (up) or 2'-hydroxy (up) - 2'-methyl (down) substitution pattern at 2'-position of sugar in pyrrolo[2,3-d]pyrimidine compounds. There is no disclosure or teaching of compounds with 2'-methyl (up) 2'-fluoro (down) substitution. WO'287 describes a general method for preparation of compounds of the present invention in scheme 1 which is reproduced herein below. The synthetic scheme does not teach fluorination at 2'-position of pyranose ring in order to have (2'R)-2'-fluoro (down) and 2'-C-methyl (up) as claimed in present application. Actually, there is not a single example for the preparation of a compound with 2'-fluoro (down) and 2'-C-methyl (up) even with pyrrolo-pyrimidine as a base. The only teaching from WO'287 is to have a 2'-hydroxy (down) and 2'-methyl (up) or 2'-methyl (down) and 2'-hydroxy (up) that too in purine based nucleoside compounds more specifically pyrrolo[2,3-d]pyrimidine compounds.



Pg = protecting group  
R = lower alkyl



In addition, please note that the illustration shown on the bottom of p. 7 of Opponent's brief does not appear in WO'287. It is a hypothetical example concocted by the Opponent and was not made, described, or even suggested in WO'287.

Further, WO'287 does not describe how to make a 2'-deoxyribonucleoside compound with a 2'-fluoro (down)-2'-C-methyl (up) substitution pattern at 2'-carbon of ribose sugar moiety or provide any data indicating that such a compound has anti-*flaviviridae* activity, let alone anti-HCV activity. Still further, the WO'287

fails to provide any guidance or suggestion as to compounds having the particular 2'-fluoro (down)-2'-C-methyl (up) substitution pattern of the instant invention.

In view of the comments above, Applicant submits that WO'287 fails as a novelty-destroying reference and that the presently pending claims are novel. Accordingly, the instant ground is liable to be rejected.

#### **10. Obviousness - Lack of Inventive Step**

The averments made in paragraph 6, subparagraphs 1-17 regarding lack of inventive step are factually and legally incorrect, misleading and are liable to be rejected.

The Opponent alleges that the claims lack inventive step in view of WO2001/90121 ("WO'121"), WO2001/92282 ("WO'282"), WO1999/43691 ("WO'691"), WO2002/57425 ("WO'425"), and WO'287. The Opponent also asserts that the alleged lack of inventive step is further substantiated by the prior art provided in Annexures 2-10. As explained below, this is not correct, and the Opponent's arguments are based on impermissible hindsight. The Opponent's averments at paragraph 6, subparagraphs 1-17 are therefore wrong and hereby denied.

##### **I. WO2001/90121 (WO'121) and WO2001/92282 (WO'282)**

The Opponent contends that WO'121 and WO'282 disclose nucleosides with 2' modifications for the treatment of HCV. The Opponent further contends that "modification at the 2' position with methyl ('up') position and hydroxyl ('down') position is known" and that "[a]dmittedly substitution of fluorine in 2' position of the sugar would bring stability and retain activity of the compound ...."

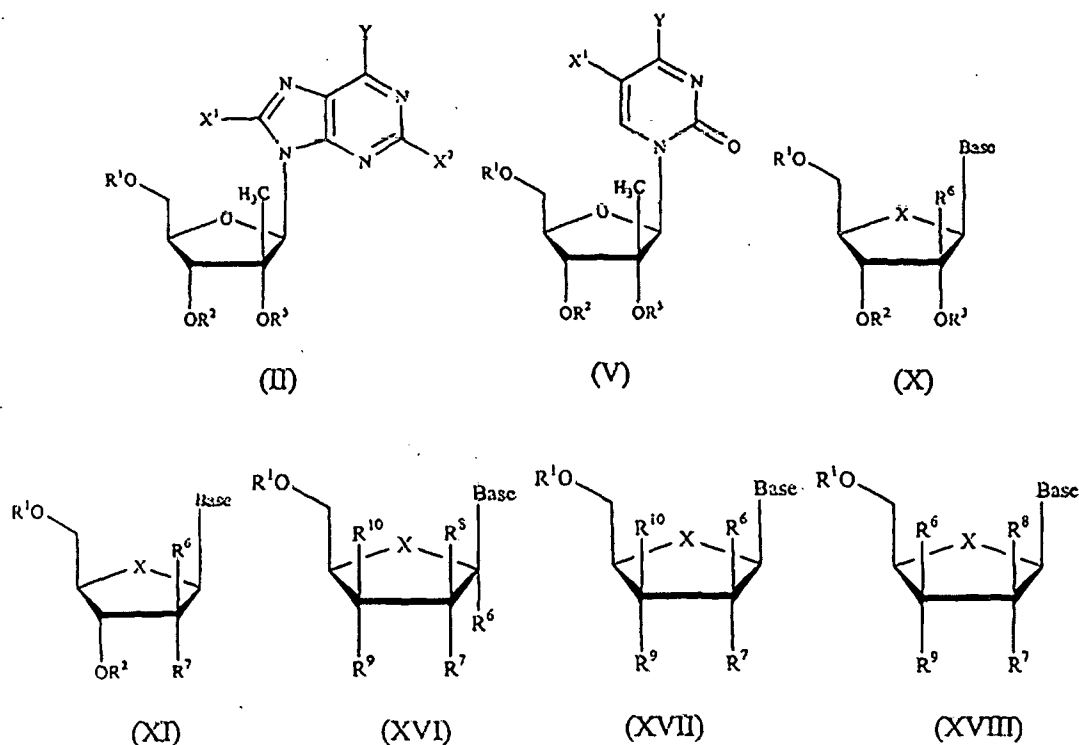
#### **Applicant's Response**

In response, Applicant respectfully disagrees. As explained below, neither WO'121 nor WO'282 discloses or suggests the presently claimed compounds.





The chemical formulae in WO'121 and WO'282 expressly omit any possibility of a 2'-fluoro (down)-2'-C-methyl (up) substitution pattern. For example, both WO'121 and WO'282 disclose the following formulae that allow for two non-hydrogen substituents at the 2' position:



WO'121 at pages 8, 11, 13-16, 23, 26, 29, 33, 40, 45; WO'282 at pages 5, 7, 9, 11-13, 20, 23, 26, 30, 37, 42. However, none of the above formulae encompass, let alone suggest, the 2' substitution pattern required by the '6087 claims. For example, none of these formulae provide for a fluorine at the 2' (down) position. For Formulae (II), (V) and (X), the 2' (down) substituent is  $-OR^3$ , i.e., not fluorine. For Formulae (XI), (XVI), (XVII) and (XVIII), chlorine, bromine and iodine are the only halogens permitted at the 2' (down)  $R^7$  position, suggesting that fluorine was omitted purposefully, which is a negative teaching or a "teaching away." The purposefulness of this omission is further indicated by the fact that, e.g., Formulae (X), (XI) and (XVII) include fluorine among the possible 2' (up)  $R^6$  substituents. WO'121 at pages 13, 16, 30, 40; WO'282 at pages 10, 12, 27, 37.

Regarding inventive step, the Applicant respectfully asserts that no *prima facie* case has been advanced. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. A prior art reference teaches away when a person of ordinary skill in the art, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. Having expressly excluded fluorine as an option for the 2' (down) substituent (e.g., R<sup>7</sup>), it cannot be said that the person with ordinary skill in the art would have come up with the current solution for the technical problem given the disclosure of WO'121 and/or WO'282.

Also, neither WO'121 nor WO'282 describes how to make any (2'R)-2'-fluoro (down)-2'-C-methyl (up) nucleoside. For example, neither contains any working example of how to make a (2'R)-2'-fluoro (down)-2'-C-methyl (up) nucleoside. In fact, both references lack even a single example teaching how to synthesize any nucleoside having a fluorine atom on the sugar ring. They do not describe fluorinated starting materials, fluorinating reagents, or compounds that could be fluorinated. They also lack any working example that one skilled in the art could have modified, without extensive experimentation, to make the claimed compounds. For example, both WO'121 and WO'282's schemes and synthetic examples are directed to making nucleosides with, e.g., 2'-hydroxy-(down)-2'-alkyl-(up) and 2'-deoxy-2'-alkyl-(up) substitution patterns. See WO'121 at pages 66-70 (Schemes 3 and 4); WO'282 at pages 62-66 (Schemes 3 and 4). These schemes would not have informed one skilled in the art regarding how to make a (2'R)-2'-fluoro-(down)-2'-C-methyl-(up) nucleoside. Accordingly, neither WO'121 nor WO'282 can anticipate or render obvious the claimed compounds. As discussed below in **Section 10.3**, the successful synthesis of 2'-deoxynucleosides having a 2'-fluoro (down)-2'-C-methyl (up) substitution pattern was extraordinarily difficult.

Additionally, WO'121 and WO'282 both lack biological testing data suggesting that the compounds claimed in the '6087 application have anti-HCV activity. The WO'121 and WO'282 examples have hydroxyl (-OH), and not fluorine (F), as the 2' (down)

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substituent. Contrary to Opponent's assertion, neither WO'121 nor WO'282 contains any teaching or suggestion that compounds of the '6087 claims, i.e., with fluorine at the 2' (down) position, would be useful as anti-HCV therapeutics.

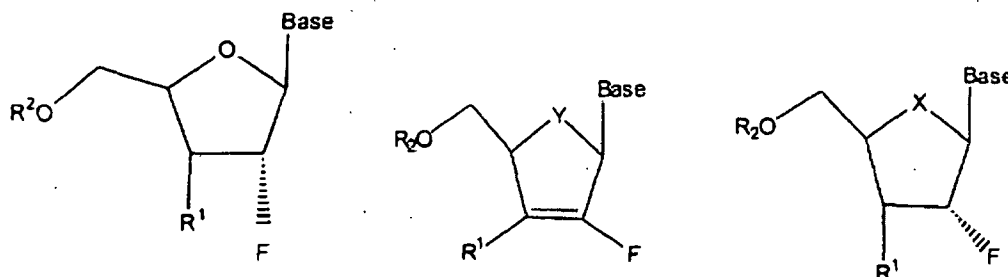
For at least the foregoing reasons, neither WO'121 nor WO'282 anticipates or renders obvious the present application's pending claims.

## II. WO1999/043691 (WO'691)

As per the opponent, the use of certain 2'-fluoronucleosides to treat HCV is disclosed in WO1999/043691 ("WO'691"). The opponent alleges that modification using fluorine at 2'-position either up or down was very well known before the priority date of the present application.

### Applicant's Response:

In response, Applicant respectfully disagrees. Compounds of WO'691 also do not have a 2'-fluoro (down)-2'-C-methyl (up) substitution pattern, as clearly seen from the structures. These compounds are mono-substituted at the 2' position of sugar moiety. The compounds of the present invention have a (2'R)-2'-fluoro (down) - 2'-C-methyl (up) substitution pattern. This substitution pattern is not disclosed in WO'691. Compounds of WO'691 are only mono-substituted at the 2' position, whereas the present invention is specifically directed to a 2'-fluoro (down)-2'-C-methyl (up) substitution pattern. WO'691 further provides no guidance to persons of ordinary skill in the art concerning the synthesis of nucleosides having a (2'R)-2'-fluoro (down) - 2'-C-methyl (up) substitution pattern.



Likewise, the other references cited by the Opponent (i.e. Eldrup et al., Bhat et al., and Olsen et al.) also provide no description of di-substituted compounds at the 2' position. These references do not provide the basis for an inventive step rejection for at least these reasons, and therefore, cannot be used to support a rejection on inventive step.

### III. Eldrup et al., Bhat et al., and Olsen et al.

The Opponent argues in paragraph 7(ii) that "[f]urther structure-activity relationship at the 2' position was also known before the priority date" as evidenced by documents from Eldrup et al., Bhat et al., and Olsen et al. at the 16<sup>th</sup> International Conference on Antiviral Research (April 27, 2003, Savannah, GA).

#### Applicant's Response

Applicant notes that Opponent did not provide copies of the documents cited in paragraph 7(ii), and its arguments should be dismissed on this basis alone.

That said, they are referenced in the present application's specification. But the Opponent has both over-simplified and over-stated its argument. Contrary to Opponent's assertion, neither Eldrup et al., Bhat et al., nor Olsen et al. give a detailed account of the "structure-activity relationship at the 2' position." Instead, they give limited accounts of nucleoside analogs that are mostly mono-substituted at the 2' position. Indeed, the only di-substituted compounds have either -OH/-methyl or -O-methyl/-methyl at the 2 position. These references do not discuss 2'-di-substituted compounds having a fluorine at the 2' (down) position.

Opponent's argument is limited to the two-part statement that "modifications at the 2' position" and "modification with fluorine at [the] 2' position" were known. Perhaps Opponent hopes that the reader will "fill in the blank" on arguments that it is unable to make, itself, since Opponent has failed to show how these references show or suggest anything else, i.e. compounds having fluorine and methyl substituents at the 2' position, let alone the particular 2'-fluoro (down)-2'-C-methyl (up) substitution pattern of the present invention.

Lastly, if anything, Eldrup et al. teaches away from the present invention as it teaches that compounds with a 2'-fluoro (down) substituent and hydrogen at the 2' (up) position showed much worse anti-HCV activity than the corresponding 2'-hydroxy (down)-2'-methyl (up) compounds (see Eldrup et al., slide 8).

These references do not provide the basis for an inventive step rejection for at least these reasons, and therefore, cannot be used to support a rejection on inventive step.

**IV. Park et al., Gumina et al., Pankiewicz et al., Middleton, and Wachtmeister et al.**

The Opponent raises several references in Section 8 of its Opposition Brief. Opponent makes very general statements in these sections and has not shown how those general statements are applicable to the invention at hand.

**Applicant's Response**

As a preliminary matter, Opponent's argument relies on gross assumptions that the Opponent makes across the entire field of medicinal chemistry without showing that it is appropriate to do so, and without applying these assumptions to the particular subject matter of invention, i.e. nucleotide analog inhibitors of HCV RNA polymerase. Opponent's arguments should be rejected on this basis alone.

With respect to Park et al. and Gumina et al., Opponent states that fluorine can have a wide variety of effects, but has not applied any of those purported effects to the context of this invention. Opponent states that Park et al. describe that "fluorine substitution can alter the chemical properties, disposition and biological activity of drugs" and mentions in "two types of impacts" namely "binding of ligands" and "drug disposition, in terms of distribution, drug clearance, routes, and extent of drug metabolism." Opponent then states that Gumina et al. shows that "fluorine substitution also has a favourable effect of increasing metabolic stability." Respectfully, Opponent's arguments are so general and broad that they have lost any meaning. Opponent has not shown specifically how Park et al. or Gumina et al.

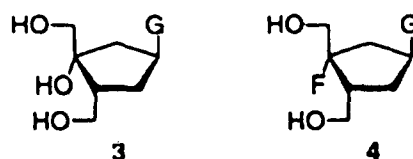
render any one particular aspect of the present invention obvious. By raising an extremely broad set of general concepts, from ligand binding to distribution and metabolism, the Opponent seems to be suggesting any and all possible concepts which *might* apply to the present invention, but have not been able to show how any specific concepts actually could or do apply.

Regarding Pankiewicz, this general review article discusses various fluorinated nucleosides, including nucleosides containing fluorine at C-2', nucleosides doubly fluorinated at C-2', 3'-deoxy-3'-fluoro nucleosides, C-4' fluorinated nucleosides and C-5' fluorinated nucleosides. Out of the many fluorinated compounds discussed in Pankiewicz et al., not a single compound is taught that has 2'-fluoro (down)-2'-methyl (up) substitution. Pankiewicz et al. also does not provide any guidance regarding how to make the presently claimed compounds, and such would not have been obvious as discussed in more detail in Section 10.3 below.

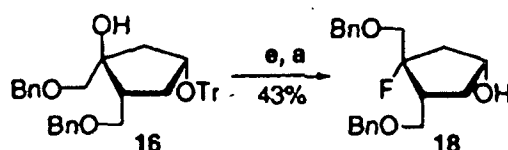
The next article, Middleton, does not discuss the use of DAST to fluorinate tertiary alcohols on nucleoside sugar rings, nor does it disclose or refer to (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides. The Opponent engages in oversimplification when asserting that, because DAST had been shown to fluorinate certain alcohols, it was therefore known how it would react with very different substrates. Rather, even if DAST had been shown to successfully fluorinate, e.g., certain straight chain alcohols, one skilled in the art could not have predicted that DAST would work to fluorinate a sterically hindered tertiary alcohol at the 2' position of a nucleoside's sugar ring. The Opponent's argument is based on impermissible hindsight gained from Applicant's present application, which was the first publication teaching the synthesis of a (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleoside using DAST.

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Finally, Wachtmeister et al. discusses the synthesis of 4-substituted carbocyclic 2,3-dideoxy-3-C-hydroxymethyl nucleoside analogues (3) and (4) shown below:



Wachtmeister et al. discloses that such compounds were made by fluorinating the 4-position of a carbocyclic intermediate 16 using Deoxofluor:



Wachtmeister et al. also states that attempting the same transformation with DAST gave a mixture of products.

Wachtmeister et al. would not have taught one skilled in the art that either Deoxofluor or DAST could be used to make the presently claimed (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides. Intermediate 16 in Wachtmeister et al. is carbocyclic and lacks a base. Thus, Wachtmeister's Intermediate 16 is structurally very different from both the presently claimed compounds and from the intermediates that Applicant's specification teaches are needed to react with DAST in order to make a (2'R)-2'-fluoro (down)-2'-methyl (up) nucleoside (see, e.g., pages 76-87 of the PCT application).

All of Opponent's arguments in Section 8 of its brief should be rejected for at least these reasons.

#### V. Maybridge MedChem and Hayakawa et al.

In Section 9 of its brief, the Opponent argues that Bioisosteres in Medicinal Chemistry, published by Maybridge MedChem ("Maybridge MedChem") (Annexure 7 to Opponent's submission) discloses that "replacement of hydroxyl group with

fluoro group extends the biological half-life and eliminates the formation of toxic metabolites and thus such type of replacement are extensively used in medicinal chemistry." Then, in a complete non sequitur, Opponents cite Hayakawa et al. for teachings about fluorination chemistry.

### **Applicant's Response**

Opponent's citation of Maybridge MedChem is not relevant to this invention. Maybridge MedChem discusses a variety of drugs and other biologically active chemicals that are very different from the compounds of the present application in terms of both chemical structure and biological function. Maybridge MedChem does not even discuss nucleosides, nucleotides, or anti-viral compounds! The Opponent's contention that an artisan would have applied teachings regarding structurally different compounds that act through very different biological mechanisms so as to arrive at the presently claimed compounds depends on oversimplifications that one skilled in the art would not have made. Opponent cites Maybridge MedChem for the notion that the "fluoro group extends the biological half-life and eliminates the formation of toxic metabolites" but makes no showing of how those concepts are relevant in the context of this invention, or how the person of ordinary skill in the art would or even could apply the teachings of Maybridge MedChem to come upon the presently claimed invention.

Hayakawa et al. discusses reactions between DAST and certain nucleosides having 2',3'-vicinal diol systems. However, Hayakawa et al. does not discuss the use of DAST to install a fluorine atom on a tertiary carbon at a nucleoside's 2' position in order to make a (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleoside as required by the present application's claims. Hayakawa et al. pertains only to reactions between DAST and certain secondary alcohols. The resulting products differ structurally from the presently claimed compounds, e.g., they lack the 2'-fluoro (down)-2'-C-methyl (up) substitution. Hayakawa et al. does not describe any DAST reaction that provides a tertiary fluoride, let alone at a nucleoside's constrained and sterically hindered 2' position. Even further, Hayakawa et al. demonstrates the



unpredictability of DAST fluorination reactions, e.g., showing that they can fail to give a fluorinated product, instead producing an unfluorinated 2'-cyclo derivatives. See Hayakawa et al., e.g. at page 1137 (conversion of Compound 14 to Compound 15) and other examples.

In relying on Hayakawa et al., the Opponent again engages in oversimplification by asserting that, because DAST had been shown to fluorinate certain alcohols, it was therefore known how it would react with very different substrates. The Opponent also uses impermissible hindsight, selecting from the prior art a reactant (DAST) that Applicant's own specification was the first to teach could be used to make the claimed compounds. See **Exhibit E** at page 22. The Patent Trial and Appeal Board (PTAB) of the United States Patent and Trademark Office (USPTO) has repeatedly rejected similar hindsight-based arguments relying on Hayakawa et al. See **Exhibit C** at pages 27, 32, 35-36; **Exhibit H** at pages 10, 11, 17-21.

If the learned Examiner is interested further in Opponent's "isosteres" argument, he may kindly refer to an article that discusses this point in the proper context of this invention. A recent study has confirmed, using one of the claimed compounds, that the 2' (down) fluorine atom does not act as an isosteric replacement for hydroxyl in the context of the present invention. The 2' (down) fluorine atom does not engage in the same type of bonding with the NS5B enzyme that a 2' (down) hydroxyl group does; rather, the fluorine atom appears to disrupt such interactions. See Appleby et al., Structural Basis for RNA Replication by the Hepatitis C Virus Polymerase, *Science* **2015** 347:771-775 at 774 (**Exhibit J**).

All of Opponent's arguments in Section 9 of its brief should be rejected for at least these reasons.

#### VI. Matsuda et al.

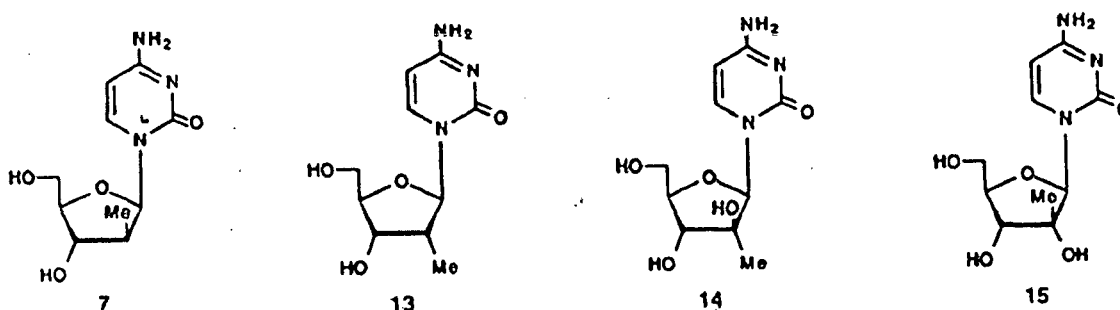
As per the Opponent, Matsuda et al. (Annexure 9 to Opponent's submission) "discloses the synthesis of 2'-deoxy-2'-(S)-methylcytidine and their use in anti-leukemic activity." According to the Opponent, nucleoside analogues with methyl



(up) and hydroxyl (down) at 2' position were known way before the priority date of the present application.

### Applicant's Response

In response, Applicant respectfully disagrees with the Opponent's assertions. Matsuda et al. discusses the synthesis of 2'-deoxy-2'(S)-methylcytidine (compound 7) along with compounds 13-15 shown below:



Matsuda et al. also discusses the inhibitory activity of these compounds against mouse leukemic cell line L1210 cells. The compounds disclosed in Matsuda et al. differ from the presently claimed compounds, e.g., Matsuda et al. does not disclose or suggest compounds with (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) substitution. In fact, Matsuda et al. does not contain any reference to fluorinated nucleosides or processes for making such compounds. Matsuda et al. also lacks any suggestion that the (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides of the present application's claims would have anti-HCV activity. In fact, Matsuda et al. does not mention any type of antiviral activity, but rather focuses only on anti-leukemic activity. In this regard, Matsuda et al. teaches that 2'-deoxy-2'-methyl compound 7 was the most active against the mouse leukemic cell line tested (page 3969-70).

The skilled artisan would also understand that an anti-leukemic (or anti-cancer) agent would be acting as DNA and that natural DNA nucleosides have a hydrogen in the 2' (down) position. The skilled artisan would understand that a nucleoside with anti-HCV (or anti-*Flaviviridae*) activity would be acting on RNA and that natural

RNA nucleosides have a hydroxyl in the 2' (down) position. Also, anti-cancer agents typically work by killing the cell, whereas anti-HCV agents must be anti-viral but retain cell viability. Matsuda et al. does not provide the basis for an inventive step rejection for at least these reasons.

#### VII. WO2002/057425 (WO'425)

As per the Opponents all the claims 1 to 10 of the present application are obvious by disclosure in WO2002/057425 (hereinafter referred to as "WO'425") (Annexure 10 to Opponent's submission). As per the opponent, the basic scaffold in WO'425 discloses a sugar attached to nitrogenous base and also sets out and encompasses various substitutions for base. It also discloses compounds and derivatives including triphosphates, monophosphates, and their stereochemical configuration. As per the opponent, all the claims are rendered obvious by disclosure of WO'425.

#### Applicant's Response

Applicant respectfully disagrees with the Opponent's characterization of the pending claims as well as the reference relied upon. An obviousness argument can be established only by showing such references as may give a person skilled in the art a reason to cause the substitution. In the absence of such a reference, mere similarity in the compounds in a general manner does not establish obviousness.

Opponent first argues, that "*425 discloses a compound of formula (I) and R1 could be C1-C4 alkyl which includes methyl and R2 includes fluorine*" and "*specific examples of uridine derivative & 5'methyluridine are provided in examples 46-51 and examples 102 and 103*". Opponent alleges that WO'425 encompasses the compounds disclosed and claimed in the present application.

We address each of these contentions in turn.

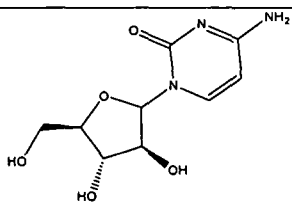
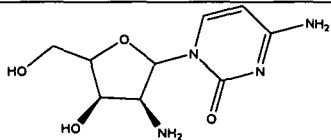
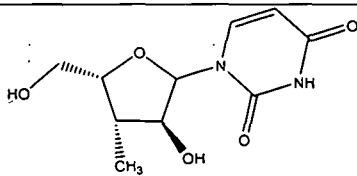
As a preliminary matter, a close perusal of WO'425 would reveal that claimed compounds cannot be deemed to be part of invention as envisaged in WO'425. It is to be noted that from the synthesis route prescribed in WO'425 claimed compounds

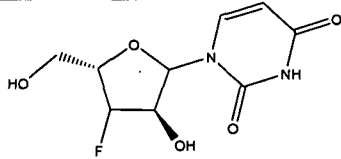
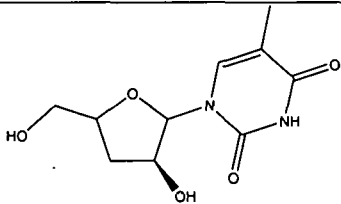
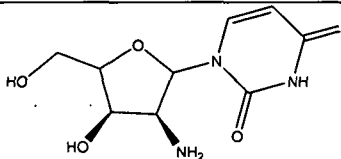
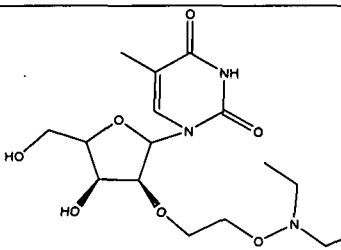
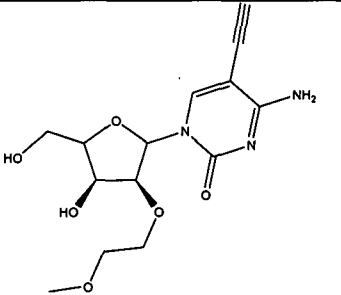
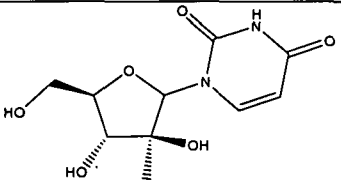
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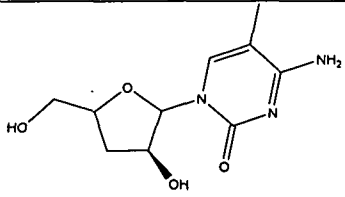
cannot be synthesized. Further, Scheme 1 provided on page 56 of WO'425 describes the general synthesis of compounds. There is no fluorination step, at all, in the synthetic route of said Scheme 1 without which fluoro substituent at 2'-position of ribose sugar is not possible. Scheme 1 also does not describe fluorinated starting materials or fluorinating reagents. This is also evident from the fact that none of the compounds mentioned in the examples 1 to 154 on pages 57 to 185 of WO'425 have the unique 2'-fluoro (down)-2'-C-methyl (up) substitution pattern as claimed in the present invention. Thus, there is neither exemplification nor enabling disclosure of the compound of the present invention. Therefore, it is misleading and incorrect to argue that WO'425 anticipates claimed compounds.

Continuing with the Opponent's argument WO'425 provide a long list of specific compounds. However, none of them have the unique 2'-fluoro (down)-2'-C-methyl (up) substitution pattern as claimed.

For convenience, the cytosine- and uridine- based compounds of the said list on pages 23-24 of WO'425 are shown here:

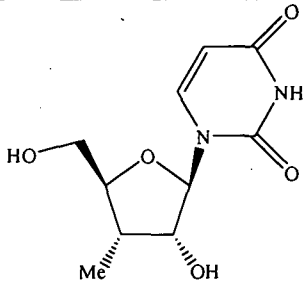
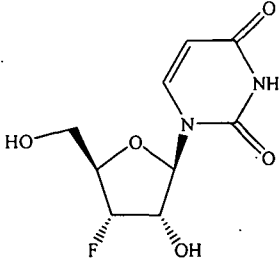
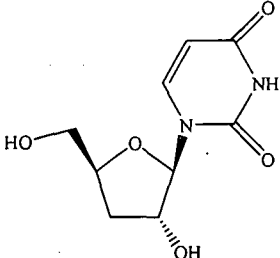
Str. No.	Compound Name	Structure
1	1-(D-arabinofuranosyl)-1H-cytosine	
2	2'-amino-2'-deoxycytidine,	
3	3'-deoxy-3'-methyl-uridine	

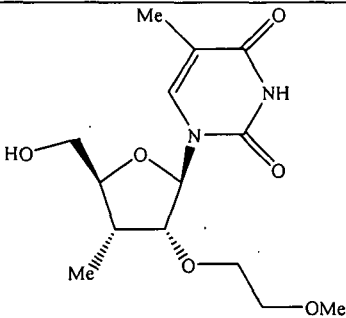
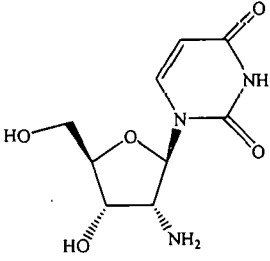
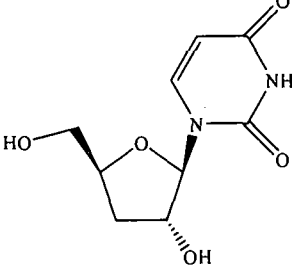
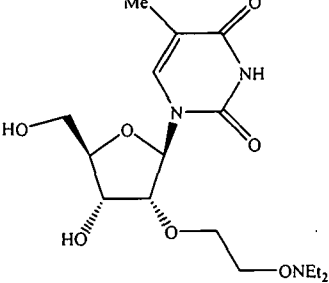
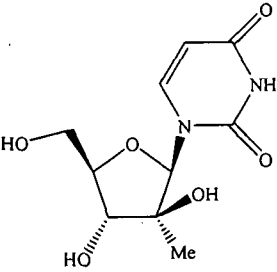
4	3'-deoxy-3'-fluorouridine	
5	3'-deoxy-5-methyl-uridine	
6	2'-amino-2'-deoxy-uridine	
7	2'-O-[2-(N,N-diethylaminoxy)ethyl]-5-methyluridine	
8	5-ethynyl-2'-O-(2-methoxyethyl)-cytidine	
9	1-(2-methyl-D-arabinofuranosyl)uracil	

10	5-methyl-3'-deoxycytidine	
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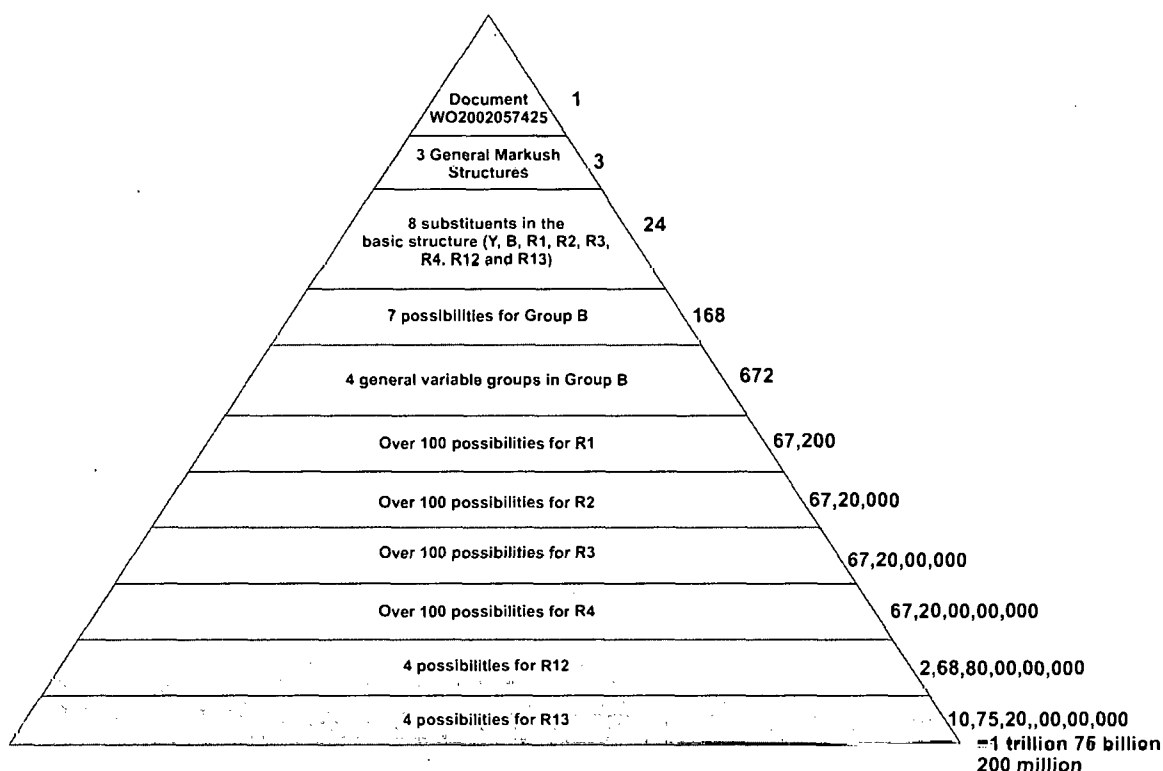
It should be immediately apparent that none of these compounds have a 2'-fluoro (down)-2'-methyl (up) substitution pattern on the sugar ring, as claimed.

Similarly, none of compounds provided in Examples 46-51, 102 and 103 have a 2'-fluoro (down)-2'-C-methyl (up) substitution pattern, as claimed, and many don't even have the same substituent at the 3' position. Please see the following chart:

Example	Compound Structure
46	
47	
48	

49	 <chem>COCCOC[C@H]1O[C@@H](c2nc(=O)c(C)c(=O)[nH]2)[C@H](O)[C@@H](C)[C@H]1O</chem>
50	 <chem>N[C@H]1[C@@H](O)[C@H](CO)O[C@H]1Nc2nc(=O)c[nH]c2=O</chem>
51	 <chem>O[C@H]1[C@@H](O)O[C@H](Nc2nc(=O)c[nH]c2=O)[C@H](CO)O1</chem>
102	 <chem>CCOC(CCOC)O[C@H]1[C@@H](O)[C@H](CO)O[C@H]1Nc2nc(=O)c(C)c(=O)[nH]2</chem>
103	 <chem>C[C@H]1[C@@H](O)[C@H](CO)O[C@H](Nc2nc(=O)c[nH]c2=O)[C@H](O)[C@H]1O</chem>

It is submitted that WO'425 provides billions of possibilities and permutations and combinations as illustrated below:



It may be noted that choosing even one Markush i.e. Formula (I) on page 4 of the description out of three general Markush structures i.e. Formula (I), Formula (IV), Formula (XII) given in WO'425 will result in 1 trillion 75 billion 200 million compounds. This extreme breadth of compounds applies to the other structural formula of WO'425 as well.

Arbitrary selections of substituents out of billions of possibilities for B, Y, R1, R2, R3, R4, R12 and R13, more so in view of the scope of invention as envisaged in WO'425 is not justified in law, at all. Opponent claims that WO'425 discloses compounds wherein R2 is F. However, the description of possibilities of R2 is very long, and likely encompasses millions of possibilities. There is not even a remote description of the possibility of existence of such a compound. Further, claim 1 of WO'425 contains no mention of R2 being fluorine. As submitted above, from synthesis route of scheme provided in WO'425, R2 can never be fluorine.



In summary, pages 23-24 and Examples 46-51 and 102-103 of WO'425 do not disclose compounds with the unique substitution pattern of present invention i.e. (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides. It should be noted that none of the compounds in WO'425 compounds have the same substitution pattern as the compounds of the present application and nor is their efficacy disclosed. This reference does not provide the basis for an inventive step rejection for at least these reasons, and therefore cannot be used to support a rejection on inventive step. Therefore, WO'425 does not render these claims obvious.

In view of the comments above, Applicant submits that the presently pending claims are inventive. Accordingly, the instant ground is liable to be rejected.

#### **VIII. WO'287**

As per the opponents, WO'287 discloses 2'-methyl (up)-2'-fluorine (down) nucleoside analogues in its embodiment I but with different base attached to sugar. As per the Opponent the WO'287 application also discloses several 2'-methyl (up) 2'-hydroxy (down) compounds which were known to have anti-HCV activity at the time of filing of the present application. Opponent submits that at the time of priority of the present application it was common general knowledge that 2'-methyl-up-2'-hydroxy-down nucleoside analogues had the potential to be therapeutically efficacious in treating HCV.

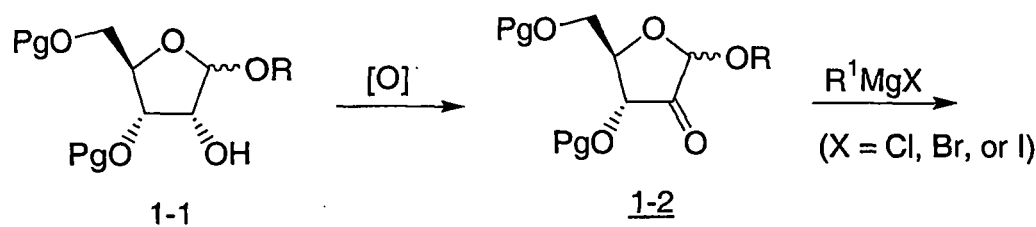
#### **Applicant's Response**

In response, Applicant respectfully disagrees. WO'287 discloses compounds wherein the sugar is attached to pyrrolo[2,3-d]pyrimidine moiety. The compounds of WO'287 are totally different compounds than the nucleoside compounds of present application. Applicant submits that a careful analysis of WO'287 reveals that the compounds of the present application are neither disclosed by the cited reference nor are obvious in view of said disclosure.

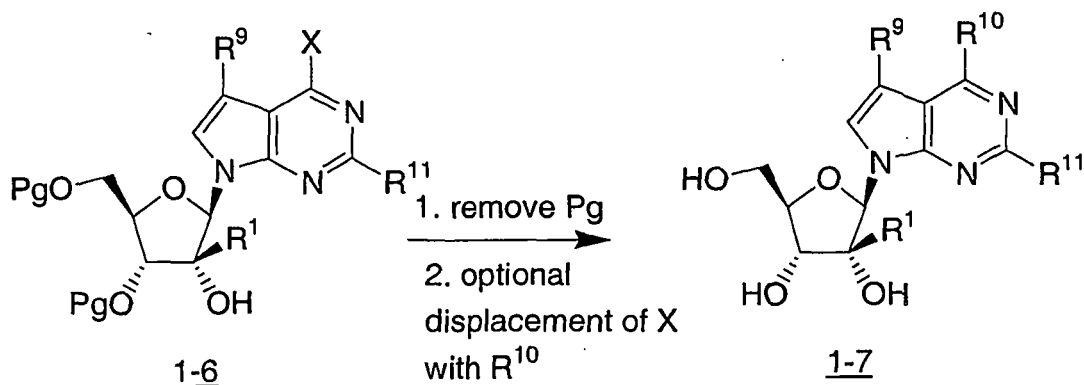
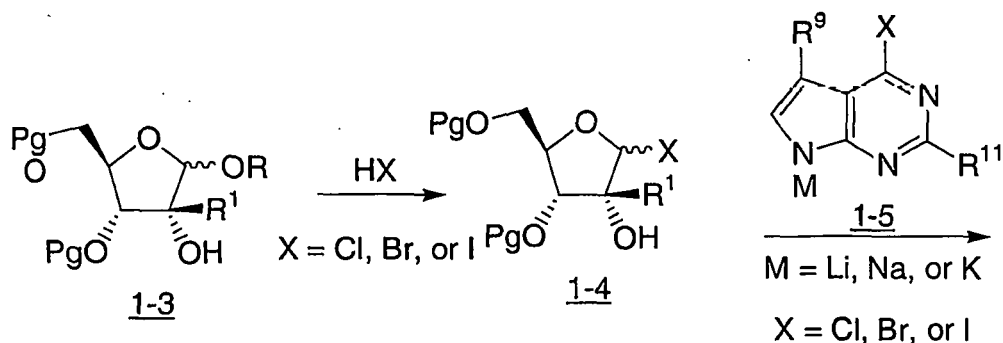
Firstly, it is to be noted that the compounds disclosed and taught by WO'287 are pyrrolo[2,3-d]pyrimidine compounds unlike the compounds of the present application.

Secondly, all the exemplified or promising compounds of WO'287 either have a 2'-hydroxy (down) - 2'-methyl (up) or 2'-hydroxy (up) - 2'-methyl (down) substitution pattern at 2'-position of sugar in pyrrolo[2,3-d]pyrimidine compounds. There is no disclosure or teaching of compounds with 2'-methyl (up) 2'-fluoro (down) substitution as claimed in the present application. Further, WO'287 describes a general method for preparation of compounds of the present invention in scheme 1 which is reproduced herein below. The synthetic scheme does not teach fluorination at 2'-position of pyranose ring in order to have 2'-fluoro (down) and 2'-C-methyl (up) substitution. Actually, there is not a single example for the preparation of a compound with 2'-fluoro (down) and 2'-methyl (up) even with pyrrolopyrimidine as a base. The only teaching from WO'287 is to have a 2'-hydroxy (down) and 2'-methyl (up) or 2'-methyl (down) and 2'-hydroxy (up) that too in pyrrolo[2,3-d]pyrimidine compounds.

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Pg = protecting group  
R = lower alkyl



It is submitted that this WO'287 does not disclose or teach 2'-deoxyribonucleosides having the unique substitution pattern of the instant invention wherein the base is a pyrimidine base.

Further, WO'287 does not describe how to make a 2'-deoxyribonucleoside compound with a 2'-fluoro (down)-2'-C-methyl (up) substitution pattern at 2'-carbon of ribose sugar moiety or provide any data indicating that such a compound has anti-flaviviridae activity, let alone anti-HCV activity. Still further, the WO'287

fails to provide any guidance or suggestion as to compounds having the particular 2'-fluoro (down) – 2'-C-methyl (up) substitution pattern of the instant invention.

This reference does not provide the basis for an inventive step rejection for at least these reasons, and therefore, cannot be used to support a rejection on inventive step.

#### **IX. No Motivation to Combine; No Expectation of Success**

The Opponent's argument is devoid of any explanation as to why one skilled in the art would have selected any of the foregoing references or would have been motivated to combine any of them to arrive at the presently claimed invention. Thus, the Opponent fails to establish a *prima facie* case of lack of inventive step. Rather, in hindsight the Opponent has attempted to identify in scientific literature the discrete structural components of the presently claimed compounds, as well as discrete chemical reagents that may be used to make them according to the Applicant's own novel methods. However, such is insufficient where there is no evidence that an artisan would have selected any of the foregoing references or any combination thereof, no evidence that an artisan would have been motivated to select and combine particular portions in the disclosure of each reference to arrive at the claimed invention, and no evidence that the artisan would have had any reasonable expectation that the presently claimed compounds would have anti-*Flaviviridae*, e.g., anti-HCV, activity and low toxicity. Accordingly, the Opponent's inventive step argument wholly fails to establish that the presently claimed invention lacks inventive step.

Furthermore, the combination of references discussed above would not have taught a skilled artisan how to make the claimed compounds. In fact, the United States Patent and Trademark Office ("USPTO") has repeatedly rejected arguments very similar to those made by the Opponent with respect to synthetic methods. For example, in Interference No. 105,871, Idenix Pharmaceuticals, Inc., et al. argued that DAST could have been routinely used to replace a hydroxyl group with a fluorine atom in a compound from related work published by Matsuda et al. so as to make a

(2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleoside. See **Exhibit H** at 7-14.

The PTAB rejected such arguments:

Specifically, Dr. Dahma [Idenix's expert witness] testifies that the literature taught fluorinating the sugar at the 2' position of a deoxy-arabinonucleoside or arabinonucleoside with the reagent DAST. (FFs 11-13). According to Dr. Dahma, because these reactions include replacing an OH group with a fluorine and inverting the stereochemistry so that the fluorine is in the "down" position, those in the art would have considered these reactions to be the same as the reactions needed to make 2'-F-2'-Me-ribonucleoside within Count 1. Dr. Dahma also testifies that even though the nucleoside fluorinations with DAST reported in the literature as of December 2001 were fluorinations of secondary alcohols, fluorinations of tertiary alcohols with DAST were also known. (FFs 15-17.)

Clark [Applicant] opposes Sommadossi's [Idenix's] argument, relying on the opinion of its witness, Dr. Marquez. According to Dr. Marquez, the evidence presented by Dr. Dahma does not show that those in the art would have considered using DAST to synthesize a 2'-F-2'-Me-nucleoside because it would have been too unpredictable. Dr. Marquez testifies that those of skill in the art would have been aware of the risks of producing elimination and anhydro products when using DAST and would have understood that DAST had not been shown to produce a tertiary fluorine on the 2' carbon of the sugar of a nucleoside. (FFs 26.)

In support, Dr. Marquez cites to correspondence between Idenix personnel and to the advice of consultants hired by Idenix, which were critical of the proposed schemes. (FFs 27-33.)

Clark also argues that Sommadossi's own diligence period attests to the lack of knowledge about how make a compound within the scope of Count 1 at the time of Sommadossi's asserted conception. (Clark Opp. 9, Paper 460, at 3:17-4:4.) Clark argues that six Ph.D. level chemists at Idenix, as well as other researchers, with the help of two consultants (Dr. Fleet (*see* Storer Deposition, Exh. 1644, 73:22-24 (describing Dr. Fleet as a "world expert on carbohydrate chemistry") and Dr. Coe (*see id.*, 74:23-24 (describing Dr. Coe as an "expert in organofluorine chemistry"))), worked for over three years to make a 2'-F-2'Me-ribonucleoside. (Clark Opp., Paper 460, at 9:5-9.) Clark also notes that at least one member of the Idenix team (Dr. Griffon and Claire Pierra, *see* Storer Decl., Exh. 1429, at ¶ 35) attended a four-day training course in fluorination chemistry to gain the necessary knowledge and, further, that Sommadossi was only able to actually reduce to practice an embodiment of the Count after the publication of a synthesis pathway in the application that became the Clark patent. (Clark Opp. 9, Paper 460, at 9:6-7 and 3:17-22.) According to Clark, this effort was not routine and demonstrates the lack of skill of any artisan at the time, as well as an incomplete conception by the Sommadossi inventors by their asserted conception dates.

We are persuaded by Clark's argument. Though Dr. Dahma presents evidence to show that each step of the synthesis of a 2'-F-2'Me-ribonucleoside would have been known to those in the art, the skepticism shown by Dr. Coe, who was consulted for his expertise, and in the communications between Drs. Storer and Stewart support Dr. Marquez's opinion that those of skill in the art would not have had the necessary skill.

In addition, we are persuaded that the length of time Idenix personnel spent trying to synthesize a 2'-F-2'Me-ribonucleoside does not exemplify routine experimentation. Sommadossi argues that it is improper to look to the activities of specific people to show what was known by a skilled artisan at the time because such analysis "is premised on the false assumption that those efforts were made by the hypothetical person instead of real people with imperfect awareness of the relevant art." (Sommadosi Reply 9, Paper 464, at 3:20-23.) According to Sommadossi, if there is an operative method of making a compound in the art, it is irrelevant that the actual inventor tried and failed, even many times, to make it. (Sommadosi Reply 9, Paper 464, at 3:20-4:10.)

Sommadosi's argument does not persuade us to ignore the evidence of the Idenix personnel's extraordinary effort. To make a determination of what the hypothetical ordinarily skilled artisan would have been able to do, we look to evidence of not only what information was publically available, but also evidence of what actual artisans did with that knowledge.

Both Drs. Dahma and Marquez agree that a hypothetical person skilled in the art of synthesizing a compound of the count would have an advanced education (Ph.D. or master's degree) and additional experience in the chemical aspects of drug discovery (*i.e.*, synthetic organic chemistry). (See Dahma Decl., Exh. 1281, ¶ 16; Marquez Decl., Exh. 2001, ¶ 70.) The members of the Idenix team were all employed as chemists and several had doctoral degrees. (See, *e.g.*, Storer Decl., Exh. 1429, ¶ 2 (testifying that he has a D.Phil. degree in chemistry); Substitute Declaration of Jean-Francois Griffon, Exh. 1471, ¶ 2 (testifying that he has a Ph.D. degree in organic chemistry); Substitute Declaration of Adel Moussa, Exh. 1428, ¶ 2 (testifying that he has a Ph.D. degree in organic chemistry); Substitute Declaration of Alistair Steward, Exh. 1241, ¶ 2-3 (testifying that he has a Ph.D. degree in organic chemistry.) Sommadossi does not argue that they were not at least ordinarily skilled artisans. On the record before us, we have no reason to exclude them as representative of ordinarily skilled artisans at the time. Thus, the evidence of the effort exerted by the Idenix team to eventually synthesize a 2'-F-2'-Me-ribonucleoside is informative of what the hypothetical skilled artisan could do.

Furthermore, the evidence of the effort exerted by the Idenix team shows that it was not just one chemist who was unable to synthesize a compound within Count 1 with routine experimentation, but a team of chemists, even after they had consulted with



others considered to be experts and had sought additional training. From this record it is reasonable to find that if after all of this effort, a compound within the scope of the count could not be synthesized easily, a hypothetical person of ordinary skill would not have known how to synthesis such a compound either.

*Id.* at 8-21.

For this additional reason, the combination cannot render the claimed invention obvious.

#### **ADDITIONAL ARGUMENTS REGARDING INVENTIVE STEP**

The Applicant submits its additional reply under Sections 10.2 and 10.3 as below:

##### **10.2 Changes in Substituents at the 2' Position of Nucleosides Result in Large Changes in Activity or Toxicity.**

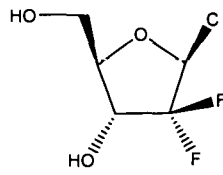
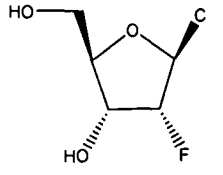
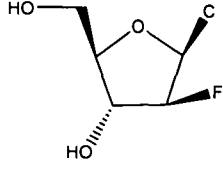
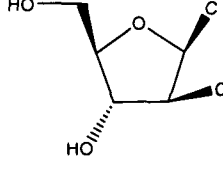
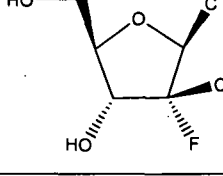
The particular substitution pattern of the claimed compounds is unique, and imparts unexpectedly high activity and low toxicity to them. In this regard, Applicant re-submits Table 1, below, which shows activity (EC<sub>90</sub><sup>2</sup>) and cytotoxicity (CC<sub>50</sub><sup>3</sup>) of various 2'-substituted nucleosides:

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<sup>2</sup> EC<sub>90</sub> refers to effective concentration to achieve 90% inhibition (see, e.g., '6087 description of FIG. 1).

<sup>3</sup> CC<sub>50</sub> refers to the concentration required to reduce the number of non-virus-infected cells by 50% (see, e.g., '6087 Example 5 (Toxicity)).

**Table 1. Activity and Cytotoxicity Comparison  
of 2'-Substituted Cytidine Analogs**

No.	Compound	HCV Activity EC <sub>90</sub> (μM)	Cytotoxicity			
			Clone A CC <sub>50</sub> (μM)	Hep G2 CC <sub>50</sub> (μM)	BxPC3 CC <sub>50</sub> (μM)	CEM CC <sub>50</sub> (μM)
1		<1	<0.1	<1	<1	<1
2		5.66	>100	400	10	6
3		Cannot determine: Toxic to cells	<50	200	5	5
4		9.73	10.47	40	<1	<1
5		4.5	>100	>1000	>1000	>1000

"C" represents cytosine.

The above table is instructive for at least the following reasons.

First, it shows that the data for Compound 5<sup>4</sup> (present invention) is unexpectedly better than that of the compared compounds. For example, the 2'-fluoro (down)-2'-hydrogen (up) compound (Compound 2) shows HCV activity but is also toxic in certain cell lines. As noted above, Compound 2 (i.e., FdC) has also demonstrated mitochondrial toxicity. See **Exhibit F** at Table 5. The 2'-fluoro (up)-2'-hydrogen (down) compound (Compound 3) is too toxic to test for anti-HCV activity. The 2'-difluoro compound (Compound 1) is more active than Compound 2 but also very toxic. Finally, the 2'-methyl (up)-2'-hydrogen (down) compound (Compound 4) has activity but is also toxic against certain cell lines.

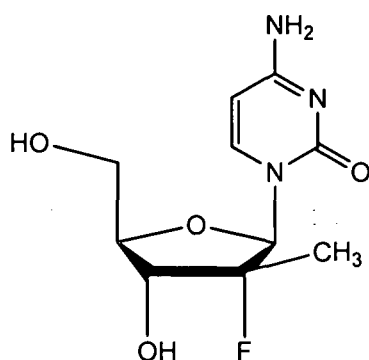
Second, these data demonstrate the high degree of unpredictability when varying the substituents at a nucleoside's 2' position. There is no clear trend in the data. Compound 5, therefore, has a very unexpected and surprising activity and toxicity profile.

Third, if one attempted to discern some trend from the foregoing data, it would suggest that a 2'-fluoro (down)-2'-methyl (up) substitution pattern would cause toxicity. Both Compound 2 (2'-fluoro (down)) and Compound 4 (2'-methyl (up)) show significant cytotoxicity against the cell lines tested. Thus, one of ordinary skill in the art would not predict the very low toxicity observed for Compound 5.

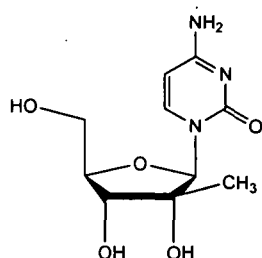
In addition, the learned Controller may refer to the experimental data already disclosed in the specification (see pages 66-71 and 87-94), which clearly indicates that 2'-deoxynucleosides with 2'-fluoro (down)-2'-methyl (up) substitution patterns are non-toxic, highly active and have other favorable characteristics as compared to the nucleoside compounds of the prior art. For example, Tables 1 to 9 of the present application compare the activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (Compound 3-6/Compound 4-6 in '6087) with the activities of 2'-C-methylcytidine and 2'-C-methyladenosine.

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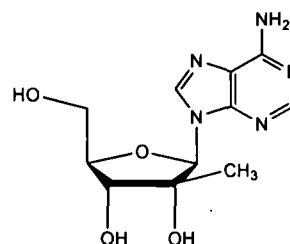
<sup>4</sup> Table 1's Compound 5 corresponds to the '6087 application's Compound 3-6/Compound 4-6, i.e., (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine.



(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (**Compound 3-6/4-6**)



**2'-C-Methylcytidine**



**2'-C-Methyladenosine**

Tables 1 and 2 in '6087 demonstrate that (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine has unexpectedly superior activity compared to 2'-C-methylcytidine in several HCV replicon assays. Tables 6 and 9 also demonstrate that (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine has unexpectedly lower toxicity, compared to 2'-C-methylcytidine and 2'-C-methyladenosine in cytotoxicity and human bone marrow cell assays. Table 8 further demonstrates (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine's PK parameters in Rhesus monkeys following a single oral dose. (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine's unexpected properties could not have been predicted and, thus, could not have been obvious from the compounds disclosed in the references upon which the Opponent relies.

Applicant asserts that, from the data presented above in Table 1 and in the specification, it is clear that the 2'-fluoro (down)-2'-C-methyl (up) substitution pattern present in the nucleosides of the present application unexpectedly imparts therapeutic activity against HCV while at the same time imparting no toxicity to the host.

In view of above, the compounds of instant invention are novel and not obvious to one skilled in the art.

**10.3 The Prior Art Did Not Enable the Synthesis of 2'-Fluoro (down)-2'-Methyl (up) Nucleosides.**

As noted above, none of the cited references describe how to make the compounds of the present application. The same is true of the prior art as a whole. Rather, Applicant's application first published on 13 January 2005 provided the first report of how to synthesize a 2'-fluoro-(down)-2'-C-methyl-(up) nucleoside.

Applicant has prevailed in contested proceedings with Idenix et al. in other countries—in particular Norway, the UK, and the United States. One issue central in these proceedings was whether the prior art would have enabled an artisan to make the claimed compounds without undue or overly burdensome experimentation. In addition to the lack of teaching in the prior art, these tribunals have considered the attempts of actual scientists in the field, specifically those at Idenix and affiliated institutions (i.e., the applicants for WO'121). Evidence of Idenix's failed attempts to make such compounds over a period of several years was first made available in U.S. Patent Interference No. 105,871, where Idenix's witnesses admitted that the first time Idenix successfully made a 2'-fluoro-(down)-2'-methyl-(up) nucleoside was only after Gilead's application published in 2005 and they repeated a procedure as written therein. See **Exhibit G** at 106-107; see **Exhibit C** at 9-10. Idenix's multi-year struggle illustrates that the prior art would have been insufficient to enable the synthesis of (2'R)-2'-fluoro-(down)-2'-C-methyl-(up) nucleosides prior to Gilead's application.

Further in this regard, the Oslo District Court panel, which included a technical judge who was a professor of chemistry, issued a decision on 21 March 2014 (**Exhibit B**) which, in part, discussed how difficult it was to make (2'R)-2'-deoxy2'-fluoro (down)-2'-C-methyl (up) nucleosides prior to the publication of Gilead's application. The Oslo District Court wrote:

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[T]he skilled person will be faced with a number of choices that have to be made in order to be able to produce or synthesise [a 2'-fluoro-2'-methyl nucleoside]. Firstly, a choice needs to be made between the sugar route and the nucleoside route. Thereafter, starting materials need to be chosen. Many alternatives will be available in respect of both route alternatives, and the choices will not be perceived as obvious. Moreover, a fluorination reagent needs to be selected. This also involves numerous alternatives. Even if one starts out from the most precise and restrictive part of the description, as well as the alternative claims, there are several options. One may for example choose both natural and synthetic bases. Finally, one needs to select reaction conditions and solvents, etc., for the various reactions. The Court notes that minor variations in chemical processes may have a major impact and be decisive in terms of whether or not one succeeds in bringing about the desired compound.

**Exhibit B** at page 32 (emphasis added). The Court then gave its judgment on whether the art was enabling, taking in account whether Idenix made any (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides before the priority date of the present application:

[T]he skilled person will, in order to carry out the invention, have to find an overall solution that will depend on the sum total of a number of partial solutions. The Court is of the view that the skilled person would not be able to carry out the invention without a considerable amount of trial and error. This conclusion is also supported by the fact that Idenix itself

would not appear to have been able to produce the compound until at a much later date.

*Id.* at page 33. The Oslo District Court concluded that the Gilead patent (equivalent to '6087) was valid and the Idenix patent based on WO2004/002999 was invalid.

The USPTO reached a similar conclusion: Gilead was the first to invent (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides. See **Exhibits C, D, E and H**. In reaching this conclusion, the USPTO considered Idenix's repeated failed attempts to make such compounds prior to the publication of Gilead's application as evidence that the prior art was not enabling. For example, the USPTO stated:

In addition, we are persuaded that the length of time Idenix personnel spent trying to synthesize a 2'-F-2'Me-ribonucleoside does not exemplify routine experimentation. Sommadossi [Idenix] argues that it is improper to look to the activities of specific people to show what was known by a skilled artisan at the time because such analysis "is premised on the false assumption that those efforts were made by the hypothetical person instead of real people with imperfect awareness of the relevant art." (Sommadosi Reply 9, Paper 464, at 3:20-23.) According to Sommadossi, if there is an operative method of making a compound in the art, it is irrelevant that the actual inventor tried and failed, even many times, to make it. (Sommadosi Reply 9, Paper 464, at 3:20-4:10.)

Sommadosi's argument does not persuade us to ignore the evidence of the Idenix personnel's extraordinary effort. To make a determination of what the hypothetical ordinarily skilled artisan would have been

able to do, we look to evidence of not only what information was publically available, but also evidence of what actual artisans did with that knowledge.

Both Drs. Dahma and Marquez agree that a hypothetical person skilled in the art of synthesizing a compound of the count would have an advanced education (Ph.D. or master's degree) and additional experience in the chemical aspects of drug discovery (*i.e.*, synthetic organic chemistry). (See Dahma Decl., Exh. 1281, 16; Marquez Decl., Exh. 2001, ¶ 70.) The members of the Idenix team were all employed as chemists and several had doctoral degrees. (See, *e.g.*, Storer Decl., Exh. 1429, ¶ 2 (testifying that he has a D.Phil. degree in chemistry); Substitute Declaration of Jean-Francois Griffon, Exh. 1471, ¶ 2 (testifying that he has a Ph.D. degree in organic chemistry); Substitute Declaration of Adel Moussa, Exh. 1428, ¶ 2 (testifying that he has a Ph.D. degree in organic chemistry; Substitute Declaration of Alistair Steward, Exh. 1241, ¶ 2-3 (testifying that he has a Ph.D. degree in organic chemistry.) Sommadossi does not argue that they were not at least ordinarily skilled artisans. On the record before us, we have no reason to exclude them as representative of ordinarily skilled artisans at the time. Thus, the evidence of the effort exerted by the Idenix team to eventually synthesize a 2'-F-2'Me-ribonucleoside is informative of what the hypothetical skilled artisan could do.

Furthermore, the evidence of the effort exerted by the Idenix team shows that it was not just one chemist who was unable to synthesize a compound within Count 1



with routine experimentation, but a team of chemists, even after they had consulted with others considered to be experts and had sought additional training. From this record it is reasonable to find that if after all of this effort, a compound within the scope of the count could not be synthesized easily, a hypothetical person of ordinary skill would not have known how to synthesis such a compound either.

**Exhibit H** at pages 20-21. The USPTO also stated "[w]e find it informative that Idenix's research team in Montpellier, France, repeatedly attempted *without success* to synthesize a 2'-methyl ('up') 2'-fluoro ('down') nucleoside during the interval between December, 2002 and September, 2004." **Exhibit C** at 14 (emphasis added); *see also id.* at pages 14-19.

Testimony by Dr. Victor E. Marquez on this point was also important. For example, in a declaration submitted to the USPTO (**Exhibit I**), Dr. Marquez described, based on his review of Idenix's internal documents, that Idenix employed a team of Ph.D. chemists, as well as consultants specializing in carbohydrate and fluorination chemistry, all of whom were unable to make the (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides for a period of several years. Dr. Marquez noted that these chemists tried numerous potential chemical routes and many different reagents in attempts to make a (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides. All of these attempts failed. It was only after the publication of the Gilead patent application (i.e., the Pharmasset PCT corresponding to '6087) that Idenix researchers were purportedly finally able to synthesize compounds of this type, thereby illustrating that the prior art was not enabling. **Exhibit I** at paragraphs 21-35.

In summary, the Applicant requests the Controller to withdraw the novelty and inventive step rejections because (A) none of the cited references describe or suggest the claimed compounds, (B) the prior art did not teach how to make the claimed compounds, as illustrated by Idenix's difficulties, and (B) the claimed compounds have unexpectedly high activity and low toxicity not suggested by the prior art. Thus, it is Applicant's position that the (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides of the present invention remain novel and inventive in view of the cited reference.

#### **11. Section 3(d)**

The averments made in **paragraph 7(a)** regarding Section 3(d) are factually and legally incorrect, and are furthermore misleading, and hence denied. As per the Opponent, the subject matter of claims 1 -7 are not patentable under Section 3(d) of the Act. The Opponent alleges that the set of claims are drawn to the nucleoside analogs. The Opponent contends that the Applicant is required to provide data showing therapeutic efficacy as compared to compounds in WO'425 and WO'287. The Opponent also contends that process claims 8 and 9 are drawn to "mere glycosylation of pyrimidine with compounds of Formula I-4," which Opponent alleges is a process already known in the art.

#### **Applicant's Response**

In response, the Applicant respectfully disagrees. It is submitted that the provisions of Section 3(d) are not applicable to the present case as detailed under:

- a) New Form: The compounds of the present invention are a new chemical entity, and are not related to any known substance in a way that would fall within Sec. 3(d).
- b) Mere Discovery: The present invention cannot be held to be a "mere discovery" within the meaning of Sec. 3(d). In fact, the present invention relates to a new chemical entity.

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- c) Known therapeutic efficacy: Without prejudice, even if it is assumed that Sec. 3(d) is applicable in present case, the Opponent has failed to point out known efficacy of any other known substance against which any comparable data is to be submitted in the present case. There is no known substance over which the present invention can be deemed to be lacking in efficacy. In fact the efficacy of the compounds of the present invention is significantly enhanced and different over any other known medicine for treatment of Hepatitis C. The reliance on section 3(d) is misplaced and untenable. Opponent has completely failed to discharge its onus of proof in respect of Sec. 3(d).

It is submitted that Sec. 3(d) does not apply to all pharmaceutical and chemical inventions, and in particular does not apply to new chemical entities (NCE). It is submitted that Sec. 3(d) was designed to make a higher bar of innovation for patentability of new salts, esters, and other derivatives (second generation compounds) of known substances (e.g. pharmaceuticals) unless they differ significantly in properties with regard to efficacy, to avoid alterations being made to the FORM of such substances and thus extending market exclusivity of known substances. It is not meant to create a higher bar for new substances by deeming all new compounds to be merely derivatives of known compounds.

The claims of the present application do not contravene Section 3(d). As explained above, the claimed compounds are novel and inventive NCEs whose properties would have been unpredictable prior to the Applicant's teachings in the present application. In particular, the presently claimed compounds have a unique and novel 2'-fluoro (down)-2'-methyl (up) substitution pattern, and they have both high potency and low toxicity as compared to comparative compounds. See Sections 12.3 and 12.2, above, discussing data for (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine and comparative compounds. They are not "new forms of known substances," such as salts, esters, ethers, polymorphs, pure forms, particle sizes, isomers, complexes,

or combinations of the type targeted by Section 3(d). The Patent Office should reject Opponents' suggestion that Section 3(d) can be used to prevent patenting every new compound by calling it a derivative of some known chemical core, despite the new compound's novelty and inventiveness in the unpredictable chemical arts.

The Applicant also respectfully submits that Section 3(d) is inapplicable to the presently pending process claims, which are directed to glycosylation methods for making the novel compounds of claim 1. Section 3(d) excludes from the meaning of "inventions," *inter alia*, "the mere use of a known process ... unless such known process results in a new product or employs at least one new reactant." Claims 14 and 15 are directed to processes that *both* result in a new product *and* employ at least one new reactant. The "new product" is a nucleoside as claimed in claim 1, which, as explained above, is a novel compound. Examples of the "new reactant" are the protected 2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) compound 1-4 recited in claim 14 and the protected 2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleoside recited in claim 15, both of which are novel reactants.

In the light of the above, the Applicant submits that the claimed compounds are completely novel and inventive. Thus, Section 3(d) cannot be applied to the claims of the instant application.

#### **12. Section 3(e)**

As per the Opponent, claim 10 is not patentable under Section 3(e) because purportedly it is directed to a composition that "is a mere admixture of known substances, which result only in aggregation of the properties of the individual components and do not demonstrate any synergistic effect."

#### **Applicant's Response**

In response, Applicant respectfully disagrees with Opponent's assertions. Claim 10 is directed to "[a] nucleoside as claimed in any of the Claims 1 to 7 as and when used for the preparation of a pharmaceutical composition or medicament." As explained above, the compounds of Claims 1 to 7 are novel, inventive and have utility.

(51)

Accordingly, claim 10 is directed to said novel and inventive compounds when used for the preparation of a pharmaceutical composition or medicament, which is also novel and inventive. In any case, the Opponent merely repeats conclusory language from Section 3(e) but fails to establish the grounds pleaded.

### **13. Insufficient or Unclear Description**

The Opponent contends that the specification fails to teach how to make the claimed compounds, lacks disclosure regarding specific pharmaceutically acceptable salts, and fails to teach how to use a nucleoside in a pharmaceutical preparation or medicament. For at least the reasons explained below, the averments made in **paragraph 8** regarding insufficient or unclear description are factually and legally incorrect, and are furthermore misleading, and hence denied.

### **Applicant's Response**

In response, Applicant respectfully disagrees. As presently amended, the '6087 claims are directed to (2'R)-2'-deoxy-2'-fluoro (down)-2'-methyl (up) nucleosides having cytosine or uracil bases, and their corresponding 5' mono-, di-, and triphosphates.

The present specification provides general schemes and procedures for preparing (2'R)-2'-deoxy-2'-fluoro (down)-2'-methyl (up) nucleosides, e.g., Schemes 1 and 2 and accompanying descriptions on pages 72-76 (original PCT application). The specification also contains working examples of (2'R)-2'-deoxy-2'-fluoro (down)-2'-methyl (up) nucleosides, such as (2'R)-2'-deoxy-2'-fluoro-2'-methylcytidine and its hydrochloride salt, including detailed synthetic procedures and characterization data for both intermediates and final compounds. See Schemes 3-6 and accompanying descriptions on pages 77-87 (original PCT application). The specification further provides biological data for (2'R)-2'-deoxy-2'-fluoro-2'-methylcytidine and its corresponding 5' triphosphate, as well as for comparative compounds, such as:

- i) Antiviral activity in HCV replicon assays (Tables 1 and 2, Figs. 1A and 1B);
- ii) Potency in NS5B polymerase assay (Table 3);
- iii) Cytotoxicity (Table 6);
- iv) Mitochondrial toxicity (Table 7);
- v) Human bone marrow toxicity (Table 9);
- vi) *In vivo* toxicity in female Swiss mice (Fig. 2);
- vii) Pharmacokinetic parameters in Rhesus monkeys (Table 8, Fig. 3); and
- viii) Antiviral activity against viruses including Rhinovirus, West Nile virus, Yellow Fever virus, and Dengue virus (Tables 4 and 5).

For example, Tables 1 to 3, 5, 6, 7 and 9 on pages 90 to 94 include activity and other biological data for of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (Compound 3-6/Compound 4-6) as compared with 2'-C-methylcytidine and 2'-C-methyladenosine. Table 4 summarizes the antiviral activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine against a variety of viruses, and Table 8 provides pharmacokinetic parameters ( $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-last}$ ,  $T_{1/2}$ , and Bioavailability) in Rhesus monkeys following a single oral dose of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine. Table 9 compares the human bone marrow toxicity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine against that of 2'-C-methylcytidine and AZT.<sup>5</sup> The foregoing data support that compounds of the present application have good anti-HCV activity and low toxicity as compared to comparative compounds.

Furthermore, with respect to pharmaceutical compositions, the specification discusses preparation of the same in Section III on pages 47-50 (original PCT application). This description includes details regarding excipients that may be used

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<sup>5</sup> Lower  $IC_{50}$  values indicate higher potential toxicity. Thus, Table 9 shows that (2'R)-2'-deoxy-2'-fluoro-2'-methylcytidine was significantly less toxic to the tested human bone marrow cells compared to 2'-C-methylcytidine and AZT.

to prepare pharmaceutical compositions of a variety of forms, including oral dosage forms, parenteral formulations and liposomal suspensions.

In view of above, the Applicant submits that the claims of the present application are described with sufficient clarity to enable a person skilled in the art to put the claimed invention to practice. The data in the patent specification as filed, in combination with the information provided in the description, allow a skilled person to put the invention into effect across the entire scope claimed.

#### **14. Section 8 Requirements**

It is denied that the Applicant has failed to furnish information as required under Section 8. It is submitted that claims similar to those presented here in 6087/DELNP/2005 have been granted in numerous countries (see Form 3 details):

Country	Patent Nos.
Australia	2004253860
Canada	2527657
China	200480019148.4
Colombia	1214
Indonesia	P0028288
Israel	172259 and 210367
Japan	4958158 and 5266357
Korea	200883703
Mexico	275935

Malaysia	138477
Norway	0333700
New Zealand	543867
Philippines	1-2005-502136
Russia	2358979
Singapore	117252
South Africa	2005-09521
Taiwan	1333956
United States	7429572 and 8415322;

Exemplary claim sets of the Granted Patent in some of these countries have been already submitted to the Indian Patent Office on 30 June 2014 and 23 July 2014.

Most of the information required under Section 8 of the Indian Patents Act at this stage of the prosecution have been provided and remaining information shall be provided accordingly in due time.

- 15. Dr. Rane's Affidavit Fails to Demonstrate that the Claimed Invention Would Have Been Obvious to One of Ordinary Skill in the Art or that the Claimed Compounds Are Derivatives of Known Prior Art Compounds**



The Opponent has submitted an affidavit of Dr. Dnyandev Ragho Rane in support of its petition. However, Dr. Rane's affidavit is insufficient to prove that the presently claimed invention would have been obvious to a person of ordinary skill in the art.

As a preliminary matter, although Dr. Rane states that he has 24 years of experience in "the field of development of chemical synthesis of nucleosides, nucleotides analogues," the Opponent has not shown that Dr. Rane has any expertise in, e.g., designing nucleosides to be used as therapeutic agents (such as anti-HCV therapeutics), or in developing syntheses of novel fluorinated nucleosides. This is evident from the fact that most of Dr. Rane's work as published in patent applications such as 2306/CHE/2006, WO2007010352 and WO2008126105 does not pertain to nucleoside or nucleotide analogues. These applications pertain to processes for the preparation of SIMVASTATIN, NEVIRAPINE and ZOPICLONE respectively—compounds that are not nucleosides, compounds that lack fluorine substituents, and compounds that are unrelated to HCV. Thus, Dr. Rane's affidavit fails to establish that he has expertise in specific issues relevant to the present application.

Dr. Rane's affidavit contains a series of conclusory statements about what was allegedly "known" in the art without explaining the basis or providing documentary evidence to support a number of his assertions. He also engages in an improper hindsight analysis, whereby he asserts that a number of features of the claimed invention were allegedly "known" and summarily concludes that it would have been obvious to arrive at the claimed invention, without explaining *why* one of ordinary skill in the art allegedly would have selected any particular prior art compound and proceeded to make the modifications necessary to arrive at the claimed invention, all with a reasonable expectation of success.

Dr. Rane refers to the following prior art references in his Affidavit:

- WO2001/90121
- WO2001/92282
- WO1999/043691
- Eldrup et al., Bhat et al. and Olsen et al
- B.K. Park and N.R. Kitteringham
- Gumina et al
- Pankiewicz et al.
- Middleton et al.
- Wachtmeister et al
- Maybridge Medchem
- Hayakawa et al.
- Matsuda et al
- WO2002/057425
- WO2002/057287

All the above prior art references were cited in Opposition petition and the Applicant has replied to all the references in sections 9 and 10 above.

Further, Dr. Rane refers to one additional document i.e. US 6348587, which is not part of this Opposition petition as such. However, this US patent is derived from PCT application WO1999/043691 which is included in Opposition Petition as prior art reference. Thus, the reply in respect of WO1999/043691 in section 10 can be referred here.

Furthermore, Dr. Rane has failed to consider relevant evidence, such as the evidence of unexpected results and the evidence of Idenix's repeated failures to synthesize (2'R)-2'-deoxy-2'-fluoro (down)-2'-methyl (up) nucleosides, discussed above in Sections 10.2 and 10.3, respectively.

With respect to Section 3(d), Dr. Rane baldly asserts that the claimed compounds are derivatives of already known prior art compounds, without explaining which prior art compounds he intends to reference, and without providing any explanation or support (e.g., scientific literature or patent documents) for his assertions.

For at least these reasons, as well as those discussed above in Applicant's response, Dr. Rane's incorrect and unsupported opinions should be ignored.

#### 16. Conclusion

In view of the above submissions, it is clear that the subject application claims compounds that are novel, inventive and patentable. The Opponent has failed to make out or substantiate any of the alleged grounds. The entire opposition is frivolous and vexatious and has been filed merely to harass this Applicant. None of the prayers prayed for by the Opponent are tenable and the same deserve to be rejected outright and the opposition should be dismissed with heavy costs. As such, the representation filed by the Opponent is frivolous and ought to be dismissed *in limine*.

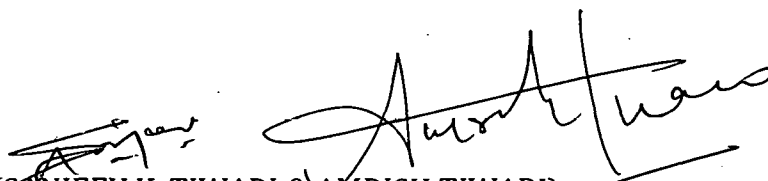
#### PRAYER

In the above premises, the Applicant prays that -

- i) the representation filed by Opponent under Section 25(1) be rejected by the Ld. Controller of Patents and Indian Application No.6087/DELNP/2005 be allowed to proceed to grant;

- ii) the applicant be allowed to file evidence as may be necessary to comply with the provisions of the Patents Act, 1970;
- iii) Costs of delays in grant of the patent and for engaging in this representation be awarded to this Applicant;
- iv) Any other relief or reliefs as the Controller may deem fit may be granted in favour of the Applicant.

Dated this 07<sup>th</sup> day of August, 2015.

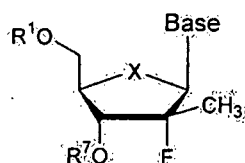
  
(SANJEEV K. TIWARI & AMRISH TIWARI)  
K&S PARTNERS  
ATTORNEYS FOR THE APPLICANT

To,  
THE CONTROLLER OF PATENTS  
THE PATENT OFFICE, NEW DELHI.

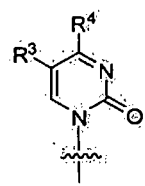
39

**We Claim:**

1. A nucleoside or its pharmaceutically acceptable salt of the structure:



wherein the Base is a pyrimidine base represented by the following formula

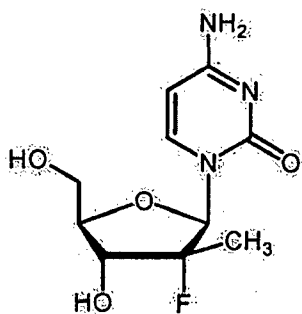


X is O; R<sup>1</sup> and R<sup>7</sup> are independently H, a monophosphate, a diphosphate, or a triphosphate; and

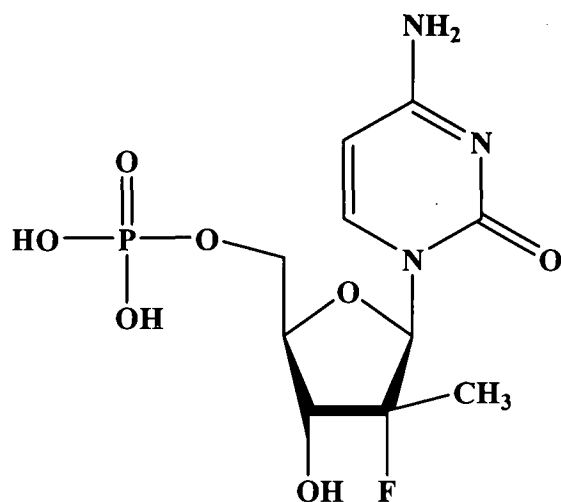
R<sup>3</sup> is H and R<sup>4</sup> is NH<sub>2</sub> or OH.

2. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, wherein R<sup>7</sup> is H and R<sup>1</sup> is a monophosphate, a diphosphate, or a triphosphate.
3. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, R<sup>7</sup> is H and R<sup>1</sup> is a diphosphate or a triphosphate.
4. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R<sup>7</sup> is H and R<sup>1</sup> is a triphosphate.
5. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R<sup>1</sup> and R<sup>7</sup> are H.

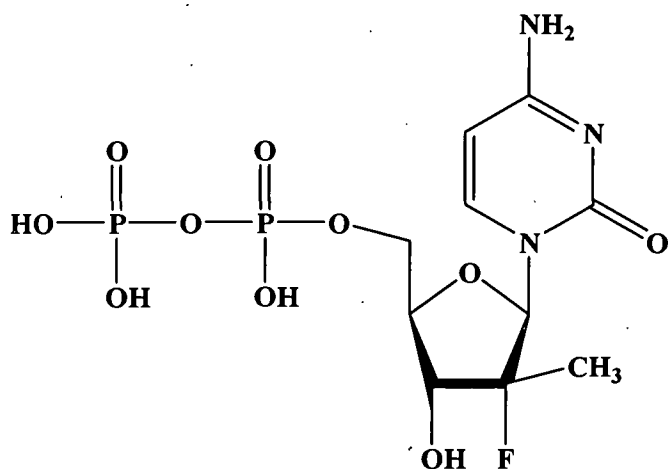
6. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:



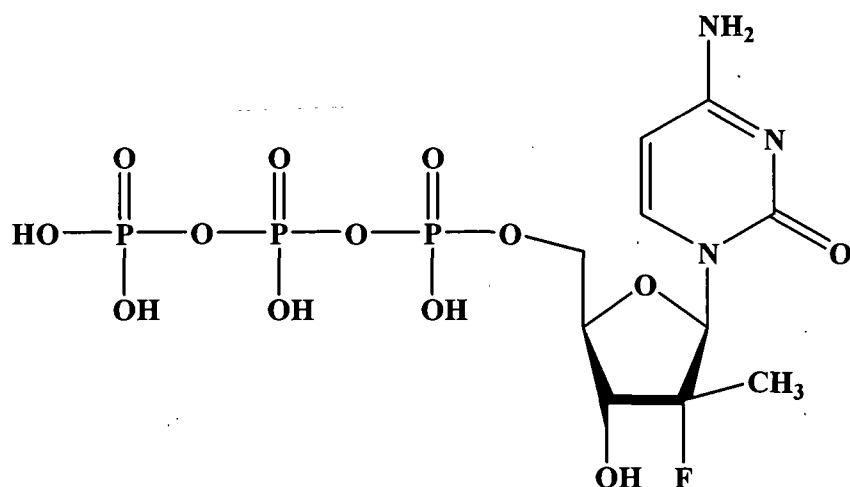
7. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula



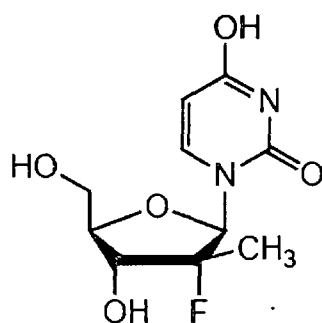
8. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula



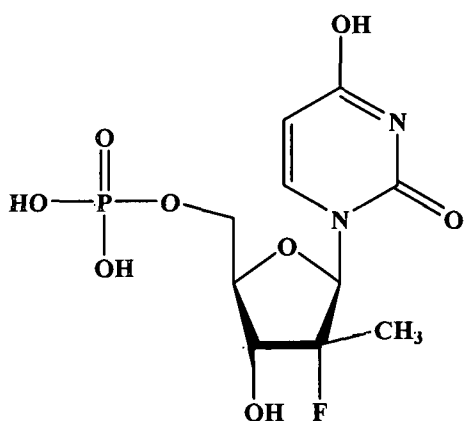
9. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula



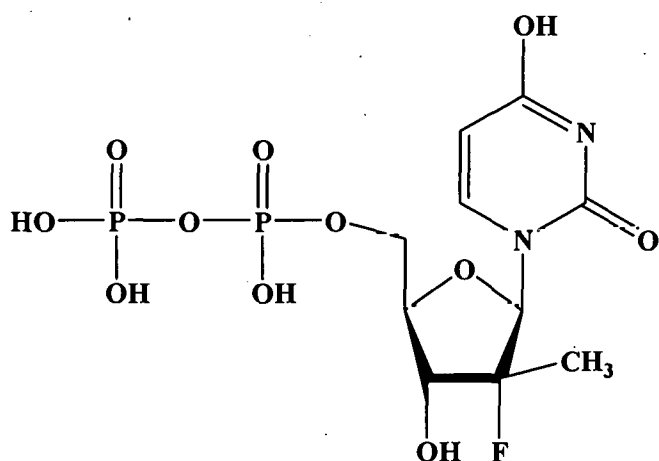
10. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:



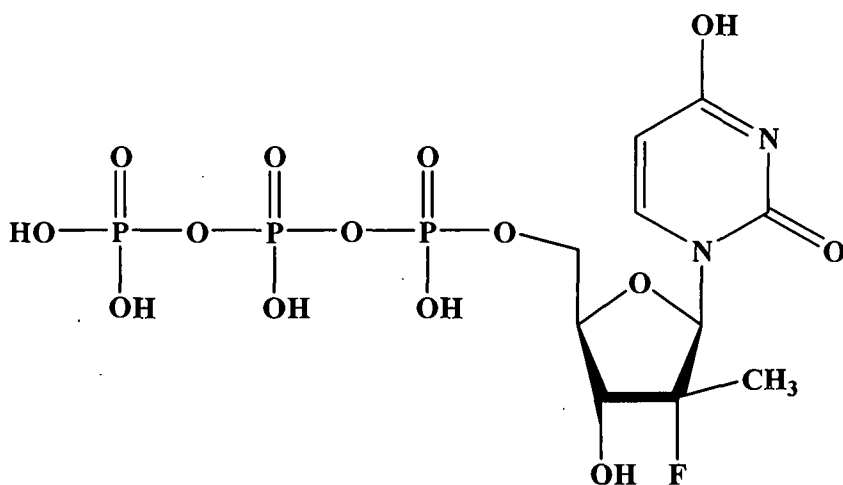
11. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula



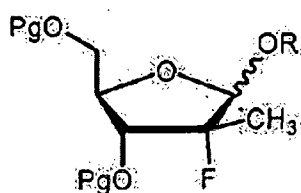
12. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula



13. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula



14. A method of synthesizing the nucleoside as claimed in claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure:

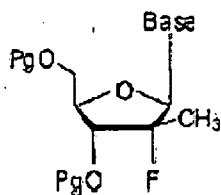


I-4



wherein R is C<sub>1</sub>-C<sub>4</sub> lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-C<sub>1</sub>-C<sub>10</sub> alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkyl, CH<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkenyl, CH<sub>2</sub>-phenyl, CH<sub>2</sub>-biphenyl, CH<sub>2</sub>-naphthyl, CH<sub>2</sub>O-C<sub>1</sub>-C<sub>10</sub> alkyl, CH<sub>2</sub>O-phenyl, CH<sub>2</sub>O-biphenyl, CH<sub>2</sub>O-naphthyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkyl, SO<sub>2</sub>-phenyl, SO<sub>2</sub>-biphenyl, SO<sub>2</sub>-naphthyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

15. A method of synthesizing the nucleoside as claimed in claim 1, which comprises selectively deprotecting a 3'-OPg or a 5'-OPg of a compound having the following structure:



wherein, each Pg is independently a protecting group selected from among C(O)-C<sub>1</sub>-C<sub>10</sub> alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH<sub>3</sub>, CH<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkyl, CH<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkenyl, CH<sub>2</sub>-phenyl, CH<sub>2</sub>-biphenyl, CH<sub>2</sub>-naphthyl, CH<sub>2</sub>O-C<sub>1</sub>-C<sub>10</sub> alkyl, CH<sub>2</sub>O-phenyl, CH<sub>2</sub>O-biphenyl, CH<sub>2</sub>O-naphthyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkyl, SO<sub>2</sub>-phenyl, SO<sub>2</sub>-biphenyl, SO<sub>2</sub>-naphthyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

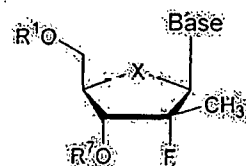
16. A nucleoside as claimed in any of the Claims 1 to 13 as and when used for the preparation of a pharmaceutical composition or medicament.

Dated this 27<sup>th</sup> day of December, 2005

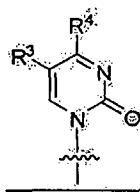
[AMRISH TIWARI]  
OF K & S PARTNERS  
ATTORNEY FOR THE APPLICANT(S)

**We Claim:**

1. A nucleoside or its pharmaceutically acceptable salt of the structure:



wherein the Base is a pyrimidine base represented by the following formula

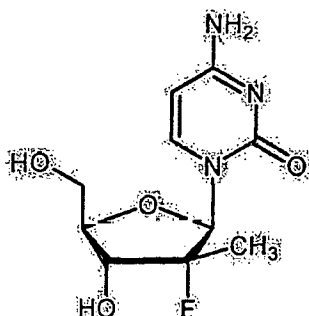


X is O; R<sup>1</sup> and R<sup>7</sup> are independently H, a monophosphate, a diphosphate, or a triphosphate; and

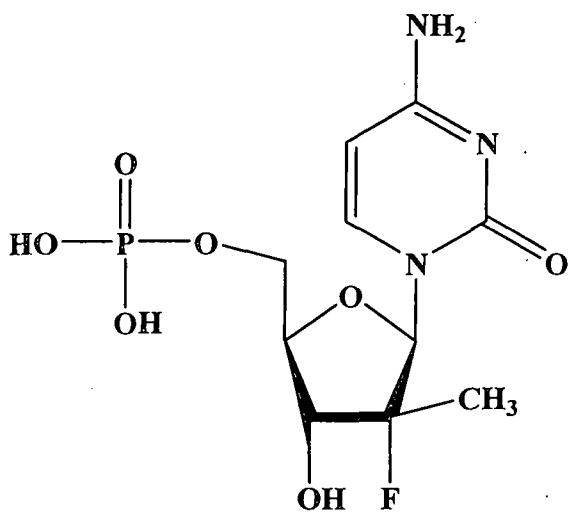
R<sup>3</sup> is H and R<sup>4</sup> is NH<sub>2</sub> or OH.

2. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, wherein R<sup>7</sup> is H and R<sup>1</sup> is a monophosphate, a diphosphate, or a triphosphate.
3. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, R<sup>7</sup> is H and R<sup>1</sup> is a diphosphate or a triphosphate.
4. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R<sup>7</sup> is H and R<sup>1</sup> is a triphosphate.

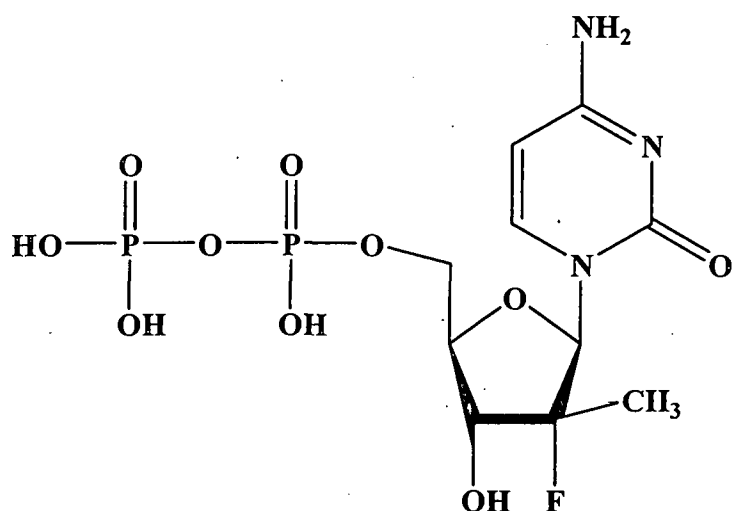
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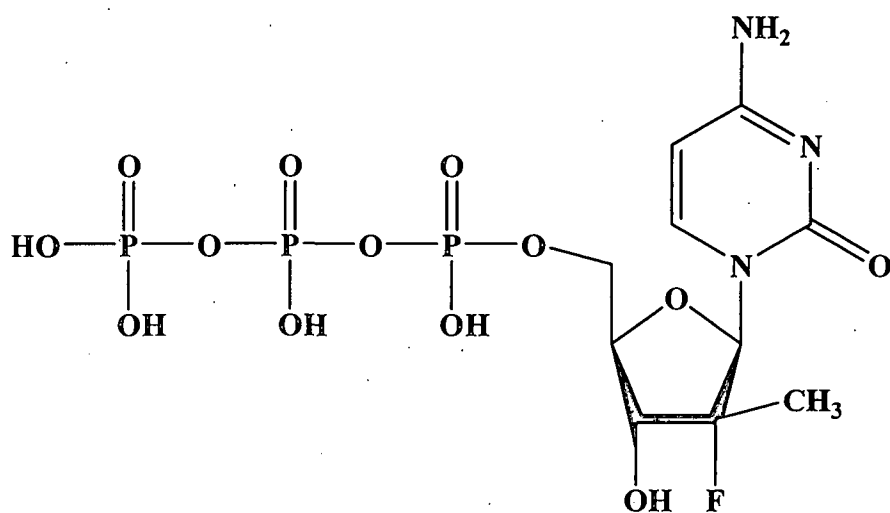
7. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula



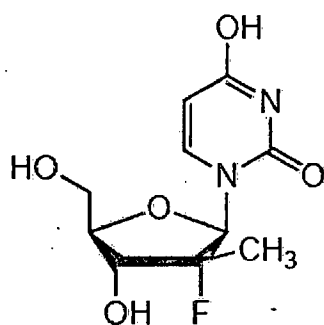
8. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula



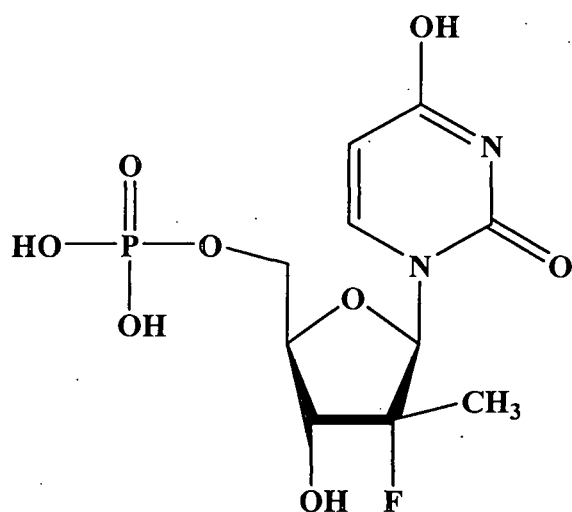
9. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula



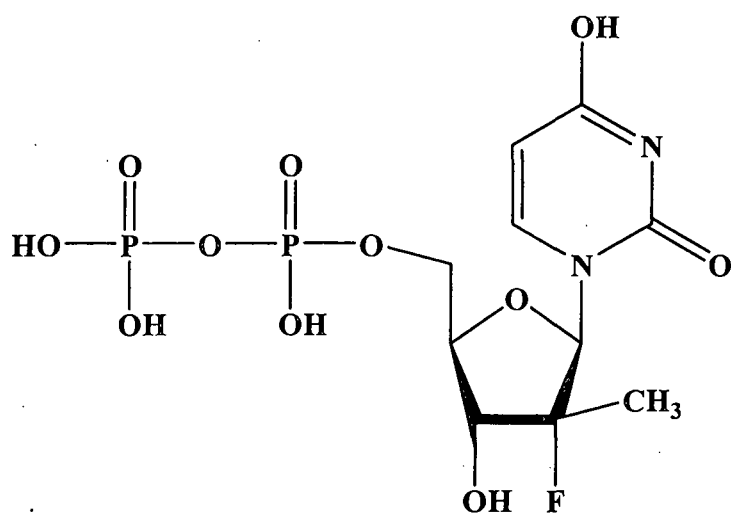
710. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:



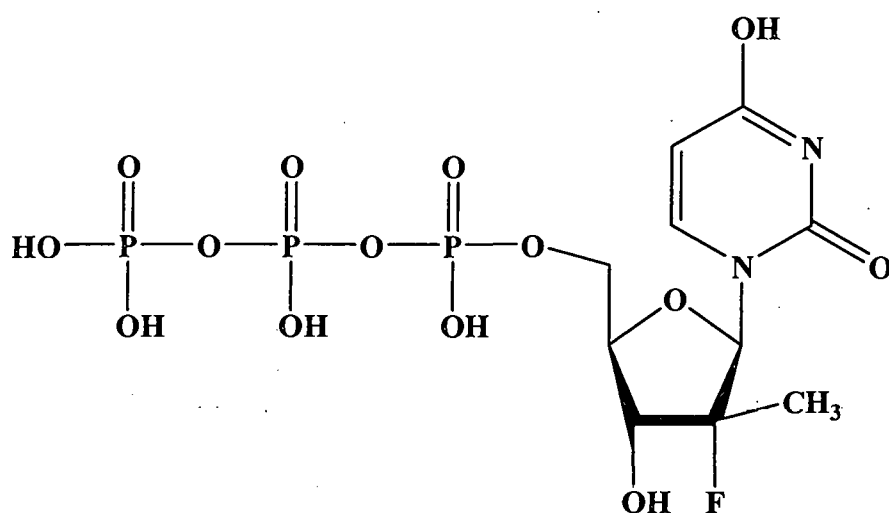
11. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula



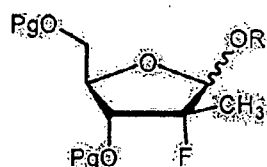
12. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula



13. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula



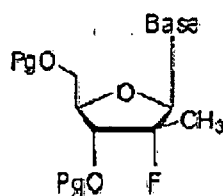
814. A method of synthesizing the nucleoside as claimed in claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure:



1-4

wherein R is C<sub>1</sub>-C<sub>4</sub> lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-C<sub>1</sub>-C<sub>10</sub> alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkyl, CH<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkenyl, CH<sub>2</sub>-phenyl, CH<sub>2</sub>-biphenyl, CH<sub>2</sub>-naphthyl, CH<sub>2</sub>O-C<sub>1</sub>-C<sub>10</sub> alkyl, CH<sub>2</sub>O-phenyl, CH<sub>2</sub>O-biphenyl, CH<sub>2</sub>O-naphthyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkyl, SO<sub>2</sub>-phenyl, SO<sub>2</sub>-biphenyl, SO<sub>2</sub>-naphthyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

915. A method of synthesizing the nucleoside as claimed in claim 1, which comprises selectively deprotecting a 3'-OPg or a 5'-OPg of a compound having the following structure:



5

wherein, each\_Pg is independently a protecting group selected from among C(O)-C<sub>1</sub>-C<sub>10</sub> alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH<sub>3</sub>, CH<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkyl, CH<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkenyl, CH<sub>2</sub>-phenyl, CH<sub>2</sub>-biphenyl, CH<sub>2</sub>-naphthyl, CH<sub>2</sub>O-C<sub>1</sub>-C<sub>10</sub> alkyl, CH<sub>2</sub>O-phenyl, CH<sub>2</sub>O-biphenyl, CH<sub>2</sub>O-naphthyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>10</sub> alkyl, SO<sub>2</sub>-phenyl, SO<sub>2</sub>-biphenyl, SO<sub>2</sub>-naphthyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

1016. A nucleoside as claimed in any of the Claims 1 to 137 as and when used for the preparation of a pharmaceutical composition or medicament.

OSLO DISTRICT COURT

[Stamped: "True copy certified:  
by authorisation:"] [Signature]  
[By hand: "28 March 2014"]  
[Stamped: "OSLO DISTRICT COURT"]

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**JUDGMENT**

**Rendered:** 21 March 2014 by the Oslo District Court

**Case Nos.:** 12-155575TVI-OTIR/01 and 13-170456TVI-OTIR/01

**Judge:** District Court Judge Inger Kjersti Dørstad

**Lay judges:** Professor Hans Einar Krokan  
Professor Jesper Wengel

**Subject-matter  
of the case:** Invalidation of Norwegian patent

Gilead Sciences Europe Ltd.

Counsel: Attorney Are Stenvik  
Of counsel: Attorney Gunnar Sørli  
and Attorney Elin Moen;

v.

1. Idenix Pharmaceuticals Inc

Counsel: Attorney Arne Ringnes  
Of counsel: Attorney Harald Ludvig  
Joachim Irgens-Jensen and  
Associate Ellen Kristina Rognlien

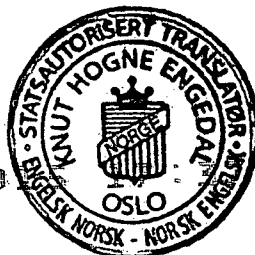
2. Centre National de la Recherche  
Scientifique

3. Università Degli Studi Di Cagliari

4. L'Université Montpellier II

Disclosure to the general public is not subject to any restrictions

True translation certified.  
2 April 2014



Knut Hogne Engedal  
Government-authorised translator  
English - Norwegian • Norwegian - English



Idenix Pharmaceuticals Inc

Counsel: Attorney Arne Ringnes  
Of counsel: Attorney Halrahd [sic]  
Irgens-Jensen and Associate Ellen  
Kristian [sic] Rognlien

v.

Gilead Pharmasset LLC

Counsel: Attorney Are Stenvik  
Of counsel: Attorney Gunna [sic]  
Sørli and Attorney Elin Moen



The present proceedings concern a dispute as to the validity of the two Norwegian patents NO 330 755 and NO 333 700, cf. Section 52, cf. Sections 2 and 8, of the Norwegian Patents Act.

The defendants in the two cases that have been consolidated for a joint hearing are each the holder of one Norwegian patent. Both of the disputed patents pertain to chemical compounds that are suitable for use in pharmaceutical products, especially for the treatment of *Flaviviridae* infections, such as hepatitis C virus infections.

The present proceedings have their origin in a disagreement between the parties to the case as to who are the rightful inventors of chemical substances of the pattern 2'-methyl-up, 2'-fluorine-down nucleosides with a natural N-bonded base. The parties also disagree on which of them first disclosed the invention in a patent application with a valid priority sequence.

Idenix Pharmaceuticals Inc., Centre National de la Recherche Scientifique, Università Degli Studi Di Cagliari and L'Université Montpellier II are joint holders of NO 330 755 (hereinafter referred to as "NO 755"). Defendant No. 1, Idenix Pharmaceuticals Inc, was founded in 1998 and is headquartered in Massachusetts, United States. It is a pharmaceuticals company engaged in research on, and development of, antiviral pharmaceutical products, including antiviral nucleosides for the treatment of, *inter alia*, HIV, HBV (hepatitis B) and HCV (hepatitis C). The company has collaborated with the three other defendants, all of which are universities or research institutions, in research on, and development of, antiviral pharmaceutical products. The said parties will be jointly referred to as "Idenix". Idenix Pharmaceuticals Inc. is the sole claimant with regard to the validity of the other patent.

Gilead Pharmasset Inc. is the holder of the other Norwegian patent, NO 333 700 (hereinafter referred to as "NO 700"), and is the defendant in the case concerning the validity of the said patent. A company within the same group, Gilead Sciences Europe Ltd., is the claimant in the case concerning the validity of patent NO 755. Both companies will be jointly referred to as "Gilead". Gilead was founded in California in 1987 and is a pharmaceuticals firm with a product portfolio encompassing several disease categories, including, *inter alia*, HIV/AIDS, hepatitis, serious respiratory diseases, cardiovascular diseases and cancer.

### The patent history

There has, as mentioned, been a race between the parties to arrive first at the invention and be the first to secure the rights by way of a patent.

Idenix first applied for a patent in the United States. Reference has been made to four US applications, but the case has been restricted to application US 60/392,350 ("US 350"). The said application was filed



on 28 June 2002. If this priority is valid, Idenix will be first in time. Gilead has disputed that Idenix can claim priority based on the said application.

Gilead applied for a patent in the United States on 30 May 2003. The application is designated as US 60/474,368 ("US 368"). If Idenix cannot claim priority from its application US 350, this application [US 368] will be first in time. Idenix has disputed that Gilead can claim priority from the said application.

Idenix filed a PCT application on 27 June 2003. It has subsequently been extended to include Norway. If Gilead cannot claim priority from its application US 368, Idenix' PCT application will be first in time. It is not contested that Idenix can claim formal priority from the said application.

Idenix' applications US 350 and PCT became available to the public on 8 January 2004.

Gilead filed a PCT application on 21 April 2004, i.e. after Idenix' applications had been published. It is not contested that Gilead can claim formal priority from the said application.

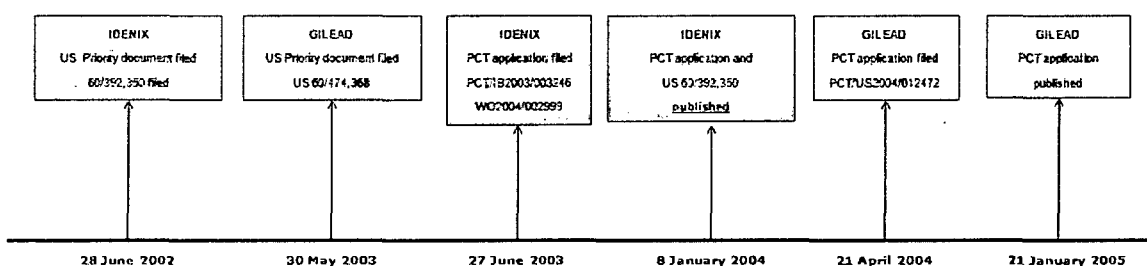
Idenix filed Norwegian patent application NO 20050465 ("NO 465") on 27 January 2005.

Gilead filed Norwegian patent application NO 20056221 ("NO 221") on 28 December 2005.

Norwegian patent NO 330 755 was granted to Idenix on 4 July 2011.

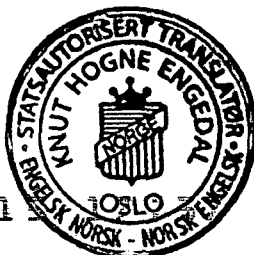
Norwegian patent NO 333 700 was granted to Gilead on 26 August 2013.

Schematically, the time sequence may be presented as follows:



### Procedural history

Case No. 12 -155575TVI-OTIR/01, which is the invalidity action pertaining to Norwegian patent NO 330 755, was brought by Gilead Sciences Europe Ltd. by way of a Writ of Summons to the Oslo District Court, dated 28 September 2012. The Notice of Intention to Defend from the four defendants Idenix Pharmaceuticals Inc., Centre National de la Recherche Scientifique, Universita Degli Studi Di Cagliari and L'Université Montpellier II, which was filed in a timely manner, is dated 20 November 2012.



Case No. 13 -170456TVI-OTIR/01, which is the invalidity action pertaining to Norwegian patent NO 333 700, was brought by Idenix Pharmaceuticals Inc. by way of a supplementary pleading to the Oslo District Court, dated 6 September 2013. The Notice of Intention to Defend from Gilead Pharmasset LLC, which was filed in a timely manner, is dated 1 October 2013. Both parties requested that the cases be consolidated for a joint hearing, despite the short time left before the scheduled main hearing. None of the parties requested postponement of [the main hearing] for reasons of necessary preparation of the case. Both parties did, on the contrary, state that the case concerned the same or corresponding issues, and that it would neither be necessary to allocate additional time for the preparation of the case, nor to schedule more time for the main hearing, for purposes of explaining the case properly. It was decided, against this background, to consolidate the cases for a joint hearing.

A number of supplementary pleadings have been submitted in the present proceedings. Besides, one written submission pursuant to Section 9-9, Sub-section 3, of the Norwegian Dispute Act has been filed by each of the parties in relation to the priority issues raised in these proceedings. A planning meeting has been held, as well as several preparatory meetings. The main hearing of the case was conducted over nine days during the period from 7 to 19 November 2013. Fourteen witnesses gave testimony, ten of whom were expert witnesses called by the parties. There was disclosed such documentation as is reflected in the court record. The Court was set with two expert lay judges, at the request of both parties. The judgment is not rendered within the statutory time limit. This is partly because the case has been very wide in scope and has raised complex issues. In addition, one of the members of the Court has been on sick leave for a protracted period of time.

**Gilead has, in the main, invoked the following:**

**In Case 12-155575TVI-OTIR/01:**

Gilead argues that patent NO 330 755 ("NO 755") is invalid.

NO 755 can neither derive valid priority from the cited priority document US 60/392,350 ("US 350"), nor from any of the other US priority documents. This can be concluded on a number of grounds, each of which are sufficient, in themselves, for the priority claim to be set aside.

Firstly, there is no formal priority. Not all inventors of US 350 had assigned the right to the invention, including the priority right, prior to the filing of the patent application, i.e. before the filing of international application PCT/IB2003/003246 (published as WO 2004/002999, hereinafter referred to as "WO '999), which led to NO '755.

Secondly, there is no substantive priority either. US 350 contains no clear and direct disclosure of the chemical compounds in respect of which protection is claimed under NO 755. Neither does US 350 describe any process for the production of the chemical compounds in respect of which protection is claimed under NO 755, nor did the prior art include any process that enabled a skilled person to produce the said compounds without undue burden or experimentation.



Nor did US 350 disclose any information that made it plausible to the skilled person that the alleged effect is achieved by any of the chemical compounds falling within the scope of the patent claims in NO 755.

When the application date, 27 June 2003, is adopted as the priority date, i.e. the date of the filing of the PCT application, the invention was anticipated by Gilead's patent application NO 20056221, which derives valid priority from US 60/474,368 (hereinafter referred to as "US 368"). This [application] was filed on 30 May 2003, i.e. before the defendants filed their EPC application.

It is argued, irrespective of which priority date is adopted, that NO 755 is invalid for the following reasons, each of which are sufficient, in themselves, for the patent to be revoked:

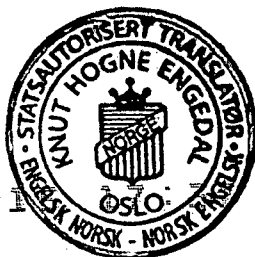
- NO 755 discloses no information that would have enabled the skilled person to identify, without undue burden or experimentation, chemical compounds which fall within the scope of the patent claims, and which can be used in the treatment of *Flaviviridae* infections.
- NO 755 discloses no process for the production of the chemical compounds in respect of which protection is claimed. Nor did the prior art include any process that enabled the skilled person to produce the said compounds without undue burden or experimentation.
- NO 755 discloses no information that made it plausible for the skilled person that the alleged effect is achieved by any the chemical compounds that fall within the scope of the patent claims in NO 755.
- Neither the dependent patent claims, nor the alternative patent claim, add anything that might justify upholding the patent.

In Case 13-170456TVI-OTIR/01:

Gilead argues that patent NO 333 700 (NO 700) is valid in its entirety.

The arguments [outlined] in following pertain to all patent claims.

NO 700 derives valid priority from US 368, filed on 30 May 2003. The patent applicant, Pharmasset, Ltd. (Barbados), had validly acquired the right to the invention in US 368, including the priority right, prior to the filing of the patent application, i.e. before the filing of international application PCT/US04/012472 (published as WO 2005/003147 A2), which led to NO 700, on 21 April 2004. WO 999 cannot derive valid priority from US 350. Hence, Idenix' application cannot be deemed to have been filed before the PCT application date of 27 June 2003. When the correct priority dates are adopted, none of the publications invoked by Idenix can be cited against NO 700.



Moreover, Gilead will argue that NO 700 is valid irrespective of which priority dates are adopted. Even if the contents of WO 999 and/or US 350 are deemed to have been known within the meaning of Section 2, Sub-section 2, of the Norwegian Patents Act, NO 700 meets the novelty and inventive step requirements under Section 2, Sub-section 1.

Each of the following grounds are sufficient, in themselves, for concluding that the cited publications do not anticipate the invention:

- The publications disclose no process for the production of the chemical compounds protected by NO 700. Nor was any production process that enabled the skilled person to produce these chemical compounds without undue burden or experimentation available from other sources.
- The publications disclose no information that made it plausible to the skilled person that the alleged effect is achieved by exercising the invention.

The invention in NO 700 also meets the inventive step requirement, i.e. it differs essentially from what could be inferred from US 350, WO 999 and other prior art. The patented invention exhibits beneficial properties.

Gilead has prayed for the following *relief*:

In Case 12-155575TVI-OTIR/01:

1. Norwegian patent NO 330 755 to be declared invalid.
2. Idenix Pharmaceuticals Inc., Centre National de la Recherche Scientifique, Universita Degli Studi Di Cagliari and L'Université Montpellier II to be ordered to pay the legal costs of Gilead Sciences Europe Ltd.

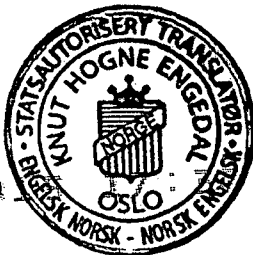
In Case 13-170456TVI-OTIR/01:

1. The Court to find in favour of Gilead Pharmasset LLC.
2. Idenix Pharmaceuticals Inc. to be ordered to pay the legal costs of Gilead Pharmasset LLC.

**Idenix has, in the main, invoked the following:**

In Case 12-155575TVI-OTIR/01:

The defendants, Idenix Pharmaceuticals, Inc., Centre National de la Recherche Scientifique, Universita Degli Studi di Cagliari and l'Université Montpellier II, argue that Claims 2-22 of their patent 330 755 (the "755 Patent") shall be upheld as valid in the form of new Claims 1-21 as shown in the principal claims set out in Exhibit 1a. Alternatively, in the event that the Court finds, contrary to expectation, the said claims to be invalid, the Court is requested to rephrase the patent claims in conformity with the alternative patent claims set out in Exhibit 1b.



Gilead asserts that patent application NO20056221 prevents novelty for the Idenix Patent. Gilead claims priority from the US application filed on 30 May 2003. However, this claimed priority is invalid, thus implying that Gilead can only claim priority from the filing of the PCT application on 21 April 2004. Consequently, Gilead's patent application NO20056221 does not qualify as prior art, irrespective of whether Idenix' claimed priority in respect of NO 755 is valid, because Idenix' PCT application has an earlier filing date, i.e. 27 June 2003.

Besides, Gilead cannot claim priority from US 368 for the following reasons:

It follows from Section 6 of the Norwegian Patents Act, which needs to be interpreted in accordance with the Paris Convention and European case law, that those inventors holding a right of priority must have assigned such right to the applicant filing the PCT application, in the form of a written document signed by both parties, before such PCT application was filed. Gilead has failed to substantiate any valid assignment from those holding the priority right to Pharmasset, Ltd. (Barbados) prior to 21 April 2004. Instead, the priority right was assigned to Pharmasset, Inc. (Georgia).

The NO 755 patent meets the prerequisite in Section 8, Sub-section 2, third sentence, of the Norwegian Patents Act, for the description to be sufficiently clear to enable the skilled person to carry out the invention on the basis thereof. A skilled person would on 28 June 2002 and 27 June 2003 have been able to synthesise the compounds in respect of which protection is claimed, based on the information disclosed in the patent and his or her general knowledge of the art. He [or she] could have done this by only conducting routine experimentation.

The skilled person would, based on his or her general knowledge of the art, have been familiar with appropriate reagents for purposes of achieving fluorination, including diethylaminosulfur trifluoride (DAST) and Deoxo-Fluor. The skilled person would also know how to get to the appropriate precursor for achieving the correct stereochemistry.

The defendants maintain that it is not a legal prerequisite for the description with regard to the product claims in Claims 1 and 2 of Exhibit 1a and Claims 1 and 2 of Exhibit 1b to be sufficient to enable the skilled person to test the activity of the compounds. However, methods for the testing of the antiviral activity of the compounds were available to the skilled person. As far as anti-HCV testing is concerned, assays based on the HCV replicon system constituted common general knowledge in the art as at the priority date. Alternatively, in vitro assays for RNA polymerase activity, which are described in the patent, were available.

As far as testing of activity against WNV, YFV, dengue fever, etc., is concerned, routine cell-based assays for viral infections were available, such as assays for the calculation/reduction of plaque. Moreover, assays for cell protection/cytopathic effect, including neutral red [dye] uptake (neutral "red dye uptake [sic]") assay, were available to the skilled person. These



assays are described in the patent, and were well known, in routine use, as well as available, on 28 June 2002.

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Nor is there any doubt that the invention does in fact exhibit technical effect and is susceptible of industrial application. Gilead discusses a "credibility test", i.e. that there is a requirement for the application in itself, in view of the common general knowledge of the skilled person as at the application date, to make the effect "plausible". However, such credibility test is only relevant to the assessment of inventive step. The Norwegian Industrial Property Office has correctly concluded that the invention has inventive step, and Gilead has not denied that such is the case. In the event that a credibility test is inherent in the technical effect requirement, this is nothing more than a requirement that the relevant type of object is likely to exhibit technical effect. Nucleoside analogues, which have long been known to exhibit antiviral effect, meet this basic requirement. Since Gilead's arguments with regard to credibility are not only legally untenable, but also lack any basis in the facts, the defendants have submitted evidence that substantiates the credibility of the invention, although this is not a legal requirement. In the event that the legal standard for documentation of the technical effect that has been invoked by Gilead is to be applied, Gilead's own patent NO 700 shall also be declared invalid, because they have not complied with such standard either.

Alternatively, it is argued that even if the Gilead Patent, NO 700, is deemed to have valid priority from US 368, of 30 May 2003, the defendants' patent NO 755 have better priority, since their priority from US 350 is valid.

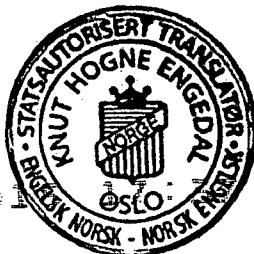
The true inventors who were entitled to the right of priority, i.e. Sommadossi, Gosselin and Storer, had validly assigned the right to claim priority to Idenix (Cayman), Ltd. and Centre National de la Recherche, the applicants under the PCT application, before the PCT application was filed. Reference is made to priority application US 350, application PCT/IB2003/003246, employment agreements with the inventors and declarations of assignment.

Moreover, the invention disclosed in the Norwegian patent is the "same invention" as the one disclosed in the US 350 application, cf. Section 6 of the Norwegian Patents Act and Article 4A of the Paris Convention. A skilled person would derive the invention directly and unambiguously from Formula IX on pp. 26-27/91-92 and Formula IV on pp. 57-58/105 of the 350 application.

In Case 13-170456TVI-OTIR/01:

Idenix Pharmaceuticals, Inc. argues that the Gilead Patent, NO 700, shall be declared invalid in its entirety due to lack of novelty and inventive step over applications PCT 346, NO 465 and US 350, which applications the defendants' patent is based on.

As mentioned, application PCT 246, which corresponds to the defendants' Norwegian patent application NO 465, has earlier priority than the Gilead Patent, NO 700. The same applies to the defendants'





priority application US 350. The subject-matter of Claims 1-12, 14, 15 and 19-60 of the Gilead Patent is disclosed in Idenix' PCT application and Norwegian application. The subject-matter of the same claims of the Gilead Patent is disclosed in Idenix' 350 application. The descriptions in the defendants' PCT application, Norwegian application and priority application are all sufficient. Consequently, the said claims of the Gilead Patent lack novelty, cf. Section 2, Sub-section 1, cf. Sub-section 2, third sentence, of the Norwegian Patents Act.

Both the defendants' application PCT 246 and priority application US 350 became available to the public on 8 January 2004. None of these were examined by the Norwegian Industrial Property Office at the time of the granting of the Gilead Patent, NO 700. Based on the description of 2'Me-up/2'F-down compounds in the said prior art, the compounds in respect of which protection is claimed in the Gilead Patent would have been obvious to the skilled person, irrespective of whether the Idenix citations meet the requirement for sufficient description in Section 8, Sub-section 2, third sentence, of the Norwegian Patents Act. Any allegedly "unexpected effect", which according to European case law is only a secondary indicator of patentability, cannot change this.

Correspondingly, the method and the pharmaceutical preparation claimed in the Gilead Patent, NO 700 (Claims 13 and 16-18) are obvious in view of the 2'Me-up/2'F-down compounds disclosed in the defendants' application PCT 246 and in priority application US 350, when taking the common general knowledge of the skilled person into consideration.

Idenix has prayed for the following relief:

In Case 12-155575TVI-OTIR/01:

1. Norwegian patent NO 330 755 to be upheld with the claims set out in Bundle 23, pages 10,558 – 10,561.
2. Alternatively: Norwegian patent NO 330 755 to be upheld with the claims set out in Bundle 23, pages 10,562 – 10,565.
3. Gilead Sciences Europe, Ltd. and Gilead Pharmasset LLC to be ordered to pay the legal costs of Idenix Pharmaceuticals, Inc., Centre National de la Recherche [sic] Scientifique, Università Degli Studi Di Cagliari and L'Université Montpellier II.

In Case 13-170456TVI-OTIR/01:

1. Norwegian patent NO 333 700 to be declared invalid.
2. Gilead Pharmasset LLC to be ordered to pay the legal costs of Idenix Pharmaceuticals, Inc.



### Technical background

Hepatitis is a disease caused by certain hepatitis viruses, including hepatitis C virus, which primarily affect the liver. Hepatitis C virus was first described in 1989. Hepatitis C virus is a positive-sense, single-stranded RNA virus. RNA is, like DNA, a macromolecule comprised of long chains of "building blocks" called nucleotides. Hepatitis C virus belongs to the Hepacivirus genus, which again belongs to the *Flaviviridae* family. The *Flaviviridae* family also includes, *inter alia*, yellow fever virus, West Nile virus, dengue fever virus and the virus causing tick-borne encephalitis (acute inflammation of the brain). Hepatitis C virus is transmitted via blood or other bodily fluids.

Most patients (about 85%) infected by hepatitis C virus do not show any symptoms, or only specific symptoms, during the acute phase. Hepatitis C virus will in many cases not show any symptoms for the first few years, not even for those who develop chronic infection after the acute phase. Chronic infection may result in cirrhosis of the liver, and evolve into liver failure, liver cancer or other fatal diseases. It is assumed that up to 130-180 million people are suffering from chronic hepatitis C virus infection worldwide, that 3-4 million people are infected each year and that about 350,000 people die each year of hepatitis C-related causes.

At present, there exists no vaccine against hepatitis C virus infection. The standard treatment of C virus infection involves administration of the active ingredients alpha interferon or pegylated alpha interferon and ribavirin. Other active ingredients are also used in some cases, such as the NS3/NS4a protease inhibitors telaprevir or boceprevir. Hepatitis C treatment with alpha interferon or pegylated alpha interferon and ribavirin typically lasts for 48 weeks, and involves frequent side effects, including bone marrow suppression, fatigue, flu-like symptoms, as well as neurological diseases and mental disorders. In general, only between 40 and 50% of patients with (genotype 1) hepatitis C virus infection achieve a sustained virologic response indicating that the treatment is effective. Those who are not cured, and who develop liver failure or liver cancer, will often need a liver transplant. This, as well as the large number of patients afflicted with the disease, has resulted in hepatitis C virus infection being one of the most widespread causes of liver transplants.

In the development of new treatment methods, extensive research has related to the hepatitis C virus replication process, which briefly summarised involves the following stages:

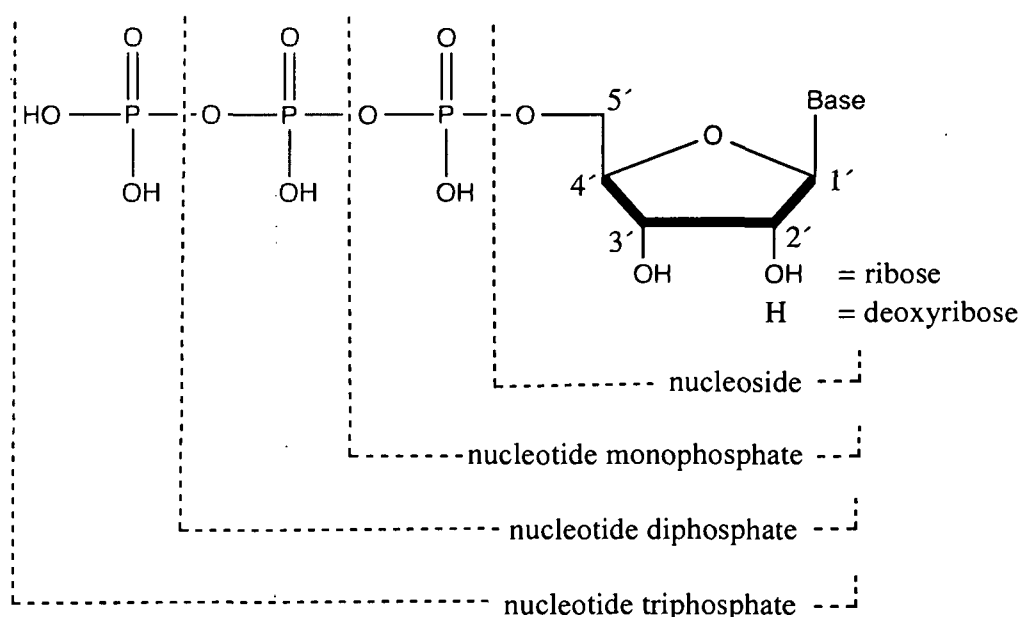
- a) The hepatitis C virus enters a host cell;
- b) the shell of the virus disintegrates and the RNA strand (the genetic material) of the virus is exposed;
- c) by using the information from the RNA strand, the host cell produces polymerase (a protein called NS5B), which is used for making new copies of the genetic material of the virus, and other proteins included in, *inter alia*, the virus particle;



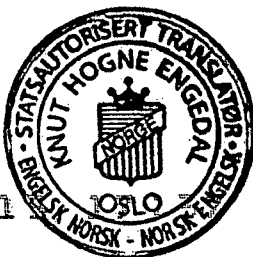
- d) the polymerase recognises and binds to so-called nucleotides, which are chemical substances that exist in the host cell, and incorporates the nucleotides into new RNA strands; and
- e) the virus builds a shell around the new RNA strand, and thereby makes a new virus particle that can leave the host cell and infect other cells.

Several strategies have been pursued with a view to preventing the replication of the hepatitis C virus. The inventions with which the present proceedings are concerned are nucleosides and nucleotides intended to influence what is referred to as stage (d) of the replication process above, and which thereby inhibit replication of the virus.

Nucleosides are chemical substances that serve as starting materials for the biological formation of nucleotides. Both nucleosides and nucleotides typically consist of a sugar ring (called ribose or deoxyribose), which is bonded with a base (nucleobase). The main difference is that nucleotides include one or more phosphate groups at the 5'-position, which are not included in nucleosides, as shown below.

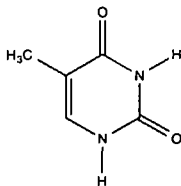
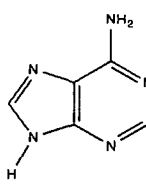
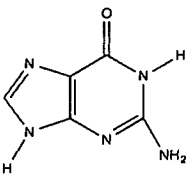
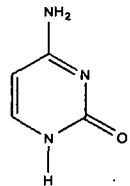
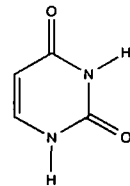
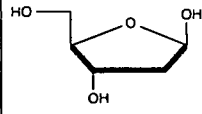
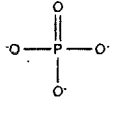
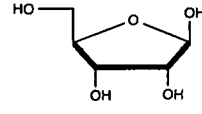


Nucleotides are molecules that constitute "building blocks" of nucleic acids (DNA and RNA). In addition, the nucleotides participate in biological processes in the cells. The most common naturally occurring nucleobases in DNA and RNA are: (1) cytosine, (2) uracil and (3) thymine, all of which are termed pyrimidines, as well as (4) adenine and (5) guanine, which are termed purines. Thymine only occurs naturally in DNA, and uracil only occurs naturally in RNA, whilst the remaining three occur naturally in both DNA and RNA. There are also differences in the sugar ring, inasmuch as the DNA ring (2'-deoxyribose) does not include the OH-group at the 2'-down



position (at the bottom right of the sugar ring). The diagram below shows the building blocks of DNA and RNA:

### The components of nucleic acids

	In DNA only	In both DNA and RNA	In RNA only
Nitrogen bases	 <p>Thymine</p>	 <p>Adenine</p>  <p>Guanine</p>  <p>Cytosine</p>	 <p>Uracil</p>
Sugar and phosphate	 <p>2-Deoxyribose</p>	 <p>Phosphate</p>	 <p>Ribose</p>

The following requirements must be met in order for a nucleoside/nucleotide compound to prevent the replication of hepatitis C virus:

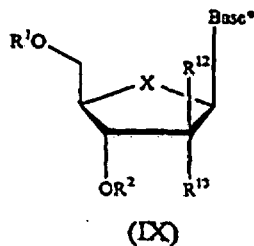
- The compound must be recognised by the hepatitis C virus polymerase (NS5B);
- it must be incorporated into new RNA strands instead of the nucleotides that occur naturally in the cells; and
- the compound must have properties that result in it preventing the completion of replication, after it has been incorporated into new RNA strands.

Ribavirin, which forms part of the current standard treatment of hepatitis C virus infection, was synthesised in 1970. It was first marketed in 1980, and has been used in the treatment of hepatitis C virus infection since 1998. Ribavirin is a nucleoside analogue that influences the replication process as described above. Ribavirin does not work specifically on hepatitis C virus, but is active against a number of DNA and RNA viruses.

#### Disputed patent NO 755 (the "Idenix Patent")

As mentioned, the disputed patent concerns chemical compounds that have turned out to be suitable as pharmaceutical products, especially in the treatment of *Flaviviridae* infections, such as hepatitis C virus infection. The patent claims pertain, according to their wording, to a group of 2'-fluorine substituted nucleoside/nucleotide compounds of the general formula:



A number of alternatives are specified for the substituents  $R^1$  and  $R^2$ . Base\* may be a "purine or pyrimidine base", which is defined in the patent as encompassing a large number of individual bases, both natural and non-natural bases.

X may, for example, be oxygen (O). Several alternatives are specified for  $R^{12}$ , including methyl ( $CH_3$ ), whilst  $R^{13}$  can only be fluorine.

Idenix has requested patent limitation in connection with these proceedings.

Idenix has limited the patent to Patent Claims 2–22. Alternatively, Idenix has moved for the patent to be upheld on the basis of a new claim that corresponds to Claim 5 of the alternative set of claims filed with the EPO on 4 July 2013.

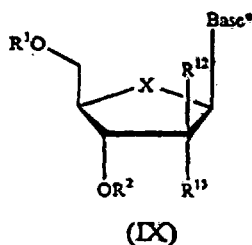
Gilead has not objected thereto, and the parties have requested the Court to base its assessment on the new claims. The Court adheres to this, although it refrains, against the background of the outcome of the case, from ruling on the limitation.

The new claims are worded as follows:

Patent Claim (1a) Patent NO 755

1.

Compound, characterised in having Formula (IX):



or a pharmaceutically acceptable salt thereof, where



R1 and R2, independently, are H; phosphate; straight-chain, branched, or cyclical C1-10 alkyl; CO-C1-10 alkyl; CO-aryl; CO-C1-10 alkoxy(C1-10)alkyl; CO-aryloxy(C1-10)alkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents chosen from fluorine, chlorine, bromine, iodine, hydroxyl, amino, C1-10 alkylamino, arylamino, C1-10 alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate; C1-10 alkylsulfonyl; arylsulfonyl; ar(C1-10 alkyl) sulfonyl; or an amino acid chosen from  $\alpha$ ,  $\beta$ ,  $\gamma$  or  $\delta$  glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine in D or L configurations;

X is O;

Base\* is a purine or pyrimidine base;

R12 is C(Y3)3;

Y3 is H; and

R13 is fluorine;

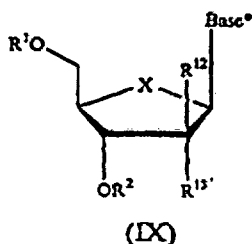
wherein aryl in each case means phenyl, biphenyl or naphthyl.

2.

Compound according to claim 1, characterised in that R1 and R2 are H.

#### Alternative Patent Claim (1b) Patent NO 755

Compound, characterised in having Formula (IX):



or a pharmaceutically acceptable salt thereof, where



R1 and R2, independently, are H; phosphate; straight-chain, branched, or cyclical C1-10 alkyl; CO-C1-10 alkyl; CO-aryl; CO-C1-10 alkoxy(C1-10)alkyl; CO-aryloxy(C1-10)alkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents chosen from fluorine, chlorine, bromine, iodine, hydroxyl, amino, C1-10 alkylamino, arylamino, C1-10 alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate; C1-10 alkylsulfonyl; arylsulfonyl; ar(C1-10 alkyl) sulfonyl; or an amino acid chosen from  $\alpha$ ,  $\beta$ ,  $\gamma$  or  $\delta$  glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine in D or L configurations;

X is O;

Base\* is cytosine, uracil, guanine, adenine, or thymine;

R12 is C(Y3)3;

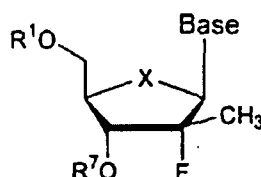
Y3 is H; and

is fluorine;

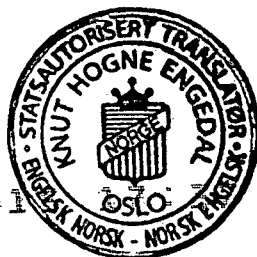
wherein aryl in each case means phenyl, biphenyl or naphthyl.

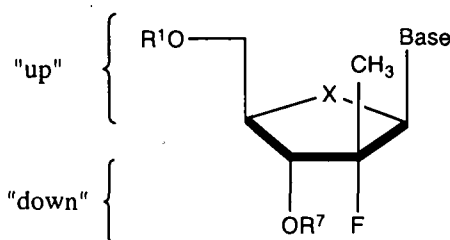
#### Disputed patent NO 700 (the "Gilead Patent")

The Gilead Patent also concerns certain nucleoside and nucleotide compounds that can be used in the treatment of *Flaviviridae* infections, especially hepatitis C. According to Patent Claim 1, filed on 30 March 2012, the patent pertains to compounds of the general formula:

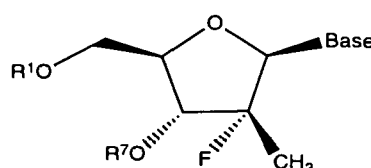


The thick lines in the above formula show the three-dimensional shape of the molecule, and indicate that the bonds between the atoms are pointing towards the viewer. For this reason, some atoms and atom groups are designated as "up" and some as "down", as illustrated in the diagram below:

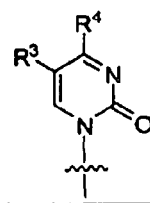




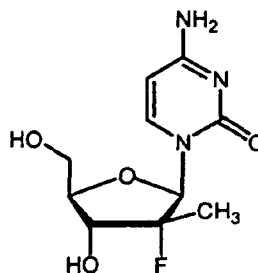
Another way of illustrating the three-dimensional shape is to use unbroken and broken [lines to represent] bonds, respectively, as in the following [diagram]:



The compounds disclosed in Claim 1 are N-nucleosides/nucleotides, i.e. compounds in which the nitrogen atom of the base is bonded with the carbon atom at the 1'-position on the sugar ring. More specifically, the patent claim pertains to compounds wherein Base is of the following formula:



The characterising features invoked in respect of Gilead's invention include, *inter alia*, the 2'-position on the sugar ring having been substituted with F (fluorine) at the 2'-down-position and CH<sub>3</sub> (methyl) at the 2'-up-position, as well as Base being cytosine or uracil bonded from a nitrogen atom of the base (i.e. N-bonded). One embodiment of the invention is shown on page 33 of the application as filed, and is illustrated in Example 1 and Example 2 (wherein the base is cytosine):





### The comments of the Court

The Court has full jurisdiction over the issue of the validity of patents. Reference is made to Section 52, Sub-section 1, of the Norwegian Patents Act, from which it follows that a patent may be invalidated by a court decision if it has been granted in spite of the fact that the requirements under Sections 1 – 2 are not complied with (1); or it relates to an invention the description of which is not sufficiently clear to enable a person skilled in the art to carry out the invention on the basis thereof (2); or after a request for patent limitation, the patent has been amended in such a way that the scope of protection has been extended (5).

Although the courts of law also have full jurisdiction over the specific discretionary assessment, the Supreme Court has stated in two cases concerning decisions to reject patent applications that the courts of law shall exercise restraint in their judicial review of the discretionary technical assessments of the Norwegian Industrial Property Office. Reference is made to the Swingball Judgment, published on p. 603 onwards of the 1975 volume of the *Norsk Retstidende* court reporter, and the Biomar Judgment, HR-2008-1991-A.

### The invalidity action with regard to NO 755

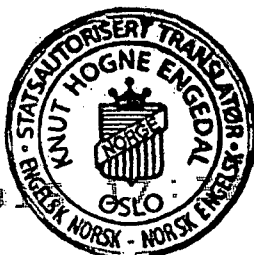
The Court will first examine Gilead's argument that patent NO 755 is not valid because the description is not sufficiently clear to enable it to be carried out by a skilled person.

*Gilead has, in the main, invoked the following in relation thereto:*

The application that forms the basis for the disputed patent contains no embodiment examples illustrating the patented invention and does not contain information that would have enabled the skilled person to identify, without undue burden or experimentation, chemical compounds within the scope of the patent claims that can be used for the treatment of *Flaviviridae* infections. Nor does the application contain any information that would have enabled a skilled person to produce and make use of the therapeutically active compounds without undue burden or experimentation. It describes no process for the production of the chemical compounds in respect of which protection is claimed. Nor did the prior art include any process that enabled the skilled person to produce the said compounds without undue burden or experimentation.

The disputed patent encompasses an enormous number of different compounds as the result of the many alternatives specified for the various substituents, without disclosing any information that would have enabled the skilled person to choose between them.

Furthermore, the description neither discloses sufficient information concerning how to conduct and interpret suitable tests, for purposes of distinguishing the alleged pharmaceutical product candidates, nor provides any guidance with regard to synthesis routes or reaction conditions that would enable the skilled person to produce the patented compounds.



Neither the dependent patent claims, nor the alternative patent claim, add anything that might justify upholding the patent.

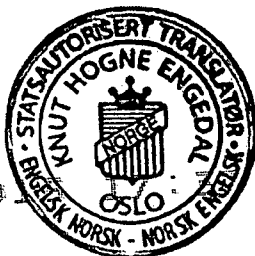
*Idenix has, in the main, invoked the following:*

The skilled person would be able to produce the compounds in the patent claims without undue burden by using information from chemical literature and the patent documents, as well as starting materials, reagents, techniques and equipment that are available to the public, together with his or her own expertise and knowhow, as well as routine experiments. As at the priority date of NO 755, the synthesis for nucleoside analogues, with both natural and non-natural bases, had been known for a long time. Both suitable starting materials and synthesis strategies were available. The same was the case with a number of methods for testing the antiviral effect of different compounds in relation to various viruses within the *Flaviviridae* family. Some of these are discussed in the patent, cf. p. 45 and pp. 180–183, whilst others, such as for example the HCV Replication System, formed part of the common general knowledge of the skilled person.

A skilled person would on 28 June 2002 and 27 June 2003 have been able to synthesise the compounds in respect of which protection is claimed, based on the information disclosed in the patent and common general knowledge in the art. The skilled person could have done this by only conducting routine experimentation. The skilled person would have been familiar with appropriate reagents for purposes of achieving fluorination, including diethylaminosulfur trifluoride (DAST) and Deoxo-Fluor. The skilled person would also know how to get to the appropriate precursor for achieving the correct stereochemistry. Reference is made to the expert opinions, incl. appendices, and the witness testimony of Professors Meier and Sydnes.

It is not a legal prerequisite for the description with regard to the product claims in Claims 1 and 2 of Exhibit 1a and Claims 1 and 2 of Exhibit 1b to be sufficient to enable the skilled person to test the activity of the compounds. However, methods for the testing of the antiviral activity of the compounds were available to the skilled person. As far as anti-HCV testing is concerned, assays based on the HCV replicon system constituted common general knowledge in the art as at the priority date. Alternatively, in vitro assays for RNA polymerase activity were available. This is described in the patent. As far as testing of activity against WNV, YFV, dengue fever, etc., is concerned, routine cell-based assays for viral infections were available, such as assays for the calculation/reduction of plaque. Moreover, assays for cell protection/cytopathic effect, including neutral red uptake assay, were available to the skilled person. These assays are described in the patent, and were well known, in routine use, as well as available, on 28 June 2002. Reference is made to the expert opinion, incl. appendices, and the witness testimony of Dr DeFrancesco.

*The Court* will base its assessment on Section 8, Sub-section 2, third sentence, of the Norwegian Patents Act, which is worded as follows:



*The description shall be sufficiently clear to enable a person skilled in the art to carry out the invention on the basis thereof.*

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The requirement with regard to the clarity of the description is a substantive prerequisite for patentability. The reasoning behind such requirement is, firstly, that the invention shall be made available to the public and clarify the scope of the exclusive right. If the requirement is not met, the patent may be declared invalid, cf. Section 52, Sub-section 1, No. 2, of the Norwegian Patents Act.

The parallel provision of the European Patent Convention ("EPC") is Article 83. It is worded as follows:

*The European patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.*

The said provision stresses that the description shall not only be clear, but also "complete". The same wording is used in Art. 5 PCT. The former Norwegian patents acts used the wording "clear and complete". Although the wording of the current act is different, it follows from the preparatory works that one did not intend to effect any amendment to the substance [of the legislation], cf. the NOU 1963:6 Green Paper, page 185. Reference is made, furthermore, to the NOU 1976:49 Green Paper, page 110, in which it is concluded that Art. 5 PCT, which we have noted corresponds to Art. 83 EPC, does not occasion any amendment to Section 8, Sub-section 2, of the Norwegian Patents Act.

There is a presumption that Norwegian law is in conformity with the EPC. This is a key factor of interpretation. It must be concluded, when read in the context of the legislative history of the provision, that the contents of Section 8, Sub-section 2, third sentence, of the Norwegian Patents Act are the same as [the contents of] Art. 83 EPC. Consequently, the description shall not only be *clear*, but also *complete*. This can also be reasonably inferred from the requirement that the skilled person shall be able to exercise ["carry out"] the invention on the basis of the description.

Neither the preparatory works of the Act, nor case law, provide further guidance with regard to the requirements for the description. It can nonetheless be concluded, against the background of case law and literature relating to Art. 83 EPC, that one must be able to directly derive the information necessary to carry out the invention, either from the description or from common general knowledge in the art. One must, on the basis of the said information, be able to solve the problem intended to be solved by the invention. One must be able to produce and make use of the invention. Claims 1 and 2 are product claims. Hence, the question is whether the skilled person can make the product. In order to make the product, the starting materials and the active ingredient need to be identified. The Court also refers, in relation hereto, to the decision of the EPO Technical Boards of Appeal in Case T 0412/93:



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*Whether this product claim can stand for the purposes of Article 83 depends on whether what is claimed can be identified, and whether a reliable method existed for making it using the teaching of the patent and common general knowledge available at the priority.*

Moreover, the EPO has concluded that everything of critical importance to understanding the invention shall be disclosed in the description. It is not sufficient to refer to publications, etc., in which it is disclosed, cf. T 276/99.

One shall be able to carry out [the invention] without undue burden or experimentation. The EPO has put it as follows:

*It must be possible to reproduce the invention on the basis of the original application documents without any inventive effort and undue burden. (T 629/05)*

Some experimentation and a reasonable amount of trial and error can be accepted, but the EPO has stated the following:

*Where the skilled person can only establish by trial and error whether or not his particular choice of numerous parameters will provide a satisfactory result, this amounts to an undue burden. (T 32/85)*

The EPO has stated the following with regard to experimentation:

*They should quickly give a reliable picture of how the products can be produced or manufactured (T 475/88).*

It is not necessary to show all steps leading to the compound, and there is no requirement that the invention can be carried out with only a small number of non-disclosed steps. However, the requirement is that each of these steps are perceived by the skilled person as sufficiently clear to make a detailed description thereof seem superfluous. Reference is made to the EPO Technical Boards of Appeal:

*Furthermore, there is in the Board's opinion, no requirement in the European Patent Convention that where it is not explicitly described how a claimed invention is to be carried out this must be practicable with the aid of only a few additional non-disclosed steps. The only essential requirement that must be fulfilled is rather that everyone of these additional steps must be so apparent to the skilled person that, in the light of his common general knowledge, a detailed description thereof is superfluous. (T 721/89)*

The skilled person must be able to know that he has achieved the outcome, and hence there must be a method for verifying whether the invention has been realised.



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It is the technical solution defined in the patent claims that shall be capable of being carried out on the basis of the description and common general knowledge in the art. The parties agree that the Court may for purposes of the present case restrict its assessment to the new patent claims. The Court bases [its assessment] on the arguments invoked by the parties, but, as the Court will revert to, [the Court] refrains from ruling on whether or not the patent limitation request is admissible.

It follows from EPO case law that any doubt as to whether or not the invention can be carried out without "undue burden" shall be resolved in favour of the patent holder.

#### Review of the patent description

the Idenix Patent, NO '755, pertains to chemical compounds that are suitable for use in pharmaceutical products, especially for the treatment of *Flaviviridae* infections such as hepatitis C virus infections.

The patent describes a very large number of nucleosides and nucleoside derivatives. According to the description, these nucleosides are branched at the 1'-, 2'-, 3'- or 4'-position and may feature  $\beta$ -D- or  $\beta$ -L-configuration. The nucleosides may contain a number of different bases and may in the 2'-, 3'- and/or 5'-position contain a biologically decomposable entity, typically a natural or synthetic D- or L-amino acid.

The description includes numerous detailed embodiments. A number of these include formulas with high chemical variability. Application NO 465 uses the term "Principal Embodiments" to designate the first six groups specified. Sub-embodiments are specified under each of these groups. Some of these are termed "preferred" and some are termed "even more preferred" or "especially preferred". The Court finds the use of these designations to be purely incidental and void of guidance. After the six principal embodiments, [the description] specifies four forms designated as "particular aspects" of the invention. Some additional embodiments are also specified, one of which is termed "another preferred embodiment", cf. application NO 465, page 42.

The said designations are not included in the description of patent NO 755 as granted. Apart from that, the contents are virtually identical. The description starts out by discussing the main formulas. The formulas are discussed anew from page 54 of the patent. This is termed "Active Compound" in the US application, and is the active part of the pharmaceutical product and thus also the key aspect of the invention. A total of 23 formulas are discussed. The patent describes a number of variants under each of these. It would appear that the grouping into the six main groups continues, although the designation "Main Group" is not used.

All of the formulas are presented with the following wording:

A compound of the Formula (..) or [its] pharmaceutically acceptable salt or prodrug [thereof], or stereoisomer, tautomer or polymer form thereof are described...



The designations "sub-embodiment groups" or "preferred embodiment", etc., are not used in the patent description either, unlike in the application, subject to certain exceptions to which the Court will revert.

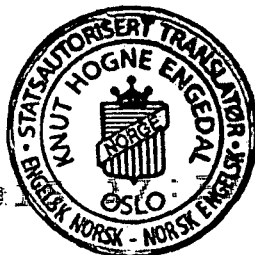
**Formula (I)** is discussed from page 19 and from page 54 of the patent description. The diagram discloses 2'-branched ribonucleosides with OR substituents in the 2'-, 3'- and 5'-position and with a synthetic/non-natural purine base with three variable substituents. The formula encompasses a very large number of chemical compounds; probably much more than one billion. The number must in reality be considered infinite since the definition of the variable substituents includes substance classes and substituents with unlimited scope for variation. One specifically described compound is identified in relation to this formula. Although the said variant represents a limitation, this description also allows for a very large number of alternative choices.

This first embodiment is of no direct relevance in relation to the invention as currently claimed, i.e. in relation to the revised principal and alternative claims, since the variant with 2'-fluorine-down is not included.

**Formula (II)** is discussed from page 19 and from page 56 of the patent description. This diagram also discloses ribonucleosides with OR substituents, "2'-OR-down, with non-natural pyrimidine bases. Likewise, this formula encompasses a very large number of chemical compounds, probably much more than one billion. The embodiment is narrowed down in one "specifically described" form, but such [form] is also likely to encompass about 1,000 embodiments.

Nor is this second embodiment of any direct relevance in relation to the compounds currently claimed as the invention, as it does not include the variant with 2'-fluorine-down either.

**Formulas (III), (IV) and (V)** are discussed from page 21 and from page 57 of the patent description. In application NO 465, these formulas were designated as the "third principal embodiment". In addition to compounds with oxygenous sugar rings, [the formulas] also allow for other nucleosides, for example carbocyclic nucleosides ( $X=CH_2$ ), thionucleosides ( $X=S$ ) or unsaturated nucleosides ( $X^*=CH$ ). In the same way as with Formulas (I) and (II), the number of chemical compounds encompassed by the description is infinitely large as the result of very considerable scope for structural variation in the base and substituent groups. The base may be chosen from a large number of bases outlined in some detail. However, it would appear to the Court that the potential choices are limited to non-natural or synthetic bases. The natural N-bonded purine and pyrimidine bases are not included. As an example, reference is made to Diagram (E) on pages 22 and 58. The diagram as presented includes cytosine (if  $Y^2 = O$ ,  $W^1 = N$ ,  $Y^1 = NH_2$ ,  $X^2 = H$ ,  $W^4 = CH$ ), uracil (in the enol form if  $Y^2 = O$ ,  $W^1 = N$ ,  $Y^1 = OH$ ,  $X^2 = H$ ,  $W^4 = CH$ ), and thymine (in the enol form if  $Y^2 = O$ ,  $W^1 = N$ ,  $Y^1 = OH$ ,  $X^2 = CH_3$ ,  $W^4 = CH$ ). Consequently, even though natural bases are encompassed at the outset,



such natural bases are specifically excluded at the bottom of page 28 and at the top of page 29 of the patent description. The same is evident from the middle of page 64. The Court is of the view that this will be perceived by the skilled person as a deliberate choice. In other words, it is not perceived as an oversight or unintentional error that it would be appropriate for the skilled person to rectify.

In Formula (IV), fluorine (F) is listed as one of many available choices for the  $R^7$  substituent (2'-down position). Fluorine is disclosed as one of four halo substituents. Halo is included at the bottom of a listing of a very large number of alternatives, cf. pages 30 and 66 of the patent. Given the structure of the description, the Court is of the view that the skilled person will not perceive fluorine as having been highlighted, and the available choices will also here be perceived as infinite in number.

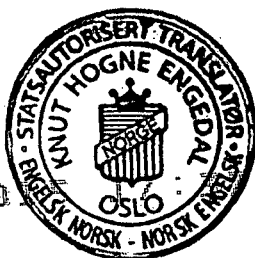
A further three embodiments are described under these three formulas. Thereafter, one additional embodiment is described under Formula IV, which is designated Formula (IV(a)), cf. page 68 of the patent. Fluorine is therein specified as the preferred  $R^7$  substituent, i.e. in position 2'-down. Formula (IV(a)) is not specified as "an especially preferred embodiment" in the patent, as was the case in the application. The said limited embodiment also encompasses a large number of chemical compounds, when considered against the background that there is very considerable scope for variation with regard to Base,  $R^1$  and  $R^2$ .

The Court is of the view that none of these embodiments are of direct relevance in relation to the revised patent claims either, inasmuch as Base, and not Base\*, is specified with regard to all of them. The Court is of the understanding that the term Base as used in the patent does not include the natural bases.

**Formulas (VI) and (VII)** are discussed from page 30 and from page 69 of the patent description. In application NO 465, these formulas were designated as the "fourth principal embodiment".

These formulas include miscellaneous branched nucleosides, including a very large number of chemical compounds with different bases. At first, one embodiment is disclosed under both of Formulas (VI) and (VII). Thereafter, eight compounds are disclosed under Formula (VI), four under Formula (VII) and an additional 15 compounds under Formula (VI). Hence, a very large number of chemical compounds are encompassed.

These formulas are not of appreciable relevance in relation to the amended patent claims. Given how these formulas are presented on pages 69 to 71, the natural N-bonded bases are not included. Given how the range of bases is disclosed on pages 71 onwards, it would appear that natural bases are also included. Fluorine and methyl might be an option under some of the outlined alternatives, but it would be very difficult for the skilled person to deduce the invention from what is disclosed here. Indeed, the parties have not focused on these formulas.



Formulas (VIII), (IX) and (X) are discussed from page 32 and from page 111 of the patent description. In application NO 465, these formulas were designated as the "fifth principal embodiment".

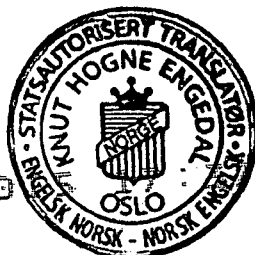
These formulas include three classes of nucleosides in which the base is designated as Base\*. Base\* is defined in the patent as "a purine or pyrimidine base as defined herein". It follows from the definition of purine or pyrimidine base on page 128 that the natural pyrimidine (cytosine, thymine and uracil) and purine (adenine and guanine) bases fall within the scope of the term Base\*. However, Base\* is not limited to the natural bases. According to the definition, a large number of non-natural bases are also included, thus implying that the total number of available base choices is very large here as well.

The first discussion of Formulas (IX) and (X), cf. page 32 and page 111, mentions fluorine as one out of a very large number of alternatives for the  $R^{13}$  substituent (2'-down position). The number of available choices for  $R^{13}$  must be characterised as infinite. Fluorine is listed as the last alternative, and the Court is of the view that the skilled person would not perceive fluorine as being highlighted here in any way as a preferred choice. The description also offers up a very large number of available choices with regard to X,  $R^1$ ,  $R^2$ ,  $R^{12}$ .  $CH_3$  (methyl up) is one of these alternatives, but it is not highlighted.

Following discussion of these three formulas, a "first aspect of the present invention" is mentioned, characterised by Formula (IX).  $R^{13}$  is therein limited to fluorine, whilst  $R^{12}$  is limited to  $C(Y^3)_3$ , cf. page 113. Thereafter, "a preferred embodiment" is disclosed, in which  $X=O$  and  $Y^3=H$ . Furthermore, "a second preferred embodiment" is disclosed, in accordance with the first aspect, in which  $R^1$  and  $R^2=H$ . As mentioned, the base is specified as Base\*, which also includes natural bases. Consequently, this embodiment encompasses the invention as currently accentuated by the limited patent claims. Reference is made to page 114 of the patent. It is noted that the said presentation of a limited version of Formula (IX) was not included in this part of the Norwegian application as originally worded in NO 465.

Thereafter follows a description of a number of nucleosides with **formulas from (XI) to (XXII)**. These formulas are not assumed to be of any relevance to the invention, as now sought protected with the pattern 2'-fluorine-down, 2'-methyl-up and a natural base. The Court therefore does not examine this part of the patent in further detail. However, it is noted that these formulas also allow for a very large number of available choices for the various substituents. An infinite number of chemical compounds fall within the scope of this part of the patent description as well.

After discussion of Formulas (XI) to (XXII), the patent reverts to Formula (IX) on its page 123. In the corresponding part of application NO 465, page 118, the designation "a preferred embodiment" is used. The patent description of NO 755 does not use the said designation. The substituents are described in the same manner as in the preceding discussion of Formula (IX) on pages 111 and 112. In addition, there is a





sub-embodiment in which  $R^1$ ,  $R^2$  and  $R^3$  are specified as H when X is O and  $Y^3$  is H. According to the said description of the formula, the chemical compound will be limited to 2'-fluorine-down, 2'-methyl-up, with only the base being variable. The base shall be a purine or pyrimidine base, but it could be either natural or non-natural.

### Description and exemplification of syntheses

The description states that the nucleosides can be synthesised (produced) through "a number of processes known in the literature". It is noted that synthesis of the disclosed nucleosides can be achieved, in particular, by either alkylation of suitable modified sugar, followed by glycosylation (the sugar route), or by glycosylation followed by alkylation of nucleosides (the nucleoside route).

Thereafter, a number of general synthesis routes to different branched nucleosides are presented, without experimental data. All of the descriptions include general protection and deprotection steps, and references to known and relevant monographs and publications are included.

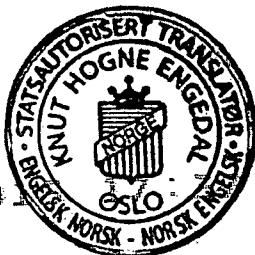
For 1'-C-branched nucleosides, the sugar route is described by two general examples. The first example includes nucleophilic attack on lactone intermediate, followed by activation and coupling with base (Diagram 1). The second example uses D-fructose as starting material. Following conversion into psicofuranose intermediate, this is coupled with base (Diagram 2). For 2'-C-branched derivatives, the sugar route is described first, including nucleophilic attack on 2-keto-sugar derivative followed by coupling with base (Diagram 3). Thereafter, it is described how the nucleoside route can alternatively be used with 2'-ketonucleoside as intermediate (Diagram 4). The corresponding general synthesis path is described for 3'-C-branched nucleosides (Diagram 5 and Diagram 6). A sugar route that includes oxidation of C5 followed by attack on electrophilic alkyl reagent is described for 4'-C-branched nucleosides. These descriptions are followed by a general description of synthesis of 2'/3'-prodrug derivatives (alkylation of hydroxy group with amino acid).

This is followed by a number of examples of specific experimental synthesis procedures. These are typical literature procedures for illustration of the preceding disclosures. The same applies to Diagrams 7 and 9, which describe synthesis of nucleoside intermediates that were also known from the literature.

None of these examples address the synthesis of fluorine substituted nucleosides.

### Common general knowledge in the art

It is a statutory requirement that the description is sufficiently clear to enable *a skilled person* to carry out the invention. The EPC uses the term *a person skilled in the art*. Consequently, it is not necessary for the description to include what is normally known or



understood by persons skilled in the art. This is termed common general knowledge in the art. The skilled person shall be representative of the general, average professional level.

Idenix has, in its Notice of Intention to Defend of 20 November 2012, provided the following description of the skilled person:

*The "skilled person" will for purposes of the present case be a team in possession of the knowledge and experience of, for example, a synthetic organic chemist who is familiar with the synthesis of nucleosides and nucleoside analogues, a medicinal chemist who is familiar with structure-activity relationships for nucleosides and nucleoside analogues, as well as a virologist who is familiar with assays for determining antiviral activity, especially with regard to Flaviviridae virus, in addition to structure-activity relationships. Each of the members of the team may have experience, knowledge and abilities that overlap with the knowledge of other members. Each of the members of the team will have appropriate education and experience, such as a Ph.D. degree within a relevant field, as well as no less than two years' experience.*

Gilead has not objected directly to this, and the Court will base its assessment on the above description.

The next question is what shall be deemed to have been known to the skilled person for purposes of the assessment to be performed herein. The Court adopts the premise that the skilled person within the meaning of Section 8 will not be in possession of the same knowledge as would be assumed for purposes of the inventive step assessment under Section 2. This follows from case law from the EPO, and also follows from the purpose of the said [statutory] provisions. The patent description shall disclose the invention in such a way as to make it understandable to the ordinary person skilled in the art. Information available from textbooks and key articles that are normally read by persons skilled in the art will be assumed to form part of common general knowledge in the art. Patent documents and other sources that are more specialised will not be included, although such information is taken into consideration for purposes of inventive step assessments.

The skilled person is assumed to be capable of drawing on common general knowledge in the art, in addition to the information in the patent. The skilled person is also presumed to be capable of rectifying errors in the description on the basis of common general knowledge in the art. Textbooks and general technical literature form part of common general knowledge in the art. *However, information which can only be obtained after a comprehensive search is not to be regarded as part of the common general knowledge, cf. T 206/83, T 654/90.* The burden of proof is on whoever asserts that something forms part of common general knowledge in the art.

The application date will be of decisive importance in assessing what information the skilled person could have inferred from his or her common general knowledge. The Court will base such assessment on the date of the European application, i.e. 27 June 2003.



As at the said date, the skilled person knew, first of all, that nucleosides could be produced by either the so-called sugar route or the so-called nucleoside route. This is also, incidentally, specified in the patent. Many examples of successful introduction of a fluorine substituent on the sugar ring, including in the 2'-position, had been published, and it had been documented that both the sugar route and the nucleoside route were viable in this context. Reference is made, in particular, to the article Fluorinated Nucleosides, Pankiewicz, published in 2000 (the "Pankiewicz Citation"). The following is stated at the beginning of the said article:

*The objective of this chapter is not to present a list of known fluorinated nucleosides but rather to show the development of the field. Since some early-synthesized 2'-deoxy-2'-fluoro nucleosides showed promising therapeutic potential (mainly antiviral and anticancer), the synthesis of new generations of 2'-fluorinated nucleosides flourished in hope of new drug discovery. Thus, more than 77% of fluorinated nucleosides synthesized to date contain fluorine atom(s) at C-2' of the sugar.*

The skilled person was also familiar with the use of protecting groups, for example via knowledge of the monographs of Greene and Kocienski. Besides, the skilled person was familiar with the article Alkyl Addition Reaction of Pyrimidine 2'-Ketonucleosides, Matsuda, et.al, published in 1988 (the "Matsuda Citation"). The said [article] describes synthesis of 2'-methyl-up, 2'-hydroxy-down and 2'-methyl-down, 2'-hydroxy-up nucleosides with pyrimidine bases. Consequently, the skilled person would be able to identify these derivatives as potential starting materials for the synthesis of 2'-methyl-up, 2'-fluorine-down nucleosides with pyrimidine bases.

Moreover, the skilled person was familiar with 2-keto carbohydrates and the alkylation thereof with C-nucleophiles into starting materials for potential syntheses of 2-methyl-up, 2-fluorine-down intermediates with a view to subsequent coupling with base into corresponding nucleoside derivatives.

The Court further assumes that the skilled person was familiar with potential stereochemical challenges in the coupling of activated carbohydrates with bases, and with heterogeneous reactivity and synthesis strategy across different bases, e.g. between pyrimidine and purine bases. The skilled person would also be aware of the need for making use of completely heterogeneous reaction types in the synthesis of N- and C-nucleosides via the so-called sugar route.

The skilled person would be aware that a decisive step in the syntheses of 2'-methyl-up, 2'-fluorine-down nucleosides would be the introduction of fluorine into the desired stereochemical configuration.

The skilled person was familiar with a number of different reagents for the replacement of a hydroxy group with a fluorine atom. Moreover, the skilled person was familiar with potential stereochemical challenges and with potential undesired side reactions when attempting the introduction of fluorine substituents.

The skilled person knew, for example, about DAST (diethylaminosulfur trifluoride) and the closely related Deoxo-Fluor (di-2-(methoxy)ethylamino(sulfur trifluoride)) as reagents



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in the replacement of a hydroxy group with a fluorine atom. The skilled person also knew that DAST had been used successfully for the introduction of fluorine substituents in the 2'-position on the sugar ring of nucleosides, via both the sugar route and the nucleoside route.

The Court has not registered any disagreement between the parties with regard to the conclusion that the [knowledge] outlined above formed part of common general knowledge in the art as at the priority date. The disagreement concerns, in particular, issues relating to the introduction of a fluorine substituent in the synthesis of the relevant 2'-methyl-up, 2'-fluorine-down nucleosides.

The respective expert witnesses called by the parties would also appear to, partly, hold highly diverging opinions, precisely with regard to issues relating to the introduction of a fluorine substituent in the synthesis of the relevant nucleosides. Idenix' expert witness Dr Mcier stated, *inter alia*, the following in his report:

*These two reagents [note: DAST and Deoxo-Fluor"] were used previously by several scientists also in nucleoside chemistry and therefore was a routine reaction.*

He further stated that:

*Taking the arguments above together, a person skilled in the art could routinely and predictably convert the 2'-OH of a 2'-Me-up nucleoside into a 2'-F-derivative with a simultaneous inversion of stereochemistry to form a 2'-F-down-2'-methyl-up nucleoside analog as shown below.*

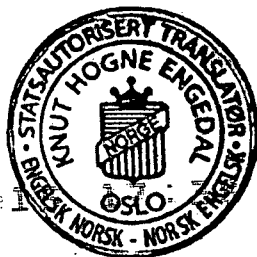
On the other hand, Gilead's expert witness Dr Marquez stated the following:

*This is because fluorination reactions often have surprising or unpredictable outcomes. This can be especially true when one is trying to synthesize a compound with different chemical features from those known in the art, for example a nucleoside with a new substitution pattern on the sugar ring.*

He further stated that:

*Accordingly, it is my opinion that an artisan as of June 27, 2003 could not have predicted whether particular methods known in the literature for making fluorinated compounds would have worked to make the compounds of the Idenix Claims.*

The Court is of the view that it follows from the abovementioned article by Pankiewicz that the skilled person knew that the necessary protection of hydroxy groups could be achieved with different protecting groups. Reference is made to Diagrams 5, 8 and 11, in which trityl and silyl protecting groups are used. The Court is of the view that the skilled person would, in 2003, be aware that



the introduction of fluorine in the C2 position of carbohydrates, as implied by the sugar route, could be complex. This is evidenced by the following quote from the Pankiewicz Citation:

*Although, the introduction of a fluorine atom at C-2 of the carbohydrate by nucleophilic displacement reaction is rather difficult, the similar reaction at C-3 is not.*

The Court also notes that common fluorination reagents such as, for example, DAST, Deoxo-Fluor, hydrogen fluoride and ammonium fluoride, are used in precisely such nucleophilic substitution reactions. The fact that the sugar route might involve challenges is also illustrated by a number of synthesis problems described in the Pankiewicz Citation under the synthesis of a sugar coupling reagent for the production of FMAU (2'-deoxy-2'-fluoro-ara-A), cf. Diagram 4 and text in the 2<sup>nd</sup> column.

Besides, it follows from the Pankiewicz Citation that it was known that ribo-configured 2'-fluorine-substituted pyrimidine nucleosides could be produced from 2,2'-anhydrous intermediate.

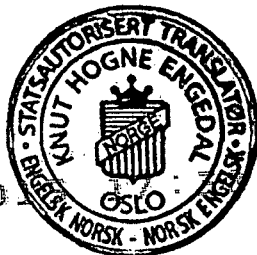
The skilled person would also be aware that an anhydrous intermediate could not be formed in respect of the natural purine nucleosides, thus implying that it would probably be necessary, as far as the nucleoside route was concerned, to make use of different synthesis strategies in the production of, respectively, pyrimidine and purine nucleosides with 2'-fluorine substituent.

The Court is of the view that the skilled person would be aware that the nucleoside route could be difficult for purposes of the synthesis of 2'-methyl-up-2'-fluorine-down nucleosides because of, *inter alia*, steric and inductive effects and the potential for undesired side reactions. This can be illustrated by the following quote from the Pankiewicz Citation:

*The direct displacement of a good leaving group at C-2' in ribo configuration with fluorine attacking from the  $\beta$ -face had not been considered to be successful due to the steric hindrance provided by the aglycone positioned above the sugar face. Also, the inductive effects from the aglycone and the lactol ring oxygen make the substitution at the C-2' position difficult.*

This quote concerns direct synthesis of 2'-F-up derivatives, but the necessity of the presence of a 2'-C-methyl-group at C2' might be expected to induce steric challenges in connection with the incorporation of a fluorine atom into the C2' atom. The same could not be excluded in connection with the sugar route.

The Court is of the understanding that Dr Meier, unlike Dr Marquez, believed that a replacement from OH to F would not result in a conformational change on the sugar ring. The Court is of the view that the presence of a 2'-C-methyl-group might entail new and not hitherto described



inductive and conformational conditions on the sugar ring, and that these might influence fluorination reactions. This might happen both when using the nucleoside route and [when using] the sugar route.

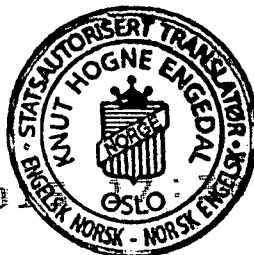
The skilled person would be aware that there did not exist many examples, if any at all, of the introduction of fluorine at the C2'-position of nucleosides by way of the replacement of a tertiary hydroxy group with a fluorine atom. Moreover, the skilled person would be aware that insertion of a fluorine atom into the carbon atom at the 2'-position; the neighbouring atom of the glycosidic centre, might be expected to influence the chemical and enzymatic stability of the glycosidic bond, as well as the preferred conformation of the furanose ring. This is supported by the Pankiewicz Citation.

Furthermore, the Court assumes that the skilled person would be aware that it was known that structure-activity relationships (SAR), relating to the anti-HCV activity of ribonucleosides, are complex. Hence, only a small number of ribo-configured nucleosides were known to exhibit antiviral activity. The Court concludes, as a result thereof, that there was no general acceptance in professional circles that 2'-hydroxy ribonucleosides, and the corresponding 2'-fluorine ribonucleosides, would exhibit uniform antiviral activity. It is noted, in support thereof, that it was known that 2'-H-up, 2'-fluorine-down nucleosides of guanine and adenine, unlike the corresponding 2'-methyl-up, 2'-hydroxy-down nucleosides, were inactive in "replicon assay". The Court is of the view that this would lead the skilled person away from choosing 2'-methyl-up, 2'-fluorine-down nucleosides on the basis of the description in the patent.

#### Further details of the assessment of the Court

As mentioned, the notional skilled person, as defined above, shall be able to both identify the product and produce it based on the reviewed description and common general knowledge in the art. Although Section 8 of the Norwegian Patents Act only refers to the description, it is assumed in case law and legal theory that the patent claims shall also be taken into consideration. Reference is made to "*Patentloven med kommentarer*" ["The Annotated Danish Patents Act"] by Lindgreen, Skchovsbo [sic], Thorsen, 2012, page 220. As far as identification of the product is concerned, the Court is of the view that the skilled person gets somewhat more guidance from the patent claims subsequent to the limitation thereof. This applies, in particular, to a limitation to the alternative claims referred to as 1b). The original claims were much broader in scope. The patent claims cannot be amended in such a way as to grant a patent on anything not encompassed by the application as filed. Such might be the case even if an amendment takes the form of a limitation. However, Gilead has not invoked any arguments in relation thereto, and hence the Court does not perform any assessment as to whether the limitation would have been lawful.

The patent is very broad in scope. The description encompasses billions, or even an infinite number, of chemical compounds. Moreover, the structure of the description is not particularly good or clarifying. A number of the diagrams are featured several times. An example is Formula IX, which the Court considers to be the only formula of direct relevance to the invention. A variant of this formula is repeated after the other formulas have been



discussed, without any explanation being provided in relation thereto. Application NO 465 includes principal embodiments and sub-embodiments, preferred and especially preferred embodiments, etc. However, this terminology does not appear to have been consistently applied, and in many cases it would seem that the terms have been used almost randomly. Indeed, this [terminology] is abandoned in NO 755.

The compounds in respect of which protection is now claimed, and which constitute the "invention" under the limited patent claims, is a compound featuring methyl up and fluorine down, as well as a natural N-bonded base. This invention is disclosed in a variant of Formula (IX). However, the said compound is not specifically highlighted, as it is one of an infinite number of compounds described at the same level of detail. The question is therefore whether the skilled person would have identified such compound without extensive trial and error. The compound has, as mentioned, been rendered more visible after the limitation.

However, it is not sufficient for the skilled person to be able to identify the compound. He or she must also be able to produce it, based on the description and common general knowledge in the art. Neither the original patent claims, nor the amended ones, provide the skilled person with any guidance in this respect. As far as the production process, or synthesis, is concerned, this is described in the form of a presentation of general synthesis paths. Corresponding descriptions can be found in earlier patent descriptions, cf. WO 121 and WO 282. Diagram 7 on page 157 has been added to [the descriptions from] WO 121 and WO 282, but this covers simple acylation of a 3'-hydroxy group, and is a synthesis known from the literature. Consequently, the said description does not provide the skilled person with any guidance on top of what he or she would already know from his or her general knowledge of the art.

Even if one were to assume that the skilled person has identified the "correct" formula; in this case a sub-embodiment of Formula IX, the skilled person will be faced with a number of choices that have to be made in order to be able to produce or synthesise the substance. Firstly, a choice needs to be made between the sugar route and the nucleoside route. Thereafter, starting materials need to be chosen. Many alternatives will be available in respect of both route alternatives, and the choices will not be perceived as obvious.

Moreover, a fluorination reagent needs to be selected. This also involves numerous alternatives. Even if one starts out from the most precise and restrictive part of the description, as well as the alternative claims, there are several options. One may for example choose both natural and synthetic bases. Finally, one needs to select reaction conditions and solvents, etc., for the various reactions.

The Court notes that minor variations in chemical processes may have a major impact and be decisive in terms of whether or not one succeeds in bringing about the desired compound.



As noted, the skilled person will here have to make a number of choices in respect of which no guidance is provided by the description. Matsuda and Pankiewicz are key citations that the skilled person is assumed to be familiar with. Despite this, the skilled person would not be able to find answers in common general knowledge in the art either, with regard to all of the choices that have to be made.

In other words, the skilled person will, in order to carry out the invention, have to find an overall solution that will depend on the sum total of a number of partial solutions. The Court is of the view that the skilled person would not be able to carry out the invention without a considerable amount of trial and error.

This conclusion is also supported by the fact that Idenix itself would not appear to have been able to produce the compound until at a much later date. It follows from Table 1 that a number of attempts had been made.

The Court refers, in particular, to attempts made by Griffon. Idenix has argued that the Court must disregard his unsuccessful attempts because his professional qualifications were inadequate. The Court finds it difficult to evaluate Griffon's qualifications on the basis of the disclosures made in the main hearing. The Court notes, however, that he formed part of a professional circle. It is also noted that he did write articles together with other skilled persons. It would seem likely, on the other hand, that Griffon alone did not possess all qualifications expected from the skilled person under Section 8 of the Norwegian Patents Act. It is assumed, as noted above, that we are here concerned with a type of invention that is usually made in cooperation between persons from several professions. Hence, the notional skilled person will be a team of persons holding different qualifications. However, it is concluded that Griffon did not operate alone, but was instead part of a research team that was working on this for Idenix.

Idenix has also argued that the Court needs to disregard Griffon's attempts for the particular reason that he used the incorrect reagents. However, the Court is of the view that the said conclusion is not obvious. Hence, the Court does not agree with Idenix' argument that the silyl protecting group (TIPDS) used by Griffon was necessarily the "incorrect" protecting group. Reference is made to the Pankiewicz Citation, in which the following is stated:

*Interestingly, this work demonstrated the usefulness of the silyl protection in the reaction with DAST.*

It is noted, in this context, that Griffon included Deoxo-Fluor reaction on 3',5'-di-O-tetraisopropylidisiloxanyl-protected starting materials. Deoxo-Fluor and DAST are closely related reagents that work through the same mechanism. As mentioned, the skilled person would know from the Pankiewicz Citation that DAST and silyl protecting groups can work together. Against that background, the attempt made by Griffon in cooperation with Chappe must be considered well founded, also as far as the use of a silyl protecting group is concerned.





The Court does not place decisive weight on the fact that Griffon, or the team to which he has belonged, did not succeed in producing the compound. As mentioned, however, the Court considers this to be an argument, in addition to what has otherwise been mentioned, in favour of concluding that the description is incomplete. Both parties have described how there was a race in research circles to arrive first at the invention. It is therefore assumed that Idenix also put a major focus on precisely this field.

The Court has also considered the deliberations of the Norwegian Industrial Property Office. However, it is not evident from the disclosed correspondence that the Norwegian Industrial Property Office has conducted an assessment as to whether the description was sufficiently clear to enable the invention to be carried out within the entire scope of the claims. The Court refers, in this context, to "*Patentloven med kommentarer*" ["The Annotated Danish Patents Act"], by Lindgreen, Skchovsbo [sic], Thorsen (2012), page 221. It is there stated that the said grounds for opposition are almost always included in connection with an opposition because such issue has not normally been considered in connection with the deliberations before the Danish Patent and Trademark Office. The Court assumes that the same will often be the case in Norway.

The Court concludes, based on the above, that the description in patent NO '755 is not sufficiently clear and complete as to enable a skilled person, as at the application date of 27 June 2003, to carry out the invention without undue burden or experimentation. This applies with regard to both Claims 1 and 2 of the claims included in Bundle 23, pages 10,558 – 10,561, and Claims 1 and 2 of the alternative claims included in Bundle 23, pages 10,562 – 10,565. The other claims are dependent claims, and thus cannot be upheld either.

Consequently, Norwegian patent NO 330 755 shall be declared invalid pursuant to Section 52, Sub-section 1, No. 2, of the Norwegian Patents Act.

#### Technical effect

Against the background that the Court has concluded that the disputed patent is invalid, it is not necessary for the Court to further address the issues relating to technical effect.

#### The validity of the Gilead Patent NO 333 700

Idenix Pharmaceuticals, Inc. has moved for patent 333 700 (the "Gilead Patent"), which was granted to the defendant's associate Gilead Pharmasset LLC on 26 August 2013, to be declared invalid, under reference to the said patent describing the same modified fluorinated nucleoside analogues for the treatment of *Flaviviridae* infections as the defendants' patent NO 330 755 (the "Idenix Patent").

*Idenix has, in the main, invoked the following:*

The Gilead Patent has been granted without Idenix' patent application having been examined by the Norwegian Industrial Property Office. During the deliberation of Gilead's patent application NO 20056221 (which resulted



in patent 333 700), neither Idenix' PCT application, nor the US 350 application, was taken into consideration as prior art. Hence, there is no reason for the Court to exercise restraint when it comes to declaring the patent invalid due to lack of inventive step in relation to Idenix' PCT application.

Idenix has earlier priority in respect of its patent than does Gilead in respect of its [patent]. Consequently, it is Idenix' patent application that prevents the Gilead Patent from meeting the novelty requirement, and not the reverse.

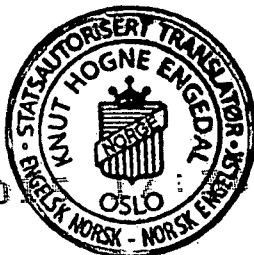
Idenix' US 350 application and PCT application both represent prior art in relation to the Gilead Patent. Gilead claims priority from the US patent application referred to as US 368. That [application] was filed on 30 May 2003, i.e. after the filing of Idenix' priority application US 350, but before the filing of Idenix' PCT application. Gilead's PCT application was filed on 21 April 2004, i.e. after both the filing and the publication of Idenix' 350 application and PCT application.

Idenix maintains that Gilead's claimed priority from the 368 application is invalid, whilst Idenix' own priority from the 350 application is valid. Hence, Idenix enjoys the best priority. Gilead is only able to claim priority from its PCT application of 21 April 2004, which was filed after Idenix' PCT application and the US 350 application had been made available to the public.

This implies that both documents are relevant prior art for purposes of the assessment of both novelty and inventive step under Section 2, Sub-section 1, cf. Sub-section 2, first sentence, of the Norwegian Patents Act. Most of the claims in the Gilead Patent lack novelty in relation to both of these documents. Under any circumstance, all of the claims in the Gilead Patent lack inventive step in relation to these citations. Hence, the patent must be declared invalid pursuant to Section 52 of the Norwegian Patents Act.

In the event that the Court holds the priority claimed by Gilead to be *valid*, Gilead's priority date will precede the date on which Idenix' PCT application and the 350 application were made available to the public. However, Idenix' valid priority from 28 June 2002 implies that Idenix' PCT application and Norwegian application remain relevant prior art for purposes of assessing the novelty of the Gilead Patent, cf. Section 2, Sub-section 2, second sentence, of the Norwegian Patents Act.

In the event that the Court concludes that Idenix' Norwegian application and PCT application do not enable the skilled person to carry out the invention, these documents will nonetheless be of relevance to the inventive step assessment, since the applications were published before Gilead filed its PCT application. It is argued that the solution in the Gilead Patent would have been obvious to the skilled person, based on Idenix' applications. Reference is made, in particular, to the statement from Dr Meier that the selection of bases does not result in any novel invention. Consequently, the compounds, the approach and the pharmaceutical production process in the Gilead Patent were obvious in relation to US'350 and PCT'246. Hence, the patent lacks inventive step and is therefore invalid.



*Gilead has, in the main, invoked the following:*

NO '700 meets all patentability requirements, and the patent has been validly granted. None of the publications invoked by Idenix constitute prior art in relation to NO '700. NO '700 derives valid priority from US '368, and hence qualifies for priority from 30 May 2003. US '350 does not constitute prior art because the document did not become available to the public until 8 January 2004, i.e. after Gilead's priority date. WO '999 does not constitute prior art because the application was filed on 27 June 2003, which is also after the priority date of NO '700. Idenix cannot derive valid priority from US '350, and hence Idenix' PCT application cannot be deemed to have been filed on the date of the filing of US '350.

Furthermore, Gilead argues that NO '700 is valid irrespective of which priority dates are adopted. Even if the contents of WO '999 and/or US '350 are deemed to have been known for purposes of Section 2, Sub-section 2, of the Norwegian Patents Act, NO '700 meets the novelty and inventive step requirements under Section 2, Sub-section 1.

It is argued that neither US '350, nor WO '999, anticipates the invention protected by NO '700, because these publications do not describe any process for the production of the chemical compounds encompassed by the patent claims in NO '700. Nor was any production process that enabled the skilled person to carry out the invention without undue burden or experimentation available from any other sources. Moreover, the publications contain no information that made it plausible to the skilled person that the alleged effect would be achieved from any of the chemical compounds encompassed by the patent claims in NO '700.

The invention in NO '700 also meets the inventive step requirement. Even if US '350 and WO '999 were deemed to have been known prior to the application date, the patented invention differs essentially from what could be inferred from the [said] publications. It is mentioned, in relation thereto, that the patented invention exhibits properties that are superior to those of US '350 and WO '999, as well as to those of other prior art. As far as Process Claim 13 is concerned, reference is made, in particular, to the fact that the compound with Structure 1-4 was not previously known, whether from US '350, WO '999 or other prior art. Nor was it obvious for the skilled person to synthesise the compound with Structure 1-4 from generally available starting materials. The description on page 124 of WO '999, to which Idenix refers, does not pertain to the production of a compound with such a structure.

*The Court* has above concluded that the Idenix Patent, NO 755, shall be declared invalid because it is not described sufficiently clearly and completely to enable the skilled person to carry out the invention without undue burden or experimentation. The Court has based such assessment on Idenix' PCT application, as it was the principal argument of Idenix that [such application] should form the basis [for the said assessment]. Consequently, the Court has not ruled on whether Idenix could have claimed valid priority from the filing of the US application referred to as US 350.

True translation certified.  
2 April 2014



Knut Hogne Engedal  
Government-authorised translator  
English - Norwegian • Norwegian - English

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First, *the Court* examines the validity of the Gilead Patent, NO 700, based on priority from the PCT application. It is not disputed that the company enjoys priority from that date, i.e. from 21 April 2004. Idenix' applications US 350 and PCT246/WO 999 had been published by the said date. These were published on 8 January 2004. Consequently, both the novelty requirement and the inventive step requirement must be examined on the basis that the skilled person had knowledge of these documents. As far as the requirements applicable to the notional skilled person are concerned, reference is made to the observations previously made under the assessment of the Idenix Patent. It is assumed that the same qualification requirements shall apply here, although with the skilled person being expected to also have knowledge of patent applications published within the field.

The Court is of the understanding that patentability can in theory be forestalled by an application that has been made available to the public, despite such application not meeting the description requirement under Section 8 of the Norwegian Patents Act. This must depend on a specific assessment as to what had been made public. The question is, in other words, what information was communicated by Idenix' applications, i.e. what the skilled person could infer from these documents.

A solution having been previously described is not sufficient to prevent novelty. It is necessary for [such solution] to have been described in such a way as to enable the skilled person to carry it out, i.e. an "enabling disclosure". The EPO has concluded that the requirement as to the contents of the description corresponds to the novelty requirement, cf. T 206/83 (1987). In other words, an invention is held to be novel if it was not described in such manner in a previous publication as to enable the skilled person to carry out the invention on the basis of such description. The publications are required to contain a plausible description that is sufficiently clear to enable the skilled person to carry out the invention on the basis thereof, without undue burden or experimentation.

The Court refers to the observations made above under the assessment of Idenix' patent application. Unlike Idenix' PCT application, there is an unequivocal core to the Gilead Patent, NO 700, i.e. derivatives of 2'-methyl-up, 2'-fluorine-down nucleosides. It describes cytosine nucleoside without scope for variations, and thereafter describes, *inter alia*, stereochemical aspects and basic methods for the production of nucleosides. It is also noted that Idenix' applications that had been published by the application date of Gilead PCT did not contain the revised claims currently invoked. Hence, disclosure of the 2'-methyl-up, 2'-fluorine-down pattern was even weaker than at present.

The Court is of the view that Idenix' application fails to disclose any process that enables the skilled person to carry out the invention. This is also different in NO 700. Biological test methods are included there, and the sections on synthesis direction contain synthesis schemes pertaining to both the sugar route and the nucleoside route. These general synthesis schemes specify starting materials and synthesis steps to 2'-methyl-up, 2'-fluorine-down nucleosides. Furthermore, the patent contains synthesis examples to render the



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general synthesis schemes specific. Experimental data are included, with all necessary details and characterisation data. The actually executed synthesis examples encompass both the sugar route and the nucleoside route, and both pyrimidine and purine bases, including the natural bases cytosine and adenine. Finally, the description contains extensive data to render the general biological experiment descriptions specific and to verify technical effect (antivirus activity).

The Court concludes, against this background, that the novelty requirement is met in relation to Idenix' patent applications.

In order for the inventive step requirement to be met, the invention shall differ essentially from what was known from before, cf. Section 2, Sub-section 2, of the Norwegian Patents Act. The Court refers to what was mentioned under the assessment of the novelty requirement. The Court finds, especially against the background of the synthesis description, that the Gilead Patent, NO 700, differs essentially from what could be inferred from Idenix' applications. Reference is also made, in this context, to the attempts made by Griffon and his team. These are described above. The Court has, as mentioned, concluded that Idenix failed, despite extensive research activity, to carry out the invention. It is not disputed that the invention can be carried out against the background of the description in the Gilead Patent. The Court concludes, against this background, that NO 700 exhibits the necessary inventive step in relation to Idenix' published patent applications.

It is noted that the Court has not performed any assessment in relation to any other citation, since no arguments have been invoked in such regard. Only Idenix' applications have been invoked as preventing novelty and inventive step. Consequently, these proceedings have not been structured around a thorough review of the Gilead Patent. The issue of the validity of the said patent was raised shortly before the main hearing, and the parties have devoted little attention thereto in these proceedings.

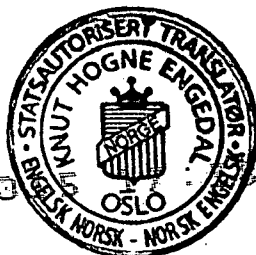
Consequently, the Court finds in favour of Gilead with regard to the claim for Norwegian patent NO 700 to be declared invalid.

#### **The priority issues**

The above implies that it is not necessary for the Court to rule of the issue of priority in relation to the US applications.

#### **Legal costs**

Gilead Sciences Europe Ltd. has prevailed with all of its claims in Case No. 12 -155575TVI-OTIR/01, which is the invalidity action pertaining to Norwegian patent NO 330 755. Gilead Pharmasset LLC has prevailed with all of its claims in Case No. 13 -170456TVI-OTIR/01, which is the invalidity action pertaining to Norwegian patent NO 333 700.



The issue of legal costs is governed by Section 20-2 (1) of the Norwegian Dispute Act. The main rule is that a party is entitled to full compensation for its legal costs from the opposite party if the former has prevailed in the action. The Court has considered the statutory exemption provisions, but does not find these to be applicable to the present proceedings.

The amount shall be determined pursuant to Section 20-5 of the Norwegian Dispute Act. The main rule is that the prevailing parties are entitled to compensation for all of their necessary costs in relation to the case. In assessing whether costs have been necessary, weight is placed on whether it was reasonable to incur them in view of the importance of the case.

Gilead Sciences Europe Ltd. and Gilead Pharmasset LLC were both represented by the same counsel in the case. Attorney Stenvik has submitted a specification of legal costs in conformity with the statutory requirements. According to the said [specification], the total cost claim in respect of both cases is NOK 14,736,373. NOK 8,069,625 is in the form of legal fees, NOK 2,247,521 is in the form of disbursements that are subject to VAT, NOK 1,839,941 is in the form of disbursements that are not subject to VAT and NOK 2,579,286 is in the form of VAT on the disbursements that are subject to VAT and on the legal fees.

Attorney Stenvik has apportioned, on a discretionary basis, 5% of the total fees to Case No. 13 - 170456TVI-OTIR/01, which is the invalidity action pertaining to Norwegian patent NO 333 700. He has apportioned the remaining 95% to Case No. 12 - 155575TVI-OTIR/01, which is the invalidity action pertaining to Norwegian patent NO 330 755.

A preliminary cost specification was submitted in Court, with the opposite party being given the opportunity to comment thereon. Attorney Stenvik has submitted two revised specifications, the last of which was received by the Court on 13 December 2013. These specifications have also been forwarded to the opposite party, which has been given the opportunity to comment thereon. No comments have been received. The cost specification from the other party is for a similar amount.

The Court notes that both parties to the proceedings have incurred high costs, and the Court has assessed whether the legal cost claims from the parties that prevailed in the case exceed what has been necessary to conduct the proceedings in a proper manner. The Court notes that the case is extensive in scope. A number of preparatory meetings have been held. The main hearing lasted for 9 full days. The case has been complex and numerous experts have been involved in the proceedings from both sides. In part, these [experts] have diverged in their views. Although the Court has not been in doubt about the conclusion reached by the Court, the [case] has raised many, and in part highly complex, issues that have not previously been addressed by the judicial system. The case has also included an examination of foreign law.

Both parties have been represented by two lawyers acting as of counsel in addition to their counsel, two of whom from each side have been very experienced patent lawyers charging high hourly rates. The Court finds, against the background of the scope and complexity of the case, that this has been necessary. It is noted that the case has been very well prepared and



presented by the attorneys on both sides. Finally, reference is also made to the very considerable financial interests that the case represents for both parties.

The Court finds, based on an overall assessment, that the costs for which compensation is claimed have been necessary and that it was reasonable to incur these in view of the importance of the case. Liability for the legal costs is allocated across the two cases in conformity with the discretionary apportionment made by Attorney Stenvik. The opposite party has not submitted any comments in relation thereto, although it has apportioned its costs in a ratio of 90% - 10%. The Court has no comments in relation to the apportionment made by Attorney Stenvik.

Idenix Pharmaceuticals Inc., Centre National de la Recherche Scientifique, Università Degli Studi Di Cagliari and L'Université Montpellier were the defendants in Case No. 12 -155575TVI-OTIR/01. The Court found against them in all respects in the said case. Hence, these parties shall be jointly and severally liable for 95% of the costs, which amounts to a total of NOK 13,999,554.

Idenix Pharmaceuticals Inc. was the claimant in Case No. 13 -170456TVI-OTIR/01. The Court also found against it in all respects in this case, and hence Idenix Pharmaceuticals Inc. shall be liable for 5% of the costs, which amounts to a total of NOK 736,819.

The court fees shall be paid by those parties that did not prevail in the case, in accordance with an invoice to be issued by the Court.

In addition, those parties that did not prevail in the case are ordered to pay the costs associated with the expert lay judges, based on the same apportionment. The amount of the costs associated with the expert lay judges will be specified in a separate ruling.

The judgment is rendered unanimously.



## CONCLUSION OF THE JUDGMENT

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### In Case 12-155575TVI-OTIR/01:

1. Norwegian patent NO 330 755 is declared invalid.
2. Idenix Pharmaceuticals Inc., Centre National de la Recherche Scientifique, Universita Degli Studi Di Cagliari and L'Université Montpellier II are ordered to pay, jointly and severally, the legal costs of Gilead Sciences Europe Ltd. in the amount of 13,999,554 – thirteen million nine hundred and ninety nine thousand five hundred and fifty four – Norwegian kroner within 2 – two – weeks of service of the present judgment.
3. Idenix Pharmaceuticals Inc., Centre National de la Recherche Scientifique, Universita Degli Studi Di Cagliari and L'Université Montpellier II shall in addition pay, jointly and severally, the costs apportioned to Gilead Sciences Europe Ltd. in relation to the Court and the expert lay judges. The amount of these costs is to be specified in a separate ruling.

### In Case 13-170456TVI-OTIR/01:

1. The Court finds in favour of Gilead Pharmasset LLC.
2. Idenix Pharmaceuticals Inc. is ordered to pay the legal costs of Gilead Pharmasset LLC in the amount of 736,819 – seven hundred and thirty six thousand eight hundred and nineteen – Norwegian kroner within 2 – two – weeks of service of the present judgment.
3. Idenix Pharmaceuticals Inc. shall in addition pay the costs apportioned to Gilead Pharmasset LLC in relation to the Court and the expert lay judges. The amount of these costs is to be specified in a separate ruling.





Court adjourned

[Signature]

Inger Kjersti Dørstad  
District Court Judge

[Signature]

Hans Einar Krokan

[Signature]

Jesper Wengel

Guidance notes on the right of appeal in civil actions are appended.

True translation certified.  
2 April 2014



Knut Hogne Engedal  
Government-authorised translator  
English - Norwegian • Norwegian - English

Exh 17-C

110

Boxinterferences@uspto.gov  
571-272-4683

Filed: January 16, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

JEREMY CLARK  
Junior Party  
(Application No. 11/854,218)

v.

RICHARD STORER, GILLES GOSSELIN, JEAN-PIERRE SOMMADOSSI,  
and PAOLA LACOLLA  
Senior Party  
(US 7,608,600 B2)

Interference No. 105,981 (JGN)  
Technology Center 1600

**Decision on Motions - Bd.R. 125**

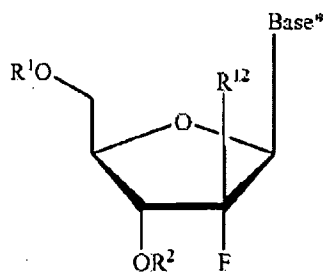
*Before* RICHARD E. SCHAFER, DEBORAH KATZ, and JOHN G. NEW,  
*Administrative Patent Judges.*

NEW, *Administrative Patent Judge.*

I. INTRODUCTION

This interference is before a merits panel for a decision on non-priority motions. The interference involves Junior Party Jeremy Clark's ("Clark") US Appl. No. 11/854,218 (the "218 application") and Senior Party Richard Storer, Gilles Gosselin, Jean-Pierre Sommadossi, and Paola LaColla's ("Storer") US Patent 7,608,600 B2 (the "600 patent"). Declaration at 1.<sup>1</sup> The subject matter of the interference is generally related to a method of using a class of 2'-methyl (or halomethyl) nucleosides with a uracil or cytosine base for the treatment of a host infected with the hepatitis C virus ("HCV"). An important aspect of the nucleosides is the position of the fluorine moiety (F) in the "down" position as shown in the image below. Count 1 of the interference is Storer claim 1 or Clark claim 164 and recites:

1. A method for the treatment of a host infected with a hepatitis C virus, comprising administering to the host infected with a hepatitis C virus an effective amount of a compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein:

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<sup>1</sup> Paper No. 1

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R<sup>1</sup> is H; mono-, di- or triphosphate; acyl; an amino acid ester; a carbohydrate; a peptide;

or a pharmaceutically acceptable leaving group which when administered *in vivo* provides a compound wherein R<sup>1</sup> is H or phosphate;

R<sup>2</sup> is H; acyl; an amino acid ester; a carbohydrate; a peptide; or a pharmaceutically acceptable leaving group which when administered *in vivo* provides a compound wherein R<sup>2</sup> is H;

Base\* is selected from the group consisting of adenine, N<sup>6</sup>-alkylpurine, N<sup>6</sup>-acylpurine, N<sup>6</sup>-benzylpurine, N<sup>6</sup>-halopurine, N<sup>6</sup>-vinylpurine, N<sup>6</sup>-acetylenic purine, N<sup>6</sup>-acyl purine, N<sup>6</sup>-hydroxyalkyl purine, N<sup>6</sup>-alkylaminopurine, N<sup>6</sup>-thioalkyl purine, N<sup>2</sup>-alkylpurine, N<sup>2</sup>-alkyl-6-thiopurine, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, 6-azacytosine, 2- and/or 4-mercaptopyrimidine, uracil, 5-halouracil, 5-fluorouracil, C<sup>5</sup>-alkylpyrimidine, C<sup>5</sup>-benzylpyrimidine, C<sup>5</sup>-halopyrimidine, C<sup>5</sup>-vinylpyrimidine, C<sup>5</sup>-acetylenic pyrimidine, C<sup>5</sup>-acyl pyrimidine, C<sup>5</sup>-hydroxyalkyl purine, C<sup>5</sup>-amidopyrimidine, C<sup>5</sup>-cyanopyrimidine, C<sup>5</sup>-iodopyrimidine, C<sup>6</sup>-iodo-pyrimidine, C<sup>5</sup>-Br-vinyl pyrimidine, C<sup>6</sup>-Br-vinyl pyrimidine, C<sup>5</sup>-nitropyrimidine, C<sup>6</sup>-amino-pyrimidine, N<sup>2</sup>-alkylpurine, N<sup>2</sup>-alkyl-6-thiopurine, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, guanine, hypoxanthine, 2,6-diaminopurine, and 6-choropurine;

R<sup>12</sup> is C(Y<sup>3</sup>)<sub>3</sub>; and

Y<sup>3</sup> is independently H or F.

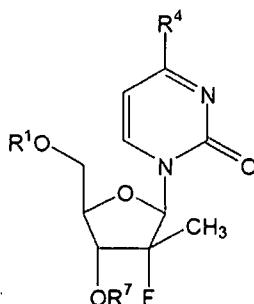
or

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164. A method for the treatment of hepatitis C infection, which comprises:

administering to a mammal in need thereof an antivirally effective amount of a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside ( $\beta$ -D or  $\beta$ -L) or its pharmaceutically acceptable salt of the structure:



wherein  $R^1$  and  $R^7$  are independently H, a monophosphate, a diphosphate, a triphosphate, a H-phosphonate, an alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl; and

$R^4$  is  $NH_2$  or OH.

Declaration at 3.

Before us are the following motions:

1. Clark Substantive Motion 1<sup>2</sup> to deprive Storer of the benefit of its US Appl. No. 60/392,350.
2. Clark Substantive Motion 2<sup>3</sup> to deprive Storer of the benefit accorded with respect to Count 1 of its U.S. Appl. No. 60/466,194.

<sup>2</sup> Paper No. 389

<sup>3</sup> Paper No. 390

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3. Clark Substantive Motion 3<sup>4</sup> to deprive Storer of the benefit accorded with respect to Count 1 of its U.S. Appl. No. 60/470,949.
4. Clark Substantive Motion 10<sup>5</sup> to deprive Storer of the benefit accorded with respect to Count 1 of US Appl. No. 10/6018,907.
5. Clark Substantive Motion 7<sup>6</sup> for judgment against Storer's US Patent No. 7,608,600 B2 on the grounds of unpatentability under 35 U.S.C. § 112, 1st paragraph, for lack of enablement and written description.
6. Clark Substantive Motion 5<sup>7</sup> to substitute Clark's proposed count 2 or, alternatively, Clark's proposed count 3, for Count 1.
7. Clark Substantive Motion 8<sup>8</sup> for judgment against Storer's US Patent No. 7,608,600 B2 on the ground of unpatentability under 35 U.S.C. § 101, for lack of utility and, accordingly, under 35 U.S.C. § 112, 1st paragraph, for lack of enablement.
8. Clark Substantive Motion 9<sup>9</sup> for judgment against Storer's US Patent No. 7,608,600 B2 on the ground of unpatentability under 35 U.S.C. §§ 102(e) or 103 as being either anticipated by, or obvious over, Clark's US Appl. No. 10/828,753.
9. Clark Miscellaneous Motion 18<sup>10</sup> to exclude evidence.

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<sup>4</sup> Paper No. 391

<sup>5</sup> Paper No. 392

<sup>6</sup> Paper No. 154

<sup>7</sup> Paper No. 162

<sup>8</sup> Paper No. 155

<sup>9</sup> Paper No. 156

<sup>10</sup> Paper No. 427

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1 10. Storer Substantive Motion 5<sup>11</sup> to substitute proposed count B for  
2 Count 1.

3  
4 11. Storer Substantive Motion 11<sup>12</sup> for judgment against Clark on the  
5 grounds of unpatentability of all of Clark's involved claims as  
6 anticipated under 35 U.S.C. § 102(e) and/or 103.

7  
8 12. Storer Contingent Motion 14<sup>13</sup> to add a new claim to the interference.

9  
10 13. Storer Contingent Motion 15<sup>14</sup> to add an application to the  
11 interference.

13 14. Storer Miscellaneous Motion 16<sup>15</sup> to exclude evidence.

14  
15 We address these motions in the order presented above.

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<sup>11</sup> Paper No. 157

<sup>12</sup> Paper No. 158

<sup>13</sup> Paper No. 327

<sup>14</sup> Paper No. 328

<sup>15</sup> Paper No. 425

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II. CLARK MOTIONS

A. Clark Substantive Motion 1<sup>16</sup>

Clark Substantive Motion 1 seeks to deny Storer benefit for Count 1 of its US Appl. No. 60/392,350, filed June 28, 2002 (the "S1" application) pursuant to 37 C.F.R. § 41.208(3). Clark Subs. Motion 1, Paper 389 at 1. As challenger of Storer's accorded benefit, Clark must demonstrate that the S1 application does not constitute a constructive reduction to practice of Count 1. Bd.R. 42.201; SO ¶ 208.4.2. Clark argues that the S1 application does not describe, enable or provide a credible utility of any of the 2'-fluoro-2'-methyl nucleosides that constitute the subject matter of Count 1.

1. Enablement of the compounds of Count 1

The first paragraph of 35 U.S.C. § 112 requires that the specification of a patent must enable a person skilled in the art to make and use the claimed invention. *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988). However, a patent

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<sup>16</sup> In addition to Clark's arguments set forth in the main body of this decision, Clark continues to argue that, despite the panel's prior decision (*see* Paper No. 350), interference estoppel should apply in this interference and that the Board should therefore reject Storer's attempts to argue issues that Storer raised, or could have raised, in the '871 interference. Motion at 8-9. Clark's attention is directed to the Federal Circuit's recent decision in *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1296-97 (Fed. Cir. 2014), holding that, because an interference action under 35 U.S.C. § 146 was pending in the district court, the Board's decision lacked requisite finality for purposes of estoppel. We therefore decline to address this argument further.



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1 need not disclose what is already well known in the art at the time of invention.

2 See *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730

3 F.2d 1452, 1463 (Fed. Cir. 1984).

4 Clark seeks relief on the basis that Storer's S1 application does not  
5 constitute a constructive reduction to practice of the subject matter of Count 1, i.e.,  
6 it does not include a described and enabled anticipatory embodiment that falls  
7 within Count 1. Count 1 is recited *supra*, and relates to methods of treating HCV  
8 infections with members of a genus of nucleosides, all of which possess a fluorine  
9 atom at the "down" position of the 2' carbon atom on the ribose ring. Both parties  
10 agree that the S1 application provides no explicit disclosure or example of how  
11 such an embodiment of Count 1 can be synthesized. See Clark Subs. Motion 1,  
12 Paper 389 at 12; Storer Opp. 1, Paper 402 at 12; see also Ex. 1194, pp. 97-99, 101,  
13 110, 121-122, 130. Failure to synthesize a single embodiment of the compounds  
14 recited in Count 1 would effectively prevent practice of the methods recited in the  
15 S1 application.

16 The question therefore devolves onto whether Clark, as challenger, can  
17 show, by a preponderance of the evidence, that a person skilled in the art, upon  
18 reading the Specification of the S1 application, and being knowledgeable  
19 concerning the prior art in the field of nucleoside synthesis, would not have been  
20 able to synthesize the 2'-fluoro ("down") nucleosides of Count 1 without undue  
21 experimentation. See *Wands*, 858 F.2d at 736-37; see also *Alcon Research Ltd. v.*  
22 *Barr Laboratories, Inc.*, 745 F.3d 1180, 1188 (Fed. Cir. 2014).

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1 Whether synthesis would require undue experimentation is a “conclusion  
2 reached by weighing many factual considerations.... includ[ing] (1) the quantity of  
3 experimentation necessary, (2) the amount of direction or guidance presented, (3)  
4 the presence or absence of working examples, (4) the nature of the invention, (5)  
5 the state of the prior art, (6) the relative skill of those in the art, (7) the  
6 predictability or unpredictability of the art, and (8) the breadth of the claims”). *In*  
7 *re Wands*, 858 F.2d 731, 737 (Fed.Cir.1988).

8 With respect to the first *Wands* factor, the quantity of experimentation  
9 necessary for a skilled artisan to arrive at the invention, Clark argues that an artisan  
10 attempting to synthesize a compound recited in Count 1 would have been required  
11 to engage in an extensive and undue amount of experimentation. Clark Subs.  
12 Motion 1, Paper 389 at 15 (citing Ex. 2001, ¶¶ 167-176, 186, 202, 214, 229-231,  
13 235, 248-250; Ex. 2044, p. 1; Ex. 2145, ¶¶ 85-101).

14 Clark points to the findings of the panel in the related 105,871 interference,  
15 which found that the Idenix team members had diligently attempted to make a 2'-  
16 fluoro-2'-methyl nucleoside as a high priority target for several years. Clark Subs.  
17 Motion 1, Paper 389 at 11. Clark observes that, during this interval, the Idenix  
18 team members were employed as chemists, several of whom hold doctoral degrees,  
19 but were nevertheless uniformly unsuccessful in synthesizing the target nucleoside.  
20 *Id.* Furthermore, argues Clark, Idenix also consulted outside experts, including  
21 individuals to whom Dr. Richard Storer, one of the Senior Party, referred to as an  
22 “expert in organofluorine chemistry” and a “world expert in carbohydrate  
23 chemistry” for advice on how to make a 2'-fluoro-2'-methyl nucleoside. However,

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1 argues Clark, Storer alleged it was successful only after Clark's C2 application was  
2 published and Idenix scientists followed a procedure described therein. Clark  
3 Subs. Motion 1, Paper 389 at 15-16. Furthermore, argues Clark, documents  
4 produced by Storer show that Idenix chemists and/or consultants tried or  
5 considered trying numerous different fluorinating reagents when unsuccessfully  
6 attempting to synthesize a 2'-fluoro-2'-methyl nucleoside during the interval 2002-  
7 2005. Clark Subs. Motion 1, Paper 389 at 11.

Clark rejects the argument of Storer, and its technical expert Dr. Masad J.  
9 Damha,<sup>17</sup> that one skilled in the art as of June 28, 2002 would "immediately see,"  
10 based on the prior art, that the fluorinating reagent N, N-Diethylaminosulfur  
11 trifluoride (Et<sub>2</sub>NSF<sub>3</sub> or "DAST") could be readily used to make a 2'-fluoro-2'-  
12 methyl nucleoside from a nucleoside substituted at the 2' position with a tertiary  
13 alcohol (OH) because DAST was a well-known and predictable reagent for  
14 fluorinating nucleosides, including those with tertiary alcohols at the 2' position.  
15 Clark Subs. Motion 1, Paper 389 at 10 (citing Storer Substantive Motion 5, pp. 18-

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<sup>17</sup> Storer's expert witness is Dr. Masad J. Damha. Dr. Damha is currently James McGill Professor of Chemistry at McGill University, Montreal, Canada, where he has been a faculty member since 1992. Ex. 1132, ¶ 2. He has also received a number of distinguished awards and is the author of approximately 150 papers and book chapters in peer-reviewed journals, many of which address the synthesis of nucleoside analogs. *Id.*, ¶ 7. Dr. Damha has also consulted for pharmaceutical companies in the United States and Canada and has presented lectures and conference presentations at academia and industry on synthesis and applications of nucleosides, oligonucleotides and their analogs. *Id.*, ¶ 9. Upon review of his curriculum vitae, we find that Dr. Damha is therefore qualified to opine as an expert on the subject matter of this interference.

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20, ll. 11-3; Storer Contingent Responsive Motion 14, p. 18-19, ll. 6-16; Ex. 1132,<sup>18</sup> ¶¶ 64, 69-76). Clark points out that Dr. Damha admitted, on cross-examination, that none of the references on which he relied for this contention actually show fluorination of a tertiary alcohol at a nucleoside's 2' position using DAST. *Id.* (citing Ex. 1194, p. 125, ll. 4-18; Ex. 2145,<sup>19</sup> ¶ 96; Ex. 1148,<sup>20</sup> pp. 10761-10770; Ex. 1160,<sup>21</sup> pp. 65-96; Ex. 1161,<sup>22</sup> pp. 574-578).

Storer argues that the S1 application provides precursor molecules and guidance that would have enabled one skilled in the art to synthesize a 2'-methyl ("up") 2'-fluoro ("down") nucleoside without undue experimentation. Storer Opp. 1, Paper 402 at 4-5. Storer points to compound 17 of Exhibit 1140, Akira Matsuda et al., *Alkyl addition reaction of pyrimidine 2'-Ketonucleosides: Synthesis of 2'-Branched-Chain Sugar Pyrimidine Nucleosides (Nucleosides and Nucleotides. LXXXI)*, 36(3) CHEM. PHARM. BULL. 945-953 (1988) ("Matsuda"). Storer contends that a skilled artisan would have recognized that compound 17 of Exhibit 1140 was a precursor to the claimed compound. *Id.* at 4-5 (citing Ex. 1200, ¶ 91; Ex. 2139, at 110-112, ll. 25-7; Ex. 1144, p 949; Ex. 2001, ¶ 323). Compound 17 of Matsuda is reproduced below:

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<sup>18</sup> Paper No. 679

<sup>19</sup> Paper No. 400

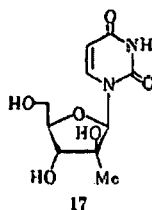
<sup>20</sup> Paper No. 345

<sup>21</sup> Paper No. 309

<sup>22</sup> Paper No. 310

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Compound 17 of Matsuda depicts 2'-hydroxy-2'-methyl cytidine

Storer argues that a skilled artisan, when looking at the structure of the claimed compound, would necessarily have recognized the need for a fluorinating reagent for synthesis and that replacement of a hydroxyl (OH) group with fluorine (deoxyfluorination) was a well-known organic transformation, as cited in such reference texts such as Richard C. Larock, *COMPREHENSIVE ORGANIC TRANSFORMATIONS: A GUIDE TO FUNCTIONAL GROUP PREPARATIONS* (2nd ed.) (1999) ("Larock 1999") (Ex. 1199). Storer Opp. 1, Paper 402 at 5 (citing Ex. 1200, ¶ 89; Ex. 2139, p. 100-101, ll. 22-15; Ex. 1248,<sup>23</sup> p. 90, ll. 13-19, p. 91, ll. 14-21, Ex. 1200, ¶ 79; Ex. 2139, p. 127, ll. 4-7; Ex. 1199, at 689 to 690 (Chapter 8, "Halogenation of Alcohols"))).

Storer also points out that Larock teaches the use of DAST in the deoxyfluorination of a "variety of chemical compounds with success" and argues that, by 2002, DAST was known as "the most convenient and powerful reagent for deoxyfluorination" reactions.<sup>24</sup> Storer Opp. 1, Paper 402 at 5-6 (citing Ex. 2014, p.

<sup>23</sup> Paper No. 549

<sup>24</sup> DAST is a nucleophilic fluorinating agent and acts by displacing the hydroxyl group and inverting the position of the methyl group. Thus, a 2'-hydroxy ("up") –

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259; Ex. 1200, ¶ 82; Ex. 1223,<sup>25</sup> p. 2357; Ex. 2139, pp. 126-127, ll. 17-3).

Therefore, argues Storer, a skilled artisan would have appreciated that DAST could have been used to transform the hydroxyl group of known nucleosides, such as Matsuda Compound 17, into the 2' ("down") fluorinated nucleosides recited in Count 1. *Id.* at 6 (citing Ex. 1200, ¶ 85). Accordingly, contends Storer, the prior art disclosed information that would have enabled a skilled artisan to synthesize a 2'-methyl ("up") 2'-fluoro ("down") nucleoside within the scope of Count 1. *Id.* (citing Ex. 1200, ¶¶ 74-99).

By way of example, Storer points out that an Idenix scientist, Jingyang Wang, synthesized the compound, using DAST, on her first attempt without the benefit of Clark's publication. Storer Opp. 1, Paper 402 at 6 (citing Ex 1232,<sup>26</sup> ¶¶ 17-20; Ex. 1233,<sup>27</sup> p. 70, ll. 5-11; *see also* Ex. 1231<sup>28</sup>). Storer argues that is also informative that Clark, a chemist without a Ph.D., was allegedly able to make a 2'-methyl (up)-2'-fluoro (down) nucleoside in just a few months using DAST. *Id.* (citing Ex. 1246,<sup>29</sup> p. 40, ll. 2-3; Ex. 1247,<sup>30</sup> ¶¶ 32, 39, 41).

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2' methyl ("down") cyclic sugar may become a 2'-methyl ("up") -2'-fluoro ("down") cyclic sugar. *See, e.g.*, Ex. 2014.

<sup>25</sup> Paper No. 527

<sup>26</sup> Paper No. 535

<sup>27</sup> Paper No. 536

<sup>28</sup> Paper No. 534

<sup>29</sup> Paper No. 547

<sup>30</sup> Paper No. 548

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1           Consequently, argues Storer, the synthesis of a 2'-fluoro-2'-methyl  
2 nucleoside would not have required undue experimentation by one skilled in the  
3 art.

4           We find it informative that Idenix's research team in Montpellier, France,  
5 repeatedly attempted without success to synthesize a 2'-methyl ("up") 2'-fluoro  
6 ("down") nucleoside during the interval between December, 2002 and September,  
7 2004. *See, generally*, Ex. 2128; 2129. Regular progress reports and  
correspondence of the Montpellier team during this interval demonstrate that  
9 synthesis of a 2'-fluoro-2'-methyl nucleoside during this interval was considered to  
10 be a high-priority result. Exs. 2026-2044; *see, e.g.*, Ex. 2037, p. 3 (report dated  
11 July, 31, 2003: stating that synthesis of a 2'-fluoro-2'-methyl nucleoside with the  
12 fluoro substituent in the "down" position "still a high priority").

13           During this interval, Idenix scientists also corresponded with consultants Dr.  
14 George Fleet and Dr. Paul Coe in an attempt to effect a synthesis of the desired  
15 compound. *See, e.g.*, Ex. 2034<sup>31</sup> ("Prioritized Summary of Idenix Meeting with  
16 G.W. J. Fleet held on 10th May 2004"); Ex. 2038 (communication from Dr. Coe to  
17 Dr. Storer entitled "Thoughts on your synthesis problems"). Dr. Richard Storer,  
one of the inventors of the S1 application, describes Dr. Fleet as "an expert in  
19 carbohydrate chemistry" and "one of the best in the world" and describes Dr. Coe  
20 as "an expert in organofluorine chemistry." Ex. 2131<sup>32</sup>, pp. 35, 74. Both  
21 consultants suggested possible schemes for the synthesis of a 2'-fluoro-2'-methyl

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<sup>31</sup> Paper No. 74

<sup>32</sup> Paper No. 625

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1 nucleoside with the fluorine substituent in the "down" position. Ex. 2034; Ex.

2 2038. In the latter communication, Dr. Coe related that:

3 [I]n our experience and indeed in that of manner [sic] other[,]  
4 particularly the de Clerc group[,] the most viable routes to fluoro  
5 nucleosides are by sugar/base condensation methods the anomer  
6 problem notwithstanding, for the very reasons you have discovered, in  
7 that leaving groups generated in situ[,] e.g.[,] in DAST reactions are  
8 readily attacked by the pyrimidine ring nucleophiles or elimination  
9 and/or participation of the blocking groups. Further migrations of  
10 groups can readily occur.

12 Ex. 2038, p. 1.

13 Idenix personnel also attended a "Scientific Update Course" entitled  
14 "Making and Using Fluoroorganic Molecules" in April, 2003, and submitted a  
15 report summarizing the course content. Ex. 2039.

16 Nevertheless, despite these consultations, the Montpellier team was never  
17 able to successfully synthesize a 2'-fluoro-2'-methyl nucleoside with the fluorine  
18 substituent in the "down" position. Dr. Jean-François Griffon,<sup>33</sup> leader of the  
19 Montpellier group, testified that he attempted at least seven different synthetic  
20 schemes, including several suggested by Dr. Coe, and in some cases employing  
DAST, without success. Ex. 2128, ¶¶ 8-64; Ex. 2132, p. 57. As Dr. Griffon  
22 reported in an email to Dr. Storer on March 4, 2003: "As I told you last week at the  
23 end of the Summary Meeting, the compound I obtained after treatment with

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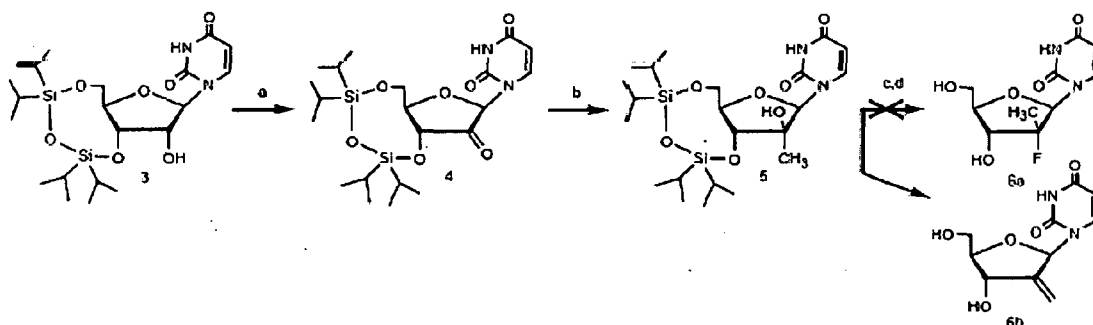
<sup>33</sup> By the standard we determined *infra*, we find that Dr. Griffon qualifies as a person skilled in the art. See Ex. 2152 (Paper No. 542).



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- 1 DeoxoFluor<sup>34</sup> and deprotection was not the (very!) expected Fluoro derivative but  
 2 the 2'-methylene derivative." Ex. 2029, p. 1. A diagram in the accompanying  
 3 report documents the failure of this synthetic scheme, the end product having a 2'-  
 4 methylene group rather than the desired 2'-methyl-2'-fluoro groups:



5  
 6 Illustration from Ex. 2029 indicating synthesis of an undesired 2'-methylene  
 7 nucleoside (6b) rather than a 2' (down) fluorination (6a).

8  
 9 *Id.*, p. 3

10 Furthermore, attempts by the Montpellier team to use DAST in the synthesis  
 11 of a 2'-fluoro-2'-methyl nucleoside produced similar failures, as this diagram from  
 12 an Idenix summary of results indicates:

<sup>34</sup> Deoxo-Fluor® is, like DAST, a nucleophilic organic fluorinating agent. See, e.g., R.P. Singh and M.S. Jean'ne, *Recent advances in nucleophilic fluorination reactions of organic compounds using deoxofluor and DAST*, 17 SYNTHESIS 2561-2578 (2002).

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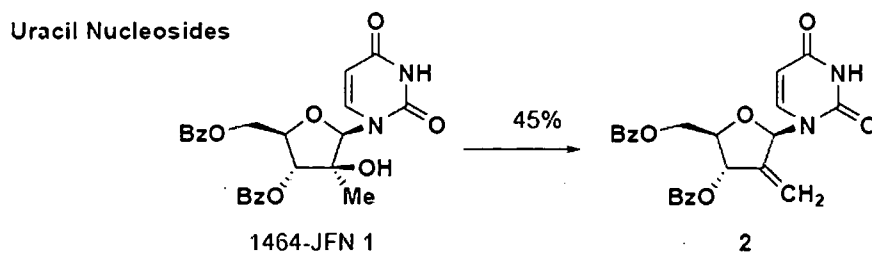


Illustration from Ex. 2041 indicating synthesis of an  
undesired 2'-methylene nucleoside via DAST reaction.

Ex. 2041, p. 2. The difficulties experienced by Idenix in synthesizing a 2'-fluoro-2'-methyl nucleoside are expressed in a November 11, 2014 email from Dr. Storer stating:

When we get this information together we'll decide what, if anything, we will do in house and how it it [sic] fits with what anyone else knows. *A lot of things which look simple on paper in related systems have been tried and don't work in this series. Having to make the tertiary fluoride is very different to having to make a secondary.*

Ex. 2044, p. 1 (emphasis added).

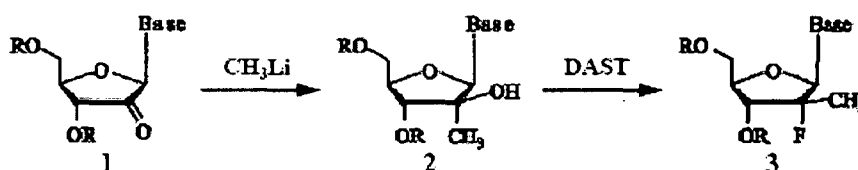
With respect to the testimony of Jingyang Wang who allegedly synthesized the desired compound in a single attempt in January, 2015, at Idenix's research facility in Cambridge, Massachusetts, we note that, prior to beginning her synthesis, Ms. Wang had received the reports from the Montpellier group as well as intermediate compositions synthesized at Montpellier. Ex. 1233, pp. 99-101. Consequently, Ms. Wang was not, as Storer seems to suggest, attempting synthesis of a 2'-fluoro-2'-methyl nucleoside *ab initio*, but rather had the hindsight benefit of the Montpellier group's efforts. *Id.*

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Similarly, Storer's expert, Dr. Damha, points in his Declaration to what he terms Scheme A, of which the first step is disclosed by the S1 application. Ex. 1132, ¶ 67; *see also* Ex. 1003, p. 120. Scheme A of Dr. Damha's declaration is reproduced below:

Scheme A



Scheme A shows a sequence of two steps by which a 2'-keto group is replaced by a 2'-hydroxyl (up) - 2'-methyl (down) nucleoside which is in turn replaced by DAST with a 2'-methyl (up)-2'-fluoro (down) nucleoside.

Ex. 1132, ¶ 67. The intermediate form 2 in Scheme A also corresponds to Matsuda compound 17. *Id.*, ¶ 69, fn. 5. According to Dr. Damha:

A person skilled in the art as of June 28, 2002 could therefore simply look at the 2'-F-2'-methyl-ribonucleoside species disclosed in the '350 Application, and synthesize it without undue experimentation using: (i) the starting materials and reagents disclosed in the '350 Application and known in the art [i.e., Matsuda compound 17], and (ii) the then-existing routine DAST chemistry. It is well known that all organic reactions produce by-product(s). As of June 28, 2002, it would not have been a surprise to a person skilled in the art that DAST fluorination might lead to elimination, rearrangement, or other by-products. However, just like all other organic reactions, the DAST fluorination does not need to be perfect to be useful in organic synthesis, as separation and purification techniques were well-known as a [sic] of June 2002.

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1 *Id.*, ¶ 76. However, Dr. Damha's opinion is not borne out by the fact that this very  
2 reaction was attempted by the Montpellier group and was not successful: attempts  
3 to fluorinate compound 17 with DAST yielded a 2'-methylene nucleoside. *See* Ex.  
4 2041, p. 2. Such a result is supported by Dr. Coe's suggestion that "leaving groups  
5 generated in ... DAST reactions are readily attacked by the pyrimidine ring  
6 nucleophiles or elimination and/or participation of the blocking groups." Ex. 2038,  
7 p. 1. The use of other fluorinating agents yielded similarly unsuccessful results.  
8 *See, e.g.*, Ex. 2029, p. 3 (using DeoxoFluor® as the fluorinating agent).

9 We therefore find, based upon the proffered evidence, that a high amount of  
10 experimentation is necessary to synthesize a 2'-fluoro-2'-methyl nucleoside with  
11 the fluoro moiety in the "down" position requiring at least two years of a high  
12 priority experimentation by persons skilled in the art, including multiple  
13 consultations with experts at the top of their fields and additional formal training.

14 With respect to the second *Wands* factor, the amount of direction or  
15 guidance presented, Clark argues, and Storer does not contest, that the S1  
16 application provides no explicit explanation or example describing synthesis of a  
17 2'-fluoro "down" nucleoside as embodied in Count 1. *See* Clark Subs. Motion 1,  
18 Paper 389 12; Storer Opp. 1, Paper 402 at 12. Clark also argues that no synthesis  
19 of a 2'-fluoro-2'-C(H/F)<sub>3</sub> nucleoside, including any 2'-fluoro-2'-methyl  
20 nucleoside, had been reported in the available art as of the S1 application's June  
21 28, 2002 filing date. Clark Subs. Motion 1, Paper 389 at 9 (citing Ex. 2001, ¶¶

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1 137, 231; Ex. 2005, p. 22, ll. 4-8; Ex. 1194,<sup>35</sup> p. 91, ll. 12-16). Rather, argues  
2 Clark, its own US Appl. Pub. No. 2005/0009737 A1 (the "C2 application"),  
3 published on January 13, 2005 (subsequent to the S1 application's June 28, 2002  
4 filing date), was the first reported synthesis of a 2'-fluoro-2'-methyl nucleoside, an  
5 embodiment of Count 1. *Id.* at 9-10 (citing Ex. 2001, ¶¶ 137, 162; Ex. 2003, ¶¶  
6 221, 222; Ex. 2005, p. 22, ll. 4-8; Ex. 2013,<sup>36</sup> cover page (item 43), ¶ [0294]-  
7 [0035]).

Furthermore, argues Clark, the S1 application's failure to disclose any  
9 specific starting materials or conditions under which such a compound could be  
10 made cannot be rectified by reliance on the prior art for all of the required  
11 teachings. *Id.* (citing *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1366  
12 (Fed. Cir. 1997); also citing Ex 2005, pp. 24-25, ll. 13-10, 26, ll. 2-5). Clark  
13 contends that Storer and its expert, Dr. Damha, argue that the S1 application  
14 discloses "starting materials" and reagents (e.g., methyl lithium) for making 2'-  
15 fluoro-2'-methyl nucleosides, and that an artisan purportedly would have  
16 "immediately identified" operative methods for making such compounds by  
17 reacting DAST with a 2'-methyl-2'-hydroxy nucleoside. Clark Subs. Motion 1,  
Paper 389 at 13.

19 However, Clark relates, Dr. Damha, on cross-examination, admitted that: (1)  
20 no such methods are found in the S1 application; (2) the S1 application does not  
21 discuss any fluorinating reagents, including DAST; (3) the S1 application does not

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<sup>35</sup> Paper No. 498

<sup>36</sup> Paper No. 56

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1 disclose intermediate Compound 2 and final Compound 3 shown in Dr. Damha's  
2 "Scheme A"; (4) nothing in Scheme 4 of the S1 application suggests isolating the  
3 intermediate Compound 2 needed for the Damha "Scheme A" route, which has a  
4 methyl group "down" and a hydroxyl group "up" at the 2' position (the opposite 2'  
5 stereochemistry from the compounds in Scheme 4); and (5) contrary to his  
6 declaration, the S1 application does not "explicitly disclose" the reagent methyl  
7 lithium. Clark Subs. Motion 1, Paper 389 at 14 (citing Ex. 1194, pp. 97, ll. 5-8, 98,  
8 ll. 11-17, 98-99, ll. 22-17, 101, ll. 15-16, 110, ll. 14-24, 121-122, ll. 19-11, 130, ll.  
9 7-16).

10 Clark also argues that Dr. Damha's opinion relies on references not  
11 mentioned in the S1 application, and he did not consider whether the S1  
12 application would have guided an artisan to such literature. Clark Subs. Motion 1,  
13 Paper 389 at 14 (citing Ex. 1194, pp. 102, ll.12-17, 133-135, ll. 24-2).

14 Storer responds that the S1 application provides adequate guidance for  
15 synthesizing compounds within Count 1. Storer Opp. 1, Paper 402 at 9-10. Storer  
16 argues that the fluorination reagent DAST was known to the skilled artisan for  
17 substituting fluorine for a hydroxyl group with inversion. *Id.* at 10. Therefore,  
18 argues Storer, recognizing that inversion will occur, a skilled artisan would have  
19 known to start with a nucleoside having a similar structure to that defined by Count  
20 1, but with a 2'-OH (up) group, in order to obtain the desired 2'-F (down) structure  
21 of the compounds within Count 1. *Id.* at 12. (citing Ex. 1200, ¶ 90).

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1 Storer points out that Clark's expert, Dr. Stanislaus Wnuk<sup>37</sup> agreed that a  
2 skilled artisan would have recognized Matsuda Compound 17 as a potential  
3 precursor to the subject matter of count 1, which is depicted at paragraph 323 of  
4 his Declaration. Storer Opp. 1, Paper 402 at 12 (citing Ex. 2001). Storer points  
5 out that Matsuda Compound 17 differs from the claimed compound in that the  
6 configuration at the 2'-position is inverted with a 2'-OH (up) instead of a 2'-fluoro  
7 (down). *Id.* at 12-13 (citing Ex. 1200, ¶ 92; Ex. 2139, pp. 107-108, ll. 18-6).

Further, alleges Storer, both parties' experts agree that the synthesis of the  
9 compound of Count 1 would have been essentially a one-step reaction of Matsuda  
10 Compound 17 with DAST. *Id.* at 13 (citing Ex. 1200, ¶ 94; Ex. 2139, p. 156, ll. 2-  
11 12). Store contends that the synthesis of Matsuda Compound 17 is the same as the  
12 product of the first steps of Scheme 4 of the S1 application which is reproduced, in  
13 part, below:

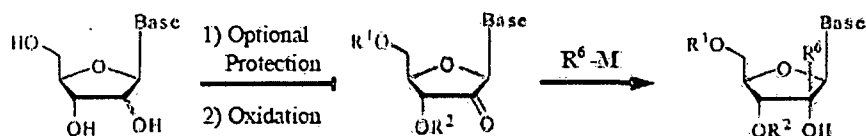
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<sup>37</sup> Clark's expert witness, Dr. Stanislaus F. Wnuk received his Ph.D. in organic chemistry from Adam Mickiewicz University in Poznan, Poland in 1983 and is currently Professor of Chemistry at Florida International University, a position he has held since 1997. Ex. 2001, ¶¶ 8-9. He is the author of over 120 publications, more than 80 of which pertain to nucleosides or nucleotides, with approximately 30 of those relating to fluorinated nucleosides or nucleotides. *Id.*, ¶ 12. He has also received a number of research and teaching awards. *Id.*, ¶ 11. Upon review of his curriculum vitae, we find that Dr. Wnuk is sufficiently qualified as an expert to opine on the synthesis of fluorinated nucleosides.

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Scheme 4



The initial reaction steps of Scheme 4 depicts synthesis of Compound 17 of Matsuda, where  $R^6$  is methyl,  $R^1$  and  $R^2$  are protective groups, and the base is uracil

*Id.* (citing Ex 1132, ¶¶ 65, 66; Ex. 1003, p. 120). Storer points out that the intermediate compound (2'-keto) of Scheme 4 is the starting material of Matsuda Compound 17, wherein  $R^1$  and  $R^2$  form protecting groups and the Base is uracil. *Id.* (citing Ex. 1132, ¶¶ 65-66; Ex. 1003, p. 120; Ex 1144, pp. 945-953).

As such, contends Storer, the specification of the S1 application teaches the starting materials and methods for making Matsuda Compound 17, which is a precursor to the claimed compound. Storer Opp. 1, Paper 402 at 13. Storer concludes that the S1 application therefore provides a skilled artisan with the starting materials and guidance for making the compounds within Count 1 without undue experimentation. *Id.* (citing Ex. 1200, ¶ 97).

We agree with Clark that the S1 application provides no explicit explanation or guidance as to how to synthesize a 2'-fluoro "down" nucleoside as embodied in Count 1. Moreover, we have related *supra* how the Idenix team identified such a molecule as a high-priority target, but failed to synthesize such a compound for approximately two years subsequent to the submission of the S1 application. Moreover, we have related how the Idenix team attempted the very syntheses that



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1 Storer's expert Dr. Damha states would be suggested by the disclosures of the S1  
2 document, but were unable to successfully synthesize the target molecule. We  
3 therefore find that the S1 application provides little in the way of direction or  
4 guidance as to how to synthesize a 2'-fluoro-2'-methyl nucleoside with the fluoro  
5 moiety in the "down" position.

6 The third *Wands* factor enquires into the presence or absence of working  
7 examples of the invention. It is uncontested by the parties that there were no  
8 examples of such a molecule reported in the art prior to submission of the S1  
9 application. Clark Subs. Motion 1, Paper 389 at 9. Clark contends, and Storer  
10 does not contest, that the S1 application lacks a single, specific example teaching  
11 how to synthesize any nucleoside having a fluorine atom substituent on the ribose  
12 ring. Clark Subs. Motion 1, Paper 389 at 12-13 (citing Ex. 2001, ¶¶ 138, 186, 202,  
13 214, 230, 249; Ex. 2049, pp. 1-5297, ll. 1-21, Figs. 1-4). Additionally, argues  
14 Clark, the S1 application lacks any working example that an artisan could have  
15 modified, without extensive experimentation, to make a compound falling within  
16 either of Count 1's chemical formulae. *Id.* at 13 (Ex. 2001, ¶¶ 138-141, 186, 202,  
17 214, 229, 230, 235, 248, 249; Ex. 2049, pp. 1, ll. 1-5297, Figs. 1-4; Ex. 2005, pp.  
18 23-24, ll. 18-3).

19 With respect to the fourth *Wands* factor, the nature of the invention, Clark  
20 contends that Count 1 is directed to methods for treating HCV infection using  
21 certain 2'-fluoro-2'-C(H/F)<sub>3</sub> nucleosides, including certain 2'-fluoro-2'-methyl  
22 nucleosides. Clark Subs. Motion 1, Paper 389 at 9 (citing Ex. 2001, ¶¶ 45-50; Ex.

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1 2003,<sup>38</sup> ¶¶ 26, 28, 31-33, 40-42; Ex 2012,<sup>39</sup> p. 2:8-17; Ex. 2098,<sup>40</sup> col. 2221, ll. 9-  
 2 52). According to Clark, because such compounds were not commercially  
 3 available as of June 28, 2002, it would have been necessary for an artisan to make  
 4 a compound falling within one of Count 1's chemical formulae. *Id.* (citing Ex.  
 5 2001, ¶ 136; Ex. 2005, p. 20, ll. 23-26).

6 Storer does not contest Clark's characterization of the nature of the  
 7 invention, but responds that the nature of the invention is such as to require a high  
 level of skill in the art, so much so that a skilled artisan would have been familiar  
 9 with the methods for synthesizing nucleosides of the type within Count 1.

10 We find that the nature of the invention, as recite in Count 1 is best  
 11 characterized as the administration of a genus of nucleosides used in the treatment  
 12 of viruses, particularly those of the family *Flaviviridae* (which includes HBV and  
 13 HCV<sup>41</sup>). We also find that, as of the time of filing of the S1 application, although  
 14 organic fluoridation mechanisms were generally well-known in the art a 2'-fluoro-  
 15 2'-methyl nucleoside with the fluoro substituent in the "down" position had not yet  
 16 been synthesized.

17 With respect to the fifth *Wands* factor, the state of the prior art, Clark argues  
 that no synthesis of a 2'-fluoro-2'-C(H/F)<sub>3</sub> nucleoside, including any 2'-fluoro-2'-  
 19 methyl nucleoside, had been reported in the available art as of S1's June 28, 2002  
 20 filing date. Clark Subs. Motion 1, Paper 389 at 9 (Ex. 2001, ¶¶ 137, 231; Ex.

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<sup>38</sup> Paper No. 47

<sup>39</sup> Paper No. 55

<sup>40</sup> Paper No. 137

<sup>41</sup> See, e.g., Clark Subs. Motion 1, Paper 398 at 2

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1 2005, p. 22, ll. 4-8; Ex. 1194,<sup>42</sup> p. 91, ll. 12-16). Rather, argues Clark, its US Appl.  
2 Pub. No. 2005/0009737 A1 (the "C2 application"), published on January 13, 2005  
3 (subsequent to the S1 application's June 28, 2002 filing date), was the first  
4 reported synthesis of a 2'-fluoro-2'-methyl nucleoside. *Id.* at 9-10 (citing Ex.  
5 2001, ¶¶ 137, 162; Ex. 2003, ¶¶ 221, 222; Ex. 2005, p. 22, ll. 4-8; Ex. 2013,<sup>43</sup>  
6 cover page (item 43), ¶ [0294]-[0035]).

7 Storer argues that the specification of the S1 application, when viewed in  
light of the prior art, discloses sufficient information to enable a skilled artisan to  
9 synthesize a 2'-methyl (up)-2'-F (down) nucleoside without undue  
10 experimentation. Storer Opp. 1, Paper 402 at 4. According to Storer, and as  
11 argued *supra*, a skilled artisan would have readily recognized that a well-known  
12 precursor to the nucleoside, such as Matsuda Compound 17, could have been  
13 transformed in a single step to a nucleoside within the scope of the count. *Id.*  
14 (citing Ex. 1132, ¶25; Ex. 1144,<sup>44</sup> p. 949; Ex 1115,<sup>45</sup> pp. 40-45). Storer argues that  
15 compounds that were one reaction step away from the compounds of Count 1, such  
16 as 2'-methyl (down)-2'-OH (up) nucleosides, were well known by June 2002. *Id.*  
17 (citing Ex. 1132, ¶ 25; Ex. 1144, p. 949; Ex. 1115, pp. 40-45).

Reviewing the evidence before us, we find, with respect to the prior art, that  
19 certain methods of organic fluoridation were well-known at the time of invention,  
20 but that synthesis of a 2'-fluoro-2'-methyl nucleoside had not yet been reported in

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<sup>42</sup> Paper No. 498

<sup>43</sup> Paper No. 56

<sup>44</sup> Paper No. 293

<sup>45</sup> Paper No. 269

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1 the prior art. See Ex. 1132, ¶ 33. The fluorinating agent DAST was well-known in  
2 the prior art to be useful in the fluorination of nucleosides and nucleoside analogs.  
3 For example, Johanna Wachtmeister et al., *Synthesis of 4-substituted carbocyclic*  
4 *2,3-dideoxy-3-C-hydroxymethyl nucleoside analogues as potential anti-viral*  
5 *agents*, 55 TETRAHEDRON 10761 (1999) ("Wachtmeister") teaches the use of  
6 DAST in the fluoridation of certain carbocyclic nucleoside analogs in which the  
7 oxygen in the five-member ribose ring is replaced with a carbon atom and  
fluoridation takes place at the C-4 position. Ex. 1148, p. 10763. Similarly, P.  
9 Herdewijn et al., *Synthesis of nucleosides fluorinated in the sugar moiety. The*  
10 *application of diethylaminosulfur trifluoride to the synthesis of fluorinated*  
11 *nucleosides*, 8(1) NUCLEOSIDES AND NUCLEOTIDES 65 (1989) ("Herdewijn")  
12 teaches using DAST for, *inter alia*, fluoridation of nucleosides at the 2' position.  
13 Ex. 1160, pp. 65-96. A. Van Aerschot et al., *2',3'-difluoro- and 3'-azido-2'-fluoro*  
14 *substituted dideoxypyrimidines as potential anti-HIV agents*, 98(12) BULL. SOC.  
15 CHIM. BELG. 937 (1989) ("Van Aerschot") teaches the use of DAST to produce  
16 various 2'-fluoro-nucleoside analogs. Ex. 1151,<sup>46</sup> pp. 938-941. Hiroyuki  
17 Hayakawa et al., *Diethylaminosulfur trifluoride (DAST) as a fluorinating agent of*  
*pyrimidine nucleosides having a 2',3'-vicinal diol system*, 38(5) CHEM. PHARM.  
19 BULL. 1136 (1990) ("Hayakawa") teaches that although "participation of the base  
20 moiety often thwarts the desired introduction of a fluorine atom ... appropriate  
21 modification of the base and/or sugar moieties allowed the desired  
22 fluorodehydroxylation to occur, giving 5'-, 3'-β, and 2'-α-fluorinated

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<sup>46</sup> Paper No. 300

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1 uracilnucleosides in good yields.” Ex. 1152, p. 1136. Consequently, we find that  
2 it was well-known in the prior art that DAST could be employed in the 2’  
3 fluoridation of nucleosides and nucleoside analogs.

4 Dr. Damha cites these prior art references, among others, as demonstrating  
5 that:

6 The fluorinating reagent, DAST, may be used to prepare a 2’-F-  
7 ribonucleoside in a single step from an “arabinonucleoside”  
8 (compound 2 of Scheme A, above). As of June 28, 2002, DAST had  
9 routinely been used in the nucleoside field to install a fluoro group at  
10 the 2’-position of nucleosides, often with an unprotected nucleobase,  
11 in a single step under very mild conditions.  
12

13 Ex. 1132, ¶ 71. However, Dr. Damha admits that none of these references teaches  
14 using DAST to convert a tertiary alcohol at a nucleoside 2’ position to a tertiary  
15 fluoride at the nucleoside 2’ position:

16 Q. [Ms. Austin] I just want to make sure the record is clear. So just  
17 maybe a yes or a no, did any of these references describe using DAST  
18 to convert a tertiary alcohol at a nucleoside 2’ position to a tertiary  
19 fluoride at the nucleoside 2’ position?  
20

21 [...]  
22

23 A. [Dr. Damha] No.

24  
25 Ex. 1194, p. 125. And Dr. Wnuk opined in response that “I believe it is an  
26 oversimplification to assert that, because DAST had been used to fluorinate certain

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1 secondary and tertiary alcohols<sup>47</sup> with inversion of stereochemistry, it was  
2 therefore well-known that it would react similarly with significantly different  
3 substrates.” Ex. 2145, ¶ 96.

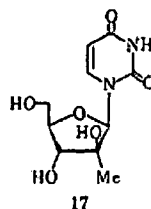
4 We consequently find, with respect to the fifth *Wands* factor, that although  
5 DAST was well-known in the prior art as fluoridating agent for nucleosides and  
6 nucleoside analogs, the prior art did not teach, or explicitly suggest, the use of  
7 DAST in the fluoridation of a tertiary alcohol to convert a tertiary alcohol at a  
nucleoside 2' position to a tertiary fluorine at the nucleoside 2' “down” position.

9 We further find that, although organic fluoridation techniques were well-known in  
10 the art at the time the S1 application was filed, fluoridation of tertiary alcohols to  
11 produce a 2' “down” tertiary fluorine was not taught or suggested by the prior art.

12 The sixth *Wands* factor is the relative level of skill of those in the art. The  
13 parties largely agree that the level of skill in the art is very high and on the

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<sup>47</sup> In a secondary alcohol, the carbon atom binding the hydroxyl group is attached directly to two alkyl groups, which may be the same or different. In a tertiary alcohol, the carbon atom binding the hydroxyl group is attached directly to three alkyl groups, any combination of same or different. By way of example, Matsuda compound 17:



is a tertiary alcohol because the 2' carbon binding the hydroxyl group is bound to three carbons: the 1' and 3' ring carbons and the carbon of the methyl (Me) group.

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1 qualifications of a person of ordinary skill. *See* Ex. 1132, ¶ 14; Ex. 2001, ¶¶ 60-61.  
2 We therefore find that a person possessing the ordinary level of skill in this art, as  
3 of the time of invention, would hold a doctoral degree in the field of organic,  
4 synthetic, or medicinal chemistry with at least a year's experience in the field of  
5 nucleoside synthesis or relevant drug discovery. Alternatively, that artisan could  
6 hold a master's degree in one of those same fields with at least three years of  
7 practical experience in the field of nucleoside synthesis or relevant drug discovery.

With respect to the seventh *Wands* factor, the predictability or  
9 unpredictability of the art, Clark argues that the fluorination chemistry involved in  
10 attempting to synthesize 2'-fluoro ("down") 2'-C(H/F)<sub>3</sub> ("up") nucleosides was  
11 unpredictable at the time of Idenix's attempts to do so, because there was no  
12 precedent in the literature for making such a substitution on tertiary carbons of the  
13 ribose ring. Clark Subs. Motion 1, Paper 389 at 12 (citing Ex. 2001, ¶¶ 154-159,  
14 231; Ex. 2005, p. 22, ll. 12-17, Ex. 2007, pp. 19, ll. 4-12, 22, ll. 5-18; Ex. 2022,<sup>48</sup>  
15 pp. 65-96; Ex. 2023,<sup>49</sup> pp. 574-78; Ex. 2024,<sup>50</sup> pp. 2315-16; Ex. 2025,<sup>51</sup> pp. 251-  
16 54; Ex. 1194, pp. 91, ll. 12-16, 92, ll. 3-93:18, 125, ll. 4-18). Clark maintains that  
17 the prior art demonstrated that attempted fluorination reactions (including those  
involving DAST) could fail, resulting in unfluorinated elimination and/or  
19 rearrangement products, or products with incorrect stereochemistry. *Id.* (citing Ex.

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<sup>48</sup> Paper No. 62

<sup>49</sup> Paper No. 63

<sup>50</sup> Paper No. 64

<sup>51</sup> Paper No. 65

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1 2001, ¶¶ 156, 231; Ex. 2014,<sup>52</sup> p. 259, ll. 15-20; Ex. 2015,<sup>53</sup> pp. 7570-7571, ll. 18-  
 2 4; Ex. 2016,<sup>54</sup> pp. 2563 (left col, ll. 11-14, Scheme 5), 2564 (Scheme 9); Ex.  
 3 2017,<sup>55</sup> pp. 1090-91; Ex. 2018,<sup>56</sup> pp. 554-55; Ex. 2139,<sup>57</sup> pp. 156-157, ll. 15-3).

4 Clark argues further that the documents that produced by Storer in the  
 5 related 105,871 Interference demonstrate that DAST treatment of tertiary and  
 6 secondary alcohols failed to produce fluorinated products. Clark points out that  
 7 Dr. Paul Coe, an expert in organofluorines expressed skepticism regarding the use  
 8 of DAST; and Dr. Richard Storer stated that “[a] lot of things which look simple  
 9 on paper in related systems have been tried and don’t work in this series. Having  
 10 to make the tertiary fluoride is very different to [sic] having to make secondary.”  
 11 *Id.* (citing Ex. 2001, ¶¶ 157, 158, 174; Ex. 2007, pp. 15-17, ll. 15-2; 20, ll. 3-8; Ex.  
 12 2029, p. 2 (numbered p. 1); Ex. 2035, p. 3 (numbered p. 2); Ex. 2038, pp. 1-3, 5-  
 13 10; Ex. 2041,<sup>58</sup> p. 1; Ex. 2042,<sup>59</sup> p. 1; Ex. 2043,<sup>60</sup> pp. 38, 40; Ex. 2044,<sup>61</sup> p. 1; Ex  
 14 2139, pp. 146, ll. 9-22, 147, ll. 14-23).

15 Storer responds that deoxyfluorination with DAST was highly predictable.  
 16 Storer Opp. 1, Paper 402 at 7 (citing Ex. 1200, ¶¶ 100-131). According to Storer,

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<sup>52</sup> Paper No. 57

<sup>53</sup> Paper No. 58

<sup>54</sup> Paper No. 59

<sup>55</sup> Paper No. 60

<sup>56</sup> Paper No. 61

<sup>57</sup> Paper No. 368

<sup>58</sup> Paper No. 81

<sup>59</sup> Paper No. 82

<sup>60</sup> Paper No. 83

<sup>61</sup> Paper No. 84



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1 the references that Clark and its expert, Dr. Wnuk, rely on in support of their  
2 argument that fluorination with DAST was unpredictable are Exhibit 2018,  
3 Krzysztof W. Pankiewicz et al., *A synthesis of 9-(2-deoxy-2-fluoro-β-D-*  
4 *arabinofuranosyl) adenine and hypoxanthine. An effect of C3'-endo to C2'-endo*  
5 *conformational shift on the reaction course of 2'-hydroxyl group with DAST*, 57 J.  
6 ORG. CHEM. 553-59 (1992)<sup>62</sup> ("Pankiewicz") and Exhibit 1152, Hiroyuki Hyakawa  
7 et al., *Diethylaminosulfur trifluoride (DAST) as a fluoridating agent of pyrimidine*  
8 *nucleosides having a 2',3'-vicinal diol system*, (38(5) CHEM. PHARM BULL. 1136-  
9 39 (1990) ("Hayakawa")<sup>63</sup>. Storer argues that Clark relies upon these references  
10 to demonstrate that using DAST in the preparation of fluoridated nucleosides may  
11 result in a "rearrangement product" and an "unfluorinated 2'-cyclo derivative." *Id.*  
12 (citing Storer Motion 1, p. 12, ll. 6-11; Ex. 2001, ¶ 156; Ex. 2145, ¶ 98). However,  
13 argues Storer, both Pankiewicz and Hayakawa teach that DAST deoxyfluorination  
14 of a nucleoside with a 2'-OH (up) proceeded with inversion to form a nucleoside  
15 with a 2'-F (down) in over 80% yields without any alleged rearrangement or  
16 unfluorinated products reported. *Id.* (citing Ex. 1152, p. 1139; Ex. 2018, p. 559;  
17 Ex. 2139, p. 149-150, ll. 10-11. Ex. 1248, p. 87, ll. 2-11).

Storer also disputes that Exhibit 2015 teaches that fluorination with DAST  
19 may proceed with double inversion resulting in a "product with unexpected  
20 stereochemistry" as Clark and its expert suggest. Storer Opp. 1, Paper 402 at 8  
21 (citing Clark Motion 1, p. 12, ll. 6-11; Ex. 2001, ¶ 156). Exhibit 2015 is Lak S.

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<sup>62</sup> Paper No. 61

<sup>63</sup> Paper No. 301

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1 Jeong et al., *Unanticipated retention of configuration in the DAST fluorination of*  
2 *Deoxy-4'-thiopyrimidine nucleosides with "up" hydroxyl groups*, 35(41)  
3 TETRAHEDRON LETTERS, 7569-72 (1994) ("Jeong"). According to Storer, the title  
4 of the article explains that the double inversion was not the norm. *Id.* According  
5 to Storer, Jeong teaches that the double inversion was a result of the sulfur atom in  
6 the thiofuranose ring, which is not present in the compounds of Count 1. *Id.*  
7 (citing Ex. 2139, p. 136, ll. 8-12).

Storer also points to Exhibits 2014, 2016, and 2017, which Clark and its  
9 expert rely upon to argue that deoxyfluorination with DAST may result in an  
10 "unfluorinated dehydration product," a "rearrangement product," or an  
11 "elimination product." Storer Opp. 1, Paper 402 at 9 (citing Storer Motion 1, p. 12,  
12 ll. 6-11; Ex. 2001, ¶ 156). According to Storer, none of the DAST reactions relied  
13 upon by Clark was performed on a nucleoside. *Id.* Nevertheless, argues Storer,  
14 Exhibit 2014 teaches that "diethylaminosulfur trifluoride (DAST) appears to be the  
15 most convenient and powerful reagent for deoxyfluorination," and Exhibit 2016  
16 teaches that "Deoxo-Fluor ...and DAST ... are widely used in one-step reactions  
17 for the introduction of fluorine into organic compounds." *Id.* (quoting Ex. 2014, p.  
18 259; Ex. 2016, p. 2561). Moreover, argues Storer, Dr. Wnuk agreed that the latter  
19 statement describes the state of the art for fluorination in 2002. *Id.* (citing Ex.  
20 2139, p. 139, ll. 13-21).

21 Having reviewed the parties' arguments, and the proffered evidence, we find  
22 that the art, with respect to fluoridation of tertiary alcohols, was highly  
23 unpredictable, as evidenced by Idenix's repeatedly unsuccessful attempts to

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1 synthesize its high-priority target nucleoside, and as further evinced by the  
2 statements of Dr. Coe and Dr. Storer. See Ex. 2038, p. 1; Ex. 2044, p. 1.

3 In summary, having reviewed the *Wands* factors argued by the parties,<sup>64</sup> we  
4 find that (1) synthesis of a 2'-fluoro-2'-methyl nucleoside with the fluoro moiety in  
5 the "down" position required at least two years of a high-priority experimentation  
6 by persons skilled in the art, including multiple consultations with experts at the  
7 top of their fields and additional formal training; (2) the S1 application provides  
8 little in the way of direction or guidance as to how to synthesize such a compound;  
9 (3) the S1 application provides no explicit example of a 2'-fluoro-2'-methyl  
10 nucleoside, nor was an example provided by the relevant art as of the S1  
11 application's filing date; (4) the invention is characterized as the administration of  
12 a genus of nucleosides used in the treatment of viruses, particularly those of the  
13 family *Flaviviridae* (which includes HBV and HCV) and an embodiment of the  
14 count requires a 2'-fluoro ("down") 2'-methyl nucleoside; (5) although organic  
15 fluoridation techniques were well-known in the art at the time the S1 application  
16 was filed, fluoridation of tertiary alcohols to produce a 2' "down" tertiary fluorine  
17 was not taught or suggested by the prior art; (6) the level of skill in the art was  
18 highly sophisticated: a person possessing the ordinary level of skill in this art, as of  
19 the time of invention, would hold a doctoral degree in the field of organic,  
20 synthetic, or medicinal chemistry with at least a year's experience in the field of  
21 nucleoside synthesis or relevant drug discovery; and (7) the art, at least with  
22 respect to fluoridation of tertiary alcohols to produce a tertiary fluorine in the 2'

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<sup>64</sup> Neither party argued the eighth *Wands* factor, the breadth of the claims.

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1 “down” position, was highly unpredictable. We therefore find that *Wands* factors  
2 1, 2, 3, 5, and 7 strongly indicate that a person skilled in the art would not arrive at  
3 the claimed invention without undue experimentation. We therefore conclude that  
4 the S1 application does not enable any species of Count 1, all of which require a  
5 fluorine atom in the 2’ “down” position.

6 A party is accorded benefit of the date of an earlier application if its earlier  
7 application constitutes a constructive reduction to practice of the count. Bd.R.  
41.201. Clark, as the party challenging Storer’s accorded benefit of the S1  
9 application, must therefore demonstrate that the S1 application does not provide a  
10 constructive reduction to practice of Count 1. SO ¶ 208.4.2. Constructive  
11 reduction to practice means a described and enabled anticipation under 35 U.S.C.  
12 102(g)(1) in a patent application of the subject matter of Count 1. Bd.R. 41.201.  
13 Thus, even if the S1 application does not describe and enable the full scope of  
14 Count 1, Storer cannot be deprived of the filing date of the S1 application if the S1  
15 application describes a single embodiment or species that meets all of Count 1’s  
16 limitations.

17 Neither party disputes that all of the species of the genus contemplated  
within the scope of Count 1 require a fluorine atom in the “down” position and a  
19 C(H/F)<sub>3</sub> moiety in the “up” position at the 2’ carbon of the sugar ring. We have  
20 found that the analysis of the factors set forth in *Wands* compel the conclusion that,  
21 at the time the S1 application was filed, a person skilled in the art would not have  
22 been able to synthesize any of the 2’-fluoro (“down”) nucleosides of Count 1  
23 without undue experimentation. We therefore conclude that the S1 application

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1 does not enable a single species of Count 1 and, consequently, the S1 application is  
2 not a constructive reduction to practice of Count 1. Because we find this issue to  
3 be dispositive of the motion, we do not reach Clark's other arguments. Clark  
4 Substantive Motion 1 to deny Storer the accorded benefit of its S1 application is  
5 granted.

6  
7 **B. Clark Substantive Motions 2 and 3**

Clark Substantive Motion 2 seeks to deprive Storer of the benefit accorded  
9 with respect to Count 1 of its U.S. Appl. No. 60/466,194 (the "S2 application")  
10 filed April 28, 2003. Clark Subs. Motion 2, Paper 390 at 1. Clark Substantive  
11 Motion 3 seeks to deprive Storer of the benefit accorded with respect to Count 1 of  
12 its US Appl. No. 60/470,949 (the "S3 application") filed May 14, 2003. Clark  
13 Subs. Motion 3, Paper 391 at 1.

14 Clark argues that although Storer was accorded benefit of the S2 and S3  
15 applications when the present interference was declared, Storer has not relied upon  
16 either in any of its motions in the present interference. Clark Subs. Motion 2,  
17 Paper 390 at 9; Clark Substantive Motion 3, Paper 391 at 9. According to Clark,  
that constitutes an admission by Storer that the S2 and S3 applications are  
19 unrelated to the subject matter in dispute between the parties. Clark Subs. Motion  
20 2, Paper 390 at 9; Clark Substantive Motion 3, Paper 391 at 9.

21 Clark argues that Count 1 of the interference pertains to a method for  
22 treating HCV infection. Clark Subs. Motion 2, Paper 390 at 10; Clark Subs.

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1 Motion 3 Paper 391 at 10 (citing Declaration,<sup>65</sup> p. 3, ll. 16-17; Ex. 2001, ¶¶ 45-50;  
2 Ex 2003, ¶¶ 26, 28, 29, 31-33; 40-42; Ex. 2012,<sup>66</sup> p. 2:8-17; Ex. 2098, col. 2221, ll.  
3 9-52). However, argues Clark, the S2 and S3 applications are deficient because it  
4 fails to mention HCV or methods for treating HCV infection, as required by Count  
5 1. *Id.* (citing Ex. 2001, ¶¶ 256-261; Ex. 2003, ¶¶ 140-141, 145-147; Ex. 2050,<sup>67</sup>  
6 pp. 1-36, Figs. 1-3). According to Clark, the S2 and S3 applications disclose  
7 processes for chemically synthesizing certain prodrugs of antiviral nucleosides. *Id.*  
(citing Ex. 2001, ¶¶ 58, 59; Ex. 2003, ¶¶ 49, 136-137; Ex. 2050, pp. 1, ll. 3-6, 6-9,  
9 ll. 24-9).

10 Clark also argues that Count 1 requires certain compounds, specifically,  
11 certain 2'-fluoro-2'-C(H/F)<sub>3</sub> nucleosides, which the S2 and S3 applications fail to  
12 disclose. Clark Subs. Motion 2, Paper 390 at 10; Clark Subs. Motion 3, Paper 391  
13 at 10 (citing Ex. 2001, ¶ 256-261; Ex. 2050, pp. 1-36, Fig. 1-3). Therefore, argues  
14 Clark, as of the filing dates of the S2 and S3 applications, an artisan would not  
15 have believed that S2 and S3's applicants were in possession of any compound(s)  
16 falling within either of Count 1's chemical formulae, or any method(s) for treating  
17 HCV infection involving such compound(s). Clark Subs. Motion 2, Paper 390 at  
11; Clark Subs. Motion 3, Paper 391 at 13 (citing Ex. 2001, ¶¶ 256-261).

19 Clark also argues that the S2 and S3 applications fail to provide an enabling  
20 anticipation of Count 1 because it does not teach an artisan as how to make any

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<sup>65</sup> Paper No. 1

<sup>66</sup> Paper No. 55

<sup>67</sup> Paper No. 112

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1 nucleoside falling within the scope of Count 1, or teach how to treat HCV infection  
2 using any such nucleoside, without undue experimentation. Clark Subs. Motion 2,  
3 Paper 390 at 11; Clark Subs. Motion 3, Paper 391 at 13 (citing Ex. 2001, ¶¶ 256-  
4 261; Ex. 2003, ¶¶ 136-147; Ex. 2050, pp. 1-36, Fig. 1-3).

5 Storer argues only that Clark has failed to establish that it is entitled to the  
6 relief requested. Storer Opp. 2, Paper 403 at 2; Storer Opp. 3, Paper 403 at 2  
7 Storer does not provide substantive argument and does not direct us to evidence to  
contradict Clark's arguments.

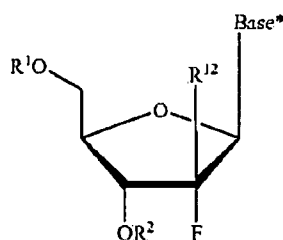
9 We have reviewed the disclosures of the S2 and S3 applications. For the  
10 reasons stated with respect of the S1 application, we agree with Clark that the S2  
11 and S3 applications do not describe either the genus of Count 1 or an embodiment  
12 that meets all the limitations of that count. Clark Substantive Motions 2 and 3 to  
13 deprive Storer of the benefit accorded with respect to Count 1 of its S2 and S3  
14 applications are granted.

15  
16 **C. Clark Substantive Motion 7**

17 Clark's Substantive Motion 7 seeks judgment against Storer on the grounds  
that involved claims 1-12, 17, 18, 20, 33, 34, 36, 38, 49-57, 62, 64, and 76-85 of  
19 Storer's involved US Patent No. 7,608,600 B2 (the "'600 Patent") are unpatentable  
20 under 35 U.S.C. § 112, 1st paragraph for lack of enablement and written  
21 description. Clark Subs. Motion 7, Paper 154 at 1. To prevail, Clark must  
22 demonstrate that the Specification of the '600 patent does not support the full  
23 scope of the claimed subject matter.

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1 Claim 1 of the '600 patent has been recited *supra* as part of Count 1 and we  
2 do not repeat it here. As we have related, Clark argues that the salient limitation of  
3 Storer claim 1, for purposes of enablement, is the fluorine atom in the 2' "down"  
4 position, thus:



5  
6 Ex. 1001-2, col. 2221, ll. 14-24. Storer's involved dependent claims 2-12, 17, 18,  
7 20, 33, 34, 36, 38, and 49 all depend from claim 1 and all claim a fluorine atom in  
8 the 2' "down" position. Ex. 1001-2. Storer's involved claims 51-57, 62, 64, and  
9 76-85 all depend from independent claim 50, which also claims a fluorine atom in  
10 the 2' "down" position, as do all of the involved claims depending from it. *Id.*

11 Storer's '600 patent issued from Storer's S4 application, which claims  
12 priority benefit of the S1 application. *See* Ex. 1001, p. 1. Clark argues that, as of  
13 June 27, 2003, the filing date of the S4 application, there was no available prior art  
reporting synthesis of a 2'-fluoro-2'-C(H/F)<sub>3</sub>. Clark Motion 7, paper 154, at 9,  
15 citing Wnuk Decl., Ex. 2001, ¶¶ 136, 137. Clark argues further that the prior art as  
16 of 27 June 2003 would not have taught an ordinarily skilled artisan how to make  
17 the recited nucleoside without undue experimentation. *Id.* at 10.

18 Storer does not argue or direct us to evidence of art available prior to the  
19 June 27, 2003 filing of the S4 application that reporting or describing synthesis of



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1 the recited nucleosides. Accordingly, because we have found *supra* that the S1  
2 application does not enable a nucleoside as recited in Count 1, we find that the  
3 specification of the '600 patent does not enable Storer's involved claims. We  
4 therefore conclude that the involved claims 1-12, 17, 18, 20, 33, 34, 36, 38, 49-57,  
5 62, 64, and 76-85 of '600 patent are unpatentable under 35 U.S.C. § 112, 1st  
6 paragraph, for lack of enablement.<sup>68</sup> Clark Substantive Motion 7 for judgment  
7 against the involved claims of Storer's '600 patent is granted.

9 **D. Clark Substantive Motion 10**

10 Clark next moves to deprive Storer of the benefit accorded with respect to  
11 Count 1 of US Appl. No. 10/608,907, filed June 27, 2003 (the "S4" application).  
12 Motion at 1. Clark contends that the S4 application S4-lacks enablement, written  
13 description, and utility for subject matter anticipating Count 1. Clark Subs. Motion  
14 10, Paper 392 at 1. Storer has opposed. Storer Opp. 10, Paper 405. Clark has  
15 replied. Clark Reply 10, Paper 422.

16 Because we have determined *supra* that Storer's involved claims -12, 17, 18,  
17 20, 33, 34, 36, 38, 49-57, 62, 64, and 76-85 are unpatentable under 35 U.S.C. §  
18 112, first paragraph, for lack of enablement, we need not reach this motion. -  
19

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<sup>68</sup> We note that all of the remaining claims of the '600 patent similarly recite a fluorine atom in the 2' "down" position and may likewise be unpatentable under 35 U.S.C. § 112, first paragraph, for the same reasons. Storer may wish to seek re-examination of these claims.

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1 **E. Clark Substantive Motion 5**

2 Clark next moves to substitute its proposed count 2 or, alternatively, its  
3 proposed count 3, for Count 1. Clark Subs. Motion 5, Paper 192 at 1. Clark's  
4 Proposed Count 2 is simply its Count 164 of its '218 application. *Id.*

5 However, because we have already determined that Storer's involved claims  
6 are unpatentable, we *sua sponte* remove Storer's unpatentable claim 1 from the  
7 count and reformulate Count 1 as Clark's claim 164.

We therefore need not reach Clark's Substantive Motion 5.

9

10 **F. Clark's Substantive Motion 8**

11 Clark's Substantive Motion 8 seeks judgment against Storer on the ground  
12 that all of Storer's involved claims, claims 1-12, 17, 18, 20, 33, 34, 36, 38, 49-57,  
13 62, 64, and 76-85 of Storer's '600 patent are unpatentable under 35 U.S.C. § 101,  
14 for lack of utility and, accordingly under 35 U.S.C. § 112, 1st paragraph, for lack  
15 of enablement. Clark Subs. Motion 8, Paper 155 at 1.

16 Our decision on Clark's Substantive Motion 7 that Storer's involved claims  
17 are unpatentable under 35 U.S.C. § 112, 1st paragraph, for lack of enablement is  
dispositive of the patentability of Storer's claims. Therefore, it is unnecessary for  
19 us to reach this motion. Clark's Substantive Motion 8 is consequently dismissed.

20

21 **G. Clark Substantive Motion 9**

22 Clark Substantive Motion 9 seeks judgment against Storer on the ground that  
23 all of Storer's involved claims, claims 1-12, 17, 18, 20, 33, 34, 36, 38, 49-57, 62,

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64, and 76-85 of Storer's '600 patent are unpatentable under 35 U.S.C. §§ 102(e) or 103 as being either anticipated by, or obvious over, Clark's US Appl. No. 10/828,753 (the "C2 application"), filed April 21, 2004. Clark Subs. Motion 9, Paper 156 at 1.

Our decision on Clark's Substantive Motion 7 that Storer's involved claims are unpatentable under 35 U.S.C. § 112, 1st paragraph, for lack of enablement is dispositive of the patentability of Storer's claims. Therefore, it is unnecessary for us to reach Clark Substantive Motion 9.

#### **H. Clark Miscellaneous Motion 18**

Clark has moved to exclude the following Storer Exhibits: 1132, 1175-76, 1177, 1200, 1201, 1228, 1229, 1231, 1232, and 1233. Clark Misc. Motion 18, Paper 427 at 1.

##### **1. Storer Exhibit 1132**

Clark argues that Storer Exhibit 1132, the Declaration of Masad J. Damha, Ph.D., (the "Damha Declaration") is inadmissible under SO ¶ 105.6 because it is an affidavit without an original signature. Clark Misc. Motion 18, Paper 427 at 1. According to Clark, Dr. Damha, Storer's declarant, testified at his deposition that he did not sign a paper copy of Exhibit 1132 in ink, but instead inserted a digital image of his signature. *Id.* (citing Ex. 1194, p. 26, ll. 14-24). Furthermore, argues Clark, there is no original copy of Exhibit 1132 with a handwritten original

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1 signature that could have been retained or made available on demand, which is also  
2 in violation of SO ¶ 105.6. *Id.* (citing Ex. 1194, pp. 26-27, ll. 25-4).

3 Alternatively, argues Clark, paragraphs 61-81 of the Damha Declaration  
4 should be excluded under Federal Rule of Evidence 702 because Dr. Damha's  
5 opinions expressed in these paragraphs are not based on sufficient facts or data.  
6 Clark Misc. Motion 18, Paper 427 at 2. According to Clark, when opining that it  
7 would have been trivial for an artisan to make 2'-fluoro-2'-methyl nucleosides, Dr.  
Damha did not take into account Storer's own documents from the prior  
9 '871 interference (e.g., Ex. 2029, Ex. 2035, Ex. 2041, Ex. 2042, and Ex. 2043).

10 Storer responds that Dr. Damha verified during his deposition that he  
11 personally inserted his digital signature into his Declaration. Storer Opp. 18, Paper  
12 29 at 1 (citing Ex. 1194, p. 26, ll. 19-24. Therefore, argues Storer, although Dr.  
13 Damha did not handwrite his signature on a paper copy of his declaration, he did  
14 verify that he personally electronically signed the declaration. *Id.* Storer submits  
15 that the Board should accept this as sufficient. *Id.*

16 Storer also argues that Clark did not timely object to Exhibit 1132 at the  
17 deposition and also failed to request a conference call with the Administrative  
Patent Judge managing the interference to seek authorization to belatedly object to  
19 Exhibit 1132. Storer Opp. 18, Paper 29 at 1 (citing 37 C.F.R. § 41.155(a)).

20 Dr. Damha has affirmed that the digital signature is a reproduction of his  
21 own signature and that the declaration was his own. We therefore decline to  
22 exclude the Exhibit on this ground.

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1 More substantially, we agree with Storer that whether Dr. Damha examined  
2 the '871 interference documents prior to forming his opinion on whether a person  
3 of ordinary skill could have synthesized 2'-fluoro-2'-methyl nucleoside  
4 compounds is a question of the probative weight of the opinion testimony and not  
5 one of admissibility. We held, *supra*, that Dr. Damha was qualified as an expert.  
6 He may express his opinions on matters relevant to this interference. Federal Rule  
7 of Evidence 702 states that a "witness who is qualified as an expert by knowledge,  
skill, experience, training, or education may testify in the form of an opinion or  
9 otherwise if ... the testimony is based on sufficient facts or data." Fed. R. Evid.  
10 702(b).

11 We therefore decline to exclude Exhibit 1132.

12  
13 2. Storer Exhibits 1175 and 1176

14 Clark next argues that Storer Exhibits 1175<sup>69</sup> and 1176<sup>70</sup>, which comprise  
15 two emails to the Patent Trial and Appeal Board concerning the '871 interference,  
16 with copies to Administrative Patent Judge New, discuss Storer's allegations of  
17 inequitable conduct and request authorization to move for additional discovery in  
the present interference, are inadmissible in their entirety because they are  
19 irrelevant under Rule 402, as well as confusing and a waste of time under Rule  
20 403. Clark Misc. Motion 18, Paper 427 at 3.

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<sup>69</sup> Paper No. 458

<sup>70</sup> Paper No. 459

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1 Storer was not authorized to file a motion asserting inequitable conduct and  
2 has not raised the issue in any of its substantive or contingent motions considered  
3 herein. Because this evidence is unrelated to any of the matters before us we  
4 decline to address the admissibility of Exhibits 1175 and 1176 as an evidentiary  
5 matter. However, because the exhibits are extraneous to this proceeding we order  
6 that they be expunged from the record. Bd.R. 7(a) & 122(c)(1)(iii).

7  
3. Storer Exhibit 1177

9 Storer Exhibit 1177<sup>71</sup> is a copy of an order (Docket No. T-1156-12) from  
10 Federal Court of Canada, regarding the litigation with respect to the Canadian  
11 versions of Storer's involved patent and Clark's involved application in that venue.  
12 Clark seeks exclusion of Exhibit 1177 on substantially the same grounds that it  
13 seeks exclusion of Exhibits 1175 and 1176. Clark Misc. Motion 18, Paper 427  
14 at 4.

15 Storer has not raised, in any of its substantive or contingent motions, any  
16 argument that relies upon this Exhibit and, having reviewed the Exhibit, we can  
17 discern no purpose for it to be included in this proceeding. Because the exhibit  
18 appears to be extraneous to this proceeding, we decline to consider it as an  
19 evidentiary matter and order that it be expunged from the record of this  
20 proceeding. Bd.R. 7(a) & 122(c)(1)(iii).

21  

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<sup>71</sup> Paper No. 460

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1 4. Storer Exhibit 1200

2 Clark next seeks exclusion of Exhibit 1200, the Second Declaration of  
3 Dr. Damha. Clark Misc. Motion 18, Paper 427 at 5. According to Clark, Dr.  
4 Damha failed to consider relevant information. Clark argues that Dr. Damha did  
5 not take into account the Storer Documents when forming his view that it would  
6 have been trivial for an artisan to make 2'-fluoro-2'-methyl nucleosides as of June  
7 28, 2002. *Id.* (citing Ex. 1244, pp. 26-40, ll. 19-15). Clark argues further that Dr.  
8 Damha testified that such evidence was not important and that there was not "any  
9 chance" that it could have affected his opinions, despite the Board having  
10 previously found it significant. *Id.* (citing Ex. 1244, pp. 31-40, ll. 15-15).

11 We have related *supra*, with respect to Storer's Exhibit 1132, why the  
12 credibility of Dr. Damha's opinion testimony is a probative question on the merits  
13 of Storer's substantive motions. The issue is one of the weight of the testimony  
14 rather than one of admissibility. We employ the same reasoning here. Clark's  
15 motion to exclude Exhibit 1200 is denied.

16  
17 5. Storer Exhibit 1201

18 Storer Exhibit 1201 is the Second Declaration of Raffaele De Francesco,  
19 Ph.D. According to Clark, Dr. De Francesco opines on an artisan's ability to  
20 perform high throughput testing of compounds for activity against hepatitis C virus  
21 ("HCV") using an HCV replicon assay during the 2000-2003 timeframe. Clark  
22 Misc. Motion 18, Paper 427 at 5 (citing Ex. 1201, ¶¶ 82, 95-101). Clark argues  
23 that Dr. De Francesco's opinions are based on unpublished techniques allegedly

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1 used in his own labs. Because the reaction conditions and experimental processes  
2 for these screening experiments were not published, argues Clark, they were not  
3 available to the artisan to utilize, test or publicly critique. Clark Misc. Motion 18,  
4 Paper 427 at 5-6 (citing Ex. 2171, ¶ 128). Therefore, contends Clark, De  
5 Francesco's testimony regarding his non-public activities within his laboratory  
6 does not provide any insight whatsoever into any issue pending in this. Motion at  
7 6.

Storer did not oppose Clark's motion to exclude Exhibit 1201. Nevertheless,  
9 we are not persuaded by Clark's arguments. As we have related *supra*, with  
10 respect to Storer's Exhibits 1132 and 1200, the credibility of Dr. De Francesco's  
11 opinion testimony is a probative question on the merits of Storer's motions. The  
12 issue is one of weight and not one of admissibility. We employ the same reasoning  
13 here. Clark's motion to exclude Exhibit 1201 is denied.

14

15 6. Storer Exhibit 1228 and 1229

16 Storer Exhibit 1228<sup>72</sup> is the transcript of the deposition of Stanley Moncrief  
17 Lemon and Storer Exhibit 1229<sup>73</sup> is the transcript of the deposition of Jeffrey Scott  
Glenn, both taken on Tuesday, July 31, 2012. Clark Misc. Motion 18, Paper 427 at  
19 7. Clark argues that both transcripts are inadmissible as hearsay under Rule 802,  
20 and under SO ¶¶ 157.1 and 157.3, because they are transcripts of depositions taken  
21 in the prior 105,871 interference. *Id.* Clark contends that if Storer wanted to rely

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<sup>72</sup> Paper No. 531

<sup>73</sup> Paper No. 532



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1 on the testimonies of Drs. Lemon and Glenn, it should have submitted a new  
2 declaration from both individuals in the present case, thereby making them subject  
3 to cross-examination in this interference. *Id.*

4 Storer points out that Clark has failed to demonstrate that Storer relies on  
5 Exhibits 1228 and 1229 to prove the truth of any statements therein. Storer Opp.  
6 18, Paper 429 at 7, 8. Storer points out that Clark has not directed the Board to any  
7 statements in either Exhibit that Storer relies on to prove the truth of an asserted  
matter. *Id.* Finally, Storer argues that that Clark was a party to the prior 105,871  
9 interference and that Clark cross-examined both deponents during their respective  
10 depositions. *Id.* (citing Exs. 1228; 1229). Moreover, contends Storer, Clark  
11 submitted the Declarations of Drs. Lemon and Glenn, which was the basis for the  
12 deposition as Exhibit 2167. *Id.* Therefore, argues Storer, Clark is not prejudiced  
13 by the introduction of Exhibits 1228 into evidence. *Id.*

14 We agree that Storer has not relied upon Exhibits 1228 and 1229 in support  
15 of any of its arguments in its substantive or contingent motions. Accordingly, we  
16 can discern no purpose for it to be included in this proceeding. We decline to  
17 consider it as an evidentiary matter and order that it be expunged from the record  
of this proceeding. Bd.R. 7(a) & 122(c)(1)(iii).

19  
20 7. Storer Exhibits 1231, 1232, and 1233

21 Storer Exhibit 1231 is the laboratory notebook by Jingyang Wang, an  
22 employee of Idenix Pharmaceuticals, Inc., one of the Storer real parties-in-interest.

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1 Clark contends that Exhibit 1231 is inadmissible under Rules 402, 403, 802, and  
2 901(a), and SO ¶¶ 152.2.2 and 157.1. Clark Misc. Motion 18, Paper 427 at 7.

3 We considered Exhibits 1232 and 1233 with respect to our conclusion that  
4 the S1 application did not enable the embodiments of a 2' fluoro "down"  
5 nucleoside within the scope of Count 1. Clark prevailed upon that issue  
6 notwithstanding the consideration of these exhibits. Exclusion of the exhibits  
7 would not influence the outcome of our review. It is therefore unnecessary for us  
8 to consider the admissibility of the exhibits.

9  
10 8. Summary

11 For the reasons set forth above, Clark's Miscellaneous Motion 18 is denied.

12  
13 III. STORER MOTIONS

14  
15 **A. Storer Substantive Motion 5**

16 Storer moves to substitute proposed Count B for Count 1 and to be accorded  
17 benefit of the S1 application. Motion at 1. All of the species encompassed by  
18 Storer's proposed Count B and disclosed in the Genus Disclosure of Storer's  
19 involved application have a fluorine atom in the 2' "down" position. See Storer  
20 Subs. Motion 5, Paper 157 at App'x 8-2 ("R<sup>7</sup> is F"; "[F is shown in the 2' "down"  
21 position of the above formula]"). We have related *supra* that the claims of Storer's  
22 involved application fail to provide an enabling disclosure for any of the  
23 embodiments of the nucleosides within the scope of its involved claims. All of

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1 those claims are characterized by a fluorine in the 2' "down" position. As a result  
2 of our determination we removed Storer's claim 1 as an alternative of the count.  
3 Storer's proposed Count B broadens the species substituents at other positions of  
4 the nucleotide but includes the fluorine in the 2' "down" position. Thus, Storer's  
5 proposed Count B is unsuitable as a vehicle for determining priority in this  
6 interference for the same reasons that Storer's Claim 1 was unsuitable. We  
7 therefore deny Storer's Substantive Motion 5.

9 **B. Storer Substantive Motion 11**

10 Storer next argues that Clark's involved claims are unpatentable under 35  
11 U.S.C. § 102(e)(2) and/or 35 U.S.C. §§ 102(e)(2)/103(a) over Storer's '600 patent.  
12 Storer Subs. Motion 11, Paper 158 at 1.—Storer does not challenge that the Clark  
13 '218 application has an effective filing date of May 30, 2003, the date Clark's '368  
14 provisional application was filed. *Id.*

15 Storer argues that its '600 patent, which it cites as prior art under 35 U.S.C.  
16 § 102(e), has an effective filing date of June 28, 2002, the filing date of its S1  
17 application, which precedes the May 30, 2003, filing date of Clark's '368  
application. Storer Subs. Motion 5, Paper 157 at 2. Therefore, argues Storer, the  
19 '600 patent is prior art to the Clark claims. *Id.*

20 We have related *supra* why Storer's involved claims are not supported  
21 by an enabling disclosure of an embodiment having a 2'-fluoro "down" nucleoside.  
22 For the same reason, the earlier S1 application fails to provide an enabling  
23 disclosure for nucleoside with the fluorine in the down position.—Storer is not

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entitled to the benefit of the June 28, 2002, filing date of the S1 application.  
Storer's '600 patent is not prior art for Clark's '638 application. We therefore  
deny Storer's Substantive Motion 11.

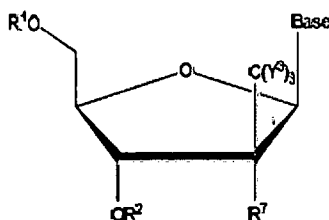
### C. Storer Contingent Responsive Motion 14

Storer Contingent Responsive Motion 14 seeks to add a new claim, claim 14  
to the interference if any of Clark Substantive Motions 7, 8, or 9 are granted.  
Storer Cont. Motion 14, Paper No. 327 at 1.

Because we have granted Clark Substantive Motion 8, we now address  
Storer Contingent Motion 14.

Storer Claim 14 recites:

14. A method for the treatment of a host infected with a hepatitis C  
virus, comprising administering to the host infected with a hepatitis C  
virus an effective amount of a compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

Base is selected from the group consisting of thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, 6-azacytosine, 2-and/or 4 mercaptopyrimidine, uracil, 5-halouracil, 5-fluorouracil, C⁵-alkylpyrimidine, C⁵-benzylpyrimidine, C⁵-halopyrimidine, C⁵-vinylpyrimidine, C⁵-acetylenic pyrimidine, C⁵-acyl pyrimidine, C⁵-

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amidopyrimidine, C<sup>5</sup>-cyanopyrimidine, C<sup>5</sup>-iodopyrimidine, C<sup>6</sup>-iodopyrimidine, C<sup>5</sup>-Br-vinyl pyrimidine, C<sup>6</sup>-Br-vinyl pyrimidine, C<sup>5</sup>-nitropyrimidine, C<sup>5</sup>-aminopyrimidine, 5-azacytidinyl, 5-azauracilyl;

R<sup>7</sup> is F;

R<sup>1</sup> is H; phosphate; monophosphate, diphosphate; triphosphate; a stabilized phosphate prodrug; acyl; lower acyl; alkyl; lower alkyl; sulfonate ester; alkyl or arylalkyl sulfonyl; methanesulfonyl; benzylsulfonyl; a lipid; a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo provides a compound wherein R<sup>1</sup> is H or phosphate;

R<sup>2</sup> is phosphate; monophosphate; diphosphate; triphosphate; a stabilized phosphate prodrug; acyl; lower acyl; alkyl; lower alkyl; sulfonate ester; alkyl or arylalkyl sulfonyl; methanesulfonyl; benzylsulfonyl; a lipid; a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo provides a compound wherein R<sup>2</sup> is H or phosphate; and wherein each Y<sup>3</sup> is H.

Motion App'x at 2-1-2. We note that all of the embodiments of Storer's proposed claim 14 possess a fluorine atom in the 2' "down" position.

Responsive motions may be filed to cure a claim defect raised on a notice of requested relief or a substantive motion. Bd.R. 41.121(a)(2). However, we have related *supra* why the S1 application fails to enable a fluorine atom in the 2' "down" position of any of the embodiments of the nucleoside species within the scope of count 1. Storer's proposed claim 14 fails to cure this defect of the Storer claims corresponding to Count 1. We therefore deny Storer's Contingent Responsive Motion 14.

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**D. Storer Contingent Miscellaneous Motion 15**

Storer Contingent Motion 15 seeks the addition to this interference of Storer US Appl. No. 14/220,534, (the "'534 application") filed March 20, 2014. Storer Cont. Motion 15, Paper 328 at 1. Storer's proposed Claim 14 is the sole claim pending in the '534 application. *Id.* The '534 application claims the benefit accorded the S1 and S4 applications. *Id.* at 2.

When Storer was authorized to file the contingent responsive motion to add Storer's new claim 14, Storer was also required to file a contingent miscellaneous motion to add the new continuation application with the new claim to the interference. *See* Order Responsive Motion Bd.R. 41.121(a)(2), Paper 326, at 3:1-3. Storer Contingent Miscellaneous Motion 15 serves that purpose. Storer Cont. Motion 15, Paper 328 at 1.

Because we have denied Storer's Contingent Responsive Motion 14 to add its new claim 14, we do not reach Storer's Contingent Motion 15 to add the '534 application to the instant interference.

**E. Storer Miscellaneous Motion 16**

Storer seeks to exclude the following Exhibits, in full or in part: Storer Exhibits 1194, 1243, 1244, and exclusion of Clark Exhibits 2088, and 2100. Storer Misc. Motion 16, Paper 425 at 1-5.

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1 1. Storer Exhibit 1194

2 Storer Exhibit 1194 is the deposition of Dr. Damha, taken on April 15, 2014.  
3 Storer argues that the questions posed by Clark's counsel at page 81, lines 9 to  
4 19 page 85, lines 14 were beyond the scope of Dr. Damha's direct testimony given  
5 in Exhibit 1132 and/or were irrelevant as to whether one of ordinary skill in the art  
6 as of June 28, 2002 would have been able to synthesize a 2'-fluoro-2'-methyl-  
7 nucleoside at issue. Storer Misc. Motion 16, Paper 427 at 1. Specifically, Storer  
8 argues that Dr. Damha did not, in his Declaration, address Idenix's post-June 28,  
9 2002 efforts to synthesize a 2'-fluoro-2'-methyl-nucleoside, which was the subject  
10 of the questions posed by Clark's counsel in the disputed pages. *Id.* at 1-2.

11 Clark responds that, first, impeachment evidence is always relevant and  
12 within the scope of permissible cross-examination. Clark Opp. 16, Paper 430 at 1  
13 (citing Fed. R. Evid. 611(b); 702).

14 Second, Clark denies that, in the disputed questions in Exhibit 1194, the  
15 questions exceeded the scope of Dr. Damha's direct testimony. Clark Opp. 16,  
16 Paper 430 at 3. Clark contends that the questions went to the bases for the  
17 opinions proffered in Exhibit 1132 and, specifically, whether those opinions took  
into account Idenix's synthesis efforts. *Id.*

19 Third, Clark points out that Storer's counsel did not object to the questions  
20 posed by Clark's counsel pp. 82, ll.11-13; 82, ll. 15-18; 82, ll. 20-21; 82, l. 23; 82,  
21 l. 25; 83, ll. 3-4; 83, ll. 6-7; and 85, ll. 10-13 of Exhibit 1194, and to which Dr.  
22 Damha at pp. 82, l. 14; 82, l. 19, 82, l. 22; 82, l. 24; 83, l. 2; 83, l. 5; 83, l. 8; and

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1 85, l. 14, respectively, responded. Clark Opp. 16, Paper 430 at 3 (citing Ex. 1194).

2 Therefore, argues Clark, these questions and answers should not be excluded. *Id.*

3 We are not persuaded by Storer's arguments. In the disputed passages of  
4 Exhibit 1132, Dr. Damha is questioned repeatedly whether, in arriving at his  
5 opinion that one of ordinary skill in the art would be aware of "a method for  
6 preparing a 2'-F-2'-methyl-ribonucleoside of the '350 Application and within the  
7 scope of Claim 38 of the Storer Patent," he had been made aware of, or considered,  
8 any of Idenix's efforts to synthesize the compound during the interval between  
9 2002 and 2005. For example, during the Dr. Damha's deposition, he responded to  
10 the questions as below:

11 Q. So you're not aware that in the prior interference Idenix put forth  
12 its story about how its chemists tried to make 2'-fluoro-2'-methyl  
13 nucleosides during the 2002 to 2005 time period?

14

15 MR. KINTON: Same objection. Beyond the scope.

16

17 A. No.

18

19 Q. So then you couldn't have considered any of Idenix's story about its  
20 attempt to make those compounds in forming your opinions?

21

A. None whatsoever.

23

24 Q. And did you consider any Idenix documents about trying to make  
25 2'-fluoro-2'-methyl nucleosides when you formed your opinion?

26

27 A. No.

28

29 Q. Did you consider any Idenix lab notebooks when forming your  
30 opinion?



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1  
2 A. On how to make these compounds, no.  
3  
4 Q. What about Idenix's meeting minutes?  
5  
6 A. No.  
7  
8 ...  
9  
10 Q. Did you ever ask to see such information when forming your  
11 opinions?  
  
13 A. No.  
14  
15 Q. Why not?  
16  
17 MR. KINTON: Objection. Irrelevant.  
18  
19 Ex. 1194, p. 82, ll. 3-24; p. 83, ll. 6-10. These, and the other disputed passages, all  
20 inquire whether Dr. Damha had reviewed, or had knowledge of, any documents  
21 concerning Idenix's research efforts between 2002 and 2005. Dr. Damha  
22 responded in the negative to this entire line of questioning:  
23 Q. Do you think what Idenix actually tried in terms of attempting to  
24 make a 2'-fluoro-2'-methyl nucleoside might be important when  
forming your opinion?  
26  
27 MR. KINTON: Objection. Irrelevant. Assumes facts.  
28  
29 A. No, not at all. I formed my opinion on literature and knowledge  
30 that I have gained as a nucleoside nucleic acid chemist. And in fact,  
31 having used procedures that are directly applied to the synthesis of the  
32 2'-methyl-2'-fluoro compounds.  
33

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1 Ex. 1194, pp. 84-85, ll. 22-9. Thus, this line of questioning by Clark inquires as to  
2 the materials that formed the basis for Dr. Damha's opinion expressed in his  
3 Declaration. As such, it is neither beyond the scope of Dr. Damha's declaration,  
4 nor is it irrelevant. Moreover, Clark is entitled to attempt to impeach the  
5 credibility of Storer's expert on cross-examination. FRE 611(b). Storer's motion  
6 to exclude the cited passages of Storer's Exhibit 1194 is consequently denied.

7  
8 2. Storer Exhibit 1243

9 Storer Exhibit 1243<sup>74</sup> is the transcript of the deposition of Dr. De Francesco.  
10 Storer moves to exclude certain passages in the Exhibit, viz., page 81, lines 12-13  
11 and 21-22 and page 82, lines 6-8 as exceeding the scope of Dr. De Francesco's  
12 direct testimony in his Declaration (Ex 1201). Storer Misc. Motion 16, Paper 427  
13 at 3. According to Storer, Dr. De Francesco did not address in his declaration the  
14 disclosure in Exhibit 1003 of the bases for particular compounds, including  
15 Formula (IV), which was the subject of the questions posed by Clark's counsel.

16 Clark responds that, first, Dr. De Francesco's testimony in the contested  
17 passages is admissible because Clark's counsel's questions were within the scope  
of Dr. De Francesco's direct testimony in his Declaration or, alternatively, went to  
19 a matter affecting Dr. De Francesco's credibility. Clark Opp. 16, Paper 430 at 4  
20 (citing FRE 611(b), 702).

21 We are not persuaded by Storer's arguments. In his Declaration, Dr. De  
22 Francesco opined:

---

<sup>74</sup> Paper No. 544

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1 The '350 and '907 applications state that the compounds of the  
2 invention exhibit antiviral activity against *Flaviviridae* viruses such as  
3 HCV, and can be used to treat infections by those viruses. Ex 1003, at  
4 44:3-4, 57:15-19; Ex 1002, at 46:3-4, 58:4-9. As of June 28, 2002 and  
5 June 27, 2003, persons skilled in the art would have believed that the  
6 Relevant Compounds could have anti-HCV activity because: (i) the  
7 Relevant Compounds are nucleoside analogs, and it was known at the  
8 time that certain nucleoside analogs exhibit antiviral activity due to  
9 interference with viral polymerases required for replication of viral  
10 genetic material (referred to herein as "genome replication"), as  
11 described in ¶¶39-40;

13 (ii) it had been shown experimentally at the time that certain 2'-  
14 modified nucleosides exhibit anti-*Flaviviridae* activity, in particular  
15 against BVDV and YFV, as described in ¶¶41-46;

16  
17 (iii) persons skilled in the art would have believed that nucleoside  
18 analogs that exhibit activity against BVDV are likely to also exhibit  
19 activity against HCV, and that nucleoside analogs that exhibit activity  
20 against BVDV and YFV are highly likely to also exhibit activity  
21 against HCV, as described in ¶¶47-67;

22  
23 (iv) as of June 27, 2003, it had been experimentally shown that certain  
24 2'- modified nucleosides exhibit anti-HCV activity, as described in  
25 ¶¶68-70; and

26  
27 (v) there were no specific reasons to doubt anti-HCV activity of the  
28 Relevant Compounds, as described in ¶71.

29  
30 Ex. 1201, ¶ 21. In the contested passages of Exhibit 1243, Dr. De Francesco  
31 states:

32 Q. Would you turn back to page 57 of the '350 application, which is  
33 Exhibit 1003?

34 ...

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1 A. Uh-huh.

2  
3 Q. And could you identify for me what the base is for that formula?

4  
5 MR. FRIEBEL: Objection, beyond the scope of his declaration.

6 ...  
7 A. (Perusing.) No. Sorry. This is — I think this is beyond my — it  
8 would require a better understanding of chemistry than I have.

9  
10 Q. So you have no idea what the base would be?

11  
12 MR. FRIEBEL: Same objection.

13  
14 A. (Perusing.) I didn't review these as part of my opinion because I  
15 don't think this was requested to me. Tentatively, I would say it's one  
16 of the group — must be one of the group of bases described in the  
17 previous pages, I guess.

18  
19 Q. So we were talking about the compounds at pages 1551 previously.  
20 Would that be previous pages?

21  
22 MR. FRIEBEL: Same objection, beyond the scope of his original —  
23 of his second declaration.

24  
25 A. (Perusing.) Yeah, I believe herein means one of the bases described  
26 in pages 48, 49 to 54, but I'm not sure. I mean, again, I'm not a  
chemist, so I don't — it's a tentative answer.

27  
28  
29 Ex. 1243, pp. 81-82, ll. 7-16.

30 Determining the scope of cross-examination is within the sound discretion of  
31 the administrative tribunal. *See, e.g., Guise v. Dep't of Justice*, 330 F.3d 1376,  
32 1379 (Fed. Cir. 2003). Dr. De Francesco has explicitly declared that he has studied  
33 Storer Exhibit 1003, the '350 application, as part of the preparation for giving his

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1 expert opinion. Ex. 1243, ¶ 10. Because Dr. De Francesco places no limiting  
2 language on this statement in his Declaration, we assume that he has reviewed the  
3 entire document and that questions concerning the contents of the document on  
4 cross-examination are not beyond the scope of his Declaration. Therefore, the  
5 contents of the '350 application are within the scope of his Declaration. The line  
6 of questioning in the disputed passages goes to the basis for the formation of that  
7 opinion, although his statements ("it would require a better understanding of  
8 chemistry than I have") may undermine his credibility as an expert witness with  
9 respect to the chemistry of nucleoside bases. Nevertheless, the credibility of a  
10 witness' opinion, and the probative weight we consequently ascribe to that  
11 testimony, is a substantive issue and not one of admissibility. We consequently  
12 deny Storer's motion to exclude the contested passages of Exhibit 1243.

13  
14 3. Storer Exhibit 1244

15 Storer Exhibit 1244<sup>75</sup> is the Second Deposition of Dr. Damha, taken on June  
16 20, 2014. Storer moves to exclude certain passages in the Exhibit, viz., page 26,  
17 line 19 to page 29, line 25; page 33, line 11 to page 36, line 2; and page 36, line 18  
to page 40, line 15 as exceeding the scope of Dr. Damha's direct testimony in his  
19 Declaration (Ex. 1200). Storer Misc. Motion 16, Paper 427 at 4. Specifically,  
20 Clark contends that Dr. Damha did not address, in his Declaration, Idenix's post-  
21 June 28, 2002 effort in synthesizing a 2'-fluoro-2'-methyl nucleoside, the subject  
22 of the questions posed by Clark's counsel in the contested passages. *Id.*

---

<sup>75</sup> Paper No. 545

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1 In response, Clark repeats the argument that it made with respect to Ex. 1195  
2 *supra*: that the testimony that Storer seeks to exclude is relevant to determining  
3 whether Dr. Damha's direct testimony in Exhibit 1200 should be given any weight,  
4 and whether it is relevant to assessing Dr. Damha's credibility, particularly with  
5 regard to Dr. Damha's opinions about whether an artisan could have made 2'-  
6 fluoro-2'-methyl nucleosides without undue experimentation. Clark Opp. 16,  
7 Paper 430 at 5. Clark also contends that Dr. Damha's alleged failure to consider  
8 Idenix's extended efforts to synthesize the compounds affects his credibility as an  
9 expert witness. *Id.*

10 We agree with Clark. As we related *supra*, the lines of questioning objected  
11 to by Storer inquire as to the materials that formed the basis for Dr. Damha's  
12 opinion, as expressed in his Declaration and the extent of Dr. Damha's knowledge  
13 of Idenix's efforts at synthesis of 2'-fluoro-2'-methyl nucleosides. Moreover,  
14 Clark is entitled to attempt to impeach the credibility of Storer's expert in cross-  
15 examination. FRE 611(b). As such, it is neither beyond the scope of Dr. Damha's  
16 declaration, nor is it irrelevant. Storer's motion to exclude the cited passages of  
17 Storer's Exhibit 1194 is denied.

19 4. Clark Exhibit 2088

20 Clark Exhibit 2088<sup>76</sup> is the Declaration and curriculum vitae of Dr. Jean-  
21 Pierre Sommadossi, one of the inventors of Storer's '600 patent. Storer Misc.  
22 Motion 16, Paper 427 at 5. Storer argues that although Exhibit 2088 refers to

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<sup>76</sup> Paper No. 568

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Exhibit 1 (a copy of Tables 4 and 5 from Chapter Two of B.N. Fields et al., *Fields Virology*, Lippincott-Raven, Philadelphia (3rd ed. 1996)) at 3, ¶ 11.), Exhibit 2088 does not in fact contain an Exhibit 1. *Id.* Therefore, argues Storer, Exhibit 2088 is incomplete and should be excluded under Federal Rule of Evidence 106. *Id.*

Storer also argues that Clark relies on Exhibit 2088, and particularly ¶ 15, to prove that one cannot predict a compound's activity against another virus without testing it. Storer Misc. Motion 16, Paper 427 at 5 (citing Clark Substantive Motion 8<sup>77</sup>, at 11, ll. 13-14). Consequently, argues Storer, Clark Exhibit 2088 is an out-of-court statement made by a declarant who has not testified in this proceeding and the statement is offered to prove its truth. *Id.* Therefore, Storer contends, Exhibit 2088 is also inadmissible as impermissible hearsay. *Id.* (citing FRE 802).

As an initial matter, Federal Rule 106 is not an exclusionary rule. Federal Rule 106 states: "If a party introduces all or part of a writing or recorded statement, an adverse party may require the introduction, at that time, of any other part--or any other writing or recorded statement--that in fairness ought to be considered at the same time." Fed. R. Evid. 106. Storer has not requested completion of the record, and we therefore consider any such request waived.

##### 5. Clark Exhibit 2100

Clark Exhibit 2100<sup>78</sup> is a document of the European Patent Office ("EPO"), purportedly reporting of a consultation by the EPO with applicant/representative

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<sup>77</sup> Paper No. 155

<sup>78</sup> Paper No. 576

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1 Idenix Pharmaceuticals, Inc., the real party-in-interest in the instant interference,  
2 with respect to EPO Application No. 03 761 744.6.

3 Storer argues that Clark relies on Exhibit 2100 to prove that Exhibit 1002's<sup>79</sup>  
4 Formula (IX) does not provide for R<sup>1</sup> to be di- or triphosphate and thus does not  
5 describe certain Storer claims. Storer Misc. Motion 16, Paper 427 at 5-6. As such,  
6 contends Storer, Exhibit 2100 constitutes impermissible hearsay and should be  
7 excluded. *Id.* at 6.

8 We do not see the relationship of Exhibit 2100 to the dispositive issue  
9 with respect to Storer's involved claims, viz., the enablement of a 2'-fluoro "down"  
10 -nucleoside. Accordingly, we can discern no purpose for it to be included in this  
11 proceeding. We decline to consider it as an evidentiary matter and order that it be  
12 expunged from the record. Bd.R. 7(a) & 122(c)(1)(iii).

13  
14 6. Summary

15 For the reasons set forth above, Storer's Miscellaneous Motion 16 is denied.  
16

17 IV. CONCLUSION

18 For the reasons set forth above:

- 19 1. Clark Substantive Motion 1 to deprive Storer of the benefit of its US  
20 Appl. No. 60/392,350 is GRANTED.  
21

---

<sup>79</sup> Papers Nos. 319-322



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- 1       2. Clark Substantive Motion 2 to deprive Storer of the benefit accorded  
2       with respect to Count 1 of its U.S. Appl. No. 60/466,194 is  
3       GRANTED.  
4
- 5       3. Clark Substantive Motion 3 to deprive Storer of the benefit accorded  
6       with respect to Count 1 of its U.S. Appl. No. 60/470,949 is  
7       GRANTED.  
8
- 9       4. Clark Substantive Motion 10 to deprive Storer of the benefit accorded  
10      with respect to Count 1 of US Appl. No. 10/608,907 is DISMISSED.  
11
- 12      5. Clark Substantive Motion 7 for judgment against Storer's US Patent  
13      No. 7,608,600 B2 on the grounds of unpatentability under 35 U.S.C. §  
14      112, 1st paragraph for lack of enablement and written description is  
15      GRANTED.  
16
- 17      6. Clark Substantive Motion 5 to substitute its proposed alternate count 2  
18      for the present Count 1 of the interference is DISMISSED.  
19
- 20      7. Clark Substantive Motion 8 for judgment against Storer's US Patent  
21      No. 7,608,600 B2 on the ground of unpatentability under 35 U.S.C. §  
22      101, for lack of utility, and accordingly under 35 U.S.C. § 112, 1st  
23      paragraph, for lack of enablement is DISMISSED.  
24
- 25      8. Clark Substantive Motion 9 for judgment against Storer's US Patent  
26      No. 7,608,600 B2 on the ground of unpatentability under 35 U.S.C.  
27      §§ 102(e) or 103 as being either anticipated by, or obvious over,  
28      Clark's US Appl. No. 10/828,753 is DISMISSED.  
29
- 30      9. Clark Miscellaneous Motion 18 to exclude evidence is DENIED. We  
31      sua sponte order that Storer Exhibits 1175, 1176, 1177, 1228, and  
32      1229 be expunged.  
33
- 34      10. Storer Substantive Motion 5 to substitute proposed count B for Count  
35      1 is DENIED.

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- 1  
2 11. Storer Substantive Motion 11 for judgment against Clark on the  
3 grounds of unpatentability of all of Clark's involved claims as  
4 anticipated under 35 U.S.C. § 102(e) and/or 103 is DENIED.  
5  
6 12. Storer Contingent Motion 14 to add a new claim is DENIED.  
7  
8 13. Storer Contingent Motion 15 to add an application to the interference  
9 is DISMISSED.  
10  
11 14. Storer Miscellaneous Motion 16 to exclude evidence is DENIED.  
12 We *sua sponte* order that Clark Exhibit 2100 be expunged.  
13  
14 15. Party Clark shall be designated Senior Party for any further  
15 proceedings according to the Redecoration issued herewith.  
16

17 IT IS SO ORDERED

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Clark v. Storer

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**Exhibit-D**

**176**

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571-272-4683

Filed: March 23, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

RICHARD STORER, GILLES GOSSELIN, JEAN-PIERRE SOMADOSSI,  
and PAOLA LACOLLA  
Junior Party  
(US 7,608,600 B2)

v.

JEREMY CLARK  
Senior Party  
(Application No. 11/854,218)

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Interference No. 105,981 (JGN)  
Technology Center 1600

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**JUDGMENT - REQUEST FOR ADVERSE  
Bd.R. 127(b)(4)**

*Before* RICHARD SCHAFER, DEBORAH KATZ, and  
JOHN G. NEW, *Administrative Patent Judges*.

NEW, Administrative Patent Judge

## I.

On January 16, 2015, a merits panel of the Board entered a decision on then-Senior Party Richard Storer, Gilles Gosselin, Jean-Pierre Sommadossi, and Paola LaColla's ("Storer") and then-Junior Party Jeremy Clark's ("Clark") substantive motions.<sup>1</sup> Paper No. 687. The panel concluded, *inter alia*, that Storer's US Appl. No. 60/392,350 (the "'350 application"), for which Storer had been accorded priority benefit, failed to enable any of the 2'-fluoro-2'-C-methyl nucleosides that are required by the count. *Id.* at 35-36. The panel consequently granted Clark's motion 1 to deprive Storer of the benefit accorded with respect to Count 1 of the '350 application. *Id.*

As a result, the interference was redeclared with Storer as the Junior Party, Clark as the Senior Party, and with Clark's involved claims 164 and 165 and Storer's involved claims 1-12, 17, 18, 20, 33, 34, 36, 38, 49-57, 62, 64, and 76-85 corresponding to the new Count 2. Paper No. 688. A scheduling order for the priority phase was also entered on January 16, 2015. Paper No. 689. Storer's priority motion was due on February 27, 2015. Paper 689, Appendix. Rather than filing its priority motion, Storer contacted the Board via email to indicate that it did not intend to file a priority motion. See Paper No. 692.

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<sup>1</sup> On January 16, 2015, the Board also entered an order for Storer to show cause why, in view of the Board's decision on the parties' substantive motions, judgment should not be entered against it. Paper 690. Storer timely responded. Paper No. 691. Although the panel finds Storer's response to the order to show cause to be insufficient, Storer's response to the order to show cause played no role in the entry of this judgment.

## II.

As Senior Party, Clark is entitled to the presumption under Bd.R. 207(a)(1) that it is the prior inventor. *See also* Bd.R. 201, definition of senior party. As the Junior Party, Storer therefore bears the burden of establishing a date of inventorship prior to Clark's accorded benefit date of May 30, 2003. *See* Bd. Rs. 121(b) and 208(b). By declining to file a priority motion and forgoing the opportunity to prove an earlier date of invention, Storer has effectively abandoned the contest. Storer's abandonment of the contest is construed as a request for adverse judgment. *See* Bd.R. 127(b)(4).

It is therefore—

ORDERED that judgment on priority be entered against Junior Party Storer for the subject matter of count 2;

FURTHER ORDERED that claims 1-12, 17, 18, 20, 33, 34, 36, 38, 49-57, 62, 64, and 76-85 of Storer's involved U.S. Patent No. US 7,608,600 B2 be CANCELED, 35 U.S.C. 135(a)<sup>2</sup>; and

FURTHER ORDERED that a copy of this judgment be entered in the administrative records of Storer's involved US 7,608,600 B2 patent and Clark's involved US Appl. No. 11/854,218.

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<sup>2</sup> As was in effect on March 15, 2013. *See* Pub. L. 112-29, § 3(n), 125 Stat. 284, 293 (2011).

1 FURTHER ORDERED that if a party seeks judicial review, the party  
2 must file a notice with the Board (37 C.F.R. § 41.8(b)) within seven days of  
3 initiating judicial review.

4  
5 We also direct the parties' attention to *Biogen Idec MA, Inc., v.*  
6 *Japanese Foundation for Cancer Research*, Civil No. 13-13061-FDS, 2014  
7 WL 2167677 (D. Mass. May 22, 2014).

8

NOTICE: "Any agreement or understanding between parties to an interference, including any collateral agreements referred to therein, made in connection with or in contemplation of the termination of the interference, shall be in writing and a true copy thereof filed in the Patent and Trademark Office before the termination of the interference as between the said parties to the agreement or understanding." 35 U.S.C. 135(c); see also Bd.R. 205 (settlement agreements).

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**Exhibit-E**

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Paper 426  
Entered: March 22, 2013

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UNITED STATES PATENT AND TRADEMARK OFFICE  
PATENT TRIAL AND APPEAL BOARD

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Patent Interference 105,871 (RPG)  
Technology Center 1600

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**JEREMY CLARK,**

Patent 7,429,572,  
Junior Party,

v.

**JEAN-PIERRE SOMMADOSSI, PAOLO LACOLLA, RICHARD STORER, and  
GILLES GOSSELIN,**

Application 12/131,868,  
Senior Party

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Before: SALLY G. LANE, RAE LYNN P. GUEST, and DEBORAH KATZ,  
*Administrative Patent Judges.*

GUEST, *Administrative Patent Judge.*

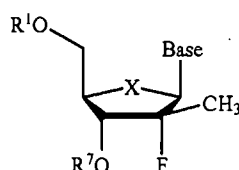
**DECISION ON MOTIONS**

### Introduction

The interference is before a merits panel for a decision on non-priority motions.

The interference involves a Clark patent and a Sommadossi patent application. Paper 1.

The subject matter of the interference is generally related to a class of 2'-methyl, 2'-fluoro nucleosides with a uracil or cytosine base. Count 1 (Paper 1, p. 8) reads: A compound of the formula:



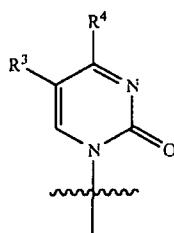
or a pharmaceutically acceptable salt thereof, wherein:

X is O;

R<sup>1</sup> is H, a monophosphate, a diphosphate, a triphosphate, an alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl;

R<sup>7</sup> is H, a monophosphate, a diphosphate, a triphosphate, an alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl; and

Base is a pyrimidine represented by the following formula:



wherein,

R<sup>3</sup> is H; and

R<sup>4</sup> is NH<sub>2</sub> or OH.

**Real parties in interest**

The real party in interest for Clark is Gilead Pharmasset LLC. Paper 8.

The real parties in interest for Sommadossi are Idenix Pharmaceuticals, Inc., Centre National De La Recherche Scientifique, L'Universite Montpellier II, and Universita degli studi di Cagliari. Paper 5.

**Motions before the panel**

Clark has filed 5 motions. Sommadossi has filed a total of 5 motions, but withdrew Sommadossi Substantive Motion 5. Paper 39. The following motions of Clark are before the Board:

- Clark Substantive Motion 1 for benefit to Clark's Provisional Application 60/474,368 (Clark's C1 Application);
- Clark Substantive Motion 2 to deny Sommadossi's accorded benefit to Sommadossi US Application 10/608,907 (Sommadosi's S4 Application);
- Clark Substantive Motion 3 for judgment by repose under 35 U.S.C. § 135(b)(1) and 135(b)(2);
- Clark Substantive Motion 6 for judgment based on unpatentability of Sommadossi's involved claims under 35 U.S.C. §§ 101 and 112, first paragraph; and
- Clark Miscellaneous Motion 7 to exclude evidence.

The following motions of Sommadossi are before the Board:

- Sommadossi Substantive Motion 1 for benefit to Sommadossi's Provisional Application 60/392,350 (Sommadosi's S1 Application);
- Sommadossi Responsive Motion 6 to substitute proposed Counts C or D for Count 1;

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- Sommadossi Miscellaneous Motion 7 to amend the specification of the involved application to clarify a cross-reference to Sommadossi US Application 10/608,907 (Sommadosi's S4 Application); and
- Sommadossi Miscellaneous Motion 8 to exclude evidence.

Pursuant to 37 C.F.R. § 41.125(a) (2007), we exercise discretion to consider the motions in the order discussed below. *See also Berman v. Housey*, 291 F.3d 1345, 1351 (Fed. Cir. 2002).

### **I. Clark Substantive Motion 3**

#### **Sommadosi's involved claims are barred under 35 U.S.C. § 135(b)**

Clark Substantive Motion 3 (Paper 34) seeks judgment that Sommadossi's involved claims are barred by repose under 35 U.S.C. § 135(b)(1) over Clark's involved patent or, alternatively, under 35 U.S.C. § 135(b)(2) over Clark's US application publication 2005/0009737 A1.

Sommadosi has opposed. Paper 70.

Clark has replied. Paper 83.

This motion is a threshold motion, in that if the motion is granted as to all of Sommadossi's involved claims then Sommadossi would lack standing to continue in the interference. Bd. R. 201.

As the moving party, Clark has the burden to show that it is entitled to the relief requested. Bd. R. 208(b).

#### *A. Repose under 35 U.S.C. § 135(b)(1)*

##### Findings of fact

Clark's involved patent, US 7,429,572 (hereinafter the '572 patent), issued on 30 September 2008. Ex. 2009. Thus, the "critical date," under 35 U.S.C. §135(b)(1), by which Sommadossi must have filed claims to the same or substantially the same subject matter as claimed in the '572 patent is 30 September 2009.

1 Sommadossi's involved claims are claims 44, 45, 48, 52, 53, 57, 58, 63, 64,  
2 72, 78, 80, 91, 92, 95, 96, 99, 100, 103, 104, 131, 133-138, and 151-154 of US.  
3 Application 12/131,868 (hereinafter the "868 application" or "S5"). Paper 1.

4 Clark argues that all of Sommadossi's involved claims are barred under 35  
5 U.S.C. § 135(b)(1). Paper 34, 1:2-9.

6 Claims 44-130 were filed in a preliminary amendment with the application  
7 on 2 June 2008. Claims 44 and 45 were the sole independent claims. Claims 44  
8 and 45 are directed to a compound having a general formula with various certain  
9 constituents. Of relevance for deciding this motion, claims 44 and 45 each  
10 included a limitation that "R<sup>7</sup> is halo, F, Cl, Br or I." Claims 59 and 60, which  
11 depended from claims 44 and 45, were also presented in the preliminary  
12 amendment and limited R<sup>7</sup> to F. Ex. 2018.

13 In response to a restriction requirement, some claims were cancelled and  
14 claims 131-150 were added on 14 December 2011. Claim 131 was the sole  
15 independent claim added and included a limitation that R<sup>7</sup> is halo, F, Cl, Br or I.  
16 Claim 132 was presented, which depended from claim 131, and limited R<sup>7</sup> to F.  
17 Ex. 2020.

18 An office action dated 3 March 2011 rejected all the pending claims under  
19 35 U.S.C. § 112, second paragraph as being indefinite on two basis. Regarding the  
20 first basis, the Examiner stated that "[t]he claims should not define the variables  
21 [R<sup>1</sup> and R<sup>2</sup>] as that which is [optionally] 'capable of' providing the groups, but  
22 which do provide the groups." Accordingly, the Examiner suggested more  
23 favorable language. The second basis is that the variable R<sup>7</sup> uses the term "halo"  
24 or alternatively specific halogens, namely "F, Cl, Br or I." Ex. 2021, p. 3.

25 Claims 44, 45 and 131 were amended on 27 May 2011 to delete "halo" from  
26 the R<sup>7</sup> options and to amend the language of variables R<sup>1</sup> and R<sup>2</sup> from including a  
27 "pharmaceutically acceptable leaving group which when administered *in vivo* is

1 capable of providing a compound wherein [R<sup>1</sup> or R<sup>2</sup>, respectively] is H or  
2 phosphate” to the language that the Examiner suggested was more favorable, i.e. a  
3 “pharmaceutically acceptable leaving group which when administered *in vivo*  
4 provides a compound wherein [R<sup>1</sup> or R<sup>2</sup>, respectively] is H or phosphate.” Ex.  
5 2022 (underlining added to emphasize the amended language); Ex. 2021, p. 3.

6 After a second office action dated 16 August 2011 based on prior art  
7 rejections, an amendment was filed 20 September 2011. In the amendment, claims  
8 44, 45 and 131 were amended to limit R<sup>7</sup> to F, claims 59, 60 and 132 were  
9 cancelled, and claims 151-154 were added. Claim 153 is independent. Ex. 2024.

10 In the amendment, Sommadossi states that the rejection under 35 U.S.C. §  
11 102(e) “is moot in view of the above amendments to the claims, in which R<sup>7</sup> has  
12 been amended to recite ‘F’ in each of the independent claims (claims 44, 45 and  
13 131).” Ex. 2024 at 12.

14 The claims of the 20 September 2011 amendment are Sommadossi’s  
15 involved claims.

16 The claims of the 2 June 2008 preliminary amendment were filed before the  
17 critical date.

18 The claims of the 14 December 2011 amendment, 27 May 2011 amendment,  
19 and 20 September 2011 amendment were all filed after the critical date.

#### Analysis

21 35 U.S.C. § 135(b)(1) reads as follows:

22 (1) A claim which is the same as, or for the same or  
23 substantially the same subject matter as, a claim of an issued patent  
24 may not be made in any application unless such a claim is made prior  
25 to one year from the date on which the patent was granted.

26 This statute acts to bar a party from claiming patented subject matter more  
27 than one year from the issuance of a patent.

1 A claim to the same or substantially the same subject matter as a claim of an  
2 issued patent is barred by §135(b)(1) unless timely presented. Thus, 135(b)(1) acts  
3 as a statue of repose placing a time limit on a patentee's exposure to an  
4 interference proceeding. *Regents of Univ. of Calif. v. Univ. of Iowa Res. Found.*,  
5 455 F.3d 1371, 1376 (Fed. Cir. 2006). A claim to the same or substantially the  
6 same subject matter filed after one year from the date on which the patent was  
7 issued, the "critical date," is barred unless the "later filed claim does not differ  
8 from an earlier [pre-critical date] claim in any 'material limitation,'" *In re Berger*,  
9 279 F.3d 975, 981-82 (Fed. Cir. 2002) (quoting *Corbett v. Chisholm*, 568 F.2d 759,  
765-66 (CCPA 1977)). What is to be considered is whether "all material  
11 limitations of the copied claim necessarily occur in the prior claims" or, in other  
12 words, whether "all material limitations of the copied claim are present in, or  
13 necessarily result from, the limitations of the prior claims." *Berger*, 279 F.3d at  
14 982 (claims are missing a particularly recited limitation of the copied claim); *see*  
15 *also Corbett*, 568 F.2d at 766 (earlier claims missing particular squeezing step).

16 We agree with Clark (Paper 34, 2:3-9) that "[w]hen an applicant adds  
17 limitations in response to an examiner's rejection, and those limitations result in  
18 allowance, there exists a well established presumption that those limitations are  
19 necessary to patentability and thus material" *Adair v. Carter*, 668 F.3d 1334, 1339  
(Fed. Cir. 2012) (citing *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*,  
21 535 U.S. 722, 734 (2002); *Corbett*, 568 F.2d at 765; *Parks v. Fine*, 773 F.2d 1577,  
22 1579 (Fed. Cir. 1985) ("The insertion of this limitation to overcome the examiner's  
23 rejection is strong, if not conclusive, evidence of materiality.")). *See also Berger*,  
24 279 F.3d at 982 (holding that a limitation added during prosecution to avoid the  
25 prior art is a "material limitation"). However, this presumption may be rebutted  
26 with explanation and supporting evidence that the limitation is not a material one.

27 It is with this understanding that we address Sommadossi's involved claims.

1 understood the claim to have the same meaning, i.e., reciting the same leaving  
2 groups, before and after the amendment. Paper 70, 5:18-24 (citing *Raz v. Davis*,  
3 2011 WL 4568986, \*9 (BPAI 2011)). Sommadossi reasons that the *in vivo*  
4 conditions of the claim are not specified, such that any leaving groups “capable of  
5 providing” a compound, necessarily “provide” the compound when the *in vivo*  
6 conditions to do so are met. *Id.*, 6:7-17. Sommadossi notes that the current claim  
7 does not require the leaving group “provides” the compound under all *in vivo*  
8 conditions, but that the language means “it provides under at least one set of *in*  
9 *vivo* conditions. *Id.*, 7:5-13. Sommadossi directs us to the identical testimony of  
Drs. Trost and Damha to support this contention. *Id.*, 6:7-17.

11 Clark responds that the “two expressions have manifestly different  
12 meanings” in that “while something that ‘provides’ necessarily is ‘capable of  
13 providing,’ the converse is not true.” Paper 83, 2:20-21. Clark argues that  
14 “capable of providing” means under at least one *in vivo* condition, while  
15 “provides” means under any, i.e. all or every, *in vivo* condition. *Id.*, 2:15-20.  
16 Clark cites to no evidence to support its interpretation of the claim language. *Id.*,  
17 2:9-23.

18 We find Sommadossi’s position that the amended language of the  $R^1$  and  $R^2$   
19 variable has the same meaning in the context of the claims to be persuasive. We  
note that the Examiner’s phrasing of the rejection supports this position. The  
21 Examiner stated that “[t]he claims should not define the variables [ $R^1$  and  $R^2$ ] as  
22 that which is [optionally] ‘capable of’ providing the groups, but which do provide  
23 the groups.” Ex. 2021, p. 3. We take this comment by the Examiner to suggest  
24 that the change in language as proposed by the Examiner did not alter the meaning  
25 of the claim itself but rather put the language into a more acceptable and definite  
26 form. In other words, Sommadossi has sufficiently rebutted Clark’s argument that  
27 the  $R^1$  and  $R^2$  option of “a leaving group which when administered *in vivo* provides



1            *Claims 44 and 45*

2            Here, current claims 44 and 45 were amended in the current S5 application  
3            in only two ways. The first we do not consider an additional limitation at all.  
4            Claims 44 and 45 originally stated “wherein R<sup>7</sup> is halo, F, Cl, Br or I.” At the same  
5            time, claims 59 and 60, which directly depended from claims 44 and 45,  
6            respectively, recited “wherein R<sup>7</sup> is F.” Thus, the amendment of claims 44 and 45  
7            changing “wherein R<sup>7</sup> is halo, F, Cl, Br or I” to read “wherein R<sup>7</sup> is F” and the  
8            concurrent deletion of claims 59 and 60 is no more than the rewriting of claims 59  
9            and 60 in independent form as claims 44 and 45. Thus, the subject matter of  
10           original claims 59 and 60, i.e., “wherein R<sup>7</sup> is F,” clearly demonstrates that a ‘2-  
11           fluoro-sugar constituent of the formula of claims 44 and 45, respectively, was  
12           initially claimed subject matter of the S5 application.

13           The second change in claims 44 and 45 is the change of variables R<sup>1</sup> and R<sup>2</sup>  
14           from optionally constituting “a leaving group which when administered *in vivo* is  
15           capable of providing a compound wherein R<sup>1</sup> and R<sup>2</sup> is H or phosphate” to  
16           optionally constituting “a leaving group which when administered *in vivo* provides  
17           a compound wherein R<sup>1</sup> and R<sup>2</sup> is H or phosphate” (underlining added to show  
18           amended language). This change was indisputably made in response to a 35  
19           U.S.C. § 112, second paragraph rejection based on indefiniteness.

20           Clark argues that the change is presumptively a “material limitation” within  
21           the meaning of *Corbett* and *Berger*. Paper 34, 9:5-10 and 18-22. Under the  
22           reasoning in *Adair*, we agree with Clark that there is a rebuttable presumption that  
23           the change in language is a material one. Thus, the issue before us is whether the  
24           differences in language between the pre- and post-critical date claims are material  
25           differences.

26           Sommadossi contends that the change does not render the current claim  
27           language to be a “material limitation” because the skilled artisan would have

1 a compound wherein R<sup>1</sup> and R<sup>2</sup> is H or phosphate” is a “material limitation”  
2 missing from the earlier claim.

3 Thus, we determine that Sommadossi may rely upon original claims 44 and  
4 45 for purposes of avoiding the bar of 35 USC 135(b), and Clark Substantive  
5 Motion 3 is denied at least with respect to claims 44 and 45 under 35 U.S.C. §  
6 135(b)(1). Because at least involved claims 44 and 45 of Sommadossi are not  
7 barred, the remainder of the arguments under 35 U.S.C. § 135(b)(1) do not present  
8 a threshold issue that might deprive Sommadossi of standing in the interference.  
9 Bd. R. 201.

*B. Repose under 35 U.S.C. § 135(b)(2)*

Findings of fact

11 Clark also argues that all the involved claims are barred by 35 U.S.C. §  
12 135(b)(2).  
13

14 Clark’s involved patent, US 7,429,572 (hereinafter “‘572 patent”), issued  
15 from US application 10/828,753 (hereinafter “‘753 application”). Ex. 2009. The  
16 ‘753 application published on 13 January 2005 as US Publication 2005/0009737  
17 A1 (hereinafter “‘737 publication”). Ex. 2008. The “critical date,” under 35 U.S.C.  
18 §135(b)(2), by which Sommadossi must have filed claims to the same or  
19 substantially the same subject matter as claimed in the ‘753 application publication  
is 13 January 2006.

21 Clark relies upon claims 10 and 25 of the ‘737 application as being the same  
22 or substantially the same subject matter as Sommadossi’s involved claims. Paper  
23 30, 18:20-19:5.

24 Published claim 10 and published claim 25 are independent claims that  
25 recite the identical compound “or its pharmaceutically acceptable salt or prodrug,”  
26 but published claim 25 was directed to “a pharmaceutical composition” comprising

1 the compound, or salt or prodrug thereof, in "a pharmaceutically acceptable  
2 carrier." Ex. 2008 at 37-38 and 42-43.

3 On January 4, 2007, Clark replaced published claim 25 with an entirely new  
4 claim reciting "[a] pharmaceutical composition comprising the nucleoside of claim  
5 10 or its pharmaceutically acceptable salt or prodrug and a pharmaceutically  
6 acceptable carrier." Ex. 1170, at 25-26. Accordingly, this amendment did not  
7 change the scope for published claim 25.

8 In an Office Action dated March 30, 2007, independent claims 10 and, now  
9 dependent, claim 25 of the '753 application were rejected under 35 U.S.C. § 112,  
first paragraph on the basis that the Specification was not enabled for "making  
11 prodrugs of the claimed compounds" and under 35 U.S.C. § 112, second paragraph  
12 on the basis that certain parenthetical phrases and the phrase "optionally  
13 substituted" were indefinite. Ex. 1172, at 6 and 9.

14 On September 12, 2007, Clark replaced claim 10 with a new claim reciting  
15 "[a] (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside ( $\beta$ -D or  $\beta$ -L) of claim 6 or  
16 its pharmaceutically acceptable salt thereof wherein  $R^1$  and  $R^7$  are H." Ex. 1173, at  
17 6-7. Clark also deleted "or prodrug" from claim 25. Ex. 1173, at 9.

18 After the September 12, 2007 amendment, claim 6 did not recite a prodrug  
19 of the compound, and the  $R^1$ ,  $R^3$ ,  $R^4$ , and  $R^7$  constituents were limited beyond that  
of published claim 10. Ex 1173 at and 2-3 and 6-7.

21 In the September 12, 2007 amendment, Clark states that the 35 U.S.C. § 112,  
22 first paragraph rejection should be withdrawn because "the term 'prodrug thereof' .  
23 . . . does not appear in the presently amended claims." Ex. 1173 at 26.

24 In the September 12, 2007 amendment, Clark states that the 35 U.S.C. § 112,  
25 second paragraph rejection should be withdrawn because "the term 'optionally  
26 substituted' . . . [does] not appear in the presently amended claims." Ex. 1173 at  
27 26.

1 In an Office Action dated February 26, 2008, the Examiner noted that the 35  
2 U.S.C. § 112, first and second paragraph rejections were overcome by applicant's  
3 amendments. Ex. 1174 at 2.

4 Analysis

5 Section 135(b)(2) reads:

6 A claim which is the same as, or for the same or substantially  
7 the same subject matter as, a claim of an application published under  
8 section 122(b) of this title may be made in an application filed after  
9 the application is published only if the claim is made before 1 year  
10 after the date on which the application is published.

11 Sommadossi directs us to no particular claim sets filed prior to 13 January  
12 2006 upon which it relies. Paper 70, 12:13-26:7.

13 Sommadossi's contends that Clark is not eligible for repose under §  
14 135(b)(2) because Clark's involved claims of the '572 patent are materially  
15 different from the published claims of the '737 publication. Paper 70, 12:13-17:23  
16 (citing *Ryan v. Young*, 2008 WL 577435 (BPAI Mar. 4, 2008) and *Steffel v.*  
17 *Schofield*, 2011 WL 1576590, at \*8 (BPAI Apr. 25, 2011)).

18 In particular, Sommadossi argues that claims 10 and 25 of the '737 patent  
19 were materially changed, after publication, in response to an Office Action  
20 rejection dated March 30, 2007. We find that there is sufficient evidence to  
21 support the position that claims 10 and 25 were successfully amended to overcome  
22 certain 35 U.S.C. § 112, first and second paragraph rejections. Clark does not  
23 oppose these findings.

24 Clark contends that *Ryan* was improperly decided because (1) it is not  
25 supported by the statute or legislative history, (2) it bars an applicant from moving  
26 for repose under 35 U.S.C. § 135(b)(2) without an issued patent, and (3) it  
27 transmutes the "material difference" test against the party who should be protected  
28 by repose. Paper 30, 18:2-8; Paper 83, 5:4-14.

1 We need not reach Clark's arguments regarding the *Ryan* decision because  
2 Sommadossi's involved claims only recite the compound or "a pharmaceutically  
3 acceptable salt thereof" and do not encompass a "prodrug." Thus, Sommadossi's  
4 allegedly "copied" claims are materially different in scope from Clark's published  
5 claims because they lack a limitation to a prodrug. Accordingly, Sommadossi's  
6 claims are not directed to the same or substantially the same subject matter as  
7 claim 10 or claim 25 of the '737 publication by virtue of the fact that they are  
8 materially narrower claims.

9 Accordingly, Clark has not met the burden of establishing that  
Sommadosi's claims are barred under 35 U.S.C. § 135(b)(2) because Clark has  
11 not shown that it is eligible for repose based on claims 10 and 25. Accordingly, we  
12 deny Clark Substantive Motion 3 with respect to 35 U.S.C. § 135(b)(2).

13 Since not all of Sommadossi's involved claims are barred under either 35  
14 U.S.C. § 135(b)(1) or § 135(b)(2), we exercise our discretion to dismiss the  
15 remainder of the motion as its consideration does not aid in resolution of the  
16 priority dispute before us and is not consistent with securing the just, speedy and  
17 inexpensive determination of the interference. Bd. R. 125(a).

#### 18 Decision on Clark Substantive Motion 3

19 Upon consideration of Clark Substantive Motion 3, and for the reasons  
given, it is

21 ORDERED that Clark Substantive Motion 3 is *denied-in-part* and  
22 *dismissed-in-part*.

#### 23 **II. Clark Substantive Motion 6**

24 **For judgment based on some of Sommadossi's involved claims for being**  
25 **unpatentable under 35 U.S.C. § 101 and 112, first paragraph**

26 Clark Substantive Motion 6 (Paper 35) seeks judgment against Sommadossi  
27 on the grounds that some, but not all, of Sommadossi's involved claims are

unpatentable under 35 U.S.C. § 101, for lack of utility, and under 35 U.S.C. § 112, first paragraph for lack of enablement and lack of written description.

Sommadossi has opposed. Paper 71.

Clark has replied. Paper 86.

Clark has not challenged all of Sommadossi's involved claims. Paper 35, 3:8-13. Even if Clark prevailed on its motion, some of Sommadossi's involved claims would remain and the interference would continue. Accordingly, we dismiss the motion as its consideration does not further resolution of the priority dispute that is the subject matter of the interference. Bd. R. 125(a).

Decision on Clark Substantive Motion 6

Upon consideration of Clark Substantive Motion 6, and for the reasons given, it is

ORDERED that Clark Substantive Motion 6 is *dismissed*.

**III. Sommadossi Responsive Motion 6<sup>1</sup>**

**To substitute Count C or Count D for Count 1**

Sommadossi Responsive Motion 6 (Paper 41) is responsive to Clark Motion 6 (Paper 37) which we dismissed. Accordingly we need not and do not reach Sommadossi Responsive Motion 6.

Decision on Sommadossi Responsive Motion 6

Upon consideration of Sommadossi Responsive Motion 6, and for the reasons given, it is

ORDERED that Sommadossi Responsive Motion 6 is *dismissed as moot*.

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<sup>1</sup> Sommadossi Responsive Motion 6 was filed incorrectly numbered as Sommadossi Responsive Motion 18. Paper 41. Clark was ordered to respond as Opposition 6, and Sommadossi was ordered to respond as Reply 6. Paper 66. Accordingly, we will refer to this Motion as Sommadossi Responsive Motion 6.

1 IV. Clark Motion 1

2 For benefit to Clark's Provisional Application 60/474,368

3 Clark Substantive Motion 1 (Paper 32) seeks to be accorded benefit for  
4 Count 1 of US Provisional Application 60/474,368, filed May 20, 2003  
5 (hereinafter "C1" or "the '368 Application").

6 Sommadossi has filed an Opposition. Paper 68.

7 Clark has replied. Paper 85.

8 As the moving party, Clark has the burden to show that it is entitled to the  
9 relief requested. Bd. R. 208(b).

Findings of Fact

11 Count 1 is as noted *supra* at Page 2 and will not be repeated here for brevity.  
12 Count 1 is limited to certain constituents for X, R<sup>1</sup>, R<sup>7</sup>, R<sup>3</sup>, and R<sup>4</sup>. Paper 1, p. 8.

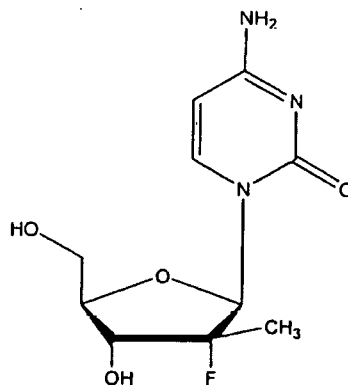
13 Count 1 is directed to a class of 2'-methyl, 2'-fluoro nucleosides with a  
14 uracil or cytosine base. *Id.*

15 The application that became Clark's involved patent was filed April 21,  
16 2004, within a year of the filing date of Clark's C1 application, May 30, 2003. Ex.  
17 2009, cover page.

18 Clark's involved application includes a cross-reference to Clark's C1  
19 application. Ex. 2009, col. 1, ll. 7-10.

Clark's involved patent and Clark's C1 application both recited Jeremy C.  
21 Clark as the sole inventor. Ex. 2009, cover page; *see* Exs. 2006 and 2007  
22 (indicating the inventorship of Clark's C1 application was corrected to recite only  
23 Jeremy C. Clark as the sole inventor).

24 Clark's C1 application discloses a compound referred therein as "beta-D-2'-  
25 methyl-2'-fluoro-2'-deoxycytidine," "2'-methyl-2'-fluorocytidine" and "Compound  
26 6," which has the chemical structure reproduced below (hereinafter referred to as  
27 "Compound 6").



Paper 32, 5:10-14; Ex. 2005, 17:1-6 and 34:12-25.

Compound 6 is encompassed by the scope of Count 1.

Clark's C1 application discloses a scheme and procedure for preparing the above described compound. Paper 32, 6:6-17; Ex. 2005, 32:17-34:25.

Clark's C1 application describes "dose-dependent reduction of the replicon HCV [hepatitis C virus] RNA" when Compound 6 above is added to hepatitis C virus culture media. Paper 32, 8:1-3, Ex. 2005, 37:20-38:6.

#### Applicable Law

In an interference, for a party to be accorded benefit for the purpose of priority, the party must establish that its "benefit" application constitutes a constructive reduction to practice of the subject matter of the count. Our applicable rule puts it this way (italics in original) "*Constructive reduction to practice* means a described and enabled anticipation under 35 U.S.C. 102(g)(1) in a patent application of the subject matter of the count." 37 C.F.R. § 41.201 (definition of constructive reduction to practice); *Hunt v. Treppschuh*, 523 F.2d 1386, 1389 (CCPA 1975) (an application need only disclose a single enabled embodiment within the scope of the count to constitute a constructive reduction to practice of the invention of the count); *see also Weil v. Fritz*, 572 F.2d 856, 9 865 n.16 (CCPA 1978). "[T]he § 112, first paragraph, requirements need only be met for an



1 *embodiment* within the count” where the count is drawn to a genus and the  
2 previously-filed application discloses only a species thereof. *Hunt*, 523 F.2d at  
3 1389.

4 Only one embodiment (as opposed to a description and enablement  
5 commensurate in scope with the breadth of a claim) is needed in a priority case  
6 because one prior art embodiment is all that is needed to *defeat* the opponent’s  
7 right to a claim on the issue of priority. In other words, one prior art species within  
8 a genus defeats an applicant’s right to the genus.

9 Analysis

10 Clark contends that the C1 application is entitled to benefit for Count 1  
11 because the C1 application describes, enables one skilled in the art to make and  
12 use, and provides utility for, a compound that falls within the scope of Count 1.  
13 Paper 32, 5:8-8:12. Clark also contends that Clark’s involved application satisfies  
14 the requirements for benefit under 35 U.S.C. § 119(e). Paper 32, 8:13-22.

15 For reasons provided by Clark in its Motion that are undisputed on this  
16 record, we are persuaded that Clark is entitled to the relief requested.

17 In particular, we credit the testimony of Clark’s expert, Dr. Victor E.  
18 Marquez. Ex. 2001. Dr. Marquez has more than 30 years of experience, authored  
19 a large number of papers, and extensively lectured on the subject of nucleoside  
chemistry. Ex. 2001, ¶ 18. In particular, Dr. Marquez has experience in  
21 fluorinated nucleosides at the 2’ and 3’ positions and in nucleosides useful for the  
22 treatment of viral infections. Ex. 2001, ¶ 15-16 and 18. We find Dr. Marquez  
23 qualified to testify regarding the chemistry involved with fluorinated nucleosides at  
24 the 2’ position.

25 Dr. Marquez testifies that “Compound 6” of Clark’s C1 application falls  
26 within the scope of Count 1, wherein R<sup>1</sup> is H, R<sup>7</sup> is H and R<sup>4</sup> is NH<sub>2</sub>. Ex. 2001, ¶  
27 87. Dr. Marquez further testifies that Scheme 1 of Clark’s C1 application (Ex.

2005, 34:17-30) and its associated description teaches a specific procedure for making Compound 6 such that the skilled artisan could make Compound 6 with only routine, if any, experimentation. Ex. 2001, ¶ 88-91. Dr. Marquez further testifies that Clark's C1 application discloses what appears to be data confirming that Compound 6 has antiviral activity. Id., ¶¶ 101-105.

Sommadossi filed an Opposition, but does not substantively contest Clark's motion. Paper 68. Rather, Sommadossi concedes that "neither party disputes the proofs offered by Clark are sufficient" and the "[m]any of these same proofs are in the Sommadossi '350 app. and the Sommadossi '907 app." See Paper 68, 7:5-7.

#### Decision on Clark Substantive Motion 1

Upon consideration of Clark Substantive Motion 1, and for the reasons given, it is

ORDERED that Clark's Substantive Motion 1 is *granted*.

FURTHER ORDERED that benefit is accorded to Clark for Clark's Provisional Application 60/474,368 filed May 30, 2003.

#### **V. Clark Substantive Motion 2**

##### **To deny Sommadossi the accorded benefit of Sommadosi's Application 10/608,907**

Clark Substantive Motion 2 (Paper 33) seeks to deny Sommadossi benefit for Count 1 of US Application 10/608,907, filed June 27, 2003 (hereinafter "S4" or "the '907 Application").

Sommadosi has opposed. Paper 69.

Clark has replied. Paper 82.

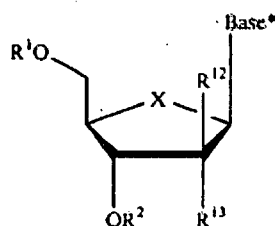
As the moving party, Clark has the burden to show that it is entitled to the relief requested. Bd. R. 208(b).

# Background of Motion

Clark seeks relief on the basis that (1) Sommadossi's S4 application does not constitute a constructive reduction to practice of the subject matter of Count 1 (i.e., does not include a described and enabled anticipatory embodiment that falls within Count 1) and that (2) Sommadossi's involved application fails to properly cross-reference Sommadossi's S4 application and thus is not entitled to benefit under 35 U.S.C. § 120.

Count 1 is as noted *supra* at Page 2 and will not be repeated here for brevity. Count 1 is directed to a class of 2'-methyl, 2'-fluoro nucleosides with a uracil or cytosine base. Paper 1, p. 8.

Sommadosi's S4 application describes a preferred genus of Formula (IX) which is a 2'-methyl, 2'-fluoro nucleoside having the following structure:



(IX)

wherein X=O, R<sup>13</sup> is fluoro, R<sup>12</sup> is CH<sub>3</sub>, R<sup>1</sup> and R<sup>2</sup> is H, and Base\* is "a purine or pyrimidine base." Ex. 3002, 100:6-29.

The S4 application includes a list of "purine" and "pyrimidine" bases that recites cytosine and uracil among other natural and synthetic bases. Ex. 3002, 104:15-32. The S4 application does not include a preference for a cytosine or uracil base.

Clark contends that this disclosure is insufficient to provide written descriptive support to an embodiment of Count 1, is not enabled, and lacks a credible utility. Paper 33. As discussed below, we conclude that Clark has shown

1 a lack of enablement for an embodiment of Count 1 and thus we need not and do  
2 not reach the utility and description issues raised by Clark.

3 Analysis

4 Enablement is a question of law involving underlying factual inquiries. *See*  
5 *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997).

6 “Although not explicitly stated in section 112, to be enabling, the specification of a  
7 patent must teach those skilled in the art how to make and use the full scope of the  
8 claimed invention without ‘undue experimentation.’” *In re Wright*, 999 F.2d 1557,  
9 1561 (Fed. Cir. 1993). The specification need not explicitly teach those in the art  
10 to make and use the invention; the requirement is satisfied if, given what they  
11 already know, the specification teaches those in the art enough that they can make  
12 and use the invention without “undue experimentation.” *Amgen, Inc. v. Hoechst*  
13 *Marion Roussel, Inc.*, 314 F.3d 1313, 1334 (Fed. Cir. 2003).

14 Whether undue experimentation is required is a “conclusion reached by  
15 weighing many factual considerations.... includ[ing] (1) the quantity of  
16 experimentation necessary, (2) the amount of direction or guidance presented, (3)  
17 the presence or absence of working examples, (4) the nature of the invention, (5)  
18 the state of the prior art, (6) the relative skill of those in the art, (7) the  
19 predictability or unpredictability of the art, and (8) the breadth of the claims.”).  
20 *In re Wands*, 858 F.2d 731, 737 (Fed.Cir.1988).

21 Accordingly, we discuss each of the *Wands* factors below.

22 *Nature of the invention and breadth of the count*

23 There does not appear to be a dispute that the nature of the invention at issue  
24 is the synthesis of a nucleoside compound with a methyl constituent in the “up” 2’-  
25 position and a fluoro constituent in the “down” 2’-position. Paper 33, 9:19-10:2;  
26 Paper 69, 9:23-10:8 (indicating the need for “stereochemical control”).

1        *Level of Skill in the Art*

2        Both Clark and Sommadossi agree that the level of skill in the art of  
3        nucleoside chemistry is high. Paper 33, 2:5-23; Paper 69, 8:21-23.

4        Clark presents evidence that the ordinary artisan would not have had  
5        expertise or experience with fluorination reactions, and would require some  
6        guidance. Paper 33, 10:3-5; Ex. 2001, ¶ 214. According to Clark's expert,  
7        fluorination chemistry is "considered a specialized field" and the ordinary chemist  
8        engaged in drug discovery did not have experience or expertise. *Id.*

9        Sommadossi does not dispute Clark's experts regarding the skilled artisan's  
10       general familiarity with fluorination reactions. Rather, Sommadossi argues that  
11       expertise with fluorination would not have been required. Paper 69, 9:21-23. This  
12       argument appears to be supported on cross-examination of Clark's expert witness:

13                Q. And now, other chemists, organic chemists can follow your  
14                publication and do the same. Is that right?

15                A. If they are interested in the field of fluorine chemistry or  
16                fluoro nucleosides, they might.

17        Ex. 2065, Marquez Tr. 64:22-65:3.

18        Accordingly, while fluorination reactions may be rare in nucleoside organic  
19        chemistry, the skilled artisan in nucleoside chemistry would likely be capable of  
20        performing a fluorination reaction in the manner described in the literature at the  
21        time of the invention.

22        *State of the prior art*

23        Sommadossi presents evidence of a scheme, "Scheme 1," that "could have  
24        been used" at the time of the invention to prepare a 2'-fluoro, 2'-methyl  
25        nucleoside. Ex. 1101, ¶ 95.

1        There appears to be no dispute that fluorinating agents and certain  
2        fluorinating reactions used in "Scheme 1," namely the DAST reagent, were known  
3        in the art as of June 27, 2003. Ex. 2001 ¶ 210-212; Ex. 1101, ¶ 100.

4        However, there also does not appear to be a dispute that Clark's published  
5        patent application on January 13, 2005, after the filing date of Sommadossi's S4  
6        application, was the first reported scheme for the synthesis of 2'-fluoro, 2'-methyl  
7        nucleosides in the art. Paper 33, 10:10-11; Ex. 2001, ¶ 219; Ex. 1191, 158:6-  
8        159:10; Ex. 2008.

9        Clark's published application describes the DAST reaction of Sommadossi's  
10        Scheme 1. Ex. 1004, 49:44-49; Ex. 1101, ¶ 101.

11        *Predictability of the art*

12        Clark argues that fluorination chemistry can be unpredictable, especially for  
13        nucleoside molecules, such as that for Count 1. Paper 33, 10:5-7. Clark relies on  
14        the testimony of Dr. Marquez, whose qualifications to testify are discussed *supra*.  
15        In fact, Dr. Marquez testifies that "attempted fluorination reactions could result in  
16        products with the wrong stereochemistry, products resulting from undesired  
17        rearrangements or products in which no fluorination occurred." Ex. 2001, ¶ 217.

18        Sommadossi argues that the DAST reaction had been extensively studied  
19        and that "replacement of hydroxyl groups by fluorine with DAST usually precedes  
20        with complete inversion of configuration" such that the conversion of hydroxy to  
21        fluoro in the 2' position would have been "routine." Paper 69, 10:2-8.

22        *Quantity of experimentation necessary*

23        Neither party discusses the quantity of experimentation that may be  
24        necessary to synthesize a 2'-methyl, 2'-fluoro nucleoside given the disclosure of  
25        Sommadossi's S4 application.

1 Clark presents evidence that the experimentation would be a "trial-and-error  
2 process" that would require determination of "appropriate starting materials,  
3 reagents and chemical transformations." Paper 33, 10:7-10; Ex. 2001, ¶ 217.

4 *Amount of direction or guidance presented and presence or absence of*  
5 *working examples*

6 It is not disputed that Sommadossi's S4 application does not include any  
7 working examples of 2'-methyl, 2'-fluoro nucleosides with a uracil or cytosine  
8 base. Admitted fact 55, Paper 33, 8:23-9:3; Paper 69, 9:9-11, Appx. 2-11; *see*  
9 *generally* Ex. 3002.

10 Sommadossi's S4 application does not appear to describe any schemes or  
11 procedures for preparing a 2'-methyl, 2'-fluoro nucleoside with a uracil or cytosine  
12 base. Paper 33, 9:11-12; Paper 69, 9:12-18; *see generally* Ex. 3002.

13 Sommadossi's S4 application does not appear to describe "fluorinating  
14 starting materials, fluorinating reagents, or compounds that could be fluorinated."  
15 In particular, Sommadossi's S4 application does not appear to describe DAST as a  
16 known or desirable fluorinating reagent. Paper 33, 9:20-22; Ex. 3002; Ex. 2001, ¶  
17 220; Ex. 1168, 156:21-157:15; Ex. 1169, 178:5-17.

18 Sommadossi's S4 application describes a reaction scheme for the synthetic  
19 production of 2'-hydroxy, 2'-methyl nucleosides. Paper 33, 9:12-15; Ex. 3002,  
124:4-5 and 125:14-15.

21 Clark's expert, Dr. Marquez, indicates that the scheme for making 2'-  
22 hydroxy, 2'-methyl described in Sommadossi's S4 application would not be  
23 directly useful for fluorination via the DAST reaction that was known in the art  
24 because it would have been expected to result in the opposite stereochemistry.  
25 Paper 82, 4:3-15; Ex. 2001, ¶ 220. We credit Dr. Marquez's testimony, which is  
26 supported by the description of the DAST reaction in Scheme 1, proposed by  
27 Sommadossi's experts, having the opposite stereochemistry as that of the 2'-

1 hydroxy, 2'-methyl scheme described in Sommadossi's S4 application. *Compare*  
2 Ex. 3002, 124:4-5 and 125:14-15 (showing a hydroxyl in the "down" 2'-position)  
3 and Ex. 1101, ¶ 100 (showing a hydroxyl in the "up" 2'-position).

#### 4 Discussion

5 Sommadossi correctly points out that the absence of working examples is  
6 not dispositive of a lack of enablement. Paper 69, 9:9-11 (citing *In re Strahilevitz*,  
7 668 F.2d 1229, 1232 (CCPA 1982) and *Martin v. Johnson*, 454 F.2d 746, 750  
8 (CCPA 1972)). Yet, in considering the *Wands* factors discussed above, we  
9 determine that, having only the disclosure provided by Sommadossi's S4  
10 application, i.e., only the structure of a 2'-methyl, 2'-fluoro nucleoside, it would  
11 have required undue experimentation for the skilled artisan to synthesize the  
12 compound.

13 "Although the knowledge of one skilled in the art is indeed relevant, the  
14 novel aspect of an invention must be enabled in the patent." *Automotive Techs.*  
15 *Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1283 (Fed. Cir. 2007).  
16 "[O]mission of minor details does not cause a specification to fail to meet the  
17 enablement requirement. However, when there is no disclosure of any specific  
18 starting material or of any of the conditions under which a process can be carried  
19 out, undue experimentation is required." *Genentech, Inc. v. Novo Nordisk A/S*, 108  
20 F.3d 1361, 1366 (Fed. Cir. 1997).

21 Here, the novel aspect appears to be the presence of a fluorine in the  
22 "down" 2'-position of a nucleoside. We agree with Clark that Sommadossi's S4  
23 application is so void of an explanation as to how to synthesize a 2'-fluoro, 2'-  
24 methyl nucleoside with the fluorine in the "down" position that the skilled artisan  
25 would have to rely on the prior art for all of the teachings necessary to make a  
26 compound of such a structure.



1           Moreover, Sommadossi's "Scheme 1" appears to be similar to Clark's own  
2   scheme for synthesis of a 2'-methyl, 2'-fluoro nucleoside, which was not prior art  
3   at the time of Sommadossi's S4 application. We are persuaded that the skilled  
4   artisan could not have relied upon the synthesis of the 2'-hydroxy, 2'-methyl  
5   compound described in Sommadossi's S4 application as a starting point for  
6   Sommadosi's "Scheme 1" and nothing in Sommadossi's S4 application would  
7   have instructed the skilled artisan to the DAST technique and the inverse  
8   stereochemistry used in Sommadossi's "Scheme 1."

9           Accordingly, Sommadossi's S4 application is not enabling for an  
10   embodiment encompassed by Count 1.

11           We need not reach a decision on whether Sommadossi's S4 Application has  
12   proper cross-reference under 35 U.S.C. § 120.

13                           Decision on Clark Substantive Motion 2

14           Upon consideration of Clark Substantive Motion 2, and for the reasons  
15   given, it is

16           ORDERED that Clark's Substantive Motion 2 is *granted*.

17           FURTHER ORDERED that Sommadossi's S4 application, US Application  
18   10/608,907, fails to describe an embodiment within the scope of Count 1.

19           FURTHER ORDERED that benefit accorded to Sommadossi in the  
20   Declaration (Paper 1, page 10) as to Sommadossi's S4 application 10/608,907,  
21   filed June 27, 2003 is *vacated*.

22                           **VI.   Sommadosi Substantive Motion 1**

23                   **For benefit to Sommadossi's Provisional Application 60/392,350**

24           Sommadosi Substantive Motion 1 (Paper 25) seeks to accord Sommadossi  
25   benefit for Count 1 of US Provisional Application 60/392,350, filed June 28, 2002  
26   (hereinafter "S1" or "the '350 Application").

27           Clark has opposed. Paper 72.

1 Sommadossi has replied. Paper 79.

2 As discussed above, we determine that Sommadossi was not entitled to  
3 benefit with respect to Count 1 of its intervening S4 Application. On this basis,  
4 priority benefit to Sommadossi's earlier filed S1 Application is not appropriate for  
5 the same reasons.

6 Decision on Sommadossi Substantive Motion 1

7 Upon consideration of Sommadossi Substantive Motion 1, and for the  
8 reasons given, it is

9 ORDERED that Sommadossi Substantive Motion 1 is *denied*.

10 FURTHER ORDERED that Sommadossi is *denied* benefit to Sommadossi's  
11 S1 application, US Provisional Application 60/392,350, filed June 28, 2002.

12 FURTHER ORDERED that party Clark shall be designated senior party for  
13 any further proceedings according to the Redecclaration issued herewith.

14 **VII. Sommadossi Miscellaneous Motion 7<sup>2</sup>**

15 **For authorization to amend the Specification of Sommadossi's involved**  
16 **application 12/131,868 to recite a cross-reference to its earlier filed application**  
17 **10/608,907**

18 Because priority to Sommadossi's earlier filed application 10/608,907 (S4  
19 Application) was denied due to lack of enablement of an embodiment within the  
20 count, and we do not reach a decision on Clark's contention that Sommadossi's S4  
Application lacked proper cross-reference under 35 U.S.C. § 120, Sommadossi's  
22 Miscellaneous Motion 7 is moot.

23  
24  

---

<sup>2</sup> Sommadossi Miscellaneous Motion 7 was filed incorrectly numbered as  
Sommadosi Miscellaneous Motion 19. Paper 58. It was ordered that these  
incorrectly numbered motion papers would hereinafter be stylized as Sommadossi  
Miscellaneous Motion 7, Clark Opposition 7, and Sommadossi Reply 7. Paper 66.  
Accordingly, we will refer to this Motion as Sommadossi Miscellaneous Motion 7.

Decision on Sommadossi Miscellaneous Motion 7

Upon consideration of Sommadossi Miscellaneous Motion 7, and for the reasons given, it is

ORDERED that Sommadossi Miscellaneous Motion 7 is *dismissed as moot*.

**VIII. Clark Miscellaneous Motion 7**

**To exclude evidence**

Clark Miscellaneous Motion 7 (Paper 95) seeks to exclude from evidence all or portions of the following exhibits: 1013, 1088, 1101, 1136, 1145, 1146, 1147, 1152, 1168, 1206, 1207, and 2065.

Sommadosi has opposed. Paper 97.

Clark has replied. Paper 102.

As the moving party, Clark has the burden to show that it is entitled to the relief requested. Bd. R. 208(b).

*Conduct during Cross-Examination*

Clark argues that pages 171:22-178:23 of Ex. 1168 (Deposition of Dr. Trost) is inadmissible under Rules 611(b) and 611(c) because it consists of deposition testimony obtained through the improper use of leading questions on re-direct, as well as questions on re-direct that were outside the scope of cross-examination. Paper 95, 8:11-9:2. Clark also argues that pages 39:20-40:6, 171:3-8, and 202:12-203:9 of Ex. 1207 (Deposition of Dr. Marquez of September 26, 2012) are inadmissible under FRE 611(a) because these portions of Ex. 1207 consist of Dr. Marquez's responses to questions that improperly mischaracterized his prior testimony. *Id.*, 10:8-11:10.

Clark also argues that pp. 174:15-16 of Ex. 2065 (Deposition of Dr. Marquez of July 27, 2012) is inadmissible under Rule 611(a). Our decision does not rely on the portions of Ex. 1168, 1207, and 2065 raised by Clark as allegedly being improper. Accordingly, this portion of the motion is dismissed as moot.

1           *Cumulative exhibits/Duplicity*

2           Clark contends that these exhibits are inadmissible under FRE 403 as  
3 cumulative and a "waste of time." *E.g.*, Paper 95, 1:17. According to Clark,  
4 Exhibits 1013 (Declaration of Dr. Lemon) and 1088 (Declaration of Dr. Glenn) are  
5 substantially identical testimony, at times verbatim. Paper 95, 1:13-24, 2:13-15,  
6 3:5-13. Likewise, according to Clark, Exhibits 1101 (Declaration of Dr. Damha)  
7 and 1136/1152 (Declarations of Dr. Trost) are substantially identical testimony, at  
8 times verbatim. *Id.*, 3:20-4:15, 5:1-24. According to Clark, Exhibits 1145  
9 (Declaration of Dr. Lemon) and 1146 (Declaration of Dr. Glenn) are likewise  
substantially identical testimony, at times verbatim. *Id.*, 6:21-7:14. Clark argues  
11 that certain paragraphs of Exhibits 1147 are substantially identical in content to  
12 certain paragraphs of Exhibit 1136. *Id.*, 7:15-23. Clark also argues that Exhibit  
13 1152 (Declaration of Dr. Trost), which is supplement evidence to Ex. 1136  
14 (Declaration of Dr. Trost) is inadmissible for the same reason as Ex. 1136. *Id.*,  
15 7:24-8:10. Clark also argues that Ex. 1206 is an unsigned version of Ex. 2094 and  
16 Ex. 1207 is an unsigned version of Ex. 2093 and, thus, duplicative. *Id.*, 9:10-10:7.  
17 Finally, Clark argues that repetitive questioning of Dr. Marquez in Ex. 2065 is  
18 cumulative and improper. *Id.*, 11:11-12:15.

19           Among other arguments, Sommadossi responds that the duplicative  
testimony reflects the fact that two experts with difference experience and  
21 backgrounds have the same opinion. Paper 97, 1:5-24, 4:14-5:6.

22           We decline to exclude the evidence solely on the basis that it is cumulative  
23 or duplicative. The evidence Clark argues to be duplicative is not excessive and  
24 appears to be used to reinforce other similar evidence. To the extent that the  
25 presentation of testimony that is verbatim identical cast doubt on the veracity of the  
26 testimony, we choose to consider this as an issue of credibility, not admissibility.  
27 We deny this portion of the motion.

1        *Relevance*

2        Clark argues that the declaration testimony of Dr. Lemon (Ex. 1013) and Dr.  
3        Glenn (Ex. 1088) directed to “the *availability* of various procedures for testing  
4        compounds as of December 11, 2001, are irrelevant to determining any issue in the  
5        interference” because “evidence regarding whether it would have been possible to  
6        test compounds for pharmacological activity does not establish utility and confuses  
7        the issues of enablement and utility.” Paper 95, 2:1-12 and 22-4.

8        This argument is moot in light of the fact that our decision did not reach the  
9        issue of utility in any application or rely on the portion of the testimony of Dr.  
10        Lemon and Dr. Glenn raised by Clark. We dismiss as moot this portion of the  
11        motion.

12       *Timeliness*

13       Clark argues that Ex. 1136 (Declaration testimony of Dr. Trost) is  
14       inadmissible under Standing Order ¶ 7.2 for being served on Clark on June 22,  
15       2012, over two weeks after the June 5, 2012, deadline for serving evidence in  
16       support of Sommadossi Substantive Motion 1. Paper 95, 6:1-13.

17       It appears that Ex. 1136 was filed in support of Sommadossi Responsive  
18       Motion 6. This motion was dismissed. Accordingly, we did not rely upon Ex.  
19       1136. This portion of the Motion is dismissed as moot.

Decision on Clark’s Miscellaneous Motion 7

21       Upon consideration of Clark’s Miscellaneous Motion 7, and for the reasons  
22       given, it is

23       ORDERED that Clark’s Miscellaneous Motion 7 is *dismissed-in-part*  
24       *and denied-in-part*.

1 **IX. Sommadossi Motion 8**

2 **To exclude evidence**

3 Sommadossi Miscellaneous Motion 8 (Paper 93) seeks to exclude from  
4 evidence all or portions of the following exhibits: 2025, 2054, 1167/1190, and  
5 1168/1191.

6 Clark has opposed. Paper 99.

7 Sommadossi has replied. Paper 101.

8 As the moving party, Sommadossi has the burden to show that it is entitled  
9 to the relief requested. Bd. R. 208(b).

10 *Exhibit 1167/1190*

11 Sommadossi argues that page 97, ll. 6-15 of Ex. 1167/Ex. 1190 (Dr. Glenn's  
12 Deposition Testimony with and without and errata sheet) should be excluded from  
13 evidence because Clark's counsel's questioning went beyond the scope of Dr.  
14 Glenn's declaration (Ex. 1088). Paper 93, 4:1-24. According to Sommadossi, this  
15 testimony addressed "the meaning of the phrases 'capable of providing' and  
16 'providing.'" *Id.*, 4:9-10.

17 We note that Clark did not rely on Dr. Glenn's testimony regarding the  
18 meaning of the terms "capable of providing" and "providing." Paper 83, 2:7-23.  
19 In fact, we note above that Clark relies on no evidence that the terms "capable of  
providing" and "providing" have different meanings.

21 Accordingly, we did not consider this testimony in rendering our decision on  
22 that issue *supra*. Thus, this portion of the Sommadossi Motion is dismissed as  
23 moot.

24 *Exhibits 2025 and 2054*

25 Sommadossi argues that Ex. 2025 (Lalezari article) should be excluded for  
26 lack of authentication and as inadmissible hearsay under F.R.E. 901 and 802.  
27 Paper 93, 1:6-3:8. According to Sommadossi, this article was submitted as

1 evidence that Clark's "Compound 6" "has been shown to be effective against HCV  
2 in human clinical trials." *Id.*

3 Sommadossi also argues that Ex. 2054 (Sommadosi declaration submitted  
4 in Interference 103,906) as inadmissible hearsay under FRE 802. *Id.*, 3:9-23.  
5 According to Sommadossi, this testimony was directed to whether "one cannot  
6 predict a compound's activity against another virus without testing it." *Id.*

7 We credit the largely uncontested testimony of Dr. Marquez as to the skilled  
8 artisan's understanding of disclosure in Clark's C1 application as evidence of the  
9 activity of Compound 6. We do not find it necessary to consider Ex. 2025 or Ex.  
10 2054 to support a finding of utility in Clark's C1 application. Accordingly, we do  
11 not consider this testimony in rendering our decision on that issue *supra*. Thus,  
12 this portion of the Sommadossi Motion is dismissed as moot.

13 *Exhibit 1168/1191*

14 Sommadossi also argues that page 188, l. 25 to page 190, l. 19 of Ex  
15 1168/Ex 1191 (Dr. Trost's Deposition Testimony with and without an errata sheet)  
16 should be excluded from evidence because the re-cross questions posed by Clark's  
17 counsel went beyond the scope of Sommadossi's counsel's redirect examination.  
18 Paper 93, 4:1-24. According to Sommadossi, Clark relied on this testimony in its  
19 Opposition 6 as evidence that Sommadossi's schemes "were created by  
Sommadosi in hindsight by copying Clark's procedures." *Id.*

21 We do not reach Sommadossi Responsive Motion 6 and as a consequence,  
22 Clark Opposition 6. According this portion of the Motion is dismissed as moot.

23 Decision on Sommadossi Miscellaneous Motion 8

24 Upon consideration of Sommadossi Miscellaneous Motion 8, and for the  
25 reasons given, it is

26 ORDERED that Sommadossi Miscellaneous Motion 8 is *dismissed*.  
27

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# Inhibition of hepatitis C replicon RNA synthesis by $\beta$ -D-2'-deoxy-2'-fluoro-2'-C-methylcytidine: a specific inhibitor of hepatitis C virus replication

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$\beta$ -D-2'-Deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) is a cytidine analogue with potent and selective anti-hepatitis C virus (HCV) activity in the subgenomic HCV replicon assay, 90% effective concentration ( $EC_{90}$ ) =  $4.6 \pm 2.0 \mu\text{M}$ . The spectrum of activity and cytotoxicity profile of PSI-6130 was evaluated against a diverse panel of viruses and cell types, and against two additional HCV-1b replicons. The S282T mutation, which confers resistance to 2'-C-methyl adenosine and other 2'-methylated nucleosides, showed only a 6.5-fold increase in  $EC_{90}$ . When assayed for activity against bovine diarrhoea virus (BVDV), which is typically used as a surrogate assay to identify compounds active against HCV, PSI-6130 showed no anti-BVDV activity. Weak antiviral activity was

noted against other flaviviruses, including West Nile virus, Dengue type 2, and yellow fever virus. These results indicate that PSI-6130 is a specific inhibitor of HCV. PSI-6130 showed little or no cytotoxicity against various cell types, including human peripheral blood mononuclear and human bone marrow progenitor cells. No mitochondrial toxicity was observed with PSI-6130. The reduced activity against the RdRp S282T mutant suggests that PSI-6130 is an inhibitor of replicon RNA synthesis. Finally, the no-effect dose for mice treated intraperitoneally with PSI-6130 for six consecutive days was  $\geq 100 \text{ mg/kg}$  per day.

**Keywords:** antiviral activity, HCV, PSI-6130

## Introduction

Hepatitis C virus (HCV), an important member of the *Flaviviridae*, is the leading cause of liver transplantation in the United States. Nearly 2% of the U.S. population and an estimated 170 million people world-wide are HCV carriers (Poynard *et al.*, 2000; Alter *et al.*, 1999). The current standard of care is a combination of pegylated interferon and ribavirin (Di Bisceglie *et al.*, 2002; Collier & Chapman, 2001; Alter *et al.*, 1999). Because of the adverse effects associated with both interferon and ribavirin (Di Bisceglie *et al.*, 2002; Collier & Chapman, 2001; Alter *et al.*, 1999), there is a need for more potent anti-HCV compounds with fewer adverse effects.

The lack of cell-based assays for HCV has hindered the discovery and development of therapies to treat HCV infection. However, surrogate models such as the HCV RNA replicon that replicates in human hepatoma cells has facilitated the identification of candidate anti-HCV drugs (Lohmann *et al.*, 1999; Blight *et al.*, 2000). Nucleoside analogues, which inhibit viral encoded polymerases, have a proven track record as therapies for viral infections caused by herpes viruses, HIV and hepatitis B virus (De Clercq, 2004). The HCV RNA-dependent RNA polymerase NS5B protein (RdRp) is considered to be essential for HCV replication and therefore is an ideal

therapeutic target for nucleoside analogues (Yamashita *et al.*, 1998; Lohmann *et al.*, 1998; Lohmann *et al.*, 1997; Ishii *et al.*, 1999; Blight *et al.*, 2000).

Recently, several 2'-modified nucleoside analogues with activity against HCV have been identified (Yamashita *et al.*, 1998; Lohmann *et al.*, 1998; Lohmann *et al.*, 1997; Ishii *et al.*, 1999; Blight *et al.*, 2000). These compounds are phosphorylated to the corresponding 5'-triphosphate which in turn inhibits the HCV RdRp. Of these compounds the valine ester of  $\beta$ -D-2'-C-methylcytidine (NM283, valopicitabine) is currently undergoing Phase II clinical trials in HCV-infected individuals (Pierra *et al.*, 2005). Here we describe the *in vitro* results of studies with  $\beta$ -D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130; Figure 1), a new, potent and specific anti-HCV compound, which shows little or no toxicity *in vitro* and *in vivo*.

## Materials and methods

### Chemistry

PSI-6130 (Figure 1) was synthesized according to the methods of Clark *et al.* (2005). 2'-C-Methylcytidine and 2'-C-methyladenosine were synthesized in our laboratories following published procedures (Eldrup *et al.*, 2004; Clark *et al.*, 2005). Interferon- $\alpha$ 2a (Roferon-A) was obtained from Hoffmann-La Roche Inc., Nutley, NJ, USA.

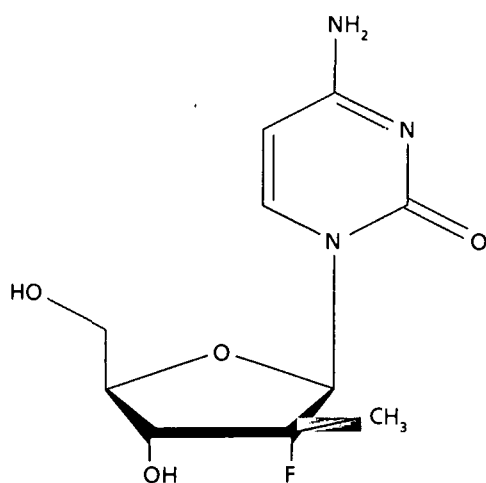
### Virology

**Viruses and cells.** The HCV subgenomic replicon RNA-containing Huh 7 cells (Clone A cells; Apath, LLC,

St. Louis, MO, USA) and the full length HCV replicon RNA-containing Huh 7 cells, 21-5, kindly provided by Dr Ralf Bartenschlager (Johannes-Gutenberg University Mainz, Mainz, Germany), were maintained in exponential growth in Dulbecco's modified Eagle's medium (high glucose and no pyruvate) containing 10% fetal bovine serum, 1 $\times$  nonessential amino acids, 100 U/ml of penicillin, 100  $\mu$ g/ml of streptomycin, 0.292 mg/ml of glutamine and 500  $\mu$ g/ml of G418. Madin-Darby bovine kidney (MDBK) cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% horse serum and 100  $\mu$ g/ml of penicillin-streptomycin. HepAD38 cells (a gift from Dr Brent Korba) were maintained in Dulbecco's modified Eagle's/F12 medium (DMEM/F12; GIBCO/Invitrogen Technologies, Carlsbad, CA, USA) supplemented with 10% heat inactivated fetal bovine serum, 50  $\mu$ g/ml of penicillin, 50  $\mu$ g/ml of streptomycin, 100  $\mu$ g/ml of kanamycin and 0.3  $\mu$ g/ml of tetracycline in a humidified 5% CO<sub>2</sub> atmosphere at 37°C. The cytopathic NADL strain of bovine diarrhoea virus (BVDV) was kindly provided by Dr Ruben Donis, University of Nebraska. The New Guinea strain of Dengue type 2 virus (DV) and the New York strain of the West Nile virus (WNV) were provided by Drs N Karabatsos and R Lanciotti, respectively, of the Centers for Disease Control and Prevention, Atlanta, GA USA. The 17D strain of yellow fever virus (YFV), CEM and HepG2 cells (HB-8065) were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA).

**Generation of NS5B S282T mutant replicon.** Clone A cells were seeded into six-well plates at  $2.4 \times 10^4$  cells/well in the presence of 1 mg/ml G418 and 5  $\mu$ M of 2'-C-Me-adenosine in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 1 $\times$  nonessential amino acids, 100 U/ml of penicillin, 100  $\mu$ g/ml of streptomycin and 0.292 mg/ml of glutamine. After 10 days, cells became confluent. Cultures were then split with a one to five dilution into fresh medium and the concentration of compound was increased to 10  $\mu$ M. On day 21, the concentration was increased to 20  $\mu$ M. On day 34, cell death was first noted, and small colonies of cells resistant to the inhibitor and the antibiotic became visible. The medium was renewed as needed. and on day 47, resistant colonies were isolated and transferred to a 24-well plate. Resistant colonies were then expanded and characterized. RNA was isolated from a representative clone using the RNeasy 96 kit (Qiagen, Valencia, CA, USA), reverse transcribed and amplified. The resulting DNA was sequenced using primers specific for NS5B to identify any mutations present in the NS5B polymerase gene. The only mutation found in the NS5B of the resistant clone was

Figure 1. Chemical structure of PSI-6130



the substitution of serine 282 with threonine (S282T), consistent with Migliaccio *et al.* (2003).

**HCV replicon assay.** The HCV replicon assay was performed as previously described by Stuyver *et al.* (2003b). Briefly, clone A cells were added to a 96-well plate at 1,000 cells/well in 50  $\mu$ l of medium without G418. Test compounds in 50  $\mu$ l (two-fold serial dilutions) were added immediately after seeding. Plates were incubated at 37°C in a 5% CO<sub>2</sub> atmosphere for 4 days. Replicon RNA was extracted and amplified in a single-step multiplex RT-PCR protocol as described (Stuyver *et al.* 2003b). Antiviral activity was determined by subtracting the average threshold RT-PCR cycle of the test compound from the average threshold RT-PCR cycle of the no-drug control ( $\Delta$ Ct<sub>HCV</sub>). A  $\Delta$ Ct of 3.3 equals a 1-log reduction (equal to the 90% effective concentration [EC<sub>90</sub>]) in replicon RNA levels. Cytotoxicity of test compounds was also determined by calculating the  $\Delta$ Ct for ribosomal RNA ( $\Delta$ Ct<sub>RNA</sub>).

**BVDV assay.** Cells were seeded in a 96-well plate at  $5 \times 10^3$  cells/well and incubated for 72 h at 37°C in a humidified 5% CO<sub>2</sub> atmosphere. The cells were then infected with the cytopathic NADL strain of BVDV at a virus dilution of 10<sup>-2</sup> and incubated for 45 min. Cell monolayers were washed three times with medium. Fresh medium containing serial dilutions of test compounds or ribavirin (positive control) was added to cultures and medium containing no drug was added to the no-drug controls. After 72 h incubation, supernatant was collected and viral RNA was extracted using the QIAmp Viral RNA Mini Kit (Qiagen). Viral load was determined by quantitative RT-PCR using primers specific for the NADL strain of BVDV (Stuyver *et al.*, 2003b).

**DV, WNV and YFV assays.** Antiviral activity against DV, WNV and YFV was determined using the neutral red dye uptake assay described by McManus (1976). A known positive control compound was included in each assay. Ribavirin was used as the positive control in the DV virus assays, and 6-azauridine was the positive control for the WNV and YFV assays.

**HIV assay.** The assay was performed using a modification of the assay described by Schinazi *et al.* (1990 & 1992). Briefly, primary human peripheral blood mononuclear (PBM) cells were isolated from sero-negative donors and activated with phytohemagglutinin A (1  $\mu$ g/ml). Cells were infected with HIV-1<sub>LAI</sub> (Centers for Disease Control and Prevention) at a multiplicity of infection of 0.1. At 1 hr post-infection, compounds were added in duplicate at concentrations of 0.1, 1.0, 10 and 100  $\mu$ M. 3'-Azido-3'-deoxythymidine (AZT) was used as a positive control.

After incubating for 6 days at 37°C in a humidified 5% CO<sub>2</sub> atmosphere, 1 ml of culture supernatant was centrifuged and the virus pellet resuspended in 100  $\mu$ l of a buffer containing 0.05 M Tris, pH 7.8, 0.5% Triton X-100, 0.8 M NaCl, 0.5 mM phenylmethylsulfonyl fluoride, and 20% glycerol. Ten microlitres of solubilized virus were added to 75  $\mu$ l of reverse transcriptase reaction mixture (0.06 M Tris at pH 7.8, 0.012 M MgCl<sub>2</sub>, 0.006 M dithiothreitol, 0.006 mg/ml poly rA-oligo dT<sub>(12-18)</sub> [Amersham Bioscience, Piscataway, NJ, USA], 96  $\mu$ g/ml dATP [Sigma-Aldrich, St. Louis, MO, USA] and 1  $\mu$ M [<sup>3</sup>H]-thymidine-5'-triphosphate [87.0 Ci/mmol; Perkin Elmer, Boston, MA, USA]) and incubated at 37°C for 2 h. The reaction was stopped and the reaction product precipitated by the addition of 10% trichloroacetic acid (100  $\mu$ l) containing 0.05% sodium pyrophosphate. The precipitate was collected using a Packard FilterMate Cell Harvester (Packard, Meriden, CT, USA) and counted in a Packard Direct Beta Counter. The 50% effective concentration was determined using the method of Belen'kii and Schinazi (1994).

**HBV assay.** The HBV quantitative-PCR assay with HepAD38 cells was performed as previously described (Stuyver *et al.*, 2002; Hassan *et al.*, 2003). HepAD38 cells replicate HBV under conditions that can be regulated with tetracycline (Ladner *et al.*, 1997). HepAD38 cells were seeded into 96-well plates at  $5 \times 10^4$  cells/well in 200  $\mu$ l of medium and incubated at 37°C in a humidified 5% CO<sub>2</sub> atmosphere. On day two, medium was removed and the cells were washed with PBS. Compounds and controls were prepared in medium without tetracycline and added at 10  $\mu$ M (final concentration) in duplicate. On day seven, HepAD38 cell supernatant was collected and stored for analysis. Supernatant containing extracellular HBV was extracted using DNeasy® 96 Tissue Kit (Qiagen, catalog #69582) in a 96-well format. DNA was eluted in 100  $\mu$ l total volume and 5  $\mu$ l was used for real time PCR in a 25  $\mu$ l reaction. HBV primers were used at 22.5 pmol/reaction and probe was used at 5 pmol/reaction (Operon, Huntsville, AL, USA/Qiagen). Taqman® Universal PCR Master Mix was added at twice the concentration (Applied Biosystems, Foster City, CA, USA/Roche, Pleasanton, CA, USA).

**Cytotoxicity assay.** Human PBM cells ( $5 \times 10^4$  cells/well), CEM cells ( $2.5 \times 10^3$  cells/well), HepG2 ( $5 \times 10^3$  cells/well), Huh-7 ( $5 \times 10^3$  cells/well) and Clone A cells ( $5 \times 10^3$  cells/well) were seeded in 96-well plates in the presence of increasing concentrations of test compound and incubated at 37°C in a humidified 5% CO<sub>2</sub> atmosphere for 3–5 days. For each assay, 50  $\mu$ l of twofold serial dilutions of test compound

were added in to each well of a 96-well plate. Final concentrations of PSI-6130 ranged from 1 to 100  $\mu\text{M}$ . A "no drug" (medium only) control and a "cells plus medium only" control were included. After 5 days incubation for PBM cells, 3 days incubation for CEM cells or 4 days incubation for all others, cell viability was determined using the CellTiter 96 AQ<sub>ueous</sub> One Solution cell proliferation colorimetric assay (Promega, Madison, WI, USA). The absorbance (490 nm) was then read on an ELISA plate reader using the 'no drug' wells as blanks. Cytotoxicity was expressed as the concentration of test compound that inhibited cell growth by 50% ( $\text{CC}_{50}$ ).

**Human bone marrow cytotoxicity assay.** Primary human bone marrow mononuclear cells were obtained from Cambrex Bioscience (Walkersville, MD, USA). CFU-GM assays were performed using a bilayer soft agar in the presence of 50 units/ml human recombinant granulocyte/macrophage colony-stimulating factor, whereas BFU-E assays used a methylcellulose matrix containing 1 unit/ml erythropoietin (Sommadossi & Carlisle, 1987). Cells were incubated in the presence of the compound for 14–18 days at 37°C with 5%  $\text{CO}_2$ . Colonies of greater than 50 cells were counted using an inverted microscope to determine 50% inhibition concentration (Sommadossi *et al.*, 1992). Each experiment was performed in duplicate using cells from three different donors. 3'-Azido-3'-deoxythymidine (AZT) was used as a positive control.

**Mitochondrial toxicity assays.** HepG2 cells (5,000 cells/well) were seeded in 96-well, collagen-coated plates. Test compound was added to the medium at selected concentrations and the plates were incubated at 37°C in a humidified 5%  $\text{CO}_2$  atmosphere for 14 days. After incubation, the supernatant was removed and cellular nucleic acids were extracted using a RNeasy 96 kit (Qiagen). The mitochondrial cytochrome C oxidase subunit II (*cox2*) gene and ribosomal DNA (rDNA) were amplified from a 5  $\mu\text{l}$  sample using a multiplex quantitative PCR protocol (Stuyver *et al.*, 2002) and the  $\Delta\text{Ct}$  (mitochondrial DNA) and  $\Delta\text{Ct}$  (rDNA) for each sample were determined. The fold difference in mitochondrial DNA normalized for rDNA relative to control was calculated.

Lactic acid quantification was performed using the D-lactic acid/ L-lactic acid test kit (Boehringer Mannheim, Indianapolis, IN, USA / R-Biopharm, South Marshall, MI, USA/ Roche). The total amount of lactic acid produced for each sample was determined as well as the fold change in lactic acid production (% of lactic acid/ % of rDNA), following a 7 day incubation in the presence of various concentrations of PSI-6130, as described in the manufacturer's instructions.

**Evaluation of toxicity in mice.** Five groups of five six-week-old female Swiss mice (SWR/J; Charles River Laboratory, Wilmington, MA, USA) were dosed intraperitoneally (i.p.) with 0, 3.3, 10, 33 or 100 mg/kg per day of PSI-6130 dissolved in pyrogen-free, sterile saline (0.85% NaCl, Sigma-Aldrich, St. Louis MO, USA). Animals were monitored daily for weight changes, general appearance and mortality up to 24 days post-treatment. The statistical significance of changes in animal weight was evaluated by one-way analysis of variance. A *P*-value of <0.05 was deemed statistically significant. These studies were conducted under the approval of the Institutional Animal Care and Use Committee (IACUC) of the Department of Veteran Affairs, Atlanta, GA, USA.

## Results

### Inhibition of HCV RNA in replicon cells

The results from the subgenomic HCV replicon assay with PSI-6130 are presented as  $\text{EC}_{90}$  values in Table 1. An  $\text{EC}_{90}$  value of  $4.6 \pm 2.0$   $\mu\text{M}$  was determined for PSI-6130. Comparing the activity of PSI-6130 with that of 2'-C-methylcytidine (2'-C-MeC), 2'-C-methyladenosine (2'-C-MeA) and 2'-deoxy-2'-fluorocytidine (2'-F-C), we found that PSI-6130 was greater than fourfold more potent than 2'-C-MeC, half as active as 2'-C-MeA and showed similar activity to 2'-F-C (Table 1). The activity of PSI-6130 was also compared with that of 2'-C-MeC and 2'-C-MeA using the full length replicon 21–5. The  $\text{EC}_{90}$  values were lower for each of the compounds, but the relative potency was similar to what was seen with the Clone A subgenomic replicon (Table 1).

It has been demonstrated that candidate antiviral agents can indirectly alter replicon RNA levels by affecting cell growth rates (Stuyver *et al.*, 2003a). To address this issue, we followed the level of HCV replicon RNA on a per cell basis over the course of 7 days in cells

**Table 1.** *In vitro* activity of PSI-6130 compared with other nucleoside analogues in the Clone A replicon, and Bovine diarrhoea virus

Compound	90% Effective concentration $\pm\text{SD}$ , $\mu\text{M}$			
	Clone A	Clone A		BVDV
	HCV Replicon	21-5 HCV Replicon	S282T Replicon	
PSI-6130	$4.6 \pm 2.0$	$1.6 \pm 0.7$	$30.7 \pm 11.7$	>100
2'-C-MeC	$21.9 \pm 4.3$	6.6*	>100	$2.3 \pm 0.1$
2'-C-MeA	$2.1 \pm 0.27$	0.6*	>100	$2.0 \pm 0.08$
2'-F-Cytidine	$6.5 \pm 1.6$	ND	ND	>100

\*Single assay performed in duplicate. ND, not determined.

treated with PSI-6130. Cells were seeded in the presence or absence of PSI-6130 (5  $\mu$ M and 25  $\mu$ M) and incubated at 37°C. On days 3–7, cells were harvested and counted using the trypan blue exclusion method, followed by total cellular RNA isolation and quantification of replicon RNA. When the  $\log_{10}$  change in HCV replicon RNA copy number was determined per cell, cells treated with PSI-6130 showed a significant and steady decrease in replicon copy number per cell compared to untreated control cells, which showed a slight increase in replicon copy number (Figure 2A). Interferon- $\alpha$ 2a and ribavirin was used as a positive and negative control, respectively (Figure 2B). Compared to the "no drug" control, interferon- $\alpha$ 2a significantly reduced the HCV replicon RNA copy numbers per

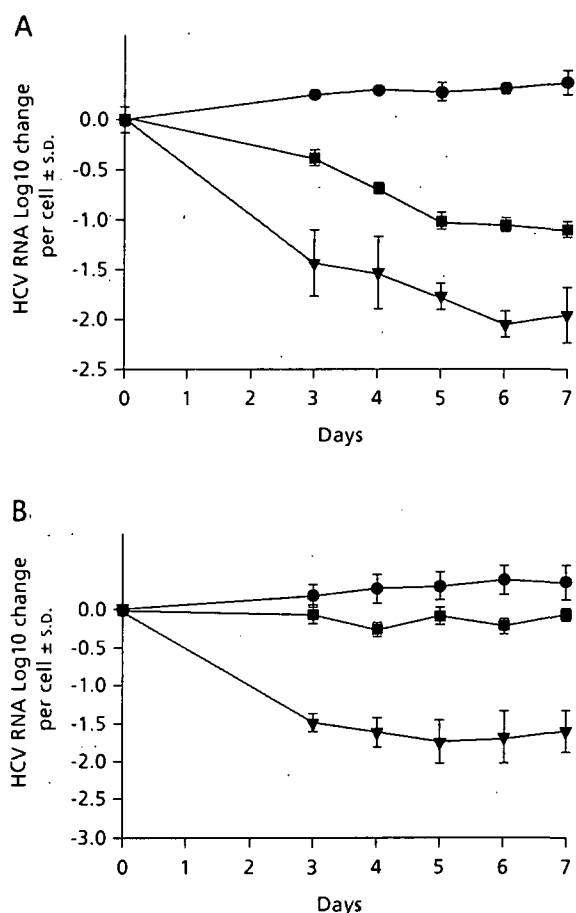
cell (Figure 2B), whereas ribavirin reduced the replicon RNA copy number per cell only minimally (Figure 2B). These results indicate that PSI-6130 selectively inhibited replication of the HCV replicon.

Migliaccio *et al.* (2003) previously isolated a resistant replicon by passaging in the presence of 2'-C-MeA and identified a serine to threonine mutation at position 282 of the HCV RdRp that conferred a loss of sensitivity to 2'-C-MeA. In contrast to 2'-C-MeA and 2'-C-MeC, which were inactive against the S282T mutant, PSI-6130 showed only a 6.5-fold increase in  $EC_{90}$  (30.7  $\pm$  11.7  $\mu$ M) with the S282T mutant replicon (Table 1).

### Prevention of PSI-6130 inhibition of HCV replicon replication

Using a real-time RT-PCR assay (Stuyver *et al.*, 2003b), the ability of natural nucleosides to prevent the anti-HCV activity of PSI-6130 was explored to gain some insight as to the mechanism by which PSI-6130 is phosphorylated in replicon cells. These reversal studies were performed with exogenously added natural nucleosides. In these studies, 5  $\mu$ M of PSI-6130 (the concentration of PSI-6130 that approximates the  $EC_{90}$  value) was incubated with natural ribo- or 2'-deoxyribonucleosides at a concentration of 50  $\mu$ M (approximately 10-times the  $EC_{90}$  of PSI-6130). Cells were incubated at 37°C in a humidified 5%  $CO_2$  atmosphere for 4 days and antiviral activity was determined by real time PCR as described in the Materials and methods. Of the natural nucleoside analogues tested, only 2'-deoxycytidine completely inhibited the antiviral activity of PSI-6130 (Table 2). Exogenous cytidine caused a partial reversal of antiviral activity whereas none of the other ribo- or

**Figure 2.** Effect of PSI-6130 (A), Ribavirin or Interferon (B) on HCV replicon RNA per cell



(A) Change in HCV replicon copy number per cell in the presence of PSI-6130. ●, no drug control; ■, 5  $\mu$ M PSI-6130; ▼, 25  $\mu$ M PSI-6130. (B) Change in HCV replicon copy number per cell in the presence of ribavirin and interferon- $\alpha$ 2a. ●, no drug control; ■, 100  $\mu$ M ribavirin; ▼, 100 IU/ml interferon- $\alpha$ 2a.

**Table 2.** Prevention of the anti-HCV activity of PSI-6130 by exogenously added nucleosides

Competing nucleoside (50 $\mu$ M)	$\Delta Ct \pm SD$	% Inhibition of HCV replication
PSI-6130 control	3.39 $\pm$ 0.11	90.4
Cytidine	0.74 $\pm$ 0.87	40.0
Uridine	3.52 $\pm$ 0.61	91.2
Adenosine	2.82 $\pm$ 0.53	85.8
Guanosine	2.90 $\pm$ 0.06	86.5
2'-Deoxycytidine	0.00 $\pm$ 0.14	0.0
2'-Deoxyuridine	3.38 $\pm$ 0.01	90.3
Thymidine	4.59 $\pm$ 0.14	95.8
2'-Deoxyadenosine	3.42 $\pm$ 0.08	90.6
2'-Deoxyguanosine	3.42 $\pm$ 0.17	89.3

$\Delta Ct$  (the average threshold RT-PCR cycle of the test compound subtracted from the average threshold RT-PCR cycle of the no-drug control) of 3.3 equals a 1-log reduction or 90% inhibition.

2'-deoxyribonucleoside analogues were effective (Table 2). These results were quite different from those obtained with 2'-C-MeC where cytidine completely reversed the anti-HCV activity of the compound (data not shown). These results suggest that there are differences in the metabolic pathways of PSI-6130 and 2'-C-MeC even though both compounds are cytidine analogues.

#### Activity of PSI-6130 against other viruses

Like HCV, BVDV, WNV, YFV and DV are members of the *Flaviviridae* family of viruses. To demonstrate the specificity of PSI-6130 for HCV, we tested the compound for activity against these other flaviviruses. BVDV is typically used as an HCV surrogate to assay for compounds for potential activity against HCV. Interestingly, unlike 2'-C-MeC and 2'-C-MeA that were active against the NADL strain of BVDV giving  $EC_{50}$  values of 2  $\mu$ M and 1.5  $\mu$ M, respectively, PSI-6130 was not active against this virus ( $EC_{50} > 100 \mu$ M; Table 1). PSI-6130 had little or no activity against WNV ( $EC_{50} = 46.3 \mu$ M), YFV (in two separate experiments  $EC_{50} = 46.3 \mu$ M and 100  $\mu$ M) and DV ( $EC_{50} > 100 \mu$ M). PSI-6130 was also found to be inactive against HIV ( $EC_{50} > 100 \mu$ M) and HBV ( $EC_{50} > 10 \mu$ M).

#### Cytotoxicity and mitochondrial toxicity of PSI-6130

In standard 3-, 4- or 5-day cytotoxicity assays with Huh7, Clone A replicon cells, HepG2 cells, CEM cells and human PBM cells, PSI-6130 did not show significant toxicity in the MTT assay at concentrations up to 100  $\mu$ M (Table 3). Bone marrow toxicity is the principal dose-limiting toxicity associated with a number of nucleoside antiviral drugs (Sommadossi *et al.* 1992; Sommadossi and Carlisle, 1987). Therefore, candidate antiviral nucleosides are typically evaluated *in vitro* for their haematopoietic toxicity potential. PSI-6130 showed inhibition of BFU-E and CFU-GM growth at concentrations  $> 80 \mu$ M, whereas 2'-C-methylcytidine inhibited these cells at twofold lower

**Table 4.** Effect of PSI-6130 and 2'-C-Methylcytidine on human bone marrow progenitor cells

Compound	$CC_{50} \pm SD, \mu$ M	
	BFU-E	CFU-GM
PSI-6130	83.6 $\pm$ 4.8	86.5 $\pm$ 6.4
2'-C-Methylcytidine	36.1 $\pm$ 6.8	33.7 $\pm$ 2.8
AZT	0.09 $\pm$ 0.01	2.9 $\pm$ 1.2

BFU-E, erythroid blast forming unit;  $CC_{50}$ , concentration of compound that inhibits cell growth by 50%; CFU-GM, granulocyte macrophage colony forming unit.

concentrations (Table 4). The AZT control was toxic and gave values similar to published results (Table 4).

As mitochondrial toxicity has been associated with several nucleoside analogues, the effect of PSI-6130 on mitochondrial DNA content was determined using HepG2 cells. In a 14-day mitochondrial toxicity assay, no significant effect on mitochondrial DNA content was observed when PSI-6130 was evaluated up to 100  $\mu$ M (Table 5). In contrast, the positive control, 2',3'-dideoxycytidine, was toxic at a concentration less than 10  $\mu$ M. In addition, the effect of PSI-6130 on lactate production, another measure of mitochondrial toxicity, was assessed. In a 7-day assay, no increase in lactic acid was noted at concentrations up to 33  $\mu$ M, the highest concentration tested (data not shown).

#### Evaluation of toxicity in mice

Swiss mice (five animals/dose) were given single i.p. injections of PSI-6130 for six consecutive days (that is, days 0–5). The doses tested were 0, 3, 10, 33.3 and 100 mg/kg administered in 500  $\mu$ l of sterile saline solution. Mortality and overall appearance (that is, ruffled fur, dehydration, etc.) of the mice were monitored daily and individual animal weights were determined on days 0, 1, 2, 3, 4, 5, 7, 9, 11, 14, 18, 21, 25, 28 and 30. As shown in Figure 3, there were no significant differences in the weight gain among the

**Table 3.** Cytotoxicity of PSI-6130 compared with other nucleoside analogues with anti-HCV activity

Compound	$CC_{50} \pm SD, \mu$ M				
	Clone A	Huh7	HepG2	CEM	PBM
PSI-6130	$> 100$	$> 100$	$> 100$	$> 100$	$> 100$
2'-C-MeC	$> 100$	$> 100$	$> 100$	29.4	24.5
2'-C-MeA	30.5	50.2	31.2	$> 100$	$> 100$
2'-F-Cytidine	$> 100$	$> 100$	$> 100$	ND	ND

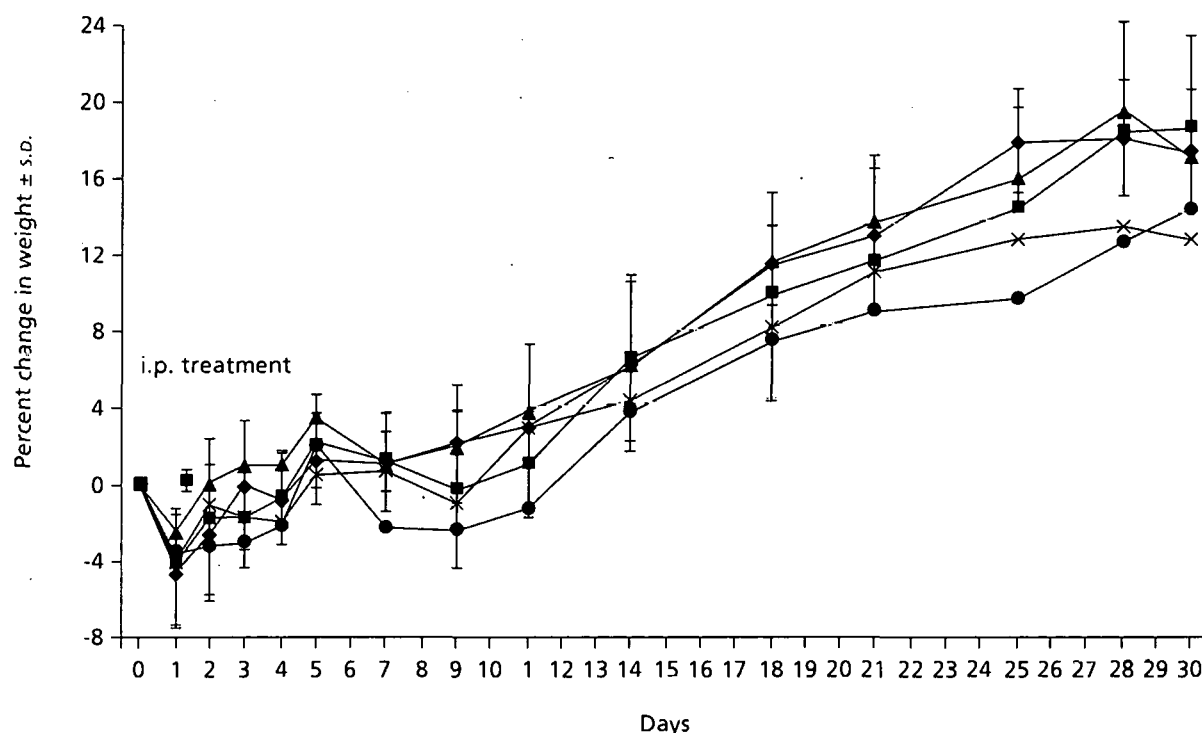
All experiments were performed in duplicate.  $CC_{50}$ , concentration of compound that inhibits cell growth by 50%; ND, not determined; PBM, peripheral blood mononuclear.

**Table 5.** Fourteen day mitochondrial toxicity assay comparing PSI-6130 with 2'-C-Methylcytidine, 2'-C-Methyladenosine and 2'-F-Cytidine

Compound	50% Inhibition concentration $\pm$ SD, $\mu$ M	
	MitCoxII	rDNA
Dideoxycytidine	$< 10$	$< 10$
PSI-6130	$> 100$	71.80 $\pm$ 33.6
2'-C-Methylcytidine	32.5 $\pm$ 11.7	43.5 $\pm$ 9.5
2'-F-Cytidine	$< 1$	$< 1$

rDNA, ribosomal DNA; mitCoxII, mitochondrial cox2 DNA.

Figure 3. Toxicity study in mice treated with PSI-6130



Swiss mice, five animals per dosing group, were injected intraperitoneally (i.p.) with PSI-6130 on day 0 to day 5 and changes in weight were monitored on the indicated days. ◆, 0 mg/kg/day PSI-6130; ●, 3.3 mg/kg/day PSI-6130; ×, 10 mg/kg/day PSI-6130; ▲, 33 mg/kg/day PSI-6130; ■, 100 mg/kg/day PSI-6130. For clarity, standard deviations (s.d.) are shown only for the 0 mg/kg/day and 100 mg/kg/day treatment groups.

different dosing groups compared to controls. No animals died or exhibited signs or symptoms of distress for the duration of the study at all doses studied. The no effect level was determined to be  $\geq 100$  mg/kg/day.

## Discussion

Recently, several modified nucleoside analogues with potent inhibitory activity against the HCV NS5B polymerase have been described (Walker & Hong, 2002; Shim *et al.*, 2003; Migliaccio *et al.*, 2003; Lai *et al.*, 2003; Eldrup *et al.*, 2004; Devos, 2002; Carroll *et al.*, 2003). These analogues can be divided into the following three classes: 2'-modifications of the ribose ring (methyl or O-methyl; Walker & Hong, 2002; Migliaccio *et al.*, 2003; Eldrup *et al.*, 2004; Carroll *et al.*, 2003); 3'-modifications – mainly 3'-deoxy (Migliaccio *et al.*, 2003; Lai *et al.*, 2003) and 4'-modifications (Devos, 2002). Among the most potent compounds are  $\beta$ -D-2'-C-methyl-cytidine and 2'-C-methyl-adenosine. In a recent publication, the synthesis and anti-HCV activity of PSI-6130 was described (Clark *et al.*, 2005). Because of the similar size and electronegativity of fluorine and oxygen, and because the hydrogen bonding

characteristics of fluorine are similar to those of a hydroxy group, substituting fluorine would be expected to allow the molecule to have biological activity. In addition, the presence of a 2'-fluoro group should stabilize the glycosidic bond (Watanabe *et al.*, 1983; Watanabe *et al.*, 1979). In this present study, PSI-6130 was found to be both a potent and a selective inhibitor of HCV RNA replication in the HCV replicon assay system. Instead of using a surrogate virus for assaying compounds of anti-HCV activity, we assayed for anti-HCV activity using a subgenomic or a full length HCV replicon.  $EC_{50}$  values of  $4.6 \pm 2.0 \mu\text{M}$  and  $1.6 \pm 0.6 \mu\text{M}$  were obtained for PSI-6130 with the subgenomic and full length replicon, respectively. Interestingly, little or no antiviral activity was observed when PSI-6130 was tested for activity using other members of the *Flaviviridae* family. This modest or lack of activity against other members of the flavivirus family, as well as HIV and HBV, suggest that PSI-6130, unlike 2'-C-MeC and 2'-C-MeA, is a specific inhibitor of HCV. The lack of significant antiviral activity seen with other flaviviruses, including BVDV, could be due to an inability of certain cells, for example, MDBK cells to phosphorylate PSI-6130. Alternatively, the RdRp of these viruses might be less

susceptible to inhibition by the 5'-triphosphate of PSI-6130. Since the differential activity of PSI-6130 extends to a number of flaviviruses in different cell lines, it is more likely a result of target sensitivity brought about by the dual substitution of methyl and fluorine at the 2' position than levels of phosphorylation.

To gain insight into the mechanism of action of PSI-6130, inhibition studies were performed using exogenously added natural ribo- and 2'-deoxyribonucleosides to determine which nucleoside could prevent the anti-HCV activity of PSI-6130. The antiviral effect was prevented strongly by 2'-deoxycytidine. This would suggest that the compound is primarily phosphorylated by the host cell's deoxycytidine kinase and not by uridine-cytidine kinase. Although deoxyadenosine and deoxyguanosine are substrates of cytosolic deoxycytidine kinase, PSI-6130 phosphorylation was not affected significantly by deoxyadenosine or deoxyguanosine. This observation could be due to the poor binding affinity of deoxyadenosine and deoxyguanosine for cytosolic deoxycytidine kinase. The weak inhibition of antiviral activity seen with cytidine could be the result of competition by cytidine which can be utilized as a weak substrate by deoxycytidine kinase (Sabini et al., 2003; Datta et al., 1989); competition of cytidine monophosphate or diphosphate with the corresponding phosphate derivatives of PSI-6130 with the cellular cytidylate kinase and/or nucleoside diphosphate kinase or competition between cytidine 5'-triphosphate and PSI-6130 triphosphate for binding to the HCV RdRp. The reduced activity of PSI-6130 seen when the compound was tested against a replicon, which carried the S282T mutation in the RdRp, is consistent with PSI-6130 being an inhibitor of the NS5B enzyme. The mechanism of action studies with purified HCV RdRp, which will be published elsewhere, indicate that the 5'-triphosphate of PSI-6130 is an alternative substrate inhibitor of the enzyme. To date, no mutations in NS5B have been selected in the *in vitro* passaging experiments with PSI-6130 (unpublished data) in the subgenomic replicon cells.

Studies were performed to assess the toxicity of PSI-6130 *in vitro* and *in vivo*. Cytotoxicity assays using several different cell types, including human bone marrow progenitor cells, indicated no toxicity associated with PSI-6130 at physiologically relevant concentrations. Mitochondria are often a target for nucleoside toxicity (Lewis & Dalakas, 1995). Mitochondrial toxicity can be determined by measuring the effect of a compound on mitochondrial DNA and the production of lactic acid in liver cells. In these studies, there was no detectable reduction in mitochondrial DNA or an increase in lactic acid production compared to untreated control cells, indicating that PSI-6130 did not produce any mitochondrial toxicity at the

concentrations tested. Finally, the no-effect dose for mice treated i.p. with PSI-6130 was 100 mg/kg per day.

In summary, we describe the *in vitro* antiviral activity of the PSI-6130. PSI-6130 demonstrated potent and specific activity in the HCV replicon assay system. PSI-6130 showed little or no cytotoxicity and no mitochondrial toxicity. Prevention studies performed with natural nucleosides suggest that PSI-6130 is phosphorylated via the 2'-deoxycytidine salvage pathway. The details of the mechanism of action remain to be determined.

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