

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GILEAD SCIENCES, INC.
Petitioner

v.

REGENTS OF THE UNIVERSITY OF MINNESOTA
Patent Owner

U.S. Patent No. 8,815,830

“Nucleosides With Antiviral and Anticancer Activity”

Inter Partes Review No.: IPR2017-01712

**PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,815,830
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.100 *et seq.***

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<i>Reactive Surfaces Ltd. LLP v. Toyota Motor Corp.,</i> Case IPR2016-01914, Paper 23 (P.T.A.B. Mar. 3, 2017)	7

EXHIBIT LIST

Exhibit No.	Exhibit Description
1001	U.S. Patent No. 8,815,830, <i>Nucleosides With Antiviral And Anticancer Activity</i> (“the ’830 patent”)
1002	File History of U.S. Patent Application No. 14/229,292, filed Mar. 28, 2014 (“NP5”)
1003	Complaint, <i>Regents of the University of Minnesota v. Gilead Sciences, Inc.</i> , Civil Action No. 0:16-cv-02915-SRN-HB (D. Minn., Aug. 29, 2016)
1004	U.S. Patent Application Publication No. 2010/0016251, <i>Nucleoside Phosphoramidate Prodrugs</i> (“Sofia”)
1005	U.S. Patent Application No. 13/753,252, <i>Nucleosides With Antiviral And Anticancer Activity</i> (“NP4”)
1006	Preliminary Amendment, U.S. Patent Application No. 11/721,325 (Jun. 8, 2007) (“NP3”)
1007	International Application No. PCT/US2005/044442, <i>Nucleosides With Antiviral And Anticancer Activity</i> (“NP2”)
1008	U.S. Provisional Application No. 60/634,677, <i>Nucleosides With Antiviral And Anticancer Activity</i> (“P1”)
1009	U.S. Patent No. 8,765,935, <i>Nucleosides With Antiviral And Anticancer Activity</i> (“the ’935 patent”)
1010	U.S. Patent No. 8,399,428, <i>Nucleosides With Antiviral And Anticancer Activity</i> (“the ’428 patent”)
1011	Declaration of Victor E. Marquez, Ph.D.
1012	<i>Curriculum Vitae</i> of Victor E. Marquez, Ph.D.
1013	Anastasi et al., <i>Current Medicinal Chemistry</i> 2003, 10: 1825-1843

Exhibit No.	Exhibit Description
1014	Calogeropoulou et al., <i>Current Topics in Medicinal Chemistry</i> 2003, 3: 1467-1495
1015	Cahard et al., <i>Mini-Reviews in Medicinal Chemistry</i> 2004, 4: 371-381
1016	Highleyman, "Lodenosine trials stopped due to safety concerns," <i>BETA</i> 12(4): 4 (1999)
1017	Sicardi et al., <i>European Journal of Pharmaceutical Sciences</i> , 22: 25-31 (2004)
1018	Kim et al., <i>Molecular Pharmaceutics</i> , 1: 102-111 (2004)
1019	2005 FDA Approved Drugs, available at: https://www.centerwatch.com/drug-information/fda-approved-drugs/year/2005
1020	Yoo et al., <i>J. Med. Chem.</i> 2008, 51: 7593-7601
1021	Pauling, <i>J. Amer. Chem. Soc.</i> , 54: 3570-3582 (1932)

MANDATORY NOTICES

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner certifies that Gilead Sciences, Inc. is the real party-in-interest.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Pursuant to 37 C.F.R. § 42.8(b)(2), U.S. Patent No. 8,815,830 is currently involved in the following proceeding: *Regents of the University of Minnesota v. Gilead Sciences, Inc.*, Civil Action No. 0:16-cv-02915-SRN-HB (D. Minn., Aug. 29, 2016).

C. Lead And Backup Counsel And Service Information Under 37 C.F.R. § 42.8(b)(3)-(4)

Petitioner hereby designates lead and backup counsel as follows:

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Service information for lead and backup counsel is provided in the designation of lead and backup counsel, above. Petitioner consents to electronic service by email at the email addresses provided above.

D. Payment of Fees Under 37 C.F.R. §§ 42.15(a) & 42.103

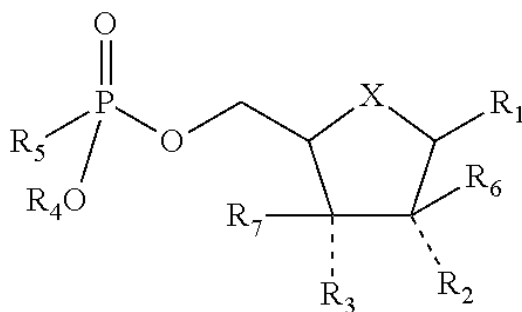
The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 50-3939. Any overpayment or refund of fees may also be deposited in this Deposit Account.

Gilead Sciences, Inc. (“Petitioner”) requests *inter partes* review (“IPR”) pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.100 *et seq.* of claims 1-9, 11-21, and 23-28 (the “Challenged Claims”) of U.S. Patent No. 8,815,830 (Ex. 1001), which issued on August 26, 2014 to Carston R. Wagner (“Applicant”) and is facially assigned to the Regents of the University of Minnesota (hereinafter “Patent Owner” for purposes of this petition).

Petitioner submits herewith the supporting declaration of Victor E. Marquez, Ph.D. (Ex. 1011), a Scientist Emeritus at the Chemical Biology Laboratory of the Center for Cancer Research, National Cancer Institute, National Institutes of Health, in Frederick, Maryland. Dr. Marquez has 40 years of experience in the area of nucleoside chemistry, including significant experience with fluorinated nucleosides and experience with designing and synthesizing nucleoside compounds. Ex. 1011, ¶ 9; Ex. 1012.

I. INTRODUCTION

The ’830 patent relates to nucleosides with purported antiviral and/or anticancer activity. ’830 patent claim 1 is represented by the following formula:

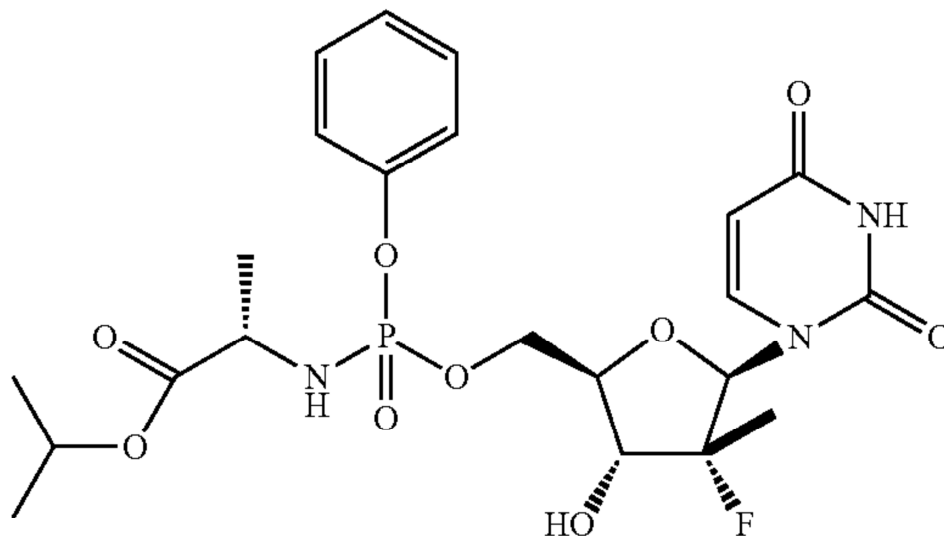


R₁ can be myriad nucleoside base options; R₂ can be any halogen; R₃ is hydroxy; R₄ can be myriad substituents; R₅ can be any amino acid, including non-naturally occurring amino acids; R₆ and R₇ can be, independently, hydrogen or (C₁-C₆)alkyl, and the (C₁-C₆)alkyl can be optionally substituted with numerous substituents; and X can be oxy, thio, or methylene. While '830 patent claim 1 covers an enormous number of potential compounds, it is still a mere subgenus of the even larger disclosure contained in the applications to which the '830 patent claims priority.

Relevant to this Petition (and to a pending litigation between Patent Owner and Petitioner) is the nucleoside referred to as sofosbuvir. Sofosbuvir was invented by scientists at Pharmasset. The lead scientist from Pharmasset, Michael Sofia, received the Lasker Award for his discovery. Sofosbuvir is the subject of patents naming Michael Sofia as inventor, including U.S. Patent No. 7,964,580. Sofosbuvir, an active ingredient in Gilead's Sovaldi®, Harvoni®, and Epclusa® medicines, is prescribed to

cure chronic hepatitis C virus infection. It is represented by the following chemical formula:

25



The structure of sofosbuvir became publicly known by at least January 21, 2010¹ with the publication of Michael Sofia et al., U.S. Patent Application Publication No. 2010/0016251 (“Sofia,” Ex. 1004).

After sofosbuvir’s unique, life-saving properties became publicly known and while the ’830 patent application was pending, on March 31, 2014, Applicant amended its claims to target sofosbuvir specifically. Ex. 1002, at 57 (Mar. 31, 2014 Preliminary Amendment, at 6). But neither the ’830 patent nor the applications to which Applicant claimed priority contain

¹ The corresponding PCT publication, WO 2008/121634, which included the same structure, was published on October 9, 2008.

a disclosure that reasonably conveys to a person of ordinary skill in the art (“POSA”) that Applicant had possession of sofosbuvir. Applicant canceled those claims and pursued broad subgenus claims to attempt to capture sofosbuvir. Ex. 1002, at 78-79 (Apr. 23, 2014 Supplemental Preliminary Amendment, at 4-5). These claims issued as the ’830 patent.

Because Patent Owner asserts that the ’830 patent claims are infringed by sofosbuvir, Sofia is novelty-destroying prior art to the ’830 patent, which is not entitled to the benefit of its asserted priority date.

To claim priority from an earlier application, each application to which priority is claimed must comply with the written description requirement. None of the alleged applications to which the ’830 patent claims priority contain written description support for the claims of the ’830 patent and, thus, the ’830 patent is not entitled to the benefit of those earlier filing dates.²

In summary, because the ’830 patent is not entitled to priority, the January 21, 2010 Sofia publication (Ex. 1004) is prior art to the ’830 patent and anticipates each of the Challenged Claims.

² Petitioner takes no position in this petition on whether the ’830 patent contains written description support for its claims.

II. IPR REQUIREMENTS (37 C.F.R. §§ 42.101, 42.104 & 42.108)

A. Grounds For Standing (37 C.F.R. § 42.104(a))

Petitioner certifies that the '830 patent is available for IPR and that Petitioner is not barred or estopped from requesting an IPR of the '830 patent on the grounds identified in this petition. This petition is being filed within one year of Petitioner being served with a complaint alleging infringement of the '830 patent (Ex. 1003), which occurred on August 29, 2016. Petitioner further certifies that the prohibitions of 35 U.S.C. §§ 315(a)-(b) are inapplicable.

B. Sovereign Immunity Is Not Applicable To These Proceedings

Patent Owner cannot duck review of the '830 patent by the Board by asserting that it has sovereign immunity from IPR under the Eleventh Amendment. First, Patent Owner consented to these proceedings by filing a patent application after the promulgation of the AIA in 2011. A patentee takes a patent "subject to the conditions and requirements of [the Patent Act]." 35 U.S.C. § 101. As of 2011, the AIA sets forth those conditions, which include post-grant proceedings, such as *ex-parte* reexam and IPR. *See* 35 U.S.C. §§ 311-319. Patent Owner filed the application that led to the '830 patent in March 2014, three years after promulgation of the AIA. The property right Patent Owner received when the '830 patent issued was

therefore subject to post grant proceedings at the Patent Office. *Cf.* 35 U.S.C. § 293 (providing jurisdiction to the Eastern District of Virginia to “take any action respecting the patent or rights thereunder” against foreign patent owners because they avail themselves of the benefits and protections this country affords by filing for a United States patent).

IPR proceedings are not an “affront to a State’s dignity.” *Fed. Mar. Com’n v. S.C. St. Ports Authority*, 535 U.S. 743, 760 (2002). Sovereign immunity does not apply in *ex parte* reexamination proceedings before the Patent Office because in such proceedings a State does not have to “answer the complaints of private parties.” *Fed. Mar. Com’n*, 535 U.S. at 760. An IPR proceeding is no different; it, like *ex parte* reexamination, allows the Patent Office to reevaluate its earlier administrative grant of a federal patent monopoly. It is not akin to “the complaints of private persons.” *Id.* Unlike in civil litigation: “An administrative agency . . . is not subject to Article III of the Constitution of the United States and related prudential limitations,” *Pfizer Inc. v. Shalala*, 182 F.3d 975, 980 (D.C. Cir. 1999), nor can Patent Owner object to post-grant proceedings on the basis that the Patent Office does not have personal jurisdiction over it. That the “relief” afforded in an IPR proceeding is a cancelation certificate, as opposed to a reexamination certificate, is no meaningful difference. *Fed. Mar. Com’n*, 535 U.S. at 769.

Two panels of the Patent Trial and Appeal Board have recently dismissed IPR proceedings on the basis of a university's sovereign immunity. *See Neochord, Inc. v. Univ. of Md., Balt. and Harpoon Med., Inc.*, IPR2016-00208, Paper 28 (P.T.A.B. May 23, 2017); *Covidien LP v. Univ. of Fla. Research Foundation Inc.*, IPR2016-01274, Paper 21 (P.T.A.B. Jan. 25, 2017). Both cases are inapposite, for at least two reasons. First, the respective patents in *Neochord* and *Covidien* were filed before promulgation of the AIA, even though they issued after. And second, in August 2016, Patent Owner voluntarily chose to exercise its patent rights by filing federal district court litigation against Petitioner alleging infringement of the '830 patent. Ex. 1003. Assuming *arguendo* sovereign immunity applies in IPR proceedings (which, Petitioner does not) Patent Owner admits its choice to file a patent infringement lawsuit amounts to waiver of any sovereign immunity it may have. *See Reactive Surfaces Ltd. LLP v. Toyota Motor Corp.*, Case IPR2016-01914, Paper 23 at 19-20 (P.T.A.B. Mar. 3, 2017). Nor would Patent Owner's potential waiver be undone by the fact that IPR proceedings occur at the Patent Office, as opposed to in the federal court where the infringement action is proceeding. *See Lapidus v. Board of Regents of Univ. System of Ga.*, 535 U.S. 613, 620 (2002) (noting that the rule governing waiver of immunity by litigation conduct rests on the need to

avoid “unfairness” and “inconsistency,” as well as to prevent a State from selectively using immunity to achieve a litigation advantage).

Finally, an IPR proceeding is initiated by the Patent Office—an arm of the United States. *See* 35 U.S.C. § 314(a). And it is the Patent Office (the United States), not Petitioner, that has the authority to address questions of “jurisdiction, patentability, or Office practice.” 37 C.F.R. § 42.74 (addressing settlement of parties); *see also* 35 U.S.C. § 303(a) (“On his own initiative, and [at] any time, the Director may determine whether a substantial new question of patentability is raised by patents and publications discovered by him or cited under the provisions of section 301 or 302); 37 C.F.R. § 90.2(a)(3)(ii) (providing the Director the right to intervene in an appeal arising out of an IPR proceeding). Sovereign immunity does not apply where, as here, IPR is instituted by the United States, as opposed to a private party. *See Fed. Mar. Com’n*, 535 U.S. at 752; *see also Vt. Agency of Nat. Resources v. U.S. ex rel. Stevens*, 529 U.S. 765, 773 (2000) (holding United States’ injury in fact conferred Article III standing on relator in qui tam civil action under FCA in face of sovereign immunity challenge).

III. OVERVIEW OF THE '830 PATENT

A. The '830 Patent Specification

The '830 patent specification provides a disclosure of an enormous number of potential antiviral or anticancer agents, specifically nucleotide phosphoramidate prodrugs³ that are potentially good substrates for human histidine triad nucleotide-binding protein 1 (“hHINT1”). Ex. 1001, col.2 ll.13-47.

The '830 patent specification asserts that these compounds are potentially active against viral infections, including but not limited to: HIV, HSV-2, varicella zoster, vaccinia, CMV, ebola, hepatitis B virus, hepatitis C virus, and the like; metabolic liver disorders; and/or various cancers including but not limited to breast, lung, ovarian, and brain cancer. *Id.*, col.4 ll.15-67, col.6 ll.13-16, col.16 ll.19-24.

B. Prosecution History

The '830 Patent issued on August 26, 2014, five months after its application was filed. *Id.* at 1. The prosecution period was extremely

³ The term “prodrug” is defined in the pharmaceutical field as a biologically inactive derivative of a drug that upon administration to the human body is converted to the biologically active parent drug according to some chemical or enzymatic pathway.

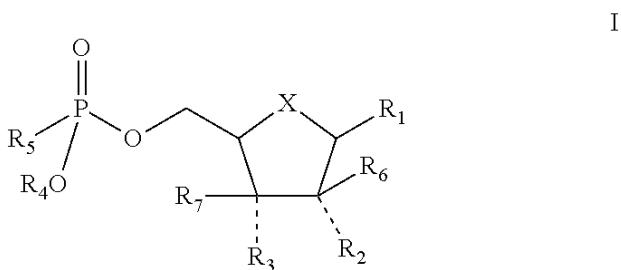
abbreviated because Applicant requested and received Track One prioritized examination. Ex. 1002, at 1 (Mar. 28, 2014 Track One Request), 106 (May 6, 2014 Track One Request Granted).

During prosecution, the Examiner conducted a search for references and, eight days later, issued a Notice of Allowance without a rejection of any kind. *Id.* (May 23, 2014 Notice of Allowance). In particular, no written description rejection or objection to the priority benefit statement was expressly made by the Examiner and there is no evidence in the prosecution history that the Examiner considered entitlement to priority.

C. The Challenged Claims

Claims 1-9, 11-21, and 23-28 are at issue in the Petition. Among the Challenged Claims, claim 1 is the only independent claim. Claim 1 is directed to a genus of nucleoside compounds:

1. A compound of formula I:



wherein:

R₁ is guanine, cytosine, thymine, 3-deazaadenine, or uracil, optionally substituted by 1, 2, or 3 U; wherein

each U is independently halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, hydroxy(C₁-C₆)alkyl, $\text{---}(\text{CH}_2)_{1-4}\text{P}(=\text{O})(\text{OR}_w)_2$, aryl, aryl(C₁-C₆)alkyl, or NR_xR_y;

R₂ is halo;

R₆ and R₇ are independently H or (C₁-C₆)alkyl;

R₃ is hydroxy;

R₄ is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl, aryl(C₁-C₆)alkyl, or 2-cyanoethyl;

R₅ is an amino acid;

X is oxy, thio, or methylene;

each R_w is independently hydrogen or (C₁-C₆)alkyl;

R_x and R_y are each independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, phenethyl, or (C₁-C₆)alkanoyl; or R_x and R_y together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino;

wherein any (C₁-C₆)alkyl of R₁, R₄-R₇, R_w, R_x, and R_y is optionally substituted with one or more halo, hydroxy, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, azido, cyano, oxo

(=O), (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkyl-S—(C₁-C₆)alkyl-, aryl, heteroaryl, alkyl(C₁-C₆)alkyl, or heteroaryl(C₁-C₆)alkyl, or NR_{aj}R_{ak}; wherein each R_{aj} and R_{ak} is independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl;

and wherein any aryl or heteroaryl may optionally be substituted with one or more substituents selected from the group consisting of halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, and amino;

or a pharmaceutically acceptable salt thereof.

Ex. 1001, col.19 ll.1-47.

Claims 2-9, 11-21, and 23-28 are dependent upon claim 1 and recite specific R group substituents (claims 2-9 and 11-12), provide a method of treating a viral infection in an animal with compounds of claim 1 (claims 13-21 and 23-27), and provide a pharmaceutical composition comprising compounds of claim 1 and a pharmaceutically acceptable vehicle or carrier (claim 28). Ex. 1001, col.19 l.49 – col.22 l.19.

D. Construction Of The Challenged Claims

The claim terms in the '830 patent are presumed to take on their ordinary and customary meaning based on the “broadest reasonable construction in light of the specification of the patent in which it appears.” 37 C.F.R. § 42.100(b). If an inventor acts as his or her own lexicographer and provides an explicit definition of a term, that explicit definition will control interpretation of that term in the claim, including under the broadest reasonable construction standard. *See In re ICON Health and Fitness, Inc.*, 496 F.3d 1374, 1379 (Fed. Cir. 2007).

The '830 patent specification offers numerous specific definitions, some of which are more broad than conventional terminology. For example, the specification defines “amino acid” as including “residues of the natural amino acids . . . as well as unnatural amino acids,” including those “protected at the carboxy terminus” and “linked to the remainder of a compound of the invention through the carboxy terminus, the amino terminus, or through any other convenient point of attachment.” Ex. 1001, col.5, ll.39-63; Ex. 1011, ¶ 23.

Other definitions offered in the specification of the '830 patent are conventional. For example, the specification defines “halo” as “fluoro, chloro, bromo, or iodo” and “peptide” as “a sequence of 2 to 25 amino acids

or peptidyl residues.” Ex. 1001, col.5, ll.15 (“halo”), col.5, ll.63-65 (“peptide”) (internal parenthetical omitted). Undefined claim terms are conventional terminology. Ex. 1011, ¶ 24.

IV. PERSON OF ORDINARY SKILL IN THE ART

The art to which the ’830 patent is directed is the field of drug discovery. Drug discovery is a multi-stage, multidisciplinary process that involves numerous people over a period of several years and draws upon a broad variety of expertise, including chemical and biological expertise. It is unlikely that any one individual could ever possess all of the relevant knowledge in the art or all of the necessary training in each of the relevant disciplines, including designing target compounds, synthesizing them, and assessing their biological activity. Ex. 1011, ¶ 33.

To accurately reflect the process of drug discovery, the POSA would encompass a team having the knowledge, education, and skills ordinarily associated with the various disciplines involved in the process of drug discovery.⁴ Ex. 1011, ¶ 34.

⁴ This POSA definition applies throughout the range of dates applicable throughout this petition, from the December 9, 2004 filing of Applicant’s

A POSA would have included someone with a doctoral degree with a background in organic, synthetic, or medicinal chemistry, or possibly a related discipline such as pharmacology, and who also had some practical experience (e.g., at least two years) in drug discovery. This person could also have been someone with a bachelor's or master's degree in one of these disciplines but with greater practical experience (e.g., at least four years) in drug discovery. This person would possess certain skills and experience relevant to conducting the chemical aspects of drug discovery. Ex. 1011, ¶ 36.

Further, the POSA would have included someone with a doctoral degree with a background in virology, microbiology, or molecular biology who also had post-doctoral experience (e.g., at least two years). This person could also have been someone with a bachelor's or master's degree in one of these disciplines but with at least four years of practical experience. This person would possess certain skills and experience relevant to conducting the biological aspects of drug discovery. Ex. 1011, ¶ 37.

provisional application through the January 29, 2013 filing of Application No. 13/753,252. Ex. 1011, ¶ 35.

V. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

Petitioner requests an Order cancelling the Challenged Claims as unpatentable under 35 U.S.C. § 102.

A. Claims For Which Review Is Requested

Petitioner requests IPR of claims 1-9, 11-21, and 23-28 of the '830 patent.

B. The Specific Art On Which The Challenge Is Based

Because the claimed subject matter in the '830 patent is entitled to a priority date no earlier than March 28, 2014 (see Section VII *infra*), Sofia (Ex. 1004), published on January 21, 2010, is prior art under either pre-AIA 35 U.S.C. § 102(b) or post-AIA 35 U.S.C. § 102(a) because it was published more than one year before March 28, 2014.

C. The Statutory Grounds On Which The Challenge Is Based

This Petition identifies the following grounds of unpatentability:

Ground 1: Sofia anticipates claims 1-9, 11-21, and 23-28 under 35 U.S.C. § 102.

VI. EXPLANATION OF GROUNDS OF UNPATENTABILITY (37 C.F.R. § 42.104(b)(4))

A. Ground 1: Sofia Anticipates Claims 1-9, 11-21, and 23-28

The Challenged Claims should be found unpatentable because they are anticipated by Sofia.

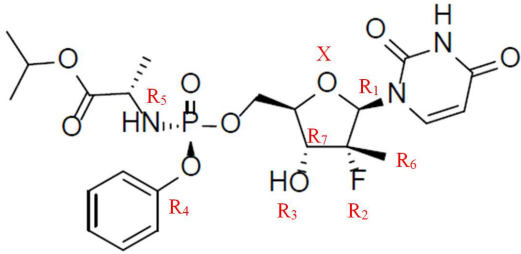
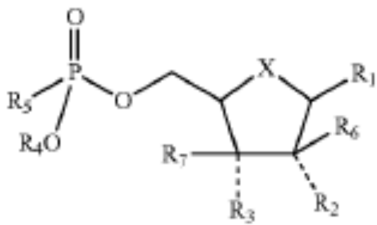
“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Federal Circuit case law “firmly establishes that a later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim.” *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 971 (Fed. Cir. 2001); *see also Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) (“When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art.”).

’830 patent claim 1 is the only independent claim, and claims a genus of nucleoside phosphoramidate prodrugs.

Sofia is directed to phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections, including hepatitis C viral infections, and specifically discloses sofosbuvir as example 25 (“Sofia 25”): “(S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-

phosphorylamino}-propionic acid isopropyl ester” (see, e.g., Ex. 1004, at 49, 58), represented by the chemical structure below:

Sofia 25	'830 patent
 The chemical structure of Sofia 25 is a complex molecule. It features a central phosphate group (P=O) linked to an isopropyl ester of L-alanine on the left and a nucleoside derivative on the right. The nucleoside part consists of a pyrimidine ring (uracil) attached to a sugar ring. Various substituents are labeled with R groups: R₁ is on the sugar ring, R₂ is a fluorine atom, R₃ is a hydroxyl group, R₄ is a phenyl group, R₅ is the isopropyl ester group, R₆ is a methyl group, and R₇ is a hydrogen atom. A substituent X is also shown on the sugar ring.	 The general chemical structure of the '830 patent is a nucleoside derivative. It shows a pyrimidine ring (uracil) attached to a sugar ring. The sugar ring has substituents R₁, R₂, R₃, R₆, and R₇. A substituent X is also shown on the sugar ring. The sugar ring is linked to a phosphate group (P=O) which is further linked to an ester group (R₄O) and another group (R₅).

Patent Owner has asserted in the above-referenced patent infringement litigation between the parties here that Sofia 25 meets every limitation of '830 patent claim 1 where:

R₁ is uracil;

R₂ is fluoro;

R₃ is hydroxy;

R₄ is phenyl;

R₅ is an amino acid (i.e., the isopropyl ester of L-alanine);

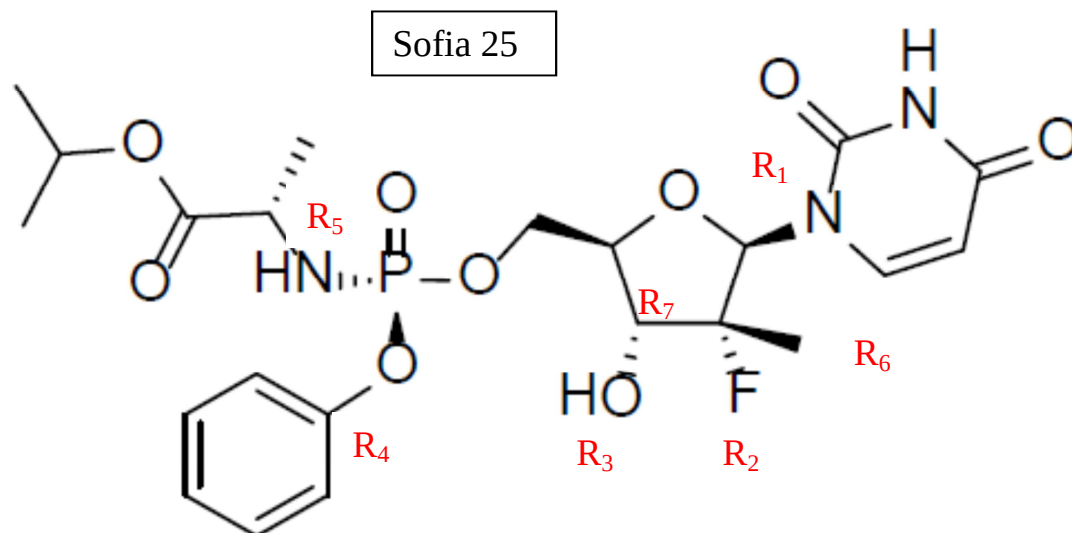
R₆ is methyl;

R₇ is hydrogen; and

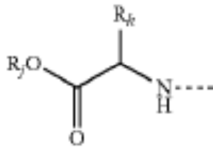
X is oxy.

Ex. 1003, ¶¶ 47-48; *see also* Ex. 1011, ¶ 143. Further, in its March 31, 2014 preliminary amendment, Applicant argued that selection of the specific classes of R group substituents of '830 patent claim 1 was supported in the applications to which the '830 patent claimed priority and, therefore, Sofia 25 is not prior art. Ex. 1002, at 84-85 (Apr. 23, 2014 Supplemental Preliminary Amendment, at 10-11, tbl.A). Thus, under Patent Owner's interpretation of the Challenged Claims, Sofia 25 anticipates '830 patent claim 1. *See In re Slayter*, 276 F.2d 408, 411 (C.C.P.A. 1960) ("It is well settled that a generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus; in other words, whatever would infringe if subsequent will anticipate if prior.") Dependent claims 2-9 and 11-12 of the '830 patent are also anticipated by Sofia 25, as shown in the claim chart below (Table 1).

TABLE 1. Anticipation of '830 Patent Dependent Claims 2-9 and 11-12 By Sofia 25



Claim	'830 Patent	Sofia 25
2	The compound or salt of claim 1 wherein R ₁ is guanine, cytosine, thymine, 3-deazaadenine, or uracil .	R ₁ =uracil
3	The compound or salt of claim 1 wherein R ₁ is cytosine, thymine, 3-deazaadenine, or uracil .	R ₁ =uracil
4	The compound or salt of claim 1 wherein R ₁ is cytosine, thymine, or uracil .	R ₁ =uracil
5	The compound or salt of claim 1 wherein R ₁ is a nitrogen linked radical of formula VI: VI	R ₁ =uracil (R _{af} and R _{ag} = hydrogen)

Claim	'830 Patent	Sofia 25
	wherein R_{af} is hydrogen , halo, (C ₁ -C ₆)alkyl, (C ₃ -C ₆)cycloalkyl, or trifluoromethyl; and R_{ag} is hydrogen , (C ₁ -C ₆)alkyl, (C ₃ -C ₆)cycloalkyl, trifluoromethyl, hydroxyl(C ₁ -C ₆)alkyl, or –(CH ₂) ₁₋₄ P(=O)(OR _w) ₂ .	
6	The compound or salt of claim 1 wherein R ₂ is fluoro .	R ₂ =fluoro
7	The compound or salt of claim 1 wherein R₅ is a nitrogen linked radical of formula III:  III wherein R_h is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkyl-S—(C₁-C₆)alkyl-, aryl, heteroaryl, aryl(C₁-C₆)alkyl, or heteroaryl(C₁-C₆)alkyl; wherein any aryl or heteroaryl may optionally be substituted with 1, 2, or 3 Z; R_j is hydrogen, (C₁-C₆)alkyl, phenyl, benzyl, or phenethyl; and wherein each Z is independently halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl,	R₅=isopropyl ester of L-alanine (R_h=methyl and R_j=isopropyl, both (C₁-C₆)alkyls)

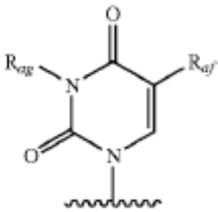
Claim	'830 Patent	Sofia 25
	trifluoromethoxy, nitro, cyano, or amino.	
8	The compound or salt of claim 7 wherein R _h is hydrogen, (C ₁ -C ₆)alkyl, phenylmethyl, or 3-indolylmethyl.	R _h =methyl
9	The compound or salt of claim 8 wherein R _j is hydrogen or (C ₁ -C ₆)alkyl.	R _j =isopropyl
11	The compound or salt of claim 1 wherein R ₅ is a (C ₁ -C ₆)alkyl ester of L-alanine.	R ₅ =isopropyl ester of L-alanine
12	The compound or salt of claim 11 wherein R ₇ is hydrogen.	R ₇ =hydrogen

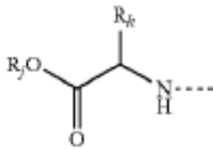
Ex. 1011, ¶¶ 144-51.

'830 patent claim 13 recites: “A method for treating a viral infection in an animal comprising administering to an animal in need of such treatment an effective amount of a compound or salt of formula I according to claim 1.” Claim 8 of Sofia recites a method of treating a subject in need thereof by administering a therapeutically effective amount of Sofia 25. Ex. 1004, at 65-66. Sofia further states that: “The present invention pertains to nucleoside phosphoramidates and their use as agents for treating viral diseases.” Ex. 1004, at 1 ¶ 0001. Thus, Sofia 25's use in a method for treating viral infections is disclosed in Sofia. Ex. 1011, ¶ 152. Dependent

claims 14-21 and 23-24 of the '830 patent are anticipated by Sofia 25 as shown in the claim chart below (Table 2).

TABLE 2. Anticipation of '830 Patent Dependent Claims 14-21 and 23-24 By Sofia 25

Claim	'830 Patent	Sofia 25
14	The method of claim 13 wherein R ₁ is guanine, cytosine, thymine, 3-deazaadenine, or uracil .	R ₁ =uracil
15	The method of claim 13 wherein R ₁ is cytosine, thymine, 3-deazaadenine, or uracil .	R ₁ =uracil
16	The method of claim 13 wherein R ₁ is cytosine, thymine, or uracil .	R ₁ =uracil
17	The method of claim 13 wherein R₁ is a nitrogen linked radical of formula VI:  VI wherein R_{af} is hydrogen, halo, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, or trifluoromethyl; and R_{ag} is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, trifluoromethyl, hydroxyl(C₁-C₆)alkyl, or – (CH₂)₁₋₄P(=O)(OR_w)₂.	R₁=uracil (R_{af} and R_{ag} = hydrogen)
18	The method of claim 13 wherein R ₂ is fluoro .	R ₂ =fluoro

Claim	'830 Patent	Sofia 25
19	The method of claim 13 wherein R₅ is a nitrogen linked radical of formula III:  III wherein R_h is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkyl-S—(C₁-C₆)alkyl-, aryl, heteroaryl, aryl(C₁-C₆)alkyl, or heteroaryl(C₁-C₆)alkyl; wherein any aryl or heteroaryl may optionally be substituted with 1, 2, or 3 Z; R_j is hydrogen, (C₁-C₆)alkyl, phenyl, benzyl, or phenethyl; and wherein each Z is independently halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, or amino.	R₅=isopropyl ester of L-alanine (R_h=methyl and R_j=isopropyl, both (C₁-C₆)alkyls)
20	The method of claim 19 wherein R _h is hydrogen, (C₁-C₆)alkyl , phenylmethyl, or 3-indolylmethyl.	R _h =methyl
21	The method of claim 20 wherein R _j is hydrogen or (C₁-C₆)alkyl .	R _j =isopropyl
23	The method of claim 13 wherein R ₅ is a (C₁-	R ₅ =isopropyl ester

Claim	'830 Patent	Sofia 25
	C₆)alkyl ester of L-alanine.	of L-alanine
24	The method of claim 23 wherein R ₇ is hydrogen.	R ₇ =hydrogen

Ex. 1011, ¶¶ 153-60.

'830 patent claim 25 recites: “The method of claim 13 wherein the viral infection is caused by HCV.” Claim 8 of Sofia recites a method of treating a subject in need thereof by administering a therapeutically effective amount of Sofia 25. Ex. 1004, at 65-66. Sofia further states that:

The present invention pertains to nucleoside phosphoramidates and their use as agents for treating viral diseases. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of HCV NS5B polymerase, as inhibitors of HCV replication and for treatment of hepatitis C infection in mammals.

Ex. 1004, at 1 ¶ 0001. Thus, Sofia 25's use in a method for treating HCV is disclosed in Sofia. Ex. 1011, ¶ 161.

'830 patent claim 26 recites: “The method of claim 13 wherein the animal is a human.” Claim 8 of Sofia recites a method of treating a subject in need thereof by administering a therapeutically effective amount of Sofia 25. Ex. 1004, at 65-66. “Subject” is defined to mean a mammal, preferably

a human, in the specification of Sofia. *See* Ex. 1004, at 32 ¶ 0817. Thus, Sofia 25's use in a method for treating viral infections in humans is disclosed in Sofia. Ex. 1011, ¶ 162.

'830 patent claim 27 recites: "The method of claim 26 wherein the compound or salt of formula I is orally administered." Claim 8 of Sofia recites a method of treating a subject in need thereof by administering a therapeutically effective amount of Sofia 25. Ex. 1004, at 65-66. The specification of Sofia states: "The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms and carriers." *See* Ex. 1004, at 30 ¶ 0801. Thus, Sofia 25's use in an orally administered formulation for treating viral infections in humans is disclosed in Sofia. Ex. 1011, ¶ 163.

'830 patent claim 28 recites: "A pharmaceutical composition comprising a compound or salt of formula I as described in claim 1 and a pharmaceutically acceptable vehicle or carrier." Claim 4 of Sofia recites: "A composition for the treatment and/or prophylaxis of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium" in combination with Sofia 25. *See* Ex. 1004, at 57-58. Thus, a

pharmaceutical composition comprising Sofia 25 in a pharmaceutically acceptable carrier is disclosed in Sofia. Ex. 1011, ¶ 164.

Because the '830 patent is entitled to a priority date no earlier than March 28, 2014 (see Section VII *infra*), Sofia 25 is an anticipatory prior art species to the genus disclosed in the '830 patent. Sofia published on January 21, 2010, more than one year before the earliest effective filing date of the '830 patent and expressly discloses each element in the Challenged Claims of the '830 patent, rendering every Challenged Claim unpatentable.

VII. EFFECTIVE FILING DATE OF THE CHALLENGED CLAIMS

The '830 patent, which issued from U.S. Patent Application No. 14/229,292 filed on March 28, 2014, asserts claims of priority to earlier applications. The related U.S. Application Data identified on the face of the '830 patent is:

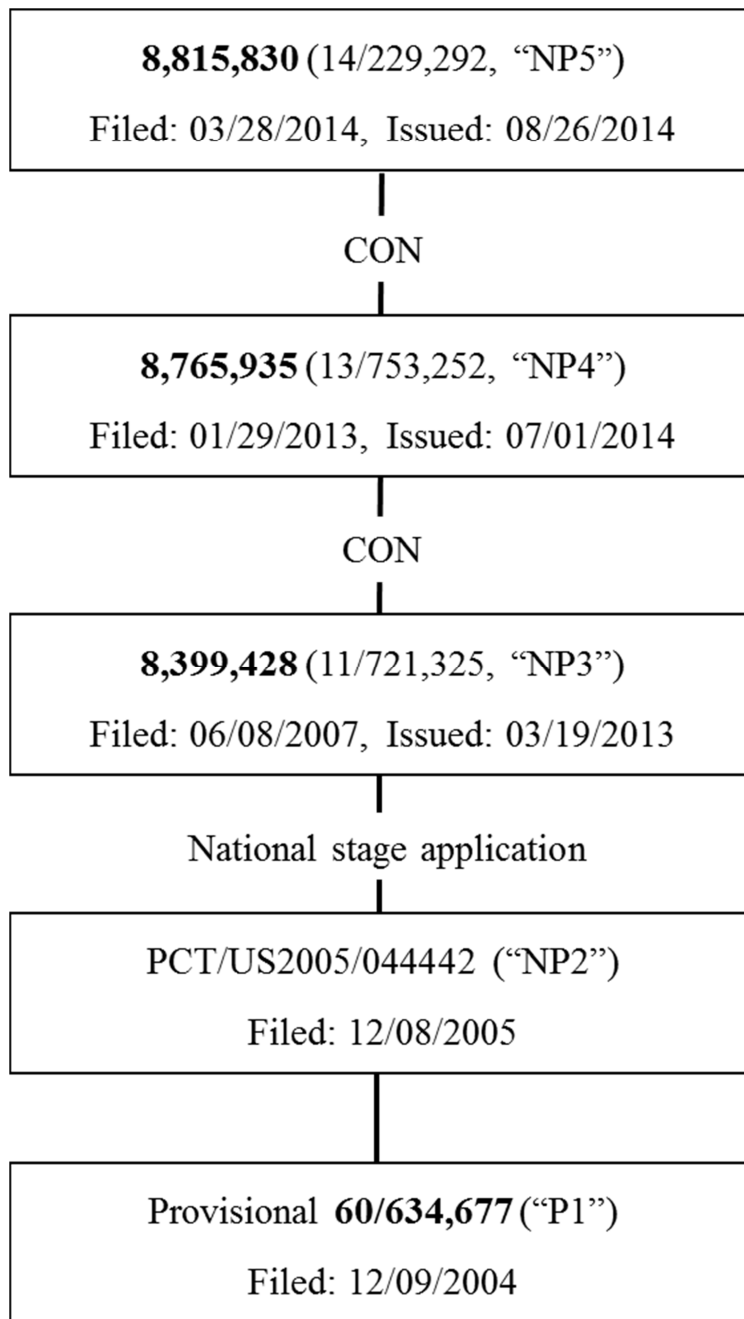
Continuation of application No. 13/753,252 [Ex. 1005, "NP4"], filed on Jan. 29, 2013, which is a continuation of application No. 11/721,325 [Ex. 1006, "NP3"], filed as application No. PCT/US2005/044442 [Ex. 1007, "NP2"] on Dec. 8, 2005, now Pat. No. 8,399,428.

Provisional application No. 60/634,677 [Ex. 1008, "P1"].

Ex. 1001, at [60], [63], *see also* col.1 ll.7-16.

NP4, filed on January 29, 2013, issued as U.S. Patent No. 8,765,935 (Ex. 1009). NP4 is an alleged continuation of NP3, filed on June 8, 2007, which issued as U.S. Patent No. 8,399,428 (Ex. 1010). NP3 was a national stage filing of NP2, filed on December 8, 2005, and contains the same disclosure as NP2 (NP3 and NP2 will hereinafter be referred to as “NP3/NP2”). NP3/NP2 claims priority to P1, filed on December 9, 2004.

NP4, NP3/NP2, and P1 are collectively referred to herein as the “Alleged Priority Applications.” For ease of reference, the following chart provides a graphical depiction of the alleged claims of priority in the chain leading to the ’830 patent.



The Challenged Claims of the '830 patent are not entitled to the benefit of the Alleged Priority Applications due to lack of written description support in the Alleged Priority Applications.

A. The Alleged Priority Applications Do Not Provide Written Description Support For The Challenged Claims And Thus They Are Not Entitled To A Priority Date Earlier Than March 28, 2014

To claim priority from an earlier application under 35 U.S.C. §§ 119 or 120, each application to which priority is claimed must comply with the written description requirement of 35 U.S.C. § 112. *Zenon Envtl., Inc. v. U.S. Filter Corp.*, 506 F.3d 1370, 1378 (Fed. Cir. 2007). In other words, “claims added during prosecution must find support sufficient to satisfy § 112 in the written description of the original priority application[s].” *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1344 (Fed. Cir. 2013).

“To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that ‘the inventor invented the claimed invention.’” *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997) (quoting *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997)); see also *Novozymes*, 723 F.3d at 1344 (“A ‘mere wish or plan’ for obtaining the claimed invention does not satisfy the written description requirement.”).

The patent specification itself must demonstrate possession of the full scope of what is claimed for written description purposes – “actual

‘possession’ or reduction to practice outside of the specification is not enough.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010); *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011) (concluding that one must make an “‘objective inquiry into the four corners of the specification’” from the perspective of a POSA to determine written description support). Therefore, the Alleged Priority Applications must demonstrate possession of the full scope of the compounds claimed in the ’830 patent.

A broad generic description of an invention does not provide written description support to that genus unless the description: (1) discloses a representative number of species falling within the scope of the genus or (2) includes preferences that narrow the genus to a sufficiently small disclosure so that a POSA can easily “visualize or recognize” the members of the genus. *Ariad*, 598 F.3d at 1349-50 (“[A]n adequate written description of a claimed genus requires more than a generic statement of an invention’s boundaries.”).

Whether the written description requirement for a genus is met by a particular disclosure is a question of fact, *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1297 (Fed. Cir. 2014), and is analyzed as of the filing date of the application at issue. *Ariad*, 598 F.3d at 1355.

Factors relevant to evaluating the written description of genus claims include the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the predictability of the aspect at issue. *Id.* at 1351.

1. P1 Does Not Provide Written Description Support For The Challenged Claims And Thus They Are Not Entitled To The Benefit Of P1

P1, the first application in the alleged chain of priority, was filed on December 9, 2004. The existing knowledge as of December 9, 2004 in the field of antiviral or anticancer nucleosides was progressing, although the state of the art progressed at different rates for different indications. For example, HIV drug discovery was progressing at a faster rate than HCV drug discovery at this time.

Researchers were investigating nucleosides and nucleotides in the fields of antiviral and anticancer therapeutics, and there was a general awareness of the desirability of using nucleotides to bypass the first kinase phosphorylation step to decrease drug resistance, and the use of nucleotide prodrugs to mask the negative charges associated with nucleotides and permit cellular delivery of the antiviral agent. Ex. 1011, ¶ 40; Ex. 1013; Ex. 1014; Ex. 1015; Ex. 1016. As of December 9, 2004 there were no FDA-approved phosphoramidate nucleoside prodrugs. Ex. 1011, ¶ 41.

A POSA understood the large and unpredictable differences in the stereoselective metabolic rate of the pronucleotide series that could profoundly affect activity and toxicity, particularly for phosphoramidates. Ex. 1011, ¶ 42; Ex. 1017. Applicant also studied AZT phosphoramidates to deliver AZT-monophosphate and found that different levels of expression of 5'-nucleotidase were cell dependent which affected the efficiency and delivery of the phosphoramidate prodrug. Ex. 1011, ¶ 43; Ex. 1018.

P1 acknowledges the uncertainties and early stage of nucleoside phosphoramidate prodrug understanding and development. See Ex. 1008, at 1 (“HINTs have been associated *only recently* with adenosine phosphoramidate activity.” (emphasis added)); *id.* at 2 (“[T]he nature of the enzyme responsible for phosphoramidate hydrolysis has not been determined.”).

For a genus to provide written description support of a particular species or subgenus, the specification must (1) disclose a representative number of species to support the full scope of the claims or (2) include preferences that narrow the genus to a sufficiently small disclosure so that a POSA can easily “visualize or recognize” the members of the genus. *Ariad*, 598 F.3d at 1349-50. P1 contains neither of these aspects of disclosure. The P1 genera encompasses an enormous number of compounds and P1 provides

no direction towards any particular combination of substituents. Ex. 1011, ¶ 52.

Notwithstanding certain similarities in the broad general formulas provided in the specifications of P1 and the '830 patent, the subgenus claimed in '830 patent claim 1, which requires R₂ to be halo; R₃ to be hydroxy; R₅ to be amino acid; and R₆ and R₇ to be independently H or (C₁-C₆)alkyl, does not have written description support in P1. There is no disclosure in P1 that would lead a POSA to conclude that Applicant had possession of this subgenus as of the filing date of P1. While the disclosures of P1 include R groups encompassing the substituents claimed in the narrowed R groups in the '830 patent claims, there are no blaze marks directing a POSA to those later claimed combinations of narrowed substituents, leaving the POSA with the insurmountable task of picking and choosing R groups from the broad genera in P1, with no guidance directing the POSA to the selections claimed in the narrowed subgenus of the '830 patent. Ex. 1011, ¶ 51. As is manifestly evident, to arrive at that later-claimed '830 patent subgenus, Applicant was guided by a compound it did not invent, sofosbuvir, in re-assembling R groups from P1.

a. **There Are No Blaze Marks In P1 That Would Direct A POSA To Compounds Falling Within**

The Full Scope Of The '830 Patent Claim 1 Subgenus

As is readily apparent, P1 discloses a large number of substituents for R₂, R₃, R₅, R₆, and R₇. See Ex. 1008, at 2:15-3:13. The possible combinations for these substituents is enormous. Ex. 1011, ¶ 59.

Differences between the genera disclosed in P1 and the subgenus claimed in '830 patent claim 1 is shown in Table 3 below.

TABLE 3. Comparison of Substituents Between P1 and the '830 patent

	P1	'830 patent claim 1
R₂	H, halo, hydroxy, (C ₁ -C ₆)alkyl, (C ₃ -C ₆)cycloalkyl, (C ₁ -C ₆)alkoxy, (C ₃ -C ₆)cycloalkyloxy, (C ₁ -C ₆)alkanoyl, (C ₁ -C ₆)alkanoyloxy, trifluoromethyl, azido, cyano, -N(R _z)C(=O)N(R _{aa})(R _{ab}), -N(R _z)C(=O)OR _{ac} , or NR _{ad} R _{ae} , provided that one of R ₂ and R ₆ is hydroxy halo, (C ₁ -C ₆)alkoxy, (C ₃ -C ₆)cycloalkyloxy, trifluoromethyl, cyano, or NR _{ad} R _{ae} ; R _z is H, (C ₁ -C ₆)alkyl, (C ₃ -C ₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 3:23-4:2]; R _{aa} and R _{ab} are each independently H, (C ₁ -C ₆)alkyl, (C ₃ -C ₆)cycloalkyl, phenyl, benzyl, or phenethyl; or R _{aa} and R _{ab} together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino [Ex. 1008, at 4: 24-26]; R _{ac} is H, (C ₁ -C ₆)alkyl, (C ₃ -C ₆)cycloalkyl, phenyl, benzyl,	halo

	P1	'830 patent claim 1
	or phenethyl [Ex. 1008, at 4: 27-28]; R_{ad} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 29-30]; R_{ae} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 5: 1-2].	
R₃	H, halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, azido, cyano, -N(R_z)C(=O)N(R_{aa})(R_{ab}), -N(R_z)C(=O)OR_{ac}, or NR_{ad}R_{ae} [Ex. 1008, at 4: 3-6]; R_z is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 3:23-4:2]; R_{aa} and R_{ab} are each independently H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl; or R_{aa} and R_{ab} together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino [Ex. 1008, at 4: 24-26]; R_{ac} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 27-28]; R_{ad} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 29-30]; R_{ae} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 5: 1-2].	hydroxy
R₅	amino acid, peptide, or NR _a R _b [Ex. 1008, at 3: 9];	amino acid

	P1	'830 patent claim 1
	The term “peptide” describes a sequence of 2 to 25 amino acids or peptidyl residues. The sequence may be linear or cyclic. A peptide can be linked to the remainder of a compound of formula I through the carboxy terminus, the amino terminus, or through any other convenient point of attachment. Preferably, a peptide comprises 2 to 25, or 5-25 amino acids. [Ex. 1008, at 8: 18-22]; Each R_a and R_b is independently H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl, or aryl(C₁-C₆)alkyl; or R_a and R_b together with the nitrogen to which they are attached form a pyrrolidino, piperidino or morpholino [Ex. 1008, at 4: 15-17].	
R₆	H, halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, azido, cyano, -N(R_z)C(=O)N(R_{aa})(R_{ab}), -N(R_z)C(=O)OR_{ac}, or NR_{ad}R_{ae}, provided that one of R₂ and R₆ is hydroxy halo, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, trifluoromethyl, cyano, or NR_{ad}R_{ae} [Ex. 1008, at 3:23-4:2]; R_z is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 3:23-4:2]; R_{aa} and R_{ab} are each independently H, (C₁-C₆)alkyl, (C₃-	H or (C ₁ -C ₆)alkyl

	P1	'830 patent claim 1
	C₆)cycloalkyl, phenyl, benzyl, or phenethyl; or R_{aa} and R_{ab} together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino [Ex. 1008, at 4: 24-26]; R_{ac} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 27-28]; R_{ad} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 29-30]; R_{ae} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 5: 1-2].	
R₇	H, halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, azido, cyano, -N(R_z)C(=O)N(R_{aa})(R_{ab}), -N(R_z)C(=O)OR_{ac}, or NR_{ad}R_{ae}; R_z is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 3:23-4:2]; R_{aa} and R_{ab} are each independently H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl; or R_{aa} and R_{ab} together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino [Ex. 1008, at 4: 24-26]; R_{ac} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 27-28];	H or (C ₁ -C ₆)alkyl

	P1	'830 patent claim 1
	R_{ad} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 29-30]; R_{ae} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 5: 1-2].	

While '830 patent claim 1 purports to narrow the scope of substituents disclosed in P1, there are no blaze marks in P1 to guide a POSA through “the forest of disclosed possibilities” toward the '830 patent claim 1 subgenus. Ex. 1011, ¶ 53. See *Novozymes*, 723 F.3d at 1345; *In re Ruschig*, 379 F.2d 990, 994-95 (C.C.P.A. 1967); see also *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996) (“In the absence of such blazemarks, simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or subgenuses.”).

The absence of blaze marks is critical in determining whether P1 demonstrates that Applicant was in possession of the subject matter claimed in '830 patent claim 1 because a combinatorial calculation based on the number of Markush elements (“classes of R group substituents”) encompassed by R₂, R₃, R₅, R₆, and R₇ in P1 formula I (the R groups narrowed in '830 patent claim 1) results in 7,441,875 possible combinations

of classes of R group substituents from which the later claimed '830 patent subgenus is derived. Ex. 1011, ¶¶ 54-60.

Further, P1 does not disclose preferred definitions for each R group substituent in Formula I (*see infra* at 43). Nor does P1 teach any improved properties, such as improved antiviral or anticancer activity for compounds with the R groups selected in the '830 patent claim 1 subgenus. The POSA is simply left to wander in a vast forest without direction to the later claimed trees reflecting the '830 patent subgenus. *See Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1326-27 (Fed. Cir. 2000) (“[O]ne cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention. In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure.”).

The '830 patent subgenus selects one substituent (halo) out of 15 possibilities for R₂, one substituent (hydroxy) out of 15 possibilities for R₃, one substituent (amino acid) out of three possibilities for R₅, two substituents [H or (C₁-C₆)alkyl] out of 15 possibilities for R₆, and two substituents [H or (C₁-C₆)alkyl] out of 15 possibilities for R₇. This is akin to selecting **seven** trees from a forest of **7,441,875** trees, with no guidance in P1 pointing the POSA to those seven particular trees. Ex. 1011, ¶ 61.

Importantly, instead of guiding a POSA to those later claimed classes of R group substituents, P1 actually directs a POSA to select other classes of R group substituents by teaching that compounds “useful in the methods of the invention” (Ex. 1008, at 7) have **hydroxy at R₂** (Ex. 1008, fig.3) and the only synthetic scheme taught in P1 for making the compounds of the invention is one that results in **hydroxy at R₂** (Ex. 1008, fig.1). Ex. 1011, ¶ 61. Taken together, a POSA would understand that the disclosure in P1 was not sufficient to demonstrate that Applicant had possession of the subgenus later claimed in ’830 patent claim 1. Ex. 1011, ¶ 62.

Where an applicant adds claims during prosecution of a later application that were not included in the original priority application, such as was done here, the Federal Circuit requires a “detailed description and identification of the later-claimed invention in that original disclosure, particularly where the specification discloses numerous possibilities with scant guidance on which to select.” *Novozymes*, 723 F.3d at 1345.

In *Novozymes*, upon learning that its competitor (DuPont) had introduced a competitor alpha-amylase product into the market, the patent applicant (Novozymes) filed a continuation application containing subgenus claims covering DuPont’s alpha-amylase product that claimed priority from an application filed nine years earlier that disclosed a broader genus. *Id.* at

1341. Novozymes filed a patent infringement action against DuPont after the patent issued. *Id.* at 1342. The Federal Circuit affirmed a finding of inadequate written description for the later claimed subgenus. The subgenus claims were directed to alpha-amylase variants having 90% sequence identity to the wild-type alpha-amylase with a specific amino acid substitution of serine at position 239, whereas the application to which applicant claimed priority described a broad genus of a “potentially wide range of alpha-amylase variants,” did not specifically recite the claimed subgenus, and gave scant guidance on which species/subgenus out of the numerous possibilities to select. *Id.* at 1340.

This is the precise set of circumstances here. Applicant previously described a broad genus of compounds in P1, nowhere reciting the later claimed '830 patent subgenus. Further, P1 gives scant guidance on which classes of R groups substituents to select out of the over 7,000,000 possibilities. Ex. 1011, ¶¶ 60-61.

b. P1 Does Not Disclose Any Compounds Or Examples Falling Within The '830 Patent Claim 1 Subgenus And The Compounds That Are Disclosed Teach Away From That Subgenus

P1 does not disclose any representative species or subgenus that falls within the scope of '830 patent claim 1. Nor does P1 contain any examples

of compounds that fall within that subgenus. *See Boston Scientific*, 647 F.3d at 1364 (“Although examples are not always required to satisfy the written description requirement, the lack of any disclosure of examples may be considered when determining whether the claimed invention is adequately described.”). Thus, there is no teaching or suggestion anywhere in P1 to select the particular combination that would result in ’830 patent claim 1. Ex. 1011, ¶¶ 63-64.

The only “illustrative” compounds defined as “useful in the methods of the invention,” or for which a synthetic scheme is provided are shown in Figures 1 and 3 of P1, and all of those compounds have **hydroxy at R_2** , which is not within the scope of ’830 patent claim 1. *See* Ex. 1008, fig.1, 3. Thus, P1’s “illustrative” compounds teach a preference for compounds that do not fall within the scope of ’830 patent claim 1 which requires **R_2 to be halo**. Instead, P1’s “illustrative” compounds would be understood by a POSA as demonstrating that Applicant was not in possession of ’830 patent claim 1 as of the filing date of P1. Ex. 1011, ¶ 65.

Further, P1 also teaches that compounds containing an electropositive group at the 2’-position are “especially good substrates for hHINT1.” Ex. 1008, at 3: 3-11. Halogens, and in particular fluorine, are electronegative,

not electropositive; indeed, *fluorine is the most electronegative element in the periodic table*. Ex. 1011, ¶¶ 66-67; Ex. 1021.

Based on P1's teaching that electropositive groups at the 2'-position are favored for phosphoramidate hydrolysis, a POSA understood that P1 did not provide any blaze marks to direct him or her to select halo, a term that encompasses some of the most electronegative atoms in the periodic table, at R₂. Therefore, a POSA understood that Applicant was not in possession of the '830 patent claim 1 subgenus which requires R₂ to be halo, as of the filing date of P1. Ex. 1011, ¶ 68.

c. **The Alleged Multiple Dependent Claim “Preferences” In P1 Do Not Provide Written Description Support Because The Large Number Of Multiple Dependent Claims That Refer Back To Other Multiple Dependent Claims Result In An Enormous Number Of Possibilities**

Patent Owner may point to P1's numerous multiple dependent claims as allegedly showing “preferences” for the classes of R group substituents claimed in the '830 patent subgenus. But such an argument can only be made using hindsight because there is nothing in P1 singling out those classes of R group substituents, either as “preferred” embodiments of the invention or as demonstrating superior antiviral or anticancer activity. Ex. 1011, ¶ 69.

Even assuming *arguendo* that the claims of P1 illustrate some “preference” for the classes of R group substituents recited in the ’830 patent claims, there are still no blaze marks directing a POSA to select those R groups from different R groups recited in other claims. Ex. 1011, ¶ 70.

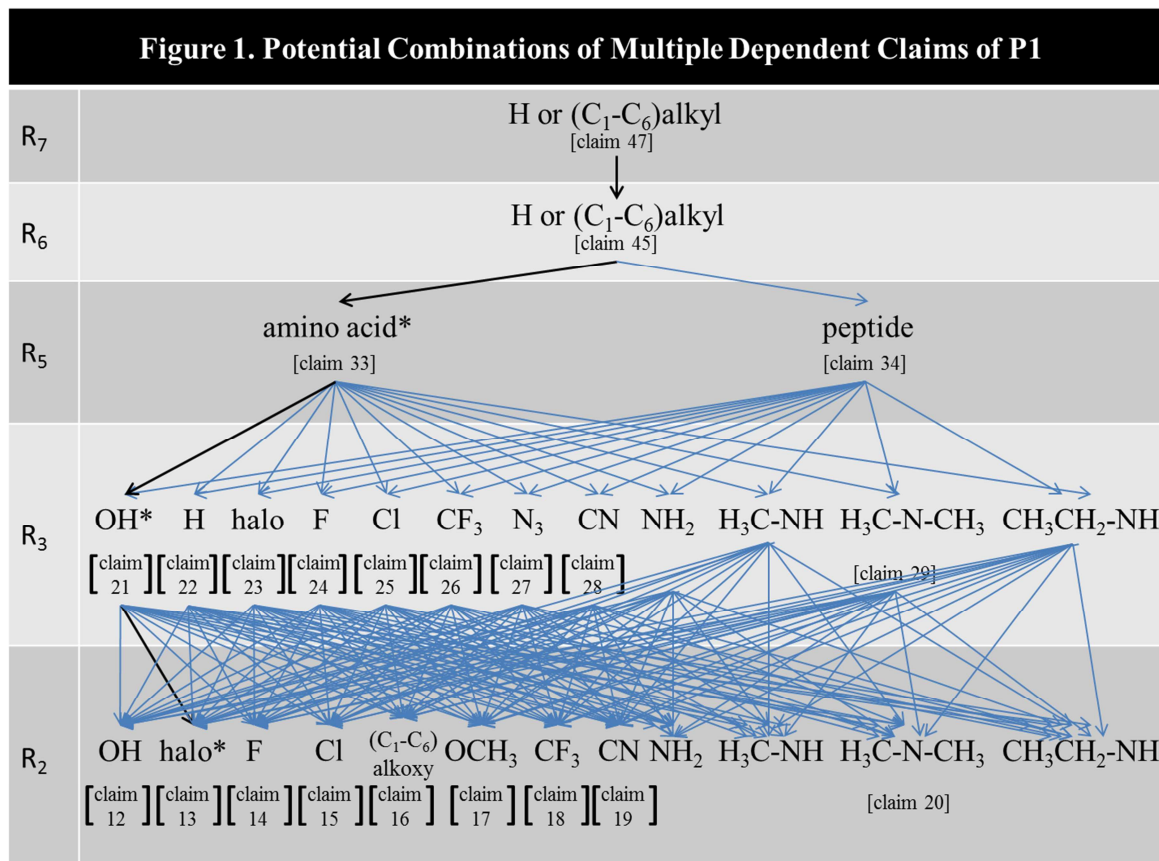
For example, while claim 13 of P1 specifies R₂ as halo, ***other claims specify R₂ can be hydroxy (claim 12); fluoro (claim 14); chloro (claim 15); (C₁-C₆)alkoxy (claim 16); methoxy (claim 17); trifluoromethyl (claim 18); cyano (claim 19); or “amino, methylamino, dimethylamino, ethylamino, or dimethylamino” (claim 20).*** Ex. 1008, at 23. While claim 21 specifies R₃ as hydroxy, ***other claims specify R₃ can be hydrogen (claim 22); halo (claim 23); fluoro (claim 24); chloro (claim 25); trifluoromethyl (claim 26); azido (claim 27); cyano (claim 28); or “amino, methylamino, dimethylamino, ethylamino, or dimethylamino” (claim 29).*** Ex. 1008, at 23-24. While claim 33 specifies R₅ as amino acid, ***other claims specify that R₅ can be a peptide (claim 34), which is defined in P1 as “a sequence of 2 to 25 amino acids . . . or peptidyl residues.”*** Ex. 1008, at 8: 18-19. See also Ex. 1011, ¶¶ 71-73.

Additionally, these claims are all multiple dependent claims which themselves depend from large numbers of other multiple dependent claims. For example, claim 47 states: “The compound of any one of ***claims 1-46***

wherein R₇ is hydrogen or (C₁-C₆)alkyl.” Ex. 1008, at 27. There are no blaze marks in this claim or any of the claims of P1 specifically pointing to the substituents recited in ’830 patent claim 1. Ex. 1011, ¶ 74. This leads to an enormous number of possible combinations. For example, even if claim 47 were to be understood by a POSA as demonstrating a “preference” for R₇ as hydrogen or (C₁-C₆)alkyl, claim 47 still represents 70,875 classes of R group substituents for R₂, R₃, R₅, and R₆ with no blaze marks in P1 to direct the POSA to the classes of R group substituents later claimed in the ’830 patent claim 1 subgenus. Ex. 1011, ¶ 74.

It would require hindsight to pick (among 46 claim possibilities in claim 47) claims 13, 21, 33, and 45 to combine with that claim. There is no disclosure in P1 pointing a POSA in the direction of choosing any of those claims over any others. A POSA could just as likely combine claim 17 (where R₂ is methoxy), claim 27 (where R₃ is azido), and claim 35 (where R₅ is a peptide), in combination with claim 47, or any other combination of claims. Ex. 1011, ¶ 75. *See Novozymes*, 723 F.3d at 1349 (concluding that written description support in a prior application must be viewed from the vantage point of a POSA with no foreknowledge of the later-claimed compound or subgenus).

Even limited by picking and choosing from P1's claims, which is a vast underestimation of the problem to be solved (giving Patent Owner the benefit of the doubt in even starting with claim 47), those combinations still present an enormous number of possibilities as shown in Figure 1 below.

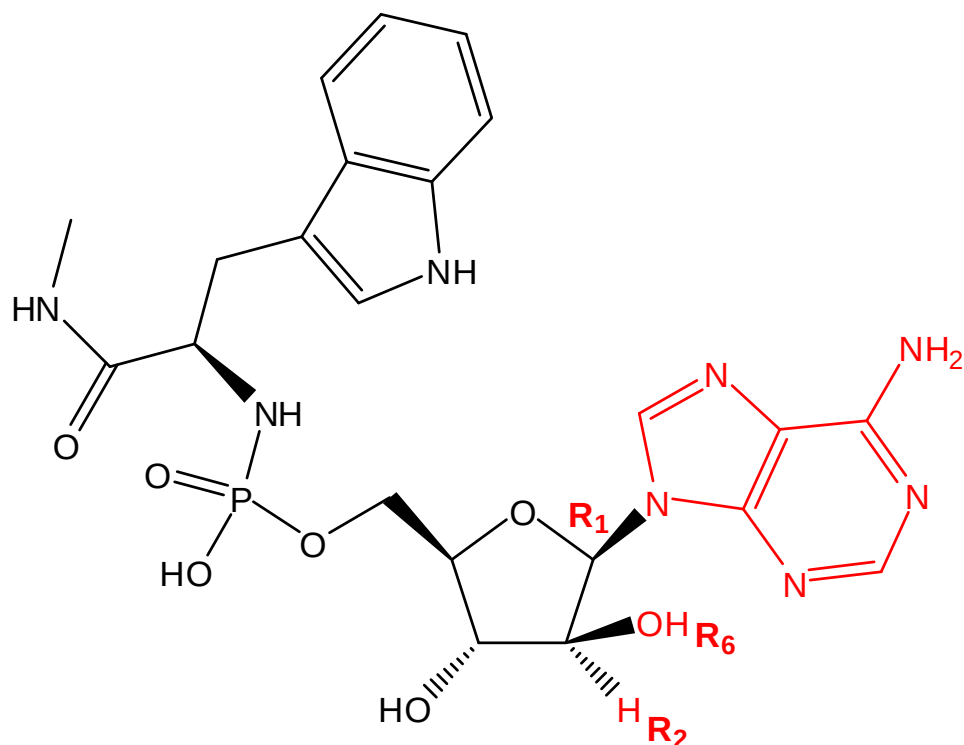


Given that P1's claims recite multiple classes of R group substituents for each of R₂, R₃ and R₅, and the lack of blaze marks in P1 to direct a POSA to select R₂ as halo, R₃ as hydroxy, and R₅ as amino acid (as specifically claimed in the '830 patent claim 1 subgenus) from the 7,441,875 other possible combinations, a POSA would understand that Applicant was not in possession of the '830 patent claim 1 subgenus as of the filing date of P1.

And, as discussed in detail in subsection (b) above, the disclosure of P1 actually points a POSA away from choosing any of the halogens at R_2 because they are strongly electronegative and the disclosure in P1 ***focused on electropositive groups at R_2*** . Ex. 1011, ¶ 76.

Another disclosure in P1 that would direct a POSA to select something other than R_2 as halogen is claim 46, which recites a subgenus which ***excludes R_2 as being halogen and excludes R_6 as being hydrogen***. Ex. 1008, at 26. This would not direct a POSA to what is claimed in the '830 patent, which limits R_2 to halogen and R_6 to hydrogen and (C_1-C_6) alkyl. Ex. 1011, ¶ 77.

And, importantly, the only compound expressly disclosed by name in P1, which is recited in claim 49 (Ex. 1008, at 27), is (2-(3-indolyl)-1(R)-methylcarbamoylethyl)phosphoramidic acid mono (1-B-arabinofuranosyladenosine)ester (illustrated below). This compound ***contains hydrogen at R_2*** , which would be understood by a POSA as directing him or her to compounds that ***do not have halogen at R_2*** . Ex. 1011, ¶ 78.



Further, the compound disclosed in claim 49 contains adenine at R_1 whereas *all of the '830 patent claims exclude adenine* at that position, and contains hydroxy at R_6 whereas *all of the '830 patent claims exclude hydroxy* at that position. Ex. 1011, ¶ 79.

In addition to directing a POSA to select a substituent at R_1 , R_2 , and R_6 that is not within the scope of the '830 patent claims, other disclosures in P1 would direct a POSA to select a substituent at R_3 that is not within the scope of those claims. For example, claim 48 of P1 recites a subgenus where *R_3 is hydrogen or alkyl*. Ex. 1008, at 27. Just as claims 46 and 49 would direct a POSA to select something other than R_2 as halogen, claim 48

would direct a POSA to select something other than R₃ as hydroxy. Ex. 1011, ¶ 80.

Taken together, the claims of P1 would direct a POSA to select substituents for the R₁, R₂, and R₃ groups that are not within the scope of the '830 patent claims. Ex. 1011, ¶ 81. Thus, only through hindsight would a POSA be directed by P1 to a subgenus with the classes of R group substituents later claimed in the '830 patent claim 1 subgenus. Ex. 1011, ¶ 82.

d. P1 Does Not Provide Written Description Support For The Dependent Claims Of The '830 Patent And Thus They Are Not Entitled To The Benefit Of P1

For similar reasons that '830 patent claim 1 does not have written description support in P1, the dependent claims of the '830 patent also do not have written description support in P1.

While the dependent claims of the '830 patent narrow some substituents, there are no “preferences” or other teachings in P1 that would provide direction to a POSA, with no foreknowledge of the later-claimed '830 patent subgenus, to select the narrowed R₂, R₃, R₅, R₆, and R₇ groups claimed in the '830 patent dependent claims. Ex. 1011, ¶ 84.

Dependent claims 2-5 of the '830 patent limit R_1 to specific bases. Ex. 1001, col.19 l.48 – col.20 l.4. While claims 8-11 of P1 also limit R_1 to the same specific bases (Ex. 1008, at 22-23), for the reasons discussed for claim 1 above, P1 provides no blaze marks to direct a POSA to select the specific narrowed R_2 , R_3 , R_5 , R_6 , and R_7 groups in the correct combination to arrive at the claimed subgenera of the '830 patent claims 2-5. Just focusing on those narrowed R groups, claims 8-11 of P1 encompass **7,441,875** possible combinations of classes of R group substituents with no guidance as to which of each of those classes at various positions should be combined. Ex. 1011, ¶ 85.

Dependent claim 6 of the '830 patent limits R_2 to fluoro. Ex. 1001, col.20 l.5. While claim 14 of P1 limits R_2 to fluoro (Ex. 1008, at 23), P1 provides no blaze marks to direct a POSA to select R_2 fluoro in combination with the other narrowed R_3 , R_5 , R_6 , and R_7 groups to arrive at the claimed subgenera of the '830 patent. Just focusing on those narrowed R groups, claim 14 of P1 encompasses **496,125** possible combinations of classes of R group substituents with no guidance as to which of each of those classes at various positions should be combined. Ex. 1011, ¶ 86. And, as discussed above, the disclosure of P1 ***points a POSA away from selecting fluoro at R_2***

because of its strongly electronegative properties that are inconsistent with NP3/NP2's preference for electropositive groups at R₂. Ex. 1011, ¶ 86.

'830 patent claims 7-9 and 11 limit R₅ to amino acids. Ex. 1001, col.20 ll.6-36. While claims 33 and 40-44 of P1 limit R₅ to amino acids (Ex. 1008, at 24-26), P1 provides no blaze marks to direct a POSA to select R₅ amino acid in combination with the other narrowed R₂, R₃, R₆, and R₇ groups to arrive at the claimed subgenera of the '830 patent. Just focusing on those narrowed R groups, claims 33 and 40-44 of P1 encompass **2,480,625** possible combinations of classes of R group substituents with no guidance as to which of each of those classes at various positions should be combined. Ex. 1011, ¶ 87.

'830 patent claim 12 limits R₇ to hydrogen. Ex. 1001, col.20 ll.37-38. There is no disclosure in P1 which limits R₇ to hydrogen. Ex. 1008, at 19-31. Thus, for the same reasons as discussed for claims 1-5, P1 provides no blaze marks to direct a POSA to select R₇ hydrogen in combination with the other narrowed R₂, R₃, R₅, and R₆ groups to arrive at the claimed subgenera of the '830 patent claim 12. Ex. 1011, ¶ 88.

Dependent claims 13-21 and 23-27 of the '830 patent are directed to a method for treating a viral infection comprising administering various subgenera of claims 1-9 and 11-12 of the '830 patent. Ex. 1001, col.20 l.39

– col.22 l.16. For the same reasons as discussed for claims 1-9 and 11-12, P1 provides no blaze marks to direct a POSA to select the specific narrowed R₂, R₃, R₅, R₆, and R₇ groups in the correct combination to arrive at the claimed subgenera of the '830 patent claims 13-21 and 23-27. Ex. 1011, ¶ 89.

Dependent claim 28 of the '830 patent is directed to pharmaceutical compositions comprising the genus of claim 1 and a pharmaceutically acceptable vehicle or carrier. Ex. 1001, col.22 ll.17-19. For the same reasons as discussed for claim 1, P1 provides no blaze marks to direct a POSA to select the specific narrowed R₂, R₃, R₅, R₆, and R₇ groups in the correct combination to arrive at the claimed subgenera of the '830 patent claim 28. Ex. 1011, ¶ 90.

Because claims 2-9, 11-21, and 23-28 of the '830 patent either further limit the R groups specified in claim 1 or claim methods or compositions of using the compounds disclosed in claim 1, P1 similarly does not provide written description support for these claims.

* * *

Given the enormous size of the genus disclosed in P1, the lack of blaze marks that would direct a POSA to the '830 patent claims and the teachings in P1 that would direct a POSA towards something other than the

R groups later claimed in the '830 patent, a POSA would have understood that Applicant was not in possession of the subject matter of the '830 patent claims. Ex. 1011, ¶ 91.

**2. NP3/NP2 Do Not Provide Written Description
Support For The Challenged Claims And Thus They
Are Not Entitled To The Benefit Of NP3/NP2**

NP2, the second application in the alleged chain of priority, was filed on December 8, 2005 and published as WO 2006/063149 on June 15, 2006. NP3, the third application in the alleged chain of priority, was the national stage filing of NP2 and, therefore, has the same disclosure as NP2. By December 8, 2005, only one new nucleoside antiviral agent, entecavir (a carbocyclic nucleotide) received FDA approval. Ex. 1011, ¶ 44; Ex. 1019.

NP3/NP2 contain additional disclosure from what is in P1. In particular, NP3/NP2 contain 24 “representative compounds” which were added after the filing of P1, and anticancer *in vitro* cell assay data was added on three of these “representative compounds.” No antiviral activity was provided for any of these “representative compounds.” ***None of these***

“representative compounds” fall within the scope of the ’830 patent

claims.⁵ Ex. 1011, ¶ 92.

Notwithstanding certain similarities in the general formulas provided in the specifications of NP3/NP2 and the ’830 patent, there is no disclosure in NP3/NP2 that would lead a POSA to conclude that Applicant had possession of the claimed invention in ’830 patent claim 1 as of the December 8, 2005 filing date of NP3/NP2. Ex. 1011, ¶ 93.

a. There Are No Blaze Marks In NP3/NP2 That Would Direct A POSA To Compounds Falling Within The Full Scope Of The ’830 Patent Claim 1 Subgenus

Like P1, NP3/NP2 recites a large number of classes of R group substituents for R₂, R₃, R₅, R₆, and R₇ that encompass an enormous number of compounds. See Ex. 1007, at 3:18-4:13. Differences between the disclosure in NP3/NP2 and ’830 patent claim 1 is the same as shown above in Table 3. As for P1, the possible combinations of substituents disclosed in NP3/NP2 is enormous and NP3/NP2 provide no direction towards any particular combination of substituents. Ex. 1011, ¶ 94.

⁵ The differences between P1 and NP3/NP2 do not cure the written description issues identified with regard to P1, as further discussed below.

While '830 patent claim 1 narrows the scope of the classes of R group substituents disclosed in NP3/NP2, similar to the disclosures in P1, there are no blaze marks in NP3/NP2 to guide a POSA to select those specific classes of R group substituents from the myriad possibilities in the broad genera disclosed in NP3/NP2. Ex. 1011, ¶ 95.

As stated above for P1, the absence of blaze marks is critical in determining whether NP3/NP2 demonstrate that Applicant was in possession of the subject matter claimed in '830 patent claim 1 because a combinatorial calculation of the number of substituents encompassed by R₂, R₃, R₅, R₆, and R₇ in NP3/NP2 formula I (the R groups narrowed in '830 patent claim 1) results in **7,441,875** classes of R group substituents from which the later claimed '830 patent claim 1 subgenus is derived. Ex. 1011, ¶ 96.

Similar to P1, there are no disclosures in NP3/NP2 that provide any direction to select any of those classes of R group substituents over others, i.e., there are no disclosures in NP3/NP2 that would direct a POSA to select: (1) R₂ as halogen from among the 15 classes of R group substituents in NP3/NP2, (2) R₃ as hydroxy from among the 15 classes of R group substituents in NP3/NP2, (3) R₅ as amino acid from among the three classes of R group substituents in NP3/NP2, and (4) R₆ and R₇ as hydrogen or (C₁-C₆) alkyl from among the 15 classes of R group substituents in NP3/NP2.

Importantly, instead of guiding a POSA to those later claimed classes of R group substituents, NP3/NP2 would instead direct a POSA to select other classes of R group substituents because the only compounds “useful in the methods of the invention” have hydroxy at R₂ (NP3/NP2 Figure 3) and the only synthetic scheme for making the compounds in NP3/NP2 is one that results in hydroxy at R₂ (NP3/NP2 Figure 1). Ex. 1011, ¶ 97.

Therefore, based on the disclosures in NP3/NP2, a POSA would understand that Applicant was not in possession of the subgenus later claimed in '830 patent claim 1 as of the filing date of NP3/NP2. Ex. 1011, ¶ 98.

b. NP3/NP2 Do Not Disclose Any Compounds Or Examples Falling Within The '830 Patent Claim 1 Subgenus And The Compounds That Are Disclosed Teach Away From That Subgenus

Similar to P1, NP3/NP2 do not disclose any representative species or subgenus that falls within the scope of '830 patent claim 1. Nor do NP3/NP2 contain any examples of compounds that fall within the scope of that subgenus. Ex. 1011, ¶ 99.

NP3/NP2 disclose 24 “representative” compounds, as shown below.

Example 2. Representative compounds of the invention can be prepared using a procedure similar to those described by T. Chou et al., *The Journal of Biological Chemistry*, **2005**, 280, 15356-15361. The following compounds were prepared using such a procedure.

Compound	Nucleotide	Amino Acid	Theoretical mass	[M-H] ⁻	Error (ppm)
100	AMP	L-TrpCOOMe	546.1508	546.1503	-0.9
101	AMP	L-TrpCONMe	547.1824	547.1851	4.9
102	AMP	L-TrpCONH ₂	533.1668	533.1669	0.3
103	AMP	D-TrpCOOMe	546.1508	546.1513	1.0

104	AMP	Tryptamine	488.1447	488.148	6.7
105	GMP	L-TrpCOOMe	562.1451	562.1468	3.0
106	GMP	L-TrpCONMe	563.1773	563.1813	7.1
107	GMP	L-TrpCONH ₂	547.146	547.1444	-3.0
108	GMP	D-TrpCOOMe	562.1451	562.1462	1.9
109	GMP	Tryptamine	504.1397	504.140	0.7
110	IMP	L-TrpCOOMe	547.1342	547.1351	1.6
111	IMP	D-TrpCOOMe	547.1342	547.1335	-1.4
112	IMP	Tryptamine	489.1288	489.1279	-1.8
113	Ara-AMP	L-TrpCOOMe	546.1508	546.1496	-2.1
114	Ara-AMP	D-TrpCOOMe	546.1508	546.1503	-0.9
115	Ara-AMP	Tryptamine	488.1447	488.1422	-5.2
116	TMP	L-TrpCONMe	520.1597	520.1592	-1.0
117	TMP	D-TrpCOOMe	521.1437	521.1426	-2.2
118	TMP	Tryptamine	463.1383	463.1396	2.9
119	CMP	D-TrpCOOMe	522.139	522.1399	1.7
120	CMP	L- TrpCONH ₂	507.1393	507.1399	1.1
121	CMP	Tryptamine	464.1335	464.1335	0.0
122	UMP	D-TrpCOOMe	523.123	523.124	1.9
123	UMP	Tryptamine	465.1175	465.1174	-0.3

A = Adenosine, G = Guanosine, I = inosine, T = thymidine, U = uridine, Ara-A = 9-beta-D-arabinofuranosyladenosine
 Trp=tryptophan COOMe=carbomethoxy ester, CONMe = methyl amide

*Most of compounds were analyzed in negative mode except compounds 101, 102, and 106.

Ex. 1007, at 26-27. Most of these compounds are phosphoramidate prodrugs of natural nucleosides that have **hydroxy at R_2** which takes them outside the scope of the '830 patent claims, all of which require halo at R_2 . Only one compound, Ara-A, is a non-natural nucleoside, but that compound contains **hydroxy at R_6 and hydrogen at R_2** (consistent with the arabino sugar indicated by the name "Ara-A"). This compound is also outside the scope of the '830 patent claims which **require hydrogen or (C_1-C_6) alkyl at R_6 and halo at R_2** . Ex. 1011, ¶ 101.

In addition, NP3/NP2 contain the same Figures 1 and 3 as in P1, which teach compounds "useful in the methods of the invention" (Figure 3) and a synthetic scheme to make compounds (Figure 1). Ex. 1007, fig.1, 3. These Figures include only compounds having **hydroxy at R_2** . None of those compounds fall within the scope of the '830 patent claims which **require halo at R_2** . Ex. 1011, ¶ 102. Thus, not only is there a complete absence of any teaching that would direct a POSA to select a compound having halo at R_2 but there is actually guidance to select compounds that do not have halo at that position. Ex. 1011, ¶ 102.

Moreover, as for P1, NP3/NP2 teach that **electropositive groups are favored at R_2** . This teaching would lead a POSA in a different direction

from selecting R₂ as halo given that halogens are among the most electronegative groups in the periodic table. Ex. 1011, ¶ 103.

Taken together, the absence of any blaze marks that would direct a POSA to select halo at R₂ (required by the '830 patent claims) combined with the disclosures in Figures 1 and 3 that compounds useful in the methods of the invention and those for which a synthetic scheme is provided do not have halo at R₂, and the fact that halo is disfavored at R₂ because of its strongly electronegative property, would not be understood by a POSA as demonstrating that Applicant was in possession of the '830 patent claim 1 subgenus at the time of the filing of NP3/NP2. Ex. 1011, ¶ 104.

c. **The Alleged Multiple Dependent Claim “Preferences” In NP3/NP2 Do Not Provide Written Description Support Because The Large Number Of Multiple Dependent Claims That Refer Back To Other Multiple Dependent Claims Result In An Enormous Number Of Possibilities**

Again, Patent Owner may point to NP3/NP2's numerous multiple dependent claims as allegedly showing “preferences” for classes of R group substituents claimed in the '830 patent subgenus. But such an argument can only be made using hindsight because there is nothing in NP3/NP2 singling out those classes of R group substituents as “preferred.” Ex. 1011, ¶ 105.

NP3/NP2 and P1 differ in the organization of their multiple dependent claims. For example, P1's claims encompass the entire range of the previous multiple dependent claims, while the NP3/NP2's claims have different dependencies. As noted above, claim 47 of P1 depends from claims 1-46 whereas as noted below corresponding claim 61 of NP3/NP2 depends from claims 1-13.

Even assuming *arguendo* that the claims of NP3/NP2 illustrate some "preference" for those classes of R group substituents, there are still no blaze marks directing a POSA to select the classes of R group substituents falling within the scope of the '830 patent claim 1 subgenus from the many other R group "preferences" recited in the NP3/NP2 claims. Ex. 1011, ¶ 106.

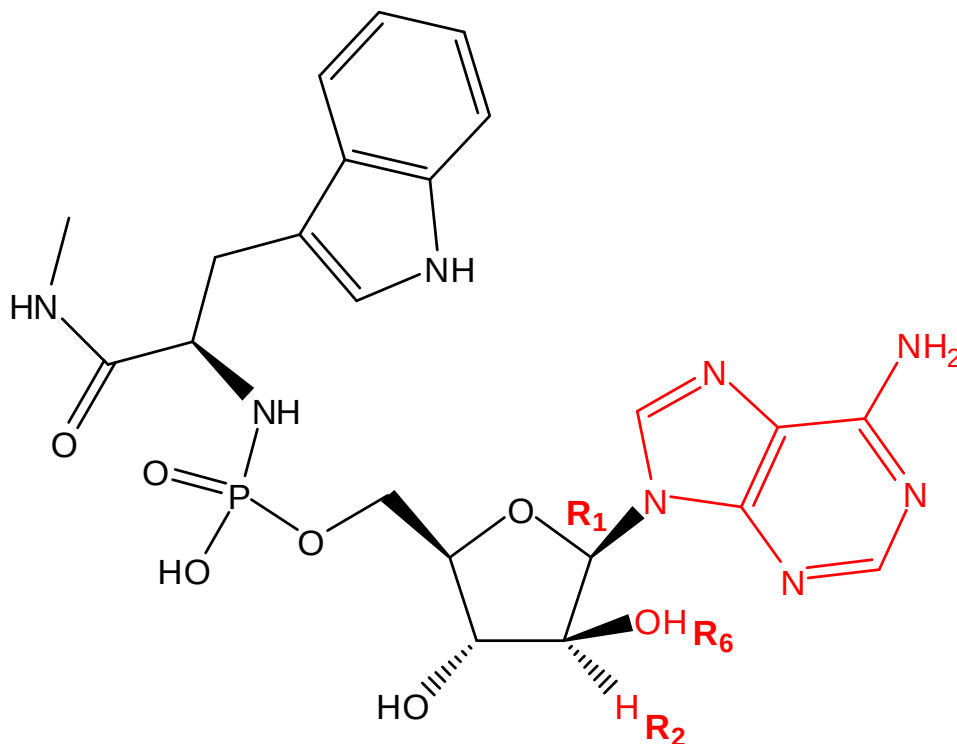
While claim 27 of NP3/NP2 specifies R_2 as halo, other claims specify *R_2 can be hydroxy (claim 26); fluoro (claim 28); chloro (claim 29); (C_1 - C_6)alkoxy (claim 30); methoxy (claim 31); trifluoromethyl (claim 32); cyano (claim 33); or "amino, methylamino, dimethylamino, ethylamino, or dimethylamino" (claim 34).* Ex. 1007, at 40. While claim 35 specifies R_3 as hydroxy, other claims specify *R_3 can be hydrogen (claim 36); halo (claim 37); fluoro (claim 38); chloro (claim 39); trifluoromethyl (claim 40); azido (claim 41); cyano (claim 42); or "amino, methylamino, dimethylamino, ethylamino, or dimethylamino" (claim 43).* Ex. 1007, at 40-41. While

claim 47 specifies R₅ as an amino acid, other claims specify that ***R₅ can be a peptide (claim 48), which is defined in P1 as “a sequence of 2 to 25 amino acids . . . or peptidyl residues.”*** Ex. 1007, at 8. See also Ex. 1011, ¶¶ 107-109.

Moreover, the NP3/NP2 claims would actually direct a POSA to select other classes of R group substituents claimed in the '830 patent claim 1 subgenus. For example, claim 61 recites: “The compound of any one of claims 1-13 wherein R₇ is hydrogen or (C₁-C₆)alkyl.” Ex. 1007, at 43. Claims 1-13 provide no “preferences” for choosing R₂ as halo, R₃ as hydroxy, R₅ as amino acid, and R₆ as H or (C₁-C₆)alkyl. Indeed, claims 3-13 recite that R₅ is NR_aR_b, and provide “preferences” for the specific ***R_a and R_b groups which exclude amino acids***, which is required at R₅ in the '830 patent claim 1 subgenus. Ex. 1007, at 34-38; Ex. 1011, ¶ 111. And claim 60 recites a subgenus which ***excludes R₂ as being halo and R₆ as being hydrogen***, both of which are required by the '830 patent claims. Ex. 1007, at 43; Ex. 1011, ¶ 112.

Importantly, as discussed for P1, a compound expressly disclosed by name in NP3/NP2, which is recited in claim 63 (Ex. 1007, at 44), is (2-(3-indolyl)-1(R)-methylcarbamoyl ethyl)phosphoramidic acid mono (1-B-arabinofuranosyladenosine)ester (illustrated below). This compound

contains hydrogen at R_2 , which would be understood by a POSA as directing him or her to compounds that ***do not have halogen at R_2*** . Ex. 1011, ¶ 113.



Further, the compound disclosed in claim 63 contains adenine at R_1 whereas ***all of the '830 patent claims exclude adenine*** at that position, and contains hydroxy at R_6 whereas ***all of the '830 patent claims exclude hydroxy*** at that position. Ex. 1011, ¶ 114.

In addition to directing a POSA to select substituents at R_1 , R_2 , and R_6 that are not within the scope of the '830 patent claims, other disclosures in NP3/NP2 would direct a POSA to select a substituent at R_3 that is not within the scope of those claims. Ex. 1011, ¶ 115. For example, claim 62 of NP3/NP2 recites a subgenus where ***R_3 is hydrogen or alkyl***. Ex. 1007, at 43.

Just as claims 60 and 63 would direct a POSA to select something other than R_2 as halogen, claim 62 directs him or her to select something other than R_3 as hydroxy. Ex. 1011, ¶ 115.

Taken together, the disclosures of NP3/NP2 would direct a POSA to select classes of R group substituents for R_1 , R_2 , and R_3 that are not within the scope of the '830 patent claims. Ex. 1011, ¶ 116.

Patent Owner may point to claim 59 as allegedly providing support for the '830 patent claim 1 subgenus. Claim 59 recites: "The compound of any one of claims 1-58 wherein R_6 is hydrogen or (C_1-C_6) alkyl." Ex. 1007, at 43: 17-18. But while R_6 in claim 59 matches R_6 in the '830 patent claim 1 subgenus, there are no blaze marks in the NP3/NP2 specification or claims that would direct a POSA to **combine** R_6 from claim 59 with the other narrowed classes of R group substituents, i.e., R_2 , R_3 , R_5 , and R_7 . Even if claim 59 were to be understood by a POSA as demonstrating a "preference" for R_6 as hydrogen or (C_1-C_6) alkyl, claim 59 still represents **70,875** possible combinations of classes of R group substituents for R_2 , R_3 , R_5 , and R_7 . And there is no teaching in claim 59 whatsoever directing a POSA to select the narrowed classes of R group substituents as recited for R_7 in the '830 patent claim 1 subgenus. Ex. 1011, ¶ 117.

This is emblematic of any argument that Patent Owner could make of any “preferences” allegedly taught by the NP3/NP2 claims: there is simply no disclosure in NP3/NP2 that would direct a POSA to combine a particular class of R group substituents recited in one claim with classes of R group substituents recited in other claims. There are no blaze marks in NP3/NP2 that would lead a POSA through the dense forest of claims and direct him or her to stop at any particular claim because there are no blaze marks in NP3/NP2 that would direct a POSA to those specific claims. Ex. 1011, ¶ 118.

Unlike the case for P1, the organization of the claims of NP3/NP2 and their relationship to one another through their dependencies, ***precludes combinations that would result in the classes of R group substituents later claimed in the '830 patent.*** Thus, even in hindsight a POSA would not be able to combine the classes of R group substituents later claimed in the '830 patent claim 1 subgenus from the disclosures and claims of NP3/NP2. Ex. 1011, ¶ 119.

d. **NP3/NP2 Do Not Provide Written Description Support For The Dependent Claims Of The '830 Patent And Thus They Are Not Entitled To The Benefit Of NP3/NP2**

For similar reasons that '830 patent claim 1 does not have written description support in NP3/NP2, the dependent claims of the '830 patent also fail to have written description support in NP3/NP2.

While the dependent claims of the '830 patent narrow the broad scope of the classes of R group substituents in independent claim 1, similar to P1, there are no “preferences” or other teachings in NP3/NP2 that would provide direction to a POSA, with no foreknowledge of the later-claimed '830 patent subgenus, to select the narrowed R₂, R₃, R₅, R₆, and R₇ groups claimed in the '830 patent dependent claims. Ex. 1011, ¶ 122.

Dependent claims 2-5 of the '830 patent limit R₁ to specific bases. Ex. 1001, col.19 l.48 – col.20 l.4. While claims 22-25 of NP3/NP2 limit R₁ to the same bases (Ex. 1007, at 39-40), for the reasons discussed above, NP3/NP2 provide no blaze marks to direct a POSA to **combine** R₁ in claims 22-25 with the exact combination of narrowed R₂, R₃, R₅, R₆, and R₇ classes claimed in '830 patent claims 2-5. Ex. 1011, ¶ 123. Just focusing on those R group classes, claims 22-25 of NP3/NP2 encompass **7,441,875** possible combinations of classes of R group substituents with no guidance as to which of those should be combined. Ex. 1011, ¶ 124.

Similarly, dependent claim 6 of the '830 patent limits R₂ to fluoro. Ex. 1001, col.20 l.5. While claim 28 of NP3/NP2 limits R₂ to fluoro (Ex. 1007, at 40), NP3/NP2 provide no blaze marks to direct a POSA to **combine** R₂ recited in claim 28 with the exact combination of narrowed R₃, R₅, R₆, and R₇ classes claimed in '830 patent claim 6. Ex. 1011, ¶ 125. Just focusing on those narrowed R groups, claim 28 of NP3/NP2 encompasses **496,125** possible combinations of classes of R group substituents with no guidance as to which of those should be combined. And, as discussed above, the disclosure of NP3/NP2 **points a POSA away from selecting fluoro at R₂** because of its strongly electronegative properties that are inconsistent with NP3/NP2's preference for electropositive groups at R₂. Ex. 1011, ¶ 126.

Dependent claims 7-9 and 11 of the '830 patent limit R₅ to amino acids. Ex. 1001, col.20 ll.6-36. While claims 47 and 54-58 of NP3/NP2 limit R₅ to amino acids (Ex. 1007, at 41-43), NP3/NP2 provide no blaze marks to direct a POSA to **combine** R₅ recited in claims 47 and 49-58 with the exact combination of narrowed R₂, R₃, R₆, and R₇ classes of R group substituents claimed in '830 patent claims 7-9 and 11. Ex. 1011, ¶ 127. Just focusing on those narrowed R groups, claims 47 and 54-58 of NP3/NP2 encompass **2,480,625** possible combinations of classes of R group

substituents with no guidance as to which of those should be combined. Ex. 1011, ¶ 128.

Dependent claim 12 of the '830 patent limits R₇ to hydrogen. Ex. 1001, col.20 ll.37-38. There is no disclosure in NP3/NP2, including the claims, which limits R₇ to hydrogen. Ex. 1011, ¶ 129. Thus, for the same reasons as discussed above for claims 1-5, NP3/NP2 provide no blaze marks to direct a POSA to select the exact combination of narrowed R₂, R₃, R₅, and R₆ groups to arrive at the claimed subgenera of '830 patent claim 12.

Dependent claims 13-21 and 23-27 of the '830 patent are directed to a method for treating a viral infection in an animal comprising administering various subgenera of claims 1-9 and 11-12 of the '830 patent. Ex. 1001, col.20 l.39 – col.22 l.16. Thus, for the same reasons as discussed above for '830 patent claims 1-9 and 11-12, NP3/NP2 provide no blaze marks to direct a POSA to select the specific narrowed R₂, R₃, R₅, R₆, and R₇ classes of R group substituents claimed in '830 patent claims 13-21 and 23-27. Ex. 1011, ¶ 130.

Dependent claim 28 of the '830 patent is directed to pharmaceutical compositions comprising the genera of claim 1 and a pharmaceutically acceptable vehicle/carrier. Ex. 1001, col.22 ll.17-19. For the same reasons as discussed above for '830 patent claim 1, NP3/NP2 provide no blaze

marks to direct a POSA to select the specific narrowed R₂, R₃, R₅, R₆, and R₇ classes of R group substituents claimed in '830 patent claim 28. Ex. 1011, ¶ 131.

Because '830 patent claims 2-9, 11-21, and 23-28 either further delineate the classes of R group substituents specified in claim 1 or claim methods or compositions of using the compounds disclosed in claim 1, NP3/NP2 also do not provide written description support for those claims.

* * *

Given the enormous size of the genera of compounds disclosed in NP3/NP2, the lack of blaze marks that would direct a POSA to the specifically narrowed R groups claimed in the '830 patent, combined with the teachings in NP3/NP2 that would direct a POSA to select something other than the later claimed R groups, a POSA would have understood that Applicant was not in possession of the subject matter of the '830 patent claims. Ex. 1011, ¶ 132.

3. NP4 Does Not Provide Written Description Support For The Challenged Claims And Thus They Are Not Entitled To The Benefit Of NP4

NP4, the fourth application in the alleged chain of priority, was filed on January 29, 2013, at which time there were still no phosphoramidate nucleoside antiviral or anticancer agents that were FDA-approved. This is

evidence that as of January 29, 2013, there was still no generally understood structure-activity relationships for phosphoramidate nucleoside prodrugs that would allow a POSA to predict, without specific data, and with any reasonable certainty, antiviral or anticancer activities for this large class of compounds. This is largely due to the continued lack of any detailed understanding of the mechanisms by which phosphoramidate prodrugs were transported and metabolized and whether the metabolic products would be cytotoxic. Ex. 1020; Ex. 1011, ¶ 45.

Prior to NP3 issuing as a patent, Applicant filed NP4, labelling that application as a “continuation” of NP3. However, the disclosures in NP4 and NP3/NP2 differed – instead of including the NP3/NP2 claims in NP4, Applicant replaced them with 16 new claims. Ex. 1005, at 30-33. These new claims do not provide written description support for the claims of the ’830 patent. Indeed, a POSA would understand from these new claims that Applicant was not in possession of the ’830 patent subgenus. Instead, these claims would direct a POSA to select something other than the subgenus claimed in the ’830 patent. Ex. 1011, ¶ 135.

None of the NP4 claims recite R_2 as halo, instead ***requiring R_2 to be hydroxy***. A POSA as of January 29, 2013 would have understood from this that Applicant was focused on nucleosides with ***hydroxy at R_2 , not halo***.

Thus, NP4 would direct a POSA to compounds that are not within the scope of the '830 patent claims – namely, compounds that contain hydroxy at R₂. Ex. 1011, ¶ 136.

Further, none of the NP4 claims recite R₅ as amino acid, instead ***requiring R₅ to be NR_aR_b***. A POSA as of January 29, 2013 would have understood from this that Applicant was focused on nucleosides with NR_aR_b at R₅, not amino acid. Thus, NP4 would direct a POSA to compounds that contain NR_aR_b at R₅, which are not within the scope of the '830 patent claims. Ex. 1011, ¶ 137.

And as the specification of NP4, absent the claims, is identical to that of NP3/NP2, there are no blaze marks in NP4 that would direct a POSA to the subgenus in the '830 patent Challenged Claims. Therefore, a POSA would understand from the disclosures in NP4 that Applicant was not in possession of the subject matter of the Challenged Claims as of the filing date of NP4. Ex. 1011, ¶ 138.

The claims of the '830 patent are not entitled to the benefit of NP4, and NP4 is an intermediate application without which there would be no copendency with NP3/NP2 and P1. For this reason alone the claims of the '830 patent cannot be entitled to NP3/NP2 or P1's filing dates.

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In conclusion, none of the Alleged Priority Applications demonstrate to a POSA that Applicant was in possession of the subject matter claimed in the '830 patent. In particular:

- There are no blaze marks in P1, NP3/NP2, or NP4 that would direct a POSA to compounds within the scope of the '830 patent claims, as demonstrated by the fact that:
 - o All of the compounds disclosed in P1, NP3/NP2, and NP4 have **hydroxy or hydrogen at R_2** whereas the '830 patent claims require **halogen at R_2** ;
 - o The only synthetic scheme disclosed in P1, NP3/NP2, and NP4 for making the claimed nucleotides results in compounds having **hydroxy at R_2** whereas the '830 patent claims require **halogen at R_2** ;
 - o P1, NP3/NP2, and NP4 teach that **electropositive** groups are favored at R_2 , whereas halogens, particularly fluorine, are strongly **electronegative**;
 - o The only compound described by name in the claims of P1 and NP3/NP2 contains substituents at R_1 , R_2 and R_6 that are **not within the scope of the '830 patent claims**;

- o The claims of P1 and NP3/NP2 recite subgenera that ***do not contain hydroxy at R₃*** whereas the '830 patent claims ***require hydroxy at R₃***; and
- o The combinations encompassed by R₂, R₃, R₅, R₆, and R₇ in P1, NP3/NP2, and NP4 result in between ***70,000 and over 7,000,000 classes of R group substituents*** from which the later claimed '830 patent subgenus selects 7 specific classes, with no blaze marks to direct a POSA to those classes. Ex. 1011, ¶ 139.

Thus, the '830 patent claims are not entitled to the benefit of any of the filing dates of the Alleged Priority Applications.

VIII. CONCLUSION

Petitioner has demonstrated that claims 1-9, 11-21, and 23-28 of the '830 patent are anticipated by the prior art. Accordingly, IPR of those claims is requested.

DATED: June 30, 2017

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I hereby certify that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,815,830 contains 13,921 words as measured by the word processing software used to prepare the document (and including the 35 words encompassed in the figure on page 29, 93 words encompassed in Figure 1 on page 47, and 232 words encompassed in the figure on page 58), in compliance with 37 C.F.R. § 42.24(a).

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CERTIFICATE OF SERVICE

I hereby certify that true and correct copies of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,815,830 and Exhibits 1001-1021 were served on June 30, 2017 via USPS EXPRESS MAIL to the following parties:

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