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I. INTRODUCTION

The year 2019 was one of stasis and change, reaction and challenges to practitioners, patentees and those discontented with patents, and the judiciary itself. The year saw a comeback of sorts for the doctrine of equivalents, which has been a quiet area of the law since the Supreme Court's last word in *Festo v. Shoketsu Kinzoku Kogyo Kabushiki Co.* in 2002.[1] In 2019 there were no fewer than seven cases decided by the Federal Circuit involving the doctrine, and its primary antithesis, the doctrine of prosecution history estoppel.[2] The perennial issue of subject matter eligibility remained uncertain with the Federal Circuit deciding that method of treatment claims were patent-eligible as being an application of a natural law (and the Supreme Court taking the Solicitor General's advice and not granting *certiorari* to review the wisdom of this dichotomy).[3] Diagnostic method claims were another matter, with the Federal Circuit maintaining its jurisprudence that claims to such methods are almost *per se* patent-ineligible. In doing so, however, its *Athena Diagnostics, Inc. v. Mayo Collaborative Services LLC* decision illustrated a court in frank internal disagreement (if not disarray) in denying patentee's petition for rehearing *en banc*.[4] The Supreme Court weighed in on the extent to which the Leahy-Smith America Invents Act changed the scope of novelty-destroying prior art (saying it didn't, despite an *amicus* brief to the contrary by the Act's co-author, Rep. Lamar Smith)[5], and Section 112(a) came under scrutiny on both written description and enablement issues.[6] Finally, as a fixed constant in an otherwise changing universe, the interference over CRISPR technology between the Broad Institute and its colleagues and the University of California, Berkeley, and its collaborators maintained its measured pace to a determination of who was first to invent CRISPR, and accordingly, who owns this important technology.[7]

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1 *See* Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 344 F.3d 1359 (Fed. Cir. 2003).

2 Dennis Crouch, *Doctrine of Equivalents at the Federal Circuit*, PATENTLY-O (Nov. 22, 2019), https://patentlyo.com/patent/2019/11/doctrine-equivalents-federal.html [https://perma.cc/29JU-24L7].

3 *See* Vanda Pharm., Inc. v. West-Ward Pharm. Int'l Ltd., 887 F.3d 1117 (Fed. Cir. 2018), *cert. denied*, No. 18-817 (Jan. 13, 2020), https://www.supremecourt.gov/docket/docketfiles/html/public/18-817.html [https://perma.cc/8QQT-H375].

4 915 F.3d 743 (Fed. Cir. 2019).

5 *See* Helsinn Healthcare S.A. v. Teva Pharm. USA, Inc., 139 S. Ct. 628 (2019).

6 Idenix Pharm. LLC v. Gilead Scis. Inc., 941 F.3d 1149 (Fed. Cir. 2019).

7 Jon Cohen, *The Latest Round in the CRISPR Patent Battle Has an Apparent Victor, But the Fight Continues*, SCIENCE MAG (Sep. 11, 2020, 6:40 PM), https://www.sciencemag.org/news/2020/09/

Admittedly, choosing the top ten judicial decisions suffers from an inevitable degree of subjectivity. However, we believe these decisions are among the most important decisions of the year in biotechnology patent law even if others might prefer to substitute a case or two for those on our list. All of the decisions discussed in this article were delivered during the 2019 calendar year.[8]

II. TOP TEN BIOTECHNOLOGY PATENT LAW CASES OF 2019

We discuss the top ten biotechnology patent decisions below. These decisions are not presented in any particular order. After consideration of individual judicial decisions, we conclude by suggesting what prospective impact these decisions may have on biotechnology patent law.

*A. *Helsinn Healthcare v. Teva Pharmaceuticals (on-sale bar)*

"Pigs fly!," "Hell has frozen over!," or less dramatically, "Supreme Court affirms Federal Circuit decision!" all would be apt subtitles for any discussion of the Supreme Court's decision in *Helsinn v. Teva*.[9] The question before the Court was whether Congress intended, by passing the Smith-Leahy America Invents Act (AIA), to change the status of "secret" sales so that they would not trigger the on-sale bar of revised Section 102 by adding the phrase "or otherwise known to the public." The Federal Circuit held it had not done so, at least not effectively,[10] and the Supreme Court agreed.[11]

The decision is short (nine pages, with the legal basis of the Court's opinion starting at page five), unanimous (9–0 vote), handed down less than seven weeks after oral argument, and authored by Justice Thomas, who often writes patent law decisions that are not particularly contentious or for which one Justice does not

latest-round-crispr-patent-battle-has-apparent-victor-fight-continues [https://perma.cc/FHV6-BY9W].

[8] Much of the discussion of biotechnology law cases in this article is adapted, with full permission, from case summaries written by Dr. Kevin E. Noonan on his leading biotechnology patent law blog, www.PatentDocs.org. The authors wish to thank Bobbie Jo Horocofsky and Mary Kate Workman for their brilliant research assistance. This article will be published in spring 2021 by the University of New Hampshire Law Review with whose permission the authors make it available in final published form.

[9] *Helsinn*, 139 S. Ct. at 628.

[10] *Id*. at 630.

[11] *Id*.

have a particular interest.[12] By way of reminder regarding the factual predicate of the case, it arose over Hatch-Waxman litigation concerning Teva's intention to market a generic version of Helsinn's intravenous formulations of palonosetron used to reduce chemotherapy-induced nausea and vomiting ("CINV").[13] There were four patents-in-suit: U.S. Patent Nos. 7,947,724, 7,947,725, 7,960,424, and 8,598,219; only the '219 Patent was allowed and granted under the AIA changes in U.S. patent law.[14]

A prior art patent (U.S. Patent No. 5,202,333)[15] taught that palonosetron was useful for treating CINV; the patents-in-suit were directed to novel formulations comprising "unexpectedly low concentrations of palonosetron."[16] Claim 2 of the '725 Patent is representative of the pre-AIA patents-in-suit:

> 2. A pharmaceutically stable solution for reducing emesis or reducing the likelihood of emesis comprising:
>
> a) 0.05 mg/mL palonosetron hydrochloride, based on the weight of the free base, in a sterile injectable aqueous carrier at a pH of from 4.5 to 5.5;
>
> b) from 0.005 mg/mL to 1.0 mg/mL EDTA; and
>
> c) mannitol in an amount sufficient to tonicify said solution, in a concentration of from about 10 mg/ml to about 80 mg/ml.[17]

Claim 1 is representative of the '219 Patent [post-AIA].

> 1. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:
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> palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;
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> from 0.005 mg/mL to 1.0 mg/mL EDTA; and
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> from 10 mg/mL to about 80 mg/mL mannitol,
>
> wherein said formulation is stable at 24 months when stored at room

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[12] *See, e.g.*, Ass'n for Molecular Pathology v. Myriad Genetics Inc., 569 U.S. 576 (providing an example of a Justice Thomas patent opinion).

[13] *Helsinn*, 139 S. Ct. at 630–31.

[14] *Id.* at 631 (discussing U.S. Patent No. 7,947,724 (filed July 21, 2005); U.S. Patent No. 7,947,725 (filed Mar. 24, 2006); U.S. Patent No. 7,960,424 (filed Mar. 24, 2006); and U.S. Patent No. 8,598,219 (filed May 23, 2013)).

[15] *Id.* (referring to U.S. Patent No. 5,202,333 (filed May 22, 1991)).

[16] *Id*.

[17] '725 Patent.

temperature.[18]

"It [was] undisputed that each asserted claim covers the 0.25 mg dose of palonosetron."[19] Helsinn entered into a contract for supplying the claimed formulation prior to the critical date, but contingent on FDA approval (which was not obtained until after the critical date).[20]

The District Court found a sale or offer for sale prior to the critical date, but that the invention was not ready for patenting with regard to the pre-AIA patents, and that the AIA had changed the on-sale bar to require a public sale or offer for sale.[21] Although the existence of the agreement and its terms were publicly known, the parties had not disclosed the 0.25 mg palonosetron dose before the critical date.[22] The District Court thus rejected Teva's invalidity contentions based on the § 102(b) on-sale bar.[23]

The Federal Circuit reversed, in an opinion by Judge Dyk joined by Judges Mayer and Moore.[24] Using the framework set forth by the Court in *Medicines Co. v. Hospira*, the panel found that the invention was "on sale" prior to the critical date by applying "the law of contracts as generally understood" and "those activities that would be understood to be commercial sales and offers for sale 'in the commercial community.'"[25] Under this analysis, the Court had little difficulty deciding that there had been a sale before the critical date.[26] The contingent nature of FDA approval did not refute this conclusion; the Court saying that commercial practices, exemplified by provisions of the Uniform Commercial Code (UCC), contemplate "'purported present sale of future goods . . . [which] operates as a contract to sell,' UCC § 2–105(2)," and that "[a] contract for sale that includes a condition precedent is a valid and enforceable contract."[27] The opinion also cited the Court's own precedent regarding the existence of a sale despite the presence of conditions precedent to commercial transfer of goods, such as *Enzo Biochem, Inc. v. Gen-Probe,*

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18 Helsinn Healthcare S.A. v. Teva Pharm. USA, Inc., 855 F.3d 1356, 1361 (Fed. Cir. 2017).

19 *Id.*

20 *Id.* at 1361–62.

21 *Id.* at 1360.

22 *Id.* at 1363.

23 *Id.*

24 *Helsinn*, 855 F.3d at 1356.

25 *Helsinn*, 855 F.3d at 1364; Kevin E. Noonan, The Medicines Company v. Hospira, Inc. *(Fed. Cir. 2016) (en banc)*, PATENT DOCS (July 12, 2016), https://www.patentdocs.org/2016/07/the-medicines-company-v-hospira-inc-fed-cir-2016-en-banc.html [https://perma.cc/6RGX-Z3LS].

26 *Helsinn*, 855 F.3d at 1364.

27 *Id.* at 1356 (citing BG Grp., PLC v. Republic of Argentina, 134 S. Ct. 1198, 1207 (2014)).

Inc. and *C.R. Bard, Inc. v. M3 Sys., Inc.*[28]

The Court also rejected Helsinn's contention that the AIA changed the on-sale bar calculus to limit its application to public sales.[29] Noting that confidential sales did not *per se* prevent application of the on-sale bar prior to enactment of the AIA, the opinion rejected arguments by Helsinn and *amici* (including the U.S. government) that the AIA changed the law. These assertions were based almost exclusively on statements from the Congressional record (which themselves were directed not to on-sale activities but to public use).[30] It did not help Helsinn's argument in this regard that the panel identified Supreme Court precedent directly contrary to their position, *i.e.*, *Pennock v. Dialogue*, 27 U.S. (2 Pet.) 1, 19 (1829).[31] Accordingly, the opinion stated that "[w]e conclude that, after the AIA, if the existence of the sale is public, the details of the invention need not be publicly disclosed in the terms of sale", and thus, invalidity of the '219 Patent was not properly determined by the District Court.[32]

With regard to the question of whether the invention claimed in the patents-in-suit was "ready for patenting" prior to the critical date, the panel decided that it was, because the invention had been reduced to practice before that date.[33] This decision depended, in part, on the parties' stipulation that "they would contest ready for patenting 'only with respect to the limitations and intended uses of "reducing emesis or reducing the likelihood of emesis" and "to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting "'of the asserted claims' and not 'for any other reason.'"[34] The panel noted that its case law distinguished the standard needed to show reduction to practice with regard to whether a pharmaceutical invention would work for its intended purpose and the standard for FDA approval of a new drug, citing *Scott v. Finney*.[35] Specifically, the standard is that the invention "works for its intended purpose 'beyond a probability of failure' but not 'beyond a possibility of failure.'"[36] The Federal Circuit found the District Court erred by applying the FDA standard rather than the proper patent standard in making its

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[28] *Id.* at 1365–66 (citing Enzo Biochem, Inc. v. Gen-Probe, Inc., 424 F.3d 1276 (Fed. Cir. 2005) and C.R. Bard, Inc. v. M3 Sys., Inc., 157 F.3d 1340 (Fed. Cir. 1998)).

[29] *Id.* at 1369–71.

[30] *Id.* at 1368–69.

[31] *Id.* at 1369.

[32] *Id.* at 1371.

[33] *Id.*

[34] *Helsinn*, 855 F.3d at 1372.

[35] *Id.* (citing Scott v. Finney, 34 F.3d 1058, 1063–64 (Fed. Cir. 1994)).

[36] *Id.* at 1372 (citing *Scott*, 34 F.3d 1062).

erroneous determination that the invention was not "ready for patenting" before the critical date.[37] This conclusion was supported by Helsinn's own documents (including portions of the patents' prosecution histories), pre-litigation statements, and testimony.[38] And the opinion noted that—if the standard applied by the District Court was correct—Helsinn could not have filed a valid application prior to the critical date, and "[s]uch a standard would preclude the filing of meritorious patent applications in a wide variety of circumstances."[39]

The Supreme Court granted *certiorari* to consider the following Question Presented: "Whether, under the Leahy-Smith America Invents Act, an inventor's sale of an invention to a third party that is obligated to keep the invention confidential qualifies as prior art for purposes of determining the patentability of the invention."[40] The Court recognized that it had "never addressed the precise question presented in this case," but voiced its opinion that "our precedents suggest that a sale or offer of sale need not make an invention available to the public."[41] The Court based its decision on the well-established principle that, under prior versions of Section 102, "secret sales" could trigger the on-sale bar.[42] These cases were as recent as *Pfaff* v. *Wells Electronics, Inc.*,[43] and as ancient as a trio of 19th Century cases[44] (although to be honest these cases stand for the proposition that a sale triggers the bar and not the issue of whether the sale was secret or public). The opinion credits the Federal Circuit (saying without apparent irony that that Court "has 'exclusive jurisdiction' over patent appeals, 28 U.S.C. § 1295(a)") with making "explicit what was implicit in our precedents" with regard to the on-sale bar, citing *Special Devices, Inc.* v. *OEA, Inc.*; *Woodland Trust* v. *Flowertree Nursery, Inc.*, in support of its conclusion.[45]

Based on this various precedent, the Court was able to reach the conclusion that Congress did not change what activities raised the on-sale bar which includes secret sales, because there was insufficient evidence of that intent, citing *Shapiro* v. *United*

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37 *Id*. at 1373.

38 *Id*. at 1373–75.

39 *Id*. at 1375.

40 *Helsinn*, 139 S. Ct. at 628, *question presented report*, No. 17-1229 (June 25, 2018).

41 *Id*. at 633.

42 *Id*.

43 525 U.S. 55 (1998).

44 *See* Smith & Griggs Mfg. Co. v. Sprague, 123 U.S. 249 (1887); Elizabeth v. Pavement Co., 97 U.S. 126 (1878); Consolidated Fruit-Jar Co. v. Wright, 94 U.S. 92 (1877).

45 *Helsinn*, 139 S. Ct. at 633 (citing Special Devices, Inc. v. OEA, Inc., 270 F. 3d 1353, 1357 (Fed. Cir. 2001), and Woodland Trust v. Flowertree Nursery, Inc., 148 F. 3d 1368, 1370 (Fed. Cir. 1998)).

States.[46] The Court relied expressly on the Solicitor General's argument that "if 'on sale' had a settled meaning before the AIA was adopted, then adding the phrase 'or otherwise available to the public' to the statute 'would be a fairly oblique way of attempting to overturn' that 'settled body of law.'"[47] In reaching this conclusion, the Court rejected Helsinn's argument, based on the "associated-words canon" of legislative intent, that the effect of construing the statute as Teva advanced—and the Court accepted—would read the amended words out of the statute.[48] The opinion points out that the catch-all phrase "otherwise available to the public" is better interpreted to capture "material that does not fit neatly into the statute's enumerated categories but is nevertheless meant to be covered"; "on-sale" having a defined meaning the Court declined to encompass its proscriptions into what constitutes being on-sale.[49]

The Court also, as can be its wont, waxed somewhat philosophical regarding the limitations on Congressional authority for patenting (reproduced here as a sage reminder of the underpinnings of much of the Court's patent jurisprudence):

> The United States Constitution authorizes Congress "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." Art. 1, § 8, cl. 8. Under this grant of authority, Congress has crafted a federal patent system that encourages "the creation and disclosure of new, useful, and nonobvious advances in technology and design" by granting inventors "the exclusive right to practice the invention for a period of years." *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 151, 109 S.Ct. 971, 103 L.Ed.2d 118 (1989).
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> To further the goal of "motivating innovation and enlightenment" while also "avoiding monopolies that unnecessarily stifle competition," *Pfaff*, 525 U.S., at 63, 119 S.Ct. 304, Congress has imposed several conditions on the "limited opportunity to obtain a property right in an idea," *Bonito Boats, supra*, at 149, 109 S.Ct. 971. One such condition is the on-sale bar, which reflects Congress' "reluctance to allow an inventor to remove existing knowledge from public use" by obtaining a patent covering that knowledge.[50]

Congressman Lamar Smith, the Chairman of the Committee on the Judiciary of the

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[46] *Id*. at 633–34 (citing Shapiro v. United States, 335 U.S. 1, 16 (1948)).

[47] *Id*. at 634.

[48] *Id*.

[49] *Id*.

[50] *Id*. at 632–33. *See Pfaff*, 525 U.S. at 64; *see also* Pennock v. Dialogue, 2 Pet. 1, 19 (1829) (explaining that "it would materially retard the progress of science and the useful arts" to allow an inventor to "sell his invention publicly" and later "take out a patent" and "exclude the public from any farther use than what should be derived under it").

U.S. House of Representatives during the pendency of the AIA, and the lead sponsor of the bill in the House filed an *amicus* brief to the Court explaining Congressional intent, which was unpersuasive to the Court.[51]

The Court's language left the door slightly ajar for a future litigant to distinguish this decision on different facts (for example, where there was *no* disclosure that the agreement existed). The Court was uncharacteristically cautious in its language ("a commercial sale to a third party who is required to keep the invention confidential *may* place the invention 'on sale' under the AIA."). [52] Congress, if sufficiently aggrieved by the Court's dismissal of Congressman Smith's *amicus* brief *explaining* Congressional intent, could decide to include an express provision into the statute overturning this decision. But it is clear that only something that express will be enough to convince the Court that their own and the Federal Circuit's extensive jurisprudence has in fact been discarded by the changes to U.S. patent law occasioned by passage of the AIA.

B. OSI Pharmaceuticals, LLC v. Apotex Inc. (Fed Cir. 2019)

The Federal Circuit overturned an obviousness determination in an *inter partes* review (IPR) proceeding by the Patent Trial and Appeal Board in *OSI Pharmaceuticals LLC v. Apotex Inc.*[53] The Court also reaffirmed its holdings in earlier-decided cases that applying the IPR portion of the Leahy-Smith America Invents Act to patents arising from applications filed before enactment of the AIA is not unconstitutional.[54]

The challenged patent, U.S. Patent No. 6,900,221, was listed in the Orange Book for OSI's cancer treatment Tarceva® (erlotinib), an epidermal growth factor receptor (EGFR) inhibitor used in the treatment of non-small cell lung cancer (NSCLC).[55] The opinion explains that NSCLC was the leading cause of cancer deaths in 2000, amounting to greater than one million cases.[56] At that time, chemotherapy was the standard therapy but was limited by the toxicity of most cancer chemotherapeutic agents, which showed little specificity by killing normal

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51 *See Helsinn*, 139 S. Ct. 628.

52 *Id.* at 630. (emphasis added).

53 939 F.3d 1375 (Fed. Cir. 2019).

54 *Id.* at 1385–86.

55 *Id.* at 1378.

56 *Id.* at 1377.

as well as cancer cells.[57]

Efforts during the timeframe of the earliest claimed priority date of the '221 Patent were directed to EGFR inhibitors, but—importantly for the Court's decision—the opinion notes that "many of these [EGFR inhibitors] failed in clinical trials."[58] One reason for these negative outcomes, according to the opinion, is that "[c]ancer treatment is highly unpredictable" and that while some promising compounds were effective *in vitro*, such successes were "a poor proxy for how effective that drug actually was in treating cancer *in vivo* (i.e., in the body)" (the opinion cites several reasons for these results).[59] The opinion also recites the regulatory hurdles prospective drugs must overcome, and that "[a] great majority of therapies for NSCLC failed in clinical trials"—including the 1631 new drugs for treating NSCLC between 1990 and 2005, and the mere seven that were approved by the FDA, one of which was OSI's erlotinib.[60]

Before the Patent Trial and Appeal Board, Petitioner challenged claims 44–46 and 53 of the '221 Patent for being unpatentable as obvious:

> 44. A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (H[P]V), Barrett's esophagus (pre-malignant syndrome), or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms, and a carrier.
>
> 45. The method of claim 44, wherein the treatment further comprises a palliative or neoadjuvant/adjuvant monotherapy.
>
> 46. The method of claim 44, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).
>
> 53. The method of claim 44 for the treatment of non-small cell lung cancer (NSCLC).[61]

The asserted prior art disclosed "a class of '4-(substituted phenylamino) quinazoline derivatives which are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals" (Schnur); a scientific review article summarizing studies related to cell signaling mechanisms and molecules like EGFR involved therein with

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[57] B.G. Peters, An overview of chemotherapeutic toxicities, *Top Hosp Pharm Manage* 14(2): 59-88 (1994).

[58] *OSI Pharmaceuticals*, 939 F.3d at 1377.

[59] *Id.* at 1377–78 (citing "poor pharmacokinetics due to poor absorption or rapid metabolism (or both), undesirable drug-drug interactions, drug toxicity due to drug binding onto healthy cells, drug toxicity due to binding onto other receptors, and metabolite toxicity").

[60] *Id*. at 1378.

[61] *OSI Pharmaceuticals*, 939 F.3d at 1378–79.

regard to malignant tumors (Gibbs); and OSI's 10-K filing with the Security and Exchange Commission.[62] Schnur discloses 105 different compounds including erlotinib (a "preferred" compound) and that this compound could be used as a treatment for cancers of many tissues, including lung (but not specifically NSCLC).[63] Gibbs discloses that erlotinib was in clinical development with "good anti-cancer activity in preclinical models."[64] The Gibbs reference discloses other references that did not disclose erlotinib for use in treating NSCLC and had no data regarding the use of erlotinib for treating NSCLC.[65] OSI's 10-K discloses the company's efforts to obtain FDA approval of erlotinib for treating NSCLC (as well as several other tumor types).[66] This disclosure was limited to Phase I and Phase II clinical trials, and there were no clinical trial data in the document.[67]

The Board held that "a person of ordinary skill 'would have combined Gibbs or OSI 10-K with Schnur and had a reasonable expectation of success of achieving the invention of challenged claims 44 and 53."[68] Specifically, the Board found that all the limitations of claims 44 and 53 were disclosed in the Schnur reference except treatment of NSCLC with erlotinib. This element of the claims was disclosed in OSI's 10-K or in the Gibbs disclosure that erlotinib "appear[s] to have good anti-cancer activity in preclinical models with an acceptable therapeutic index particularly in patients with non-small cell lung cancer" (albeit without any disclosure of clinical data to support these activities).[69] The Board entered judgment in the IPR that claims 44–46 and 53 were invalid for obviousness, and OSI appealed.[70]

The Federal Circuit reversed, in an opinion by Judge Stoll, joined by Judges Newman and Taranto.[71] While acknowledging that the Board's factual findings were due deferential "substantial evidence" review, citing *Dickinson v. Zurko*, "'[m]ere

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62 *Id*. at 1379–80.

63 *Id*. at 1379.

64 *Id*.

65 *Id*. at 1379–80.

66 *Id*. at 1380.

67 *Id*.

68 *Id*. at 1381.

69 *OSI Pharmaceuticals*, 939 F.3d at 1383 (emphasis omitted).

70 *Id*.

71 *Id*. at 1377.

speculation' is not substantial evidence" according to the opinion.[72] The panel used the District Court standard to illustrate that "substantial evidence is not a fixed quantum of evidence, and may only be determined with respect to the standard of proof"[73] (although the relevance to the issue before the Court is not immediately apparent). Nevertheless, the opinion states that "[t]he same point logically applies to review of the Board's finding."[74] Applying these standards, the panel held that the Board's finding was not supported by substantial evidence because:

> As an initial matter, in reaching its conclusion, the Board misinterpreted the asserted references to teach more than substantial evidence supports. When the references are properly read, the Board's finding that the asserted references provide a reasonable expectation of success also is not supported by substantial evidence. To be clear, the claims require only treatment of a *mammal* with erlotinib—efficacy in humans is not required. But the asserted references do not disclose *any* data or other information about erlotinib's efficacy in treating NSCLC. The record does not contain any clinical (human) data or pre-clinical (animal) data. It does not even include *in vitro* (test tube) data regarding erlotinib's effect on NSCLC. At the same time, it is undisputed that NSCLC treatment was highly unpredictable with an over 99.5% rate of failure for drugs entering Phase II clinical studies. On this record, we are not persuaded that a reasonable factfinder could conclude that a person of ordinary skill would have reasonably expected success based on the combination of Schnur and Gibbs or Schnur and OSI's 10-K.[75]

The opinion then sets out, for each reference, the deficiencies in the Board's understanding of the references and why alone or in combination they don't support an obviousness determination by substantial evidence. Gibbs, according to the panel, is merely a review article with no independent data of its own, and the data of others it does disclose does not include data showing that erlotinib could be used to treat NSCLC.[76] The references cited by Gibbs (who submitted a declaration in support of patentee during the IPR) that disclosed erlotinib did not disclose its use for treating NCSLC, and the references disclosing NSCLC treatments did not disclose erlotinib, according to the opinion.[77]

Turning to the question of whether the cited art would provide the required reasonable expectation of success, the panel held that "properly read" the cited art

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[72] *Id.* at 1382 (citing Dickinson v. Zurko, 527 U.S. 150, 162 (1999), and Intellectual Ventures I LLC v. Motorola Mobility LLC, 870 F.3d 1320, 1331 (Fed. Cir. 2017)).

[73] *Id.* (citing Eli Lilly & Co. v. Aradigm Corp., 376 F.3d 1352, 1363 (Fed. Cir. 2004)).

[74] *Id.* (citing In re Hotels.com, L.P., 573 F.3d 1300, 1302 (Fed. Cir. 2009)).

[75] *Id.* at 1382–83 (emphasis in original).

[76] *OSI Pharmaceuticals*, 939 F.3d at 1383–84.

[77] *Id.*

did not.[78] Regarding the combination of the Schnur and Gibbs references, "the asserted references do not disclose any information about erlotinib's efficacy in treating NSCLC in a mammal," according to the Court.[79] The Schnur reference "fails to disclose any *in vitro* or *in vivo* efficacy data for erlotinib or otherwise suggest the use of erlotinib to treat NSCLC"," and Gibbs, "[p]roperly read in context,[] discloses only that erlotinib inhibits the EGFR and has good anticancer activity in some cancers, *not* including NSCLC."[80] The absence of any data "or other promising information regarding erlotinib's efficacy in treating NSCLC," combined with the "highly unpredictable nature of treating NCSLC" precluded, in the Court's view, these references from providing the skilled worker with a reasonable expectation of success regarding the claimed inventive methods.[81]

With regard to the combination of the Schnur reference and OSI's 10-K document, the Court found fault with the Board's reliance on the existence of Phase I and Phase II clinical trials in the 10-K document—again without any data or reference to data showing that erlotinib could successfully treat NSCLC.[82] The panel also placed the Board's reliance on the 10-K statements in the context of the failure of 1630 putative EGFR-directed anti-cancer compounds (a 99.5% failure rate) and faulted the Board for not considering this evidence when weighing the reasonableness of any likelihood for success the 10-K disclosed information would have had on the skilled artisan.[83] "These references provide no more than hope—and hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art such as this," according to the opinion.[84]

The United States intervened over OSI's other grounds for appeal, questioning the constitutionality of subjecting to *inter partes* review proceedings patents arising from applications filed before passage of the Leahy-Smith America Invents Act.[85] The opinion notes that only after oral argument in this case did the Federal Circuit decide that applying IPR to pre-AIA patents is not a constitutional violation.[86] In

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78 *Id*. at 1384.

79 *Id*.

80 *Id*.

81 *Id*.

82 *OSI Pharmaceuticals*, 939 F.3d at 1385.

83 *Id*.

84 *Id*.

85 *Id*. at 1385–86.

86 *Id*. at 1386 (citing Celgene Corp. v. Peter, 931 F.3d 1342, 1362 (Fed. Cir. 2019), and Arthrex, Inc. v. Smith & Nephew, Inc., 935 F.3d 1319, 1331 (Fed. Cir. 2019)).

the face of this precedent, OSI conceded and the panel entered judgment in accordance with its earlier decisions that applying the IPR statute to pre-AIA patents is not unconstitutional.[87]

*C. *Amgen v Sandoz (en banc)*

The latest chapter (and perhaps last) in the long-running dispute between Amgen and Sandoz over Sandoz's Zarxio® biosimilar to Amgen's Neupogen® biologic drug came to a close when the Federal Circuit affirmed grant of summary judgment against Amgen in *Amgen Inc. v. Sandoz Inc.*[88]

To recap, Amgen's Neupogen® product (filgrastim) is "a recombinant analog of granulocyte-colony stimulating factor ('G-CSF'), a naturally-occurring human glycoprotein that stimulates the production of neutrophils and stem cells and their release into the bloodstream."[89] It is used to treat patients with a deficiency of white blood cells (neutropenia), typically caused by treatment with certain cancer chemotherapeutic agents.[90] In 2014, Sandoz filed an abbreviated biologic license application (aBLA) under the provisions of § 351(k) of the Public Health Service Act (42 U.S.C. §262(k)) for approval of its Zarxio® biosimilar.[91] However, Sandoz refused to comply with provisions of the Biologic Price Control and Innovation Act (BPCIA) requiring a biosimilar applicant to disclose its application and any relevant manufacturing information to reference product sponsor Amgen.[92] Amgen brought suit, but the District Court denied Amgen's motion for preliminary injunction, ruling that such disclosure was not mandatory.[93] Amgen appealed to the Federal Circuit, who in a fractured decision agreed with Sandoz.[94] The Supreme

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87 *Id*.

88 923 F.3d 1023 (Fed. Cir. 2019).

89 *Id*. at 1025.

90 *Id*.

91 *Id*.

92 *Id*.

93 Order on Cross Motions for Judgment on the Pleadings and Denying Motion for Preliminary Injunction, Amgen Inc. v. Sandoz Inc., No. 14-cv-04741-RS (N.D. Cal. Mar. 19, 2015); *see also* Andrew Williams, *Gotta Dance? Apparently Not – A Biosimilar Update*, PATENT DOCS (Mar. 19, 2015), https://www.patentdocs.org/2015/03/gotta-dance-apparently-not-a-biosimilar-update.html [https://perma.cc/TS46-ZLUB].

94 Amgen Inc. v. Sandoz Inc., 794 F.3d 1347, 1350 (Fed. Cir. 2015); *see* Kevin E. Noonan, *Amgen v. Sandoz* (Fed. Cir. 2015), PATENT DOCS (July 22, 2015), https://www.patentdocs.org/2015/07/amgen-v-sandoz-fed-cir-2015.html [https://perma.cc/Y27L-WRUD]; and Kevin E. Noonan, *Federal Circuit Decides* Amgen v. Sandoz *(in an opinion that will make neither party happy)*, PATENT DOCS (July 21,

Court granted *certiorari* and also agreed with Sandoz.[95] And upon remand to the Federal Circuit, Amgen lost any chance of obtaining an injunction on the ground that the state law claims (unfair competition among them) asserted by Amgen were preempted by the BPCIA, which contained no provision for an injunction under these circumstances.[96] During this time, the FDA had approved Zarxio®[97] and Sandoz was marketing the Neupogen® biosimilar.[98]

Amgen pursued its patent case on the merits, asserting U.S. Patent Nos. 6,162,427 and 8,940,878.[99] The '427 Patent is directed to methods for treating patients in need of peripheral stem cell transplantation; Amgen asserted claim 1 in the District Court action:

> 1. A method of treating a disease requiring peripheral stem cell transplantation in a patient in need of such treatment, comprising
>
> administering to the patient a hematopoietic stem cell mobilizing-effective amount of G-CSF; and
>
> thereafter administering to the patient a disease treating-effective amount of at least one chemotherapeutic agent.[100]

The '878 Patent is directed at protein purification methods using adsorbent chromatography; claim 7 was at issue before the District Court:

> 7. A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising:
>
> (a) expressing a protein in a non-native limited solubility form in a non-mammalian cell;
>
> (b) lysing a non-mammalian cell;

2015), https://www.patentdocs.org/2015/07/federal-circuit-decides-amgen-v-sandoz-in-an-opinion-that-will-make-neither-party-happy.html [https://perma.cc/4B4C-36FF].

95 Sandoz Inc. v. Amgen Inc., 137 S. Ct. 1664 (2017); *see* Kevin E. Noonan & Andrew Williams, *Sandoz Inc. v. Amgen Inc.* (2017), PATENT DOCS (June 12, 2017), https://www.patentdocs.org/2017/06/sandoz-inc-v-amgen-inc-2017.html [https://perma.cc/YR5T-EZLL].

96 *Sandoz*, 137 S. Ct. at 1669.

97 *See* Kevin E. Noonan, *FDA Approves Sandoz Filgrastim Biosimilar*, PATENT DOCS (Mar. 8, 2015), https://www.patentdocs.org/2015/03/fda-approves-sandoz-filgrastim-biosimilar.html [https://perma.cc/7KWA-P64A].

98 *See* Kevin E. Noonan, *Sandoz' NEUPOGEN® Biosimilar Now on the Market*, PATENT DOCS (Sept. 7, 2015), https://www.patentdocs.org/2015/09/sandoz-neupogen-biosimilar-now-on-the-market.html [https://perma.cc/XPE9-CPBJ].

99 Amgen Inc. v. Sandoz Inc., No. 14-CV-04741-RS, 2016 WL 4137563, at *1 (N.D. Cal. Aug. 4, 2016) (deciding U.S. Patent No. 8,940,878 (filed June 24, 2010); U.S. Patent No. 6,162,427 (filed Nov. 12, 1998).

100 *Amgen Inc.*, 923 F.3d at 1026 (reviewing '427 Patent).

> (c) solubilizing the expressed protein in a solubilization solution comprising one or more of the following:
>
> (i) a denaturant;
>
> (ii) a reductant; and
>
> (iii) a surfactant;
>
> (d) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following:
>
> (i) a denaturant;
>
> (ii) an aggregation suppressor;
>
> (iii) a protein stabilizer; and
>
> (iv) a redox component;
>
> (e) directly applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;
>
> (f) washing the separation matrix; and
>
> (g) eluting the protein from the separation matrix, wherein the separation matrix is a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.[101]

Central to the issues on appeal was the District Court's claim construction where the Court construed "disease treating-effective amount of at least one chemotherapeutic agent" in claim 1 of the '427 Patent to be limited to "[a]n amount sufficient to treat a disease for which at least one chemotherapeutic agent is prescribed." The Court thereby rejected Amgen's asserted construction that the amount must be merely sufficient to mobilize stem cells regardless of its effect on the underlying disease.[102] Under this construction, Amgen stipulated Sandoz did not infringe claim 1 of the '427 Patent pending appeal to the Federal Circuit.[103]

The District Court construed the terms relating to the "washing" and "eluting" steps of the method claimed in the '878 Patent specifically, subparts (f) and (g)) as being separate steps that required the washing step to be performed before the eluting step.[104] Again, under this construction Amgen conceded it could not prevail on infringement because Sandoz performed these steps concurrently with step (e) (regarding application of the refolding solution).[105] This appeal followed.

The Federal Circuit affirmed, in an opinion by Judge Lourie joined by Judges

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101 *Amgen Inc.*, 923 F.3d at 1026.

102 *Id.* at 1027.

103 *Id.*

104 *Id.*

105 *Id.*

O'Malley and Reyna.[106] Regarding construction of the claims of the '878 Patent, the panel credited Sandoz's argument that the claim "logically requires a series of steps," citing (as did Sandoz) *Mformation Technologies, Inc. v. Research in Motion Ltd.*[107] The Federal Circuit, like the District Court, rejected Amgen's argument that washing and eluting could be performed simultaneously, for example, under circumstances where "washing may occur toward the bottom of the matrix at the same time that elution occurs toward the top."[108] The Court's reasoning was based in part on the ordered (and sequentially lettered) steps (a) through (g), which "logically" implies they be performed in sequence.[109] This ordered performance of the steps was also consistent with how the process was described in the specification.[110]

Having determined that the District Court's construction was correct as a matter of law (and thus that Sandoz process did not literally infringe claim 7 of the '878 Patent, the Federal Circuit then considered infringement under the doctrine of equivalents.[111] Using language that arguably was at least in part responsible for energizing the Supreme Court to review more closely the Federal Circuit's stewardship of the Court's patent jurisprudence (*inter alia*, in *Warner-Jenkinson v. Hilton Davis Chemical Co.* and *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.* almost a generation ago),[112] the panel dismissed Amgen's doctrine of equivalents argument. The panel stated "[t]he doctrine of equivalents applies only in exceptional cases and is not 'simply the second prong of every infringement charge, regularly available to extend protection beyond the scope of the claims.'"[113] More correctly (and less provocatively), the panel based its decision on the sound reasoning that "Sandoz does not infringe claim 7 under the doctrine of equivalents because its one-step, one-solution purification process works in a substantially different way from

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106 *Amgen Inc.*, 923 F.3d at 1024.

107 *Id.* at 1028 (citing Information Technologies, Inc. v. Research in Motion Ltd., 764 F.3d 1392, 1398–1400 (Fed. Cir. 2014) ("a process claim is properly limited to a certain order of steps 'when the claim language, as a matter of logic or grammar, requires that the steps be performed in the order written, or the specification directly or implicitly requires' an order of steps.")).

108 *Id.* at 1028–29.

109 *Id.*

110 *Id.*

111 *Amgen Inc.*, 923 F.3d at 1029.

112 *See* Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17 (1997); *Festo Corp.*, 344 F.3d at 1359.

113 *Amgen Inc.*, 923 F.3d at 1029 (citing its *pre-Warner Jenkinson* precedent in London v. Carson Pirie Scott & Co., 946 F.2d 1534, 1538 (Fed. Cir. 1991).

the claimed three-step, three-solution process" recited in Amgen's claims.[114]

The opinion also rejected Amgen's argument that the District Court abused its discretion in not denying or postponing summary judgment under Federal Rule of Civil Procedure 56(d) because Sandoz "intends" (undisputedly), sometime in an uncertain future, to change its purification protocol to (perhaps) an infringing one, but has provided neither Amgen nor the FDA with details of its plans.[115] As the Court held in *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, while district courts cannot ignore amendments to ANDA or aBLA applications in determining whether there is (artificial) infringement under § 271(e)(2), they also have "a broad mandate to render a 'just, speedy, and inexpensive' decision."[116] The opinion discounted Amgen's argument that failure to postpone judgment would deny them of a remedy if Sandoz changed its process to an infringing one, on the grounds that Amgen could pursue a remedy for infringement to the extent that principles of *res judicata* and collateral estoppel were not violated, citing *Bayer AG v. Biovail Corp.*[117] Under the circumstances before the Court in this case (particularly because the possible changes Sandoz might make would still not result in an infringing process), the Federal Circuit held the District Court did not abuse its discretion in declining to postpone entry of summary judgment.[118] This aspect of the decision highlights a disparity in information first encountered when Sandoz refused to disclose either its aBLA or manufacturing information under Paragraph 2 of the BPCIA (42 U.S.C. § 262 (l)(2)).[119] The District Court (expressly), the Federal Circuit, and the Supreme Court evinced their presumption that all requisite information could be obtained during discovery in an ensuing lawsuit (disregarding the disadvantage their interpretation of the statute propagated regarding *which* patent(s) a reference product sponsor such as Amgen should sue on in the absence of this information).[120] Again, here, the Federal Circuit presumed that Amgen will be able to obtain the information necessary to file a well-pleaded complaint in the event Sandoz begins practicing an infringing version of its purification method. The court's

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114 *Id.*

115 *Id.* at 1029–30.

116 *Amgen Inc.*, 923 F.3d at 1030; *see* Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc., 731 F.3d 1271, 1279–80 (Fed. Cir. 2013) (citing *In re* Micron Tech., Inc., 875 F.3d 1091, 1100 (Fed. Cir. 2017) (quoting Dietz v. Bouldin, 136 S. Ct. 1885, 1891 (2016)).

117 *Amgen Inc.*, 923 F.3d at 1031; *see* Bayer AG v. Biovail Corp., 279 F.3d 1340, 1349–50 (Fed. Cir. 2002).

118 *Amgen Inc.*, 923 F.3d at 1031.

119 *Id.* at 1025.

120 *Sandoz Inc.*, 137 S. Ct. 1664; *Amgen Inc.*, 923 F.3d at 1023; *Amgen Inc.*, 2016 WL 4137563 at *1.

presumption did not address Amgen's argument that there is a possibility that they will not have and will not be able to obtain the information, under circumstances where the Court had at least some leverage to obtain binding representations from Sandoz that this information would be made available should that time come.[121]

Turning to the '427 Patent, the panel also affirmed the District Court's construction of the term "disease treating-effective amount of at least one chemotherapeutic agent" to be limited to "an amount sufficient to treat a disease for which at least one chemotherapeutic agent is prescribed."[122] The Federal Circuit rejected Amgen's argument that the amount need not be effective to treat the underlying disease but only be sufficient to mobilize stem cells in blood or bone marrow.[123] The opinion based this construction on the preamble ("[a] method of treating a disease")"), and (according to the Court) "neither the claim nor the specification lends support to Amgen's interpretation." [124] Under Amgen's construction, the claim would encompass activities directed solely at mobilizing stem cells, which would require the "disease treatment" to correspond to stem cell mobilization *per se*.[125] There is no basis for this interpretation in the panel's view, and thus the Court affirmed the District Court's grant of summary judgment.[126]

Four months later, the Federal Circuit issued an order modifying its opinion to read: "The doctrine of equivalents ~~applies only in exceptional cases and~~ is not 'simply the second prong of every infringement charge, regularly available to extend protection beyond the scope of the claims,'" thus removing the Court's latest provocation of the Supreme Court.[127]

D. Ajinomoto v. ITC

The Federal Circuit again reviewed a determination of infringement under the doctrine of equivalents, in this instance by the International Trade Commission (ITC)—again finding that one of the Supreme Court's exceptions to the preclusive effects of prosecution history estoppel (the "tangential relationship" test) applied—

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121 *Amgen Inc.*, 923 F.3d at 1031.

122 *Id.* at 1027.

123 *Id.*

124 *Id.*

125 *Id.*

126 *Id.* at 1031–32.

127 Order on Petition for Panel Rehearing, Amgen Inc. v. Sandoz Inc., No. 2018-1551 (Fed. Cir. 2019).

and affirmed the ITC's finding of infringement under the doctrine.[128]

Ajinomoto petitioned the ITC under Section 337 (19 U.S.C. § 1337) for an exclusion order against CJ Cheiljedang for importing animal feed-grade L-tryptophan amino acid products produced by several different strains of *Escherichia coli*, which Ajinimoto alleged infringed its U.S. Patent No. 7,666,655.[129] The relevant claim of the '655 Patent (claim 20) is directed to "method[s] for producing an aromatic L-amino acid, which comprises cultivating the bacterium *according to any one of* claims 9–12, 13, 14, 15–18, or 19."[130] With regard to the claimed bacteria, claims 9 and 15 are relevant to the Commission's (and the Court's) decision:

> 9. A recombinant *Escherichia coli* bacterium, which has the ability to accumulate aromatic L-amino acid in a medium, wherein the aromatic L-amino acid production by said bacterium is enhanced by enhancing activity of a protein in a cell of said bacterium beyond the levels observed in a wild-type of said bacterium,
>
> ***[1]*** and in which said protein consists of the amino acid sequence of SEQ ID NO: 2
>
> ***[2]*** and said protein has the activity to make the bacterium resistant to L-phenylalanine, fluoro-phenylalanine or 5[-]fluoro-DL-tryptophan,
>
> ***[3]*** wherein the activity of the protein is enhanced by ***[3a]*** transformation of the bacterium with a DNA encoding the protein to express the protein in the bacterium, ***[3b]*** by replacing the native promoter which precedes the DNA on the chromosome of the bacterium with a more potent promoter, ***[3c]*** or by introduction of multiple copies of the DNA encoding said protein into the chromosome of said bacterium to express the protein in said bacterium.[131]

Claim 15 differs from claim 9 with regard to the protein limitation [1], wherein the protein is limited by nucleotide sequence encoding the amino acid sequence rather claim being limited by the amino acid sequence *per se*; important to the Court's decision is that claim 15 limits the species of nucleotide sequences to those that hybridize to the sequence corresponding to the amino acid sequence under specified hybridization conditions.[132]

The claimed bacteria have been genetically engineered to increase L-aromatic amino acid production by fermentation and in particular production of L-tryptophan.[133] The basis for this increased production depends on an *E. coli* gene,

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128 Ajinomoto Co. v. USITC, 932 F.3d 1342 (Fed. Cir. 2019).

129 *Id.* at 1345 (reviewing U.S. Patent No. 7,666,655 (filed Nov. 25, 2002)).

130 *Id.* at 1346.

131 *Id.* at 1346–47 (boldface numbers were added by the Court in the opinion).

132 *Id.* at 1347.

133 *Ajinomoto*, 932 F.3d at 1346.

yddG, that encodes the YddG protein.[134] This protein is an aromatic amino acid transporter that causes the bacteria to excrete these amino acids into the culture medium.[135] This is achieved in one of three ways: either by introducing (via plasmid transduction) additional copies of the gene into the bacteria ([3a]); integrating additional copies of this gene into the bacterial chromosome ([3b]); or using a transcriptionally "stronger" promoter to express the endogenous *yddG* gene ([3c]).[136]

After an investigation, the Commission found that there were three groups of *E. coli* strains that CJ used to make the imported product:

> "[E]arlier strains" contained both the native *E. coli yddG* gene and the native *E. coli yddG* promoter, except that the first nucleotide of the promoter was changed through chemical mutagenesis, resulting in a stronger promoter . . . a first "later strain," which contained two copies of a *yddG* gene: (1) the native *E. coli yddG* gene with the native *E. coli yddG* promoter; and (2) a non-*E. coli yddG* gene with two promoters—(2a) a native non-*E. coli yddG* promoter and (2b) an *rmf* promoter . . . [and a] second "later strain" which also contained two copies of a *yddG* gene: (1) the native *E. coli yddG* gene with the native *E. coli yddG* promoter; and (2) a codon-randomized non-*E. coli yddG* gene with two promoters—(2a) an *rmf* promoter and (2b) an *rhtB* promoter[; the latter two of these strains first having been used after Ajinomoto brought its complaint].[137]

The Administrative Law Judge (ALJ) made a final initial determination where the phrase, "replacing the native promoter . . . with a more potent promoter" was construed to mean "removing the native upstream region of the *yddG* gene and inserting one of a class of promoters that controls expression of a different gene."[138] Under this construction, the ALJ held that the claims of the '655 Patent were invalid for failure to satisfy the written description requirement of 35 U.S.C. § 112(a) and that the imported products did not infringe the '655 Patent claims, either literally or under the doctrine of equivalents.[139] The full Commission reviewed this decision, affirming the ALJ's claim construction and determination of noninfringement of the imported products made by the earlier strain, and reversing as to the invalidity determination and infringement for products made using the later strains under the doctrine of equivalents.[140] An exclusion order as to the latter two products ensued, and this appeal followed.

The Federal Circuit affirmed the Commission's decision in an opinion by Judge

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134 *Id.*

135 *Ajinomoto Co.*, 932 F.3d at 1346.

136 *Id.*

137 *Id.* at 1347–48.

138 *Id.* at 1348.

139 *Id.*

140 *Ajinomoto Co.*, 932 F.3d at 1348.

Taranto joined in full by Judge Moore; Judge Dyk concurred in part and dissented in part. Beginning with the Commission's claim construction, the panel unanimously affirmed that construction and rejected Ajinomoto's argument that the term "encompasses mutagenesis of individual nucleotides within the native promoter" rather than being limited to replacement of the native promoter with a "stronger" one.[141] The Court found that this construction was supported by the ordinary and customary meaning of the claim language.[142] The opinion asserts that "context matters," stating that "[i]n many contexts, one would not refer to swapping out one small component of a larger unit as 'replacing' the unit or as providing a 'substitute' for the unit, even though the net result is a differently constituted larger unit."[143] This interpretation is consistent with the disclosure in the specification of the '655 Patent, which tellingly does not recite the term "replacing" but does recite the word "substituting," which the Court held was consistent with the Commission's construction of the phrase.[144] And nothing in the prosecution history was to the contrary.[145] The opinion recapped the course of prosecution, amendments, and argument relevant to the construction, saying that even though patent applicants may have restricted the scope of their claims to a greater extent than necessary, "there is no principle of patent law that the scope of a surrender of subject matter during prosecution is limited to what is absolutely necessary to avoid a prior art reference that was the basis for an examiner's rejection."[146] Applying this principle to rejections under § 112, the Court affirmed the Commission's construction.

Turning to the Commission's infringement determinations, the panel agreed that imported product made from CJ's earlier strain did not infringe (either literally or under the doctrine of equivalents) but split on whether product made using either of the later strains infringed under the doctrine of equivalents.[147] With

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141 *Id*.

142 *Id*. at 1349 (using as examples of "replacing" an object "a laptop computer, a bicycle, a sailboat, a blender," comprising an interesting Markush group).

143 *Id.* at 1349.

144 *Id*. (even reciting in an express example that the promoters were substituted).

145 *Id*.

146 *See Ajinomoto Co.*, 932 F.3d at 1351 (citing Norian Corp. v. Stryker Corp., 432 F.3d 1356, 1361 (Fed. Cir. 2005); Biogen Idec, Inc. v. GlaxoSmithKline LLC, 713 F.3d 1090, 1095–96 (Fed. Cir. 2013)); *see also* Donald Zuhn, *Biogen Idec, Inc. v. GlaxoSmithKline LLC (Fed. Cir. 2013)*, PATENT DOCS (April 17, 2013)), https://www.patentdocs.org/2013/04/biogen-idec-inc-v-glaxosmithkline-llc-fed-cir-2013.html [https://perma.cc/569L-6C82].

147 *Id.* at 1348, 1352; see *id.* at 1361 (Dyk, J., concurring in part).

regard to the second of the two later strains, the Commission had "found that the YddG protein encoded by the codon-randomized non-*E. coli yddG* gene of this strain is an equivalent of SEQ ID NO:2" recited in claim 9.[148] CJ challenged this ruling on two grounds: that the amendments made during prosecution raised an estoppel against infringement under the doctrine of equivalents, and that the protein expressed in CJ's second strain failed to satisfy the "structure-way-result" rationale for infringement under the doctrine.[149] Citing *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, the majority recognized three exceptions to the scope of prosecution history estoppel, with the second of these (that "the rationale underlying the amendment may bear no more than a tangential relation to the equivalent in question") being dispositive to the issue before the Court.[150] The basis for the majority's view is that, during prosecution, patentees made an amendment to distinguish over prior art that narrowed the scope of the claim from alternatives to the protein having an amino acid sequence identified as SEQ ID NO: 2 that differed by "deletion, substitution, insertion, or addition of several amino acids."[151] The amendment changed the claim language to recite instead "a protein which comprises an amino acid sequence that is encoded by a nucleotide sequence that hybridizes with the nucleotide sequence of SEQ ID NO:1 under stringent conditions."[152] The majority considered the circumstances "unusual" because "the original claim provided two alternatives; only the second was modified by amendment; and only the first is asserted as the basis for infringement by CJ's second later strain."[153] The standard to apply in determining whether the "tangential relationship" test is adequate to rebut the estoppel "focuses on the patentee's objectively apparent reason for the narrowing amendment."[154] The majority held that Ajinomoto had satisfied this standard:

> The objectively evident rationale for the amendment was to limit the set of proteins within the claim's scope so that it no longer included the prior-art *E. coli* YfiK protein and, more generally, no longer allowed as wide a range of *amino acid* alterations (hence changes in the protein) as original alternative (B), which had allowed "deletion, substitution, insertion or addition of one or several amino acids in the amino acid

148 *Id.* at 1352 (majority opinion).

149 *Id.*

150 *Id.* at 1353–56 (citing *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 740 (2002)).

151 *Id.* at 1353.

152 *Ajinomoto Co.*, 932 F.3d at 1353.

153 *Id.*

154 *Id.* at 1354.

> sequence shown in SEQ ID NO: 2." . . . The reason for the amendment had nothing to do with choosing among several DNA sequences in the redundant genetic code that correspond to the same protein.[155] Indeed, it was undisputed that the non-*E. coli* YddG protein produced without codon randomization remains within the literal claim scope even after the amendment and that the non-*E. coli* YddG protein is identical whether produced from the codon randomized or the non-codon-randomized version of the non-*E. coli yddG* gene.[156]

"Accordingly," according to the opinion, "the reason for the narrowing amendment—limiting the amino-acid makeup of the proteins included in one of the alternatives covered by the claim—is unrelated to differences among the several DNA sequences that encode a given protein."[157]

Regarding CJ's second ground of appeal, the majority further found that the non-*E. coli* YddG protein of CJ's second later strain satisfied the "structure-way-result" test for infringement under the doctrine of equivalents compared to the claimed *E. coli* YddG protein.[158] This conclusion was supported by expert testimony as to the function of the two proteins (as "'export protein[s] that actively export[] aromatic L-amino acids and aromatic L-amino acid analogs' out of the bacterial cell"),"); as was the "way" prong of the test (based on the 85-95% identical structure of the two proteins); and the result (that the consequence of the biochemical activity of each protein was for L-tryptophan to accumulate extracellularly).[159] The majority also rejected CJ's contention that its strains did not become "resistant" to L-tryptophan (*i.e.*, could grow in its absence) based on CJ's own fermentation evidence.[160] The majority found no error in any of these conclusions and thus affirmed the Commission's conclusion that the product produced by CJ's two later bacterial strains infringed under the doctrine of equivalents.[161]

Finally, the panel unanimously held that asserted claim 20 of the '655 Patent was not invalid for failure to satisfy the written description requirement.[162] The panel found that patentees had disclosed a "representative number" of stronger promoters and the person of ordinary skill would be cognizant of other members of

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155 *Id.* at 1355 (citation omitted).

156 *Id.*

157 *Ajinomoto Co.*, 932 F.3d at 1355.

158 *Id.* at 1356.

159 *Ajinomoto Co.*, 932 F.3d at 1356.

160 *Id.* at 1356–57.

161 *Id.*

162 *Id.* at 1358; *see also id.* at 1361 (Dyk, J., concurring in part).

this group from, *inter alia*, prior art disclosures thereof.[163] "[T]he genus of more potent promoters was already well explored in the relevant art by the time of the '655 Patent's invention. In these circumstances, the Commission permissibly found in the specification, read in light of the background knowledge in the art, a representative number of species for the genus of more potent promoters," according to the panel.[164]

Judge Dyk's dissent was limited to the application of the tangential relationship exception to preclude prosecution history estoppel from negating infringement under the doctrine of equivalents.[165] For Judge Dyk, the amendments to the claims of the '655 Patent had a direct relationship to the elements at issue (non-*E. coli* YddG protein of CJ's second later strain), and thus L-tryptophan produced by either of CJ's later two bacterial strains did not infringe under the doctrine.[166]

*E. *iNo Therapeutics LLC v. Praxair Distribution Inc.*

Albert Einstein once famously (albeit perhaps apocryphally) said that "the power of compound interest is the most powerful force in the universe."[167] Not to contradict the creator of 20th Century physics, but it is just as likely that the most powerful force in the universe is the power of unintended consequences. The Federal Circuit illustrated this power in its decision in *iNo Therapeutics LLC v. Praxair Distribution Inc.* with regard to Justice Breyer's exhortation in his *Mayo Collaborative Serv. Inc. v. Prometheus Laboratories, Inc.* opinion, regarding the need to beware of "interpreting patent statutes in ways that make patent eligibility 'depend simply on the draftsman's art' without reference to the 'principles underlying the prohibition against patents for [natural laws].'"[168]

Plaintiffs iNO Therapeutics, LLC; Mallinckrodt Hospital Products Inc.; and Mallinckrodt Hospital Products IP Inc. asserted U.S. Patent Nos. 8,282,966; 8,293,284; 8,795,741; 8,431,163; and 8,846,112, which the opinion "collectively [termed the] 'heart failure patents' or 'HF patents'" against Praxair Distribution Inc. and

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[163] *Id*. at 1358–59 (majority opinion) (four, exactly: P*L* promoter of lambda phage, the *lac* promoter, the *trp* promoter, and the *trc* promoter).

[164] *Id*. at 1359.

[165] *Ajinomoto Co.*, 932 F.3d at 1361 (Dyk, J., concurring in part).

[166] *Id*. at 1361–63.

[167] Allan Roth, *Compound Interest – The Most Powerful Force in the Universe?*, CBS NEWS (June 7, 2011, 9:48 AM), https://www.cbsnews.com/news/compound-interest-the-most-powerful-force-in-the-universe/ [https://perma.cc/7X4E-Z6TX].

[168] 566 U.S. 66, 73 (2012) (citing Parker v. Flook, 437 U.S. 584, 593 (1978); *see generally* 782 Fed. Appx. 1001 (Fed. Cir. 2019).

Praxair Inc.[169] Plaintiffs also asserted U.S. Patent Nos. 8,573,209; 8,776,794; 8,776,795; 9,265,911; and 9,295,802, which the opinion "collectively [termed the] 'delivery system infrared patents' or 'DSIR patents'" and which were directed to devices for administering nitric oxide gas.[170] As explained in the opinion, inhaled nitric oxide (iNO) gas had been "used to treat infants experiencing hypoxic respiratory failure" since at least the early 1990's.[171] However, in certain cases this treatment results in increased pulmonary edema for infants having a congenital defect, left ventricular hypertrophy.[172] The patents-in-suit were directed to methods and a gas delivery device to ameliorate this side-effect, as exemplified by the following claims:

Claim 1 of the '741 Patent:

> 1. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising: (a) *identifying* a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment; (b) *determining* that a first patient of the plurality does not have left ventricular dysfunction; (c) *determining* that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide; (d) *administering 20 ppm inhaled nitric oxide* treatment to the first patient; and (e) *excluding the second patient* from treatment with inhaled nitric oxide, *based on the determination that the second patient has left ventricular dysfunction*, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide.[173]

And claim of the '794 Patent:

> 1. A gas delivery device comprising:
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> *a gas source* to provide therapy gas comprising nitric oxide;
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> a valve attachable to the gas source, the valve including an inlet and an outlet in

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[169] *iNO Therapeutics*, 782 Fed. Appx. at 1002; *see also* U.S. Patent No. 8,846,112 (filed Nov. 21, 2012); U.S. Patent No. 8,795,741 (filed Nov. 21, 2012); U.S. Patent No. 8,431,163 (filed Oct. 15, 2012); U.S. Patent No. 8,293,284 (filed June 22, 2010); U.S. Patent No. 8,282,966 (filed June 22, 2010).

[170] *iNO Therapeutics*, 782 Fed. Appx. at 1002; *see also* U.S. Patent No. 9,295,802 (filed Feb. 24, 2015); U.S. Patent No. 9,265,911 (filed Oct. 29, 2013); U.S. Patent No. 8,776,795 (filed Oct. 29, 2013); U.S. Patent No. 8,776,794 (filed Oct. 29, 2013); U.S. Patent No. 8,573,209 (filed Jan. 6, 2011).

[171] *iNO Therapeutics*, 782 Fed. Appx. at 1002.

[172] *Id.* at 1002–03.

[173] '741 Patent.

> fluid communication and a valve actuator to open or close the valve to allow the gas through the valve to a control module that delivers the therapy gas comprising nitric oxide in an amount effective to treat or prevent hypoxic respiratory failure; and
>
> a circuit including:
>
> a memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration; and
>
> a processor and a transceiver in communication with the memory to send and receive signals to communicate the gas data to the control module that controls gas delivery to a subject and to *verify one or more of the gas identification, the gas concentration and that the gas is not expired*.[174]

The opinion also notes that the Court had earlier affirmed the PTAB's invalidation of the '112 Patent in *inter partes* review.[175] The District Court held the claims of the HF patents to be directed to patent-ineligible subject matter under 35 U.S.C. § 101 and that Praxair did not infringe the claims of the DSIR patents.[176] Mallinckrodt appealed.

The Federal Circuit affirmed-in-part, vacated-in-part, and remanded, in an opinion by Chief Judge Prost joined by Judge Dyk; Judge Newman concurred-in-part and dissented-in-part (but the thrust of her opinion dissented from the majority's routine and now conventional, but not capable of being well-understood, affirmance that the claims were not eligible for patenting under § 101).[177] The Court applied its now well-worn (and unnecessarily expansive) interpretation of the Supreme Court's *Mayo/Alice* test in affirming the District Court.[178] Dissecting the claims in furtherance of its patent-invalidating efforts, the panel majority first states that:

> It is undisputed that treatment of infants experiencing hypoxic respiratory failure with iNO gas has existed for decades. The inventors observed an adverse event that iNO gas causes for certain patients. The patent claim does no more than add an instruction to withhold iNO treatment from the identified patients; it does not recite giving any affirmative treatment for the iNO-excluded group, and so it covers a method in which, for the iNO-excluded patients, the body's natural processes are simply allowed to take place. Consequently, the claim here is directed to the natural phenomenon. The claim,

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[174] *iNO Therapeutics*, 782 Fed. Appx. at 1003–04 (where the italicized limitations are relevant to the Court's decision).

[175] *Id.* at 1002 (citing Praxair Distribution, Inc. v. Mallinckrodt Hospital Products IP Ltd., 890 F.3d 1024, 1028 (Fed. Cir. 2018)); *see also id.* at 1015 n. 1 (Newman, J., concurring in part) (citing *Praxair Distribution*, 890 F.3d 1024).

[176] *Id.* at 1004 (majority opinion).

[177] *See generally iNO Therapeutics*, 782 Fed. Appx. 1001.

[178] *Id.* at 1005.

> apart from the natural phenomenon itself, involves only well-understood, routine, and conventional steps. For the reasons below, claim 1 of the '741 [P]atent fails to recite eligible subject matter.[179]

What follows is the majority's justification for this conclusion. The natural phenomenon is "undisputed" (because the majority defines it as such), the majority saying "[a] neonate patient's body will react to iNO gas in a certain way depending on whether or not the patient has a congenital heart condition called LVD," followed by a recitation of the consequences thereof.[180] The panel majority then parsed the claim language to find that the claims are "directed to" an observation of the natural phenomenon they have defined, because the exclusion (from treatment) step "merely restates the natural law" (nature it seems providing a caregiver who can give the gas as well as knowing without benefit of the invention when to refrain from giving it).[181] According to the majority:

> Properly understood, this added step [characterized by Mallinckrodt as an "exclusion" step] is simply an instruction *not* to act. In effect, the claim is directed to detecting the presence of LVD in a patient and then doing nothing but leaving the natural processes taking place in the body alone for the group of LVD patients. Accordingly, the claim is directed to the natural phenomenon.[182]

And to avoid any correspondence with Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International Ltd.,[183] the majority asserted:

> Indeed, Mallinckrodt cannot dispute that the patented method does not propose a new way of *treating* LVD patients that leverages this discovery (e.g., by titrating the iNO dose).[184] Instead, the claim simply requires that the patient *not* be treated with iNO. This is significant because a claim not to treat—i.e., not to disturb these naturally-occurring physiological processes within the LVD patient's body—risks monopolizing the natural processes themselves.[185]

And returning to the opinion's theme:

> A closer look at the claim language as a whole confirms that the focus of the invention is not on a new way of actually treating the underlying condition of hypoxic respiratory failure. Nor does it recite a way of reducing the risk of pulmonary edema while providing *some* level of treatment to those patients. Rather, the focus of the invention is

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179 *Id.*

180 *Id.* at 1005–06.

181 *See id.* at 1006.

182 *Id.*

183 *See* 887 F.3d 1117 (Fed. Cir. 2018).

184 *iNO Therapeutics*, 782 Fed. Appx. at 1006.

185 *Id.* at 1006–07 (citing *Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743, 752 (Fed. Cir. 2019)).

> screening for a particular adverse condition that, once identified, requires iNO treatment be withheld. A treatment step of administering a prior art dosage is also present. But that step is plainly not the focus of the claimed invention. Mallinckrodt concedes this step is not innovative. Mallinckrodt does not point to "any innovation other than its [purported] discovery of the natural law."[186]

The opinion also cites *Nat. Alternatives Int'l, Inc. v. Creative Compounds, LLC*, and *Endo Pharm. Inc. v. Teva Pharm. USA, Inc.*, in support of the majority's distinction between these claims and what it considers "method of treatment" claims.[187] The panel further distinguished these claims from the patent-eligible claims in *Rapid Litigation Management Ltd. v. CellzDirect, Inc.*, (a decision also written by the Chief)—again on the grounds of "a careful reading of the claim language" in those claims and these.[188]

With regard to the second step of the *Mayo/Alice* test, the panel majority rejected Mallinckrodt's argument that the claims possess an "inventive concept."[189] Following their wont, the majority found nothing sufficiently novel to warrant satisfaction of the second step inquiry.[190] It is a tribute to the essential blurring of statutory lines engendered by Justice Breyer's *Mayo* decision[191] that the discussion revolves expressly on lack of novelty in performing the eligibility analysis.[192] Understandably, the majority took frank recourse to what they perceive to be the parallels between these claims and the claims in *Mayo* to support their decision. And the majority characterized as a "red herring" Mallinckrodt's, contentions that their claims do not entirely preempt the putative natural phenomenon, surprising in view of the role preemption plays in justifying the Supreme Court's eligibility requirements in the first place.[193]

The majority's consideration of infringement of the DSIR patents is more

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[186] *iNO Therapeutics*, 782 Fed. Appx. at 1006–07 (citing Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 915 F.3d 743, 752 (Fed. Cir. 2019)).

[187] *Id.* at 1008 (citing Nat. Alternatives Int'l, Inc. v. Creative Compounds, LLC, 918 F.3d 1338 (Fed. Cir. 2019); Endo Pharm. Inc. v. Teva Pharm. USA, Inc., 919 F.3d 1347 (Fed. Cir. 2019)).

[188] *Id.* at 1008–09 (citing Rapid Litigation Management Ltd. v. CellzDirect, Inc., 827 F.3d 1042 (Fed. Cir. 2016)).

[189] *Id.* at 1010–11.

[190] *Id.* at 1011.

[191] Albeit much less understandable or forgivable when the nation's "patent court" does so.

[192] For example, the opinion states: "[t]his would be quite a different case if the inventors had invented a new way of titrating the dose" and, citing the District Court (which doesn't take a putatively specialized appellate court to do), "[p]laintiffs cannot seriously contend that it is a new practice to exclude certain patients from treatment with a drug when those patients are at an increased risk of experiencing negative side effects from the drug." *See id.* at 1011–12.

[193] *iNO Therapeutics*, 782 Fed. Appx. at 1012.

legally conventional involving Mallinckrodt's disagreement with the District Court's construction of the term "verify" in the phrase "verify one or more of the gas identification, the gas concentration[,] and that the gas is not expired."[194] The majority correctly noted that the District Court didn't formally construe the word—giving it its plain and ordinary meaning.[195] The opinion characterizes this argument as Mallinckrodt "attempt[ing] to undo its loss on infringement by redrawing the metes and bounds of the claim" and finds this effort "unavailing."[196]

Providing one basis for Judge Newman to agree with her colleagues, the opinion reversed a "technical error" by the District Court and remanded for correction of the Court's "clerical error" (specifically, issuing a "blanket" judgment on all the claims of the asserted patents rather than limiting it to the asserted claims).[197]

Judge Newman's dissent is directed to the eligibility portion of the decision. In her view, the inventors observed a natural phenomenon and then developed a treatment method that took advantage of that observation to avoid adverse events.[198] "The method that is described and claimed does not exist in nature; it was designed by and is administered by humans" as the Judge saw things.[199] Procedurally, Judge Newman faults her colleagues because "[t]he majority improperly separates the claims into old and new steps, describes some claim steps as a 'natural phenomenon' and some steps as 'well-understood, routine, and conventional steps,' and avoids the requirement that a claimed invention is considered as a whole."[200] And "[t]oday's change of law adds to the inconsistency and unpredictability of this area of patent-supported innovation."[201] In Judge Newman's view, "the majority's ruling conflicts with extensive precedent" (which she extensively cites) as well as "the national interest":[202]

> The majority [states that] "we emphasize the narrowness of our holding today, which is limited to the particular claims at issue and is driven by the particular circumstances here." This disclaimer appears at the end of a lengthy exposition, whose wide-ranging pronouncements of law and policy are not tied to narrow circumstances or claims. The

194 *Id.*

195 *Id.*

196 *Id.* at 1013.

197 *iNO Therapeutics*, 782 Fed. Appx. at 1014; *see also id.* (Newman, J., concurring in part).

198 *Id.* (Newman, J., concurring in part).

199 *Id.*

200 *Id.*

201 *Id.* at 1015 (Newman, J., concurring in part)

202 *iNO Therapeutics*, 782 Fed. Appx. at 1016–17.

> persistent theme of the majority's analysis is that if a claim contains limitations that concern human physiology, ineligibility arises under section 101, whether or not the claimed method of medical treatment meets the requirement of patentability.[203]

Judge Newman further opined that the majority's broad pronouncement of ineligibility of medical treatment that relates to human physiology not only contravened precedent but contravened the national interest in achieving new methods of medical treatment with the assistance of the patent incentive.[204]

Reaching back more than two centuries, Judge Newman reminded her colleagues that patents do not function to "impede scientific and technological advance," citing *Whittemore v. Cutter*, 29 F. Cas. 1120, 1121 (C.C.D. Mass. 1813); based on common law and statutory research exemptions, citing her dissent in *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 875 (Fed. Cir. 2003); and Giles Sutherland Rich in *Principles of Patentability*, 28 Geo. Wash. L. Rev. 393, 400 (1960) ("It should never be forgotten that *patented* inventions are published and become a part of the technical literature. This publication itself promotes progress in the useful arts and it is the prospect of patent rights which induces disclosure and the issuance of the patent which makes it available.")."[205]

The majority's blessedly non-precedential opinion will bring cold comfort to patent-divested patentees to the extent it leads patent prosecutors to the inevitable conclusion that the Federal Circuit is counseling exactly what Justice Breyer cautioned against in *Mayo*—to beware of the clever draftsman who attempts (or worse, succeeds) in obtaining claims based predominantly on such claim-drafting cleverness.[206] This is not the first time that this has been the outcome of the Federal Circuit's patent eligibility jurisprudence. For example, in *In re Roslin*, Judge Dyk's opinion held patent-ineligible claims to Dolly the sheep which was, after all, just a sheep (notwithstanding being a sheep unlike any sheep that had ever lived).[207] But a careful review of that opinion leads ineluctably to the conclusion that had the draftsman been clever enough (or prescient enough to realize before the fact the quantum and quality of cleverness required) to have claimed a *flock* of genetically

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[203] *Id.* at 1017.

[204] *Id.*

[205] *iNO Therapeutics*, 782 Fed. Appx. at 1017–18 (Newman, J., concurring in part) (citing Integra Lifesciences I, Ltd. v. Merck KGaA, 331 F.3d 860, 875 (Fed. Cir. 2003) (Newman, J., dissenting)); Giles Sutherland Rich, *Principles of Patentability*, 28 Geo. Wash. L. Rev. 393, 400 (1960)).

[206] Mayo Collaborative Services v. Prometheus Laboratories, Inc., 566 U.S. 66, 69 (2013) (citing Parker v. Flook, 437 U.S. 584, 593 (1978)).

[207] *See In re* Roslin Inst. (Edinburgh), 750 F.3d 1333, 1334, 1339 (Fed. Cir. 2014).

identical sheep, the Court's objections to patent ineligibility would have perforce fallen, because it would be undeniable that flocks of genetically identical sheep do *not* occur in nature. This state of affairs is frankly Byzantine and antithetical to Congress's purpose (uniformity and predictability in U.S. patent law) for creating the Federal Circuit, as well as being contrary to the principles of clarity and the creation of "bright line rules" that arguably prompted the Supreme Court to begin its heightened scrutiny of the Court and its opinions (if not philosophy). The Federal Circuit's current path is contrary to the idea that patent claims should be readily understandable to well-intended business people and frank (or in current parlance, "efficient") infringers alike and also contrary to the Founders' attitudes regarding patenting as a way to encourage disclosure of new inventions for the public good. Having such a path will give little relief to those who have lost patent rights under the current regime, but at least it provides a way for inventors to obtain patent-eligible claims no matter what other branches of government do in addressing this issue. Innovation, especially in the diagnostic and life sciences arts, requires no more and is entitled to no less.

*F. *Athena Diagnostics v. Mayo Collaborative Services (February 12, 2019) and (July 3, 2019) (per curiam, from denial for rehearing en banc)*

The Athena case illustrated in the starkest of terms the consequences of the Supreme Court's ill-advised *Mayo*/*Alice* test for subject matter ineligibility and the Federal Circuit's failure to apply the test in a manner that would reign in its innovation-inhibiting effects.[208]

The claims at issue were claims 6–9 of U.S. Patent No. 7,267,820,[209] which recite:

> 6. A method for diagnosing neurotransmission or developmental disorders related to muscle specific tyrosine kinase (MuSK) in a mammal comprising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase (MuSK), wherein said method comprises the steps of: a) contacting said bodily fluid with muscle specific tyrosine kinase (MuSK) or an antigenic determinant thereof; and b) detecting any antibody-antigen complexes formed between said receptor tyrosine kinase or an antigenic fragment thereof and antibodies present in said bodily fluid, wherein the presence of said complexes is indicative of said mammal suffering from said neurotransmission or developmental disorders, wherein said antibody-antigen complex is detected using an anti-IgG antibody tagged or labeled with a reporter molecule, whereby the intensity of the signal from the anti-human IgG antibody is indicative of the relative amount of the anti-MuSK autoantibody in the

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[208] *See generally* Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 915 F.3d 743 (Fed. Cir. 2019), *petition for reh'g denied per curiam*, 927 F.3d 1333 (Fed. Cir. 2019).

[209] *Athena Diagnostics*, 915 F.3d at 746; *see also* U.S. Patent No. 7,267,820 (filed June 15, 2001).

> bodily fluid when compared to a positive and negative control reading.
>
> 7. A method according to claim 1, comprising contacting MuSK or an epitope or antigenic determinant thereof having a suitable label thereon, with said bodily fluid, immunoprecipitating any antibody/MuSK complex or antibody/MuSK epitope or antigenic determinant complex from said bodily fluid and monitoring for said label on any of said antibody/MuSK complex or antibody/MuSK epitope or antigen determinant complex, wherein the presence of said label is indicative of said mammal is suffering from said neurotransmission or developmental disorder related to muscle specific tyrosine kinase (MuSK).
>
> 8. A method according to claim 7 wherein said label is a radioactive label.
>
> 9. A method according to claim 8 wherein said label is I.[210]

These claims were invalidated at the District Court on a motion to dismiss under Fed. R. Civ. Pro. 12(b)(6).[211] This decision was affirmed by a Federal Circuit panel on February 19, 2019, in an opinion by Judge Lourie joined by Judge Stoll and over a vigorous dissent by Judge Newman. As has been the frustrating reality over the course of several years, the majority rendered its decision as being mandated by the Supreme Court's decisions in *Mayo* and *Alice*, despite maintaining a philosophical position that such an application of this jurisprudence was wrong, and inhibited rather than promoted innovation and progress.[212]

It is unnecessary to belabor these opinions by the panel, because the Federal Circuit's salient illustration of the disjointed opinions on its own, and the Supreme Court's eligibility jurisprudence was put on frank and open display when the court, *per curiam*, denied Athena's petition for rehearing *en banc*.[213] This opinion was accompanied by four concurrences and four dissents, representing the thinking of every member of the court. Comparisons of some of the thinking of the judges provides insights into how the members of the Court view their role in the judicial scheme regarding patent law.

Judge Lourie, joined by Judges Reyna and Chen, voiced the view, first enunciated by Judge Linn in *Ariosa Diagnostics, Inc. v. Sequenom, Inc*,[214] that, as an

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210 U.S. Patent No. 7,267,820 (the italicized portions set forth in claim 6 were derived from claims 1, 2, and 3, from which claim 6 ultimately depended).

211 *Athena Diagnostics*, 915 F.3d at 746–47.

212 *See id.* at 749.

213 *See* Donald Zuhn, *Athena Diagnostics, Inc. v. Mayo Collaborative Services, LLC (Fed. Cir. 2019)*, PATENT DOCS (July 09, 2019), https://www.patentdocs.org/2019/07/athena-diagnostics-inc-v-mayo-collaborative-services-llc-fed-cir-2019.html#comments [https://perma.cc/V3JN-3ZHE].

214 Kevin E. Noonan, *Ariosa Diagnostics, Inc. v. Sequenom, Inc. (Fed. Cir. 2015)*, PATENT DOCS (June 22, 2015), https://www.patentdocs.org/2015/06/ariosa-diagnostics-inc-v-sequenom-inc-fed-cir-2015.html [https://perma.cc/TWL2-WCT3].

inferior appellate court, its hands are tied by the Supreme Court's decisions in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*,;[215] *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*,[216] and *Association for Molecular Pathology v. Myriad Genetics, Inc.*[217]:

> If I could write on a clean slate, I would write as an exception to patent eligibility, as respects natural laws, only claims directed to the natural law itself, *e.g.*, $E=mc^2$, F=ma, Boyle's Law, Maxwell's Equations, etc. I would not exclude uses or detection of natural laws. The laws of anticipation, obviousness, indefiniteness, and written description provide other filters to determine what is patentable . . . . But we do not write here on a clean slate; we are bound by Supreme Court precedent.[218]

This view is apparently shared by seven of the Court's twelve members.

Judge O'Malley enunciated the countervailing view regarding what the Court should do to change this state of affairs. In her opinion the Court has gone astray in slavishly and too stringently applying the Supreme Court's precedent to unnecessarily restrict the scope of what is eligible (particularly with regard to diagnostic method claims, including the ones at issue before the Court in *Athena*):

> I agree with all my dissenting colleagues that our precedent applies the Supreme Court's holding in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66, 132 S.Ct. 1289, 182 L.Ed.2d 321 (2012) too broadly. I write separately, however, because I believe that confusion and disagreements over patent eligibility have been engendered by the fact that the Supreme Court has ignored Congress's direction to the courts to apply 35 U.S.C. sections 101, *et seq* ("Patent Act") as written. Specifically, the Supreme Court has instructed federal courts to read into Section 101 an "inventive concept" requirement—a baffling standard that Congress removed when it amended the Patent Act in 1952. I encourage Congress to amend the Patent Act once more to clarify that it meant what it said in 1952.[219]

It is clear that Congress is the ultimate (or perhaps only) solution. But if Judge O'Malley identifies the Federal Circuit's complicity in engendering the current situation, Judge Newman (joined by Judge Wallach) in dissent enumerated the Court's application of Supreme Court precedent to diagnostic method claims, all of

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215 Kwame Mensah, *Mayo Collaborative Services v. Prometheus Laboratories, Inc. (2012)*, PATENT DOCS (Mar. 20, 2012), https://www.patentdocs.org/2012/03/mayo-collaborative-services-v-prometheus-laboratories-inc-2012.html [https://perma.cc/22YS-3Q3C].

216 Kevin E. Noonan, *Supreme Court Issues Decision in Alice Corp. v. CLS Bank*, PATENT DOCS (June 19, 2014), https://www.patentdocs.org/2014/06/supreme-court-issues-decision-in-alice-corp-v-cls-bank.html [https://perma.cc/SS3U-XYJM].

217 Donald Zuhn, *Supreme Court Issues Decision in AMP v. Myriad*, PATENT DOCS (June 13, 2013), https://www.patentdocs.org/2013/06/supreme-court-issues-decision-in-amp-v-myriad.html [https://perma.cc/QU49-GB37].

218 *Athena*, 927 F.3d at 1335 (Lourie, Rena, Chen, JJJ., concurring).

219 *Id*. at 1371 (O'Malley, J., dissenting).

these decisions invalidating the patents at issue:

1. *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation*, 774 F.3d 755 (Fed. Cir. 2014). The claimed invention is a method for screening for genes linked to inherited breast and ovarian cancer, by analyzing for certain mutations in the DNA. The court held the claims ineligible under section 101 as directed to a law of nature, and also held that identifying genetic mutations is an ineligible abstract idea.[220]

2. *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015). The claimed invention is a method for detecting paternally inherited fetal abnormalities by analyzing the blood or serum of a pregnant female. The court held the claims ineligible under section 101, while recognizing that "detecting cffDNA in maternal plasma or serum that before was discarded as waste material is a positive and valuable contribution to science." *Id.* at 1380."[221]

3. *Genetic Technologies Ltd. v. Merial L.L.C.*, 818 F.3d 1369 (Fed. Cir. 2016). The claimed invention is a method for detecting a coding region of DNA based on its relationship to non-coding regions, by amplifying genomic DNA with a primer spanning a non-coding sequence in genetic linkage to an allele to be detected. The court stated that "the patent claim focuses on a newly discovered fact about human biology."[222]

4. *Cleveland Clinic Foundation v. True Health Diagnostics LLC*, 859 F.3d 1352 (Fed. Cir. 2017). The claimed invention is a method for diagnosing risk of cardiovascular disease by analyzing for the enzyme myeloperoxidase ("MPO"). The court held that even though prior methods for detecting MPO were inferior, the discovery of how to directly analyze for MPO, and discovery of the relation to the risk of cardiovascular disease, although "groundbreaking, 'even such valuable contributions can fall short of statutory patentable subject matter.'"[223]

5. *Roche Molecular Systems, Inc. v. CEPHEID*, 905 F.3d 1363 (Fed. Cir. 2018). The claimed invention is a method for detecting the pathogenic bacterium *Mycobacterium tuberculosis* (MTB), based on nucleotide content and a novel method of analysis. The court stated that the method is new, unobvious, and "both faster and more accurate than the traditional MTB detection methods," *id.* at 1366, but held that the method is ineligible

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[220] *Id.* at 1367 (Newman, J., dissenting); *see also* Kevin E. Noonan, *In re BRCA1- and BRCA2-based Hereditary Cancer Test Patent Litigation (Fed. Cir. 2014)*, PATENT DOCS (Dec. 17, 2014), https://www.patentdocs.org/2014/12/in-re-brca1-and-brca2-based-hereditary-cancer-test-patent-litigation-fed-cir-2014.html [https://perma.cc/W2L7-UBF3].

[221] *Athena*, 927 F.3d at 1367 (Newman, J., dissenting); *see also* 788 F.3d 1371 (Fed. Cir. 2015).

[222] *Athena*, 927 F.3d at 1367 (Newman, J., dissenting); *see also* Kevin E. Noonan, *Genetic Technologies Ltd. v. Merial L.L.C. (Fed. Cir. 2016)*, PATENT DOCS (Apr. 10, 2016), https://www.patentdocs.org/2016/04/genetic-technologies-ltd-v-merial-llc-fed-cir-2016.html [https://perma.cc/V6A6-NMWG].

[223] *Athena*, 927 F.3d at 1367 (Newman, J., dissenting); *see also* Kevin E. Noonan, *Cleveland Clinic Foundation v. True Health Diagnostics LLC (Fed. Cir. 2017)*, PATENT DOCS (June 26, 2017), https://www.patentdocs.org/2017/06/cleveland-clinic-foundation-v-true-health-diagnostics-llc-fed-cir-2017.html [https://perma.cc/QTM9-G9A5].

under section 101.[224]

> 6. *Cleveland Clinic Foundation v. True Health Diagnostics LLC*, 760 F. App'x 1013 (Fed. Cir. 2019). The claimed invention is the novel immunoassay to detect the correlation between blood MPO levels and cardiovascular disease. The court held that the claims are for a law of nature and ineligible under section 101.[225]

Conversely, as Judge Newman notes in her dissent, the Federal Circuit has repeatedly affirmed eligibility of "method of treatment" claims, in *Rapid Litigation Management Ltd. v. CellzDirect, Inc.*; *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International Ltd.*; *Natural Alternatives Int'l, Inc. v. Creative Compounds, LLC*; and *Endo Pharmaceuticals Inc. v. Teva Pharmaceuticals USA, Inc.*[226]

Both Judge Moore (writing in dissent) and Judge Chen (concurring) also recognize the problematic nature of the Court's jurisprudence on patent eligibility. And each agree with Judge O'Malley' that Congress alone can address the issue, Judge Moore stating that:

> In the wake of *Mayo*, we have painted with a broad brush, suggesting that improved diagnostic techniques are not patent eligible. *Mayo* did not go so far, and given the import of diagnostic techniques, we should reconsider this case and clarify our precedent. Because my colleagues have declined to do so, there are no more options at this court for diagnostic patents. 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.[227]

Judge Hughes, joined by Chief Judge Prost and Judge Taranto, concurred with the *per curiam* denial of *en banc* review, albeit not without some reservations:

> I, for one, would welcome further explication of eligibility standards in the area of diagnostics patents. Such standards could permit patenting of essential lifesaving

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224 *Athena*, 927 F.3d at 1367–68 (Newman, J., dissenting); *see also* Kevin E. Noonan, *Roche Molecular Systems, Inc. v. Cepheid (Fed. Cir. 2018)*, PATENT DOCS (Oct. 10, 2018), https://www.patentdocs.org/2018/10/roche-molecular-systems-inc-v-cepheid-fed-cir-2018.html [https://perma.cc/7H2C-D2H9].

225 *Athena*, 927 F.3d at 1368 (Newman, J., dissenting) (including *Athena* there are seven such cases); *see also* Donald Zuhn, *Cleveland Clinic Foundation v. True Health Diagnostics LLC (Fed. Cir. 2019)*, PATENT DOCS (Apr. 07, 2019), https://www.patentdocs.org/2019/04/cleveland-clinic-foundation-v-true-health-diagnostics-llc-fed-cir-2019.html [https://perma.cc/3MML-W2VL].

226 *Athena*, 927 F.3d at 1368 (Newman, J., dissenting) (citing 827 F.3d 1042 (Fed. Cir. 2016); 887 F.3d 1117 (Fed. Cir. 2018); 918 F.3d 1338 (Fed. Cir. 2019); 919 F.3d 1347 (Fed. Cir. 2019).

227 *Athena*, 927 F.3d at 1362 (Moore, J., dissenting).

> inventions based on natural laws while providing a reasonable and measured way to differentiate between overly broad patents claiming natural laws and truly worthy specific applications. Such an explication might come from the Supreme Court. Or it might come from Congress, with its distinctive role in making the factual and policy determinations relevant to setting the proper balance of innovation incentives under patent law.[228]

Judge Chen also concurred:

> When it comes to applying the judicial exceptions, it bears noting that the *Mayo* analytical approach is considerably harder to apply consistently than the *Diehr* framework, and more aggressive in its reach. Consider the claim in *Mayo*. If that claim had recited just the single step of administering a synthetic drug to a patient, that single-step claim would be patent-eligible, but lack novelty under § 102. And if that claim added a second step for determining the subsequent level of a non-naturally occurring metabolite in a patient, that claim also would pass muster under § 101, but lack novelty. But when the claim further recites a relationship between a metabolite level and its efficacy in a patient, that claim suddenly would be invalid under § 101 for violating the law of nature exception. In other words, steps 1 and 2 now get pushed aside and declared insignificant, and the last step is designated as the "focus" of the claim, *i.e.*, the heart of the invention. The notion that adding claim language can convert an otherwise patent-eligible claim into a patent-ineligible claim is counterintuitive and a very difficult thing to explain to 8,000 patent examiners. Moreover, the process of determining what the claim is "really about" when the claim is viewed in pieces, rather than as a whole, can be highly subjective and impressionistic.[229]

Judge Dyk wrote most extensively, joined by Judge Hughes and in part by Judge Chen. Informative nuggets of this opinion include:

> [T]here is tension between *Mayo* and the Supreme Court's later decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 133 S.Ct. 2107, 186 L.Ed.2d 124 (2013), and that the holding of *Mayo* may be overbroad. The language of § 101 does cover "discover[ies]," 35 U.S.C. § 101, and there is no doubt that determining the relationship between specific genetic abnormalities and specific diseases constitutes an important discovery with proven utility. There is much to be said for the patentability of claims to such discoveries, if not drafted overbroadly.[230]

But he also sees some benefits in the Court's approach to subject matter eligibility:

> In the realm of abstract ideas, the *Mayo/Alice* framework has successfully screened out claims that few would contend should be patent eligible, for example, those that merely apply well-known business methods and other processes using computers or the Internet. The *Mayo/Alice* framework has thus proven to be both valuable and effective

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228 *Id.* at 1337 (Hughes, J., concurring).

229 *Id.* at 1348–49 (Chen, J., concurring).

230 *Id.* at 1340 (Dyk, J., concurring).

> at invalidating overly broad, non-inventive claims that would effectively "grant a monopoly over an abstract idea."[231]

Judge O'Malley provided an additional avenue for Congressional intervention. The Judge notes the Supreme Court's resurrection of the "inventive concept" trope, which many believed was relegated to the dustbin of history by Section 103 in Giles Sutherland Rich's revision resulting in the 1952 Patent Act.[232] She provides an alternative to Senator Tillis' and Coons' proposed statutory abrogation of the judicial exceptions (which raises its own issues on Congressional authority and the Supreme Court's oversight on *ultra vires* legislative actions). Judge O'Malley's suggestion is direct:

> Had the Supreme Court not disregarded Congress's wishes for a second time [by introducing "inventive concept" into its Section 101 calculus], perhaps the outcome in this case would be different. . . . Indeed, claims directed to uses of natural laws rather than the natural laws themselves would be eligible under § 101 as written. Because the Supreme Court judicially revived the invention requirement and continues to apply it despite express abrogation, I dissent to encourage Congress to clarify that there should be no such requirement read into § 101; to clarify that concepts of novelty and "invention" are to be assessed via application of other provisions of the Patent Act Congress designed for that purpose.[233]

And Judge Moore is characteristically direct in setting forth the consequences of the Federal Circuit's refusal to consider the eligibility of Athena's claims *en banc*:

> 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 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.[234]

For those keeping score, it appears that all (or almost all) of the members of the Court believe that their patent eligibility cases have been wrongly decided. Chief Judge Prost, joined by Judges Lourie, Dyk, Reyna, Hughes, Taranto, and Chen, believe the Court's hands are tied by Supreme Court precedent, while Judges Newman, Moore, O'Malley, Wallach, and Stoll believe the Federal Circuit has the basis to distinguish Supreme Court precedent and hold these claims (or at least

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231 *Id.* at 1337.

232 *See Athena*, 927 F.3d at 1371 (O'Malley, J., dissenting).

233 *Id.* at 1373.

234 *Id.* at 1363 (Moore, J., dissenting).

claims 7–9 of Athena's claims at issue) are patent eligible.

The issue for the Federal Circuit is not just that their views are so fractured, but that the dissension between the Judges has precluded the benefits envisioned when the Federal Circuit was created. The Judges apparently cannot decide whether they should simply apply Supreme Court precedent (even incorrectly) until such time as the Supreme Court deigns to address the issue, or whether their "special expertise" and Congressional mandate creates a responsibility to distinguish the Supreme Court's precedent when it does not properly apply. And the dissension prevents the Court from at least providing incentive to the Supreme Court to provide (in its view) the correct interpretation of what is and what is not patent eligible. In at least the view of five of the judges (and many in the patent bar) the Federal Circuit has failed in exercising its responsibility, to the extent that many openly speculate whether U.S. patent law needs the Federal Circuit at all.

G. Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals Int'l. Ltd. (Fed Cir. 2018)

The Federal Circuit's decision in *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals Int'l. Ltd.* that the method of treatment claims were likely to be patent eligible provided a ray of hope with regard to the fraught nature of subject-matter eligibility in life sciences patenting.[235]

The case arose in ANDA litigation over Vanda's methods for treating schizophrenia with Fanapt® (iloperidone), particularly directed to adjusting (reducing) dosages in patients expressing a variant of a cytochrome P450 2D6 gene (CYP2D6) that metabolizes this and other drugs more poorly than other alleles of the gene. [236] This genotype is significant because it is associated with a predisposition to cause QT_c prelongation, a condition that can result in serious heart problems.[237] On inspection, the parallels with the facts in *Mayo Collaborative Services v Prometheus Labs* are evident.

Vanda asserted two patents, Reissue Patent RE 39,198 and U.S. Patent No. 8,586,610, The '610 Patent issued after ANDA litigation had been initiated over the '198 Patent and expires significantly later. This procedural posture raised a jurisdictional issue over whether the District Court could include this patent in the ANDA litigation (the Federal Circuit ruled that it could).[238]

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[235] *See generally Athena*, 927 F.3d 1333; *see generally* 887 F.3d 1117 (Fed. Cir. 2018).

[236] *Id.* at 1122.

[237] *Id.* at 1121.

[238] *Vanda*, 887 F.3d 1120–22; *see also* U.S. Patent No. 8,586,610 (filed Sep. 30, 2005); U.S. Patent No. RE 39,198 (filed Nov. 15, 2000).

Claim 1 of the '610 Patent was considered representative by the Court:

> A method for treating a patient with iloperidone, wherein the patient is suffering from schizophrenia, the method comprising the steps of:
>
> determining whether the patient is a CYP2D6 poor metabolizer by:
>
> obtaining or having obtained a biological sample from the patient;
>
> and
>
> performing or having performed a genotyping assay on the biological sample to determine if the patient has a CYP2D6 poor metabolizer genotype; and
>
> if the patient has a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount of 12 mg/day or less, and
>
> if the patient does not have a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day,
>
> wherein a risk of QTc prolongation for a patient having a CYP2D6 poor metabolizer genotype is lower following the internal administration of 12 mg/day or less than it would be if the iloperidone were administered in an amount of greater than 12 mg/day, up to 24 mg/day.[239]

The District Court found the '198 and '610 Patents not invalid and the '198 Patent infringed by West-Ward's ANDA filing under 35 U.S.C. § 271(e)(2.). West-Ward also was liable of inducing infringement under 35 U.S.C. § 271(b). Infringement was dependent on West-Ward's proposed label, which was substantially identical to Vanda's Fanapt® label and recited a "recommendation" that (1) "practitioners use iloperidone to treat patients suffering from schizophrenia"; (2) "oral administration of iloperidone tablets at 12 to 24 mg/day to nongenotypic CYP2D6 poor metabolizers and 12 mg/day or less to genotypic CYP2D6 poor metabolizers"; and (3) "practitioners perform or have performed a genotyping assay to determine whether patients are CYP2D6 poor metabolizers." [240]

Regarding West-Ward's invalidity contentions, the District Court rejected challenges based on §§ 101, 103, and 112(a) (written description). Specifically with regard to subject-matter eligibility, the District Court held that while the asserted claims depended upon laws of nature they were not directed to those laws. They thus satisfied the subject matter eligibility requirements under the Supreme Court's *Mayo*/*Alice* test:

> First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. If so, we then ask, "[w]hat else is there in the claims before us?" To answer that question, we consider the elements of each claim both individually and "as an ordered combination" to determine whether the additional elements "transform the

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239 *Vanda*, 887 F.3d at 1121.

240 *Id*. at 1122–23.

> nature of the claim" into a patent-eligible application. We have described step two of this analysis as a search for an "inventive concept"— *i.e.*, an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."[241]

Finally, the District Court held that the provisions for delaying FDA approval until after expiration of patents asserted in ANDA litigation under 35 U.S.C. § 271(e)(4)(A) were not available remedies for infringement of the '610 Patent under 35 U.S.C. § 271(b). Therefore, the court was able to exercise its "general equitable power" to impose an equivalent injunction.[242]

The Federal Circuit affirmed, in an opinion by Judge Lourie joined by Judge Hughes, with Chief Judge Prost dissenting on the subject-matter eligibility question. The opinion affirmed the resolution of the procedural issues that had arisen in the ANDA litigation context and the District Court's determination that the asserted claims were not invalid under §§ 103 and 112(a).[243] But it is the majority's opinion on the § 101 question that is of particular interest here.

Judge Lourie refuted West-Ward's analogy of these claims to the claims in *Mayo* ("This case, however, is not *Mayo*"). First, in his view the Mayo claims "were not directed to a novel method of treating a disease," but rather they "were directed to a diagnostic method based on the 'relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm.'"[244] The Supreme Court interpreted the *Mayo* claims to merely recite a relationship that is "a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes. And so a patent that simply describes that relation sets forth a natural law."[245] Importantly, the opinion notes the distinction that the *Mayo* claims "w[ere] not directed to the application of a drug to a particular disease" (again, the administering step being well-known in the art).[246] And even the Supreme Court in its *Mayo* decision recognized the distinction between the *Mayo* claims and "method of [medical] treatment" claims here, wherein the Supreme Court stated "[u]nlike,

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241 *Id.* at 1133–34 (citing *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (citations omitted) (alteration in original) (quoting *Mayo*, 566 U.S. at 72-73, 75-79))).

242 *Id.* at 1123.

243 *See id.* at 1123, 1136, 1140.

244 *Vanda Pharm.*, 887 F.3d at 1134 (The frank reliance on other sections of the patent statute in arriving at eligibility determinations, while once jarring and even now of dubious doctrinal provenance should be expected by now).

245 *Id.*

246 *Id.*

say, a typical patent on a new drug or a new way of using an existing drug, the patent claims do not confine their reach to particular applications of those laws."[247]

Here, the majority notes, while the inventors recognized the relationships between "iloperidone, CYP2D6 metabolism, and QTc prolongation," that is not what they claimed; "[t]hey claimed an application of that relationship."[248] The majority recognizes this to be an example of "a new way of using an existing drug" that had received, albeit in *dicta*, the Supreme Court's imprimatur of eligibility in *Mayo*.[249] The opinion also notes that the claims at issue here do not implicate undue preemption that was a concern (perhaps *the* concern) in *Mayo*, because the Mayo claim was *not* a treatment claim and could (at least in theory) be infringed even if a doctor did not change treatment decisions as a consequence of practicing the claimed method.[250] This distinction was significant for the court because it "did not involve doctors *using* the natural relationship between the metabolite level and lessening 'the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm.'"[251]

The majority found support for these distinctions in the court's *Rapid Litigation Management v. Cellzdirect* opinion.[252] There, "a method of producing a desired preparation of multi-cryopreserved hepatocytes cells" was determined to be patent eligible because it employed "the natural ability of the subject matter to *undergo* the process," which did not make those claim "directed to" the natural phenomenon under the *Mayo*/*Alice* principles.[253]

The crux (and perhaps the genius) of Judge Lourie's distinctions between the invention claimed by Vanda and the patent-ineligible claims in *Mayo* is best identified by a litany of specificities. Namely, "the claims here are directed to a *specific* method of treatment for *specific* patients using a *specific* compound at *specific* doses to achieve a *specific* outcome (emphases added)."[254]

The panel majority held that these claims recited more than the natural relationship, in distinction with *Mayo*, but rather a method of using these relationships to treat patients, beneficially reducing the risk of developing

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247 *Id*. at 1134–35.

248 *Vanda Pharm.*, 887 F.3d at 1135 (reviewing U.S. Patent No. 8,586,610 (filed Sep. 30, 2005)).

249 *Id.*

250 *Id.*

251 *Id.*

252 *Vanda Pharm.*, 887 F.3d at 1142 (citing Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc., 827 F.3d 1042, 1049 (Fed. Cir. 2016)).

253 *See id*. at 1142–43.

254 *Id*. at 1136.

treatment complications.[255]

Chief Judge Prost did not see these distinctions and believed that these claims were indistinguishable from the claims in *Mayo* and hence should be patent-ineligible.[256]

The Supreme Court denied *certiorari*; thus, for now, method of medical treatment claims fall outside the proscription on life sciences patenting as applied, for example, to diagnostic method claims (see, *Athena Diagnostics*).[257]

*H. *Idenix Pharma v. Gilead Sciences*

Section 112 of the Patent Act as codified, entitled "Specification" in the statute, specifies the amount of disclosure required to support a patent claim, among other requirements.[258] Section 112(a) contains three requirements: written description, enablement, and best mode.[259] In *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, the Federal Circuit held that Idenix's patent was invalid on two grounds, affirming the District Court's overturning of a jury verdict on enablement and the District Court's post-trial denial of judgment as a matter of law (JMOL) regarding satisfaction of the written description requirement.[260] In doing so, the Court illustrated ways in which it has been able to impose its views on both aspects of Section 112 requirements despite its reliance on fact finding by the jury or district court below (with Judge Newman characteristically dissenting from what she viewed as appellate court overreach by her brethren).[261]

The case arose in litigation over Idenix's U.S. Patent No. 7,608,597 that was directed to drugs for treating hepatitis C virus (HCV), which Idenix alleged Gilead would infringe by launch of its sofobuvir (Solvadi®) HCV treatment.[262] Independent claim 1 of the '597 Patent is representative of Idenix's invention: "1. A method for the treatment of a hepatitis C virus infection, comprising administering an effective amount of a purine or pyrimidine β-D-2'-methyl-ribofuranosyl nucleoside or a phosphate thereof, or a pharmaceutically acceptable salt or ester

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255 *Id.* (reviewing '610 Patent).

256 *Id.* at 1143 (Prost, J., dissenting) (reviewing '610 Patent).

257 *Athena*, 915 F.3d at 750.

258 35 U.S.C. § 112 (2012).

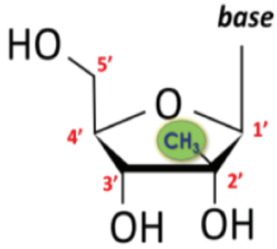
259 *Id.* § 112(a) (although the latter has been in something of a state of limbo since the Leahy-Smith America Invents Act (AIA) disabled it as a defense).

260 *See generally Idenix Pharm.* 941 F.3d 1149.

261 *Id.* at 1154, 1163, 1166 (Newman, J., dissenting).

262 *Id.* at 1153 (reviewing U.S. Patent No. 7,608,597 (filed June 20, 2003)).

thereof."[263] The opinion illustrates the structure of the purine or pyrimidine β-D-2'-methyl-ribofuranosyl nucleoside as disclosed in the '597 Patent:



which differs from naturally occurring embodiments by the substitution of a methyl group at the 2' position on the ribofuranosyl sugar, *cis* to the nitrogenous base (or in the "up" position as understood by the Federal Circuit).[264] Gilead argued (and the District Court and Federal Circuit agreed) that the '597 Patent specification did not provide guidance regarding the "billions" of possible molecules falling within the scope of the claims.[265] This argument was based on the acknowledged difference between the compounds exemplified in the '597 Patent (having a hydroxyl, -OH, group at the 2' "down" position), while Gilead's accused infringing compound had a fluorine atom at that position.[266] After protracted ("years," according to the opinion) litigation, the District Court conducted a jury trial in which Gilead conceded infringement but challenged the '597 Patent claims as failing to satisfy the Section 112(a) enablement requirement.[267] This trial resulted in a jury verdict that Idenix's '597 Patent claims were not invalid for lack of enablement under Section 112(a).[268] The Court granted Gilead's JMOL motion overturning the jury's verdict but denied Gilead's JMOL motion that the claims were invalid for failing to satisfy the written description requirement.[269] This appeal followed.

The Federal Circuit affirmed the District Court's JMOL decision on enablement and reversed the District Court's denial of JMOL on written description, in an opinion by Chief Judge Prost joined by Judge Wallach; Judge Newman dissented.[270] The majority rendered its decision under the *de novo* review standard applied to JMOL motions, which permitted the appellate panel to more easily dismiss the jury's

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263 U.S. Patent No. 7,608,597 (filed June 20, 2003).

264 *Idenix Pharm.*, 941 F.3d at 1155 (reviewing U.S. Patent No. 7,608,597 (filed June 20, 2003)).

265 *Id.*

266 *Id.*

267 *Id.* at 1161.

268 *Id.* at 1153.

269 *Idenix Pharm.*, 941 F.3d at 1153.

270 *See id.* at 1149, 1166 (Newman, J., dissenting).

factual determinations.[271] The majority opinion characterized the issue before the Court as "whether a person of ordinary skill in the art would know, without undue experimentation, which 2'-methyl-up nucleosides would be effective for treating HCV."[272] The majority held that the answer to this question is no, because "a reasonable jury would not have had a legally sufficient basis to find otherwise."[273] The opinion rendered its decision by applying the factors delineated in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988): (1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention.[274]

For context in appreciating how the majority applied the *Wands* factors, it is relevant to consider that the chemical arts have traditionally been considered unpredictable as compared with, for example, mechanical inventions. A mechanical device comprising a fastener, for example, could have as embodiments a handful of alternatives (*e.g.*, a screw, a nail, a rivet, a bolt, glue, Velcro®). Chemical compounds, in contrast, can have a multiplicity of substituents at a multiplicity of positions in a molecule, wherein the permutations can quickly exceed hundreds of thousands to millions, while but a few hundred exemplary compounds are disclosed in the specification.[275] The biotechnological arts are even more complex, for at least two reasons. First, the molecules are even larger and have the capacity for additional substitutions, and the effects of those substitutions on function of biological molecules are themselves unpredictable.[276] These scientific facts engendered the Federal Circuit's explication of the application of the written description requirement of Section 112 that culminated in the Court's *en banc Ariad v. Eli Lilly* decision (as well as earlier promulgation of Guidance from the U.S. Patent and Trademark Office in 2001).[277] Paradoxically, biotechnology patents (unlike chemical patents) do not disclose hundreds of exemplars (and frequently only one

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[271] *Id.* at 1154.

[272] *Id.* at 1156.

[273] *Id.*

[274] *Id.*

[275] *See id.* at 1157.

[276] *See Idenix Pharm.*, 941 F.3d at 1161.

[277] *See Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1357-58 (Fed. Cir. 2010); Kevin E. Noonan, *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co. (Fed. Cir. 2010) (en banc)*, PATENT DOCS (Mar. 22, 2010), https://www.patentdocs.org/2010/03/ariad-pharmaceuticals-inc-v-eli-lilly-co-fed-cir-2010-en-banc.html. [https://perma.cc/K4EZ-TX6Q].

or a few), which has led to the scope of biotechnology claims to be relatively narrow.[278]

These considerations provide an opportunity for the Federal Circuit to apply the factors set out in *Wands* stringently to find failure to satisfy the enablement requirement of Section 112(a), as the Court did here. Going in order, the majority agreed with the District Court that the amount of experimentation required to support the "billions and billions" of putative species was high, supported by Gilead's expert testimony.[279] The District Court and the majority held that experimentation was too high even if mitigating circumstances would have presented a much smaller number of species (thousands) to the person of ordinary skill in the art.[280] This aspect of Idenix's argument was contradicted by its own evidence that "the field of modifying nucleosides for anti-HCV activity was 'in its infancy' and 'unpredictable.'"[281] This conclusion was also supported by evidence that "many" of the candidate nucleosides would need to be synthesized because they were not commercially available, although the majority acknowledges that such synthesis was routine.[282]

The majority then turned to the "working examples" and "amount of guidance" factors, which the opinion not surprisingly held supported non-enablement.[283] The opinion asserts in support of this conclusion that "Claim 1 requires more than just an identification of 2'-methyl-up: it requires identification of which 2'-methyl-up nucleosides will effectively treat HCV" and that "[w]ithout specific guidance on that point, the specification provides 'only a starting point, a direction for further research.'"[284] The (un)predictability prong of the factors was supported by trial testimony from both parties' experts, and the claim scope prong (essentially overbreadth) followed from the majority's conclusions regarding the rest of the factors.[285] The opinion's discussion characterized the situation as the person of skill in the art "the 'large number' of 2'-methyl-up nucleosides falls into the 'small' group of candidates that effectively treats HCV."[286]

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278 *See Idenix Pharm.*, 941 F.3d at 1161.

279 *See id.* at 1157.

280 *See id.*

281 *Id.* at 1159.

282 *Id.*

283 *Id.* at 1160.

284 *Idenix Pharm.*, 941 F.3d at 1160 (citing ALZA Corp. v. Andrx Pharms., LLC, 603 F.3d 935, 941 (Fed. Cir. 2010)) (reviewing '597 Patent).

285 *Id.* at 1160–61.

286 *Id.* at 1162.

As a consequence of these analyses, the majority readily concluded that the District Court correctly granted JMOL because no reasonable jury could conclude anything other than that Idenix did not satisfy the written description requirement.[287] The opinion notes that their decision has "striking similarities" to *Wyeth and Cordis Corp. v. Abbott Laboratories* based on the "millions of compounds made by varying the substituent groups" in that case wherein "only a 'significantly smaller' subset of those compounds would have the claimed 'functional effects.'"[288] The opinion says that the decision here, as in *Wyeth*, "rests on the 'limits on permissible experimentation,'" and states the somewhat new principle that "[w]here, as here, 'practicing the full scope of the claims would have required excessive experimentation, even if routine,' the patent is invalid for lack of enablement."[289]

Turning to the written description issue, the majority readily pivoted from its enablement decision to hold that the '597 Patent specification fails to provide an adequate written description because there was insufficient evidence that the Idenix inventors possessed the invention throughout its full scope.[290] In particular, the majority held that there was no evidence that the '597 Patent inventors were in possession of Gilead's product.[291] As has been the case since the Federal Circuit's seminal decision in *Regents of the University of California v. Eli Lilly*, the absence of explicit disclosure of this species, in the further absence of a sufficient number of species to define a genus comprising Gilead's species, or structure/function relationships that would ensnare this species within the scope of the species expressly disclosed, was enough for the majority to conclude that the specification failed to satisfy the written description requirement.[292]

The majority rejected Idenix's argument that the specification provided "abundant traditional blazemarks for the claims—working examples, formulas, data, synthesis routes, and the target," stating that the flaw in this analysis was that Idenix provided "lists or examples of supposedly effective nucleosides, but do not explain what makes them effective, or why."[293] In almost the reverse of the

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287 *Id.* at 1162, 1164.

288 *Id.*

289 *Idenix Pharm.*, 941 F.3d at 1163 (citing Wyeth & Cordis Corp. v. Abbott Labs., 720 F.3d 1380, 1384 (Fed. Cir. 2013)).

290 *Id.* at 1164 (reviewing '597 Patent).

291 *Id.* at 1165.

292 *See Idenix Pharm.*, 941 F.3d at 1165; *see* Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997).

293 *See id.* at 1164.

majority's reasoning regarding enablement, the opinion states that "the specification lists tens or hundreds of thousands of possible nucleosides, substituent-by-substituent, with dozens of distinct stereochemical structures, and yet the compound in question is conspicuously absent."[294]

Judge Newman dissented; the tone of the dissent, and that of a footnote in the majority opinion regarding the dissent, denotes a certain impatience on the part of both authors with the opinions of the other. Judge Newman contends that "[t]he large number of unclaimed chemical variants in the specification are not described, not synthesized, and not tested for antiviral activity", and thus "[i]t is incorrect to include these variants in the claims and then to invalidate the claims because these variants are not described and not enabled."[295] The Judge believes that a reasonable jury could have considered the claims as being limited to the much smaller number of species exemplified in the specification and thus both enabled and adequately described.[296] She characterizes the majority's enablement theory as flawed for requiring description of "unclaimed and unsupported subject matter," and states that "a reasonable jury could have understood that subject matter that is unclaimed is irrelevant to validity under Section 112."[297]

In Judge Newman's view, the claims are limited by what is exemplified in the specification; interpreting claim scope necessarily restricts the scope to that disclosure.[298] This is certainly a more parsimonious interpretation than the majority's and has the advantage that it would guard against a patentee expanding the scope of a claim to encompass species that a conscientious competitor pursues in an effort to avoid the claim. The dissent recites copiously (eighteen separate citations, with the opinion stating there are "much more") from the expert testimony in this regard.[299] Judge Newman asserts that:

> It was undisputed that the '597 Patent specification did not describe and enable products other than those whose synthesis and antiviral properties were shown in the specification, all of which had the narrow formula of three OH groups and a CH3 group

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294 *Id*. at 1165.

295 *Id*. at 1165–66 (Newman, J., dissenting) (reviewing '597 Patent) (this argument harkens back to the facts in *Wands*, where the Patent and Trademark Office contended experimentation was undue because only 4 of 143 monoclonal antibodies showed the claimed activity, whereas the Federal Circuit reversed because only 9 of the 143 clones had been tested, raising the percentage from less than 3% to about 44%).

296 *Idenix Pharm*, 941 F.3d at 1166.

297 *Id.*

298 *Id*. at 1168 (Newman, J., dissenting) (reviewing '597 Patent).

299 *Id*. at 1165–1173.

as pictured. A reasonable jury could have so viewed the claims.[300]

She further states the jurisprudential principle that "[c]ourts are not free to reweigh the evidence and set aside the jury verdict merely because the jury could have drawn different inferences or conclusions or because judges feel that other results are more reasonable."[301] Judge Newman concludes her dissent by stating that, despite Gilead's stipulation of infringement, the proper outcome of this case would be that the '597 Patent claims were not invalid (when properly cabined to the scope supported by the specification) and not infringed by Gilead's fluorinated product (based on testimony as well as the absence of this species in the '597 Patent disclosure).[302]

In her own way, Judge Newman is putting her appellate thumb as heavily on the scale as did the majority. In contrast, her jurisprudence would preserve the patent within the scope of the disclosure while absolving Gilead of infringement, while the majority's approach seems to be to interpret the claims broadly to reach the conclusion that they are invalid. This decision continues the appearance, illustrated most starkly in the court's decision denying rehearing *en banc* in *Athena Diagnostics v. Mayo Collaborative Services*,[303] that the court is seriously fractured in how it approaches its role as principal arbiter of U.S. patent law.

I. Nalpropion Pharmaceuticals, Inc. v. Actavis Laboratories FL, Inc. (Fed. Cir. 2019)

In *Nalpropion Pharmaceuticals, Inc. v. Actavis Laboratories FL, Inc.*, the Federal Circuit reversed findings of non-obviousness and affirmed (over Chief Judge Prost's dissent) a finding that claims asserted in ANDA litigation were not invalid for failure to satisfy the written description requirement.[304]

ANDA litigation arose over Nalpropion Pharma's Contrave® extended-release tablets of the combination of naltrexone hydrochloride and buproprion hydrochloride, for treatment of obesity, and Orange Book-listed U.S. Patent Nos. 7,375,111; 7,462,626; and 8,916,195.[305] The following claims were at issue in this

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[300] *Idenix Pharm*, 941 F.3d at 1171.

[301] *Id*. (citing Tennant v. Peoria & P.U. Ry. Co., 321 U.S. 29, 35 (1944)).

[302] *Id*. at 1173.

[303] *See* Donald Zuhn, *Athena Diagnostics v. Mayo Collaborative Services -- The Dissents*, PATENT DOCS (July 17, 2019), https://www.patentdocs.org/2019/07/athena-diagnostics-v-mayo-collaborative-services-the-dissents.html. [https://perma.cc/BZ3H-3QH2].

[304] 934 F.3d 1344, 1346 (Fed. Cir. 2019).

[305] *Nalpropion Pharm.*, 934 F.3d at 1346; *see* U.S. Patent No. 7,375,111 (filed Apr. 21, 2004); U.S. Patent No. 7,462,626 (filed Feb. 17, 2006); U.S. Patent No. 8,916,195 (filed June 4, 2007).

litigation:

Claim 11 of the '195 Patent:

> A method of treating overweight or obesity having reduced adverse effects comprising orally administering daily about 32 mg of naltrexone and about 360 mg of bupropion, or pharmaceutically acceptable salts thereof, to a person in need thereof, wherein the bupropion or pharmaceutically acceptable salt thereof is administered as a sustained release formulation, wherein the naltrexone or pharmaceutically acceptable salt thereof is ad- ministered as a sustained release formulation, and wherein said sustained release formulation of naltrexone has an in vitro naltrexone dissolution pro- file in a dissolution test of USP Apparatus 2 Paddle Method at 100 rpm in a dissolution medium of water at 37° C. of:
>
> a) between 39% and 70% of naltrexone re- leased in one hour;
>
> b) between 62% and 90% of naltrexone re- leased in two hours; and
>
> c) at least 99% in 8 hours;
>
> wherein about 16 mg of said sustained re- lease formulation of naltrexone or a pharmaceutically acceptable salt thereof is administered twice daily, and about 180 mg of said sustained release formulation of bupropion or a pharmaceutically acceptable salt thereof is administered twice daily.[306]

Claim 1 of the '111 Patent:

> A composition for affecting weight loss comprising:
>
> (a) a sustained release formulation of bupropion or a pharmaceutically acceptable salt thereof in an amount effective to in- duce weight loss in an individual; and
>
> (b) a sustained release formulation of naltrexone or a pharmaceutically acceptable salt thereof in an amount effective to enhance the weight loss effect of the bupropion or salt thereof;
>
> wherein said composition is in a single oral dosage form fixed combination.[307]

And claims 26 and 31 of the '626 Patent:

> *A method of treating overweight or obesity, comprising administering a weight loss effective amount of a first and second compound to an individual who has been diagnosed as suffering from overweight or obesity in order to treat said overweight or obesity, wherein said first compound is bupropion, or a pharmaceutically acceptable salt thereof, and said second compound is naltrexone, or a pharmaceutically acceptable salt thereof, and wherein the weight loss activity of said first and second compounds is enhanced compared to the administration of the same amount of either compound alone,* wherein said naltrexone, or a pharmaceutically acceptable salt thereof, and said bupropion, or a pharmaceutically acceptable salt thereof, are administered together.

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306 '195 Patent.

307 '111 Patent.

> *A method of treating overweight or obesity, comprising administering a weight loss effective amount of a first and second compound to an individual who has been diagnosed as suffering from overweight or obesity in order to treat said overweight or obesity, wherein said first compound is bupropion, or a pharmaceutically acceptable salt thereof, and said second compound is naltrexone, or a pharmaceutically acceptable salt thereof, and wherein the weight loss activity of said first and second compounds is enhanced compared to the administration of the same amount of either compound alone, wherein at least one of said maltrexone, or parmaceutically acceptable salt thereof, and said bupropion, or pharmaceutically acceptable salt thereof are in a sustained-release formulation,* wherein said bupropion, or a pharmaceutically acceptable salt thereof, and said naltrexone, or a pharmaceutically acceptable salt thereof, are administered in a single oral dosage form.[308]

The District Court found that defendant Actavis had not established that claim 11 of the '195 Patent was invalid for failure to satisfy the written description requirement of 35 U.S.C. § 112(a) with regard to the claim limitation reciting USP dissolution methods ("USP1" versus "USP2").[309] The claims expressly recited the USP 2 Paddle Method, but Actavis argued that the specification disclosed only the UPS 1 Basket Method.[310] The District Court based its decision on the fact that a skilled worker would have no doubt that the inventors had possession of the invention based on the nature of the dissolution method disclosed in the specification.[311] The Court held that disclosure of a "substantially equivalent method" was sufficient to satisfy the requirement.[312]

The District Court also rejected Actavis' arguments that claims 26 and 31 of the '626 Patent and claim 1 of the '195 Patent were obvious, on the grounds that Actavis' argument that "it would have been obvious for a person of skill to combine bupropion and naltrexone for treating overweight and obesity because both drugs were known to cause weight loss," amounted to "a classic case of hindsight bias."[313]

The Federal Circuit reversed the District Court regarding its obviousness decision in an opinion by Judge Lourie, joined by Chief Judge Prost and Judge Wallach, and affirmed the District Court on its written description determination over Chief Judge Prost's dissent. The majority's written description decision was based in part on the "peculiarity" of the structure of claim 11. This claim is directed

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[308] '626 Patent at col. 40 l. 20–30, 45–48 (filed Feb. 17, 2006) (where the italicized portions of these claims were recited in independent and/or dependent claims related to asserted claims 26 and 31).

[309] *See Nalpropion Pharm.*, 934 F.3d at 1348 (reviewing '195 Patent).

[310] *Id.*

[311] *Id.*

[312] *Id.*

[313] *See Nalpropion Pharm.*, 934 F.3d at 1348 (reviewing '626 Patent and '195 Patent).

to a method for treating obesity using specific amounts of the two drugs and reciting the method for determining the dissolution profile of what the majority termed "resultant in vitro parameters," which were not the "operative steps to treat overweight or obesity."[314] The majority found no clear error in the District Court's holding that "irrespective of the method of measurement used, the specification shows that the inventors possessed the invention of treating overweight or obesity with naltrexone and bupropion in particular amounts and adequately described it."[315] The majority noted that this determination by the District Court was supported by more credible testimony from Nalpropion Pharma's expert and "untrustworthy, self-serving statements by Actavis's expert."[316] The majority stated that it refused to disturb the District Court's weighing of witness credibility in the performance of its "fact-finding function."[317] The majority further recognized (in the face of the Chief Judge's dissent) that "[w]hile as a general matter written description may not be satisfied by so-called equivalent disclosure," under these facts the District Court had not clearly erred.[318]

Turning to the District Court's non-obvious determination for claims 26 and 31 of the '626 Patent and claim 11 of the '111 Patent, the panel unanimously held these determinations to be error as a matter of law.[319] The opinion sets forth the teachings of the asserted references, characterizing them as disclosing the use of an opioid antagonist like naltrexone and "withdrawal attenuating agents," including buproprion for minimizing weight gain, *inter alia*, during smoking cessation, and bupropion or naltrexone alone in weight loss regimes.[320] The Federal Circuit disagreed with the District Court's conclusion of non-obviousness, stating that:

> The prior art here discloses the claimed components of the composition claims and the steps of the method claims including the use claimed by the method . . . . The references teach that bupropion causes weight loss . . . . Likewise, the record indicates that naltrexone can cause weight loss . . . . Given that both drugs had shown weight loss effects, we conclude that a person of ordinary skill would have been motivated to combine them. In fact, such persons did so.[321]

The panel rejected as unpersuasive Nalpropion Pharma's argument that the FDA

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314 *Id.* at 1350 (reviewing '195 Patent).

315 *Id.*

316 *Id.*

317 *Id.*

318 *Id.* at 1351.

319 *Nalpropion Pharm.*, 934 F.3d at 1356 (reviewing '626 Patent and '195 Patent).

320 *Id.* at 1353.

321 *Id.*

would not and had not approved buproprion for weight loss. The panel found that this was not dispositive to the question of whether the skilled worker would have had a motivation to combine the asserted references.[322] Further, the opinion states:

> The inescapable, real-world fact here is that people of skill in the art *did combine* bupropion and naltrexone for reductions in weight gain and reduced cravings—goals closely relevant to weight loss. Contrary to Nalpropion Pharma's view, persons of skill *did combine* the two drugs even without understanding bupropion's' mechanism of action but with an understanding that bupropion was well-tolerated and safe as an antidepressant. . . . ("The precise mechanism for bupropion SR that is responsible for effects on weight loss is unknown.") . . . Thus, we conclude that skilled artisans would have been motivated to combine the two drugs for weight loss with a reasonable expectation of success [citations to the record omitted].[323]

The Court found "every limitation of the claims at issue" was found in the asserted art. The panel also rejected Nalpropion Pharma's purported evidence for secondary considerations (failure of others, unexpected results) to rebut their finding that these claims were obvious.[324] According to the Court, "the inventors only combined two drugs known to affect weight loss. Both drugs were known to affect weight loss, and combining them for this known purpose as claimed in the patents yields no unpredictable result."[325] The Federal Circuit thus found claim 11 of the '195 Patent and claims 26 and 31 of the '626 Patent to be invalid for obviousness.

The Chief Judge's dissent on the written description question was based on the majority's reliance on "substantially equivalent disclosure" to support claim language not having clear and explicit support in the specification.[326] The Chief Judge characterizes the majority's decision as "add[ing] what appears to me to be a new rule to this court's long-standing written description jurisprudence."[327] She sets forth three reasons for her disagreement with the majority: "[f]irst, the USP 2 clause is limiting. Second, the majority's 'substantially equivalent' rule is inconsistent with this court's precedent. Third, the district court clearly erred in finding that the '195 Patent's written description includes a disclosure 'substantially equivalent' to USP 2."[328]

Important to the Chief Judge's' reasoning, *inter alia*, were arguments from the

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322 *Id.* at 1354.

323 *Id.* at 1354–55.

324 *Id.* at 1355–56.

325 *Nalpropion Pharm.*, 934 F.3d at 1348 (reviewing '111 Patent and '626 Patent).

326 *Id.* at 1356 (Prost, J., dissenting).

327 *Id.*

328 *Id.* (reviewing '195 Patent).

prosecution history where the patentee appeared to rely on the dissolution profile (and the manner of determining it) to distinguish the claims from the prior art.[329] The Chief also disagreed with the District Court's' (and the majority's) disregard for defendant's expert testimony. The Chief asserted that that the USP1 and USP2 methods would not have produced the same dissolution profile results to have been relevant to the written description issue before each court.[330]

J. Nuvo Pharmaceuticals (Ireland) Designated Activity Co. v. Dr. Reddy's Laboratories Inc. (Fed. Cir. 2019)

There are provisions and interpretations of U.S. patent law that can be in tension depending on the circumstances under which they are argued, whether before an Examiner or during litigation. One of these is the dichotomy between arguing that the prior art would provide insufficient expectation of success to render an invention obvious, while at the same time relying on what was known by a person of skill in the art to minimize the extent of the written description provided in a specification that satisfies the written description requirement of 35 U.S.C. § 112(a). This tension proved fatal to the claims at issue in *Nuvo Pharmaceuticals v. Dr. Reddy's' Laboratories*, decided by the Federal Circuit.[331]

The case arose as ANDA litigation against Dr. Reddy's' Labs (and Mylan and Lupin entities) over non-steroidal anti-inflammatory drugs (NSAIDs) formulated to diminish recognized gastrointestinal irritation side effects these drugs can cause; the formulations being claimed in Orange Book-listed U.S. Patent Nos. 6,926,907 and 8,557,285 and sold by Nuvo as Vimovo®.[332] The prior art disclosed efforts to avoid these side effects by co-administration of NSAIDs with proton pump inhibitors (PPIs), because stomach acid was believed to contribute to them.[333] These efforts were disadvantageous, *inter alia*, because stomach acid degraded the PPIs before they could be absorbed in the small intestine and have their acid-diminishing effect in the stomach.[334] The art showed attempts to remedy these shortcomings by enterically coating PPIs to resist stomach acid. These efforts did not entirely solve the problem because the NSAID was degraded if released into the stomach before

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329 *Id.* at 1357.

330 *Id.* at 1358 (reviewing '195 Patent).

331 923 F.3d 1368, 1371 (Fed. Cir. 2019).

332 *Nuvo Pharm.*, 923 F.3d at 1371; U.S. Patent No. 6,926,907 (filed May 31, 2002); U.S. Patent No. 8,557,285 (filed Aug. 23, 2011).

333 *Nuvo Pharm.*, 923 F.3d at 1372.

334 *Id.*

the PPI could reduce stomach acid (*e.g.*, raising the pH by inhibiting the proton pump responsible for producing the acidic environment therein).[335]

The inventor of the '907 Patent invented a new formulation "that coordinated the release of an acid inhibitor and an NSAID in a single tablet," the formulation comprising a core of an NSAID, enterically coated so that the coating dissolves only at an elevated pH, and then providing an amount of a PPI sufficient to provide pH elevated to the enteric cost dissolving level.[336]

Claim 1 of the '907 Patent and claim 1 of the '285 Patent are each set forth as representative in the Federal Circuit's opinion, respectively:

> 1. A pharmaceutical composition in unit dosage form suitable for oral administration to a patient, comprising:
>
> (a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms;
>
> (b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;
>
> and wherein said unit dosage form provides for coordinated release such that:
>
> i) said NSAID is surrounded by a coating that, upon ingestion of said unit dosage form by said patient, prevents the release of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher;
>
> ii) at least a portion of said acid inhibitor is not surrounded by an enteric coating and, upon ingestion of said unit dosage form by said patient, is released regardless of whether the pH of the surrounding medium is below 3.5 or above 3.5.

> 1. A pharmaceutical composition in unit dosage form comprising therapeutically effective amounts of:
>
> (a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating; and
>
> (b) naproxen surrounded by a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher;
>
> wherein said unit dosage form provides for release of said esomeprazole such that upon introduction of said unit dosage form into a medium, at least a portion of said esomeprazole is released regardless of the pH of the medium.[337]

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335 *Id.*

336 *Id.* (reviewing '907 Patent).

337 *Nuvo Pharm.*, 923 F.3d at 1372–73 (reviewing '907 Patent and '285 Patent).

While the specification (according to the panel opinion) disclosed many features of the claimed invention, "[i]t is undisputed that there is no experimental data demonstrating the therapeutic effectiveness of any amount of uncoated PPI and coated NSAID in a single dosage form," nor is there any disclosure of formulations wherein uncoated PPI could be used to raise gastrointestinal pH.[338]

The District Court found that Defendants had not shown the asserted claims to be obvious under 35 U.S.C. § 103 nor not enabled or inadequately described under 35 U.S.C. § 112, and thus, that one of Dr. Reddy's generic products did not infringe the '907 Patent (granting summary judgment to Dr. Reddy's on its noninfringement motion).[339] Specifically, the Court found that it would not have been obvious to use a PPI according to the asserted claims to prevent gastrointestinal injury from an NSAID, *inter alia*, because the art would have discouraged attempting such formulations due to the known acid sensitivity of PPIs.[340] Moreover, the District Court held that the claims were enabled because the specification disclosed how to make and use the invention. The Court relied on expert testimony in deciding that the skilled worker would have recognized the usefulness of the claimed formulations.[341]

With regard to Dr. Reddy's written description challenges, the District Court found that the use of the transition term "comprising" in the '285 Patent claims did not cause the claims to encompass (undisclosed) embodiments having uncoated, immediately released naproxen (an exemplified NSAID).[342] The Court also rejected a second challenge, that the claims encompass sustained-release as well as delayed-release NSAID formulations not supported by the specification, because the claims recited "inhibiting" rather than "preventing" NSAID release prior to achieving the claimed raised pH levels.[343] Finally, the District Court rejected Defendants" argument that "ordinarily skilled artisans would not have expected [the claimed formulation] to work and the specification provides no experimental data or analytical reasoning showing the inventor possessed an effective uncoated PPI."[344] The Court held that "experimental data and an explanation of why an invention works are not required, the specification adequately describes using uncoated PPI,

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338 *Id.* at 1373 (reviewing '907 Patent).

339 *Id.* at 1374 (reviewing '907 Patent and '285 Patent).

340 *Id.* at 1374–75.

341 *Id.* at 1375.

342 *Id.* at 1374–75 (reviewing '285 Patent).

343 *Nuvo Pharm.*, 923 F.3d at 1375 (reviewing '907 Patent and '285 Patent).

344 *Id.*

and its effectiveness is necessarily inherent in the described formulation."[345]

This appeal followed, limited to the District Court's findings on the first and third written description arguments; Nuvo cross-appealed on the District Court's grant of summary judgment of non-infringement by Dr. Reddy's second formulation.

The Federal Circuit reversed the District Court's' decision and dismissed Nuvo's cross-appeal, in an opinion by Judge Clevenger, joined by Chief Judge Prost and Judge Wallach. The opinion states that the panel's' analysis "begins and ends" with Defendants' third written description argument related to a failure to show "efficacy" of the claimed formulation.[346] According to the Federal Circuit, the issue was raised by Nuvo's argument (related to Defendants' obviousness assertions) that "ordinarily skilled artisans would not have expected uncoated PPIs to be effective."[347] Inconsistently, "nothing in the specification would teach a person of ordinary skill in the art otherwise," and this failure to disclose what was not found in the art (and indeed, Nuvo affirmatively contended was not known in the art with regard to the obviousness issue) amounts to a failure to describe how the inventors were in possession of the claimed invention.[348] The District Court's error, according to the Federal Circuit, was that its written description analysis on this point "does not support its conclusions."[349] Because of the "clear error" standard of review imposed on the Federal Circuit on questions of fact (as the adequacy of disclosure sufficient to satisfy the written description requirement is), the opinion asserts that the panel "scour[ed] the record created below for evidence supporting the District Court's written description finding."[350]

To no avail. In part, the panel came to this conclusion because they appreciated that Nuvo raised "at least five arguments" ("for the first time on appeal, and as its lead argument") directed to reading any effectiveness language or requirement from the asserted claims.[351] These arguments were, in the panel's view, contradicted by the plain language (and plain meaning thereof) of the claims (claim 1 of the '907 Patent recites ". . . in an amount *effective to raise the gastric pH of said patient to at least 3.5*," and claim 1 of the '285 Patent recites ". . . comprising *therapeutically*

345 *Id.*

346 *See Nuvo Pharm.*, 923 F.3d at 1376.

347 *Id.* at 1377.

348 *Id.* at 1377–83.

349 *Id.* at 1377.

350 *Id.*

351 *Id.*

effective amounts of [the PPI].")[352] But the opinion sets forth and rejects each one.

First, Nuvo argued that the dosage form *as a whole* does not need to be effective in raising gastric pH; the Federal Circuit agreed but did not find any of Defendants' argument to be to the contrary.[353]

Second, Nuvo argued that the claims do not require the NSAID and PPI to be in a single dosage form but "only amounts of each component effective on their own."[354] Defendants argued that the claim "requires coordinated release achieved by an effective amount of uncoated PPI that raises the gastric pH to at least 3.5 and an effective amount of naproxen that is released to treat pain when the pH reaches the desired level"; the panel held that Nuvo had not presented this argument below, and thus it was forfeited.[355]

Third, Nuvo contended that the claim didn't require the uncoated PPI to be effective to raise gastric pH, just that the formulation contained an effective amount of uncoated PPI.[356] In addition to holding Nuvo had also forfeited this argument by not raising it below, the panel termed it "nonsensical to read the claims to require effective amounts of uncoated PPI without specifying the result effectively achieved."[357]

Fourth, Nuvo asserted that the claims encompassed "multiple dosage forms," and thus, the specification did not need to expressly describe any particular effective dosage form.[358] Rather than summarily dismissing this argument, the opinion expressly disagreed with it: the '285 Patent "does not allow for more than one dosage form" and "[e]ven if it were true that the '907 [P]atent allows more than one dosage form to effectively raise the gastric pH to at least 3.5 using uncoated PPI, the specification would still need to provide support for the notion that uncoated PPI is effective," according to the Court.[359]

Finally, the panel rejected Nuvo's' argument that the Examiner interpreted the claims in a manner consistent with their argument, that "the '907 [P]atent claims [] merely require[d] certain amounts of PPI and NSAID effective on their own rather

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352 *Nuvo Pharm.*, 923 F.3d at 1377–78 (emphasis added) (reviewing '907 Patent and '285 Patent).

353 *Id.* at 1378.

354 *Id.*

355 *Id.*

356 *Id.*

357 *Id.*

358 *Nuvo Pharma.*, 923 F.3d at 1379.

359 *Id.* (reviewing '907 Patent and '285 Patent).

than requiring an overall efficacy for the combined drug."[360] The panel found Nuvo's argument relied in this regard on arguments the Court had already rejected and besides, in their view "the Examiner appears to have interpreted the claims to require an amount of PPI, whether coated or uncoated, effective to raise the gastric pH to the desired level" and that was the written description required (and lacking) in Nuvo's specification.[361]

Having decided what the law requires the written description to be, the panel then reported its failure to find such support in the specification. Nuvo's attempt to rely on expert testimony was unavailing, in part because this testimony was sufficiently particular that the Court was able to review and reject it. Specifically, the opinion states that:

> The statements [the expert] points to recite the claim limitation by simply calling generally for effective amounts of uncoated PPI, but our precedent clearly establishes that is not enough . . . . We have expressly rejected the "argument that the written description requirement . . . is necessarily met as a matter of law because the claim language appears *in ipsis verbis* in the specification."[362]

Experimental evidence is not required,[363] nor is there any requirement for a "theory or explanation of how or why a claimed composition will be effective,"[364] nor does an invention need to be reduced to practice.[365] But here, "there is nothing in the specification of the patents-in-suit showing 'that the inventor *actually invented* the invention claimed.'"[366] The Court concluded that the specification is "fatally flawed" with regard to providing an adequate written description of the requisite efficacy recited in the claims and reversed the District Court's finding that Defendants had not established that the '907 and '285 Patents were invalid for failure to satisfy the requirements of 35 U.S.C. § 112.[367]

III. CONCLUSIONS

Many other biotechnology patent court cases were decided in 2019. The patent

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360 *Id*. (reviewing '907 Patent).

361 *Id*.

362 *Id*. at 1380 (citing Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 968 (Fed. Cir. 2002)).

363 *See In re* '318 Patent Infringement Litig., 583 F.3d 1317, 1324 (Fed. Cir. 2009).

364 *Nuvo Pharm.*, 923 F.3d at 1380 (citing Allergan, Inc. v. Sandoz, Inc., 796 F.3d 1293, 1308 (Fed. Cir. 2015)).

365 *Id.* (citing Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 926 (Fed. Cir. 2004)).

366 *Id.* (citing Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341, 1348 (Fed. Cir. 2011).

367 *Id*. at 1381, 1384 (reviewing '907 Patent and '285 Patent).

interference dispute over CRISPR/Cas9 inventions continued, with Sigma Aldrich attempting to provoke an interference that would surely render this dispute even more complicated. Congress turned its attention again to 35 U.S.C. § 101, though without tangible results, while the Supreme Court refused to grant *certiorari* on several petitions concerning § 101. Many other issues of patent doctrine were explored, such as public use, on-sale bars to patentability, and experimental use exceptions,[368] but did not make our cut of the top 10 biotechnology patent decisions of 2019.

For half a century, biotechnology patent law has occupied a niche in the wider realm of patent law. Highlighting fascinating scientific discoveries, promising new approaches to solving human problems at some undefined point in the future, and posing various interesting challenges to existing legal doctrine; biotechnology has nevertheless been widely regarded as a small and eccentric niche of patent law. The SARS-CoV-2 virus and the COVID-19 pandemic it has caused has shone a bright light on the clear and present importance of biotechnology and how patent law ought to approach it to ensure humanity receives full benefits from its powerful discoveries. Suddenly, biotechnology stands at the vanguard of patent law, transforming the sound crafting, interpretation, and application of biotechnology law high on the list of societal priorities. Vaccines offer a vivid example of this, with new and innovative approaches, such as mRNA-based methods, raising worldwide hopes for a cure to COVID-19 and to the economic and social ravages it has caused. Biotechnology patent law will play an increasingly important role in helping to respond to societal issues. Understanding it better is an immediate imperative.

We began our effort to choose and describe the 10 most important biotechnology patent decisions in *Biotechnology Patent Law Top Ten of 2018 - Broad Wins, Sovereignty Loses, and Patents Dance*.[369] We intend to continue this effort each year, with our next article covering the 10 most important biotechnology patent decisions of 2020.

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368 *See* Barry v. Medtronic, Inc., 914 F.3d 1310, 1320–21 (Fed. Cir. 2019).

369 Kevin E. Noonan & Andrew W. Torrance, *Biotechnology Patent Law Top Ten of 2018 - Broad Wins, Sovereignty Loses, and Patents Dance*, 52 AKRON L. REV. 637, 637–38 (2018).