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BIOTECHNOLOGY PATENT LAW TOP TEN OF 2022: INDUCEMENT, CLEAR ERROR, AND INTERFERENCES GALORE

*Kevin E. Noonan and Andrew W. Torrance**

ABSTRACT

Five-year anniversaries are symbolized by a product of natural biotechnology: wood. This article marks the wood anniversary of the "Top Ten Biotechnology Patent Cases" series that began in 2018. Imagining the world in 2018 is challenging, in part because it was, indeed, a different world. There had not been a major pandemic in one hundred years. Inflation was low. The economy hummed along. No individual war appeared to threaten more than regional stability. *O tempora, o mores!* The year 2022 was quite different. SARS-CoV-2 continued to stalk the land, having had a monumentally mortiferous effect for several years. High inflation was rampant. The economy was still recovering from one of the deepest declines in history, with imbalances across many sectors. Moreover, eastern Europe had let slip the dogs of war, threatening peace worldwide.

Biotechnology also has seen changes of significant magnitude. Venture capital investment in biotechnology was small compared to what it is now. Efficient genome editing was restricted to first-generation CRISPR-Cas9 systems, while now it may be accomplished using more powerful and accurate methods, like base editing and prime editing (the latter offering hope for treatment in almost 90% of genetic diseases). Courts had declared that diagnostic methods did not constitute patentable subject matter, which remains the case today, although clever draftswomen continue their efforts to obtain claims protecting such methods to some extent.

Over the course of 2022, courts decided a generous selection of cases covering a wide variety of biotechnology patent law issues. These cases ran the gamut, from patent doctrines concerning satisfaction of the written description requirement for antibody claims to mechanisms for augmenting patent terms using either Patent Term Extension, or Patent Term Adjustment, or both. This article has chosen ten of the most important, though, as is the case every year, our choice of only ten was difficult, and, by necessity, left worthy cases on the cutting room floor.

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I. INTRODUCTION[1]

Five-year anniversaries are symbolized by a product of natural biotechnology: wood. This article marks the wood anniversary of the "Top Ten Biotechnology Patent Cases" series that began back in 2018. Imagining the world in 2018 is challenging, in part because it was, indeed, a different world. There had not been a major pandemic in one hundred years. Inflation was low. The economy hummed along. No individual war appeared to threaten more than regional stability. *O tempora, o mores!* The year 2022 was quite different. SARS-CoV-2 continued to stalk the land, having had a monumentally mortiferous effect for several years. High inflation was rampant. The economy was still recovering from one of the deepest declines in history, with imbalances across many sectors. Moreover, eastern Europe had let slip the dogs of war, threatening peace worldwide.

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II. DECISIONS

1. GlaxoSmithKline LLC v. Teva Pharmaceuticals USA (Fed. Cir. 2022) (Decided February 11, 2022)

The 2020 decision by a divided Federal Circuit panel in *GlaxoSmithKline LLC v. Teva Pharmaceuticals USA* regarding the extent to which an ANDA applicant who obtained regulatory approval under the Section viii carve-out

1. Portions of this article are adapted from blog posts written by Kevin E. Noonan. *See generally* Kevin E. Noonan, *CVC Files Response and Reply Brief in Interference No. 105,115 Appeal*, PatentDocs (Aug. 27, 2023), www.patentdocs.org [https://perma.cc/FD5P-J26B].

2. *See* Andrew V. Anzalone et al., *Search-and-Replace Genome Editing Without Double-Strand Breaks or Donor DNA*, 576 Nature 149, 149 (2019).

provisions of the statute could be liable for inducement of infringement under 35 U.S.C. § 271(b) caused something of an uproar, leading to a panel rehearing on the matter but ultimately coming to the same conclusion (albeit containing somewhat modified reasoning).[3] Both decisions were issued in the face of a strong dissent by Judge Prost, in the first decision while she was Chief Judge. Upon request for rehearing *en banc*, the Court decided not to grant rehearing over the dissenting opinions of three of the judges (including Judge Prost).

The matter arose in litigation over GSK's Coreg® product (carvedilol) for the treatment of hypertension (the initial approved indication; U.S. Patent No. 4,503,067), congestive heart failure (CHF) (the subject of U.S. Patent No. 5,760,069) and left ventricular dysfunction following myocardial infarction (LVD-MI).[4] The '069 patent recites a method of treating CHF with a combination of carvedilol and "one or more of an angiotensin-converting enzyme ("ACE") inhibitor, a diuretic, and digoxin."[5]

Teva's ANDA was filed with a Paragraph III certification over the '067 patent and a Paragraph IV certification over the '069 patent.[6] The FDA tentatively approved Teva's generic product for the "treatment of hypertension and heart failure," which Teva launched upon expiration of the '067 patent.[7] Teva's label indicated that the product was approved for treatment of LVD-MI and hypertension and announced that the FDA had given its product an "AB rating" (which the opinion explained "allow[s] users to determine quickly whether the Agency has evaluated a particular approved product as therapeutically equivalent to other pharmaceutically equivalent products").[8] Thereafter, the FDA required Teva to amend its label to be identical to the GSK label for Coreg®, which introduced treatment of heart failure into the approved treatments recited in Teva's label.[9]

GSK filed for reissue of the '069 patent which was duly granted by the U.S. Patent and Trademark Office as Reissue Patent No. RE40,000; claim 1 is representative of the invention as claimed in the '000 reissue patent:

> 1. A method of decreasing mortality caused by congestive heart failure in a patient in need thereof which comprises administering a therapeutically acceptable amount of carvedilol in conjunction with one or more

3. *See* GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 976 F.3d 1347, 1355 (Fed. Cir. 2020).

4. GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 7 F.4th 1320, 1323 (Fed. Cir. 2021) (per curiam).

5. *Id.*

6. *Id.*

7. *Id.* at 1324.

8. *See id.* at 1324–36.

9. *Id.* at 1324–25.

> other therapeutic agents, said agents being selected from the group consisting of an angiotensin converting enzyme inhibitor (ACE), a diuretic, and digoxin,
>
> *wherein the administering comprises administering to said patient daily maintenance dosages for a maintenance period to decrease a risk of mortality caused by congestive heart failure, and said maintenance period is greater than six months.*[10]

GSK filed suit against Teva for inducement of infringement based on the Teva label, in view of direct infringement by physicians prescribing the drug for the label indications.[11] Teva argued that it had "carved out" the indication for CHF pursuant to 21 U.S.C. § 355(j)(2)(A)(viii), resulting in a "skinny label" with regard to this indication.[12] Thereafter, however, the FDA compelled Teva to amend its label to include that indication.[13] In addition, liability for inducement attaches only if GSK could show that Teva had "directly communicated with the direct infringers and 'caused' them to directly infringe the method in the '000 [reissue] patent."[14] In an instruction, the District Court informed the jury that circumstantial evidence could be used to satisfy this burden.[15]

The jury found that Teva induced infringement of the '000 reissue patent both before and after the label amendment (albeit infringing several claims after but not before that change).[16] The District Court granted Teva's motion for judgment as a matter of law (JMOL) on the basis that GSK had not "caused" physicians to prescribe their product for the infringing uses.[17] Because proof of such causation was required, according to the District Court, its absence precluded the jury from basing its decision on substantial evidence.[18] The Court relied on the existence of "many sources of information available to prescribing physicians" other than Teva's label (including paradoxically GSK's label and promotion of its Coreg® product) in finding this evidentiary deficiency.[19]

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10. *GlaxoSmithKline LLC*, 7 F.4th at 1324–25 (where the italicized portion of the claim represents the modifications introduced in prosecution of the reissue application).

11. *See id.* at 1325.

12. *Id.*

13. *Id.* at 1324–25.

14. *GlaxoSmithKline LLC*, 976 F.3d at 1355.

15. *GlaxoSmithKline LLC*, 7 F.4th at 1339.

16. *Id.* at 1325.

17. *Id.*

18. *Id.*

19. *See GlaxoSmithKline LLC*, 976 F.3d at 1351.

Also, the Court based its decision on physician testimony that their prescribing behavior relied on "guidelines and research, as well as their own experience" and not Teva's label.[20] In sum, the Court said, "substantial evidence [did] not support the jury's finding on causation, and therefore [did] not support its verdict that Teva is liable for induced infringement, during both the skinny and full label periods."[21]

On its first appeal, the Federal Circuit reversed, in an opinion by Judge Newman joined by Judge Moore; Chief Judge Prost provided a lengthy, comprehensive dissent. The panel majority relied on the Supreme Court's decision in *Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754 (2011), that copying is evidence of inducement, and found compelling evidence from Teva's website regarding its product's AB rating with GSK's Coreg® product and other promotional content, as well as testimony from GSK's witnesses regarding physician reliance on information from generic drug makers.[22]

The panel majority opined that the District Court erred by applying the incorrect legal standard, stating that "precedent makes clear that when the provider of an identical product knows of and markets the same product for intended direct infringing activity, the criteria of induced infringement are met."[23] Considering this precedent, the majority held that "[t]here was ample record evidence of promotional materials, press releases, product catalogs, the FDA labels, and testimony of witnesses from both sides, to support the jury verdict of inducement to infringe the designated claims for the period of the '000 reissue patent."[24]

Then-Chief Judge Prost dissented based on her objections to the quanta of evidence adduced and policy consequences should the majority's position be sustained.[25] In the then-Chief's view, the majority's decision undermined these policy goals, embodied in the provisions of the law regarding skinny labels, for a balance between the incentives patents provide for pharmaceutical innovation and the public's need for access to that innovation once the patent term has expired.[26] In her view, the majority's decision undermined these policy goals by finding Teva induced infringement by marketing its generic drug product

20. GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 313 F. Supp. 3d 582, 594–95 (D. Del. Mar. 28, 2018).

21. *Id.* at 597.

22. *GlaxoSmithKline LLC*, 976 F.3d at 1352–53 (citing Global-Tech Appliances, Inc. v. SEB S.A., 563 U.S. 754 (2011)).

23. *Id.* at 1355.

24. *Id.*

25. *See id.* at 1358 (Prost, C.J., dissenting).

26. *See id.* at 1357–58.

for *unpatented* uses (emphasis in dissent) using its skinny label.[27] The dissent not only disagreed with the majority's decision but apprehended it to "nullif[y] Congress's statutory provision for skinny labels—creating liability for inducement where there should be none," contrary to Congressional intent, and, as a result, "slowing, rather than speeding, the introduction of low-cost generics."[28]

The original majority opinion occasioned an outpouring of outrage from industry groups (particularly generic ones) who latched onto the then-Chief Judge's rhetoric in her dissent to the effect that the opinion eviscerated the congressional sanctioning of skinny labels.[29] The Court granted panel rehearing that resulted in the second opinion that was the subject of the Court's denial of *en banc* review.[30]

The outcome did not change in that second opinion (although the explication of the process aspects of the majority, *per curiam* opinion were perhaps more explicit). After reciting the procedural posture of this decision (as a panel rehearing), the majority addressed *amici*'s concerns (amply represented in eleven *amicus* briefs, including a brief by one of the architects of the generic's law, former Representative Henry Waxman).[31] The opinion recited with approval the behavioral distinctions underpinning the majority's decision based on the law with regard to skinny labels:

> Generics *could* be held liable for actively inducing infringement if they marketed a drug with a label describing a patented therapeutic use or if they took active steps to encourage doctors or patients to use the drug in an infringing manner. But generics could *not* be held liable for merely marketing and selling under a 'skinny' label omitting all patented indications, or for merely noting (without mentioning any infringing uses) that FDA had rated a product as therapeutically equivalent to a brand-name drug (emphasis in original).[32]

Stating that the panel (or at least the majority) agreed to rehear arguments "to make clear how the facts of this case place it clearly outside the boundaries of the concerns expressed by *amici*," the opinion stated that the basis for their decision that the jury correctly found Teva liable for inducing infringement was that Teva was "marketing a drug with a label *encouraging*

27. *Id.* at 1357.

28. *GlaxoSmithKline LLC*, 976 F.3d at 1358.

29. *See id.* at 1359.

30. *GlaxoSmithKline LLC*, 7 F.4th at 1326.

31. *Id.* at 1326, 1342 (Prost, J., dissenting).

32. *Id.* at 1326 (majority opinion).

a patented therapeutic use" (emphasis in opinion).[33] The opinion also stated more precisely the procedural basis for their opinion: "This is a case in which substantial evidence supports a jury finding that the patented use was on the generic label at all relevant times and that, therefore, Teva failed to carve out all patented indications."[34] The majority also emphasized that their decision was a "narrow, case-specific review of substantial evidence [that] does not upset the careful balance struck by the Hatch-Waxman Act regarding section viii carve-outs."[35] The remainder of the majority opinion set forth (extensively) the evidentiary basis for their opinion that there was sufficient evidence (including expert testimony and marketing efforts occurring both before and after FDA-mandated changes to Teva's label) to satisfy the substantial evidence standard, and that the District Court erred in granting Teva JMOL to the contrary (*inter alia* including specific errors in treating factual questions as legal ones that the majority state were "not [for] this court or the district court, to resolve").[36]

Former Chief Judge Prost remained unconvinced, in large part because this outcome (in her view) undermined the congressionally sanctioned skinny label regime (if only by rendering it much more case- and fact-specific than she perceived Congress intended). The outcome-based philosophy of the dissent was presaged in its first sentence, where Judge Prost reminded the reader that "GSK's patent on carvediol expired in 2007" followed by the statement that "[b]ecause the FDA cannot authorize a generic version of a drug that would infringe a patent, this one remaining patented use could have prevented a less-expensive, generic carvedilol from coming to market altogether—even though the drug *itself* and other uses of it were unpatented" (emphasis in opinion).[37] The skinny label regime was Congress's solution to a "problem" it "saw coming" in Judge Prost's view.[38] The majority's decision thwarted this intent, according to Judge Prost, based on evidence of inducement that was "thin to nonexistent."[39] The District Court had properly exercised its supervisory role in remedying a situation where a jury came to the wrong conclusion Judge Prost concluded, based on her evaluation of the evidence before it.[40] The Judge sets forth her motivation for writing (once again) in dissent (and that the majority's attempt to provide a comforting standard falls short in her opinion):

33. *Id.*

34. *Id.*

35. *Id.*

36. *GlaxoSmithKline LLC*, 7 F.4th at 1330–31.

37. *Id.* at 1342 (Prost, J., dissenting).

38. *Id.*

39. *Id.*

40. *Id.*

> I write in this case because far from being a disagreement among reasonable minds about the individual facts, this case signals that our law on this issue has gone awry. I am particularly concerned with three aspects of the majority's analysis. First, even setting aside the majority's willingness to glean intentional encouragement from a label specifically designed to avoid encouragement, the majority further weakens the intentional-encouragement prong of inducement by effectively eliminating the demarcation between describing an infringing use and encouraging that use in a label. Second, the majority defies basic tort law by eviscerating the causation prong of inducement. The upshot of these two moves is that a plaintiff now has to show very little for a jury to speculate as to the rest. Third, the majority creates confusion for generics, leaving them in the dark about what might expose them to liability. These missteps throw a wrench into Congress's design for enabling quick public access to generic versions of unpatented drugs with unpatented uses.[41]

The decision not to grant rehearing *en banc* by the full Court was announced in a simple Order to that effect, noting that Judges Lourie and Cunningham did not participate in the decision.[42] The Order was accompanied by three written dissents: one by Judge Prost, joined by Judges Dyk and Reyna; another by Judge Dyk writing alone, and the third by Judge Reyna; the majority comprised Chief Judge Moore and Judges Newman (who was the third member of the original panels), O'Malley, Taranto, Chen, and Stoll.[43] Judge Prost's dissent calls the decision not to rehear the case *en banc* "disappointing," insofar as the issues "affect[] millions of Americans," and she terms the Court's refusal to rehear en banc "an abdication of the responsibility (to review issues at the intersection of patent law and pharmaceutical regulation)".[44] This dissent characterizes the majority's treatment of the regulatory and statutory processes involved in obtaining skinny label regulatory approval as "quite unsatisfactory," saying the majority "refuses to confront the obvious question: how could this label, which faithfully followed what the brand said about its own patents and which the FDA required Teva to use, itself be evidence that Teva intentionally encouraged something it knew would infringe?"[45] As a consequence of the majority decision, "no skinny-label generic is safe" in Judge

41. *Id.* at 1343.

42. GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 25 F.4th 949, 949 (Fed. Cir. 2022) (per curiam).

43. *Id.*

44. *Id.* at 953–54 (Prost, J., dissenting).

45. *Id.* at 955.

Prost's view.[46] This is because "most skinny labels contain language that (with clever expert testimony) could be pieced together to satisfy a patent claim," as asserted by several *amici* (one of whom, Mylan Pharmaceuticals, termed this the "Where's Waldo" approach).[47] This outcome is contrary to Congressional intent, Judge Prost maintained, which was for generic companies to *avoid* inducement liability under skinny-label circumstances (emphasis in dissent).[48] Generic drug companies who follow FDA guidelines for skinny labels are "play[ing] by the skinny-label rules" she writes, and "[e]ven if remaining label language might be pieced together to 'meet' the elements of a patent claim, the extent to which that's true is an unreliable gauge of a generic's 'intent' in this highly regulated area; it can't meaningfully separate the liable from the lawful."[49] And she notes the consequences stemming from the generic drug maker's economic model by illustration: Teva's revenues ("having made no profit," which is a bit curious), according to the dissent, were $74 million but the judgment below for inducing infringement was $234 million.[50] Under these circumstances, the Judge asserts, "generics simply won't play."[51] Judge Prost concludes her dissent by addressing what she considers inaccuracies in the majority's concurrence regarding arguments she believes were made but that the concurrence asserts were not, and its characterizations of her concerns to be fairness, when Judge Prost maintains those concerns are based on "what inducement law permits in view of the Hatch-Waxman Act."[52]

Judge Dyk's writes in dissent "to further elaborate why there cannot be infringement liability for using a label required by the FDA during the partial label period at issue in this case."[53] These elaborations are based on the extent to which Teva was obligated under law to accept the label mandated by the FDA in making its Section viii carve-out which it did (" . . FDA provided Teva with a redline for its skinny label, carving out the patented indication for congestive heart failure from GSK's branded label and keeping the remaining uses in the label").[54] Judge Dyk points out that "[i]n similar circumstances where states have sought to impose tort liability on generic drug manufacturers for using the label required under federal law, the Supreme Court has made

46. *Id.*

47. *Id.*

48. *GlaxoSmithKline LLC*, 25 F.4th at 955.

49. *Id.*

50. *Id.*

51. *Id.* at 951 (Moore, C.J., concurring).

52. *Id.* at 958 (Prost, J., dissenting).

53. *Id.* (Dyk, J., dissenting).

54. *GlaxoSmithKline LLC*, 25 F.4th at 959.

clear that federal law preempts tort liability on the part of the manufacturers."[55] There is, in Judge Dyk's view a conflict between "FDA-required labeling" and the law of infringement, and using "[c]anons of statutory construction" concludes that the "more specific and later-enacted provisions of the Hatch-Waxman Act override the general infringement provisions of the Patent Act."[56] And Judge Dyk disagrees with the concurring majority substantially along the same lines as Judge Prost does in her dissent.

Finally, Judge Reyna in a brief dissent asserts that "the briefs, the majority opinion, the dissent, and the number of amicus briefs filed to date" satisfy the provisions of the Court's Internal Operating Procedure No. 13(2)(b) for rehearing *en banc* issues of "exceptional importance."[57]

Chief Judge Moore's concurring opinion illustrates her interpretation of Judge Prost's dissent that the majority and the dissenting judges had interpreted very differently regarding what had gone on below and before the Federal Circuit in the two prior appearances before the panel. Judge Moore begins by the simple assertion that the dissent's basis for *en banc* review was "legal positions that Teva has not asserted or developed," reciting a litany.[58] The issue before the court, according to now-Chief Judge Moore, was simply "whether, considering all the facts, substantial evidence supports the jury's verdict that Teva actively encouraged infringement."[59] But Chief Judge Moore affirmatively asserts that "Teva never argued that there was a conflict between the FDA regulatory framework and patent law (as the dissents now claim); nor did it argue that the partial label was not evidence relevant to or otherwise impermissible for deciding inducement (as the dissents now suggest)."[60] She characterizes the majority's opinion as being "narrow and fact dependent," supported by how one district court has interpreted the opinion.[61] But the "cobbling together" argument made in Judge Prost's dissent *was* considered by the panel, the Chief asserts, because Teva made that argument, which in a footnote the Chief terms "a non-starter" based on instances where the Court "regularly allow[s] claim elements to be found in different portions of a label" and citing

55. *Id.* (citing Mut. Pharm. Co. v. Bartlett, 570 U.S. 472, 476 (2013), and PLIVA, Inc. v. Mensing, 564 U.S. 604, 609 (2011)).

56. *Id.* (citing United States v. Estate of Romani, 523 U.S. 517, 532 (1998); Morton v. Mancari, 417 U.S. 535, 550–51 (1974); Bulova Watch Co. v. United States, 365 U.S. 753, 758 (1961); and Rodgers v. United States, 185 U.S. 83, 87–89 (1902)).

57. *Id.* at 960 (Reyna, J., dissenting).

58. *Id.* at 950 (Moore, C.J., concurring).

59. *Id.*

60. *GlaxoSmithKline LLC*, 25 F.4th at 950.

61. *Id.* at 951; *see generally* Amarin Pharma, Inc. v. Hikma Pharms. USA Inc., No. 1:20-cv-1630 (D. Del. Jan. 4, 2022) (mem. op).

as an example *Sanofi v. Watson*.[62] The concurrence apprehends the dissents' arguments to be grounded in fairness (a characterization Judge Prost's dissent directly rejects), based on the label not supporting the intent required by the statute (quoting extensively from Judge Prost's rhetoric about "playing by the skinny-label rules").[63] While expressing concern that "GSK's representations to the FDA are at odds with its enforcement efforts in this case" and "[i]t would be troubling to hold Teva liable for relying on GSK's representations to the FDA," "that concern does not readily fit the standards governing inducement."[64] The concurrence sees a possible solution in the doctrine of equitable estoppel, which could provide a remedy on remand, the Chief suggests. And while Judge Prost thinks little of this use of equitable estoppel in this or any skinny-label instance, Chief Judge Moore asserts that the principles of equitable estoppel ("misleading conduct, reliance, and prejudice") "track this three-element framework precisely" and provide an analysis of this argument (saying "[t]his theory fits the textbook structure of an equitable estoppel argument").[65] Chief Judge Moore believes it better to permit this argument to be asserted on remand and then, under appropriate circumstances, return to the Court for review than to hear this case *en banc*.[66]

These considerations on remand suggest that for the parties it isn't over. And to the extent that the Chief is correct that district courts (albeit using a N=1) have interpreted the panel decision parsimoniously, perhaps Judge Prost's concerns about the effect the panel opinion will have on generic manufacturers' use of skinny labels are overblown. Also, perhaps these sentiments, although not binding, will help define the contours of the District Court's application of the opinion and its effect on skinny-label practices. Provided the panel decision does not significantly inhibit skinny-label practice these issues are sure to recur and be the subject of additional Federal Circuit decisions, which will make the consequences of this decision, and the Federal Circuit's decision not to review the panel opinion *en banc*, more evident.

2. In re Cellect (PTAB 2022) (Appeal filed December 22, 2021)

The Federal Circuit had the opportunity to decide a question left open during a recent spate of opinions involving the judicially created doctrine of obviousness-type double patenting (OTDP): the effect patent term adjustment (PTA) can (or should) have on creating circumstances where OTDP will operate to find a patent invalid in the absence of a timely filed terminal disclaimer.

62. *GlaxoSmithKline LLC*, 25 F.4th at 951 n.2; Sanofi v. Watson Lab'ys Inc., 875 F.3d 636, 646 (Fed. Cir. 2017).

63. *GlaxoSmithKline LLC*, 25 F.4th at 951, 957.

64. *Id.* at 952.

65. *Id.*

66. *Id.* at 953.

The issue arose in a series of *ex parte* reexaminations over five patents owned by Cellect, U.S. Patent Nos. 6,424,369; 6,452,626; 6,982,742; and 7,002,621, that involve "solid state image sensors which are configured to be of a minimum size and used within communication devices specifically including video telephones" according to the '621 patent (only 4 of these patents were invalidated, the fifth not having any PTA that raised the issue).[67] The chronological situation is set forth in Cellect's brief in its Federal Circuit appeal brief.

There was no dispute that the claims in these applications were patentably indistinct. The Board issued four Decisions on Appeal affirming the reexamination division's invalidation of the '369, '626, '621, and '742 patents, all on the grounds that the provisions of 35 U.S.C. § 154(b)(2)(B), ("No patent the term of which has been disclaimed beyond a specified date may be adjusted under this section beyond the expiration date specified in the disclaimer") mandated that a terminal disclaimer be filed under circumstances where obviousness-type double patenting arose due to extension of patent term by PTA, *i.e.*, that OTDP must be determined *after* application of PTA.[68] Because all of these patents had expired (but Cellect retained the right to sue for prior infringement under 35 U.S.C. § 286), the Board's decision invalidated these patents with no available remedy for Cellect. In its consolidated decision, the Board emphasized the potential inequities to the public due to the possibility of harassment by different parties owning patents to obvious variants of one another (in the absence of a terminal disclaimer preventing this potentiality) and as representing an unjust extension of patent term to the public's detriment.[69] Finally, the Board rejected arguments that the Federal Circuit's jurisprudence did not rely on whether or not there was gamesmanship or the potential thereof under *Gilead Sciences, Inc. v. Natco Pharma Ltd.*, but that under *In re Longi*, the public was entitled to the assumption that it is free to practice what is claimed in the patent and obvious modifications and variants thereof once the patent has expired.[70]

The questions before the Court, according to Cellect, are summarized in five arguments. The first is based on the Board's putative legal error in interpreting the statute to justify treating term extension under PTA differently

67. Brief for Appellant, at *69; *In re* Cellect, LLC, 2023 WL 5519716 (Fed. Cir. 2021) (No. 22-1293).

68. *Id.* at *36. (It will be recalled that the Federal Circuit reached a different conclusion with regard to patent term extension (PTE) under 35 U.S.C. § 156 in Novartis AG v. Ezra Ventures, 909 F.3d 1367, 1372–75 (Fed. Cir. 2018), where the Court expressly refused to permit "a judge-made doctrine to cut off a statutorily-authorized time extension.").

69. *Id.* at *136; *see In re* Fallaux, 564 F.3d 1313, 1319 (Fed. Cir. 2009).

70. Brief for Appellant, *supra* note 67, at *53; *In re* Longi, 759 F.2d 887, 889 (Fed. Cir. 1985); Gilead Scis., Inc. v. Natco Pharma Ltd., 753 F.3d 1208, 1208 (Fed. Cir. 2014).

from term extension under PTE.[71] Second, Cellect argued that application of OTDP in this case was inequitable, due to the lack of remedy as well as there being no unjust extension because Cellect had engaged in no gamesmanship in obtaining the extension to which it was entitled by statute.[72] Third, Cellect argued as a fallback position that OTDP should be used here to cancel the term extended by PTA rather than invalidating the patents in their entirety.[73] The final two arguments were that the reexamination had been improperly instituted because there was no substantial new question of patentability asserted and that any ancillary obviousness rejections raised in the reexamination were ultimately based on the OTDP of these patents (which argument the Board argued Cellect had waived).[74]

Cellect's first argument was based on statutory interpretation. Cellect argues that both PTA and PTE are statutory grounds for extending a patent term and there was no legal nor logical basis for treating them differently, *i.e.*, the Court should interpret the PTA statute here as the Court had interpreted the PTE statute in *Ezra*.[75] Further, Cellect argues that the statutory language for PTA is that the term "shall" be extended.[76] Cellect argues that the provisions the Board relied upon were intended for situations where a terminal disclaimer *had been* filed, not one where PTA creates OTDP (emphasis added).[77] The consequence of the Board's interpretation creates a situation requiring "preemptive" terminal disclaimer filings, Cellect argues which Congress had not intended.[78] Cellect also cited several district court cases, including *Amgen, Inc. v. Sandoz Inc.*, No. 18-11026, 2021 WL 5366800, at *26-27 (D.N.J. 2021), and *Mitsubishi Tanabe Pharma Corp. v. Sandoz Inc.*, 533 F. Supp. 3d 170, 214 (D.N.J. 2021), that had interpreted the Court's *Ezra* decision to support giving statutory deference to respecting PTA over a "judge-made doctrine."[79]

71. Brief for Appellant, *supra* note 67, at *28–29.

72. *Id.* at *29.

73. *Id.* at *30.

74. *Id.*

75. *Id.*; Novartis AG, 909 F.3d at 1367.

76. Brief for Appellant, *supra* note 67, at *33 (although there have been other instances regarding provisions of the BPCIA, *see* Sandoz Inc. v. Amgen Inc., 796 F.3d 1293, 1303 (Fed. Cir. 2015), where "shall" has not been given commanding effect).

77. Brief for Appellant, *supra* note 67, at *37, (compare the language of the statute regarding a "patent the term of which has been disclaimed" to how Cellect argues the Board interpreted the language regarding a "patent the term of which [may need to be] disclaimed [if adjustment is granted].").

78. *Id.* at *38.

79. *Id.* at *43, *46–47.

Regarding the equities, Cellect argues that the purpose of OTDP was to prevent "unjust timewise extension of patent term" and to prevent "harassing litigation filed by multiple patent owners" for patents on "not-patentably-distinct" inventions.[80] Cellect's argument emphasizes the *unjust* extension aspect, which Cellect ties to the gamesmanship the Court recognized in *Gilead*.[81] And in this case, Cellect contends that "[t]he Board used an equitable doctrine to achieve an inequitable result" because the circumstances provided no basis or opportunity for Cellect to cure.[82] In an effort to avoid this outcome, Cellect argues that applying the Board's interpretation to retroactively disclaim the PTA-extended term but *not* invalidate the patents would not only cure the inequitable effects of the Board's decision but also as precedent notify future applicants who could have the opportunity to decline PTA to avoid invalidation on OTDP grounds (emphasis added).[83]

The Solicitor's argument emphasized the inequities to the public occasioned by *any* extension of patentably-indistinct inventions (in view of the government's interpretation of the statute) (emphasis added).[84] The brief cites in opposition the Court's decision in *Abbvie Inc. v. Mathilda & Terence Kennedy Institute of Rheumatology Trust*, that OTDP applies whenever there is an extension of patent term for patents claiming patentably-indistinct inventions.[85] The Solicitor also notes that under circumstances where OTDP would invalidate a patent having PTE will not save it, and that the differences in the statutes permit PTA to produce OTDP where PTE cannot.[86] Regarding Cellect's arguments for forswearing PTA but preserving the patent, the PTO cites *Boehringer Ingelheim Int'l. GmbH v. Barr Laboratories Inc.* that a patentee that had benefited from notice to the public of the later expiration date has already obtained an "unjustified advantage."[87] Finally, the Solicitor argues that the term-extension issue here is not dispositive because OTDP also prevents potential harassment by multiple assignees.[88]

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80. *Id.* at *40.

81. *See generally id.* at *53; *see also Gilead Scis.*, 753 F.3d at 1210.

82. Brief for Appellant, *supra* note 62, at *17.

83. *See id.* at *62.

84. *See generally* Brief for Appellee at *1, *In re Cellect*, 2022 WL 4396273 (No. 22-1293).

85. *Id.* at *1; Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust, 764 F.3d 1366, 1373 (Fed. Cir. 2014).

86. Brief for Appellee, *supra* note 84, at *2 (because § 156 does not contain the "disclaimer" in § 154(b)(2)(B)).

87. *Id.* at *38 (citing Boehringer Ingelheim Int'l. GmbH v. Barr Lab'ys Inc., 592 F.3d 1340, 1347–1348 (Fed. Cir. 2010)).

88. *Id.* at *35.

A number of *amici* filed briefs in favor and against the Board's decision. Briefs in opposition to the Board's application of OTDP in these circumstances were filed by the Intellectual Property Owners (IPO), the Pharmaceutical Research and Manufacturers of America (PhRMA), and the Biotechnology Innovation Organization (BIO). The IPO's brief emphasized that the only reason OTDP arose in this case was the application of PTA, and that the statute mandates extension (and accordingly the Board's decision was contrary to congressional intent).[89] PhRMA's brief focused on the purpose of OTDP, which was to avoid unjust enrichment and that the PTO's "speculative" harassment rationale was inconsistent with Federal Circuit precedent.[90] BIO's brief discussed the Board's statutory interpretation errors and that the inequitable outcome in this case is inconsistent with the equitable underpinnings of OTDP.[91]

Briefs in favor of the Board's decision were filed by Alvogen, the Association for Accessible Medicines (AAM), and Samsung. Alvogen's brief argued that there was no reason OTDP should not apply to PTA because the doctrine was intended to establish term limits on patents to patentably-indistinct inventions.[92] Gamesmanship is not required under the doctrine and is an "unstable benchmark" in Alvogen's view.[93] AAM's brief was entirely outcome-oriented, based on the *amici*'s perspective that patents increase drug costs, and the Board's decision was a good one because it reduced patent term (no matter that the patents at issue were not related to drug products).[94] Finally, Samsung's brief argued that the decision was consistent with the policy bases for the OTDP doctrine and that accordingly there was no inequitable result.[95] (It should be noted that Samsung is a competitor and is involved in litigation with Cellect on other patents.)

The Federal Circuit affirmed the PTAB's *In re Cellect* (2022) decision, in *In re Cellect*, __ F.4th ___(2023), a decision likely to be discussed in the 2023 edition of this series (see, https://www.patentdocs.org/2023/08/in-re-cellect-fed-cir-2023.html).

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89. Brief for Intell. Prop. Owners Ass'n as Amici Curiae Supporting Neither Party Urging Reversal at *10, *In re Cellect*, 2023 WL 5519716 (No. 22-1293).

90. Brief for Pharm. Rsch. and Mfrs. of Am. (PhRMA) as Amici Curiae Supporting Appellant at *20, *In re Cellect*, 2023 WL 5519716 (No. 22-1293).

91. Brief for Intell. Prop. Owners Ass'n, *supra* note 89, at 5–6.

92. Brief for Alvogen PB Rsch. & Dev. LLC as Amici Curiae Supporting the Director and Affirmance at *4, *In re Cellect*, 2023 WL 5519716 (No. 22-1293).

93. *Id.* at *27.

94. Brief for The Ass'n for Accessible Meds. as Amicus Curiae Supporting Appellee at *9, *In re Cellect*, 2023 WL 5519716 (No. 22-1293).

95. Brief for Samsung Elecs. Co., Ltd. and Samsung Elecs. Am., Inc. as Amicus Curiae Supporting the Director of The U.S. Pat. and Trademark Off. at *14, *In re Cellect*, 2023 WL 5519716 (No. 22-1293).

3. *Pharmacyclics LLC v. Alvogen, Inc*. (Fed. Cir. 2022) (Decided November 15, 2022)

Late in the year, the Federal Circuit handed down its opinion affirming all aspects of the district court's decision in *Pharmacyclics LLC v. Alvogen, Inc.* The case illustrates once more the importance of the clear error standard in support of factual aspects of a district court's decision, even regarding ultimate questions of law, such as enablement and obviousness (that are based on such factual considerations).

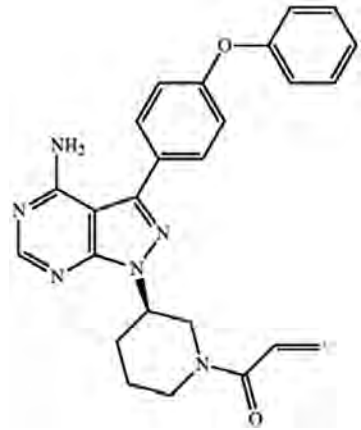
The case arose as ANDA litigation between Pharmacyclics LLC and Janssen Biotech, Inc., whose patents for the compound ibrutinib (an inhibitor of Burton's tyrosine kinase (BTK) and the basis for their Imbruvica Product) was challenged by Alvogen and Natco Pharma Ltd.[96] The drug is used for treatment of immune system cancer, specifically relapsed/refractory mantle cell lymphoma (RR/MCL).[97] At trial, Pharmacyclics asserted five claims:

Claim 10, U.S. Patent No. 8,008,309 ("the '309 patent"):

> 10. The compound of claim 1 [which claims a genus of BTK inhibitor compounds] having the formula 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.[98]

Claim 2, U.S. Patent No. 8,754,090 ("the '090 patent"):

> 1. A method for treating mantle cell lymphoma in an individual who has already received at least one prior therapy for mantle cell lymphoma comprising administering to the individual once per day between about 420 mg to about 840 mg of an oral dose of an inhibitor of Bruton's tyrosine kinase (Btk) having the structure:



96. Pharmacyclics LLC v. Alvogen Pine Brook LLC, 556 F. Supp. 3d 377, 385 (D. Del. Aug. 19, 2021).

97. Pharmacyclics LLC v. Alvogen, Inc., No. 2021-2270, 2022 WL 16943006, at *1 (Fed. Cir. 2022).

98. *Id.*

> 2. The method of claim 1, wherein the once per day oral dose is about 560 mg.[99]

Claim 5, U.S. Patent No. 9,725,455 ("the '455 patent"):

> 1. A crystalline form A of [ibrutinib] that has an X-ray powder diffraction (XRPD) pattern comprising 2-Theta peaks at 5.7±0.1°, 18.9±0.1°, and 21.3±0.1°.
>
> 5. The crystalline form of claim 1, wherein the X- ray powder diffraction (XRPD) pattern further comprises 2-Theta peaks at 13.6±0.1°, 16.1±0.1°, and 21.6±0.1°.

Claim 30, U.S. Patent No. 9,655,857 ("the '857 patent"):

> 30. The high-load solid tablet formulation of claim 1 [which recites a genus tablet formulation for ibrutinib], consisting essentially of:
> a) about 70% w/w of ibrutinib,
> b) about 14% w/w of lactose monohydrate,
> c) about 5% w/w of microcrystalline cellulose,
> d) about 2% w/w of polyvinylpyrrolidone,
> e) about 7% w/w of croscarmellose sodium,
> f) about 1% w/w of sodium lauryl sulfate,
> g) about 0.5% w/w of colloidal silicon dioxide, and
> h) about 0.5% w/w of magnesium stearate.[100]

Claim 37, the '857 patent:

> 37. The solid tablet formation of claim 27 [which recites a genus tablet formulation for ibrutinib in an amount of about 70 mg to about 840 mg] consisting essentially of
> a) about 69% w/w to about 71% w/w of ibrutinib,
> b) about 13% w/w to about 15% w/w of lactose monohydrate,
> c) about 2% w/w to about 5% w/w of microcrystalline cellulose,
> d) about 1% w/w to about 3% w/w of polyvinylpyrrolidone,
> e) about 6% w/w to about 8% w/w of croscarmellose sodium,
> f) about 1% w/w to about 4% w/w of sodium lauryl sulfate,
> g) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and
> h) about 0.4% w/w to about 0.6% w/w of magnesium stearate.[101]

The parties stipulated to infringement of the asserted '309, '090, and '455 patent claims and the District Court found Alvogen's proposed generic ibrutinib would infringe the asserted claims of the '857 patent.[102] The District Court found against Alvogen on all arguments of invalidity (only some of which

99. *Id.*

100. *Id.* at *1–2.

101. *Id.*

102. *Id.*

were the subject of this appeal, and none of these other arguments raised any additional significant issues). Alvogen and Natco appealed.[103]

The Federal Circuit affirmed, in an opinion by Judge Bryson joined by Judges Hughes and Chen.[104] The opinion addressed each ground of appeal raised against each asserted claim *seriatim*, noting initially that in an appeal from a bench trial the Court reviews factual determinations for clear error, citing *UCB, Inc. v. Watson Lab'ys Inc.*, for the principle and *Biogen Int'l GmbH v. Mylan Pharms. Inc.*, for the standard (*i.e.*, that the Court finds clear error only when it has a "definite and firm conviction that a mistake has been made").[105]

Regarding claim 2 of the '090 patent, the opinion addresses the District Court's finding that this claim was supported by an adequate written description, with an enabling specification and was not obvious.[106] The basis for the Court's affirmance on the adequate written description question was that the '090 specification disclosed two related clinical trial protocols for using a BTK inhibitor to treat R/R MCL.[107] The first of these taught using a variety of such inhibitors at dosages based on patient weight, and the other used a broader range of such inhibitors as a specific dosage ("about 560 mg/day").[108] In addition, the Summary of the Invention section of the patent expressly disclosed ibrutinib for treating R/R MCL.[109] Applying its "blazemarks" analysis,[110] the Court held it was not clearly erroneous for the District Court to find an adequate written description where ibrutinib was "'the only BTK inhibitor identified by name in the Summary of the Invention and is the only BTK [inhibitor] identified for the treatment of R/R MCL' in the '090 patent."[111] The Court expressly distinguished the circumstances here from its decision in *Biogen* (a failure to satisfy the written description requirement) because there the only disclosure of the claimed dosage was as one end of a broader disclosed range (in the context of "a long series of ranges") whereas here the claimed dosage was "expressly recited by itself" both in the claim and the specification

103. *Pharmacyclics LLC*, 2022 WL 16943006, at *2.

104. *Id.* at *1.

105. *Id.* at *7 (citing *Biogen Int'l GmbH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1341 (Fed. Cir. 2021); *UCB, Inc. v. Watson Lab'ys Inc.*, 927 F.3d 1272, 1286 (Fed. Cir. 2019)).

106. *Id.*

107. *Id.* at *3.

108. *Id.*

109. *Pharmacyclics LLC*, 2022 WL 16943006, at *3.

110. *See* Novozymes A/S v. DuPont Nutrition Biosciences APS, 723 F.3d 1336, 1349 (Fed. Cir. 2013) (quoting *In re* Ruschig, 379 F.2d 990, 994–95 (C.C.P.A. 1967).

111. *Pharmacyclics LLC*, 2022 WL 16943006, at *3.

as filed.[112] Regarding Alvogen's similar arguments on enablement, that the specification disclosed exactly 560 mg/d and claimed "about" 560 mg/d, the Federal Circuit found no clear error in the District Court's determination that there was sufficient disclosure in the specification for the skilled artisan to follow the disclosed protocol and practice the claimed method.[113]

As for obviousness, the Federal Circuit rejected Alvogen's argument that the District Court incorrectly determined that the skilled worker would not have been motivated to treat R/R MCL with ibrutinib from prior art references teaching treatment of MCL with the drug, in light of the District Court's finding of fact that disclosure of treating MCL would not be interpreted by the skilled worker as evidence of effective treatment of RR/MCL.[114] The panel also refused to find any error in the District Court's finding that disclosure of two R/R MCL patients having experienced a "partial response" to ibrutinib in a press release, in view of the small sample size and the propensity for oncology drugs to have a low frequency of receiving FDA approval ("less than five percent of oncology drugs that enter a Phase I trial ultimately receive FDA approval").[115]

Another asserted and rejected obviousness argument was that the skilled worker was capable of finding the recited dose (560 mg/d) as a therapeutically effective amount by routine experimentation, based on evidence that "typical" dose escalation studies would have involved dosages greater than 560 mg/d and would require "a study using pharmacodynamic endpoints" that was not disclosed in Alvogen's combination of references.[116] With regard to the question of whether there was a motivation to combine the cited references, the panel recognized that Alvogen's expert testified to safety concerns in 2006 rather than 2010 (when the application was filed), and Pharmacyclics asserted contrary expert testimony that the District Court found persuasive.[117] The panel also affirmed the District Court's decision regarding lack of a "presumption of obviousness" from the cited prior art teachings, on two grounds. The first was that such a presumption is proper "when the only difference from the prior art is a difference in the range or value of a particular variable",[118] which was not the case here, and second that Pharmacyclics "would have rebutted any [such] presumption."[119] Finally, the Court did not reach the question of secondary

112. *Id.* at *7. (Undiscussed were the decidedly different circumstances arising during prosecution of the patent-in-suit in Biogen supporting the Court's opinion).

113. *Id.*

114. *Id.*

115. *Id.* at *8 (citing *Pharmacyclics*, 556 F. Supp. 3d at 403).

116. *Id.*

117. *Pharmacyclics LLC*, 2022 WL 16943006, at *9.

118. *Id.* (citing *In re* Kumar, 418 F.3d 1361, 1366 (Fed. Cir. 2005)).

119. *Id.*

considerations because the District Court's non-obviousness determination made this argument unnecessary in the panel's view.[120]

Turning to claim 5 of the '455 patent, the Federal Circuit affirmed the District Court's determination that the claim was neither inherently anticipated nor obvious over the cited art.[121] Alvogen's inherent anticipation argument was grounded in an assertion that the Form A polymorph of ibrutinib (recited in claim 5) was the only polymorph used in clinical trials disclosed in the art, wherein Alvogen relied upon *Abbott Laboratories v. Geneva Pharmaceuticals, Inc.*, 182 F.3d 1315 (Fed. Cir. 1999) (an on-sale bar case).[122] The Federal Circuit distinguished the circumstances here from those in the *Abbott* case, and cited *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003), as the more apt precedent.[123] According to the opinion, the circumstances before the District Court in this case were more analogous to those in *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1382 (Fed. Cir. 2018), upon which the District Court relied, there being no evidence in this case that the only therapeutically effective polymorph of ibrutinib was Form A, and that the District Court's factual determinations in this regard were not clearly erroneous.[124] As for Alvogen's obvious arguments, the Federal Circuit affirmed the District Court based on, *inter alia*, there being no clear error in that court's reliance on Pharmacyclics' expert over one of Alvogen's experts (another one agreeing with Pharmacyclics), based on the District Court's appreciation that production of polymorphs and their physical properties was unpredictable.[125] The panel held as not clearly erroneous the District Court's finding that "given the lack of teaching in the art regarding crystalline forms of ibrutinib and the expert testimony that polymorph screening can produce unpredictable results, a skilled artisan would not have reasonably expected success in producing Form A of ibrutinib."[126]

Next, the Federal Circuit held as not clearly erroneous the District Court's finding that claims 30 and 37 of the '875 patent were adequately supported by the written description.[127] Alvogen's argument was that the specification of the '875 patent disclosed one species in a range of species recited in these

120. *Id.*

121. *Id.*

122. *Id.*

123. *Pharmacyclics LLC*, 2022 WL 16943006, at *7.

124. *Id.* at *9–10.

125. *Id.* at *10.

126. *Id.* (citing Grunenthal GmbH v. Alkem Lab'ys Ltd., 919 F.3d 1333, 1344 (Fed. Cir. 2019)).

127. *Id.* at *11.

claims.[128] Alvogen's "problem" with their argument, according to the Federal Circuit, was that "the precise ranges recited in the claims are found in formulations disclosed in the specification," and on this basis the Federal Circuit affirmed the District Court's determination that these claims were adequately described.[129]

Finally, the Federal Circuit affirmed the District Court's decision that claim 10 of the '309 patent was not anticipated by the cited art, Alvogen arguing that a skilled worker could not have synthesized a needed intermediate without undue experimentation and accordingly, the '309 patent was not entitled to its earliest priority date.[130] Alvogen's assertion of error in this regard was that the District Court should not have relied upon Pharmacyclics' testimony that his undergraduate students could have produced the intermediate without undue experimentation based on the disclosure in the priority documents.[131] The District Court also relied upon the intermediate having been known in a prior art reference upon which the skilled artisan could have relied, and Alvogen argued that the District Court did not apply the proper legal standard for incorporating this document by reference.[132] The panel found this argument not dispositive because "a skilled artisan could have synthesized Intermediate 2 and thus ibrutinib" without recourse to the reference.[133] Moreover, the opinion states that "formal incorporation by reference is not necessary if the material being incorporated is background art."[134] On these grounds, the Federal Circuit held that the District Court committed no clear error in rejecting Alvogen's argument.[135]

To the extent there is any question about the importance of the standard of review in the Federal Circuit's opinion, mere casual perusal thereof finds 15 instances of some version of "clear error" and "clearly erroneous" recited by the Court.[136] A cautionary tale indeed.

4. Par Pharmaceutical, Inc. v. Eagle Pharmaceuticals, Inc. (Fed. Cir. 2022) (Decided August 18, 2022)

This case arose in ANDA litigation over Eagle's application to market a generic version of Par's Vasostrict® product, an injectable form of vasopressin

128. *Id.*

129. *Pharmacyclics LLC*, 2022 WL 16943006, at *11.

130. *Id.*

131. *Id.*

132. *Id.*

133. *Id.* at *12.

134. *Id.* (citing Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1365 (Fed. Cir. 2006)).

135. *Pharmacyclics LLC*, 2022 WL 16943006, at *12.

136. *See generally id.* at *1–12.

used to treat patients with critically low blood pressure.[137] Par Orange Book-listed U.S. Patent Nos. 9,744,209 and 9,750,785, the '785 patent claiming vasopressin compositions and the '209 patent claiming methods for raising blood pressure using the claimed compositions.[138] Relevant to the issues before the Court was a limitation in all asserted claims that the vasopressin compositions were to have a pH of between 3.65 and 3.94, rounded to 3.7 and 3.9.[139] Eagle in its Paragraph IV assertions under 35 U.S.C. § 355(j)(2)(A)(vii)(IV) contended its product would not infringe because it had a pH of between 3.36-3.64 (rounded to 3.4-3.6) upon market release and throughout its shelf life, as well as allegations that the '209 and '785 patents were invalid.[140] Par brought suit under 35 U.S.C. § 271(e)(2) and for a declaratory judgment of infringement under §§ 271(a) and (b).[141]

At trial, Eagle stipulated that its product satisfied all limitations of the asserted claims except the pH of the claimed compositions, and Par argued that despite the difference in pH there were two "undisputed facts" that weighed in favor of a finding of infringement.[142] The first was purportedly "real world" evidence that the pH of Eagle's product "drifts up" over time, and the second was that Eagle had sought approval to market compositions having a pH of 3.64, "just 0.01 beneath the infringing range."[143] Par contended that these facts supported its argument that by a preponderance of the evidence ("more likely than not") Eagle's compositions would "inevitably drift into Par's claimed [pH] range" and thus infringe.[144]

The District Court ruled against Par on this argument, finding the asserted facts "neither undisputed nor correct," particularly that the "drift" in pH values for Eagle's product did not have "any discernible trend" into the claimed range (calling them "minor fluctuations") nor that any such drift was "steady and inevitable."[145] The District Court further found that while the release specification permitted Eagle's product to have a pH as high as 3.64, the stability specifications required the product to maintain a pH no higher than 3.6.[146] The

137. Par Pharm., Inc. v. Eagle Pharms., Inc., 44 F.4th 1379, 1382 (Fed. Cir. 2022).

138. *Id.*

139. *Id.*

140. *Id.*

141. *Id.*

142. *Id.*

143. *Par Pharm., Inc.*, 44 F.4th at 1382.

144. *Id.*

145. *Id.* at 1383.

146. *Id.*

District Court held that Par had not established infringement under 35 U.S.C. §§ 271(a), 271(b), nor 271(e)(2), and this appeal followed.[147]

The Federal Circuit affirmed in an opinion by Chief Judge Moore joined by Judges Prost and Hughes.[148] The basis for the Court's affirmance was the clear error standard for factual determinations by a district court that applies to appellate review.[149] *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1303 (Fed. Cir. 2015), and *Scanner Techs. Corp. v. ICOS Vision Sys. Corp. N.V.*, 528 F.3d 1365, 1374 (Fed. Cir. 2008). The same standard applies to questions of infringement, under *Alzo Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006).[150] Applying this standard, the Court made short work of Par's arguments. The opinion notes that an ANDA applicant is constrained upon approval to market its generic product "by strict statutory provisions to sell only those products that comport with the ANDA[]," and if the ANDA "defin[es] a proposed generic drug in a manner that directly addresses the issue of infringement, [it] control[s] the infringement inquiry."[151] Thus, in ANDA litigation comparison between the claimed invention and the specifications of the proposed generic product "directly resolves the infringement question" according to the opinion.[152] In this case, the infringement inquiry "begins and ends" with Eagle's ANDA specification according to the Court.[153] The opinion asserts that this specification mandates that the pH of the generic product remain outside the pH range claimed in the '785 and '209 patents upon release and throughout the shelf life of the product accused of infringement.[154] To prevail, the opinion indicates that Par would have had to establish that Eagle would *not* remain bound by its product specification, an assertion the opinion characterizes as "unsupported conjecture" that is not sufficient to establish infringement under *In re Brimonidine Patent Litig.*, 643 F.3d 1366, 1378 (Fed. Cir. 2011).[155] Thus, Par failed to establish infringement under 35 U.S.C. § 271(e)(2), and the Federal Circuit affirmed the District Court's determination thereof.[156]

147. *Id.*

148. *Id.* at 1381.

149. *Par Pharm., Inc.*, 44 F.4th at 1383; *see* Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1303 (Fed. Cir. 2015); Scanner Techs. Corp. v. ICOS Vision Sys. Corp. N.V., 528 F.3d 1365, 1374 (Fed. Cir. 2008).

150. *Id.*

151. *Id.* (citing Abbott Labs. v. TorPharm, Inc., 300 F.3d 1367, 1373 (Fed. Cir. 2002)).

152. *Id.* at 1383–84 (citing Ferring B.V. v. Watson Labs., Inc.-Fla., 764 F.3d 1401, 1409–10 (Fed. Cir. 2014)).

153. *Id.* at 1384.

154. *Id.*

155. *Par Pharm., Inc.*, 44 F.4th at 1384.

156. *Id.*

Turning to Par's declaratory judgment cause of action under 35 U.S.C. §§ 271(a) and 271(b), the panel held that because the District Court did not commit clear error in deciding that Eagle's generic vasopressin product would not infringe, it was not an abuse of discretion to refuse to find in Par's favor on the declaratory judgment question because Par would only be entitled to a declaratory judgment of infringement if it had established that Eagle was "engaged in activity directed toward an infringing activity or is making meaningful preparation for such activity" and Par had not done so.[157]

Accordingly, the Federal Circuit affirmed the District Court's judgment and awarded costs to Eagle.[158]

5. Mayor and City Council of Baltimore v. AbbVie Inc. (7th Cir. 2022) (Decided August 1, 2022)

Early in summer 2020, U.S. District Court Judge Manish Shah, sitting in the Northern District of Illinois, held that AbbVie did not violate Sections 1 or 2 of the Sherman Antitrust Act by amassing a large number (132) of patents to protect its best-selling drug, Humira® (adalimumab).[159] In August, 2022, the Seventh Circuit Court of Appeals affirmed the District Court's decision to dismiss the complaint in a unanimous verdict that took the Court sixteen months to hand down, in *Mayor and City Council of Baltimore v. AbbVie Inc.*[160]

To recap, the issue arose in a class action lawsuit against AbbVie and AbbVie Biotechnology Ltd. by consumer groups, drug wholesalers, and unions (including the City of Baltimore, Miami Police Department insurance trust fund, and a Minnesota-based employee welfare benefits plan for workers in the pipe trade industries), as well as corresponding state law causes of action for Alaska, California, District of Columbia, Georgia, Illinois, Nevada, New Hampshire, North Carolina, Utah, and West Virginia.[161] The basis of the complaint was AbbVie's actions in seeking and obtaining additional patents when the patent on the adalimumab molecule itself (U.S. Patent No. 6,090,382) was set to expire on December 31, 2016.[162] AbbVie filed 247 patent applications, resulting in 132 patents, and this behavior was sufficiently anticompetitive,

157. *Id.* at 1384–85.

158. *Id.* at 1385–86.

159. *See In re* Humira (Adalimumab) Antitrust Litig., 465 F.Supp.3d 811 (N.D. Ill. June 8, 2020); *see also* Kevin E. Noonan, *An Analysis of a Failed Biosimilar Antitrust Class Action*, PatentDocs (June 22, 2020), https://www.patentdocs.org/2020/06/an-analysis-of-a-failed-biosimilar-antitrust-class-action.html [https://tinyurl.com/ywfzdsxj].

160. Mayor of Balt. v. Abbvie Inc., 42 F.4th 709, 716 (7th Cir. 2022).

161. *In re Humira*, 465 F.Supp.3d at 820, 825, 848–53.

162. *Abbvie Inc.*, 42 F.4th at 711.

plaintiffs argued, that it rose to the level of an antitrust violation under the Sherman Act.[163]

The District Court discerned the following allegations in the class action Plaintiffs' complaint:

- that AbbVie "cornered the market" on Humira (and other, unnamed biosimilar drugs) by "anticompetitive conduct";[164]
- that AbbVie obtained and asserted patents "to gain the power it needed to elbow its competitors" out of the Humira market;[165] and
- that AbbVie then entered into agreements with those competitors "to keep their competing drugs off the market" (and then, paradoxically, "gave those competitors permission to market their drugs in Europe";[166] unremarked is that AbbVie gave those same competitors permission to enter the U.S. market a few years thereafter, without having to face the patents purportedly comprising the thicket.

The District Court dismissed the complaint under the rationale that:

> Plaintiffs say that AbbVie's plan to extend its power over Humira amounts to a scheme to violate federal and state antitrust laws. But what plaintiffs describe is not an antitrust violation. AbbVie has exploited advantages conferred on it through lawful practices and to the extent this has kept prices high for Humira, existing antitrust doctrine does not prohibit it. Much of AbbVie's petitioning was protected by the *Noerr Pennington* doctrine, and plaintiffs' theory of antitrust injury is too speculative.[167]

The District Court agreed with AbbVie that "there is nothing illegal about amassing a broad portfolio of legitimate patents" under Sherman Act § 2 and, to the extent that some of these patents may turn out to be improvidently granted, "the *Noerr–Pennington* doctrine immunizes them from liability."[168] Regarding the Section 1 allegations, the District Court agreed with Defendants that these settlement agreements don't violate the Sherman Act because "they[] allow AbbVie's competitors to enter the market before the expiration of AbbVie's patents; do not involve any reverse payments from AbbVie (the patentee) to Amgen, Samsung Bioepsis, and Sandoz (the alleged infringers); and

163. *Id.* at 712.

164. *In re Humira*, 465 F.Supp.3d at 819.

165. *Id.*

166. *Id.*

167. *Id.*

168. *See id.* at 826, 834.

only divvy up the market in ways consistent with AbbVie's patent rights."[169] The District Court further agreed with AbbVie that if even a single one of AbbVie's patents is not invalid and infringed, that would have been sufficient to keep the biosimilar applicants from marketing Humira biosimilars until that patent expired (a date that would have been very much later than January 2023). Under these circumstances for Plaintiffs' antitrust allegations to create liability against Defendants, Plaintiffs would need to show that AbbVie had obtained each and every one of its patents "unlawfully," which the Court found was unlikely, as a "but-for" cause of Plaintiffs' alleged injury.[170]

The 7th Circuit affirmed, in an opinion by Judge Easterbrook joined by Judge Wood and Judge Kirsch.[171] The opinion begins with a litany of precedent that the parties did *not* rely on (for AbbVie, *Illinois Brick Co. v. Illinois*, 431 U.S. 720 (1977) on jurisdictional grounds, and for plaintiffs, *Walker Process Equipment, Inc. v. Food Machinery & Chemical Corp.*, 382 U.S. 172 (1965) for inequitable conduct or "fraud on the Patent Office").[172] But the heart of the Court's opinion can be found in almost its first legally substantive sentence, where the Court asks plainly "what's wrong with having lots of patents"?[173] Further, the Court states that "[t]he patent laws do not set a cap on the number of patents any one person can hold—in general, or pertaining to a single subject."[174] Tellingly, the opinion goes on to note that "[t]ech companies such as Cisco, Qualcomm, Intel, Microsoft, and Apple have much larger portfolios of patents" and "Thomas Edison alone held 1,093 U.S. patents."[175] Finally, in this regard the Court notes that the Federal Trade Commission tried, and failed, to establish antitrust liability against Qualcomm based on the sheer number of patents that the company had amassed.[176]

The Court recognized the distinction between valid and invalid patents but notes that Plaintiffs did not allege that they will invalidate all 132 of AbbVie's patents.[177] Nor was the Court persuaded by the fact that "the 132 patents can be traced to continuation applications from 20 root patents" (which "seem

169. *See id.* at 826, 835–42.

170. *See In re Humira*, 465 F.Supp.3d at 826–46.

171. *Abbvie Inc.*, 42 F.4th at 716.

172. *Id.* at 711–12.

173. *Id.* at 712.

174. *Id.* (citing *In re* Brand Name Prescription Drugs Antitrust Litigation, 186 F.3d 781 (7th Cir. 1999)).

175. *Id.*

176. *Id.* (citing FTC v. Qualcomm Inc., 969 F.3d 974 (9th Cir. 2020)).

177. *Abbvie Inc.*, 42 F.4th at 713.

neither here nor there" to the panel).[178] As for the argument that these patents are "weak" the Court says this "leaves us cold" because a weak patent is just one having limited scope not one that is "illegitimate."[179] Those arguments are appropriate in proceedings like *inter partes* review, the opinion states, for which the Patent Trial and Appeal Board have found more consistently that challengers have failed (13 instances) to satisfy the statutory requirements for challenge than it has found a challenged patent invalid (3) (and noting that in still other instances AbbVie has prevailed before the Board).[180]

The Court further recognized the disjointed nature of Plaintiffs' argument that, while eschewing *Walker Process*-based allegations maintained its Section 2 challenge merely because AbbVie obtained the (presumptively) valid patents and asserted them against competitors.[181] While the law recognizes that "objectively baseless petitions" to the government can raise an antitrust violation,[182] like the District Court the panel noted that AbbVie had a "batting average" of .534 for patent procurement (a 53.4% allowance rate), which "cannot be called baseless."[183] But without this ground, "[t]rying to conjure liability out of successful petitions for governmental aid in blocking competition runs into the *Noerr-Pennington* doctrine" according to the opinion."[184] Other grounds for finding antitrust liability[185] did not exist under the circumstances before the Court (although the panel recognized there may be ways for AbbVie to assert their patents that the *Noerr-Pennington* doctrine would not protect).[186]

Turning to the Section 1-based allegations arising from the settlement agreements, the opinion first notes that those settlement agreements permitted biosimilar entry much earlier than the expiration date of at least some of AbbVie's patents.[187] The Court views these agreements as "compromises" and that the agreements do not violate the Sherman Act under Supreme Court

178. *Id.*

179. *Id.*

180. *Id.*

181. *Id.*

182. *Id.* (citing Pro. Real Est. Invs., Inc. v. Columbia Pictures Indus., Inc., 508 U.S. 49 (1993)).

183. *Abbvie Inc.*, 42 F.4th at 712.

184. *See id.* (citing Eastern Ry. Presidents Conf. v. Noerr Motor Freight, Inc., 365 U.S. 127 (1961); Mine Workers v. Pennington, 381 U.S. 657 (1965)).

185. "Such as unsuccessful petitioning that increases competitors' costs, such as filing frivolous lawsuits." *See* BE&K Constr. Co. v. NLRB, 536 U.S. 516 (2002).

186. *Abbvie Inc.*, 42 F.4th at 713–14.

187. *Id.* at 714.

precedent in favor of settlements in litigation.[188] But the opinion states that the basis of one such possible antitrust violation, falling under the Court's *FTC. v. Actavis* decision, cannot arise here because there is no exclusivity period for the first biosimilar filer as there was in *Actavis* for the first ANDA filer.[189] "The payors do not contend that there is anything fishy or anticompetitive about the settlements allowing entry in 2023 without any payment from AbbVie to the potential entrants," the opinion asserts, and acknowledges Plaintiffs' argument that the differential entry date of Humira biosimilars in Europe (2018) and the U.S. (2023) could produce a similar "reverse-payment deal" here.[190] Neither the District Court nor this panel were persuaded because there was no "pay-for-delay" ("0+0=0") in these settlements.[191] There were also factual distinctions between the settling parties and the legal and regulatory conditions in the European countries that were contrary to Plaintiffs' arguments that somehow, somewhere, someone had or could make money they should not have been able to make under these agreements.[192] To the extent Plaintiffs' argument sounded in the economic theory of "opportunity costs" the panel understood the Supreme Court's *Actavis* decision to have "considered, and rejected, the argument that an opportunity cost is the same as a reverse-payment settlement."[193]

The District Court characterized Plaintiffs' arguments as "a new kind of antitrust claim" that "brings together a disparate set of aggressive but mostly protected actions to allege a scheme to harm competition and maintain high prices."[194] Attorneys making novel legal theories of course is how the law progresses. Indeed, the current Chair of the Federal Trade Commission became something of an *enfant terrible* based on her law review article on antitrust in the technological age.[195] A risk in some legal theories arises when they are excessively outcome-oriented to the extent that they ignore traditional legal principles in search of the desired outcome. (The dissent by Chief Justice Roberts in *Actavis* is illustrative of the dangers attendant thereupon.)[196] The mantra of the undesirability if not illegality *per se* of so-called patent thickets for blockbuster drugs can appear politically expedient but is not supported by

188. *Id.*

189. *Id.*

190. *Id.*

191. *Id.* at 715.

192. *Abbvie Inc.*, 42 F.4th at 715.

193. *Id.*

194. *In re Humira, supra* note 150, at 819.

195. *See* Lina M. Khan, *Amazon's Antitrust Paradox*, 126 (3) Yale L.J. 710, 710–805 (2017).

196. *See* F.T.C. v. Actavis, 570 U.S. 136, 160 (2013) (Roberts, C.J., dissenting).

the facts, as shown *inter alia* by Mossoff.[197] For now, this latest flight of legal fancy has crashed on the rocks of antitrust jurisprudence reality, but it would be imprudent not to expect other attempts prompted by patent protection of blockbuster drugs (and their related costs) to arise.

6. *CareDx, Inc. v. Natera, Inc.* (Fed. Cir. 2022) (Decided July 18, 2022)

Judge Moore, in *Athena Diagnostics, Inc. v. Mayo Collaborative Services, LLC*, stated the obvious when she said in her dissent:

> My colleagues' refusal deflates the Amici's hopeful suggestion that our precedent leaves the eligibility of a diagnostic claim in front of the Federal Circuit "uncertain." It is no longer uncertain. Since *Mayo*, every diagnostic claim to come before this court has been held ineligible. While we believe that such claims should be eligible for patent protection, the majority of this court has definitively concluded that the Supreme Court prevents us from so holding. No need to waste resources with additional *en banc* requests.[198]

Since that decision it has become clear that even asking the Court to provide any answer other than an affirmance of a district court decision below invalidating claims to diagnostic methods is too much to ask, a reality made evident once again by the Court's decision in *CareDx, Inc. v. Natera, Inc.*

To recap proceedings below, the case arose over the claims in U.S. Patent Nos. 8,703,652, 9,845,497, and 10,329,607 directed to "methods to help predict the status or outcomes of transplant recipients through sequencing of cell-free nucleic acids ("cfDNA") found in the bodily fluids of a recipient." The rationale behind the invention is rejection of a transplanted organ in a recipient is accompanied by cell death, which releases donor-specific DNA into the recipient's bodily fluids.[199] Claim 1 of the '652 patent, claim 1 of the '497 patent, and claim 1 of the '607 patent were illustrative:

Claim 1 of the '652 patent recites:

1. A method for detecting transplant rejection, graft dysfunction, or organ failure, the method comprising:
   (a) providing a sample comprising cell-free nucleic acids from a subject who has received a transplant from a donor;

197. *See* Adam Mossoff, *Unreliable Data Have Infected the Policy Debates over Drug Patents*, Hudson Inst. (Jan. 19, 2022), https://www.hudson.org/technology/unreliable-data-have-infected-the-policy-debates-over-drug-patents [https://perma.cc/N3TP-VNFC].

198. *See* Athena Diagnostics, Inc. v. Mayo Collaborative Serv., 927 F.3d 1333, 1363 (Fed. Cir. 2019).

199. CareDx, Inc v. Natera, Inc., 40 F.4th 1371, 1372–73 (Fed Cir. 2022).

(b) obtaining a genotype of donor-specific polymorphisms or a genotype of subject-specific polymorphisms, or obtaining both a genotype of donor-specific polymorphisms and subject-specific polymorphisms, to establish a polymorphism profile for detecting donor cell-free nucleic acids, wherein at least one single nucleotide polymorphism (SNP) is homozygous for the subject if the genotype comprises subject-specific polymorphisms comprising SNPs;
(c) multiplex sequencing of the cell-free nucleic acids in the sample followed by analysis of the sequencing results using the polymorphism profile to detect donor cell-free nucleic acids and subject cell-free nucleic acids; and
(d) diagnosing, predicting, or monitoring a transplant status or outcome of the subject who has received the transplant by determining a quantity of the donor cell-free nucleic acids based on the detection of the donor cell-free nucleic acids and subject cell-free nucleic acids by the multiplexed sequencing,

wherein an increase in the quantity of the donor cell-free nucleic acids over time is indicative of transplant rejection, graft dysfunction or organ failure, and wherein sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV).[200]

Claim 1 of the '497 patent recites:

1. A method of detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient, the method comprising:
   (a) genotyping a solid organ transplant donor to obtain a single nucleotide polymorphism (SNP) profile of the solid organ transplant donor;
   (b) genotyping a solid organ transplant recipient to obtain a SNP profile of the solid organ transplant recipient, wherein the solid organ transplant recipient is selected from the group consisting of: a kidney transplant, a heart transplant, a liver transplant, a pancreas transplant, a lung transplant, a skin transplant, and any combination thereof;
   (c) obtaining a biological sample from the solid organ transplant recipient after the solid organ transplant recipient has received the solid organ transplant from the solid organ transplant donor, wherein the biological sample is selected from the group consisting of blood, serum and plasma, and wherein the biological sample comprises circulating cell-free nucleic acids from the solid organ transplant; and
   (d) determining an amount of donor-specific circulating cell-free nucleic acids from the solid organ transplant in the biological

200. *Id.* at 1373.

> sample by detecting a homozygous or a heterozygous SNP within the donor-specific circulating cell-free nucleic acids from the solid organ transplant in at least one assay, wherein the at least one assay comprises high-throughput sequencing or digital polymerase chain reaction (dPCR), and wherein the at least one assay detects the donor-specific circulating cell-free nucleic acids from the solid organ transplant when the donor-specific circulating cell-free nucleic acids make up at least 0.03% of the total circulating cell-free nucleic acids in the biological sample.[201]

Claim 1 of the '607 patent recites:

> 1. A method of quantifying kidney transplant-derived circulating [cfDNA] in a human kidney transplant recipient, said method comprising:
>   (a) providing a plasma sample from said human kidney transplant recipient, wherein said human kidney transplant recipient has received a kidney transplant from a kidney transplant donor, wherein said plasma sample from said human kidney transplant recipient comprises kidney transplant-derived circulating [cfDNA] and human kidney transplant recipient-derived circulating [cfDNA];
>   (b) extracting circulating [cfDNA] from said plasma sample from said human kidney transplant recipient in order to obtain extracted circulating [cfDNA], wherein said extracted circulating [cfDNA] comprises said kidney transplant-derived circulating [cfDNA] and human kidney transplant recipient-derived circulating [cfDNA];
>   (c) performing a selective amplification of target [DNA] sequences, wherein said selective amplification of said target [DNA] sequences is of said extracted circulating [cfDNA], wherein said selective amplification of said target [DNA] sequences amplifies a plurality of genomic regions comprising at least 1,000 single nucleotide polymorphisms, wherein said at least 1,000 single nucleotide polymorphisms comprise homozygous single nucleotide polymorphisms, heterozygous single nucleotide polymorphisms, or both homozygous single nucleotide polymorphisms and heterozygous single nucleotide polymorphisms, and wherein said selective amplification of said target deoxyribonucleic acid sequences is by polymerase chain reaction (PCR);
>   (d) performing a high throughput sequencing reaction, wherein said high throughput sequencing reaction comprises performing a sequencing-by-synthesis reaction on said selectively-amplified target [DNA] sequences from said extracted circulating [cfDNA], wherein said sequencing-by-synthesis reaction has a sequencing error rate of less than 1.5%;

201. *Id.* at 1373–74.

> (e) providing sequences from said high throughput sequencing reaction, wherein said provided sequences from said high throughput sequencing reaction comprise said at least 1,000 single nucleotide polymorphisms; and
> (f) quantifying an amount of said kidney transplant-derived circulating [cfDNA] in said plasma sample from said human kidney transplant recipient to obtain a quantified amount, wherein said quantifying said amount of said kidney transplant-derived circulating [cfDNA] in said plasma sample from said human kidney transplant recipient comprises using markers distinguishable between said human kidney transplant recipient and said kidney transplant donor, wherein said markers distinguishable between said human kidney transplant recipient and said kidney transplant donor comprises single nucleotide polymorphisms selected from said at least 1,000 single nucleotide polymorphisms identified in said provided sequences from said high throughput sequencing reaction, and wherein said quantified amount of said kidney transplant-derived circulating [cfDNA] in said plasma sample from said human kidney transplant recipient comprises at least 0.03% of the total circulating [cfDNA] from said plasma sample from said human kidney transplant recipient.[202]

The Magistrate Judge resolved the issue of whether these claims were ineligible for patenting under 35 U.S.C. § 101 using the first step of the Supreme Court's test enunciated in *Mayo* and *Alice Corp. v. CLS Bank Int'l.*[203] Defendants argued (as they must) that the claims in the patents-in-suit were directed to one of the judicial exceptions (a natural phenomenon, specifically "the correlation between transplant rejection and the presence of naturally occurring [cfDNA] in the bodily fluids of transplant recipients").[204] The Magistrate, relying on Federal Circuit precedent permitting a court to consider the patent specification in determining "what a patent claim is really directed to at step one [of the *Mayo/Alice* test]" (*Enfish LLC v. Microsoft Corp.*) found that:

> [T]he patents' [related] specification repeatedly and consistently states that this basic "correlation" between the presence of increased levels of donor-specific cfDNA and transplant rejection . . .—i.e., the thing that, according to Defendants, the asserted claims were

202. *Id.* at 1374–75.

203. *See* CareDx, Inc. v. Natera, Inc., No. CV 19-1804-CFC-CJB, 2020 U.S. Dist. WL 616305, (D. Del. Feb. 10, 2020); *report and recommendation vacated*, No. 19-567-CFC, 2020 U.S. Dist. WL 8186462 (D. Del. Mar. 13, 2020); *report and recommendation adopted sub nom.* CareDx, Inc. v. Eurofins Viracor, Inc., No. CV 19-1804-CFC-CJB, 2020 WL 1923726 (D. Del. Apr. 21, 2020).

204. *See id.*

> purportedly "directed to"—had already been well-known in the art for quite a long time.[205]

The District Court, while granting parties the opportunity for discovery and expert testimony, ultimately granted Natera's motion for summary judgment that the claims were invalid under Section 101 for lack of subject matter eligibility, and this appeal followed.[206]

The Federal Circuit affirmed, in an opinion by Judge Lourie joined by Judges Bryson and Hughes. The reasoning is depressingly predictable: the claims fail the first prong of the *Alice* eligibility test for being directed to a natural phenomenon and fail the second prong of the test by reciting only conventional, well-understood, and routine methods that did not rise to the ineluctable "something more" required for eligibility. In this, patentees fell into the trap that was sprung on unwary applicants ever since *Ariosa v Sequenom*.[207] As in that case, the particular petard upon which patentees' eligibility hopes were hoisted was the disclosure in the specification regarding this conventionality, the opinion setting out in a footnote in detail the extent of what the Court found was an admission:

> *See, e.g.*, '652 patent at col. 9 ll. 8–14 (stating that "[d]etection, identification and/or quantitation of the donor-specific markers (e.g.[,] polymorphic markers such as SNPs) can be performed using real-time PCR, chips (e.g., SNP chips), high throughput shotgun sequencing of circulating nucleic acids (e.g.[,] [cfDNA]), as well as other methods known in the art"); *id.* at col. 10 ll. 11–12 (stating that, to obtain cfDNA samples, "any technique known in the art may be used, e.g., a syringe or other vacuum suction device"); *id.* at col. 13 ll. 51–53 (stating that step 2 of claimed methods can be performed "using existing genotyping platforms know[n] in the art"); *id.* at col. 15 ll. 6–8 (stating that techniques recited in step 2 of claimed methods "can be accomplished through classic Sanger sequencing methods which are well known in the art"); *id.* at col. 13 ll. 58–61 (stating that "[c]ompanies (such as Applied Biosystems, Inc.) currently offer both standard and custom designed TaqMan probe sets for SNP genotyping that can in principle target any desired SNP position for a PCR based assay"); *id.* at col. 20 ll. 31–34 (stating that genotyping recited in claimed methods "may be performed by any suitable method known in the art including those described herein such as sequencing, nucleic acid array or PCR"); id. at col. 15 ll. 22–65 (discussing commercial high throughput sequencing products); *id.* at col. 14 ll. 58–67 (citing articles from

205. *Id.* at *3.

206. *See* CareDx, Inc. v. Natera, Inc., 563 F.Supp.3d 329, 347 (D. Del. Sept. 28, 2021), *aff'd*, 40 F.4th 1371 (Fed. Cir. 2022).

207. Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir. 2015).

> 2006 and 2007 as supporting the statement that "digital PCR is a much more accurate and reliable method to quantitate nucleic acid species"); *id.* at col. 18 l. 55–col. 19 l. 2 (stating that "[m]ethods for quantifying nucleic acids," including high throughput genotyping, "are known in the art"); id. at col. 21 ll. 5–9 (stating that "[t]he presence or absence of one or more nucleic acids from the transplant donor in the transplant recipient may be determined by any suitable method known in the art including those described herein such as sequencing, nucleic acid arrays or PCR").[208]

Here, the opinion states summarily that "[t]he claimed methods are indistinguishable from other diagnostic method claims the Supreme Court found ineligible in *Mayo* and that we found ineligible on multiple occasions."[209] Natera recites and the panel agrees with the familiar litany of cases coming to the same conclusion.[210] The similarity to the *Ariosa* decision (which in some ways propelled the Court down this path of *per se* ineligibility) is express:

> Here, as in *Ariosa*, the claims boil down to collecting a bodily sample, analyzing the cfDNA using conventional techniques, including PCR, identifying naturally occurring DNA from the donor organ, and then using the natural correlation between heightened cfDNA levels and transplant health to identify a potential rejection, none of which was inventive. The claims here are equally as ineligible as those in *Ariosa*.[211]

> To the extent there is anything remotely new in this opinion, it is the acknowledgment that conventionality is an element of step one of the *Alice* eligibility test, citing *Athena* and *Cleveland Clinic* decisions for the principle.[212]

With regard to that conventionality, the opinion illuminates the logical error of its treatment of this part of the equation. The opinion asserts that the methods are conventional because:

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208. *See Natera, Inc.*, 40 F.4th at 1378 n.1.

209. *Id.* at 1378.

210. *Id.* at 1379; *see, e.g.*, Athena Diagnostics, Inc. v. Mayo Collaborative Servs., 915 F.3d 743 (Fed. Cir. 2019); Genetic Veterinary Sci., Inc. v. LABOKLIN GmbH & Co. KG, 933 F.3d 1302 (Fed. Cir. 2019); Roche Molecular Sys., Inc. v. Cepheid, 905 F.3d 1363 (Fed. Cir. 2018); Cleveland Clinic Found. v. True Health Diagnostics, 859 F.3d 1352 (Fed. Cir. 2017); *Ariosa Diagnostics, Inc.*, 788 F.3d at 1371.

211. *Natera, Inc.*, 40 F.4th at 1379.

212. *Id.*

> "CareDx does not actually claim any improvements in laboratory techniques—rather, as previously discussed, the actual claims of the patent merely recite the conventional use of existing techniques to detect naturally occurring cfDNA. Furthermore, the specification admits that the laboratory techniques disclosed in the claims require only conventional techniques and off-the-shelf technology" . . . [and] "the asserted claims add nothing inventive because they merely recite standard, well-known techniques in a logical combination to detect natural phenomena."[213]

The case also contains a convenient mantra for this rationale: "[w]e have repeatedly held that applying standard techniques in a standard way to observe natural phenomena does not provide an inventive concept," citing *Ariosa*, *Athena*, and *Roche*.[214] According to the Court, a conclusion of ineligibility is justified because the claimed combination of steps adds nothing inventive, analogous to the factual circumstances in *Mayo v. Prometheus*.[215]

But what the Court has consistently ignored is the difference between the claims in *Mayo* and the ones in *Ariosa* and the Court's other diagnostic method cases. That difference is that the detection methods recited in the *Prometheus* claims were conventional *because* they were actually being performed in the prior art on the subject matter and for the purpose (assessing the amount of drug in a patient's blood after administration) recited in the claims before the priority date(s) of the patents-in-suit. The only distinction from these conventional methods in those claims was the recognition that there were boundary levels of detected drug concentrations that indicated whether the dosage should be increased or decreased. In contrast, in all the diagnostic method cases that have fallen under the Court's ineligibility ax since *Mayo* there had been no recognition, much less practice, in the prior art of these methods on this subject matter to detect this natural phenomenon that has been used to satisfy step one of the *Alice* test. The inventiveness resides *there*, and the refusal to recognize that distinction is the principal reason for the Court's continuing invalidity jurisprudence.

In her dissent in *Athena*, Judge O'Malley noted that:

> Since *Mayo*, every diagnostic claim to come before this court has been held ineligible. While we believe that such claims should be eligible for patent protection, the majority of this court has definitively concluded that the Supreme Court prevents us from so holding. No need to waste resources with additional *en banc* requests. Your only hope lies with the Supreme Court or Congress. I hope that

213. *Id.*

214. *Id.*

215. *Id.*

> they recognize the importance of these technologies, the benefits to society, and the market incentives for American business. And, oh yes, that the statute clearly permits the eligibility of such inventions and that no judicially-created exception should have such a vast embrace. It is neither a good idea, nor warranted by the statute.[216]

In view of the Supreme Court's denial of *certiorari* in *American Axle v. Neapco*, it appears Congress (other than reliance on trade secret protection) remains the only source of any respite from the scourge of ineligibility for diagnostic methods claims. Furthermore, on October 4, 2023, the Supreme Court denied CareDx' petition for certiorari.

7. *Biogen Int'l GmbH v. Mylan Pharmaceuticals Inc.* (Fed. Cir. 2022) (Denial decided March 16, 2022)

In a decision (and opinion) that illustrates the tensions that can arise in the application of the obviousness and written description requirements, the Federal Circuit denied Biogen's petition for panel rehearing and rehearing *en banc* in *Biogen Int'l GmbH v. Mylan Pharmaceuticals Inc.*[217] Judges Cunningham and Stoll did not participate in the decision, which was issued *per curiam* and supported by Judges Dyk, Prost, Reyna, Taranto, Chen, and Hughes.[218] Judge O'Malley (who dissented in the panel decision) participated (and putatively supported it) in the decision to deny the petition for panel rehearing (perhaps related to her decision to leave the Court on March 11th).[219] Judge Lourie, joined by Chief Judge Moore and Judge Newman (constituting two of the remaining most senior Judges on the Court) wrote an opinion in dissent.[220]

To recap, the case arose over Mylan's attempt to get regulatory approval and come to market with a generic equivalent of Biogen's Tecfidera® (dimethyl/monomethyl fumarate) multiple sclerosis drug.[221] Biogen asserted Orange Book-listed U.S. Patent Nos. 6,509,376; 7,320,999; 7,619,001; 7,803,840; 8,399,514; and 8,759,393, but the parties dismissed their causes of action on all patents except the '514 patent, where Biogen asserted claims 1-4, 6, 8-13, and 15-16; Claim 1 is representative:

1. A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount

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216. *Athena Diagnostics, Inc.*, 927 F.3d at 1363 (O'Malley, J., dissenting).

217. Biogen Int'l GmbH v. Mylan Pharms. Inc., 28 F.4th 1194, 1195 (Fed. Cir. 2022).

218. *Id.*

219. *Id.*

220. *Id.*

221. Biogen Int'l GmbH v. Mylan Pharms. Inc., No. 1:17CV116, 2020 U.S. Dist. LEXIS 107743, at *10 (N.D. W. Va. June 18, 2020).

of dimethyl fumarate, monomethyl fumarate, or a combination thereof, and (b) one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is *about 480 mg per day*.[222]

(wherein the italicized limitation was the entirety of the basis for the District Court's decision and the Federal Circuit majority's affirmance).

The District Court held that the asserted claims were invalid for failure to satisfy the written description requirement of 35 U.S.C. § 112(a).[223] The grounds for the District Court's decision, and the bases for Mylan's arguments that were persuasive, stemmed from certain characteristics of the prosecution history, which Mylan used to create an impression that Biogen had obtained claims based on clinical trial results for an invention not adequately disclosed in the application as filed in its earliest priority document (without such priority the claims perhaps would have been obvious).[224] Moreover, certain claim limitations (importantly, those specifying the effective dose) were recited only as part of a range and only once in the specification, which in the main was directed to methods for identifying compounds for treating neurological diseases and mentioned the specific disease treated by the claimed method, multiple sclerosis, only as one disease amongst many.[225] The District Court summed up the basis for its opinion, stating "[i]n sum, Biogen has attempted to satisfy the written description requirement of § 112 by selectively plucking specific words from the specification that correspond to each element of the claimed invention."[226]

The Federal Circuit affirmed, in an opinion by Judge Reyna joined by Judge Hughes, with Judge O'Malley dissenting.[227] Biogen was hampered by its burden of showing clear error by the District Court as well as the apparent "equities" between their position and Mylan's.[228] The majority considered Biogen to have "cast[] a wide net for a myriad of neurological disorders, including neuro-degenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, and Huntington's disease; demyelinating neurological diseases, such as various forms of MS and at least twenty-eight other disorders related to demyelination; polyneuritis; and mitochondrial disorders with demyelination" (something Judge O'Malley herself termed a

222. *Id.*

223. *Biogen Int'l GmbH*, 2020 U.S. Dist. LEXIS 107743, at *42 (N.D. W. Va. 2020).

224. *Id.* at *18.

225. *Id.* at *21.

226. *Id.* at *33.

227. *Biogen Int'l GmbH*, 18 F.4th at 1335.

228. *Id.* at 1337.

"laundry list" form of disclosure).[229] The relevant elements of the claim (the disease treated, the drug used, and the dose) were each recited once in the specification, according to the majority, and those citations were scattered in different portions therein.[230]

Judge O'Malley's dissent was based on her appreciation of the majority misunderstanding the differences between therapeutic and clinical efficacy and the differences between what is required to obtain a patent and what is required for FDA approval of a drug.[231] This error, she contended, led the majority to apply the Court's *Nuvo Pharms. (Ireland) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc.*, 923 F.3d 1368, 1377, 1381 (Fed. Cir. 2019), precedent, also in error according to the Judge.[232] The Judge stated that, in her view, the specification contained an adequate written description based on this reasoning:

> The majority's decision affirming the district court partially rests on the fact that the '514 patent only mentions the claimed DMF480 dose once. . . . But the majority cites no case law (and I know of none) for the proposition that the written description requirement demands that a patentee recite a claim element repeatedly to pass written description muster. The majority does not, and cannot, deny that the claimed DMF480 dose is expressly disclosed. To the extent the majority's opinion may be read to establish a requirement that a claim element must be disclosed multiple times, I dissent from that holding as well.[233]

Judge Lourie's dissent from the Court's decision not to rehear the case *en banc* cites four grounds of error by the District Court.[234] This dissent begins by noting that a proper written description analysis rests on the Court's *en banc* decision in *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010), but Judge Lourie sets out Federal Circuit precedent involving the variety of cases where an adequate written description was not found (many of them written by the Judge himself) and based, according to the dissent, on the CCPA case *In re Ruschig*, 379 F.2d 990, 995 (C.C.P.A. 1967), and (somewhat provocatively) on *O'Reilly v. Morse*, 56 U.S. 62, 113 (1853).[235] This case, according to the dissent, is an "outlier" "at the farthest end of the spectrum"

229. *Id.*

230. *Id.*

231. *Id.* at 1346 (O'Malley, J., dissenting).

232. *Id.* at 1349 (O'Malley, J., dissenting).

233. *Biogen Int'l GmbH*, 18 F.4th at 1351 n.4 (O'Malley, J., dissenting).

234. *See Biogen*, 28 F.4th at 1198–1202 (Lourie, J., dissenting).

235. *Id.* at 1196.

because "every claim limitation is expressly described in the disclosure."[236] And the consequence is that the Court has "let a panel majority opinion stand that imports extraneous considerations into the written description analysis and blurs the boundaries between the written description requirement and the other statutory requirements for patentability. In doing so, the court has contributed to the muddying of the written description requirement."[237]

The basis for an adequate written description is always what is disclosed, according to Judge Lourie, and here Example 4 was expressly directed to treating MS; accordingly, "from any perspective, including that of a person of ordinary skill in the art, the '514 patent describes the invention of a method for treating multiple sclerosis."[238] What is recited in claim 1, the dissent asserts, is "precisely what the specification discloses—treatment of multiple sclerosis with a 480 mg per day dose of DMF [dimethyl fumarate] or MMF [monomethyl fumarate]."[239] "Whatever shortcomings exist in this unfocused patent specification, failure of written description with respect to claim 1 is not one of them" according to Judge Lourie's dissenting opinion.[240]

So why did the panel majority go so astray in the dissenting Judges' opinions? The dissent sets out the four grounds of error by the District Court and the panel majority that provide the basis for *why* the District Court's opinion should have been reversed by the panel. The first is the "undue emphasis that the panel majority and the district court placed on unclaimed disclosures in the specification," engaging in "irrelevant comparisons between the amount of disclosure of the claimed subject matter versus the unclaimed subject matter," reciting as examples the majority's focus on the number of other neurological diseases set forth in the specification and the frequency (once) with which the 480mg dose was set forth.[241] Agreeing with Judge O'Malley's dissent, Judge Lourie faults the panel majority for relying on *In re Ruschig* for the use of "blaze marks" in performing a written description requirement, because they thereby neglected the important distinction that in *Ruschig* the specification did *not* disclose the claimed embodiment.[242] Discussing the extent of disclosure in genus/species claims, Judge Lourie recited portions of the body of precedent developed by the Court for making sufficiency determinations (a "representative number of species falling within the scope of the genus or structural features common to members of the genus so that one of skill in

236. *Id.*

237. *Id.*

238. *Id.* at 1197.

239. *See Biogen*, 28 F.4th at 1198 (Lourie, J., dissenting).

240. *Id.*

241. *Id.*

242. *Id.* at 1199.

the art can 'visualize or recognize' the members of the genus.)".[243] It is only when a claimed species is *not* expressly disclosed in the context of a disclosed genus that a blazemarks analysis is needed according to the dissenting Judges, something the court expressly set forth in *Novozymes A/S v. DuPont Nutrition Biosciences APS*.[244] That is not the case here, Judge Lourie asserts, where the disease to be treated, the drug used for the treatment, and the administered dose are all expressly disclosed.[245] In such cases, whatever else is disclosed in the specification does not support a finding of inadequate disclosure according to this dissent,[246] nor is the fact that there was only a single mention of the 480 mg dose contrary to a finding of an adequate written description ("once is enough" according to the dissent).[247] Summing up this ground of error, the dissent states:

> The panel majority opinion implies that a patent fails the written description requirement of 35 U.S.C. § 112 when it contains too much disclosure beyond the claimed invention, which is incorrect. The opinion implies that a patentee must disclose the claimed subject matter more than once, which is also incorrect. And the opinion implies that a court may arbitrarily count the number of times the claimed subject matter is disclosed in the specification relative to the number of times unclaimed subject matter is disclosed, which is incorrect.[248]

The second ground of error (again in agreement with Judge O'Malley) is that Federal Circuit precedent does not require a patentee to show that "the specification proves the efficacy of the claimed pharmaceutical composition."[249]

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243. *Id.* (citing Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1568–69 (Fed. Cir. 1997)).

244. *Biogen*, 28 F.4th at 1199 (Lourie, J., dissenting) (citing Novozymes A/S v. DuPont Nutrition Biosciences APS., 723 F.3d 1336, 1349 (Fed. Cir. 2013) ("'[b] laze marks' are not necessary where the claimed species is expressly described in the specification.")).

245. *Id.*

246. *Id.* (citing ScriptPro, LLC v. Innovation Assocs., Inc., 762 F.3d 1355, 1359 (Fed. Cir. 2014)).

247. *Id.* (citing Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd., 887 F.3d 1117, 1137 (Fed. Cir. 2018)).

248. *Id.* at 1200.

249. *Id.* (citing Nuvo Pharms. (Ir.) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc., 923 F.3d 1368, 1384 (Fed. Cir. 2019); *see In re* Brana, 51 F.3d 1560, 1567 (Fed. Cir. 1995) (noting the requirements for patenting and the requirements for drug marketing approval were different); *see also* Scott v. Finney, 34 F.3d 1058, 1063 (Fed. Cir. 1994)).

Merely stating the claimed dose is enough, according to Judge Lourie because it "leaves nothing for the skilled artisan to deduce; it expressly states that 480 mg per day is an effective amount."[250]

The third error made by the District Court and panel majority was importing "extraneous legal considerations into the written description analysis[,]" contrary to the court's holding in *Ariad*.[251] For example, the dissent notes that while operability can be raised with regard to enablement, *Ariad* stands for the distinction between the written description and the enablement requirements of the statute:[252]

> By focusing on whether the patentee *proved* that 480 mg per day is an effective amount to treat multiple sclerosis—as distinct from whether the '514 patent specification *discloses* that 480 mg per day is an effective amount to treat multiple sclerosis—the panel majority and the district court erroneously imported operability considerations into the written description analysis. (*emphasis* in dissenting opinion).[253]

Even further, the dissent criticizes the District Court and the panel majority for considering inventorship issues, which is also separate from a proper written description requirement analysis.[254] The dissent also appreciates that the majority introduced a best mode issue, in reference to whether the skilled artisan would have been "*drawn to*" the 720 mg dose (emphasis in dissenting opinion).[255] Once again, the dissent asserts that "[b]y incorporating extraneous legal standards into the analysis, the panel majority opinion creates confusion for future patent applicants and litigants regarding what is required to meet the written description requirement of 35 U.S.C. § 112."[256]

The fourth point of error in the dissenting Judges' view was the consideration of extrinsic evidence by the District Court and the panel majority.[257] Under *Ariad*, "[t]he test for written description 'requires an objective inquiry into the four corners of the specification.'"[258] While considerations outside the

250. *Biogen*, 28 F.4th at 1200.

251. *Id.* (citing Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1344 (Fed. Cir. 2010)).

252. *Id.*

253. *Id.* at 1201.

254. *Id.*

255. *Id.*

256. *Biogen*, 28 F.4th at 1201.

257. *Id.*

258. *Id.* at 1202.

four corners can be relevant (regarding, for example, the understanding of one or ordinary skill in the art), such considerations need to be limited to "an objective inquiry into what is meant by the disclosure in the patent specification" according to the dissent.[259] Where, as here, "the disclosure in a patent's specification plainly corresponds to what is claimed, extrinsic evidence should not be used to cast doubt on the meaning of what is disclosed."[260]

The dissent concludes by stating that the best reason for the *en banc* Court to hear this case is that the panel majority had "affirmed a district court's erroneous broadening of the written description inquiry" and by denying rehearing the case the Court "lost an opportunity to provide clarity for future litigants by reaffirming the proper boundaries of the written description requirement in 35 U.S.C. § 112."[261]

It would be good to remember that satisfaction of the written description requirement is a question of fact, and such questions do not easily lend themselves to readily applied, rigid rules.[262] Thus, the strength of Judge O'Malley's dissent in the panel decision as well as the strength of the dissenting Judges here is directed at the proper application of the law to the question before the Court,[263] which if in the unlikely event it ever arises again would be persuasive but is not likely to be binding precisely because such future facts are unlikely to be entirely on all fours with the question before the Court here. More significant, perhaps, is that the Court has trended towards a more stringent application of written description questions during Judge Prost's tenure as Chief Judge,[264] and with the appointment of Judges Cunningham and Stark and Judge Moore taking the position of Chief Judge that may change, perhaps to greater consistency with what was presumed to be settled Federal Circuit law.

III. A CRISPR INTERFERENCE *POT POURRI*

8. Part A: PTAB Grants Priority for Eukaryotic CRISPR to Broad in Interference No. 106,115 (Decided February 28, 2022)

In an 82-page decision, the Patent Trial and Appeal Board granted priority for eukaryotic CRISPR to the Broad Institute, Harvard University, and MIT (collectively, "Broad") as Senior Party and against Junior Party the University of California/Berkeley, the University of Vienna, and Emmanuelle Charpentier

259. *Id.* (quoting *Ariad Pharm., Inc.*, 598 F.3d at 1351).

260. *Id.*

261. *Id.* at 1203.

262. *See Biogen*, 28 F.4th at 1196–98.

263. *See id.* at 1198.

264. *See, e.g., Biogen*, 28 F.4th at 1203.

(collectively, "CVC").[265] Accordingly, all of Broad's patents and applications in interference remain in force and CVC's applications having claims directed to eukaryotic CRISPR are finally rejected for lack of priority.[266]

The Board was convinced by Broad's arguments that CVC's attempts to reduce eukaryotic CRISPR to practice were unavailing until after Broad's reduction to practice as evidenced by a manuscript submitted on October 5, 2012.[267] Operating on the legal principle that "priority of invention goes to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice,"[268] the Board was unconvinced that CVC's March 1, 2012 conception satisfied the requirements of "complete" conception.[269] Using much of the same argument (albeit for different purposes) as it had to prevail in Interference No. 106,048,[270] the Broad persuasively argued that the evidence of CVC's attempts to reduce eukaryotic CRISPR to practice showed sufficient uncertainty and failures for the Board to conclude that CVC did not satisfy the requirements for conception.[271] On this evidence, the Board was unpersuaded that all that had been needed was the application of routine experimentation using the sgRNA detailed in CVC's March 1st priority statement.[272] Nor was the Board convinced that Broad derived the embodiments of eukaryotic CRISPR that they reduced to practice embodying sgRNA only after Dr. Marraffini obtained it from CVC and disclosed it to the Broad inventors.[273]

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265. Regents of the Univ. of Cal. v. the Broad Inst., Inc., No. 106,115, at 2 (P.T.A.B. Feb. 28, 2022); *see* Document No. 2863.

266. *Id.*

267. *Id.*; *see also* Kevin E. Noonan, *CRISPR Battle Joined Again*, PatentDocs (July 1, 2019), https://www.patentdocs.org/2019/07/crispr-battle-joined-again.html [https://perma.cc/5W2M-ZEFY].

268. *Regents of the Univ. of Cal.*, No. 106,115, at 8 (P.T.A.B. Feb. 28, 2022) (quoting Cooper v. Goldfarb, 154 F.3d 1321, 1327 (Fed. Cir. 1998)).

269. *Id.*

270. *See* Kevin E. Noonan, *PTAB Decides CRISPR Interference in Favor of Broad Institute – Their Reasoning*, PatentDocs (Feb. 16, 2017), https://www.patentdocs.org/2017/02/ptab-decides-crispr-interference-in-favor-of-broad-institute-their-reasoning.html [https://perma.cc/J8UA-7HWH].

271. *Regents of the Univ. of Cal.*, No. 106,115, at 2 (P.T.A.B. Feb. 28, 2022).

272. *Id.* at 33.

273. *Regents of the Univ. of Cal.*, No. 106,115, at 70 (P.T.A.B. Feb. 28, 2022); *see* Kevin E. Noonan, *CVC Files Reply to Broad's Opposition to CVC's Priority Motion*, PatentDocs (May 25, 2021), https://www.patentdocs.org/2021/05/cvc-files-reply-to-broads-opposition-to-cvcs-priority-motion.html [https://perma.cc/8SRG-4JXY].

It must be said that this decision is not particularly surprising in light of the tenor of questioning by the Board in the Oral Hearing on February 4th or by reading the hearing transcript.[274]

In addition to the decision on priority, the Board denied CVC's motion for improper inventorship under 35 U.S.C. § 102(f)[275] for evidentiary deficiencies, and in their discretion, refused to consider CVC's allegations of inequitable conduct against the Broad.[276]

Thus, the status of eukaryotic CRISPR is where the parties left it after the '048 Interference decision but with Broad in a decidedly better position, having been granted priority on the merits here.[277]

Having lost its priority to Broad, it is possible that Interferences Nos. 106,127 and 106,132 naming CVC as Junior Party in each will be dissolved, but those decisions remain to be rendered.[278]

The Board was careful to note that CVC retained its patents on CRISPR without any cell-specific limitations, but that is almost certainly ephemeral with regard to eukaryotic CRISPR; CVC is likely to be estopped from asserting those claims against Broad's licensees (or anyone else) practicing eukaryotic CRISPR.[279] Whether CVC's inequitable conduct allegations provide a roadmap for anyone challenging Broad's eukaryotic CRISPR estate remains

274. *Regents of the Univ. of Cal.*, No. 106,115, at 5 (P.T.A.B. Feb. 28, 2022); *see* Kevin E. Noonan, *PTAB Hears Oral Argument in Interference No. 106,115*, PatentDocs (Feb. 7, 2022), https://www.patentdocs.org/2022/02/ptab-hears-oral-argument-in-interference-no-106115.html [https://perma.cc/PB6A-A3G8].

275. *Regents of the Univ. of Cal.*, No. 106,115, at 82 (P.T.A.B. Feb. 28, 2022); *see* Kevin E. Noonan, *CVC Files Substantive Motion No. 3 (for Improper Inventorship) and Broad Opposes*, PatentDocs (Dec. 30, 2020), https://www.patentdocs.org/2020/12/cvc-files-substantive-motion-no-3-for-improper-inventorship-and-broad-opposes.html [https://perma.cc/V7TT-QDMA].

276. *Regents of the Univ. of Cal.*, No. 106,115, at 81-82 (P.T.A.B. Feb. 28, 2022); *see* Kevin E. Noonan, *Inequitable Conduct by Senior Party Broad Alleged in Interference No. 106,115 (and PTAB May Finally Hear Evidence About It)*, PatentDocs (Dec. 6, 2021), https://www.patentdocs.org/2021/12/inequitable-conduct-by-senior-party-broad-alleged-in-interference-no-106115-and-board-may-finally-he.html [https://perma.cc/TNB5-DQAH].

277. *Regents of the Univ. of Cal.*, No. 106,115, at 68 (P.T.A.B. Feb. 28, 2022).

278. *See supra* Section II; discussions infra Part B; *see also* Kevin E. Noonan, *Separate Interferences Declared between ToolGen and Broad and CVC over CRISPR Priority Question*, PatentDocs (Jan. 13, 2021), https://www.patentdocs.org/2021/01/separate-interferences-declared-between-toolgen-and-broad-and-cvc-over-crispr-priority-question.html [https://perma.cc/VA4F-PSQW]; Kevin E. Noonan, *Sigma-Aldrich Joins the CRISPR Interference Fray*, PatentDocs (Dec. 13, 2021), https://www.patentdocs.org/2021/12/sigma-aldrich-joins-the-crispr-interference-fray.html [https://perma.cc/P9RD-7ZUA].

279. *Regents of the Univ. of Cal.*, No. 106,115, at 14 (P.T.A.B. Feb. 28, 2022).

speculative, and interferences involving Broad against both ToolGen (No. 106,126) and Sigma-Aldrich (No. 106,133) remain pending.[280]

CVC timely filed a notice of appeal to the Federal Circuit and that appeal is on-going.

All of this means the provenance of eukaryotic CRISPR has not yet been settled for good by the Board's decision.

8. Part B: PTAB Holds for Broad in CRISPR Interference: The Reasoning (Decided February 28, 2022)

Inventorship determinations have been called, in some of their incarnations, "one of the muddiest concepts in the muddy metaphysics of patent law."[281] Whatever complications may arise in "simple" inventorship determinations are amplified in interferences. These determinations are further burdened by over a century of case law, both in the U.S. Patent and Trademark Office and the courts, which can be charitably characterized as arcane. And these considerations are evident in the Patent Trial and Appeal Board's decision giving priority to CRISPR technology in eukaryotic cells to inventors at The Broad Institute, Harvard University, and MIT (collectively, "Broad") over inventors at the University of California, Berkeley, the University of Vienna, and one of the inventors herself, Emmanuelle Charpentier (collectively, "CVC").[282]

The basis for Board's decision was that CVC failed to provide sufficient, persuasive evidence of an earlier reduction to practice or conception, as they are legally defined, of each and every element of Count 1 before Broad's evidence of actual reduction to practice.[283] The Board cited its legal grounds for this determination: "priority of invention goes to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice."[284] Further, the Board opined "[a]n actual reduction to practice requires proving that the inventors constructed an embodiment of the count, meeting all its limitations, and that they determined the invention would work for its intended purpose."[285]

In applying these rubrics to the facts adduced by the parties, the Board cited with particularity testimony and contemporaneous statements regarding

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280. *See* Noonan, *supra* note 267.

281. Mueller Brass Co. v. Reading Indus., 352 F. Supp. 1357, 1372 (E.D. Pa. Dec. 21, 1972), *aff'd*, 487 F.3d 1395 (3d Cir. 1983); *see In re* VerHoef, 888 F.3d 1362, 1365 (Fed. Cir. 2018) (quoting *Mueller Brass Co.*, 352 F. Supp. at 1372).

282. *See supra* Section II; *see also Regents of the Univ. of Cal.*, No. 106,115, at 2 (P.T.A.B. Feb. 28, 2022).

283. *Regents of the Univ. of Cal.*, No. 106,115, at 23–24 (P.T.A.B. Feb. 28, 2022).

284. *Id.* at 24 (citing *Cooper*, 154 F.3d at 1327).

285. *Id.* at 9 (citing *Cooper*, 154 F.3d at 1327).

an August 9, 2012 zebrafish experiment performed by collaborator Florian Raible, Ph.D., to wit: "In his supporting testimony, Dr. Raible's indicates that one of the 30 embryos he injected with one concentration of the test solution showed the characteristic eyeless morphological phenotype expected for the homozygous *rx3/chokh/chk* mutant fish."[286] Specifically quoted in the Board's opinion was this excerpt from in Dr. Raible's declaration:

> [Dr. Raible testified that he] prepared [an animal with the homozygous *rx3/chokh/chk* phenotype] on August 8, 2012, on behalf of the CVC inventors by injecting into the animal a preformed complex of the Cas9 protein and two single-guide RNAs that included crRNA and tracrRNA sequences where the crRNA sequence targeted the *rx3/chokh/chk* locus. This fish indicated to me that there was successful site-specific DNA cleavage in a zygote injected with the inventors' CRISPR-Cas9 system. The inventor's CRISPR-Cas9 system thus worked as predicted in zebrafish using previously known methods for delivery and analysis.[287]

Unfortunately for CVC, the Board found that "CVC does not direct us to contemporaneous evidence showing that Dr. Raible considered the results of the 9 August 2012 experiment to have been successful."[288] In addition to this absence of evidence (which would not otherwise be evidence of absence), the opinion quotes what it considered to be contrary contemporaneous evidence, including an e-mail from Dr. Chylinski (Dr. Raible's collaborator) to inventor Charpentier, which states:

> *Potentially* good news about fish. We tested the NLS-tagged Cas9 that we just got from Martin as the normal protein was *not giving anything conclusive*. It looks like GFP expression in medaka is much lower in the embryo although *there are still problems* with toxicity and so on, so it *will require some more* optimization from their site. Anyway, there is a *hint it might work* but *we shouldn't be overexcited now* [italics added].[289]

This e-mail was sufficient for the Board to conclude that "*by itself*, neither Dr. Chylinski's e-mail of 9 August, nor Dr. Charpentier's response demonstrates that either recognized and appreciated Dr. Raible's August 2012 experiment was an actual reduction to practice of an embodiment of Count 1" (emphasis added).[290]

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286. *Id.* at 11.

287. *Id.* at 12 (quoting Raible Decl., Ex. 4294, ¶ 56).

288. *Id.*

289. *Regents of the Univ. of Cal.*, No. 106,115, at 13 (P.T.A.B. Feb. 28, 2022).

290. *Id.* at 14.

Further quoting Dr. Chylinski's testimony, the opinion contains this excerpt:

> We believed that these effects were the result of our sgRNA CRISPR-Cas9 system's activity in the fish, *though we had not confirmed an effect on the targeted regions* by sequencing. Ex. 4916. While my fish experiment result summary noted that the effects of possible incomplete GFP loss in the medaka *might be the result* of "heterozygotes" or "unspecific" effects, the zebrafish eyeless phenotype indicated that we had successfully used our sgRNA CRISPR-Cas9 system to target and cleave target DNA within the zebrafish. Ex. 4916. The reference to repeating experiments indicated that a journal publication would require multiple experiments and a second molecular detection assay [emphasis added].[291]

But, to the contrary in the Board's view is a contemporaneous slide presentation which states:

> **Fish Experiment Results**
>
> - Pretty high toxicity observed (death or misdevelopment)
> - *Small amount of putative mutants* (1 in 30-50) seen in some of the experiments
> - "Less green" embryos for Medaka [a zebrafish relative], no eyes or misdeveloped eyes for Zebrafish - *might be heterozygotes, might be unspecific*
> - Mutants tested for the mutations in the gene by PCR amplification of the targeted regions (repair of dsDNA breaks is usually connected with trimming of the DNA) - *no effect visible*
> - *Experiments are still being repeated* (emphasis added)[292]

The Board concluded that "[w]e agree with Broad and find that, contrary to CVC's argument, Exhibit 4916 does not indicate an acknowledgement of positive results by Dr. Chylinski."[293] And contemporaneous statements by Dr. Charpentier that she was "convinced" the zebrafish experiments would work are not supported by any reference to any actual zebrafish experiments, the Board stated.[294] The Board's conclusions are summarized in the opinion thusly:

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291. *Id.* at 15.

292. *Id.*

293. *Id.* at 16.

294. *Id.* at 18.

> In general, we find that CVC over-emphasizes isolated words by its inventors to argue that they recognized and appreciated Dr. Raible's results. We are further persuaded that CVC over-interprets the inventors' recognition and appreciation of Dr. Raible's results because neither Dr. Doudna nor Dr. Jinek remembers learning of them at the time . . . . We note, too, that no zebrafish experiments were included in CVC's provisional applications filed 19 October 2012 and 28 January 2013 . . . . The lack of communication by Drs. Chylinski and Charpentier regarding Dr. Raible's 9 August 2012 zebrafish experiment and lack of reference to it later indicates to us that the CVC inventors did not consider it to be a success or a reduction to practice of Count 1 because Dr. Raible did not communicate any success to them.[295]

Additional evidence persuasive to the Board that Dr. Raible did not appreciate that the experiments were a success was that no scientific research paper was forthcoming; Dr. Raible testified that:

> While I was happy to have helped the inventors validate their sgRNA CRISPR-Cas9 system in zebrafish, I did not believe that merely showing successful cleavage in a eukaryote using only routine techniques, with no special parameters to introduce a nuclease into eukaryotic cells, would be a publication-worthy discovery. That was a trivial and expected result. I felt that to justify expending additional resources on these experiments, I needed results suggesting that the efficiency of CRISPR-Cas9 *in vivo* could compete with ZFNs and TALENs. I believed that other labs with more resources would likely generate such data before I would be able to, for instance by being able to perform massive parallel sequencing on targeted gene loci, bypassing the need to rely on the presence of length variants identified by PCR.[296]

Which would be fine as it goes, but the Board was able to contrast this testimony with Dr. Raible's contemporary statements (before the experiments had been performed) to the contrary (in their view):

> Given the massive interest in simple methods for genome editing, we would expect that the establishment of a CRISPR/CAS-based genome editing system in any fish system would be of broad interest, and therefore a short article in a high-impact journal would not be unlikely as a result (provided the results match the expectations based on the in vivo data).[297]

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295. *Regents of the Univ. of Cal.*, No. 106,115, at 18–19 (P.T.A.B. Feb. 28, 2022).

296. *Id.* at 22.

297. *Id.*

The Board concluded that this contrast indicated that Dr. Raible's 2012 behavior was more consistent with abandoning the zebrafish CRISPR project because he did not think it had worked rather than, as he maintains today, being consistent with an appreciation of success.[298] And for the Board, while CVC provided evidence that Dr. Raible's results had been communicated to Drs. Chylinski and Charpentier, there was no evidence that this information had been communicated to the other two CVC inventors, Dr. Doudna and Dr. Jinek.[299]

The Board eschewed reliance on a "battle of the zebrafish experts" because "'there is no conception or reduction to practice where there has been no recognition or appreciation of the existence of new subject matter."[300]

Turning to CVC's arguments regarding contemporaneous reduction to practice by other research groups (including Broad), the Board rejected them because all evidence regarding reducing eukaryotic CRISPR to practice *by CVC* had dates – "31 October 2012, 1 November 2012, 5 November 2012, and 18 November 2012"—later than the 5 October 2012 date when Broad submitted its manuscript to Science (that the Board relied upon as evidence of actual reduction to practice).[301]

With regard to any question of diligence, the Board recognized that CVC could have prevailed if it showed conception prior to Broad and reduction to practice with the "exercise of reasonable diligence."[302] Importantly, the opinion reminds that "[an] inventor need not know that the invention will work for conception to be complete because determining it works is part of reduction to practice."[303] The standard the Board applied for incomplete conception is taken from *Alpert v. Slatin*,[304] and *Burroughs Wellcome*.[305] The issue, according to

298. *Id.* at 22–23.

299. *Id.* at 23.

300. *Id.* at 20 (citing Silvestri v. Grant, 496 F.2d 593, 597 (CCPA 1973); *accord* Invitrogen Corp. v. Clontech Lab'ys, Inc., 429 F.3d 1052, 1065 (Fed. Cir. 2005)) ("[the Board] look[s] for an appreciation of the results *by the inventors* . . ." (italics in opinion)).

301. *Regents of the Univ. of Cal.*, No. 106,115, at 24 (P.T.A.B. Feb. 28, 2022).

302. *Id.*

303. *Id.* at 25 (citing Burroughs Wellcome Co. v. Barr Lab., Inc., 40 F.3d 1223, 1228 (Fed. Cir. 1994)).

304. *Id.* (quoting Alpert v. Slatin, 305 F.2d 891, 894 (CCPA 1962) ("'[W]here results at each step do not follow as anticipated, but are achieved empirically by what amounts to trial and error' there has not been a complete conception.")).

305. *Id.* (quoting Burroughs Wellcome Co. v. Barr Lab., Inc., 40 F.3d 1223, 1228 (Fed. Cir. 1994) ("Conception is complete only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation," with the Board further noting that, "a conception may not be complete 'if the subsequent

the Board, is whether there is "factual uncertainty" about whether the inventor had a complete conception, rather than uncertainty in a field of endeavor.[306] The Board cites *Hitzeman v. Rutter*, 243 F.3d 1345, 1357 (Fed. Cir. 2001), for the analogous factual predicate that there, "statements made by the inventor during prosecution and subsequent publications . . . revealed he had not conceived of the complete subject matter of the count and considered it not to have been reasonably expected by one of ordinary skill in the art."[307] The Board supported its finding of the requisite degree of uncertainty to indicate incomplete conception by CVC inventor Doudna's statements in an e-mail exchange with Inventor Jinek:

> I'm very excited about the Csn-1/Cas9-based genome targeting ideas we discussed yesterday, this will be fabulous *if it works* [emphasis added].
>
> [I]t would be good to demonstrate that the single-RNA guide works to direct DNA cleavage by Csn1/Cas9 in vitro ASAP, . . . and then proceed with the experiments necessary to show that this strategy *will actually work in mammalian cells* [emphasis added].[308]

CVC argues that conception was "definite and permanent" on March 1, 2012, because "it did not change between conception and subsequent reduction to practice" and that this "blueprint" was expected to work using conventional methods.[309] But according to the Board:

> The IDF [Invention Disclosure Form] demonstrates that the CVC inventors planned to use their sgRNA CRISPR-Cas9 system in eukaryotic cells but does not provide many details of how the inventors envisioned such a system would be operable. Instead, the IDF and Dr. Jinek's testimony indicates that as of 1 March 2012 the inventors assumed that what was known about other genome editing systems such as TALENs and zinc fingers would be applicable to a CRISPR-Cas9 system.[310]

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course of experimentation, especially experimental failures, reveals uncertainty that so undermines the specificity of the inventor's idea that it is not yet a definite and permanent reflection of the complete invention as it will be used in practice.'").

306. *Id.* at 26.

307. *Id.*

308. *Id.* at 27.

309. *Id.* at 29–33 (The opinion reproduces pages from Jinek's laboratory notebook memorializing the plans for these experiments).

310. *Regents of the Univ. of Cal.*, No. 106.115, at 35 (P.T.A.B. Feb. 28, 2022).

Specifically, CVC set out evidence of experimental designs targeting genes in human cells and that they had produced sgRNAs for the purpose by May 28, 2012 and a plan to inject zebrafish embryos by June 28, 2012.[311] Broad asserted purported evidence of failures, including an e-mail from August 16, 2012 of "unfortunate results" in failure to achieve CRISPR cleavage of CTLA gene in human cells and a response from Dr. Doudna of "Shucks! I guess it would have been too easy of it worked the first time . . . I'll think on this and get back to you - my quick take is maybe try again with improved Cas9 expression?"[312] Also asserted by Broad was an e-mail from September 14, 2012 entitled "no good news" that said, "[u]nfortunately no cleavage for any RNA chimeras despite using the codon-optimized Cas9 constructs this time."[313] This e-mail also contained what the Board characterized as "generalized suggestions about repeating the experiment with increased amount of plasmid" and included the quotation:

> Since there are so many variables in these experiments I think we have to try to move forward in a stepwise fashion as much as possible.
>
> As for RNA localization I think we're hoping that the Cas9 protein binds the RNA such that the RNP is transported into the nucleus I wonder if having a too-efficient NLS on Cas9 is actually counterproductive if it means that Cas9 is transported before it has a chance to find and bind the guide RNA . . . . Thoughts?[314]

A colloquy of further e-mails beginning on October 11, 2012 between Dr. Doudna and Inventor Jinek regarding the CTLA cleavage experiments (after the date Broad submitted its paper) are also reproduced in the opinion:

> Hi Alex and Aaron - thanks for sending your results although it's *disappointing not to see* Cas9-mediated cleavage in these experiments. Aaron I'm wondering if you think there is *anything different* about the way you did the experiment back in August when it appeared that there was *some cleavage* with the CLTA6 guide? Or could that result have been due to a contamination, say with the ZFN sample -? And it will be interesting to see the result from the RNA transfection experiment. Is it *worth trying* the transfections again with the codon-optimized Cas9? As we have discussed I still think *the problem may be* with the assembly and localization of the Cas9 RNP - either due to degradation of the guide RNA failure to

311. *Id.* at 36.

312. *Id.* at 38.

313. *Id.*

314. *Id.*

> assemble with Cas9 or failure of the RNP nuclear localization. I will think on this on my way back to SF tonight and we can meet soon to discuss [emphasis added].[315]

And on the same day in an e-mail from Dr. Jinek to Dr. Doudna:

> Re mammalian cells - Based on the latest set of results, I *suspect we have a problem* with our RNA design. Either we are not targeting the right piece of DNA (due to chromatin structure etc.), or the problem lies with the RNA design per se. Given that the ZFN has no problems cleaving the same region (+/- 30 bp), the former is probably the lesser concern at this point. On the other hand, *there could be* a number or reasons for the latter including:
>
> -RNA is not made at sufficient levels
>
> -RNA is expressed strongly but turns over too fast to associate with Cas9 possibly due to degradation by exonucleases
>
> -RNA is stable but does not associate with Cas9 at the right place and at the right time.
>
> For the next set of experiments I think we should switch to CMV vectors cloning today and explore alternatives to our first-generation RNA design - e.g. modify the hairpin length introduce extensions at the 5' and 3' termini. Or possibly block potential degradation from either end by introducing hairpins etc. [emphasis added].[316]

To which Dr. Doudna responded:

> As for Cas9 in mammalian cells I completely agree with your analysis and suspect that one or more aspects of the RNA expression/stability/Cas9 assembly/localization are *problematic*.
>
> It would be great to test some alternate designs of the guide RNA *in vitro* - perhaps this is something Alex could do using target plasmids you already have available? Maybe we could also try this in cell extracts? We can discuss further tomorrow - 10 am OK? [emphasis added][317]

315. *Id.* at 39.

316. *Regents of the Univ. of Cal.*, No. 106,115, at 39–40 (P.T.A.B. Feb. 28, 2022).

317. *Id.* at 40.

Followed by a further response by Dr. Jinek:

> I agree that we *should explore* various alternate RNA designs for targeting in cells. As for the in vitro experiments - I thought that this was what Steve Lin was going to do. Maybe it would be good to bring him on board for this as well at this stage. Then things could be parallelized and Alex could focus more on the mammalian cell work. When Enbo gets back he could then help out with IPs and Northerns because we will need to check whether the RNAs are associating with Cas9 in vivo. Anyway, let's talk tomorrow [emphasis added].[318]

Broad argued, and the Board agreed, that these e-mails indicated that "instead of having a definite and permanent idea of an embodiment of Count 1, the CVC inventors were engaged in 'guesswork' and 'returned to the drawing board'" and that "the CVC inventors had to redesign their components and strategy beyond what would have been routine techniques for one of ordinary skill in the art and did not have a definite and permanent idea of the invention by 1 March 2012."[319] The Board rejected CVC's contentions that Broad had fabricated an "illusion of doubt" in the CVC inventors based on the language and content of *inter alia* the cited testimony and contemporary documentary evidence, and also noted the apparent disparities between their testimony in this interference and confidence that CRISPR cleavage would be achieved in eukaryotic cells merely by the exercise of conventional methods and the difficulties encountered in attempting to reduce eukaryotic CRISPR to practice:

> We find the facts related to the CVC's inventors' asserted conception on 1 March 2012 and the further evidence of 11 April 2012, 28 May 2012, and 28 June 2012 to be different from the facts of inventorship presented in *Burroughs*. In that case, the confirmatory testing was "brief" and followed the "normal course of clinical trials." *Burroughs*, 40 F.3d at 1230. In contrast, CVC argues its inventors had the materials for an actual reduction to practice in human cells on 28 May 2012, but allegedly completed it, after diligent work, on 31 October 2012 – over five months later – after encountering many problems and trying many times. Contrary to CVC's argument, we find that the CVC inventors engaged in a "prolonged period of extensive research, experiment, and modification" following the alleged conception on 1 March 2012. *Burroughs*, 40 F.3d at 1230. The evidence shows that, at best, the CVC inventors encountered one unrecognized positive result and several failures with zebrafish embryos and several months of failed experiments and doubt with human cells. Given that the scientists performing these experiments

318. *Id.*

319. *Id.* at 41.

> were of at least ordinary skill, we are persuaded that the communications surrounding these experiments reflect "uncertainty that so undermines the specificity of the inventor's idea that it [was] not yet a definite and permanent reflection of the complete invention as it [would] be used in practice." *Id.* at 1229 [citations to the record omitted].[320]

The Board rejected CVC's argument that, in the end they were correct that the invention conceived on March 1, 2012 was reduced to practice using "only routine materials and techniques," because "[the Board] look[s] to what the CVC inventors understood as evidence of their conception, not what others might have understood later."[321] And by focusing on the limitation in Count 1 that CRISPR cleavage must be achieved to satisfy the requirements of the Count, the Board included the requirement for conception that CVC's inventors "must have had a definite and permanent idea of an operative invention, that is of a system they knew would produce the effects on genes in a eukaryotic cell recited in Count 1."[322]

Turning to Broad's evidence for priority, while the opinion sets forth evidence Broad proffered for its activities from 2011 through the fall 2012, it was the manuscript Broad submitted to *Science* (for which favorable reviews supported the Board's decision) on October 5, 2012 that established Broad's date of actual reduction to practice.[323] As set forth above, because this date was earlier than CVC's activities that the Board might have considered to be an actual reduction to practice, the Board required no other evidence to grant priority to Broad.

The opinion also addressed (and rejected) CVC's argument that Broad derived its (successful) sgRNA eukaryotic CRISPR embodiments from CVC *via* communications from Dr. Marraffini.[324] In doing so, the Board applied the rubrics of derivation, which required CVC to "establish prior conception of the claimed subject matter and communication of the conception to the adverse claimant," which standard immediately doomed CVC's argument in view of the Board's determination that their March 1, 2012 conception was incomplete.[325] The Board makes abundantly clear that CVC must fail based

320. *Id.* at 45–46.

321. *Id.* at 48 (applying cases involving *nunc pro tunc* invention which may not be completely relevant in this situation).

322. *Regents of the Univ. of Cal.*, No. 106,115, at 49 (P.T.A.B. Feb. 28, 2022). (It will be appreciated that this standard comes very close to the "simultaneous conception and reduction to practice" requirement Broad earlier argued was the proper basis for determining priority).

323. *Id.* at 61.

324. *Id.*

325. *Id.* at 64–65 (citing Price v. Symsek, 988 F.2d 1187, 1190 (Fed. Cir. 1993)).

on their priority determination, saying "[t]hus, to prove derivation, CVC must first establish that its inventors conceived of the claimed subject matter before the Broad inventors."[326] But "CVC does not direct us to evidence that overcomes our determination, discussed above" [of the Board purported evidence of] "multiple experimental failures" and did not address them in its opposition asserting derivation.[327] To CVC's attempt to establish conception based on Broad's rapid achievement of actual reduction to practice close upon Dr. Marraffini's disclosure of CVC's sgRNA embodiment, the Board states that "[r]egardless of any success by the Broad inventors, the preponderance of the evidence presented by the parties demonstrates that the CVC inventors' experimental failures reveal uncertainty undermining a definite and permanent idea of an sgRNA CRISPR-Cas9 system that edits or cleaves DNA in a eukaryotic cell" and accuses CVC of "attempt[ing] to shift our focus to the activities of other, competing inventors, rather than on the activities of its own inventors," which attempt was unavailing.[328] Broad's activities, whatever they were, "do not inure to CVC" according to the Board because to do so would require CVC to have "submitted" something to Broad for testing, citing *Genentech, Inc. v. Chiro Corp.* (which appears inapposite under the scenario underlying CVC's allegations).[329] And the Board concludes that "there *must have been* [technical] differences" between Broad's activities to reduce eukaryotic CRISPR to practice and CVC's, based on CVC's failures prior to Broad's success on October 5, 2012 (emphasis added).[330] These technical features, which are not recited in the Count, were necessary according to the opinion in order to satisfy the Count limitation for "a *functional* fused or covalently linked RNA CRISPR-Cas9 system in eukaryotic cells that alters the expression of at least one gene product, cleaves or edits a target DNA molecule, or modulates transcription of a one gene encoded by the target DNA molecule" (emphasis in opinion).[331] And the same "failures" relied upon by the Board in negating CVC's conception on the priority issue doomed CVC's arguments on derivation, because the Board similarly was "not persuaded that the CVC inventors could have divulged the complete subject matter of Count 1 to the Broad inventors."[332]

The Board also denied CVC's Motion No. 3 that Broad's involved patents and applications are invalid under 35 U.S.C. § 102(f). The Board's basis for this decision was that "[a] determination of inventorship requires two steps

326. *Id.* at 65.

327. *Id.* at 66.

328. *Regents of the Univ. of Cal.*, No. 106,115, at 66 (P.T.A.B. Feb. 28, 2022).

329. *Id.* at 67 (citing Genentech, Inc. v. Chiro Corp., 220 F.3d 1345, 1353 (Fed. Cir. 2000)).

330. *Id.* at 68.

331. *Id.* at 68–69.

332. *Id.* at 70.

performed as a claim-by-claim analysis: first a construction of each asserted claim to determine the subject matter encompassed and then a comparison of the alleged contributions of each asserted co-inventor with the subject matter of the properly construed claim to determine whether the correct inventors were named."[333] On this basis, the Board held CVC's evidence was insufficient to support its argument.[334] This evidence, appreciated by the Board to be limited to a declaration by Broad's former patent counsel submitted in a European Patent Office Opposition, "does not provide an analysis of individual claims and does not list or discuss Broad's currently involved patents or applications."[335] The disparities alleged by CVC arose solely in a comparison between the testimony in the declaration to the EPO and CVC's list of individuals that it contends "should have been named" as inventors.[336] CVC's argument that these patents and involved applications all "originate from a common source" (*i.e.*, the same original provisional application) was ("completely") unpersuasive before the Board because "[c]laiming benefit to the same provisional application says nothing about what is claimed in later applications . . . [w]ithout an actual analysis of Broad's involved claims and the alleged contributions of each asserted co-inventor."[337] The opinion sets forth several instances of uncertainty or lack of specificity in the declaration regarding inventive contributions of various individuals, which motivated the Board to "decline to adopt the CVC attorney's assumptions" as to misjoinder of inventorship.[338] Because CVC bore the burden of proving improper inventorship under 37 C.F.R. § 41.208(b), the Board denied the Motion.[339]

Except for dismissing motions to exclude evidence from both parties, the remaining decision contained in the opinion was that the Board exercised its discretion not to consider CVC's assertion of inequitable conduct. The Board's grounds were that CVC's allegations in this regard "are not directly related to the issue of priority for the subject matter of the current count" and that it was within the sound exercise of the Board's discretion to refuse to consider CVC's motion.[340]

While the Board's citation to the record provides sufficient evidence to satisfy the substantial evidence standard for review before the Federal Circuit,

333. *Id.* at 72. (citing Trovan, Ltd. v. Sokymat SA, Irori, 299 F.3d 1292, 1302 (Fed. Cir. 2002)).

334. *Regents of the Univ. of Cal.*, No. 106,115, at 73 (P.T.A.B. Feb. 28, 2022).

335. *Id.* at 75.

336. *Id.* at 73.

337. *Id.*

338. *Id.* at 74–75.

339. *Id.* at 78.

340. *Regents of the Univ. of Cal.*, No. 106,115, at 81 (P.T.A.B. Feb. 28, 2022).

the implication of the outcome produces a certain level of disquiet. *If* in fact the use of the sgRNA embodiment was the basis for successful practice of CRISPR in eukaryotic cells (despite Broad's purported evidence for successful dual-molecule CRISPR embodiments that were not considered in this interference because the Count was limited to single-molecule versions thereof), then the apparent basis for the Board's decision is that Broad's inventors were more technically proficient than CVC's at achieving successful reduction to practice more quickly. Under circumstances where both inventors reduced eukaryotic CRISPR to practice within 4-5 months of the Marraffini disclosure (and less than 8 months from CVC's asserted March 1, 2012 conception date, a timeframe CVC's counsel Dr. Ellison characterized at the Oral Hearing as "lightning quick") no issue of diligence arose. The Board speculated that certain differences between Broad's experimental setup and CVC's (*e.g.*, using a U6 promoter or Broad's sgRNA species having an oligonucleotide linker length 2 nucleotides longer than CVC's) were responsible, with the only apparent basis for its speculation the logical fallacy of *post hoc ergo propter hoc* ("there *must have been* [technical] differences" to explain why Broad achieved actual reduction to practice before CVC).[341] But none of these putative differences are required to satisfy the Count.

Whether CVC can mount a legal challenge to the Board's reasoning supporting what can be anticipated to be an assertion of fundamental injustice in the Board's decision will likely be dispositive of the question of who controls eukaryotic CRISPR technology. And while the opinion states that "[t]here is no dispute in this proceeding over the patentability of those claims [that are not limited to cell type] or that the CVC inventors were the first to invent a CRISPR-Cas9 system with a single guide RNA to cleave DNA in a generic environment," this may provide cold comfort to CVC if, as can be anticipated, CVC will not be able to assert those patents against Broad's (or others') licensees over the practice of eukaryotic embodiments of CRISPR in view of the Board's priority determination in this Interference.[342]

9. *Broad et al. v. ToolGen*, Interference No. 106,126; *California et al. v. ToolGen*, Interference No. 106,127; *California et al. v. Sigma-Aldrich*, Interference No. 106,132; *Broad et al. v. Sigma-Aldrich*, Interference No. 106,133

The Patent Trial and Appeal Board declared four other interferences involving disputes over CRISPR technology patents. On December 14, 2020, in separate proceedings the Board declared Interference No. 106,126 naming ToolGen as Senior Party and Broad Institute, Harvard University, and MIT (collectively, "Broad") as Junior Party,[343] and in Interference No. 106,127

341. *Id.* at 68.

342. *Id.* at 3.

343. Broad v. Toolgen, No. 106,126 (P.T.A.B. Dec. 14, 2020).

naming ToolGen as Senior Party and the University of California/Berkeley, the University of Vienna, and Emmanuelle Charpentier (collectively, "CVC") as Junior Party.[344] On June 21, 2021 the PTAB named Sigma-Aldrich as Senior Party and the University of California/Berkeley, the University of Vienna, and Emmanuelle Charpentier (collectively, "CVC") as Junior Party in Interference No. 106,132[345] and Broad Institute, Harvard University, and MIT (collectively, "Broad") as Junior Party in Interference No. 106,133.[346] In each of these interferences all or substantially of Broad's granted CRISPR patents and related pending applications sharing priority with them were designated as corresponding to the Count, and all or substantively all of CVC's patent applications were so designated.[347]

In each of these interferences, the initial "motions" phase has been completed with no significant consequence to the posture of the interference (i.e., the parties status as Senior or Junior Party has not changed). However, the Board's decision in the '115 Interference in favor of Broad's priority right, and CVC's appeal thereof, was cited by the Board in each instance as the basis for an order suspending the priority phase until appeals in that earlier interference have been decided and the priority status of the parties resolved.[348] It can be expected that affirmance of the Board's decision by the Federal Circuit will lead to judgment in interferences between CVC and ToolGen (in the '127 Interference) and Sigma-Aldrich (in the '133 Interference) in favor of the Senior Party in each, and that the interferences between each Senior Party and Broad will proceed to a decision.

Illustration of CVC and Broad patents/applications versus Sigma-Aldrich CRISPR patent estate:

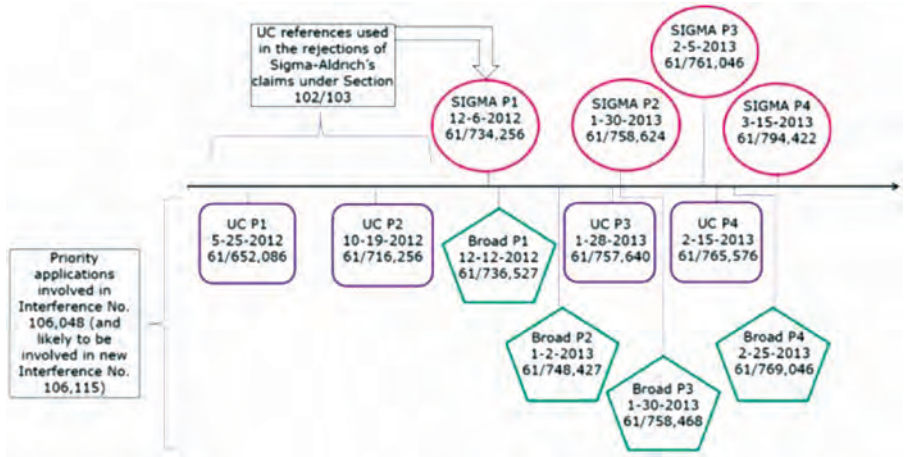
344. Regents of the Univ. of Cal. v. Toolgen, Inc., No. 106,127 (P.T.A.B. Dec. 14, 2020).

345. Regents of the Univ. of Cal. v. Sigma-Aldrich Co., No. 106,132 (P.T.A.B. June 21, 2021).

346. Broad Inst. v. Sigma-Aldrich, No. 106,133 (P.T.A.B. June 21, 2021).

347. *See generally Toolgen, Inc.*, No. 106,127 (P.T.A.B. Dec. 14, 2020); Sigma-Aldrich Co., No. 106,132 (P.T.A.B. June 21, 2021); Broad Inst., No. 106,133, (P.T.A.B. June 21, 2021) (In each case, these patents and applications were also named in Interference No. 106,115 between Broad and CVC.).

348. *Id.*



10. *Moderna v. Pfizer/BioNTech* (Complaint filed August 26, 2022)

On Friday, August 26th, Moderna Tx, Inc. and Moderna US, Inc. filed a complaint for patent infringement in Federal district court for the District of Massachusetts against Pfizer, Inc., BioNTech SE, BioNTech Manufacturing GmbH, and BioNTech US, Inc.[349] (A parallel suit was filed in Germany asserting Moderna's corresponding German patents.) There are several interesting aspects to this complaint, and perhaps of even greater interest has been the reaction to the filing in light of Moderna's earlier "pledge" to refrain from asserting any of its patents "during the pandemic."[350]

The complaint asserts three patents, identified herein in the context of the claims set forth in the complaint itself:

U.S. Patent No. 10,898,574

Claim 2. A pharmaceutical composition comprising:

a plurality of lipid nanoparticles comprising a cationic lipid, a sterol, and a PEG-lipid,

wherein the lipid nanoparticles comprise an mRNA encoding a polypeptide,

wherein the mRNA comprises one or more uridines, one or more cytidines, one or more adenosines, and one or more guanosines and wherein substantially all uridines are modified uridines.

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349. Complaint at 1, Modernatx, Inc. v. Pfizer Inc., 2023 WL 4907602 (D. Mass. Aug. 1, 2023) (No. 22CV11378).

350. Press Release, Moderna, Statement by Moderna on Intell. Prop. Matters during the COVID-19 Pandemic (Oct. 8, 2020), https://investors.modernatx.com/Statements–Perspectives/Statements–Perspectives-Details/2020/Statement-by-Moderna-on-Intellectual-Property-Matters-during-the-COVID-19-Pandemic/default.aspx [https://perma.cc/2XBP-AQMX].

Claim 9. The pharmaceutical composition of claim 2, wherein the modified uridine is 1-methyl-pseudouridine.

U.S. Patent No. 10,702,600:

Claim 1. A composition, comprising:

a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle.

U.S. Patent No. 10,933,127:

Claim 1. A method comprising administering to a subject

a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle

in an effective amount to induce in the subject an immune response to the BetaCoV S protein or S protein subunit

wherein the lipid nanoparticle comprises 20-60 mol% ionizable cationic lipid, 5-25 mol% neutral lipid, 25-55 mol% cholesterol, and 0.5-15 mol% PEG-modified lipid.[351]

Of these three asserted patents, the '574 patent has the broadest claims, not being limited to a particular virus or antigenic protein thereof, while the '600 and '127 patents expressly recite mRNAs encoding a b-coronavirus Spike protein; these claims would encompass vaccines to SARS-CoV-1 (the original SARS pandemic vaccine) as well as MERS and SARS-CoV-2 (COVID19). These claims in particular form a basis for Moderna's allegations of infringement by the Pfizer/BioNTech Comirnaty® vaccine, as recited in several paragraphs in the complaint.[352] In particular, Moderna alleges that the Comirnaty® vaccine was a direct copy of their vaccine (a path taken over three other competing candidate vaccines), citing public statements by Pfizer CEO Albert Bourla on June 9, 2020, at Goldman Sachs Virtual 41st Annual Global Healthcare Conference.[353]

Perhaps in recognition of the post-pandemic patent *zeitgeist*, the complaint has two remarkable features. The first is an extensive expostulatory section explaining the long antecedents of the technology Moderna was able to apply towards making its Spike mRNA SARS-CoV-2 vaccine (and the skepticism those efforts elicited pre-pandemic).[354] This portion of the complaint includes a history of Moderna's development of the underlying mRNA technology as well as its efforts to develop its vaccine (unnoted is that Moderna

351. Complaint at 17, *Modernatx*, 2023 WL 4907602 (D. Mass. Aug. 1, 2023) (No. 22CV11378).

352. *See id.*

353. *Id.* at 3.

354. *See id.* at 1–5.

abjured participation in "Operation Warp Speed" with its attendant Federal government financial support) during the pandemic (and makes the point that their technology is not limited to vaccines against COVID infections).[355] The complaint also makes the case that the company's IP was both the technical foundation for its successful and rapid development of the COVID vaccine and provided protection against the significant financial and investment risk occasioned by Moderna's development of its vaccine.[356]

The second remarkable feature of the complaint, and Moderna's strategy in bringing suit, is in the Prayer for Relief (and certain sections explaining the limitations of the remedy Moderna asks the Court to grant). In addition to a judgment that Pfizer and BioNTech infringe by sales of its Comirnaty® vaccine (and that such infringement was willful), Moderna seeks money damages that expressly exclude damages it would be entitled to from "sales to the U.S. government that are subject to 28 U.S.C. § 1498 or to the 92 low- and middle-income countries in the Gavi COVAX Advance Market Commitment (AMC)."[357] And in the litany of other remedies routinely requested in patent infringement cases (a finding that this is an exceptional case, with an award of attorneys' fees, costs, and expenses under 35 U.S.C. § 285, and treble damages for willful infringement under 35 U.S.C. § 284), also expressly excluded is an injunction from "such other relief the Court may deem just and proper."[358] Deigning to forego compensation for sales to the government under 28 U.S.C. § 1498 is likely done in an effort to avoid any attempt by Pfizer or BioNTech to have the case adjudicated in the Court of Federal Claims. Disclaiming any interest in sales outside the U.S. to countries falling within the scope of the COMAX AMC avoids (or at least tries to) allegations that Moderna is putting its profits and patent rights over the health and lives of the citizens of those countries.

The complaint also addresses Moderna's promises regarding assertion of its IP, specifically quoting its October 8, 2020 press release[359] stating that "*while the pandemic continues*, Moderna will not enforce our COVID-19 related patents against those making vaccines intended to combat the pandemic."[360] The

355. *Id.*

356. *Id.*

357. Complaint at 4, *Modernatx*, 2023 WL 4907602 (D. Mass. Aug. 1, 2023) (No. 22CV11378).

358. *Id.* at 19.

359. Press Release, Moderna, Statement by Moderna on Intell. Prop. Matters during the COVID-19 Pandemic (Oct. 8, 2020), https://investors.modernatx.com/Statements-Perspectives/Statements-Perspectives-Details/2020/Statement-by-Moderna-on-Intellectual-Property-Matters-during-the-COVID-19-Pandemic/default.aspx [https://perma.cc/2XBP-AQMX].

360. Complaint at 4, *Modernatx*, 2023 WL 4907602 (D. Mass. Aug. 1, 2023) (No. 22CV11378).

complaint provides Moderna's rationale and justification[361] for filing this complaint at this time:

> By early 2022, however, the collective fight against COVID-19 had entered a new endemic phase and vaccine supply was no longer a barrier to access in many parts of the world, including the United States. In view of these developments, Moderna announced on March 7, 2022, that it expected companies such as Pfizer and BioNTech to respect Moderna's intellectual property and would consider a commercially-reasonable license should they request one. This announcement was widely publicized, including through coverage in The Wall Street Journal. Critically, however, and to further its belief that intellectual property should never be a barrier to access, as part of this announcement, Moderna committed to never enforce its patents for any COVID-19 vaccine used in the 92 low- and middle-income countries in the Gavi COVAX Advance Market Commitment ("AMC"). This includes any product manufactured outside the AMC countries, such as the World Health Organization's project in South Africa, with respect to COVID-19 vaccines destined for and used in the AMC-92 countries. Although they have continued to use Moderna's intellectual property, Pfizer and BioNTech have not reached out to Moderna to discuss a license.[362]

The complaint has nonetheless raised the issue of the status of Moderna's promise in the context of patent pledges in other industries, notably for standard-essential patents (SEP) and FRAND ("fair, reasonable, and non-discriminatory") agreements.[363] Academics (in particular, Jacob Sherkow from the University of Illinois Law School and Jorge Contreras, S.J. Quinney College of Law, University of Utah Law School) have raised the specter of successful suit by Moderna in the face of its earlier promise as creating a challenge threatening the substantial edifice of patent pledges used in these other contexts.[364] Some distinctions immediately come to mind, however. One is that the patent pledges in the SEP/FRAND context are associated with consideration

361. Press Release, Moderna, Moderna's Updated Patent Pledge (Mar. 07, 2022), https://investors.modernatx.com/Statements-Perspectives/Statements-Perspectives-Details/2022/Modernas-Updated-Patent-Pledge/default.aspx [https://perma.cc/Q5SC-LWE7].

362. Complaint at 4, *Modernatx*, 2023 WL 4907602 (D. Mass. Aug. 1, 2023) (No. 22CV11378).

363. *See id.*

364. *See* Jacob S. Sherkow, *Immaculate Conception? Priority and Invention in the CRISPR Patent Dispute*, 5 The CRISPR J. XX (2022); Jorge L. Contreras, *Is CRISPR Different? Considering Exclusivity for ResearchTools, Therapeutics, and Everything In Between*, 18 The Am. J. of Bioethics 59, 59-61 (2018).

for the pledging party, that consideration consisting of, *inter alia*, compliance by companies licensing SEPs owned by the pledging patentee that provide stability and consistency in licensing regimes and create impediments against non-compliant companies.[365] Moderna received no such consideration for its pledge (and the effects of any "goodwill" it might have hoped to gain was ephemeral; after all, all the pledges in the world did not deter the WTO from adopting a patent waiver agreement at the behest of India, South Africa, and other countries who could expect to benefit and did benefit from agreements like the one in Moderna's complaint exempting sales to the COVAX AMC countries from any damages claims sought by Moderna).[366] Another distinction is that a fair reading of Moderna's promise-by-press-release was its essentially contingent nature; forgoing (or postponing exercise of) its patent rights was always limited to *during the pandemic* (although it is a fair question to ask who decides when the pandemic is over).[367] Finally it is not unfair to say that the SEP/FRAND situation is vastly different from patenting vaccines against a pandemic virus. After all, there is no analogous risk to global health and welfare arising from patent pledges relating to such patents.[368]

On the other hand, if a court does hold Moderna's patent promise to be enforceable (under the doctrine of promissory estoppel, for example), it most likely will be the last time any biotechnology or pharmaceutical company makes such a promise.

There is one other consideration here that may explain Moderna's willingness to file suit at this time that abjures the lion's share of any damages it could reasonably have expected to receive. Moderna has achieved something of a Holy Grail of patenting: true platform patents that can be and will be used for the next vaccine, and the one after that, etc. Bringing a successful suit might result in a healthy damages award but these may pale compared with what could happen during the ~10 -15 years of patent life remaining. Of course, any suit brings risks and it is not unlikely that Pfizer/BioNTech will petition for *inter partes* review; indeed, at least one patent owned by the University of Pennsylvania, U.S. Patent No. 8,691,966 (naming BioNTech principal Katalin Kariko as an inventor), discloses and claims mRNA modifications comprising 1-methylpseudouridine (albeit outside the SARS context) and this patent has an earliest priority date about 4 years prior to Moderna's patents asserted in the litigation, making an IPR proceeding supportable (at least in theory).[369]

365. *See supra*, note 342.

366. *Id.*

367. *Id.*

368. *Id.*

369. U.S. Patent No. 8,691,966 (filed Apr. 8, 2014).

IV. CONCLUSIONS

In Arthur Conan Doyle's story, *Silver Blaze*, Sherlock Holmes draws the attention of Scotland Yard Detective Gregory "to the curious incident of the dog in the night-time."[370] Confused, Gregory points out that "The dog did *nothing* in the night-time." Holmes replies, "That was the curious incident."[371] In biotechnology patent law, the year 2022 offered several of its own curious incidents. Despite a loud chorus of complaints from industry, neither the Federal Circuit nor the Supreme Court restored diagnostic methods, or even theranostic methods, to the status of patentable subject matter. The Supreme Court was given the opportunity, in *Amgen v. Sanofi*, to delineate written description and enablement, but chose not to decide that fundamental issue in the appeal. Perhaps most surprisingly, given a fever pitch of global pressure, patents claiming aspects of mRNA vaccines against SARS-CoV-2 were not "broken" or forced to operate under compulsory licensing schemes. In fact, as the world appeared to return to a degree of public health normalcy, with both infection rates and virus rhetoric calming down substantially, 2022 did not end up a watershed year for biotechnology patent law decisions. Yes, the Broad Institute advanced on the CRISPR ownership front, specifically with regard to eukaryotic genome editing, and courts shed useful light on some patent law issues. However, overall 2022 was a calm year for biotechnology patent law. Only time will tell whether it was the calm before the storm.

370. Arthur Conan Doyle, SILVER BLAZE 9 (1893).

371. *Id.*