

Filed on behalf of: Gilead Sciences, Inc.

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

Case IPR2017-01712
Patent 8,815,830

PETITIONER'S REPLY

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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. (“Marquez”)
1012	<i>Curriculum Vitae</i> of Victor E. Marquez, Ph.D.

1013	Anastasi et al., <i>Current Medicinal Chemistry</i> 2003, 10: 1825-1843
1014	Calogeropoulou et al., <i>Current Topics in Medicinal Chemistry</i> 2003, 3: 1467-1495
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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)
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1021	Pauling, <i>J. Amer. Chem. Soc.</i> , 54: 3570-3582 (1932)
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1025	Declaration of Robert S. Schwartz
1026	Transcript of Conference Call with the Board, on September 11, 2017
1027	Preliminary Amendment, U.S. Patent Application No. 14/229,292, (Mar. 31, 2014)
1028	Order, <i>Regents of the University of Minnesota v. Gilead Sciences, Inc.</i> , Civil Action No. 0:16-cv-02915-SRN-HB, D.I. 139 (D. Minn. Jun. 9, 2017)

1029	Stipulated Case Management Statement, <i>Regents of the University of Minnesota v. Gilead Sciences, Inc.</i> , 17-cv-6056-VC, D.I. 275 (N.D. Cal. Jan. 2, 2018)
1030	January 26, 2018 Email from Gerald Hrycyszyn (Counsel for Patent Owner) to Board and Counsel for Petitioner
1031	January 26, 2018 Email Chain Between Frederick Millett (Counsel for Petitioner) and Gerald Hrycyszyn (Counsel for Patent Owner)
1032	January 28, 2018 Email from Alicia Russo (Counsel for Petitioner) to Board and Counsel for Patent Owner
1033	Stipulation and Proposed Order to Exclude Filings From IPR Proceedings, <i>Regents of the Univ. of Calif. v. St. Jude Medical, LLC</i> , Case No. 4:16-CV-06210-YGR, D.I. 85 (N.D. Cal. Feb. 2, 2018)
1034	Order, <i>Regents of the University of Minnesota v. AT&T Mobility LLC</i> , No. 14-cv-4666 (JRT/TNL), D.I. 237 (D. Minn. May 19, 2017)
1035	Gilead's Motion to Stay Pending <i>Inter Partes</i> Review, <i>Regents of the University of Minnesota v. Gilead Sciences, Inc.</i> , 17-cv-6056-VC, D.I. 297 (N.D. Cal. Feb. 7, 2018)
1036	Declaration of Dr. Gerardus Josephus Petrus Henricus Boons
1037	World Intellectual Property Organization (WIPO) FAQs: Amendments to the PCT Regulations (April 1, 2007)
1038	Transcript of the October 8, 2020 Deposition of Dr. Andrea Brancale ("Brancale Dep.")
1039	Second Declaration of Dr. Gerardus Josephus Petrus Henricus Boons ("Boons")
1040	Judith Howard et al., <i>How Good is Fluorine as a Hydrogen Bond Acceptor?</i> , TETRAHEDRON 52(38):12613-22 (1996)

1041	Florante A. Quioco, <i>Protein-carbohydrate interactions: basic molecular features</i> , PURE & APPL. CHEM. 61(7):1293-1306 (1989)
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I. INTRODUCTION

Sofosbuvir, a nucleoside phosphoramidate compound prescribed to cure hepatitis C, is one of the most groundbreaking advances in medicine in the past half-century. Sofosbuvir's development took years and cost billions of dollars. Central to this effort was the development of fluorination chemistry enabling the creation of new nucleoside compounds. *See Storer v. Clark*, 860 F.3d 1340, 1351 (Fed. Cir. 2017). While other pharmaceutical companies tried to create these compounds, all failed to do so before Gilead's own patent application published in 2005. *See, e.g., Idenix Pharm. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1162-63 (Fed. Cir. 2019) (invalidating patent on § 112 grounds and discussing failures of others).

The University now alleges that, unbeknownst to the world and contrary to his own publications, Dr. Wagner was "in possession" of these new nucleoside compounds in 2004. That belies both common sense and what is actually written in the alleged priority documents. Not one of the examples, figures, schemes, specific values, citations, or claims in the priority documents describes the subgenera claimed in the '830 patent or any nucleoside phosphoramidate compounds within them. Instead, the first mention of what the applicant was allegedly in possession of in 2004 appears in 2014, when the University attempted to claim sofosbuvir itself. Ex. 1002, at 57. As the Federal Circuit warns, close scrutiny for actual

possession is “particularly important when, as here, claims are added later during prosecution in response to development by others.” *FWP IP ApS v. Biogen MA, Inc.*, 749 F. App’x 969, 974 (Fed. Cir. 2018).

The University’s task was straightforward: identify words, figures, or data in the alleged priority applications from which a skilled artisan could reasonably infer possession of the subgenera claimed in the ’830 patent. Because there is no *ipsis verbis* disclosure, *Fujikawa v. Wattanasin* instructs—and the parties seemingly agree—that a “blaze marks” analysis is necessary. 93 F.3d 1559 (Fed. Cir. 1996).

The University puts forward three alleged blaze marks: (1) a proviso that defines the boundaries of the broadest disclosed genus; (2) a combination of selective pathways through no less than seven original claims in P1 (many of which use improper multiple dependency) and corresponding specific values in NP2; and (3) 24 example compounds in NP2, none of which are species of the claimed subgenera.

But these alleged blaze marks are convoluted and nonintuitive, as evidenced by the University’s reliance on 300+ pages of expert opinion to support its theories. What the University identifies is in no way an indication of “special interest” by the applicant; it is a hindsight analysis plain and simple. *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013) (the “proper vantage point” for written description is from the perspective of one

with “no foreknowledge”). The alleged priority applications describe quadrillions of possible subgenera. And even a conservative calculation incorporating a variety of hindsight assumptions still encompasses millions—a metaphorical forest from which the trees representing the ’830 patent’s subgenera cannot be found.

What blaze marks exist do not point towards the ’830 patent’s claims. Whether considered alone or in combination, each burns a trail to subgenera without halo at R₂. Every specific compound identified in the alleged priority applications has hydrogen or hydroxy at the 2’-position. The specification confirms the applicant’s interest in such compounds with its statement that an “electropositive group” at the 2’-position is an “especially good substrate[] for hHINT1,” the enzyme whose activity is allegedly central to Dr. Wagner’s patentable “discovery.” NP2, 3:11-14; POR, 1-3. And all experts in this case agree, halogens are not “electropositive group[s].”

Dr. Wagner’s so-called possession of compounds with halo at R₂ is illusory; the alleged priority documents suggest nothing more than an effort at an after-the-fact land grab to profit off of the research and development of others.

II. THE LAW OF BLAZE MARKS

The University repeatedly argues that Gilead misstates the law. POR, 22-24, 59-62. But there is no real dispute over the applicable standard. Whether described as a “preference” (Gilead) or of “special interest” (University), the task is to search

for blaze marks that guide a skilled artisan to the claimed subgenera.¹ *Fujikawa*, 93 F.3d at 1571. Description of the broadest genus does not meet the test. *Id.* The real dispute is whether there are sufficient blaze marks in the alleged priority applications. Under controlling caselaw, there are not.

A. Federal Circuit Precedent Rejects the University’s “Blaze Marks”

The Federal Circuit has repeatedly found insufficient written description in circumstances such as this one—improper multiple dependent claims (*FWP*), disclosures in the specification that must be pieced together (*Novozymes*, *Purdue v. Faulding*, *Fujikawa*), and examples that fall outside the scope of later claimed subject matter (*Novozymes*, *Ruschig*). This Board should do the same.

In *FWP*, the Board and Federal Circuit rejected as sufficient description the seven original claims, pieced together just like the University is trying here. *FWP*, 749 F. App’x at 977. As here, the patent owner “contend[ed] that locating the now-claimed invention require[d] just simple tracing through its now cancelled original claims.” *Id.* at 978. The Federal Circuit found the task anything but simple,

¹ The University’s own expert acknowledges that there is no meaningful difference between such words: there are “different word[s] for ‘preference’ that we can use, so – but it’s –it’s clearly a statement from – from the inventor to point out a preference that he has.” Brancale Dep. 97:21-24.

however, given “the morass of possible combinations of the impermissibly-drafted [multiple dependent] original claims” and “the complex network of cross-referencing ... that must be navigated.” *Id.* While a person of skill could cobble those claims together to result in the claim at issue, there was no guidance in the specification for how (or why) to do so.

Novozymes concerned a subgenus of enzyme variants that lacked written description, even though the separate limitations were each “literally described in the disclosure of the [] application.” 723 F.3d at 1349. The Federal Circuit held that *Novozymes* could not “derive written description support from an amalgam of disclosures plucked selectively from the [] application,” as that exercise was infected with hindsight. *Id.* The applicant “nowhere describe[d] the actual functioning, thermostable alpha-amylase variants that those limitations together define.” *Id.*; see also *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326 (Fed. Cir. 2000) (claims to a specific concentration ratio were not supported, despite the fact that the ratio could be “piece[d] together” from data in the patent because nothing in the specification “emphasize[d]” the ratio to guide a skilled person to do so); *Fujikawa*, 93 F.3d at 1570 (no description for a subgenus specifying the selection of cyclopropyl at one “R” group, when cyclopropyl was listed among three other options in the specification’s disclosure of the broadest genus); *Purdue Pharma L.P. v. Iancu*, 767 F. App’x 918, 924-25 (Fed. Cir. 2019)

(affirming Board’s conclusion that no written description support existed in the “laundry list disclosures” of provisional applications).

In *In re Ruschig*, the specification disclosed a genus of at least half a million compounds, and the Court found that genus did not support a claim to a species within it. 379 F.2d 990, 993 (C.C.P.A. 1967). The Court rejected the argument that an original claim of the application provided a blaze mark, even though a skilled person could “readily determin[e]” each of the compounds of the original claim. *Id.* at 994. The Court also rejected as blaze marks a table of example compounds, even though “a simple change” to the example compounds would have resulted in the claimed species. *Id.* at 995. “[I]maginary specific example[s]” that are not actually disclosed cannot be blaze marks; they are the product of hindsight. *Id.*²

² The University relies on *Smith v. Horne* and *Heymes v. Takaya* to argue that examples outside the claimed subgenus can be blaze marks. POR, 51. But in *Heymes*, the outside-the-scope examples were accompanied by data showing that “thiazolyl compounds resulted in superior activity than the phenyl compounds”—a teaching that “motivated” a skilled person to make the claimed thiazolyl compounds. *Heymes v. Takaya*, 6 U.S.P.Q.2d 1448, 1453 (B.P.A.I. Feb. 10, 1988). No such teaching in P1 or NP2 directs a skilled artisan to replace hydroxy with

B. The University Cannot Distinguish the Controlling Cases

Rather than grappling with the implications of this precedent, the University half-heartedly attempts to distinguish *FWP*, *Novozymes*, *Purdue v. Faulding*, *Ruschig*, and *Fujikawa* on “factual finding[s].” POR, 33, 48, 60-61. The University argues:

- *Ruschig* “did not require preferences,” POR, 60, ignoring the fact that *Ruschig* found the description of 48 possible compounds insufficient for any one species not “mentioned in any manner.” 379 F.2d at 994-95. The same is true here, given that the priority applications identify species, just not the “imaginary examples” the University creates. In fact, no identified compound in the written description is inside the scope of the ’830 patent claims.

halo at R₂. Similarly, the application in *Smith* included an outside-the-scope example (using TiCl₄) alongside a statement that tetrahalides “are especially preferred” catalysts (a subgenus that included just four compounds, including TiI₄ and TiCl₄). *Smith v. Horne*, 450 F.2d 1401, 1403-04 (C.C.P.A. 1971). Taken together, the specification expressed “a preference for all the limitations,” including a TiI₄ catalyst. *Id.*

- The applicant in *Fujikawa* did not identify what compounds “other than those disclosed as preferred, might be of special interest.”
POR, 60. But again, the same is true in this case. The priority applications identify certain compounds—those containing hydrogen and/or hydroxy at R₂ and R₆—and lack any indication of special interest as to others.
- *Novozymes* and *Purdue* are distinguishable because each involved claims to “specific variants” or “characteristics” not called out in the written description. But contrary to the University’s characterization, the individual limitations of those claims were present, just never pulled together into the subgenus of interest. So too here. The alleged priority documents nowhere describe, pulled together, the now-claimed subgenera.
- *FWP* concerned a “never disclosed 480 mg” dose for a multiple sclerosis treatment. POR, 61. That is not so. The “specification [in *FWP*] refers to a 480 mg/day dosage three times.” 749 F. App’x at 972. Making that case a closer call than this one, in which the alleged priority documents never disclose a species or subgenera within the challenged claims.

The question is not whether this precedent involved different “factual finding[s].” That is always true in our common law system. The question is why the legal holdings are distinguishable—the University has no answer for that.

III. THE ALLEGED PRIORITY DOCUMENTS DO NOT CONTAIN BLAZE MARKS TO THE '830 PATENT SUBGENERA

There should be no dispute that the alleged priority documents do not contain written description for the subgenera of compounds claimed in the '830 patent. There is no “specific value,” claim, or described embodiment containing in one place their selections. Nor are there any examples, representative species, data, figures, or schemes that illustrate compounds within the '830 patent claims' scope. Even the literature cited by the applicant includes only compounds outside the now-claimed subgenera.

Instead of relying on these traditional “blaze marks,” the University insists that a skilled artisan would find the subgenera of the '830 patent through a highly curated combination of original claims, specific values, and “examples” plucked from the priority applications. But neither the Federal Circuit nor this Board have ever condoned “picking and choosing” from disparate sections of the written description without any guidance. *FWP*, 749 F. App'x at 969.

A. Language Defining the Broadest Disclosed Genus (Formula I) Cannot Blaze a Trail to the Claimed Subgenera

Fujikawa instructs that “simply describing a large genus of compounds is not sufficient to satisfy the written description requirement.” 93 F.3d at 1571. Here, that large genus of compounds is described in Formula I. NP2, 3:15-5:25. Formula I contains between 10^{16} and 10^{18} possible subgenera, and countless more actual compounds. Boons ¶¶44-58.

The University argues that a proviso in Formula I allegedly “limits choices” at the R₂ and R₆ positions. POR, 20. Far from providing a narrowing disclosure, however, the proviso is part of the description of the broadest genus. *Id.* It defines all possibilities at the 2'-position and is itself the “laundry list disclosure” that *Fujikawa* instructs is insufficient absent some other blaze mark. This list simply allows for 15 substituent group options at R₂ or R₆, provided that one of seven options is selected for the other position. *See* Sec. V, *infra* (establishing that even accepting the proviso results in a vast number of options).

The University tries to imbue this proviso with larger meaning, suggesting it teaches a skilled artisan of some special interest in polar substituents at R₂. POR, 38. Indeed, the University uses the coined phrase “polar proviso” more than fifty times in its response. But again, the University’s arguments and the actual written description diverge. The written description mentions polarity only once:

Inspection of the active site of hHINT1 has revealed that hydrogen bonding, ion pairing or polar interactions at the 2'- and 3'-positions preferentially interact with the active site residue Asp-43, which is consistent with the reduced ability of 2'-deoxy nucleoside phosphoramidates to serve as substrates.

NP2, 3:5-9. Contrary to the University's focus on R₂, the written description discusses polar interactions with regard to the "2'- and 3'-positions," consisting of four variable groups: R₂, R₃, R₆, and R₇. And contrary to the University's emphasis on polarity above all else, the written description identifies "ion pairing" and "hydrogen bonding" as notable, more so than "polar interactions." Boons ¶35, n.5.

The proviso itself does not mention polarity, despite the label the University has provided it. And an examination of the substituents identified within the proviso (hydroxy, halo, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, trifluoromethyl, cyano, or NR_{ad}R_{ae}) compared to those outside of it (hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, azido, -N(R_z)C(=O)N(R_{aa})(R_{ab}), or -N(R_z)C(=O)OR_{ac}) does not provide any further direction to the skilled artisan. This is in part because the information provided by the grouping of substituents in the proviso leads only to a listing of groups, not to some broader meaning, see Boons ¶¶32-43:

- If polar means a substituent containing polarized bonds, as the University's expert says, Brancale ¶88, then five of the eight excluded

groups are also polar, and $-N(R_z)C(=O)N(R_{aa})(R_{ab})$

and $-N(R_z)C(=O)OR_{ac}$ (both excluded) contain more polar bonds than any of the seven substituents in the proviso (Brancale Dep. 136:8-145:7; Boons ¶¶36-38);

- If polar means a substituent capable of forming hydrogen bonds, the $-N(R_z)C(=O)N(R_{aa})(R_{ab})$ and $-N(R_z)C(=O)OR_{ac}$ substituents (both outside the proviso) are capable of accepting and donating hydrogen bonds in a more substantive way than all but the hydroxy and NH_2 substituent in the proviso (Brancale Dep. 150:16-152:1; Boons ¶42);
- If polar means a substituent that is electronegative, azido (outside the proviso) is more electronegative (>3) than cyano, trifluoromethyl, NH_2 , iodine and bromine (≤ 3), all of which are substituents in the proviso (Brancale Dep. 156:11-161:10; Boons ¶¶40-41); and
- If polar means a substituent capable of ion pairing, then a skilled artisan might think of $NR_{ad}R_{ae}$, OH, and $-N(R_z)C(=O)OR_{ac}$, as able to take on a charge. But those substituents appear both inside and outside of the proviso (Boons ¶39).

Dr. Wagner's own prior art, U.S. Patent No. 6,475,985, undermines the University's characterization of the proviso. The University highlights the '985 patent as teaching substituents "incapable of polar interactions around the 2'-

carbon.” Brancale ¶¶114-15. But the ’985 patent includes a list of “specific values” at that position and a claim to those values that almost identically mirrors the substituent list in the so-called “polar proviso” of P1/NP2. Ex. 2027 (’985 Patent), 9:39-40 (R_2 is attached at the 2’-carbon); 40:7-67 (claim 24, derived from claim 20); Brancale Dep. 278:23-279:8. The same list of substituents cannot teach non-polarity in the prior art and—at the same time—suggest a preference for polarity in the alleged priority applications. What the ’985 patent and its “specific values” at the 2’-position in fact indicate is that the so-called “polar proviso” is simply a list of substituents, not evidence of some larger teaching.

In sum, the insinuation that the applicant had a “special interest in meeting the Polar Proviso at R_2 ,” POR, 50, is nothing more than a red herring. The proviso itself is a laundry list defining the broadest possible genus, and therefore every tree within the proverbial forest meets its terms. Demonstrating the applicant had a special interest in the entire forest is, by definition, inadequate under the law.

Fujikawa, 93 F.3d at 1571.

B. P1’s Improper Multiple Dependent Claims and NP2’s Corresponding Specific Values Do Not Guide a Skilled Artisan to the Claimed Subgenera

According to the University, P1’s claims and NP2’s specific values allow a skilled artisan to both “visualize” the ’830 patent subgenera and “distinguish [them] from other materials.” POR, 45. These arguments smack of hindsight. They

require the skilled artisan to selectively pick and choose certain options over others, without justification in the alleged priority applications. Boons ¶¶8-31. Mere textual reference for individual limitations scattered throughout the written description has never been a litmus test for possession. *Novozymes* explicitly holds that. 723 F.3d at 1349. The pertinent question is what P1's claims and NP2's specific values, when read as a whole, convey to the skilled artisan.

1. P1's claims and NP2's specific values are not reinforcing.

As a threshold matter, the University asserts that because P1's claims are incorporated by reference in NP2, the disclosure in P1 and NP2 are "interlocking markers collectively reinforc[ing]" one another. POR, 55-56. This argument is a straw man, as "faithfully replicat[ing]," POR, 7, P1's claims in NP2's specific values does not substantively narrow the disclosure or blaze a trail towards the claimed subgenera. Boons ¶¶4-7.

Moreover, by rule a PCT applicant should rely on incorporation-by-reference only where application portions "are, or appear to be, missing" and were "accidentally omitted." *See* Ex. 1037; PCT Rules 4.18, 20.4-20.8. In this instance, NP2 presents different claims relative to P1, and thus the omission of P1's claims cannot be inadvertent. Moreover, a PCT applicant must perfect incorporation-by-reference by timely filing, e.g., "a written notice confirming [an omission] is incorporated by reference in the [PCT] application," "a sheet ... embodying" such

omission, and “an indication as to where that part is contained in the earlier application.” PCT Rules 20.6(a), 20.7. The University made no such filing in NP2.

The University’s decision to present different claims in NP2 in light of the PCT rules informs what should be considered a blaze mark. Boons ¶¶67-72. There is no basis for combining P1’s claims with NP2’s specific values when NP2 has its own unique claims—claims from which the ’830 patent subgenera cannot be constructed, Boons ¶72, and conspicuously absent from the University’s response.

2. P1’s claims and NP2’s specific values do not significantly narrow the possibilities in Formula I.

Notwithstanding the improper incorporation-by-reference, the University severely undercounts the subgenera encompassed by P1’s claims and NP2’s specific values. Even putting aside the fact that many “selections” such as “(C₁-C₆)alkoxy” themselves reflect more than a dozen possible substituents, P1’s claims and NP2’s specific values present at least five options at R₁ (which could be “optionally substituted by 1, 2, or 3” times from a list of thirteen options), fourteen options at R₂, thirteen options at R₃, four options at R₄, at least five options at R₅ (plus more than 100 sub-options for substituents R_h and R_k), nine options at R₆, and fifteen options at R₇. Boons ¶¶120-38; Brancale Dep. 239:2-10. The combinations of these options (and corresponding subgenera) are enormous, and do not significantly narrow the possibilities in Formula I. Boons ¶¶137-38. *Fujikawa* plainly precludes an inference that Dr. Wagner possessed all of these subgenera.

The University argues, however, that a skilled artisan would identify a small subset (168) of these possible subgenera. POR, 45. This number is derived from multiplying seven selections at R₂/R₆, eight selections at R₃/R₇, and three selections at R₅, that the University says are “of special interest.” *Id.*

To begin, 168 is still too many options to reasonably convey that the applicant had possession of them all. *Ruschig* concerned a small genus of 48 compounds, which the Federal Circuit held was insufficient support for any one species. 54 C.C.P.A. at 1556 (“something more than the disclosure of a class of 1000, or 100, or even 48, compounds is required”). If 48 is too many, so is 168.

There are numerous flaws with the University’s reasoning that impugn the credibility of their calculation, *see* Boons ¶¶120-138:

- Ignoring the R₁, R₄, and X variables at which a skilled artisan would have to make selections (and to which several P1 claims and NP2 specific values are directed). Brancale ¶202.
- Counting some options at R₂ and R₃, but not all. Brancale ¶¶241-43, 259-61 (excluding P1 claims 14, 15, 17, three possibilities from claims 20, 24, 25, and three possibilities from claim 29).
- Treating all options described at R₆ and/or R₇ as one single choice. *Id.* (excluding possibilities identified in P1 claims 46 and 48).

- Counting only “three classes of options for R₅,” while ignoring all possibilities for the variables R_a and R_b, many of which are specifically identified in P1’s claims and NP2’s specific values. Brancale ¶¶265, 286.
- Selecting multiplication to calculate the number of combinations possible as opposed to the standard factorial equation to do so; undercounting the total number of combinations. Brancale ¶287.

Finally, the University’s math requires a skilled artisan to ignore the open-ended nature of most of P1’s claims. For example, P1 claims 12-20 define choices for R₂; they place no limitations on Formula I’s choices at any other position. P1, 23-24 (depending on “any one of claims 1-11”); 19-21 (defining claim 1 as “a compound of formula I”). In order to arrive at 168, the University argues P1 claims 12-20 must be limited to combinations with P1 claim 45, which defines choices for R₆. POR, 6. Nothing in the written description teaches this artificial constraint on what P1 claims 12-20 expressly allow. Nor does combining P1 claims 12-20 with P1 claim 45 place any further limitations on other positions, e.g. R₃, R₄, R₅, and R₇. For those, the University derives similar unsupported constraints: for example, with respect to P1 claims 21-29 (defining choices for R₃), limiting to combinations with P1 claim 47 (choices for R₇). POR, 7. Taken at face value, P1 claims 12-29 allow for the full range of choices in Formula I at positions other than R₂ and R₃—subgenera left wholly unaccounted for in the University’s 168.

3. A skilled artisan would not choose the claimed subgenera from P1's claims or NP2's specific values without hindsight.

The University baldly asserts P1 claim 47—through a string of no less than six multiple dependencies—“encompasses Challenged Claim 1’s *exact* subgenus.” POR, 32-33 (stating same regarding the associated seven specific values in NP2); Brancale Dep. 163:17-164:11. Choosing this path to the exclusion of all others does not adequately show possession.

'830 Patent Subgenus =

The image displays a grid of patent claim pages from the '830 Patent Subgenus. The grid shows various claims with arrows pointing to specific subgenus definitions. Claim 1 defines X and R4. Claim 2 narrows R1. Claim 13 narrows R2. Claim 21 narrows R3. Claim 33 narrows R5. Claim 45 narrows R6. Claim 47 narrows R7. A chemical structure diagram is shown in the bottom right corner, illustrating the relationship between the R groups and the core structure.

P1 claim 47 states: “[t]he compound of any one of claims 1-46 wherein R₇ is hydrogen or (C₁-C₆)alkyl.” P1, 27:1-2. This claim does not include options for R₁-R₆; a skilled artisan would have to select those from any one of P1 claims 1-46. In turn, P1 claim 47 encompasses innumerable subgenera and many multiply dependent paths that lead to compounds outside the challenged claims. Boons ¶¶8-

31, n.3 (calculating 1.9×10^{12} subgenera). In fact, any combination (including combinations starting with claim 47) that includes any one of P1 claims 12, 16-20, 22-29, 34, 35-39, 46, or 48-49 results in subgenera different than those claimed in the '830 patent. *See* Brancale Dep. 167:3-172:6.

There is no text, language, or other form of teaching in the priority applications that guides a skilled artisan to P1 claim 47 as opposed to any of the other 48 original compound claims. Nor does the University put forward any credible explanation—because none exists—as to why a skilled artisan would start from P1 claim 47 and then work backwards, cobbling together selected claim elements from seven different original claims, as it has. Brancale Dep. 166:2-21. The same is true of the University's subsequent selection of dependent claims. Picking any one of the 23 original claims identified above after choosing P1 claim 47 as a starting point leads to compounds outside the scope of the '830 patent. Boons ¶¶21-31. And most of P1's dependent claims require multiple selections from long lists of options, almost all of which result in subgenera outside the challenged claims. Brancale Dep. 167:3-172:6.

The task of locating the '830 patent subgenera is made more difficult by the nature of the original claims, which are written in cascading improper multiple dependencies. For example, P1 claim 47 depends on any one of claims 1-46. Brancale Dep. 166:22-167:2. Other P1 claims use similar language. *See, e.g.*, P1,

23-27 (claims 12-35, 39-40, 44-48). P1 claim 37 depends on claim 35, which then depends on “any one of claims 1-32.” P1, 24-25. Indeed, P1 claims 12-48 all include impermissible multiple dependencies. *See* 35 U.S.C. § 112(e). As was true in *FWP*, P1’s claims and their “intermixing dependencies presents an overall picture of a set of claims designed to preempt a conspicuously large number ..., which is disconnected from a written description that is far more limited in its disclosure.” *FWP*, 749 F. App’x at 978. P1 claim 47 does not evince possession of the subgenera of the ’830 patent. Boons ¶¶15-17.

4. P1’s claims and NP2’s specific values blaze a trail away from the ’830 patent.

Only one specific value in NP2 includes selections for all variables (R_1 - R_7 and X) within it: the value corresponding to the only compound specifically identified in P1’s (and NP2’s) claims: (2-(3-indolyl)-l(R)-methylcarbamoylethyl)phosphoramidic acid mono (1-B-arabinofuranosyladenosine)ester. P1, 27:9-11 (claim 49); Boons ¶¶79-93. That compound falls outside the ’830 patent subgenera because it possesses hydrogen at R_2 , hydroxy at R_6 , and adenosine at R_1 —a fact the University elides. *Brancale Dep.* 62:2-14; 174:11-17.

The University spends pages trying to describe the “inter-relationship between the R_2/R_6 selections at the 2’-position and between the R_3/R_7 selections at the 3’-position” highlighted by P1’s claims and NP2’s specific values. *POR*, 31,

35-43. But the University ignores that only P1 claims 46 and 48 (and their corresponding specific values) actually specify selections for R₂ or R₆ and R₃ or R₇ together. Boons ¶¶82-84, 108-119. And both limit choices at those positions to options outside the '830 patent's claimed subgenera. *Id.*

P1's claims and NP2's specific values do not identify challenged claim 1's subgenus as being of "special interest." In fact, the "slew of competing possibilities" they present blaze a trail away from it. *Novozymes*, 723 F.3d at 1349.

C. NP2's Examples Are Not a Blaze Mark to the '830 Patent

The University argues that NP2's example compounds "blaze an undeniable trail to [a] **single** combination of choices" at the 3'-position, and ultimately a "special interest in six subgenera within Formula I" POR, 49-53. To get to this "undeniable trail," the University inconsistently cherry-picks only a portion of R groups in NP2's compounds to create an imaginary example found nowhere in the written description.

NP2 includes twenty-four examples (compounds 100-123), none within the challenged claims. Brancale Dep. 34:13-35:1. Twenty-one examples are within the scope of Formula I. Boons ¶¶94-105. The remaining three are 2'-deoxy compounds (compounds 117-119)—compounds described as having a "reduced ability" to serve as substrates of hHINT1. NP2, 3:5-9. Of the twenty-one examples within

Formula I, all have either hydrogen or hydroxy at R₂. Brancale Dep. 36:3-14. Zero have halo. *Id.* 177:21-178:10.

The University's efforts to make NP2's examples into blaze marks is pure hindsight. On the one hand, the University suggests a skilled artisan would not look beyond the specific substituents contained in NP2's examples at every position other than R₂/R₆. POR, 51; Boons ¶¶73-78. On the other hand, the University broadens R₂ and R₆ beyond the substituents reflected in each example (hydrogen and hydroxy) in order to manufacture imaginary possibilities where R₂ is halo. POR, 51. There is no reasonable justification for interpreting the examples as teaching the selections made at some positions (R₃ and R₇) but not at others (R₂ and R₆); either NP2's examples blaze a trail to selections actually made, or they blaze no trail at all. Whatever the case, NP2's examples do not lead a skilled artisan to the subgenera claimed in the '830 patent. Boons ¶¶103-105.

The examples are telling for other reasons. Across all four alleged priority applications, there is biological data on only three compounds: 113, 114, and 115. Brancale Dep. 199:20-23. Each has hydroxy at R₆, hydrogen at R₂, and an adenine at R₁, making them multiple selections removed from the challenged claims. *Id.* at 58:12-61:2; Boons ¶103, n.11. Moreover, compound 115, which had the most promising biological data of the group, includes tryptamine at R₅, yet another

selection outside the scope of the challenged claims. Brancale ¶¶180, 320; Brancale Dep. 60:4-12.

The University's expert concedes that the biological data presented in the priority applications investigates selections on the phosphoramidate prodrug (R₄ and R₅), not on the antiviral nucleoside (X, R₁-R₃, and R₆-R₇), portion of the compounds claimed. Brancale Dep. 60:13-61:2. Without data for selections other than H or OH at the 2'-position, there is no marking to indicate to a skilled artisan that they should "leave the trail" to investigate compounds with substitutions other than those described in NP2's examples. *See Fujikawa*, 94 F.3d at 1571.

Nowhere does the University address why (or how) a skilled artisan would extrapolate from NP2's examples (actually possessed and with biological data) to an inference of possession of imaginary compounds patterned off the challenged claims. That is, by definition, hindsight. *See Ruschig*, 379 F.2d at 995.

IV. THE APPLICANT HAD A SPECIAL INTEREST IN ELECTROPOSITIVE GROUPS AT 2'

The "discovery" leading to the alleged priority applications concerns study of the hHINT1 enzyme and "especially good substrates for hHINT1." NP2, 3:11-14. P1 and NP2 describe Dr. Wagner's investigation as revealing that "hydrogen bonding, ion pairing or polar interactions at the 2'- and 3'- positions preferentially interact with the [hHINT1] active site." P1, 3:3-6; NP2, 3:5-9. The applications then conclude by stating unambiguously—"consequently"—that

“compounds containing [] an electropositive group at the 2’-position, ... are especially good substrates for hHINT1.” P1, 3:8-11; NP2, 3:11-14. All experts in this proceeding agree that halogens are not electropositive groups. Brancale Dep. 263:12-20; Boons ¶149.

The disclosures of P1 and NP2 (examples, data, representative species, claimed compounds), read in light of the hHINT1 investigation described, point uniformly to subgenera with hydroxy at R₂ or R₆.³ See Boons Dep. 195:17-19; Boons ¶¶139-150; Exs. 1040-41. That is because a compound’s 2’-OH can, according to the written description, “preferentially interact” with hHINT1 via “hydrogen bonding interactions.” P1, 3:3-6; 1:22-25; *see also* Boons ¶145.

The University rewrites these statements by saying there is a difference between Dr. Wagner’s work described in the “background of the invention” and application of that work to compounds with antiviral and anticancer activity. POR, 68-69. But the actual written description contradicts this position. As the University’s own expert admits, the written description links the need for

³ While OH groups are sometimes electronegative, they may also be electropositive depending on the particular chemical context. Boons Dep. 194:1-17. Halogens are always electronegative. Brancale Dep. 263:12-20.

electropositive groups at 2' with the identification of those compounds as good substrates of hHINT1, and thus candidates for antiviral and anticancer therapeutics. Brancale Dep. 261:10-263:10.

V. EVEN IN HINDSIGHT THERE ARE MILLIONS OF POSSIBILITIES

Throughout its response, the University improperly insinuates that Gilead's "priority attack turns on the assertion" that NP2 describes 7,441,875 possible combinations of R₂-R₃ and R₅-R₇ substituents. POR, 27-28. That is not true. As an initial matter and as described above, NP2's broadest genus discloses quadrillions of subgenera. Boons ¶¶47-58. The 7,441,875 number conservatively limited the number of Markush elements at each position in Formula I to those found in the '830 patent claims (e.g., the number of different possible 2-option combinations for R₆ and R₇). Marquez ¶96. In other words, the 7,441,875 number was determined (for illustrative purposes) using hindsight assumptions the skilled artisan would not make.

The University argues that the 7,441,875 overstates the possible combinations in "NP2's broadest genus." POR, 4. That argument does not pass the straight face test given the hindsight assumptions baked into 7,441,875. The actual combinations in NP2's broadest disclosed genus is at least nine orders of magnitude larger. Boons ¶¶47-58. And even incorporating the "polar proviso" into the calculation (to the extent that is the University's issue) still leaves 4,266,675

subgenera—a number far too large for any skilled artisan to wade through and find within it the '830 patent claims. Boons ¶¶58-66.

VI. CONCLUSION

The University would have this Board believe that Dr. Wagner invented all nucleoside phosphoramidate compounds with a polar group at the 2'- or 3'-positions. The scope of that invention would be breathtaking and represent one of the largest land grabs in patenting history, especially given the limited number of example compounds and biological data provided in the alleged priority applications.

Dr. Wagner's contemporaneous literature tells a more modest story. The University points to three references Dr. Wagner published from 2005 to 2007, years after his so-called invention. POR, 17. None includes a nucleoside phosphoramidate with a halogen at R₂. *See* Exs. 2022, 2053, 2054. Indeed, the University does not cite any original research by Dr. Wagner that includes such compounds. *See* Exs. 1018, 2008, 2013, 2017, 2052, 2073, 2078. The reason is simple: Dr. Wagner was not studying, and was not in possession of, nucleoside phosphoramidates with a halogen at R₂ in 2004.

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I hereby certify that the foregoing Reply Brief contains 5586 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(a).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4) and 42.105, the undersigned certifies that on this date, a true and correct copy of the foregoing Petitioner's Reply and accompanying exhibits was served via email on the Patent Owner at the following email addresses:

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