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BIOTECHNOLOGY PATENT LAW TOP TEN OF 2021. EXPERIMENTATION, BLAZE MARKS, AND UNSPECIFIED RANGES

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EXPERIMENTATION, BLAZE MARKS, AND UNSPECIFIED RANGES

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Biotechnology has never demonstrated its benefits to society more than in 2021. The SARS-CoV-2 virus that caused the CoVID-19 pandemic met a formidable opponent in mRNA vaccines developed and supplied by Moderna and Pfizer/BioNTech. These vaccines are claimed in myriad – not Myriad – patents and patent applications, many of which are destined to be litigated over the coming years, not least inspired by the many billions of dollars that have been, and will continue to be, earned by their owners. While the world waits for this storm of patent litigation, federal courts continue to be busy with ownership, licensing, validity, and infringement disputes arising from other biotechnologies, including, perhaps, up-and-coming CAR-T therapies. For the fourth year in a row (of what has become a tradition), we discuss, in this article, the ten most consequential, important, and interesting court decisions involving biotechnology patents. Our top ten decisions may not be the same as top tens compiled by others. However, to quote an expression commonly heard in courts hearing patent cases, à chacun son goût. Patent decisions delivered during 2021 tackled a diverse group of doctrinal issues. As discussed in the article, these ranged from how much experimentation is to be considered undue à la In re Wands, to what level of detail of disclosure is sufficient to satisfy the ever- written description requirement, to which types of behavior may rise to the level of inducement to infringe, not to mention assignor estoppel. Patent litigations filed in federal district court rose to 3,798, a number not seen since 2016. In contrast, the 1,333 patent actions filed with the Patent

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Biotechnology has never demonstrated its benefits to society more than in 2021. The SARS-CoV-2 virus that caused the COVID-19 pandemic met a formidable opponent in mRNA vaccines developed and supplied by Moderna and Pfizer/BioNTech. These vaccines are claimed in myriad – not Myriad – patents and patent applications, many of which are destined to be litigated over the coming years, not least inspired by the many billions of dollars that have been, and will continue to be, earned by their owners. While the world waits for this storm of patent litigation, federal courts continue to be busy with ownership, licensing, validity, and infringement disputes arising from other biotechnologies[2], including, perhaps, up-and-coming CAR-T therapies[3]. For the fourth year in a row (of what has become a tradition), we discuss the ten most consequential, important, and interesting court decisions involving biotechnology patents. Our top ten decisions may not be the same as top tens compiled by others. However, to quote an expression commonly heard in courts hearing patent cases, *à chacun son goût*.

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[2] Jack Karp, *COVID's Impact On Litigation To Persist In 2022,* LAW360 (Jan. 4, 2022, 12:02 PM)

[3] Irena Royman and Daniel Williams, *CAR T-Cell Therapy Takes Off and Brings on Patent Litigation*, KRAMER LEVIN: BIO LAW BLOG (Feb. 19, 2020), https://www.kramerlevin.com/en/perspectives-search/car-t-cell-therapy-takes-off-and-brings-on-patent-litigation.html.

district court rose to 3,798, a number not seen since 2016.[4] In contrast, the 1,333 patent actions filed with the Patent Trial and Appeal Board ("PTAB") represented a substantial decline from 2020.[5] In short, despite the challenges of the COVID-19 pandemic, patent litigation in 2021 evinced considerable vim and vigor. Described and analyzed below are the vimmiest and most vigorous of 2021 patent decisions.

I. TOP TEN BIOTECHNOLOGY PATENT LAW CASES OF 2022

A. Biogen Int'l GmbH v. Mylan Pharmaceuticals Inc.

Congress established the Federal Circuit as a circuit court of appeals to harmonize U.S. patent law in an environment where regional circuit courts had developed their own judicial interpretations of the patent statute.[6] Consequently, formerly it was often to a party's benefit to choose to litigate in a circuit where the law was favorable to their case. The resulting disharmony was occasionally and variably corrected by the Supreme Court. However, Congress perceived the High Court's capacity for concentrating on patent law to be insufficient to the country's needs for consistent application in this area of the law. For a generation, the Federal Circuit was able, with little interference from the Supreme Court, to create something of the harmony Congress mandated, assisted by judges who understood the law and the precedential roots thereof (as well as understanding Congress's mandate and the need for doctrinal consistency). Recently, however, the Court seems to have

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[4] Scott Graham, *Just 1 Judge Accounted for Nearly 25% of Patent Infringement Filings in 2021, New Report Says*, THE NATIONAL LAW JOURNAL (Jan. 4, 2022, 3:59 PM), https://www.law.com/nationallawjournal/2022/01/04/just-one-judge-accounted-for-25-of-patent-infringement-filings-in-2021-new-report-says/?slreturn=20220407234833; *What 15 Years of US Patent Litigation Data Reveal About the IP Market,* RPX (Jan. 25, 2021), https://insight.rpxcorp.com/news/65081-what-15-years-of-us-patent-litigation-data-reveal-about-the-ip-market.

[5] Logan Murr, *Unified Report: Reexaminations Double; Samsung, Apple and Google Dominate PTAB Filings*, IPWATCHDOG (Jan. 8, 2022, 12:15 PM), https://www.ipwatchdog.com/2022/01/08/unified-report-reexaminations-double-samsung-apple-google-dominate-ptab-filings/id=142622/.

[6] 28 U.S.C. § 1295

morphed (along with the composition of the judges) into a *soi-disant* court of equity, more concerned with doing what at least two judges on any particular panel have been convinced is "the right thing" (for the parties or the law) than with ruling consistently with the Court's precedent. That tendency (which could be termed "equity creep") explains in part the Court majority's decision in *Biogen Int'l GmbH v. Mylan Pharmaceuticals Inc*. and Judge O'Malley's vigorous and cogent dissent.

To briefly recapitulate the proceedings before the District Court, the case arose over Mylan's attempt to get regulatory approval and come to market with a generic equivalent of Biogen's Tecfidera® (dimethyl/monomethyl fumarate) multiple sclerosis drug.[7] Biogen asserted Orange Book-listed U.S. Patent Nos. 6,509,376; 7,320,999; 7,619,001; 7,803,840; 8,399,514; and 8,759,393,[8] but the parties dismissed their causes of action on all patents except the '514 patent, where Biogen asserted claims 1-4, 6, 8-13, and 15-16;[9] claim 1 is representative:

> 1. A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof, and (b) one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is *about 480 mg per day*.[10]

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[7] Biogen Int'l GMBH v. Mylan Pharms. Inc., 18 F.4th 1333, 1336 (Fed. Cir. 2021).

[8] Biogen Int'l GmbH v. Mylan Pharms. Inc., No. 1:17CV116, 2020 WL 3317105, at *1 n.2 (N.D.W. Va. June 18, 2020), aff'd, 18 F.4th 1333 (Fed. Cir. 2021).

[9] *Id.* at *1.

[10] Biogen Int'l GMBH v. Mylan Pharms. Inc., 18 F.4th 1333, 1337 (Fed. Cir. 2021) (emphasis added wherein the italicized limitation was the entirety of the basis for the District Court's decision and the Federal Circuit majority's affirmance).

While this litigation was proceeding, Mylan successfully petitioned the PTAB to institute an *inter partes* review proceeding, on the ground that the asserted claims of the '514 patent were obvious.[11] The Board issued a Final Written Decision that Mylan had not shown obviousness by a preponderance of the evidence, and the District Court held that Mylan was collaterally estopped from asserting obviousness as a basis for invalidating the '514 patent in this litigation.[12] Accordingly, the only ground for invalidating the '514 patent that Mylan pursued before the District Court was that the patent specification did not satisfy the written description requirement of 35 U.S.C. § 112(a).[13]

Mylan's arguments on its written description defense were grounded on certain characteristics of the '514 specification and its prosecution history. The '514 patent specification reflected Biogen's more general research goal of finding treatments for neurological disorders, including but not limited to multiple sclerosis ("MS").[14] Mylan noted that the original named inventor, Dr. Lukashev, was not a clinician but rather a research scientist investigating the mechanism of action of the claimed compound.[15] Specifically, the research underlying the '514 patent disclosure showed that DMF could activate a particular metabolic pathway (the Nrf2 pathway).[16] One important consequence of this inventor's testimony is that he "denied that his research could be extrapolated to a clinical dose of DMF; it 'was never the focus of [his] work to inform the clinical dosing of [DMF].'"[17] Dr. Lukashev was the only named inventor on the earliest applications from which the '514 patent claimed priority.[18]

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[11] Biogen Int'l GmbH v. Mylan Pharms. Inc., No. 1:17CV116, 2020 WL 3317105, at *1 n.2 (N.D.W. Va. June 18, 2020), aff'd, 18 F.4th 1333 (Fed. Cir. 2021).
[12] *Id.*
[13] *Id.*
[14] *Id.* at *5.
[15] *Id.* at *3.
[16] Biogen Int'l GmbH v. Mylan Pharms. Inc., No. 1:17CV116, 2020 WL 3317105, at *3 (N.D.W. Va. June 18, 2020), *aff'd*, 18 F.4th 1333 (Fed. Cir. 2021).
[17] *Id*. (alterations in original).
[18] *Id.*

As originally filed, the claims of the application that matured into the '514 patent did not recite methods of treatment but rather were drawn to methods for identifying compounds that affected the Nrf2 pathway.[19] However, in April 2011, Biogen received the results of a Phase III clinical study showing that a 480mg/day dose of DMF was effective in treating MS.[20] Apparently, in response, Biogen replaced the then-pending claims with claims that eventually issued, changed the title of the application, and added as an inventor the scientist who posited that this dosage would be particularly effective as an MS treatment.[21] Significantly to the written description calculus, Biogen did not supplement its specification, which permitted it to rely on a February 8, 2007 earliest priority date.[22]

Mylan's position was simple: the invention described in the specification filed in 2007 "bears no resemblance to the invention claimed in 2011."[23] Mylan supported this assertion with two arguments. First, Mylan argued that "a POSA [person of skill in the art] would not have expected the claimed invention—a 480mg/day dose of DMF (BID)—to effectively treat MS" and "that nothing in the specification of the '514 Patent teaches otherwise."[24] Second, Mylan argued that "when viewed as an integrated whole, the combination of selectively plucked disclosures in the specification of the '514 Patent fails to sufficiently describe the claimed invention—a method of treating MS with a therapeutically effective amount of DMF, i.e., 480mg/day of DMF (BID)."[25] According to Mylan, the reason for this situation is that "Biogen grafted the '514 claims onto a specification written to cover an entirely different set of inventions, conceived of by an entirely different inventor, and filed more than four years before Biogen's 2011 Phase III trial

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[19] *Id.*
[20] *Id.* at *4.
[21] Biogen Int'l GmbH v. Mylan Pharms. Inc., No. 1:17CV116, 2020 WL 3317105, at *4 (N.D.W. Va. June 18, 2020), *aff'd*, 18 F.4th 1333 (Fed. Cir. 2021).
[22] *Id.* at *5.
[23] *Id.* at *7.
[24] *Id.*
[25] *Id.*

results demonstrated the effectiveness of the 480[mg/day] dose."[26]

The District Court held that the '514 specification failed to satisfy the written description requirement because it did not show that the inventors possessed the invention on its earliest claimed priority date.[27] The Court noted that in the '514 specification only the first of its 30 columns focused on MS and that only one of the five methods expressly disclosed in the '514 specification was directed at treating a neurological disease by administering to the subject in need thereof at least one compound that is partially structurally similar to DMF (or a closely related compound, monomethylfumate).[28] The District Court understood even this method to "broadly describe[] treating neurological diseases with a therapeutically effective amount of DMF; MS is merely one such disease 'among a slew of competing possibilities."[29] As further indicia of the lack of necessary specificity of the '514 patent disclosure, the District Court cited "an exhaustive list of 'diseases suitable for the [five] methods described' in the '514 Patent."[30] In view of this listing of a plethora of neurological diseases, the Court held that there were no "blaze marks" that would teach the skilled worker to treat MS with DMF at this dosage.[31] The Court particularly rejected Biogen's contention that the specification would teach the POSA that the '480 mg/day dosage was the preferred dosage, crediting Mylan's expert Dr. Greenberg's testimony to the contrary in this regard.[32] The Court focused on the fact that the specification mentioned the 480 mg/day dosage only once, as part of a preferred range ("from about 480 to about 720 mg per

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[26]Biogen Int'l GmbH v. Mylan Pharms. Inc., No. 1:17CV116, 2020 WL 3317105, at *7 (N.D.W. Va. June 18, 2020), *aff'd*, 18 F.4th 1333 (Fed. Cir. 2021).
[27] *Id.* at *13.
[28] *Id.* at *8–9.
[29] *Id.* at *10 (citing Novozymes A/S v. DuPont Nutrition Biosciences APS by analogy in support of the inadequacy of the '514 patent disclosure).
[30] *Id.*
[31] Biogen Int'l GmbH v. Mylan Pharms. Inc., No. 1:17CV116, 2020 WL 3317105, at *10 (N.D.W. Va. June 18, 2020), *aff'd*, 18 F.4th 1333 (Fed. Cir. 2021).
[32] *Id*. at *11-12.

day").[33] The Court found neither credible nor persuasive Biogen's argument that a POSA would understand that using the lowest effective dose of the narrowest range was preferred.[34] The Court found it more consistent with what was known at the time the application was filed that dosages of 720 mg/day were effective in treating MS, and 120 and 360 mg/day were ineffective.[35] And in the battle of the experts, the Court was unpersuaded by Biogen's expert (whose credibility Mylan impeached on cross-examination, according to the Court) and was clearly persuaded by Mylan's expert.[36]

From the evidence presented at trial, the District Court found that "[i]n sum, Biogen has attempted to satisfy the written description requirement of § 112 by selectively plucking specific words from the specification that correspond to each element of the claimed invention."[37] Citing *Nuvo Pharm. (Ir.) Designated Activity Co. v. Dr. Reddy's Labs. Inc*. and *Novozymes A/S v. DuPont Nutrition Biosciences APS*, the Court stated that the Federal Circuit has squarely rejected the approach Biogen has taken.[38] Biogen appealed.[39]

The Federal Circuit affirmed, in an opinion by Judge Reyna joined by Judge Hughes, with Judge O'Malley (the only Federal Circuit judge who had also been a district court judge) dissenting.[40] A good portion of the majority opinion is devoted to an explication of the scientific background of MS, the procedural mechanics of Hatch-Waxman litigation, and a primer on the Court's written description jurisprudence.[41] The majority is cognizant (and applies it partly in justification) of the high burden Biogen has to show clear error by the District Court over the factual issues underlying its determination that the '514

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[33] *Id*. at *11.
[34] *Id*.
[35] *Id.*
[36] Biogen Int'l GmbH v. Mylan Pharms. Inc., No. 1:17CV116, 2020 WL 3317105, at *11 (N.D.W. Va. June 18, 2020), *aff'd*, 18 F.4th 1333 (Fed. Cir. 2021). .
[37] *Id.* at *13.
[38] *Id.*
[39] Biogen Int'l GmbH v. Mylan Pharm. Inc., No. 2020-1933, 2021 U.S. App. LEXIS 35254, at **1-2 (Fed. Cir. Nov. 30, 2021).
[40] *Id.* at **1.
[41] *Id.* at **2–5, **16–17.

patent does not satisfy the written description requirement.[42] But in explicating its reasons for affirmance, the majority indicates it believes that Biogen did what the District Court determined, "attempted to satisfy the written description requirement of § 112 by selectively plucking specific words from the specification that correspond to each element of the claimed invention."[43]

In this vein, the opinion states that the specification "casts a wide net for a myriad of neurological disorders, including neuro-degenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, and Huntington's disease; demyelinating neurological diseases, such as various forms of MS and at least twenty-eight other disorders related to demyelination; polyneuritis; and mitochondrial disorders with demyelination"[44] The Court further enunciates a repeated enumeration of how many times the specification mentions MS, DMF, and the 480 mg/day dose (tellingly, exactly once, where once for the majority is clearly not enough), saying "consistent with the disclosure's original title concerning Nrf2 screening, the totality of the specification focuses primarily on drug discovery."[45] The majority noted in conjunction with this statement that "[i]ndeed, the invention's title was only amended to "Treatment for Multiple Sclerosis" in 2011 after Biogen acquired Phase III clinical data for the use of DMF480 in treating MS."[46]

Focusing on Example 4, which the majority and dissent as well as the District Court, recognized is the portion of the specification most closely related to using DMF to treat MS, the majority opinion sets forth the one paragraph of the specification that "teach[es] potential dosage levels for DMF monotherapy"[47]:

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[42] *Id.* at *15–16.
[43] Biogen Int'l GmbH v. Mylan Pharms. Inc., No. 1:17CV116, 2020 WL 3317105, at *13 (N.D.W. Va. June 18, 2020), *aff'd*, 18 F.4th 1333 (Fed. Cir. 2021).
[44] Biogen Int'l GMBH v. Mylan Pharms. Inc., 18 F.4th 1333, 1337-8 (Fed. Cir. 2021) (Judge O'Malley terms this type of disclosure "laundry list" disclosure).
[45] *Id.* at 8.
[46] *Id.*
[47] *Id.* at 9.

> Effective doses will also vary, as recognized by those skilled in the art, dependent on route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatments including use of other therapeutic agents. For example, an effective dose of DMF or MM[F] to be administered to a subject orally can be from about 0.1 g to 1 g per pay, 200 mg to about 800 mg per day (e.g., from about 240 mg to about 720 mg per day; or ***from about 480 mg to about 720 mg per day***; or about 720 mg per day). For example, the 720 mg per day may be administered in separate administrations of 2, 3, 4, or 6 equal doses.[48]

In this context, the panel majority further recognizes "two crucial aspects of the invention"[49]:

> First, the above paragraph features the *one and only* reference to DMF480 in the entire specification, which puts the DMF480 dose that the '514 Patent claims at the bottom end of the spectrum of a DMF 480–720 mg/day range. Second, the specification defines the term "effective" within a therapeutic, rather than drug-discovery, context. Thus, according to the specification, the terms "'therapeutically effective dose' and 'therapeutically effective amount' refer to that amount of a compound which results in at least one of *prevention* or *delay* of onset or *amelioration of symptoms* of a neurological disorder in a subject or an attainment of a *desired biological outcome, such as reduced neurodegeneration* (e.g., de-myelination, axonal loss, and neuronal death) or *reduced inflammation* of the cells of the CNS."[50]

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[48] *Id.* 9–10 (emphasis in opinion).
[49] Biogen Int'l GmbH v. Mylan Pharm. Inc., No. 2020-1933, 2021 U.S. App. LEXIS 35254, at 10 (Fed. Cir. Nov. 30, 2021).
[50] *Id*.

The second aspect the majority finds "crucial" is an important, factual source of Judge O'Malley's disagreement with her brethren and the District Court[51].

The majority opinion is replete with instances showing the influence the history of the development of the claimed invention (and their implied suspicions about its origins) had on their opinion including, *inter alia*, mention of Biogen adding as an inventor the clinical scientist who advocated for the 480 mg/day dose and his exclusion in the application originally filed in favor of a laboratory, not clinical, scientist who was involved in developing methods for identifying compounds that acted on biological basis for MS, the Nrf2 pathway. Also important for the majority are the facts that by naming this scientist as an inventor they were able to "claim a priority date of February 8, 2007, despite filing wholly new claims alongside the [inventorship] amendments."[52] On the law, the majority is willing to concede:

> assuming that a skilled artisan would understand the disclosure to be unambiguously focused on MS despite its inclusion among approximately three-dozen neurological disorders—a determination we need not reach in this case—the specification may arguably provide adequate information to convey to a skilled artisan that the invention supports method-of-treatment claims directed to MS and, perhaps, that the use of DMF may be therapeutically linked to MS treatment.[53]

Although, in a footnote, the majority note that the only method directed to the claimed invention "is devoid of any specific reference to MS".[54]

But the important point for the majority is the disclosure in the specification of dosage amount. Here, the majority agrees with the District Court (or is unwilling to find clear error in its

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[51] Biogen Int'l GMBH v. Mylan Pharms. Inc., 18 F.4th 1333, 1339 (Fed. Cir. 2021).
[52] *Id*. at 13
[53] *Id.* at 19.
[54] *Id.* at 19 n.6.

determination) that "[t]he DMF480 dose is listed only once in the entire specification."[55] From this (and the more extensive disclosure of ranges of DMF dosages and 720 mg/day dosage in particular), the majority opines that "the specification's focus on basic research and broad DMF dosage ranges show that the inventors did not possess a therapeutically effective DMF480 dose at the time of filing in 2007."[56] This assessment was supported, according to the majority, by Dr. Lukashev's testimony regarding the extent to which (*i.e.*, none) his research could be used to arrive at the 480 mg/day dose despite the majority's recognition that Dr. Lukashev was *not* a clinical scientist.[57] According to the majority,

> [w]hat matters for purposes of the inquiry in this case is whether, at the time of filing the disclosure—well before the Phase III study even commenced—a skilled artisan could deduce simply from reading the specification that DMF480 would be a therapeutically effective treatment for MS. As to this point, the specification's focus on drug discovery and basic research further buttresses the district court's conclusion that the specification lacks an adequate written description to support the DMF480 claims.[58]

As set forth above, it is a fact that the application resulting in the '514 patent was filed *before* the clinical trials that established that the 480 mg/day dose was clinically effective at ameliorating the symptoms of MS.[59] It is also the case that the original focus of the claims was not directed to this dose (indeed, those claims were directed to methods for *finding* a therapeutically effective dose), and this temporal disjunction *inter alia* (*vide infra*) created the impression at the District Court

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[55] Biogen Int'l GmbH v. Mylan Pharm. Inc., No. 2020-1933, 2021 U.S. App. LEXIS 35254, at 19 (Fed. Cir. Nov. 30, 2021).
[56] *Id.* at 20.
[57] *Id*.
[58] *Id.* at 22.
[59] *Id.* at 21–23.

and perhaps for the majority that Biogen was not entitled to claims reciting this dose.[60]

At the end of the opinion, the majority broaches the issue upon which Judge O'Malley bases her dissent:

> Based on the record, including at least the specification's definition of a "therapeutically effective dose" and the witness and expert testimony, the district court did not find it necessary to distinguish between therapeutic effects and clinical efficacy with respect to its patentability determination, instead electing to consider both under the specification's definition of "therapeutically effective dose." We determine that such a finding was not clearly erroneous.[61]

This is where Judge O'Malley believes the majority and the District Court got off on the wrong foot as a "threshold error" that the majority dismisses (in error, in her opinion).[62] The District Court's error (an "original sin" in the dissent) was its decision to hold Biogen judicially estopped from making a distinction between clinical efficacy and therapeutic effects, based on positions that party took in the *inter partes* review[63] instituted by Mylan on obviousness (where Biogen prevailed on the basis of whether a POSA would have had a reasonable expectation of success in achieving the claimed invention.[64]

The basis for that error was, according to Judge O'Malley, not appreciating that:

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[60] Biogen Int'l GmbH v. Mylan Pharm. Inc., No. 2020-1933, 2021 U.S. App. LEXIS 35254, at 21-23 (Fed. Cir. Nov. 30, 2021).
[61] *Id.* at 28.
[62] *Id*. at 30.
[63] In a companion, nonprecedential opinion the Court affirmed the PTAB decision without analysis in view of their precedential decision here. Mylan Pharmaceuticals Inc. v. Biogen MA, Inc., No. 2020-1673, 2021 WL 5571658 (Fed. Cir. Nov. 20, 2021), *rehearing granted*, Mylan Pharmaceuticals Inc. v. Biogen MA, Inc., 2022 WL 1089900 (Fed. Cir. Apr. 8, 2022).
[64] Biogen Int'l GmbH v. Mylan Pharm. Inc., No. 2020-1933, 2021 U.S. App. LEXIS 35254, at 43 (Fed. Cir. Nov. 30, 2021) (O'Malley, J., dissenting).

> [c]linical efficacy involves the type of scientific rigor associated with Phase III clinical trials: the investigative DMF480 dose must produce superior clinical endpoints to the standard of care for MS, Rebif®. Therapeutic effects, by contrast, "do not require efficacy on clinical endpoints or superior efficacy to existing drugs." It, instead, "refer[s] to the amount of [DMF480] which results in . . . prevention or delay of onset or amelioration of symptoms of a neurological disorder" like MS.[65]

This distinction is important because the failure to appreciate it, by the District Court and the majority, was the basis, in Judge O'Malley's view, of the determination that "the '514 patent lacked written description support because 'a person of ordinary skill in the art would not have a reasonable expectation that the 480 mg/day [DMF] dose would provide statistically significant and clinically meaningful effectiveness for treating MS.'"[66] But as Biogen argued and Judge O'Malley agreed, that would be true only if the claims required *clinical* efficacy when instead they only covered *therapeutic* effects, *i.e*., a different albeit related property.[67] In addition to imposing judicial estoppel in these circumstances being an abuse of discretion by the trial court under Fourth Circuit law (in a two-sentence footnote in its opinion), Judge O'Malley takes recourse in Biogen's post-trial briefing for the nature of this error as a matter of fact.[68] In her dissent, Judge O'Malley argues that *this* error led to the District Court's *next* error, finding that the '514 patent claims were not supported by an adequate written description.[69] This is because, according to Judge O'Malley, "the district court's refusal to acknowledge the difference between *therapeutic* and *clinical* effects evinces a fundamental misunderstanding of what is claimed."[70] Judge O'Malley

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[65] *Id.* at 30 (alterations in original) (citations to the record omitted).
[66] *Id.* at 31.
[67] *Id.*
[68] *Id*. at 31.
[69] Biogen Int'l GmbH v. Mylan Pharm. Inc., No. 2020-1933, 2021 U.S. App. LEXIS 35254, at 35 (Fed. Cir. Nov. 30, 2021) (O'Malley, J., dissenting).
[70] *Id.* at 32 (emphasis in dissenting opinion).

supports her view with an explication of what the '514 specification says and how the specification uses the term "therapeutic efficacy," and how this definition is tied to just the type of research applications that seems to have disquieted the majority.[71] But both Biogen and Judge O'Malley have a point: the written description begins and ends with the question, "a written description of what?". That "what" is the claimed invention as the invention is claimed, *i.e*., by the language of the claim, which, Judge O'Malley reminds us and the majority defines as a "bedrock principle of patent law."[72]

According to Judge O'Malley, this conflation of therapeutic and clinical efficacy led the District Court, and the Federal Circuit majority, to improperly apply the Court's *Nuvo Pharmaceuticals (Ireland) Designated Activity Co. v. Dr. Reddy's Laboratories Inc.*, precedent.[73] Judge O'Malley states that "[t]he district court's reliance on *Nuvo* to conclude that Mylan could use Biogen's own obviousness defenses against it in the written description context is, therefore, legally erroneous,"[74] This erroneous reading of Federal Circuit precedent was not something on which the Court needed to defer, its review of the District Court in this regard being *de novo*.

Judge O'Malley reaches a critical issue (otherwise unmentioned) when she discusses the question of whether Biogen provided sufficient "blaze marks" in its specification regarding the specific 480 mg/day dosage (which the District Court and the majority determined it did not), using the colorful imagery from *In re Ruschig*, 379 F.2d 990, 994–995 (C.C.P.A. 1967). But this analytical tool "does not apply in every case concerning written description," Judge O'Malley reminds us, but "instead[] provides a useful framework to analyze whether written description has been met in cases involving patents

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[71] *Id*. at 32-34.
[72] *Id.* at 34 (citing Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed. Cir. 2005) (*en banc*)).
[73] *Id.* at 35-36 (citing Nuvo Pharms. (Ir.) Designated Activity Co. v. Dr. Reddy's Labs. Inc., 923 F.3d 1368, 1377, 1381 (Fed. Cir. 2019)).
[74] Biogen Int'l GmbH v. Mylan Pharm. Inc., No. 2020-1933, 2021 U.S. App. LEXIS 35254, at 38 (Fed. Cir. Nov. 30, 2021) (O'Malley, J., dissenting) (alteration in original).

containing laundry list disclosures." [75] Judge O'Malley's identification of the majority's error in this regard is relegated to a footnote:

> [t]he majority's decision affirming the district court partially rests on the fact that the '514 patent only mentions the claimed DMF480 dose once. . . . But the majority cites no case law (and I know of none) for the proposition that the written description requirement demands that a patentee recite a claim element repeatedly to pass written description muster. The majority does not, and cannot, deny that the claimed DMF480 dose is expressly disclosed. To the extent the majority's opinion may be read to establish a requirement that a claim element must be disclosed multiple times, I dissent from that holding as well.[76]

This is not a case where blaze marks are needed, according to Judge O'Malley, who states "[the specification] does not provide a laundry list disclosure of therapeutically effective doses" but rather provides one "range with the exact DMF 480 dose that is claimed" and thus blaze marks should not be required or an issue in deciding satisfaction of the written description requirement.[77]

This portion of Judge O'Malley's dissent raises the issue in a way not otherwise addressed expressly in either opinion, but one that seems relevant to the Court's precedent and consideration of it in this case. It has long been the case that claims must not need *in haec verba* support in the specification.[78] This decision, for the first time, may be one where claims that unambiguously *have in haec verba* support have been found not to satisfy the written description requirement. As with many of the Court's precedents, the current Court seems to show in its

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[75] *Id.* at 40–41 (citing Fujikawa v. Wattanasin, 93 F.3d 1559, 1571 (Fed. Cir. 1996)).
[76] *Id.* at 41 n.4.
[77] *Id.* at **43 (emphasis in dissenting opinion).
[78] *See*, *e.g.*, Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1352 (Fed. Cir. 2010) (en banc).

opinions a slow, disquieting tendency to have them spread from their doctrinal boundaries to encompass more and more circumstances that in past precedent would have been inconceivable. This is an embodiment of a specialized patent court that it is easy to apprehend Congress did not intend to create.

B. Indivior UK Ltd. v. Dr. Reddy's Laboratories S.A.

The Leahy-Smith America Invents Act prescribed two very different post-grant review proceedings in U.S. patent law. The first, post-grant review (PGR), had some analogies with European opposition practice, in that petitions for PGR could be filed no later than nine months after the patent had granted and any ground of patentability was available as the basis for challenge.[79] The other proceeding, *inter partes* review ("IPR"), a uniquely American invention, was available throughout an unexpired patent term but the subject matter of challenge was limited to anticipation under 35 U.S.C. § 102 and obviousness under 35 U.S.C. § 103.[80] However, Section 112 issues can be considered in an IPR as a part of construing the claims when questions of priority are raised, and this was the basis for the PTAB to find invalid all but one of the challenged claims in *Indivior UK Ltd. v. Dr. Reddy's Laboratories S.A*.[81]

Dr. Reddy's petitioned IPR of U.S. Patent No. 9,687,454 on the ground that all claims were anticipated by U.S. Patent Publication 2011/0033541 to Myers.[82] The claims are directed to therapeutic agent-containing films that can be orally dissolved as an administration route for various medicines.[83] The '454 patent is the latest in a series of related applications, the earliest (U.S. Patent Application 12/537,571) dating to 2009.[84] At issue in this IPR was whether the challenged claims were entitled to this earliest filing date, which antedated the publication of the '541 application asserted by Dr. Reddy's for anticipation.[85]

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[79] *See* 35 U.S.C. § 321 *et seq*.
[80] *See* 35 U.S.C. § 311 *et seq*.
[81] Indivior UK Ltd. v. Dr. Reddy's Labs. S.A., 18 F.4th 1323, 1326 (2021).
[82] *Id.* at 1324-25.
[83] *Id.* at 1325.
[84] *Id.*
[85] *Id.*

The opinion sets forth claims 1, 7, 8, and 12 as representative of the issues before the Board.

> Claim 1. An oral, self-supporting, mucoadhesive film comprising:
>
> (a) **about 40 wt % to about 60 wt %** of a water-soluble polymeric matrix;
>
> (b) about 2 mg to about 16 mg of buprenorphine or a pharmaceutically acceptable salt thereof;
>
> (c) about 0.5 mg to about 4 mg of naloxone or a pharmaceutically acceptable salt thereof; and
>
> (d) an acidic buffer;
>
> wherein the film is mucoadhesive to the sublingual mucosa or the buccal mucosa;
>
> wherein the weight ratio of (b):(c) is about 4:1;
>
> wherein the weight ratio of (d):(b) is from 2:1 to 1:5; and
>
> wherein application of the film on the sublingual mucosa or the buccal mucosa results in differing absorption between buprenorphine and naloxone, with a buprenorphine Cmax from about 0.624 ng/ml to about 5.638 ng/ml and a buprenorphine AUC from about 5.431 hr*ng/ml to about 56.238 hr*ng/ml; and a naloxone Cmax from about 41.04 pg/ml to about 323.75 pg/ml and a naloxone AUC from about 102.88 hr*pg/ml to about 812.00 hr*pg/ml.
>
> Claim 7. The film of claim 1, wherein the film comprises **about 48.2 wt % to about 58.6 wt %** of the water-soluble polymeric matrix.
>
> Claim 8. The film of claim 7, wherein the film comprises **about 48.2 wt %** of the water-soluble polymeric matrix.
>
> Claim 12. The film of claim 1, wherein the weight ratio of (d):(b) is from about 1:1 to 1:5; wherein the weight ratio of (b):(a) is from about 1:3 to about 1:11.5; and wherein the film comprises **about 48.2**

> **wt % to about 58.6 wt %** of the water-soluble polymeric matrix.[86]

As is evident from the emphasized limitations, the distinction between claim 8 and the other claims is that claim 8 has a particularly specified composition of the water-soluble polymeric matrix making up the film while the other claims have a broader range of values for this parameter.[87]

The Board considered whether the written description in the '571 priority specification had support for these features.[88] The Board found express disclosure for the "about 48.2 wt %" limitation in the '571 specification (albeit as the result of calculation by the skilled artisan); the Tables containing these data were reproduced in the Federal Circuit opinion.[89] While express disclosure of a claimed range can readily satisfy the written description requirement, inherent disclosure of such ranges by example is also in some cases adequate for written description purposes.[90] The ranges of water-soluble polymer in the films recited by the other claims did not find support in the '571 specification, according to the Board.[91] Moreover, the Board did not find Indivior's expert witness testimony to be credible on this issue.[92] Finally, the Board held that a person of ordinary skill in the art would have strayed from these ranges based on the '571 disclosure that "[t]he film may contain any desired level of self-supporting film forming polymer."[93] Accordingly, the Board held that the challenged claims of the '454 patent were not entitled to the priority date of the '571 application and thus claims 1-5, 7, and 9-14 were invalid for being anticipated by the teachings of the prior art '541

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[86] Indivior UK Ltd. v. Dr. Reddy's Labs. S.A., 18 F.4th 1323, 1325-26 (2021) (emphasis in each instance being set forth in the opinion).
[87] *See id.* at 1326.
[88] Indivior UK Ltd. v. Dr. Reddy's Labs. S.A., 18 F.4th 1323, 1326 (2021)
[89] *Id.*
[90] *See* Union Oil of Cal. v. Atl. Richfield Co., 208 F.3d 989, 997 (Fed. Cir. 2000).
[91] Indivior UK Ltd. v. Dr. Reddy's Labs. S.A., 18 F.4th 1323, 1326 (2021).
[92] *Id.*
[93] *Id.*

application while claim 8 was not anticipated.[94] Both parties appealed the Board's decision.[95]

The Federal Circuit affirmed, in an opinion by Judge Lourie joined by Judge Dyk and joined in part by Judge Linn, who dissented in part.[96] Regarding Indivior's appeal of the Board's invalidation of claims 1-5, 7, and 9-14, the panel majority agreed with the Board that the portions of the '571 specification Indivior attempted to rely upon did not disclose, expressly or inherently, the ranges recited in claims 1-5, 7, or 9-14.[97] Instead, there are instances in the disclosure that are "only specific, particular examples" but they are not ranges according to the opinion.[98] The panel majority expressly rejected Indivior's argument that a written description is adequate when the skilled worker would need to "pluck[] out the polymer components and create[] a range from the percentage totals" which the opinion states "amounts to cobbling together numbers after the fact."[99] And "[a] written description sufficient to satisfy the requirement of the law requires a statement of an invention, not an invitation to go on a hunting expedition to patch together after the fact a synthetic definition of an invention" because "a patent is not a hunting license..."[100] The Federal Circuit illustrated the doctrinal difficulties of applying the written description requirement consistently by rejecting Indivior's resort to its case law by stating "written description cases are intensively fact-oriented, and the cases vary, just as ranges vary."[101]

Because Indivior did not dispute that the '541 application would anticipate claims 1-5, 7, and 9-14 if the '454 patent was not entitled to the priority date of the '721 application, the Court affirmed the Board's decision that these claims were invalid for being anticipated.[102]

Turning to Dr. Reddy's cross-appeal, the panel understood the argument to be that the skilled worker "would not

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[94] *Id.*
[95] *Id.*
[96] Indivior UK Ltd. v. Dr. Reddy's Labs. S.A., 18 F.4th 1323, 1323 (2021).
[97] *Id.* at 1327–28.
[98] *Id.* at 1329.
[99] *Id.*
[100] *Id.* (citing Brenner v. Manson, 383 U.S. 519, 536 (1966).
[101] Indivior UK Ltd. v. Dr. Reddy's Labs. S.A., 18 F.4th 1323, 1329 (2021).
[102] *Id.* at 1330.

have immediately discerned that the '571 application discloses a polymer component comprising 48.2 wt % of a film because the tables do not state the total polymer weight of various formulations."[103] The panel agreed with Dr. Reddy's that the 48.2 wt% is not expressly disclosed but deferred to the Board's fact-finding as being supported by substantial evidence.[104] As to the possibility that this decision be perceived as being contrary if not contradictory to the Court's decision affirming invalidity of the other claims in the '454 patent, the opinion states that "given that claim 8 does not recite a range, but only a specific amount, which can be derived by selection and addition of the amounts of selected, but identified, components, we accept that there is substantial evidence to support the Board's decision concerning claim 8" and accordingly affirmed.[105]

Judge Linn's dissent illustrated the difficulties of analyzing compliance with the written description requirement. Citing some of the same case law Indivior unsuccessfully relied upon, including *Nalpropion Pharms., Inc. v. Actavis Labs. FL, Inc*., 934 F.3d 1344 (Fed. Cir. 2019), and *In re Wertheim*, 541 F.2d 257 (C.C.P.A. 1976), Judge Linn contended the majority was incorrect in failing to find written description support in the '571 specification for the '454 patent's claims 1-5, 7, and 9-14, saying the panel majority had "applie[d] an overly demanding standard for written description for ranges" contrary to this precedent.[106] His dissent then illustrates the Judge's assessment of the '571 disclosure and comes to a conclusion opposite from that of the panel majority. In Judge Linn's assessment, the reason for this difference with the panel majority is that Judges Lourie and Dyk took statements in the specification out of context and considered the specification to contain "inconsistent language" that Judge Linn is at a loss to perceive.[107] Indeed, Judge Linn chides the panel majority for doing just what the majority opinion states should not be done, applying a "strict rule" to show

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[103] *Id.*
[104] *Id.*
[105] *Id.*
[106] Indivior UK Ltd. v. Dr. Reddy's Labs. S.A., 18 F.4th 1323, 1331 (2021) (Linn, J., dissenting).
[107] *Id.*

possession of the claimed range(s).[108] Judge Linn also states that in his analysis the Tables set forth in the '571 application (and reproduced in the opinion) disclose the 48.2 wt% and 58.6 wt% in the recited ranges and required no "cobbling together numbers after the fact" as the majority had asserted in support of their decision.[109] Finally, Judge Linn found the *Wertheim* and *Nalpropion* opinions to be directly on point and in support of his opinion that the '571 specification provided an adequate written description of the challenged claims of the '454 patent.[110]

C. Pacific Biosciences of California, Inc. v. Oxford Nanopore Technologies, Inc.

The Federal Circuit continued its recent run of decisions extending the reach of the enablement requirement of 35 U.S.C. §112(a) to invalidate patents in *Pacific Biosciences of California, Inc. v. Oxford Nanopore Technologies, Inc.*, albeit in this case, affirming denial of a motion for JMOL in the face of a jury verdict of non-enablement.[111]

The matter arose when Pacific Biosciences asserted U.S. Patent Nos. 9,546,400 and 9,772,323 directed to methods for sequencing nucleic acid (DNA) using nanopore technology.[112] As explained in the opinion, the DNA being sequenced passes through the nanopores, causing a change in electrical current specific for each nucleotide base (which is then recognized by the machine).[113] Pacific Biosciences asserted Claim 1 of the '400 patent:

> Claim 1. A method for sequencing a nucleic acid template comprising:
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> a) providing a substrate comprising a nanopore in contact with a solution, the solution comprising a template nucleic acid above the nanopore;

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[108] *Id.*
[109] *Id.* at 1332.
[110] *Id.*
[111] Pac. Biosciences of Cal., Inc. v. Oxford Nanapore Techs, Inc., 996 F.3d 1342 (Fed. Cir. 2021).
[112] *Id.* at 1345.
[113] *Id.*

> b) providing a voltage across the nanopore;
> c) measuring a property which has a value that varies for N monomeric units of the template nucleic acid in the pore, wherein the measuring is performed as a function of time, while the template nucleic acid is translocating through the nanopore, wherein N is three or greater; and
> d) determining the sequence of the template nucleic acid using the measured property from step (c) by performing a process including comparing the measured property from step (c) to calibration information produced by measuring such property for 4 to the N sequence combinations.[114]

A jury found that Oxford infringed the asserted claims but that the claims were invalid for failure to satisfy the enablement requirement, based in part on conflicting testimony from each party's experts.[115] The District Court denied Pacific Biosciences' post-trial motion for judgment as a matter of law (JMOL), leading to this appeal.[116]

The Federal Circuit affirmed, in an opinion by Judge Taranto, joined by Judges Lourie and Stoll.[117] According to the opinion, "[w]hat matters is the scope of the asserted claims," which in relevant part extended to determining the sequence of a template nucleic acid without any limitation regarding the "character" of the nucleic acid, including differentiating between "particular types of DNA.[118] What the Court understood any of this to mean is unclear. The opinion discusses the relevance of the "N nucleotides" limitation in the claims, which was one basis for Oxford's expert's testimony that the claims were not enabled.[119] The opinion also notes testimony from more than one

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[114] *Id.* at 1347.
[115] *Id.* at 1349.
[116] Pac. Biosciences of Cal., Inc. v. Oxford Nanapore Techs, Inc., 996 F.3d 1342, 1349 (Fed. Cir. 2021).
[117] *Id.* at 1342.
[118] *Id.* at 1350.
[119] *Id.* at 1351.

witness that nanopore sequencing technology was not performed in the art until 2011 (after the 2009 priority dates of the patents at issue) and not based on the disclosures of those patents.[120] The opinion notes also that Pacific Biosciences' specification was constructive and that there was no real-world reduction to practice achieved at the time of filing.[121] (There was also evidence presented to the jury that Pacific Biosciences had intended to "'tangle . . . up' and 'fool' competitors with its patents" which the opinion understood might have pointed the jury away from deciding that Pacific Biosciences had an enabled method.)[122] The remainder of the panel's opinion on enablement was focused on whether the District Court properly denied Pacific Biosciences' motion for JMOL and whether the jury could reasonably have arrived at its verdict in view of the conflicting testimony of the witnesses. [123] The panel stated that in its opinion "there was ample evidence to support a finding that, before the 2009 priority date of the '400 and '323 patents, relevant artisans did not know how to perform nanopore sequencing for more than a narrow range of the full scope of nucleic acids covered by the asserted claims," citing *Idenix Pharms. LLC v. Gilead Sciences Inc.*, 941 F.3d 1149 (Fed. Cir. 2019), *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362 (Fed. Cir. 1999), and *Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co.*, 308 F.3d 1167 (Fed. Cir. 2002), in support.[124]

But as Paul Harvey used to say, here's the rest of the story (which has nothing to do with patent law and as such is discussed herein subservient to the patent law aspects of the decision). The trial was held beginning on March 9, 2020, and Pacific Biosciences was concerned that Oxford would intimate to the jury that finding its patents infringed and not invalid would hamper efforts to combat COVID-19 (specifically based on Pacific Biosciences' status as a non-practicing entity or its patent being a "paper patent").[125] To this end, Pacific Biosciences

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[120] *Id.* at 1352.
[121] Pac. Biosciences of Cal., Inc. v. Oxford Nanapore Techs, Inc., 996 F.3d 1342, 1352 (Fed. Cir. 2021).
[122] *Id.*
[123] *Id*. at 1353 *et seq*.
[124] *Id.*
[125] *Id.* at 1347.

sought and received a motion *in limine* that Oxford not be able to make or hint any such conclusion to the jury.[126] Both parties mentioned the pandemic in their opening statements, but Pacific Biosciences objected to *how* Oxford made its mention of the issue and obtained a curative instruction from the Court the next day.[127] The judge also admonished both parties not to ''turn this really into a trial about an ongoing global health crisis that has to be on the minds of the jury,' which would be 'unfair' and 'improper' and would 'inflam[e] the jury' and 'would create a real risk of a verdict' not based on the evidence.[128] Pacific Biosciences raised similar objections to Oxford's closing argument.[129] In addition to its motion for JMOL, Pacific Biosciences moved under Rule 59 for a new trial, based on undue prejudice caused by Oxford's violation of the motion *in limine*; the District Court denied this motion because Pacific Biosciences did not provide evidence that Oxford had violated the *in limine* motion or that the jury had been inflamed by those statements.[130]

The Federal Circuit also affirmed the District Court's denial of the motion for a new trial. One solid basis for this decision is that the panel opined that the District Court's views of the matter should be given "considerable weight" in view of that court's being in a better position to observe the demeanor of the jury, party counsel, and witnesses, citing *Draper v. Airco, Inc.*, 580 F.2d 91, 97 (3d Cir. 1978) (the Federal Circuit applying Third Circuit law to this question).[131] Another basis in the opinion was that Pacific Biosciences did not object when presented with advance notice that Oxford intended to make the purportedly inflammatory statements.[132] Further, the opinion notes that the District Court gave just the curative instruction Pacific Biosciences requested the day after the purported violation occurred and required each party to inform each other of any further instances of argument or testimony related to

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[126] *Id.*
[127] Pac. Biosciences of Cal., Inc. v. Oxford Nanapore Techs, Inc., 996 F.3d 1342, 1353 (Fed. Cir. 2021).
[128] *Id.* at 1348.
[129] *Id*. at 1347-1349.
[130] *Id.* at 1349.
[131] *Id.* at 1353.
[132] Pac. Biosciences of Cal., Inc. v. Oxford Nanapore Techs, Inc., 996 F.3d 1342, 1353 (Fed. Cir. 2021).

COVID-19 before eliciting testimony or making arguments to the jury.[133] Accordingly, the opinion asserts that "[g]iven all the circumstances, we do not see a basis for disturbing the district court's assessment that there was an insufficient likelihood that the improper opening remarks had an adverse impact on the ultimate verdict to justify a new trial in this case."[134]

D. Bayer Healthcare LLC v. Baxalta Inc.

In March, the Federal Circuit affirmed a jury verdict against Baxalta Inc., Baxalta US Inc., and Nektar Therapeutics for infringing Bayer Healthcare's patent to human blood clotting factor conjugates in *Bayer Healthcare LLC v. Baxalta Inc.*[135]

Bayer Healthcare sued Defendants on U.S. Patent No. 9,364,520, alleging willful infringement by Baxalta's product, Adynovate®.[136] This product is a recombinant human Factor VIII (the blood clotting factor responsible for causing Hemophilia A) having the protein structural domains A1-A2-B-A3-C1-C2, wherein the B portion was specifically modified by addition of polyethylene glycol (PEG).[137] PEGylation is important because Factor VIII has an 11-hour half-life which requires frequent injections and leads to reduced patient compliance.[138] The prior art had disclosed random modification of Factor VIII with PEG, which had several drawbacks due to the multiplicity of PEGylations sites ("158 lysines, the two N-termini, and multiple histidines, serines, threonines, and tyrosines") in the Factor VIII protein, which led to heterogeneity in the species produced, including ones having deleterious effects on Factor VIII activity and ones having a multiplicity of PEG residues conjugated to the protein.[139]

The '520 patent specification disclosed site-specific PEGylation at a site not at an N-terminal amine; claim 1 is representative:

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[133] *Id.* at 1353-54.
[134] *Id.*
[135] Bayer Healthcare LLC v. Baxalta Inc., 989 F.3d 964 (Fed. Cir. 2021).
[136] *Id.* at 969-70.
[137] *Id.* at 970.
[138] *Id.*
[139] *Id.* at 970-71.

> Claim 1. *An isolated polypeptide conjugate* comprising a functional factor VIII polypeptide and one or more biocompatible polymers, wherein the functional factor VIII polypeptide comprises the amino acid sequence of SEQ ID NO: 4 or an allelic variant thereof and has a B-domain, and further wherein the biocompatible polymer comprises polyalkylene oxide and is covalently attached to the functional factor VIII polypeptide *at the B-domain*.[140]

At trial, the District Court construed the term "isolated polypeptide conjugate" to mean "a polypeptide conjugate where conjugation was not random."[141] Specifically, the District Court held that during prosecution of the '520 patent, Bayer had disclaimed embodiments having random PEGylation of Factor VIII.[142] Further, the District Court construed the term "at the B-domain" to mean "attachment at the B-domain such that the resulting conjugate retains functional factor VIII activity," rejecting Baxalta's proposed construction that the phrase should be construed to mean "at a site that is not any amine or carboxy site in factor VIII and is in the B-domain."[143] The District Court granted Defendants' pre-trial motion as a matter of law that there was no willful infringement, and a jury found that Defendants infringed claims 1-3 and 8 of the '520 patent.[144] The jury found against Defendants' counterclaim of non-enablement, and awarded Bayer $155,190,264 in reasonable royalty damages, based on a 17.78% royalty rate for $872,836,128 in Defendants' profits.[145] The District Court also denied Defendants' JMOL motions on the issues of infringement, enablement, and damages.[146] Bayer filed a motion under Federal Rule of Civil Procedure 59(a) for pre-verdict supplemental damages, which the

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[140] Bayer Healthcare LLC v. Baxalta Inc., 989 F.3d 964, 971 (Fed. Cir. 2021) (wherein the italicized portions of the claim identify claim language disputed in the litigation).
[141] *Id.* at 977.
[142] *Id.* at 978.
[143] *Id.* at 972.
[144] *Id.*
[145] Bayer Healthcare LLC v. Baxalta Inc., 989 F.3d 964, 972 (Fed. Cir. 2021)
[146] *Id.* at 972–93.

District Court granted and awarded Bayer another $18,324,562.[147] The District Court also denied Bayer's motion for JMOL on willful infringement.[148] Both parties appealed.[149]

The Federal Circuit affirmed, in an opinion by Judge Stoll, joined by Judges Newman and Linn.[150] The opinion first opined on the District Court's claim construction, which because the District Court had not relied upon extrinsic evidence, was performed *de novo* with regard to the interpretation of the terms "at the B-domain" and "random" PEGylation of the B portion of Factor VIII.[151] The opinion rejected Defendants' argument that the term "at the B-domain" should have been interpreted to exclude amine/lysine PEG conjugation.[152] The opinion sets forth its claim construction analysis by way of the factors enunciated in *Phillips v. AWH Corp*., 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*): plain meaning of the claim terms, the specification, and the prosecution history.[153] The Federal Circuit found the plain meaning of the term "'[a]n isolated polypeptide conjugate' in which PEG 'is covalently attached to the functional factor VIII polypeptide at the B-domain'" does not require any particular amino acid residue to be PEGylated, saying that the claim "broadly requires PEGylation at the B-domain as a region."[154] The panel identified statements in the specification that supported this construction, and while acknowledging that PEGylation at cysteine residues was expressly disclosed, held that this disclosure did not limit the scope of site-specific PEGylation to just cysteine residues.[155]

The Federal Circuit also disagreed with Defendants that the specification disparaged amine/lysine PEG conjugation, expressly based on *Indivior Inc. v. Dr. Reddy's Laboratories, S.A.*, 930 F.3d 1325 (Fed. Cir. 2019); *Gaus v. Conair Corp.*, 363

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[147] *Id.*
[148] *Id.*
[149] *Id.* at 973.
[150] Bayer Healthcare LLC v. Baxalta Inc., 989 F.3d 964, 964 (Fed. Cir. 2021)
[151] *Id.* at 973.
[152] *Id.*
[153] *Id*. at 973, citing Hologic, Inc. v. Minerva Surgical, Inc., 957 F.3d 1256, 1269 (Fed. Cir. 2020) (citing Trs. of Columbia Univ. v. Symantec Corp., 811 F.3d 1359, 1362 (Fed. Cir. 2016)).
[154] *Id.*
[155] *Id.* at 973–74.

F.3d 1284 (Fed. Cir. 2004); and *SciMed Life Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337 (Fed. Cir. 2001), although the opinion states that it was a close question.[156] Rather than disparaging or disclaiming any particular type of conjugation with PEG, the panel held that the '520 patent specification disparaged random PEGylation, which is not the same thing.[157] Finally, the opinion held that nothing in the prosecution history was to the contrary, specifically in that it did not contain "a clear and unmistakable surrender of claims directed to non-random amine/lysine PEGylation."[158] While art cited by the USPTO included amine/lysine conjugation sites, taken as a whole and as understood by a person of ordinary skill in the art, the Federal Circuit held that the rejection and cited art was directed to random PEGylation.[159] Defendants' citation of statements made in the prosecution of related European Patent Application No. 11153287.4 were unavailing,[160] both on the merits and, in agreement with the District Court, because "varying legal and procedural requirements for obtaining patent protection in foreign countries might render consideration of certain types of representations inappropriate for consideration in a claim construction analysis of a United States counterpart."[161]

Regarding the term "random," the Federal Circuit rejected Defendants' argument that the District Court had erred by not expressly defining the term, thus improperly leaving construction of this term to the jury. The panel held that the District Court had resolved the parties' differences with regard to this term by addressing (and rejecting) Defendants' arguments "(1) that 'random' conjugation means any conjugation at amines or carboxy sites; and (2) that 'random' conjugation means all heterogenous conjugation."[162] The Federal Circuit understood the District Court's construction did not exclude *any* degree of heterogeneity from PEG conjugation but rather that Bayer had disparaged embodiments with "a high degree of heterogeneity"

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[156] Bayer Healthcare LLC v. Baxalta Inc., 989 F.3d 964, 974 (Fed. Cir. 2021).
[157] *Id.* at 975.
[158] *Id.*
[159] *See id.* at 975–76.
[160] *Id.* at 976 n.3.
[161] Bayer Healthcare LLC v. Baxalta Inc., 989 F.3d 964, 977 (Fed. Cir. 2021).
[162] *Id.* at 978.

which was the problem with prior art embodiments of PEGylated Factor VIII preparations that distinguished Bayer's invention.[163] Reciting the District Court's construction, the opinion states that the District Court found correctly that "non-random conjugation neither required that each FVIII protein in a product such as Adynovate® be PEGylated in the same places (homogeneity among conjugates in the product) nor required that every PEG on each FVIII protein be in the B-domain (homogeneity within each conjugate)."[164] Accordingly, the Federal Circuit held that limiting the term "random" with reference to construction of the term "isolated polypeptide conjugate" to mean "a polypeptide conjugate where conjugation was not random" sufficiently defined the meaning of the word "random" in the claimed context, and that this was consistent with other district court decisions, including denial of Defendants' motion *in limine* on this issue.[165]

The panel also affirmed as being supported by substantial evidence the jury's infringement decision, and consequently, that the District Court did not err in denying Defendants' motion for JMOL. The opinion provided a synopsis of the parties' evidence, including differing expert witnesses on infringement, supported by Baxalta's submissions to FDA regarding the specificity with which its Factor VIII product comprised "*controlled*, *targeted* chemical addition of 20 [kilodalton] PEG conjugates to this FVIII B-domain," statements inconsistent with random PEGylation.[166]

Similarly, the Federal Circuit held that there was substantial evidence for the jury's rejection of Defendants' non-enablement defense, particularly regarding embodiments comprising non-random lysine PEGylation. According to the opinion:

> Bayer presented substantial evidence from which a reasonable juror could find that the specification's disclosure of instructions as to the reaction conditions required to practice the claimed

[163] *Id.*
[164] *Id.*
[165] *Id.*
[166] Bayer Healthcare LLC v. Baxalta Inc., 989 F.3d 964, 979 (Fed. Cir. 2021) (emphasis in opinion).

> invention using cysteine PEGylation were sufficient to enable not only non-random cysteine PEGylation at the B-domain, but also non-random lysine PEGylation at the B-domain.[167]

Somewhat in contrast to recent, more stringent applications of the Federal Circuit's standards for enablement[168], this panel held that "the specification need not include a working example of every possible embodiment to enable the full scope of the claims,".[169]

Defendants also appealed the jury's damages calculations and the basis thereof. While agreeing with the District Court in rejecting Bayer's expert's 50-50 split royalty rate, the panel disagreed with several other assertions of error by Defendants.[170] These included the basis for the 17.78% reasonable royalty rate, which Defendants' argued relied on "a flawed and speculative methodology—namely, asking the jury to pick a rate between the range of feasible rates presented by [Bayer's expert] as the reasonable rate."[171] The Federal Circuit held that "[t]he district court properly exercised its discretion in allowing Bayer to ask the jury to select a rate between the range presented," within the confines of a damages expert using "reliable methodology for determining the range of possible hypothetical negotiation royalty rates."[172] When, as here, a jury's damages award "fell within the range suggested by the patentee's damages expert" the Federal Circuit stated it was supported by substantial evidence, citing *Rembrandt Wireless Techs., LP v. Samsung Elecs. Co.*, 853 F.3d 1370, 1382 (Fed. Cir. 2017), and that the District Court had not erred in permitting the jury to receive Bayer's damage expert's testimony.[173] According to the opinion, Defendants had

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[167] *Id.* at 982.
[168] *See e.g.,* Amgen Inc. v. Sanofi, 987 F.3d 1080 (Fed. Cir. 2021) and Idenix Pharmaceuticals LLC v. Gilead Sciences Inc, 941 F.3d 1149 (Fed. Cir. 2019).
[169] Bayer Healthcare LLC v. Baxalta Inc., 989 F.3d 964, 982 (Fed. Cir. 2021) (citing Alcon Rsch. Ltd. v. Barr Labs., Inc., 745 F.3d 1180, 1189–90 (Fed. Cir. 2014), and Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1336–37 (Fed. Cir. 2003)).
[170] *Id*. at 983.
[171] *Id.* at 983.
[172] *Id.*
[173] *Id.*

(and had exercised) the opportunity to cross-examine Bayer's expert on his methodology and damages calculation, and "ultimately, the jury evaluated his opinions and adopted a rate within his proposed range."[174] In the Federal Circuit's opinion there was nothing improper about the jury's damages calculation or award.

Finally, Defendants argued that the District Court had violated their Seventh Amendment rights by awarding pre-judgment damages under Fed R. Civ. P. 59. In doing so, according to the Federal Circuit, the District Court used actual sales data instead of projected amounts and applied the same 17.78% royalty rate on the amount of these actual sales.[175] "Under these circumstances," said the Federal Circuit, "we are not persuaded that the District Court's award constitutes an impermissible additur or an otherwise 'bald addition of something which in no sense can be said to be included in the verdict."[176] The remainder of the Court's opinion makes it clear that its judgment was limited to the facts in this case.

Regarding Bayer's appeal on the District Court's grant of Defendants' motion for JMOL on willful infringement, the panel held that there was insufficient evidence of the necessary state of mind having "a specific intent to infringe at the time of the challenged conduct" to support willfulness.[177] The panel affirmed the District Court's decision even though "there was no dispute that Baxalta was 'aware of the '520 patent,'" because "Bayer merely 'assume[d] that [Baxalta] knew Adynovate[®] infringed because it involved pegylation at the B-domain of factor VIII."[178] The Federal Circuit rendered this opinion even in the face of testimony by Defendants' witnesses "concerning their awareness of the patent application that issued as the '520 patent" and representations to FDA regarding non-random PEGylation in Defendants' Adynovate® product.[179]

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[174] *Id.*
[175] Bayer Healthcare LLC v. Baxalta Inc., 989 F.3d 964, 986 (Fed. Cir. 2021).
[176] *Id.* (citing Dimick v. Schiedt, 293 U.S. 474, 486 (1935)).
[177] *Id.* at 987 (citing Halo Elecs., Inc. v. Pulse Elecs., Inc., 136 S. Ct. 1923, 1933 (2016) for the proposition that the conduct warranting enhanced damages is "willful, wanton, malicious, bad-faith, deliberate, consciously wrongful, flagrant, or—indeed—characteristic of a pirate").
[178] *Id.*
[179] *Id.*

E. GlaxoSmithKline LLC v. Teva Pharmaceuticals USA

Most judicial outcomes, particularly on appeal, are broadly based on varying combinations of process and outcome. The law is replete with process-based decisions (standing, jurisdiction, waiver, to name a few) and of course even more frequently perhaps coming to the "correct" outcome is a major decisive factor in a court's opinions. Rarely are these two features of judicial consideration juxtaposed in opposition (albeit not so rarely that the aphorism that "hard cases make bad law" is not appreciated in practice). Such a case is illustrated in this second Federal Circuit decision in *GlaxoSmithKline LLC v. Teva Pharmaceuticals USA*.[180]

The matter arose in litigation over GSK's Coreg® product (carvedilol) for the treatment of hypertension (the initial approved indication; U.S. Patent No. 4,503,067), congestive heart failure (CHF) (the subject of U.S. Patent No. 5,760,069) and left ventricular dysfunction following myocardial infarction (LVD-MI).[181] The '069 patent recites a method of treating CHF with a combination of carvedilol and "one or more of an angiotensin-converting enzyme ("ACE") inhibitor, a diuretic, and digoxin."[182]

Teva's ANDA was filed with a Paragraph III certification over the '067 patent and a Paragraph IV certification over the '069 patent.[183] The FDA tentatively approved Teva's generic product for "treatment of heart failure and hypertension" which Teva launched on expiration of the '067 patent.[184] Teva's label indicated that the product was approved for treatment of LVD-MI and hypertension, and announced that FDA had given its product an "AB rating", which the opinion explained "allow[s] users to determine quickly whether the Agency has evaluated a particular approved product as therapeutically equivalent to other pharmaceutically equivalent products".[185] Thereafter, FDA required Teva to amend its label to be identical to the GSK label

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[180] GlaxoSmithKline LLC v. Teva Pharm. USA, 7 F.4th 1320 (Fed. Cir. 2021).
[181] *Id.* at 1323.
[182] *Id.*
[183] *Id*. at 1333.
[184] *Id.* at 1324.
[185] GlaxoSmithKline LLC v. Teva Pharm. USA, 7 F.4th 1320, 1335 (Fed. Cir. 2021).

for Coreg®, which introduced treatment of heart failure into the approved treatments recited in Teva's label.[186]

GSK filed for reissue of the '069 patent which was duly granted by the U.S. Patent and Trademark Office as Reissue Patent No. RE40,000;[187] claim 1 is representative of the invention as claimed in the '000 reissue patent:

> Claim 1. A method of decreasing mortality caused by congestive heart failure in a patient in need thereof which comprises administering a therapeutically acceptable amount of carvedilol in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of an angiotensin converting enzyme inhibitor (ACE), a diuretic, and digoxin, *wherein the administering comprises administering to said patient daily maintenance dosages for a maintenance period to decrease a risk of mortality caused by congestive heart failure, and said maintenance period is greater than six months.*[188]

GSK filed suit against Teva for inducement of infringement based on the Teva label, and on direct infringement by physicians prescribing the drug for the label indications.[189] Teva argued that it had "carved out" the indication for CHF pursuant to 21 U.S.C. § 355(j)(2)(A)(viii), resulting in a "skinny label" with regard to this indication.[190] Thereafter, the FDA compelled Teva to amend its label to include that indication.[191] In addition, Teva argued that it could be liable for inducement only if GSK could show that Teva had "successfully communicated with the direct infringers and 'caused' them to

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[186] *Id.* at 1324.
[187] *Id.*
[188] *Id.* at 1324 (emphasis in original) (where the italicized portion of the claim represents the modifications introduced in prosecution of the reissue application).
[189] *Id.* at 1325.
[190] GlaxoSmithKline LLC v. Teva Pharm. USA, 7 F.4th 1320, 1325-26 (Fed. Cir. 2021).
[191] *Id.* at 1324-25

directly infringe the method in the '000 patent."[192] In a jury instruction the court informed the jury that circumstantial evidence could be used to satisfy this burden.[193]

The jury found that Teva induced infringement of the '000 reissue patent both before and after the label amendment (albeit infringing several claims after but not before that change).[194] The District Court granted Teva's motion for judgment as a matter of law (JMOL) on the basis that GSK had not "caused" physicians to prescribe their product for the infringing uses.[195] Because proof of such causation was required, according to the District Court, its absence precluded the jury from basing its decision on substantial evidence.[196] The Court relied on the "many sources of information available to prescribing physicians" other than Teva's label, including paradoxically GSK's label and promotion of its Coreg® product, in finding this evidentiary deficiency.[197] Also, the Court based its decision on physician testimony that their prescribing behavior relied on "guidelines and research, as well as their own experience" and not Teva's label.[198] "In sum," the Court said, "substantial evidence [did] not support the jury's finding on causation, and therefore [did] not support its verdict that Teva is liable for induced infringement, during both the skinny and full label periods."[199] This appeal followed.[200]

The Federal Circuit reversed, in an opinion by Judge Newman joined by Judge Moore; Chief Judge Prost provided a lengthy, comprehensive dissent.[201] The panel majority relied on the Supreme Court's decision in *Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754 (2011), that copying is evidence of

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[192] *Id.* at 1339.
[193] *Id.* at 1340.
[194] *Id.* at 1325.
[195] GlaxoSmithKline LLC v. Teva Pharm. USA, 7 F.4th 1320, 1325 (Fed. Cir. 2021).
[196] *Id*.
[197] GlaxoSmithKline LLC v. Teva Pharm. USA, Inc., 976 F.3d 1347, 1351 (Fed. Cir. 2020), *reh'g granted, opinion withdrawn* (Feb. 9, 2021), *on reh'g*, 7 F.4th 1320 (Fed. Cir. 2021).
[198] *Id.*
[199] *Id.*
[200] *Id.* at 1347.
[201] *Id.*

inducement, and also found compelling evidence from Teva's website regarding its product's AB rating with GSK's Coreg® product and other promotional content, as well as testimony from GSK's witnesses regarding physician reliance on information from generic drug makers.[202]

The panel majority opined that the District Court erred by not applying the correct legal standard, stating that "precedent makes clear that when the provider of an identical product knows of and markets the same product for intended direct infringing activity, the criteria of induced infringement are met."[203] Considering this precedent, the majority held that "[t]here was ample record evidence of promotional materials, press releases, product catalogs, the FDA labels, and testimony of witnesses from both sides, to support the jury verdict of inducement to infringe the designated claims for the period of the '000 reissue patent."[204]

Chief Judge Prost dissented, as the majority noted, based on her objections to the quanta of evidence adduced and policy consequences should the majority's position be sustained.[205] In the (then) Chief's view, the majority's decision undermines the policy goals embodied in the provisions of the law regarding skinny labels, for balance between the incentives patents provide for pharmaceutical innovation and the public's need for access to that innovation once the patent term has expired.[206] In Judge Prost's view, the majority's decision undermined these policy goals by finding Teva induced infringement by marketing its generic drug product for *unpatented* uses (emphasis in dissent) using its skinny label.[207] The dissent not only disagreed with the majority's decision, but apprehended it to "nullify Congress's statutory provision for skinny labels—creating liability for

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[202] GlaxoSmithKline LLC v. Teva Pharm. USA, Inc., 976 F.3d 1347, 1352-53 (Fed. Cir. 2020), *reh'g granted, opinion withdrawn* (Feb. 9, 2021), *on reh'g*, 7 F.4th 1320 (Fed. Cir. 2021).
[203] *Id.* at 1355.
[204] *Id.*
[205] GlaxoSmithKline LLC v. Teva Pharm. USA, Inc., 976 F.3d 1347, 1352-57 (Fed. Cir. 2020), *reh'g granted, opinion withdrawn* (Feb. 9, 2021), *on reh'g*, 7 F.4th 1320 (Fed. Cir. 2021) (Prost, J., dissenting).
[206] *Id.* at 1357–58.
[207] *Id.*

inducement where there should be none,"[208] contrary to Congressional intent and "slowing, rather than speeding, the introduction of low-cost generics."[209]

The original majority opinion occasioned an outpouring of outrage from industry groups (particularly generic ones) who latched onto the then-Chief Judge's rhetoric in her dissent to the effect that the opinion eviscerated the congressional sanctioning of skinny labels. The Court granted panel rehearing in February that resulted in this second opinion.[210]

In which the outcome has not changed (although the explication of the process aspects of the majority, *per curiam* opinion are perhaps more explicit). After reciting the procedural posture of this decision as a panel rehearing, the majority addressed *amici*'s concerns amply represented in eleven *amicus* briefs, including a brief by one of the architects of the generic's law former Representative Henry Waxman.[211] The opinion recites with approval the behavioral distinctions underpinning the majority's decision based on the law regarding skinny labels:

> Generics *could* be held liable for actively inducing infringement if they marketed a drug with a label describing a patented therapeutic use or if they took active steps to encourage doctors or patients to use the drug in an infringing manner. But generics could *not* be held liable for merely marketing and selling under a 'skinny' label omitting all patented indications, or for merely noting (without mentioning any infringing uses) that FDA had rated a product as therapeutically equivalent to a brand-name drug.[212]

Stating that the panel (or at least the majority) agreed to rehear arguments "to make clear how the facts of this case place it clearly outside the boundaries of the concerns expressed by

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[208] *Id*. at 1358.
[209] *Id.* at 1358.
[210] GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 7 F.4th 1320, 1326 (Fed. Cir. 2021).
[211] *Id.*
[212] *Id.* (emphasis in original).

amici," the opinion states succinctly that the basis for their decision that the jury correctly found Teva liable for inducing infringement was "by marketing a drug with a label *encouraging a patented therapeutic use*."[213] The opinion also states more precisely the procedural basis for their opinion: "[t]his is a case in which substantial evidence supports a jury finding that the patented use was on the generic label at all relevant times and that, therefore, Teva failed to carve out all patented indications" and that this decision is a "narrow, case-specific review of substantial evidence does not upset the careful balance struck by the Hatch-Waxman Act regarding section viii carve-outs."[214] The remainder of the majority opinion sets forth the evidentiary basis for their opinion, that there was sufficient evidence including expert testimony and marketing efforts occurring both before and after FDA-mandated changes to Teva's label to satisfy the substantiality standard and that the District Court erred in granting Teva JMOL to the contrary (*inter alia* including specific errors in treating factual questions as legal ones that the majority state were "not this court or the district court, to resolve").[215]

The majority also affirmed the jury's damages calculations, which apparently played a much less significant part of the controversy surrounding this appeal, albeit likely being at least as important to the parties.[216] Adding insult to injury, the majority awarded costs to GSK.[217]

Former Chief Judge Prost remained unconvinced in her dissent to this second majority opinion, in large part because this outcome undermines the congressionally sanctioned skinny label regime if only by rendering it much more case- and fact-specific than she perceives Congress intended.[218] The outcome-based philosophy of the dissent is presaged in its first sentence, where Judge Prost reminds the reader that "GSK's patent on carvediol expired in 2007" followed by the statement that "[b]ecause the FDA cannot authorize a generic version of a drug that would

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[213] *Id.* (emphasis in original).
[214] *Id.*
[215] GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 7 F.4th 1320, 1327-31 (Fed. Cir. 2021).
[216] *Id*. at 1340-41.
[217] *Id.* at 1341-42.
[218] *Id*. at 1342-43.

infringe a patent, this one remaining patented use could have prevented a less-expensive, generic carvedilol from coming to market altogether—even though the drug *itself* and other uses of it were unpatented."[219] The skinny label regime was Congress's solution to the problem it saw coming in Judge Prost's view. The majority's decision thwarts this intent, in Judge Prost's view, based on evidence of inducement that was "thin to nonexistent."[220] The District Court had properly exercised its supervisory role in remedying a situation where a jury comes to the wrong conclusion, based on Judge Prost's evaluation of the evidence before it.[221] The Judge sets forth her motivation for writing (once again) in dissent and that the majority's attempt to provide a comforting standard falls short in her opinion:

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

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[219] GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 7 F.4th 1320, 1342 (Fed. Cir. 2021) (Prost, J., dissenting).
[220] *Id.*
[221] *Id*. at1349.

> access to generic versions of unpatented drugs with unpatented uses.[222]

The contrasting opinions by the majority and the dissent raise the issue (outside the policy one) of the extent to which a reviewing court can make judgments on the substantiality of the evidence upon which a jury bases its verdict. The substantial evidence standard is intentionally deferential ("more than a scintilla"), based on the prudent principle that a jury has had the opportunity to hear evidence from witnesses and gauge the weight their testimony is given, based on considerations (demeanor, for example) unavailable to a court on appeal.[223] JMOL includes additional considerations including the district court's opportunity for observing this same inferential evidence. Here, the majority applied Third Circuit law on the standard for reviewing JMOL decisions, which according to the opinion was that JMOL should be granted "sparingly" and "only if, viewing the evidence in the light most favorable to the nonmovant and giving it the advantage of every fair and reasonable inference, there is insufficient evidence from which a jury reasonably could find liability.").[224] The majority, both based on the standard of review as well as the conventional deference given to jury verdicts, felt bound by these procedural considerations to reinstate against Teva the jury verdict of induced infringement liability. Judge Prost, viewing the matter on outcome for policy grounds once again disagreed. The only aspect that has changed, to the extent it has, is a perhaps comforting and more informative recitation of the standard the Federal Circuit will apply to induced infringement in the context of skinny labels; by itself this may be, and of course has to be, enough.

F. Amgen Inc. v. Sanofi

About four years ago, the Federal Circuit rendered a decision in *Amgen Inc. v. Sanofi* that brought clarity to how the

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[222] *Id.* at 1343.

[223] *See*, *e.g.*, Casey et al., *Standards of Appellate Review in the Federal Circuit: Substance and Semantics,* 11 FED. CIR. BAR J. 279 (2002).

[224] GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 7 F.4th 1320, 1326 (Fed. Cir. 2021) (citing Marra v. Phila. Hous. Auth., 497 F.3d 286, 300 (3d Cir. 2007)).

Court (and U.S. Patent and Trademark Office) should apply the written description requirement in 35 U.S.C. § 112(a) to properly circumscribe the scope of claims to monoclonal antibodies. On an appeal from remand, the Court took aim at the enablement requirement for antibody claims, with similar, scope-limiting results.

The case arose when Amgen sued Sanofi and Regeneron over sales of Praluent® (alirocumab), which allegedly competes with Amgen's Repatha™ (evolocumab); Amgen's asserted patents, U.S. Patent Nos. 8,829,165 ("'165 patent") and 8,859,741 ("'741 patent"), claim a genus of antibodies that encompass Praluent®.[225] As background, blood plasma contains low-density lipoproteins that bind cholesterol and are associated with atherosclerotic plaque formation.[226] Liver cells express receptors for LDL (LDL-R), wherein binding thereto reduces the amount of LDL cholesterol in blood and reduces the risk of plaque formation and cardiovascular disease.[227] PCSK9 (proprotein convertase subtilisin/kexin type 9) is a molecule that binds to and causes liver cell LDL-R to be destroyed, thus reducing the capacity and effectiveness of the liver cell's ability to reduce serum LDL-cholesterol.[228] The antibodies at issue in this suit bind to PCSK9 and prevent PCSK9 from binding to LDL-R, preventing their destruction and resulting in lower serum cholesterol.[229]

The following claims of the '165 patent were recited in the opinion as being relevant to the issues before the Court:

> Claim 1. An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following

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[225] Amgen Inc. v. Sanofi, Aventisub LLC, 987 F.3d 1080, 1082 (Fed. Cir. 2021).

[226] *See* Boren et al., *Low-density Lipoproteins Cause Atherosclerotic Cardiovascular Disease: Pathophysiological, Genetic, and Therapeutic Insights: A Consensus Statement from the European Atherosclerosis Society Consensus Panel*, EUROPEAN HEART J. 41: 2312-2330 (2020).

[227] *See e.g.,* Goldstein et al., *Receptor-Mediated Endocytosis: Concepts Emerging from the LDL Receptor System,* ANN. REV. CELL BIOL. 1:1-39 (1985).

[228] *Id.* at 1083.

[229] *Id.*

> residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDL[-]R.
>
> Claim 19. The isolated monoclonal antibody of claim 1 wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO:3.
>
> Claim 29. A pharmaceutical composition comprising an isolated monoclonal antibody, wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO: 3 and blocks the binding of PCSK9 to LDLR by at least 80%.[230]

Claims of the '741 patent:

> 1. An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.
>
> 2. The isolated monoclonal antibody of claim 1, wherein the isolated monoclonal antibody is a neutralizing antibody.
>
> 7. The isolated monoclonal antibody of claim 2, wherein the epitope is a functional epitope.[231]

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[230] Amgen Inc. v. Sanofi, Aventisub LLC, 987 F.3d 1080, 1083 (Fed. Cir. 2021).
[231] *Id.*

It is important to note that, while reciting the structure of the residues on PCSK9 (the *antigen*) that are bound by the claimed antibody, the claim does not recite any structural limitations of the *antibody*.[232] The only antibody characteristics recited as limitation are functional, *i.e*., the ability to bind (and not even specifically bind) to at least one of the recited PCSK9 residues and block PCSK9's interaction with the LDL-R.[233]

Evidence at the first trial showed that Amgen had produced a plurality of anti-PCSK9 antibodies and screened them for the ability to inhibit PCSK9 binding to LDL-R.[234] This screening was done using a "trial and error" process that reduced 3,000 human monoclonal antibodies down to 85 antibodies that "blocked interaction between the PCSK9 . . . and the LDLR [at] greater than 90%," of which the specification illustrated the three-dimensional binding arrangement for two (one of which became the Repatha™ antibody) by x-ray crystallography.[235] The specification of the Amgen patents in suit discloses amino acid sequence information for twenty-two human anti-PCSK9 antibodies able to compete for PCSK9 binding with these two more fully characterized antibodies.[236] Regeneron's patents (not at issue here) recited antibody-specific amino acid sequences for its claimed anti-PCSK9 antibodies.[237]

The jury in the earlier case found Amgen's patents not to be invalid.[238] The District Court had excluded evidence relating to written description and enablement based on Praluent® and other post-priority-date antibodies (*i.e*., that were produced after Amgen's earliest priority date).[239] The District Court, relying on *Noelle v. Lederman* as precedent, instructed the jury that an applicant can be entitled to claim scope encompassing generically described antibodies (as was the case for Amgen's

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[232] *Id.*
[233] Amgen Inc., v. Sanofi, 872 F.3d 1367, 1372 (Fed. Cir. 2017).
[234] *Id.*
[235] *Id.*
[236] *Id.*
[237] *Id.*
[238] Amgen Inc., v. Sanofi, 872 F.3d 1367, 1371 (Fed. Cir. 2017).
[239] *Id.*

claims) *provided that* the applicant disclosed a fully characterized, novel antigen.[240]

The Federal Circuit reversed in part, affirmed in part, vacated in part, and remanded, in an opinion by then-Chief Judge Prost, joined by Judges Taranto and Hughes.[241] With regard to the written description question, the Court vacated and remanded on the ground that the District Court had instructed the jury based on the Court's pre-*Ariad* precedent (i.e., *Noelle v. Lederman*), which was inconsistent with the Court's later *en banc* decision in *Ariad v. Eli Lilly & Co*.[242] The Court also found it to be error for the District Court to have excluded evidence regarding enablement related to the "lengthy and potentially undue experimentation" Amgen needed to employ to arrive at its antibodies that fell within the scope of the claims of the '165 and '741 patents.[243] The Federal Circuit ordered a new trial for the District Court to consider post-priority-date evidence for the purposes of both enablement.[244] The Federal Circuit remanded to the District Court for a new trial on written description as well, based on the jury instruction and evidentiary errors.[245]

On remand, the jury found that claim 7 of the '741 patent and claims 19 and 29 of the '165 patent were not invalid.[246] The District Court granted Sanofi's motion for JMOL regarding enablement for these claims but denied JMOL on written description.[247] This appeal followed.

In the instant appeal, the Federal Circuit affirmed in an opinion by Judge Lourie, joined by Chief Judge Prost and Judge Hughes.[248] The panel grasps the nettle of the question before it immediately, stating that "[t]he claimed antibodies are defined by their function: binding to a combinations of sites (residues) on the PCSK9 protein, in a range from one residue to all of them;

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[240] *Id.* at 1367, 1376-7.
[241] *Id.* at 1371.
[242] *Id.* at 1377.
[243] Amgen Inc., v. Sanofi, 872 F.3d 1367, 1375 (Fed. Cir. 2017).
[244] *Id.* at 1371.
[245] *Id.*
[246] Amgen Inc. v. Sanofi, Civil Action No. 14-1317-RGA, 2019 U.S. Dist. LEXIS 146305, at *3 (D. Del. Aug. 28, 2019).
[247] *Id.*
[248] Amgen Inc. v. Sanofi, 987 F.3d 1080, 1082 (Fed. Cir. 2021).

and blocking the PCSK9/LDLR interaction."[249] This aspect of the issue before the Court was just as important and dispositive for the enablement question as it has become for the question of written description under the reasoning set forth in this opinion. The panel reverted (as it must) to its decision in *In re Wands* (and its famous "*Wands* factors"), the dispositive factor in the Court's decision being the amount of experimentation required to encompass the full scope of the claims at issue.[250] Albeit being a question of law, enablement depends particularly on the facts from which conclusions of law are based. The opinion is sensitive to the requirement for patenting that the specification enable practice of the claimed invention throughout its full scope, and with the *Wands* rubrics that the scope of the claims can determine the extent of experimentation required and whether such experimentation is undue.[251] The opinion then focused on claims 19 and 29 of the '165 patent and claim 7 of the '741 patent in rendering its decision.[252]

Amgen's arguments were grounded in disclosure of the specification regarding the type of experimentation required and the guidance provided therein on the extent of such experimentation, while Defendants argued that the scope of these claims encompassed "millions of antibody candidates," that antibody production was unpredictable, and that the specification lacked sufficient guidance because, *inter alia*, "practicing the full scope of the claims requires substantial trial and error."[253] Defendants emphasized not the antibodies Amgen had actually made but "the number of candidates that must be made and tested to determine whether they satisfy the claimed function."[254]

Calling *In re Wands* the Court's "go to" precedent, the opinion states that while itself a monoclonal antibody case, "*Wands* did not proclaim that all broad claims to antibodies are necessarily enabled" because "[f]acts control."[255] Here, the panel considered the facts (and the findings of invalidity) in more

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[249] *Id.* at 1083.
[250] *Id.* at 1084.
[251] *Id*. at 1084-5
[252] *Id.* at 1082.
[253] Amgen Inc. v. Sanofi, 987 F.3d 1080, 1085 (Fed. Cir. 2021).
[254] *Id.*
[255] *Id.* at 1086.

recent cases, including *Wyeth & Cordis Corp. v. Abbott Laboratories*, *Enzo Life Sciences, Inc. v. Roche Molecular Systems, Inc.*, and *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc*.[256] In all these cases, of course, the Federal Circuit found that the claims were not enabled, due to the broad scope of embodiments the claims in these cases encompassed and the amount of undue experimentation required to satisfy the enablement requirement throughout its full scope.[257] The panel set forth its synthesis of the Federal Circuit's analysis regarding satisfaction of the enablement requirement arising from these cases:

> What emerges from our case law is that the enablement inquiry for claims that include functional requirements can be particularly focused on the breadth of those requirements, especially where predictability and guidance fall short. In particular, it is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim.[258]

And cited a footnote in *McRO, Inc. v. Bandai Namco Games Am. Inc*.:

> In cases involving claims that state certain structural requirements and also require performance of some function (e.g., efficacy for a certain purpose), we have explained that *undue experimentation can include undue experimentation in identifying, from among the many concretely identified compounds that meet the structural requirements, the compounds that satisfy the functional requirement*.[259]

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[256] *Id.*
[257] *Id.*
[258] Amgen Inc. v. Sanofi, 987 F.3d 1080, 1086 (Fed. Cir. 2021).
[259] *Id.* at 1087 (emphasis added).

This precedent was controlling here: "[w]hile functional claim limitations are not necessarily precluded in claims that meet the enablement requirement, such limitations pose high hurdles in fulfilling the enablement requirement for claims with broad functional language."[260] As applied to Amgen's claims, the panel recognized each of them to be "a composition claim defined, not by structure, but by meeting functional limitations."[261] This outcome is consistent with *Wands*, according to the opinion, because the "functional breadth" of these claims is "indisputably broad" and "the claims are far broader in functional diversity than the disclosed examples."[262] Taking a real property analogy from *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc*., the opinion states that "[i]f the genus is analogized to a plot of land, the disclosed species and guidance 'only abide in a corner of the genus.'"[263] The opinion also referenced the unpredictability of the antibody arts as a relevant and supportive *Wands* factor in favor of invalidity.[264] The *Wands* quantum of guidance factor was also deficient, according to the opinion, because "any reasonable factfinder would conclude that the patent does not provide significant guidance or direction to a person of ordinary skill in the art for the full scope of the claims."[265]

Importantly, the panel cabined its decision by stating that while the "substantial amount of time and effort" required to produce the scope of antibodies claimed here is undue, "[w]e do not hold that the effort required to *exhaust* a genus is dispositive").[266] The Court struck a balance: "[t]he functional limitations here are broad, the disclosed examples and guidance are narrow, and no reasonable jury could conclude under these facts that anything but 'substantial time and effort' would be required to reach the full scope of claimed embodiments."[267] But the facts here (which distinguish this decision from *Wands*) are

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[260] *Id.* at 1087.
[261] *Id.* at 1088.
[262] *Id.* at 1087.
[263] Amgen Inc. v. Sanofi, 987 F.3d 1080, 1087 (Fed. Cir. 2021).
[264] *Id.* at 1085–86.
[265] *Id.* at 1088.
[266] *Id*. (emphasis in opinion)
[267] *Id.*

that "the evidence showed that the scope of the claims encompasses millions of candidates claimed with respect to multiple specific functions, and that it would be necessary to first generate and then screen each candidate antibody to determine whether it meets the double-function claim limitations."[268] Under these facts, the substantialness of such time and effort was sufficient to be considered undue experimentation by the Court.

While providing yet another fact-bound basis for invalidating (or limiting the scope of) claims to biotechnological inventions, it is unlikely to have been a coincidence that the opinion is authored by Judge Lourie, the architect of the Court's emphasis on structure in applying the written description requirement to biotechnology claims. As the Judge emphasized in his seminal *Regents of the University of California v. Eli Lilly* case:

> Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention."[269]
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention.[270] Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it;

[268] Amgen Inc. v. Sanofi, 987 F.3d 1080, 1088 (Fed. Cir. 2021).
[269] Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997) (quoting Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997).
[270] Fiers v. Revel 984 F.2d 1164, 1171 (Fed. Cir. 1993).

> what is required is a description of the DNA itself."[271]
>
> A written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials. *Fiers*; *In re Smythe* ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus.").[272]

This precedent is thus well-grounded in the Federal Circuit's concern that a patentee must satisfy the *quid pro quo* of the patent grant, so that the specification supports its claims throughout their entire scope, whether on enablement or written description grounds. It has been a bane for the biotechnology industry that the courts (and to a lesser extent, Congress) have played "catchup" in determining the proper application of these standards to biotechnology inventions, resulting in claims that are either invalidated under such changing standards or fail to encompass the activities of accused infringers. But this decision provides a consistent standard ("structure, structure, structure," as recited by former Chief Judge Rader on several occasions) and one that can be applied with consistency even though the resulting scope may prove insufficient to provide enough support to justify the costs of commercialization. And this will be a bane on everyone.

G. Juno Therapeutics, Inc. v. Kite Pharma, Inc.

Dominating the entering gallery of the Impressionists exhibit at the Art Institute of Chicago is Georges Seurat's *A*

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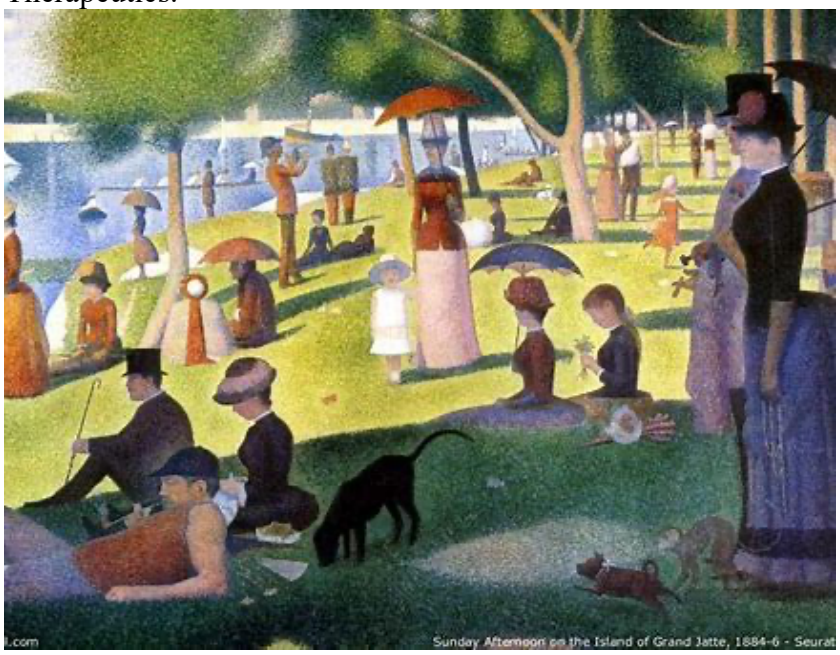
[271] *Id.* at 1170.

[272] Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997).

Sunday on La Grande Jatte (*see* below). Painted in the pointillist style, the work comprises millions of individual paint dots reminiscent of photos taken with late 20th Century technology made up of hundreds of individual photographs. Both these examples of "from many, one" come to mind when considering the Federal Circuit's opinion in *Juno Therapeutics, Inc. v. Kite Pharma, Inc*.; here, the Court overturned a jury's factual determination that Kite had not shown by clear and convincing evidence that the asserted claims were invalid for failure to satisfy the written description requirement of 35 U.S.C. § 112(a).[273] The decision also brings to mind how some inventions are a collection of many individual components or species tied together by basic similarities, without which the patency to be recognized as an invention fails. But when it fails it can, as here, have disastrous consequences for the disappointed patentee; in this case, the Court vacated a $1.2 billion judgment to Juno Therapeutics.[274]



The case arose over Juno's allegations that Kite infringed claims 3, 5, 9, and 11 of U.S. Patent No. 7,446,190 by "the use, sale, offer for sale, or importation of [Kite's] YESCARTA®"

[273] Juno Therapeutics Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021).
[274] *Id.*

product;[275] claim 1 is representative (although the opinion is directed to grounds of invalidation for all asserted claims):

> Claim 1. A nucleic acid polymer encoding a chimeric T cell receptor, said chimeric T cell receptor comprising
>
> (a) a zeta chain portion comprising the intracellular domain of human CD3 ζ chain,
>
> (b) a costimulatory signaling region, and
>
> (c) a binding element that specifically interacts with a selected target, wherein the costimulatory signaling region comprises the amino acid sequence encoded by SEQ ID NO:6.[276]

As explained in the opinion, the invention is related to so-called "CAR-T" anticancer therapy, wherein a chimeric antigen receptor (CAR) directed to T cells is used to stimulate a patient's own immune response against tumor cells in the body causing disease.[277] The components of the claimed invention include the intracellular domain of human CD3 ζ, "a signaling domain that, when the T cell binds to an antigen, is activated to create an initial immune response."[278] This is linked to a costimulatory signaling region, which has a specific amino acid sequence (SEQ ID NO: 6) that is part of naturally occurring CD28 expressed in T cells.[279] Stimulation of this sequence enhances an immune response by, *inter alia*, causing T cells to multiply.[280] The final portion is a specific binding element that binds to an antigen expressed by a target cell such as a tumor.[281] A nucleic acid encoding CAR is introduced into a patient's T cells after isolation from the patient and then returned to the patient's body, wherein these altered T cells specifically bind to the tumor cell, causing the

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[275] Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1334 (Fed. Cir. 2021).
[276] *Id.* at 1333-34.
[277] *Id.* at 1333.
[278] *Id.*
[279] *Id.*
[280] Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1333 (Fed. Cir. 2021).
[281] *Id.*

multiplication of these tumor-specific T cells and resulting in tumor cell death.[282]

A species of the specific binding element at issue in this case is a single chain antibody variable fragment or scFv, produced by linking together antigen-binding portions of the heavy and light chain of an antibody's variable region to form the binding element.[283] Important to the Court's decision, "[e]ach variable region has a unique amino acid sequence that can dictate whether and how an antibody, and thus an scFv, binds to a target."[284] The '190 patent specification discloses only two such svFvs, one that binds CD19 (a protein expressed on the cell surface of diffuse large B-cell lymphoma cells) and one that binds to PSMA, an antigen that is expressed at the cell surface of prostate cancer cells.[285] The specification does not disclose the amino acid sequence of either of these scFvs.[286]

A jury determined that Kite had not shown by clear and convincing evidence that Juno's asserted claims were invalid under the written description requirement of § 112(a) and the District Court denied Kite's motion for judgment as a matter of law directed at overturning this verdict.[287] This appeal followed.

The Federal Circuit reversed in an opinion by Chief Judge Moore, joined by Judges Prost and O'Malley.[288] While the opinion is based on several Federal Circuit opinions rendered in this century, the fundamental (doctrinal) basis for the decision is the Court's opinion in *Regents of the Univ. of Cal. v. Eli Lilly & Co*. which states "[a] written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials.[289]

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[282] *Id.* at 1333–34.
[283] *Id.* at 1333.
[284] *Id.*
[285] Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1333 (Fed. Cir. 2021).
[286] *Id.*
[287] *Id.* at 1334.
[288] *Id.* at 1330.
[289] *Id.* at 1335 (citing Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997) (quoting Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993))).

It will be recalled that this decision stemmed from a time when isolating a gene was a daunting, if not herculean, experimental task, fraught with unpredictability regarding the similarity between a gene isolated from one organism (in the *Lilly* case, the gene encoding rat insulin) compared with another (human insulin). The Court prudently ruled it improvident to hold that a party should be able to claim the undiscovered nucleic acid based on success in discovering a different one.[290] This factual predicate has not existed for almost a generation.

The panel agreed with Kite's contention that "the '190 patent discloses neither representative species nor common structural features of the claimed scFv genus to identify which scFvs would function as claimed."[291] The claims cover an enormous number (millions or billions) of scFv candidates, only a fraction of which satisfy the functional binding limitation for any given target, and that the written description does not meet the written description requirement for this functional binding limitation [and] the scFv field is unpredictable since an scFv's binding ability depends on a variety of factors.[292]

The opinion assesses the failure to satisfy the written description requirement for dependent claims 3 and 9, which the Court properly identifies as "[t]he broadest asserted claims."[293] These claims recite scFv binding elements that "specifically interact[] with a selected target."[294] The specification discloses that "[t]he target . . . can be *any target of clinical interest* to which it would be desirable to induce a T cell response," or as the opinion paraphrases "*any* scFv for binding *any* target."[295] Rarely has a validity kiss of death been stated in fewer words. The opinion states in this context that the specification's written description "fails to provide a representative sample of species within, or defining characteristics for, that expansive genus," *i.e*.,

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[290] Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997)
[291] Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1336 (Fed. Cir. 2021).
[292] *Id*.
[293] *Id.*
[294] *Id.*
[295] *Id.* (emphasis in opinion).

it utterly fails to satisfy the *Eli Lilly* test for satisfying the written description requirement.[296]

The opinion then explicates the degree to which the '190 patent specification is deficient in its disclosure, being limited to two examples of this "expansive genus."[297] In particular, the specification designates the targets merely by their "alphanumeric designations" (*i.e.*, providing no sequence information), while noting elsewhere that this feature is not dispositive.[298] The panel rejects Juno's argument that this disclosure constitutes a representative number of species of the scFv genus, if only because "there is no limit as to the particular target" encompassed by claims 3 and 9, asserting "the patent needed to demonstrate to a skilled artisan that the inventors possessed and disclosed in their filing the particular species of scFvs that would bind to a representative number of targets."[299]

The panel was not convinced that the expert testimony Juno adduced to counter Kite's invalidity allegations was sufficient (again, disregarding factual determinations by a jury having the conventional opportunity to judge demeanor, believability, and other aspects of testimony usually kept somewhat sacrosanct within the province of the jury). Yet the opinion is careful to distinguish its decision here from the Court's opinion in *Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005), based on the error by the Board of Patent Appeals and Interference in that case to require an applicant to recite in its specification sequences "already known in the prior art."[300] The opinion adheres to the requirement set forth in *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336 (Fed. Cir. 2010) (*en banc*), that the purpose of the written description requirement is to "lead a person of ordinary skill in the art to understand that the inventors possessed the entire scope of the claimed invention,"[301] something that the Court held Juno's specification did not do.

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[296] Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1336 (Fed. Cir. 2021).
[297] *Id.*
[298] *Id.*
[299] *Id.*
[300] *Id.* at 1337 (citing Capon v. Eshhar, 418 F.3d 1349, 1357 (Fed. Cir. 2005)).
[301] Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1336 (Fed. Cir. 2021) (citing Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc)*.

And the Court further rejected Juno's contention that the fact that scFvs were generally known was sufficient (this being essentially an argument sounding in enablement rather than in written description jurisprudence).[302] The Court sets forth the impossible standard: "[t]o satisfy written description, however, the inventors needed to convey that they possessed the claimed invention, which encompasses all scFvs, known and unknown, as part of the claimed CAR that bind to a selected target. Even accepting that scFvs were known and that they were known to bind, the specification provides no means of distinguishing which scFvs will bind to which targets.[303]

The opinion then turns to the alternative *Lilly* basis for satisfying the written description requirement, disclosure of common structural features, and finds the '190 specification similarly wanting. While acknowledging that scFvs have "structural commonalities,"[304] the differences in amino acid sequences are what determine different specificities to different antigens, and thus the '190 specification "fails to disclose a way to distinguish those scFvs capable of binding from scFvs *in*capable of binding those targets."[305] This situation is reminiscent of the (frankly very much different) circumstances in the *Ariad* case, because the '190 patent is claiming a "problem to be solved while claiming all solutions to it . . . cover[ing] any compound later actually invented and determined to fall within the claim's functional boundaries."[306]

The opinion then asserts as a basis of its recent (and philosophical twin) opinion in *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149 (Fed. Cir. 2019), as well as the more distant (but more antibody-related) decision in *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014), that the broader principle that functional similarities are not enough to satisfy the written description requirement

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[302] *Id.*
[303] *Id.*
[304] *Id.* at 1336-7.
[305] Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1339 (Fed. Cir. 2021 (emphasis in opinion).
[306] *Id.*

absent "an established correlation between the structure and the claimed function."[307]

The opinion next turns to asserted claims 5 and 11, which recite the further limitations that the scFv bind to CD19.[308] This limitation does nothing to satisfy the written description requirement, the panel stating that while there are "four or five" scFvs that bind to CD19 known in the prior art, "the universe of possible sequences for scFvs is in the range of 'millions or billions'" according to Kite.[309] This is enough, accompanied with the total lack of any disclosure (such as "exemplary amino acid sequence") for the panel to determine that the '190 specification lacks disclosure of any general structural characteristics and thus would not be considered by the skilled artisan to show possession of the invention having the scope claimed.[310] The panel expressly rejects both expert and inventor testimony to the contrary, characterizing some of it as "circular reasoning" with regard to testimony that the witness was not aware of any functional CD19-specific svFv that was not functional in the CAR-T context.[311] At most, the panel was willing to concede that the "invention" was the "backbone" comprising the combination of the intracellular domain of human CD3 ζ and the costimulatory sequence identified by SEQ ID NO: 6.[312] But, of course, the satisfaction of the written description requirement for these claims requires *all* components of the claimed invention to be sufficiently disclosed, and the deficiencies in disclosure of the svFv portions was enough to invalidate all asserted claims.[313]

To continue the artistic analogy, the situation with all antibody-related claims (and in truth a great many chemical claims; see *Idenix*) is that there are sufficiently large combinatorial universes of species that only a vanishingly small number of them are (or practically can be) disclosed in a

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[307] *Id.* (citing AbbVie Deutschland GmbH v. Janssen Biotech, Inc., 759 F.3d 1285, 1301-02) (Fed. Cir. 2014).
[308] *Id.* at 1340.
[309] *Id.*
[310] Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1340 (Fed. Cir. 2021).
[311] *Id.* at 1341.
[312] *Id.*
[313] *Id.* at 1341–42.

specification, like only dozens of the millions of paint dots making up Seurat's masterpiece. Under these conditions, the painting would be rendered as something perhaps more akin to Jackson Pollock's work, and the picture produced thereby lacking entirely the characteristics that have made it a masterpiece. Returning to patent law, the scope of claims relating to antibodies (and soon perhaps more mundane chemical species) will likely be limited to a "what you see (*i.e*., disclose expressly) is what you get (patented)" model, which will no doubt (by reducing valid claim scope) allow copyists to piggyback on others' inventions to make their own competing species of valuable therapeutic agents. This will likely increase the universe of potential commercial embodiments for antibody-related inventions; whether first mover advantages will be enough to make advantageous commercialization by inventors and their companies is another question.

H. Belcher Pharmaceuticals, LLC v. Hospira, Inc.

Imposition of liability under the equitable doctrine of inequitable conduct (as it has been variously defined) can result in a patent being held unenforceable. It is for this reason that former Chief Judge Rader called it the "atomic bomb of patent law".[314] The Federal Circuit's most recent attempt to cabin the application of the doctrine arose in *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276 (Fed. Cir. 2011) (*en banc*), and has generally led to narrowing the application of the doctrine by requiring a showing of materiality and intent to deceive, each under a clear and convincing evidentiary standard.[315] However, sometimes even under this more exacting standard, the patency of the violation is evident, as was the case in *Belcher Pharmaceuticals, LLC v. Hospira, Inc.* As the Christian Bible says, "no one can serve two masters,"[316] at least not well. But the attempt to satisfy the statutory requirements for patenting, particularly non-obviousness, can invite contradictory attempts

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[314] *See* Aventis Pharma S.A. v. Amphastar Pharms., Inc., 525 F.3d 1334, 1349 (Fed. Cir. 2008) (Rader, J., dissenting).
[315] *See* Regeneron Pharma., Inc. v. Merus N.V., 864 F.3d 1343, 1350 (Fed. Cir. 2017).
[316] Matthew 6:24.

to satisfy regulatory requirements before the FDA. And that can (and did) lead to the outcome in this case.

The case arose in ANDA litigation involving Belcher Pharmaceuticals' 1 mg/mL injectable L-epinephrine formulation, for which Hospira filed an ANDA and certified under 21 U.S.C. § 355(b)(2)(A)(iv) (a Paragraph IV certification) that Belcher's U.S. Patent No. 9,283,197 was invalid, not infringed, or unenforceable.[317] The '197 patent addressed compositions of L-epinephrine formulated using methods to avoid oxidation of L-epinephrine to adrenalone (which reduced its potency), and to avoid racemization, a separate basis for loss of potency.[318] Both these chemical reactions are related to the pH of the formulation solution, with oxidation increasing with higher pH conditions and racemization increasing at lower pH levels.[319] As stated in the opinion, "[i]n other words, when an epinephrine solution becomes more acidic (i.e., pH decreases), racemization increases and oxidation decreases, and when the solution becomes more basic (i.e., pH increases), oxidation increases and racemization decreases."[320] This led to the prior art understanding that the optimum pH to minimize the effects of racemization and oxidation was between pH 3.0-3.8.[321]

Belcher's NDA specified that its formulation differed from prior art formulations that included sodium metabisulfite as an antioxidant and an amount of L-epinephrine in 10% excess (to account for losses of potency for whatever reason).[322] Belcher's NDA specified that its product did not contain sulfite antioxidants or other preservatives but rather contained an increased amount of sodium chloride and 15% overage of L-epinephrine at a pH of between 2.8 and 3.3.[323] Importantly for the inequitable conduct question in this litigation, Belcher responded to FDA inquiries as follows:

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[317] Belcher Pharms., LLC v. Hospira, Inc., 1 F.4th 1345, 1350 (Fed. Cir. 2021).
[318] *Id.* at 1347.
[319] *Id.*
[320] *Id.*
[321] *Id.*
[322] Belcher Pharms., LLC v. Hospira, Inc., 1 F.4th 1345, 1349-50 (11th Cir. 2021).
[323] *Id.* at 1347.

> Addressing the FDA's question on racemization, Belcher explained that "[r]acemization of the enantiomerically pure L-Epinephrine isomer in injectable formulations of epinephrine is a well-known process," citing literature authored by Fylligen and Stepensky. Responding to the FDA's inquiry on manufacturing process for the stability validation batches, Belcher stated that the only difference between the relied-upon Sintetica batches and Belcher's proposed formulation "is related to the in[-]process pH" and that it "consider[ed] the in[-] process pH change to be a very minor change not requiring additional stability studies." Belcher also explained that the release specification of 2.2 to 5.0 "complies with [the] USP specification and stays unchanged between all the batches.".[324]

In addition, Belcher's consultants advised that the pH maintained during formulation be kept at the art-recognized pH of 2.8-3.3; "Belcher followed that advice," according to the opinion.[325]

Belcher asserted claims 6 and 7 of the '197 patent in the ensuing ANDA litigation:

> Claim 6. An injectable liquid pharmaceutical formulation of l-epinephrine sterile solution; said liquid pharmaceutical formulation having a pH between 2.8 and 3.3; said injectable liquid pharmaceutical formulation compounded in an aqueous solution as 1.0 to 1.06 mg/mL l-epinephrine, and further including a tonicity agent; said liquid pharmaceutical formulation including no more than about 6% d-epinephrine and no more than about 0.5% adrenalone at release, and no more than about 12% d-epinephrine and no more than

[324] *Id.* at 1348.
[325] *Id.*

> about 0.5% adrenalone over a shelf-life of at least 12 months.[326]
>
> Claim 7. The said injectable liquid pharmaceutical formulation of claim 6 further having a concentration of 1 mg per mL l-epinephrine.[327]

In the single Office Action during prosecution, Belcher argued that their claims were non-obvious over a prior art reference that disclosed "a 1 mg/mL epinephrine injection that was free of preservatives and antioxidants, was made in an oxygen free (i.e., nitrogen) environment, and had a pH range of 2.2 to 5.0" because the pH range of 2.8-3.3 "was unexpectedly found to be critical by the Applicant to reduce the racemization of l-epinephrine" and produced unexpected results.[328] These arguments were noted in the resulting Notice of Allowance as the basis upon which the Examiner allowed the claims, making subsequent establishment at trial of the materiality of Applicant's arguments in this regard rather easy.[329]

Hospira's inequitable conduct allegations centered on the knowledge and actions, =including failing to disclose to the Examiner, of three pieces of information by Belcher's Chief Science Officer who, by his own admission, was "involved in the development of Belcher's NDA product and participated in drafting the NDA," and "involved in the prosecution of the '197 patent" which included helping in application drafting and responding to the Examiner's Office Action (despite being neither a patent agent nor patent attorney).[330] The three pieces of information undisclosed to the patent Examiner were: (1) a label by third party (JHP) for a 1mg/mL epinephrine product; (2) Sintetica's prior art product (0.1 mg/mL l-epinephrine formulation); and (3) the 2004 Stepensky reference, *Long-term stability study of L-adrenaline injections: kinetics of sulfonation and racemization pathways of drug degradation*, 93(4) J.

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[326] *Id.* at 1349.
[327] Belcher Pharms., LLC v. Hospira, Inc., 1 F.4th 1345, 1349 (11th Cir. 2021).
[328] *Id.* at 1349–50.
[329] *Id*. at 1350.
[330] *Id.* at 1351.

PHARM. SCI. 969–80.[331] Hospira's expert testified persuasively that this information was but-for material on the issues of the pH range and the level of impurities.[332] As for intent to deceive, the District Court cited Belcher's CSO's behavior (it being evident that he was under the duty of candor set forth in 37 C.F.R. § 1.56) before the FDA that "[Belcher's CSO] knew that Belcher described the claimed pH range of 2.8 to 3.3 as 'old'; that Belcher disclosed Stepensky, which teaches an overlapping pH range of 3.25 to 3.70; that Belcher had submitted data on Sintetica's and JHP's products showing a pH within the claimed range; and that Belcher switched from a lower pH range to the claimed 2.8 to 3.3 pH range at least in part to expedite FDA approval because that range matched the pH range of Sintetica's products," none of which he disclosed to the patent Examiner.[333]

In contrast, the District Court found that "[Belcher's CSO] did not merely withhold this information but also used emphatic language to argue that the claimed pH range of 2.8 to 3.3 was a 'critical' innovation that 'unexpectedly' reduced racemization."[334] With regard to intent, the District Court found it "implausible" that Belcher's CSO considered this information to be irrelevant and also asserted that his "repeated efforts to evade questioning and inject attacks of the prior art into his answers [while testifying] raised serious questions as to his credibility."[335] On this basis, the District Court held the '197 patent to be unenforceable for inequitable conduct.[336] This appeal followed.

The Federal Circuit affirmed, in an opinion by Judge Reyna, joined by Judges Taranto and Stoll.[337] The panel opinion made short work of the materiality prong of inequitable conduct, *inter alia* because the District Court held claims 6 and 7 to be invalid for obviousness over cited references that included one of the withheld pieces of information, JHP's epinephrine product.[338]

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[331] *Id.*
[332] Belcher Pharms., LLC v. Hospira, Inc., 1 F.4th 1345, 1349 (11th Cir. 2021).
[333] *Id.* at 1351.
[334] *Id.* at 1352.
[335] *Id.*
[336] *Id.*
[337] Belcher Pharms., LLC v. Hospira, Inc., 1 F.4th 1345, 1345 (11th Cir. 2021).
[338] *Id.* at 1352–53 (citing Aventis Pharma S.A. v. Hospira, Inc., 675 F.3d 1324, 1334 (Fed. Cir. 2012)).

Regarding the intent-to-deceive prong of the *Therasense* test, the Court noted that Belcher's CSO was aware that the pH 2.8-3.3 range was known in the art and that Belcher had reverted to that range (after originally pursuing formulations having a pH range of 2.4-2.6) as a means to obtain FDA approval more expeditiously because, in part, that range had been used in the Sintetica prior art product.[339] Nevertheless, Belcher's CSO affirmatively asserted (in the '197 specification and in argument before the Examiner) that the pH 2.8-3.3 range was "a 'critical' innovation contrary to the knowledge of a person of ordinary skill in the art that yielded 'unexpected results,' namely reducing racemization of l-epinephrine."[340] These representations were "false" and "a fiction" according to the District Court and the Federal Circuit saw no reason to disagree.[341] Belcher maintained before the District Court – and before the Federal Circuit on appeal – that Belcher's CSO's representations were based on a genuine belief that the withheld information was irrelevant due to the high overage amounts used in their product.[342] The Federal Circuit, like the District Court, rejected what it called these "post hoc rationales," citing *Aventis* for similar circumstances and crediting the District Court for its firsthand assessment of Belcher's CSO's lack of credibility, stating that this conclusion was also supported by other evidence of record such as the substance of his representations to the FDA and patent Examiner and differences if not outright contradictions between them.[343]

Having found no clear error in the District Court's assessment and factual findings on either materiality or intent, the Federal Circuit affirmed the District Court's finding of inequitable conduct and resulting unenforceability of the '197 patent.[344]

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[339] *Id.* at 1353.
[340] *Id.* at 1353-54.
[341] *Id.* at 1354.
[342] Belcher Pharms., LLC v. Hospira, Inc., 1 F.4th 1345, 1354 (11th Cir. 2021).
[343] *Id.*
[344] *Id*.

I. Bio-Rad Laboratories, Inc. v. International Trade Commission

In April, the Federal Circuit affirmed the imposition of an exclusion order under 19 U.S.C. § 1337 (Section 337 of the Tariff Act of 1930) by the Federal Trade Commission against 10X Genomyx (an intervenor in this appeal) over the importation of patented microfluidic chips, in *Bio-Rad Laboratories, Inc. v. International Trade Commission*.[345] 10X Genomyx obtained a similar exclusion order against Bio-Rad in a case appealed last month.[346]

In this action, Bio-Rad filed a complaint against 10X Genomyx, alleging that the importation of certain microfluidics chips infringed claims of U.S. Patent Nos. 9,500,664, 9,636,682, and 9,649,635.[347] Representative claims set forth in the opinion are these:
The '664 patent:

> Claim 1. A system for forming a plurality of ***sample***-containing droplets suspended in a background fluid, comprising:
>
> a substrate having a bottom surface and a top surface;
>
> a ***sample*** well, a background fluid well, and a droplet well each having an upper region protruding from the top surface of the substrate;
>
> a network of channels formed in the bottom sur- face of the substrate and fluidically interconnecting the ***sample*** well, the background fluid well, and the droplet well; and

[345] Bio-Rad Laboratories, Inc. v. Int'l. Trade Comm., 998 F.3d 1302, 1322-23 (Fed. Cir. 2021)
[346] *See* Kevin E. Noonan, *Bio-Rad Laboratories, Inc. v. Int'l Trade Comm. (Fed. Cir. 2021)*, PATENT LAW WEBLOG (May 19, 2021), https://www.patentdocs.org/2021/05/bio-rad-laboratories-inc-v-intl-trade-comm-fed-cir-2021.html.
[347] Bio-Rad Laboratories, Inc. v. Int'l. Trade Comm., 998 F.3d 1302, 1323 (Fed. Cir. 2021).

> a ***droplet generation region*** defined by the network of channels and configured to generate sample-containing droplets suspended in the background fluid;
>
> wherein the ***droplet generation region*** is defined by the intersection of a first channel, a second channel, and a third channel;
>
> wherein the first channel is configured to transport ***sample***-containing fluid from the ***sample*** well to the droplet generation region, the second channel is configured to transport background fluid from the background fluid well to the ***droplet generation region***, and the third channel is configured to transport ***sample***-containing droplets from the d***roplet generation region*** to the droplet well; and
>
> wherein the substrate and the upper region of each well are injection molded as a single piece.[348]

The '682 patent:

> Claim 14. A system for generating droplets, comprising:
>
> a device including a row of sample wells each configured to receive sample-containing fluid, a row of continuous-phase wells each configured to receive continuous-phase fluid, and a row of droplet wells, the device also including a corresponding channel network for each sample well, the channel network including a ***droplet-generation region*** and fluidically connecting the sample well to one of the continuous-phase wells and one of the droplet wells;

[348] *Id.* at 1324.

> a holder for the device;
>
> a gasket configured to be attached directly to the holder, such that the gasket extends over each sample well, each continuous-phase well, and each droplet well; and
>
> an instrument configured to
> (a) receive an assembly including the device, the holder, and the gasket,
> (b) engage the gasket with a manifold, and
> (c) apply positive pressure and/or negative pressure to the device via the manifold, such that ***sample***-containing fluid flows from each sample well to the corresponding ***droplet-generation region***, continuous-phase fluid flows from each continuous-phase well to the corresponding ***droplet-generation region***, and sample-containing droplets flow from each ***droplet-generation*** region to the corresponding droplet well.[349]

The '635 patent:

> Claim 1. A system to form and concentrate an emulsion, comprising:
>
> A device including a ***sample*** well configured to receive ***sample***-containing fluid, a continuous-phase well configured to receive continuous-phase fluid, and a droplet well, the device also including a channel network having a first channel, a second channel, and third channel that meet one another in a ***droplet-generation region***; and
>
> an instrument configured to operatively receive the device and to create

[349] *Id.*

> (a) a first pressure differential to drive ***sample***-containing fluid from the ***sample*** well to the ***droplet-generation region*** via the first channel, continuous-phase fluid from the continuous-phase well to the ***droplet-generation region*** via the second channel, and ***sample***-containing droplets from the ***droplet-generation region*** to the droplet well via the third channel, such that the droplet well collects an emulsion including ***sample***- containing droplets disposed in continuous-phase fluid, and
> (b) a second pressure differential to decrease a volume fraction of continuous-phase fluid in the emulsion, after the emulsion has been collected in the droplet well, by selectively driving continuous-phase fluid, relative to ***sample***-containing droplets, from the droplet, from the droplet well via the third.[350]

The technology at issue was related to microfluidics chips for performing bioanalytic assays using small amounts of sample contained in microdroplets, defined in the opinion as "a contiguous amount of one type of fluid that is encapsulated within a different fluid," wherein "the inner fluid is aqueous or water-based, while the outer fluid is oil" in typical embodiments.[351] Generally, the sample is contained in the aqueous inner fluid.[352] An advantage of this arrangement was that each sample could be subject to chemical reactions in its own droplet (a "mini-test tube" according to the '664 patent) and that a larger number of chemical reactions can be performed in parallel.[353] Such reactions are performed on microfluidic chips as claimed in the patents-at-issue (the opinion noting that such

[350] *Id.* at 1324–25 (wherein the text in italics and boldface is the claim term at issue).
[351] *Id.* at 1323.
[352] Bio-Rad Laboratories, Inc. v. Int'l. Trade Comm., 998 F.3d 1320, 1323 (Fed. Cir. 2021).
[353] *Id.*

microchips were known in the art at the priority dates of these patents).[354]

As set forth in the opinion, the named inventors of the asserted patents previously worked for a company, QuantaLife, Inc., that was thereafter acquired by Bio-Rad. These inventors had agreed in their employment contracts with QuantaLife to promptly assign to the company their rights to the provisional applications that matured into the three patents-in-suit, which they assigned to Bio-Rad after the acquisition.[355] These inventors later left Bio-Rad and formed 10X Genomics, where they developed the technology asserted by Bio-Rad to infringe the patents-in-suit. Two embodiments of these chips were at issue in this case: (1) GEM Chips having

> Input wells for three different materials—gel beads, sample, and oil—and one output well to collect droplets. The microfluidic channels on the GEM Chips intersect each other such that the gel bead and sample fluid are mixed at a first intersection, the resulting mixture enters into a microfluidic channel referred to as a 'singulation channel,' and the mixture then mixes with the oil at a second intersection.[356]

and (2) Chip GB, which 10X Genomyx utilizes

> to generate droplets that are used to make the gel beads that are packaged with the GEM Chips and sold to customers. The Chip GB contains one input well that holds an aqueous monomer solution, a second input well that holds oil, and channels from each of the wells that intersect each other to allow for the formation of droplets that are collected in a droplet well. Over time, the monomers within each

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[354] *Id.*
[355] *Id.* at 1326.
[356] *Id.*

> droplet polymerize, and the droplet becomes a gel bead.[357]

Responsive to Bio-Rad's complaint, an Administrative Law Judge (ALJ) granted summary determination that the doctrine of assignor estoppel precluded 10X Genomyx from challenging the validity of the asserted patents.[358] The ALJ then construed the claims with regard to the term "droplet-generation region" to mean "the intersection of (1) a sample-containing dispersed phase fluid inlet channel, (2) a continuous phase fluid inlet channel, and (3) a droplet outlet channel."[359] The parties agreed that the term "sample" meant "a compound, composition, and/or mixture of interest, from any suitable source(s)."[360]

Under this construction, the ALJ determined that 10X Genomyx's GEM Chips infringed the three patents and that while the GB Chips infringed the claims of the '682 and '635 patents they did not infringe asserted claims 1 and 14 of the '664 patent because the monomer solution used with those chips was not a "sample" under the agreed-upon construction.[361] The Commission reviewed and adopted the ALJ's findings that the GEM chips infringed the three asserted patents (either literal, induced, or contributory infringement) but the GB chips did not literally infringe the '644 patent.[362] The parties appealed each of the adverse determinations against them.

The Federal Circuit affirmed, in an opinion by Judge Lourie, joined by Judges Newman and Dyk.[363] With regard to Bio-Rad's appeal, the panel addressed two erroneous assertions made by the ALJ. The first was that because the GB chips did not involve a sample, they did not have structures corresponding to "a 'sample well,' a sample channel, sample-containing droplets, or the claimed 'droplet generation region.'"[364] Second,

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[357] Bio-Rad Laboratories, Inc. v. Int'l. Trade Comm., 998 F.3d 1320, 1326 (Fed. Cir. 2021).
[358] *Id*.
[359] *Id.*
[360] *Id.* at 1327-28.
[361] *Id.* at 1334-35.
[362] Bio-Rad Laboratories, Inc. v. Int'l. Trade Comm., 998 F.3d 1320, 1327 (Fed. Cir. 2021).
[363] *Id.*
[364] *Id.* at 1328.

Bio-Rad argued that due to the structural nature of the elements of the claims (wells and channels), infringement could not depend on what was in those wells and channels.[365] The "sample" limitation was assessed based on the parties' agreed-upon definition which was taken from the '664 specification, and the Federal Circuit found no error in the ALJ relying on witness testimony that what was encapsulated in 10X Genomyx's GB Chip was not a sample under the agreed-upon definition but rather was "an input for a reagent production process."[366] This determination was also consistent with distinctions made in the '664 specification regarding the differences between a sample ("something that the customer cares about and wants to analyze") and a reagent ("which 'are of no interest'").[367] This interpretation was also consistent with exemplified samples ("blood and plasma, and research samples such as culturued [sic] cells or bacteria") and reagents, defined as ""a compount [sic], set of compounds, and/or composition that is combined with a sample in order to perform a particular test(s) on the sample").[368] Bio-Rad's challenge was on these definitions, which they argued imported unsupported additional limitations into the claim term and were based on faulty conclusions, such as the monomer being "of no interest" under circumstances where "10X carefully designed the monomer solution with particular concentrations of ingredients to serve as a gel bead precursor solution".[369] The Court agreed with the Commission and 10X Genomyx that Bio-Rad's arguments in this regard were directed to the Commission's factual determinations, and that under the Administrative Procedures Act the Commission's factual determinations were entitled to deference and "substantial evidence" review, which Bio-Rad did not satisfactorily challenge.[370] In this regard, the opinion states that "[t]he compelling factor here is the distinction between 'samples' and 'reagents'" as set forth (and relied upon by the Commission) in

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[365] *Id.*
[366] *Id.*
[367] Bio-Rad Laboratories, Inc. v. Int'l. Trade Comm., 998 F.3d 1320, 1328 (Fed. Cir. 2021).
[368] *Id.* (emphasis in opinion).
[369] *Id.*
[370] *Id.* at 1329.

the '664 patent specification.[371] In particular, the panel did not find that consideration of the term "of interest" in construing the meaning of the claims and applying that construction to 10X Genomyx's GB chips imported any untoward subjectivity to the analysis.[372]

Turning to Bio-Rad's second argument, the Federal Circuit considered this argument to "fail[]" for several substantive and procedural reasons.[373] The opinion states that it is "not clear" that Bio-Rad made this argument before the Commission, and accordingly should be precluded from presenting it on appeal in the first instance.[374] Even if this procedural hurdle had been overcome, the panel asserted Bio-Rad would not prevail because its argument rested on "rewriting the claims in an oversimplified form and removing all limitations that differentiate the recited structures from each other."[375] The opinion illustrates this defect in Bio-Rad's argument by comparing the description of what is claimed in their brief with the actual claims, saying that the former "is not remotely close to what the claim says" it is.[376] "Inventors are masters of their claims, and the words they use to describe and claim their invention are decisive and binding," said the Court, and in the panel's view the '664 inventors did not claim their invention as broadly as it would needed for Bio-Rad to prevail in its infringement argument here.[377] It was the inventors' decision "to characterize the wells and channels based on the material contained within them," according to the Court, and this choice cannot be "escaped" by recourse to the principle that "apparatus claims cover what a device is, not what a device does."[378]

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[371] *Id.*
[372] Bio-Rad Laboratories, Inc. v. Int'l. Trade Comm., 998 F.3d 1320, 1329 (Fed. Cir. 2021).
[373] *Id.*
[374] *Id.* at 1331 (citing Interactive Gift Express, Inc. v. CompuServe Inc., 256 F.3d 1323, 1346 (Fed. Cir. 2001)).
[375] *Id.*
[376] *Id.*
[377] Bio-Rad Laboratories, Inc. v. Int'l. Trade Comm., 998 F.3d 1320, 1331 (Fed. Cir. 2021).
[378] *Id.* (quoting Hewlett-Packard Co. v. Bausch & Lomb, Inc., 909 F.2d 1464, 1468 (Fed. Cir. 1990)) (emphasis in original opinion).

10X Genomyx's appeal challenged the Commission's determination that its GEM chips infringed the asserted claims of the three patents-in-suit. The first of two challenges by 10X Genomyx was based on whether the accused GEM chips contained the "droplet-generating region" required by the claims.[379] 10X Genomyx's other challenge was directed at whether the evidence supported the Commission's determination regarding indirect infringement.

The challenge regarding whether GEM chips comprised the "droplet-generating region" was on claim construction, where 10X Genomyx asserted this alternative construction of the term:

> the intersection of the sample input channel that receives the dispersed phase fluid from the sample well, the oil input channel that receives the continuous-phase or background fluid from the oil well, and the droplet outlet channel that outputs to the droplet well, at which droplets are generated.[380]

Bio-Rad (and the Commission) countered that 10X Genomyx had waived this argument three times: "first, by failing to propose it in the parties' Joint Claim Construction Chart; second, by failing to seek review by the Commission of the ALJ's waiver finding; and third, by failing in its principal brief to ask this court to overturn the ALJ's waiver finding."[381] The Court was not convinced, citing instances in the record including that the construction proposed here was identical to 10X Genomyx's initial construction asserted before the ALJ and maintained before the Commission, and that this consistent assertion of its construction did not constitute a waiver that would preclude 10X Genomyx from making its alternative claim construction argument on appeal.

Nevertheless, on the merits, the panel found that the ALJ had correctly construed the term based on the plain meaning of the claims and the specifications of the patents-in-suit. The Court held that 10X Genomyx's proposed alternative construction would impermissibly impose requirements on the claimed

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[379] *Id.*
[380] *Id.* at 1332.
[381] *Id.*

invention not supported by the intrinsic evidence.[382] The Court also rejected 10X Genomyx's argument that the ALJ erred by applying the doctrine of assignor estoppel to preclude it from challenging construction based on the prior art for the simple reason that the Court found evidence in the record that the ALJ had permitted these art-based challenges and that they had failed (which is not the same thing).[383] The opinion states that the ALJ had properly construed the claims using the intrinsic evidence under *Phillips v. AWH Corp*., 415 F.3d 1303, 1312–15 (Fed. Cir. 2005) (en banc), and the fact that prior art considerations did not make their way into the Commission's opinion which the Court termed less relevant arguments did not indicate error.[384]

Regarding the Commission's finding of indirect infringement, the Federal Circuit recognized 10X Genomyx's argument to be a factual one – was there enough evidence presented to support the determination? – that is entitled to the substantial evidence standard of review. The facts at issue revolved around whether 10X Genomyx had knowledge of the patents (in contrast to the priority applications, where such knowledge was not in doubt). In finding that the Commission's determination was supported by substantial evidence, the opinion states that "10X's various arguments attempt to distract from the reality of this case: named inventors of the asserted patents sold their company and patent rights to Bio-Rad, worked for Bio-Rad for a short time, left Bio-Rad to start a new company, and launched new products that have been determined to infringe the patents they assigned to Bio-Rad."[385] In addition, the opinion states that 10X Genomyx's arguments "largely attack the ALJ's credibility determinations and weighing of the evidence" (which fails the substantial evidence challenge), particularly with regard to the ALJ's credibility determinations of the witnesses (including the named inventors).[386] And regarding the existence of non-infringing uses relevant to the Commission's contributory infringement determination, the Court rejected 10X Genomyx's

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[382] Bio-Rad Laboratories, Inc. v. Int'l. Trade Comm., 998 F.3d 1320, 1334 (Fed. Cir. 2021).
[383] *Id.*
[384] *Id.*
[385] *Id.* at 1335.
[386] *Id.*

assertion of "hypothetical" systems, which 10X Genomyx asserted were relevant due to the statutory language that an accused product be "suitable" for non-infringing use, as being contrary to precedent (for which the panel sets forth examples including *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1330–31 (Fed. Cir. 2010), and *Golden Blount, Inc. v. Robert H. Peterson Co.*, 438 F.3d 1354, 1363 (Fed. Cir. 2006).[387] In sum, because "[i]t is not within [the Court's] purview to reweigh the evidence or to question the ALJ's credibility determinations," the Court affirmed the Commission's infringement determinations against 10X Genomyx.[388]

In the interim, 10X Genomyx obtained an exclusion order against Bio-Rad's importation of certain of their microfluidic chips over 10X Genomyx's patents; Bio-Rad has obtained an exclusion order against 10X Genomyx's importation of certain of their microfluidic chips over Bio-Rad's patents. The relationship and history between the companies argues against settlement, but under these circumstances, settlement seems a sensible solution for both parties (depending of course on the relative market share and competitive positions of the parties excluded goods).

J. Becton, Dickinson & Co. v. Baxter Corp. Englewood

In *Becton, Dickinson & Co. v. Baxter Corp. Englewood*, the Federal Circuit overturned a decision by the PTAB in an *inter partes* review that claims in the challenged patent were not invalid for obviousness.[389]

The patent at issue, U.S. Patent No. 8,554,579, is directed at telemedicine methods and particularly at methods for preparing patient-specific doses of pharmaceuticals. Claim 8 was considered representative by the Court:

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[387] Bio-Rad Laboratories, Inc. v. Int'l. Trade Comm., 998 F.3d 1320, 1336 (Fed. Cir. 2021).
[388] *Id.*
[389] Becton, Dickinson & Co. v. Baxter Corp. Englewood, 998 F.3d 1337, 1345 (Fed. Cir. 2021).

> Claim 8. A system for preparing and managing patient-specific dose orders that have been entered into a first system, comprising:
>
> . . .
>
> a dose preparation station for preparing a plurality of doses based on received dose orders, the dose preparation station being in bi-directional communication with the order processing server and
>
> having an interface for providing an operator with a protocol associated with each received drug order and specifying a set of drug preparation steps to fill the drug order, the dose preparation station including an interactive screen that includes prompts that can be highlighted by an operator to receive additional information relative to one particular step and includes areas for entering an input;
>
> . . . and wherein each of the steps must be verified as being properly completed before the operator can continue with the other steps of drug preparation process, the captured image displaying a result of a discrete isolated event performed in accordance with one drug preparation step, wherein verifying the steps includes reviewing all of the discrete images in the data record . . . .[390]

The claim terms at issue, both of which are recited in representative claim 8, are "highlighting" and various forms of the concept of "verification," as indicated in the claim as set forth above.[391] Becton, Dickinson asserted three prior art references in support of its IPR challenge sounding in obviousness: U.S. Patent No. 8,374,887 ("Alexander"), U.S. Patent No. 6,581,798 ("Liff"), and U.S. Patent Publication No. 2005/0080651 ("Morrison").[392] The Board found that the skilled artisan would

[390] *Id.* at 1338-39.
[391] *Id.* at 1338.
[392] *Id.* at 1339.

have been motivated to combine the Alexander and Liff references or even to combine all the references.[393] Similarly, the Board found Baxter's evidence of secondary considerations to be weak, according to the Federal Circuit's opinion.[394] Nevertheless, the Board found that the Alexander reference, taken alone, did not render obvious the "verification" limitation, nor did the combination of the references render obvious the "highlighting" limitation of the challenged '579 patent claims.[395]

The Federal Circuit reversed the Board's determinations in an opinion written by Judge Dyk, joined by Judges Prost and Clevenger.[396] The panel first addressed the "verification" limitation. According to the Court, the Board's application of its construction was not supported by substantial evidence.[397] Specifically, the Court held that the Board erred in concluding that the primary reference, Alexander, only disclosed that the remote pharmacist *may* verify but not that she *must* verify "each and every step before the operator is allowed to proceed."[398] The opinion states that in the panel's view, "'may' does not mean 'occasionally,' but rather that one 'may' choose to systematically check each step."[399] This is significant because the Court found that in the context of the prior art and the Alexander specification "[t]here is no significant difference between that teaching of Alexander and the '579 patent's verification requirement, which the Board construed as requiring that 'the system will not allow the operator to proceed to the next step until the prior step has been verified.'"[400] The Court rejected Baxter's arguments to the contrary that unverified prescription filling was within the scope of the Alexander teaching (which argument was based on deposition testimony of Becton's expert), and that the use of the term "the system" in the Alexander process implicated a

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[393] *Id.*
[394] Becton, Dickinson & Co. v. Baxter Corp. Englewood, 998 F.3d 1337, 1339 (Fed. Cir. 2021).
[395] *Id.*
[396] *Id.* at 1345.
[397] *Id.* at 1340.
[398] *Id.*
[399] Becton, Dickinson & Co. v. Baxter Corp. Englewood, 998 F.3d 1337, 1340 (Fed. Cir. 2021).
[400] *Id.* at 1340-41.

mechanical "hard stop"[401] to the prescribing function. The Court stated that "[n]othing in the construction requires a mechanical stop as opposed to requiring authorization from a pharmacist to continue."[402] Accordingly, the panel held that the Board's determination to the contrary was not supported by substantial evidence.[403]

Regarding the "highlighting" limitation, the opinion notes that this limitation is tied to embodiments having "an interactive screen that includes prompts that can be highlighted by an operator to receive additional information relative to one particular step,"[404] as illustrated by Figure 10 of the '579 patent:

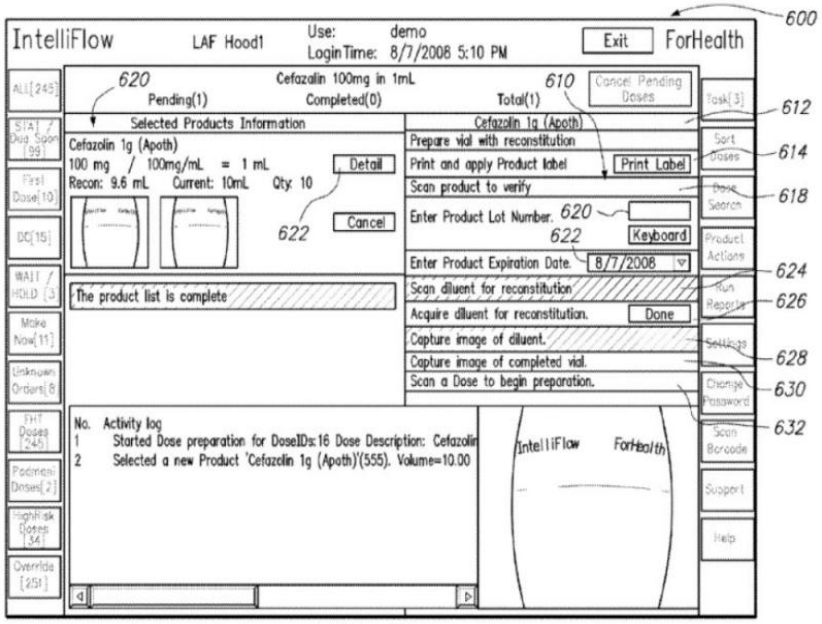

FIG. 10

The Court's understanding of the Board's construction of this term was that "the only missing element of this limitation [in the Alexander reference] is the ability to highlight prompts to receive more information concerning drug preparation steps."[405] And this feature was disclosed in the Liff reference in the panel's

[401] *Id.* at 1340 n.4.
[402] *Id.* at 1341.
[403] *Id*. at 1339
[404] Becton, Dickinson & Co. v. Baxter Corp. Englewood, 998 F.3d 1337, 1349 (Fed. Cir. 2021).
[405] *Id.* at 1342.

assessment (albeit in the physical rather than the virtual, computer realm).[406] The Liff system was illustrated by Figure 14F of that patent:

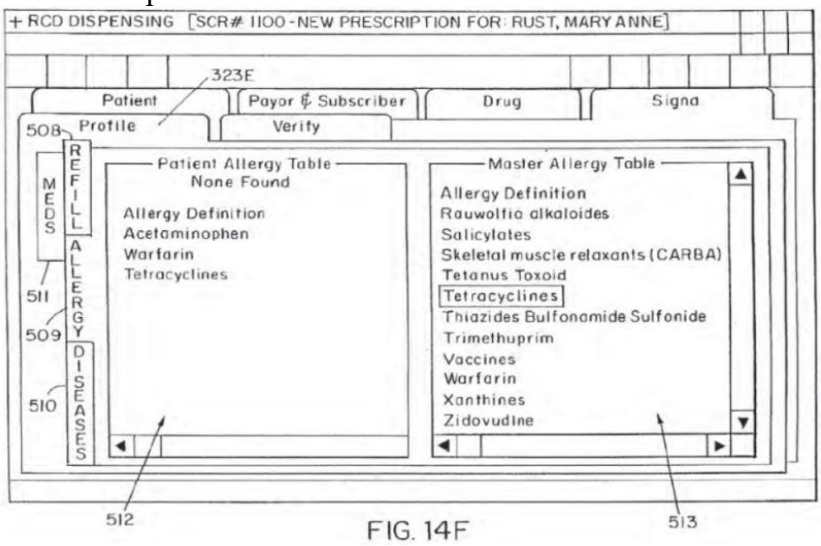

FIG. 14F

The Board had characterized its non-obviousness determination based on the highlighting limitation as a "close case";[407] the Court disagreed. To the panel, the Liff patent's teachings regarding highlighting for one purpose (*i.e.*, patient characteristics) clearly would not have precluded the skilled worker from applying the highlighting function to another feature (*e.g.*, information regarding the prescription order).[408] In the panel's view, their decision was predicated on the Supreme Court's teachings in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007), that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."[409] In addition, the panel relied on *KSR* for the principle that "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton" with regard to the question of whether the "additional information that

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[406] *Id.* at 1343 (as stated in the opinion, the system disclosed in the Liff reference comprises "a cabinet adapted to store a variety of prepackaged pharmaceuticals in a plurality of bins for filling patient prescriptions").
[407] *Id.* at 1344.
[408] *Id*. at 1343.
[409] Becton, Dickinson & Co. v. Baxter Corp. Englewood, 998 F.3d 1337, 1343 (Fed. Cir. 2021).

might be relevant" was limited to what the Liff reference expressly disclosed.[410]

In an interesting aside, the Court considered the issue of whether the Alexander reference was properly prior art under 35 U.S.C. § 102(e) because all claims in that patent were subsequently canceled in an IPR.[411] Baxter argued that this eliminated the statutory requirement that the reference be "granted" and hence § 102(e) no longer applied.[412] The panel rejected that interpretation of the statute, saying that the Alexander reference satisfied the statutory terms because "the grant[] had occurred" and the statute did not require the patent to be currently valid to qualify as prior art.[413]

Finally, the panel addressed Baxter's secondary considerations evidence, agreeing with the Board that it was "weak" and did not rebut the prima facie case.[414]

The Court's invalidation outcome is rare regarding an obviousness determination by the PTAB because it is equally rare that the Board does not amass sufficient evidence to be considered substantial and thus not to be entitled to deference under *Dickerson v. Zurko*. But where, as here, an IPR petitioner can demonstrate sufficient paucity of factual basis supporting the PTAB's non-obviousness determination, the outcome is unsurprising no matter how infrequent it may be in practice.

CONCLUSIONS

Restricting oneself to ten top biotechnology patent decisions inevitably means depriving some important patents cases and issues of the limelight they deserve. One of those excluded was *Minerva v. Hologic*.[415] Although not strictly a biotechnology or pharmaceutical patent law decision, the technology at its heart – a device whose moisture-permeable head is efficacious in treating abnormal uterine bleeding – does lie in

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[410] *Id.*
[411] *Id.* at 1345.
[412] *Id.*
[413] *Id.*
[414] Becton, Dickinson & Co. v. Baxter Corp. Englewood, 998 F.3d 1337, 1345 (Fed. Cir. 2021).
[415] *See* Minerva Surgical, Inc. v. Hologic Inc. 141 S. Ct. 2298 210 L. Ed. 2d 689 (2021).

the cognate field of medical devices. The central legal issue was whether an inventor or owner of a patent could assign her rights in the patent, then defend herself against an allegation of infringement on the grounds that the asserted patent claims had always been invalid.[416] The Supreme Court did recognize that this doctrine of "assignor estoppel" had long prohibited assertion of such a defense but invoked the equitable character of the doctrine to limit its application to situations in which the assignor had assured the assignee that the patent claims were valid.[417]

In *Minerva*, an inventor named Csaba Truckai filed a patent application claiming a medical device having a moisture-permeable head.[418] After selling the Hologic, the firm he founded which owned the patent, Truckai founded a second company, named Minerva Surgical, which developed a similar, competing, device having a moisture-*impermeable* head.[419] The successor to Hologic filed a continuation application to claim a version of the device also having a moisture-impermeable head.[420] Once this continuation patent issued, the successor sued Minerva for patent infringement.[421] When Minerva alleged that asserted claims of the continuation patent were invalid, the successor invoked assignor estoppel to preclude this defense.[422] Both the federal district court and Court of Appeals for the Federal Circuit held against Minerva, leading to a finding of infringement.[423]

The Supreme Court disagreed, holding that assignor estoppel should be available "only when its underlying principle of fair dealing comes into play."[424] As in the case of Minerva, where "the assignor has made neither explicit nor implicit representations in conflict with an invalidity defense, then there

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[416] Minerva Surgical, Inc. v. Hologic Inc. 141 S. Ct. 2298, 2299, 210 L. Ed. 2d 689 (2021).
[417] *Id.* at 2299-2301
[418] *Id.* at 2299.
[419] *Id.*
[420] *Id.*
[421] Minerva Surgical, Inc. v. Hologic Inc. 141 S. Ct. 2298, 2299, 210 L. Ed. 2d 689 (2021).
[422] *Id.*
[423] *Id.*
[424] *Id.* at 2309-10.

is no unfairness in its assertion".[425] The Supreme Court rejected Minerva's invitation to end assignor estoppel, instead narrowing it to situations in which "the assignor's claim of invalidity contradicts explicit or implicit representations he made in assigning the patent."[426] The Supreme Court vacated the decision of the Federal Circuit and remanded it for reconsideration consistent with the clarified rule of assignor estoppel.[427]

Despite much *Sturm und Drang* inside and outside Congress about amending U.S. patent law, the Patent Act escaped statutory reform in 2021. Nor did 2021 see the World Trade Organization ("WTO") actually achieve the waiver on SARS-CoV-2 vaccine patent rights it first called for back in 2020, despite having received support for this action from U.S. President Joseph Biden in April 2021. In the absence of explicit changes made with much fanfare by Congress or the WTO, biotechnology patent law instead changed through the quotidian common law mechanism of judicial decisions driven by plaintiffs, defendants, juries, and judges. Whatever 2022 and the lingering COVID-19 pandemic bring for biotechnology patent law, this latter mode of legal evolution will continue to mold the major legal incentives inventors have for enriching the world with new and useful biotechnologies.

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[425] *Id*. at 2310.
[426] Minerva Surgical, Inc. v. Hologic Inc. 141 S. Ct. 2298, 2302 210 L. Ed. 2d 689 (2021).
[427] *Id.* at 2311.