APPENDICES

APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

No. 2020-1933

BIOGEN INTERNATIONAL GMBH,
BIOGEN MA, INC.,
Plaintiffs-Appellants,
v.

MYLAN PHARMACEUTICALS INC.,
Defendant-Appellee.

Appeal from the United States District Court for the Northern District of West Virginia in No. 1:17-cv-00116-IMK-JPM, Judge Irene M. Keeley.

Decided: November 30, 2021

Before O'MALLEY, REYNA, and HUGHES,
Circuit Judges.

Opinion for the Court filed by
Circuit Judge REYNA.

Dissenting Opinion filed by
Circuit Judge O'MALLEY.

REYNA, *Circuit Judge*.

This appeal from the United States District Court for the Northern District of West Virginia concerns a

patent-infringement dispute between Biogen International GmbH, Biogen MA, Inc., and Mylan Pharmaceuticals, Inc. Biogen owns United States Patent 8,399,514 (the '514 Patent), which claims a method of treating multiple sclerosis with a drug called dimethyl fumarate. In 2017, Biogen filed a lawsuit against Mylan alleging patent infringement. Mylan counterclaimed for declaratory judgment that the patent was invalid and not infringed. Following a bench trial, the district court determined that the asserted claims of the '514 Patent were invalid for lack of written description. Biogen challenges the district court's decision on appeal.

For the reasons set forth in this opinion, we hold that the district court did not clearly err in determining that Mylan has established its burden of showing, by clear and convincing evidence, that the asserted '514 Patent claims are invalid for lack of written description under 35 U.S.C. § 112. Accordingly, we affirm the judgment of the district court.

I. BACKGROUND

Under the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act), a manufacturer of a new generic drug that is bioequivalent[1] to a previously approved drug may seek

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[1] For purposes of Hatch-Waxman litigation, a generic drug is considered bioequivalent to a brand-name drug if:

> (i) the rate and extent of absorption of the [generic] drug do not show a significant difference from the rate and extent of absorption of the listed [brandname] drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or
>
> (ii) the extent of absorption of the [generic] drug does not show a significant difference from the extent of ab-

approval from the US Food and Drug Administration (FDA) to market the generic product by filing an Abbreviated New Drug Application (ANDA). *See* Pub. L. No. 98-417, § 101, 98 Stat. 1585, 1585–86 (1984) (codified as amended at 21 U.S.C. § 355(j)(2)(A)). The statute requires the generic-drug manufacturer to submit a certification regarding the status of any patent that purportedly protects the brand-name drug, including information as to whether no such patent exists or the patent already expired, and if the patent has not expired the manufacturer must indicate the date on which the patent will expire. 21 U.S.C. § 355(j)(2)(A)(vii)(I)–(III).

If a patent that covers the brand-name drug has not expired, the generic-drug manufacturer may file what is known as a paragraph IV certification, attesting that the "patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." *Id.* § 355(j)(2)(A)(vii)(IV). The manufacturer filing the ANDA and paragraph IV certification must promptly notify the owner of any patent subject to the certification. *Id.* § 355(j)(2)(B)(iii). And the FDA must approve the ANDA, unless the patent owner objects by filing an action for patent infringement against the generic-drug manufacturer

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> sorption of the listed [brand-name] drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

21 U.S.C. § 355(j)(8)(B)(i)–(ii).

within forty-five days of receiving notice of the paragraph IV certification. *Id.* § 355(j)(5)(B)(iii). If the patent owner brings the infringement suit under the Hatch-Waxman Act within the statutory period, the law triggers an automatic, thirty-month stay in the FDA approval process of the generic drug, pending the outcome of the litigation. *See id.* § 355(j)(5)(B)(iii).

Mylan Pharmaceuticals, Inc. (Mylan) filed an ANDA seeking to manufacture, use, and market a generic dimethyl fumarate (DMF) product for the treatment of multiple sclerosis (MS) before the expiration date of the '514 Patent. J.A. 6001–02. On June 30, 2017, Biogen International GmbH and Biogen MA, Inc. (collectively Biogen) sued Mylan for patent infringement in the Northern District of West Virginia pursuant to the Hatch-Waxman Act. *Id.* In its original complaint, Biogen asserted six patents[1] purportedly covering Tecfidera®, Biogen's trademarked DMF-capsule formulation for the treatment of patients suffering from relapsing-remitting forms of MS. *Id.* Only the '514 Patent is at issue in this appeal. *See* J.A. 2–3.

A. The '514 Patent

The '514 Patent claims priority to United States Provisional Application 60/888,921 (the '921 Application), which Biogen filed on February 8, 2007. U.S. Patent No. 8,399,514, at [60] (filed Feb. 13, 2012) (issued Mar. 19, 2013). As issued, the patent is entitled "Treatment for Multiple Sclerosis." '514 Patent, at [54].

MS is a disabling autoimmune disease that affects the central nervous system (CNS) and involves an abnormal inflammatory response, which leads to damage

[1] In addition to the '514 Patent, Biogen asserted US Patents 6,509,376; 7,320,999; 7,619,001; 7,803,840; and 8,759,393. J.A. 6002.

and the eventual destruction of the myelin sheath that surrounds neuronal axons—the nerve fibers that transmit electrical signals across CNS nerve cells. *See* '514 Patent col. 1 ll. 15–20. The myelin sheath, which comprises a mixture of proteins and lipids, is a substance that acts as a protective covering to insulate nerve fibers—much like the insulation material that surrounds and protects an electrical wire—and permits nerve cells to adequately conduct the electrical signals. *See* John S. O'Brien, *Stability of the Myelin Membrane*, 147 SCIENCE 1099, 1099 (1965); J.A. 4–5. MS-induced deterioration of the myelin sheath interferes with the proper transmission of such electrical signals across nerve cells and eventually contributes to neurodegeneration, death of neurons, and progressive neurological dysfunction in individuals suffering from the disease. *See* '514 Patent col. 1 ll. 17–20, 29–30; J.A. 4–5.

In its action alleging patent infringement against Mylan, Biogen asserted claims 1–4, 6, 8–13, 15, and 16 of the '514 Patent. J.A. 15–17. Claim 1 is representative and recites:

> 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 [milligrams] per day [(mg/day)].

Id. col. 27 ll. 59–67. Relevant to this appeal is Biogen's use of DMF, a fumaric-acid ester compound, at a specific dose of 480 mg/day (DMF480) under the brand name Tecfidera® for the treatment of MS.

The '514 Patent specification largely tracks that of the original '921 Application, which Biogen entitled "Nrf2 Screening Assays and Related Methods and Compositions."[1] J.A. 3289–92. The specification casts a wide net for a myriad of neurological disorders, including neurodegenerative 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. *See* '514 Patent col. 16 ll. 18–63. Although the specification does not focus exclusively on MS, it discusses MS-related background information in two paragraphs that appear in the first column. *See id.* col. 1 ll. 15–52.

The specification further describes five methods to explore a potential protective role for the activation of the Nrf2 pathway in neurodegenerative and neuroinflammatory diseases. J.A. 66–67. Methods 1–3 relate to screening, evaluating, and comparing the bioequivalence of compounds for their use against neurological diseases. J.A. 68–69. Methods 4 and 5 relate to the *treatment* of such neurological diseases. J.A. 69. Consistent with the disclosure's original title concerning

[1] On February 7, 2008, Biogen filed International Patent Application PCT/US2008/0016902 (the '902 Application), which maintained the same title, claims, and inventor as the '921 Application but added to its specification. J.A. 10. On August 7, 2009, the international '902 Application entered the national phase and became US Patent Application 12/526,296 (the '296 Application). *Id.*

Nrf2 screening, the totality of the specification focuses primarily on drug discovery. Indeed, 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. *See* J.A. 12–13; J.A. 3490–91.

Because the claims at issue concern methods to treat MS, we must look to methods 4 and 5 as disclosed in the specification. Method 5 is largely irrelevant for our purposes because it relates to combination therapy comprising the administration of a compound that upregulates the Nrf2 pathway with at least one other compound that cannot upregulate the pathway. '514 Patent col. 8 ll. 54–63. But method 4 is instructive, as it discloses "methods of treating a neurological disease by administering to the subject in need thereof at least one compound that is at least partially structurally similar to DMF and/or [monomethyl fumarate (MMF)]," as well as "a method of treating a mammal who has or is at risk for a neurological disease … [by] administering to the mammal a therapeutically effective amount of at least one neuroprotective compound" such as DMF or MMF, and "a method of slowing or preventing neurodegeneration" induced by demyelination or the death or neurons. *Id.* col. 8 ll. 35–53.

Save for one paragraph in the specification, the disclosure does not teach potential dosage levels for DMF monotherapy. The sole DMF-dosage paragraph is not linked to treatment of any specific disease but recites:

> 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.

Id. col. 18 ll. 54–64 (emphasis added). As shown above, the specification explicitly mentions "effective doses" at various concentration ranges within an overall DMF dosage range of 100–1,000 mg/day.

Importantly for this appeal, the specification reveals two crucial aspects of the invention. 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., demyelination, axonal loss, and neuronal death) or *reduced inflammation* of the cells of the CNS." *Id.* col. 5 ll. 52–59 (emphases added).

B. Clinical Development and Procedural History

Between 2004 and 2006, Biogen conducted a Phase II, clinical, dose-ranging study to test the efficacy of

DMF at 120, 360, and 720 mg/day concentrations (DMF120, DMF360, and DMF720, respectively) for the treatment of MS. J.A. 2184–91. The May 2006 results of this study showed that DMF720 was efficacious in treating MS, but DMF120 and DMF360 were not. J.A. 7. In August 2006, the FDA recommended that Biogen add a DMF480 dosing regimen in the Phase III study because the lower dose "might improve patient compliance and/or minimize dropouts from adverse effects during the study." J.A. 1724–25. According to Biogen, the Phase II lead scientist, Dr. O'Neill, had conceived the idea of using DMF480 as early as 2003 and advocated testing the DMF480 dose as part of the trial in February 2004. J.A. 7. At the time, Biogen had decided not to include the DMF480 dose in the study for commercial reasons. *See* J.A. 1364. Although Biogen told the FDA that DMF720 was the best option, it eventually included DMF480 in the Phase III clinical testing. *See* J.A. 1726. The Phase III results showed efficacy for the DMF480 and DMF720 doses. J.A. 2060.

Based on the 2006 Phase II results—and before starting the Phase III trial to test the DMF480 dose—Biogen filed the provisional '921 Application on February 8, 2007. The original application listed Dr. Lukashev, a Biogen scientist who, at the time, focused on research related to the Nrf2 pathway, as the sole inventor. J.A. 8–10. O'Neill was not listed as a co-inventor on the '921 Application; his name was added in 2011 as part of an amendment refocusing the invention on methods of treatment for MS, which Biogen filed after gathering the Phase III results that demonstrated therapeutic efficacy of DMF480.[1] J.A. 3437–39; J.A.

[1] Biogen amended the '296 Application—the national-phase application filed in 2009, *see supra* note 3—after acquiring its

3481–86. O'Neill, however, had not been involved with any of the Nrf2 research that led to the '514 Patent. When asked during trial, Lukashev testified that he did not know why O'Neill was added as an inventor. J.A. 1318. Lukashev also corroborated the original application's emphasis on drug discovery by noting that his work had encompassed "a more exploratory nature. It[was] to explore potential for follow-on compound discovery … ." J.A. 9 (alteration in original). And, more importantly, 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].'" *Id.* (alterations in original). Besides the amendments related to inventorship and the invention's title, Biogen did not make any other changes to the specification. This enabled Biogen to claim a priority date of February 8, 2007, despite filing wholly new claims alongside the amendments. J.A. 13.

In 2017, Biogen filed its patent infringement suit against Mylan in the Northern District of West Virginia. J.A. 6001. Biogen sued after Mylan sought ANDA approval to market a generic DMF product for treating MS. Mylan counterclaimed for declaratory judgment that the '514 Patent was invalid and not infringed. J.A. 6136–44. The district court held a four-day bench trial

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Phase III clinical-data results in April 2011. J.A. 10. Biogen left the specification of the '296 Application unchanged, but it amended the invention's title and claims on June 20, 2011. J.A. 47. On October 28, 2011, Biogen subsequently amended the '296 Application again to add O'Neill as an inventor. *Id.* Biogen then abandoned the '296 Application in favor of US Patent Application 13/326,426 (the '426 Application), a continuing application filed on February 13, 2012. J.A. 11. The '426 Application eventually led to issuance of the '514 Patent on March 19, 2013. *Id.* Biogen claims a February 8, 2007 priority date for the '514 Patent based on the '921 Application. *Id.*

starting on February 4, 2020. J.A. 1001. On February 5, 2020, the Patent Trademark and Appeal Board (Board) issued a final written decision in a related inter partes review (IPR) proceeding, which Mylan initiated on July 13, 2018 and is the subject of a companion case to this appeal. *See Mylan Pharms. Inc. v. Biogen MA Inc.*, No. IPR2018-01403, 2020 WL 582736 (P.T.A.B. Feb. 5, 2020). In the IPR case, the Board rejected an obviousness challenge to the asserted '514 Patent claims, which estopped Mylan from litigating obviousness issues in the trial court. *See* J.A. 3 n.2.

During trial, the parties agreed that, for purposes of this case, a person of ordinary skill in the art (POSA) is someone with "at least a medical degree, at least three years of training in neurology, and at least three years of clinical experience treating multiple sclerosis patients." J.A. 20. The parties presented expert testimony from two neurologists who treat patients with MS—Dr. Greenberg for Mylan and Dr. Wynn for Biogen. J.A. 20. At the conclusion of the trial, the district court found that the specification did not reasonably convey to a POSA that the '514 Patent inventors had "actually invented" a method of treating MS with a therapeutically effective dose of DMF480 as of February 8, 2007. J.A. 45. The court also found that Biogen's arguments and Wynn's testimony that a POSA would be drawn to the DMF480 dose upon reading the patent specification were "neither credible nor persuasive," J.A. 30–31, and noted that Wynn conceded during cross examination that the sole DMF-dosage paragraph in the specification did not teach a POSA that DMF480 would be therapeutically effective for treating MS, J.A. 31.

The district court opined that Biogen's attempt to "combin[e] a few selectively[ ]plucked disclosures from

the specification … has been squarely rejected by the Federal Circuit." J.A. 45. Based on the testimony offered at trial, the context of the '514 Patent prosecution history, and "significant omissions from the specification," the district court ultimately concluded that Mylan had satisfied its burden of showing by clear and convincing evidence that the asserted '514 Patent claims were invalid for lack of written description under 35 U.S.C. § 112. *Id.* Biogen now appeals the district court's decision.

II. STANDARD OF REVIEW

Whether a claim meets the written-description requirement is a question of fact, which this court reviews for clear error on appeal from a bench trial. *Nuvo Pharm. (Ireland) Designated Activity Co. v. Dr. Reddy's Laboratories Inc.*, 923 F.3d 1368, 1376 (Fed. Cir. 2019), *cert. denied*, 140 S. Ct. 902 (2020). The clear-error standard requires courts to exercise deference when reviewing findings of fact, unless there is a "definite and firm conviction that a mistake has been made." *Scanner Techs. Corp. v. ICOS Vision Sys. Corp. N.V.*, 528 F.3d 1365, 1374 (Fed. Cir. 2008) (internal quotation marks and citation omitted). Patent invalidity under the written-description doctrine must be established by clear and convincing evidence. *Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1351 (Fed. Cir. 2011). Courts of appeals cannot reweigh a district court's assessment of witness credibility, *Advanced Magnetic Closures, Inc. v. Rome Fastener Corp.*, 607 F.3d 817, 832 (Fed. Cir. 2010), and must take into account the "unchallenged superiority" of a district court's ability to make witness-credibility determinations and findings of fact, *see Salve Regina Coll. v. Russell*, 499 U.S. 225, 233 (1991).

III. DISCUSSION

A. The Written-Description Requirement

To secure a patent for an invention under the laws of the United States, an inventor must comply with the written-description requirement outlined in 35 U.S.C. § 112, which prescribes:

> The [patent] specification shall contain a *written description* of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.[1]

35 U.S.C. § 112 (emphasis added). The statutory mandate for a written description as a prerequisite for patenting an invention has been a fixture of our laws for more than two centuries. The Supreme Court recognized, as far back as 1822, that the purpose of requiring a written description under the Patent Act of 1793 was to "put the public in possession of what the party claims as his own invention, so as to ascertain if he claim[s] anything that is in common use, or is already known …." *Evans v. Eaton*, 20 U.S. 356, 434 (1822).

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[1] Following the enactment of the Leahy–Smith America Invents Act (AIA), Pub. L. No. 112-29, 125 Stat 284 (2011), the first paragraph of § 112 was redesignated as § 122(a). The AIA amendments, which took effect on September 16, 2012, replaced the words "of carrying out his invention" in the pre-AIA § 112 with "or joint inventor of carrying out the invention" in the current § 112(a). 125 Stat. at 296–97. The amendments bear no significance for purposes of our written-description analysis.

"[P]ossession as shown in the disclosure," therefore, represents the hallmark of written description. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The written-description statutory language has undergone little change despite the enactment and revisions of numerous patent statutes since the Founding era. *See Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925 (Fed. Cir. 2004).

This court's precedents dictate that the § 112 written description "requirement is satisfied only if the inventor 'convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,' and demonstrate[s] that by disclosure in the specification of the patent." *Nuvo*, 923 F.3d at 1376–77 (quoting *Centocor Ortho Biotech, Inc. v. Abbott Laboratories*, 636 F.3d 1341, 1348 (Fed. Cir. 2011)). A precise definition of the invention is pivotal to establishing possession. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1373 (Fed. Cir. 2017). An applicant may show possession of the claimed invention by describing it with all of its limitations using "such descriptive means as words, structures, figures, diagrams, formulas, etc." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The term "possession" in the context of written-description jurisprudence entails an "objective inquiry into the four corners of the specification from the perspective of a [skilled artisan]." *Ariad*, 598 F.3d at 1351.

Whether a claimed invention satisfies the written-description requirement of § 112 will depend on the nature of the invention. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 963 (Fed. Cir. 2002) (citations omitted). Thus, the written-description analysis is highly dependent on the facts of each case. *Nuvo*, 923 F.3d at 1383 (citations omitted). In general, "written descrip-

tion is judged based on the state of the art as of the priority date. … [E]vidence illuminating the state of the art subsequent to the priority date is not relevant to written description." *Amgen*, F.3d at 1373–74 (internal citation omitted).

B. Possession of the Claimed Invention

The core issue in this appeal is whether the specification Biogen filed on February 8, 2007 supports the 2011 claims that issued in the '514 Patent. Even more precisely, the narrow ground on which this question turns is whether the original specification describes "possession" of the claimed therapeutically effective DMF480-dose limitation to treat MS.

The district court began by properly noting that "it is the specification itself that must demonstrate possession." J.A. 23 (quoting *Ariad*, 598 F.3d at 1352). The specification covers a broad array of nearly three dozen neurological disorders, and MS may arguably constitute an important element of the disclosure from the start. *See* '514 Patent col. 1 ll. 12–52 (explaining that the overall purpose of the invention is to treat "demyelinating neurological diseases," such as MS). Next, DMF appears more than two-dozen times throughout the specification, including in the three examples listed in the disclosure. The prior art demonstrates the existence of a link between DMF-mediated activation of the Nrf2 pathway and the neuroprotective and therapeutic effects of said activation, which could be exploited for the treatment of certain neurological disorders such as MS. *See id.* col. 5 ll. 20–24. Thus, 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.[1]

The skilled artisan would then look in the specification for guidance vis-à-vis a suitable therapeutic-DMF dosage. This is where the district court noted the lack of written description, upon which it primarily based its finding of invalidity. The DMF480 dose is listed only once in the entire specification. *See* '514 Patent col. 18 l. 62. The specification's sole reference to DMF480 constitutes a significant fact that cuts against Biogen's case, particularly because it appears at the end of one range among a series of ranges, including DMF concentrations of 100–1,000, 200–800, 240–720, and 480–720 mg/day. That is in stark contrast to DMF720, which is referenced independently as one dose and was known to be effective as of the February 2007 priority date. The '514 Patent, as issued, features multiple claims that are drawn exclusively to the specific DMF480 dose, but 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. On this point, Lukashev, the original inventor listed in the '921 Application, offered testimony in which he "denied that his research could be extrapolated to a clinical dose of DMF; it 'was never the

[1] We note, however, that method 4, which is the only relevant method to this appeal, is devoid of any specific reference to MS. *See* '514 Patent col. 8 ll. 35–53; J.A. 27 (noting that MS is merely listed as one of a slew of neurological diseases). The district court further found that Mylan's expert "credibly testified" that nothing in the specification "ties an effective dose of DMF specifically to the treatment of MS." J.A. 29.

focus of [his] work to inform the clinical dosing of [DMF].'" J.A. 9 (alterations in original); *see also* J.A. 34 (noting that the district court found Lukashev's testimony credible as to the fact that all the examples listed in the specification were part of his research and would not have been "helpful in identifying a therapeutically effective" DMF dose). Likewise, the district court credited Mylan's expert testimony at trial that the paragraph containing the sole DMF480 reference fails to specifically link an effective dose of DMF to the treatment of MS. J.A. 29.

This court has previously held that "[s]atisfaction of the description requirement [e]nsures that … a claim subsequent to the filing date of the application was sufficiently disclosed at the time of filing so that the prima facie date of invention can fairly be held to be the filing date of the application." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562 (Fed. Cir. 1991) (quoting *In re Smith & Hubin*, 481 F.2d 910, 914 (CCPA 1973)). An inventor need not "prove that a claimed pharmaceutical compound actually achieves a certain result. But when the inventor expressly claims that result, our case law provides that [such] result must be supported by adequate disclosure in the specification." *Nuvo*, 923 F.3d at 1384. Based on the evidence in the record, the district court did not clearly err in determining that Mylan established its burden of showing, by clear and convincing evidence, that the specification does not adequately support the asserted claims of the '514 Patent. More specifically, the district court did not clearly err in finding that a skilled artisan would not have recognized, based on the single passing reference to a DMF480 dose in the disclosure, that DMF480 would have been efficacious in the treatment of MS, particularly because the specification's only reference to DMF480 was part

of a wide DMF-dosage range and not listed as an independent therapeutically efficacious dose.

That Biogen later established the therapeutic efficacy of DMF480 is of no import to the written-description analysis. What 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. At the time of filing the original disclosure in 2007, the Nrf2 insights that proved critical in the Phase III study had not yet been translated to clinical use. *See* J.A. 35 (finding that, based on the evidence presented at trial, Lukashev's research related to Nrf2 activation and small-molecule screening "had nothing to do with the clinical development of Tecfidera®"). Regardless of whether O'Neill had in fact hypothesized or even conceived the idea of treating MS with a DMF480 dose as early as 2003, *see* J.A. 1586–87, the law is clear that a patent cannot be awarded for mere theoretical research without more, *see Ariad*, 598 F.3d at 1353. The written-description requirement limits patent protection only to individuals who perform the difficult work of producing a complete and final invention featuring all its claimed limitations and publicly disclose the fruits of that effort. *Id.* We therefore determine that, based on the evidence in the record, the district did not clearly err in finding that Biogen did not possess an invention directed to the specific use of a therapeutically effective DMF480 dose for the treatment of MS as of 2007.

Confronted with the lack of a specific reference to DMF480, Biogen and its expert argued that a skilled artisan would be drawn to the DMF480 dose because it was "anchored" to the effective DMF720 dose. J.A. 1548–49. But the very same sentence in the specification that discloses the DMF 480–720 mg/day range also "anchors" DMF240 (a known ineffective dose) to DMF720 (according to the DMF 240–720 mg/day range). *See* '514 Patent col. 18 ll. 54–64. Not only does the specification anchor an ineffective dose, it also expands the purported range of therapeutic efficacy from DMF100 and DMF200 (doses that a skilled artisan would expect to be ineffective) to DMF1,000 (a dose well above the therapeutically effective DMF720 mg/day dose). *See id.* col. 18 ll. 54–64; Appellee's Br. 26. That column 18 of the '514 Patent specification recites several DMF doses in the 100–1,000 mg/day range as "effective" without even identifying a target disease is further indicative that the inventors were not in possession of a complete and final invention as of February 2007.

Lastly, the court noted that Mylan had impeached Wynn's credibility by pointing out his inconsistent statements and evasiveness when asked, during the district court proceedings, why a skilled artisan would be drawn to the purported DMF480 efficacy upon reading the patent specification—all while consistently maintaining that a skilled artisan would not have reasonably expected DMF480 to provide the therapeutic efficacy claimed in the patent during the IPR proceeding. J.A. 31–33. After hearing live testimony from the parties' experts at trial, the district court found that the Biogen expert's opinion that a skilled artisan would be drawn to a DMF480 dose was "neither credible nor persuasive." JA 30–31. We discern no principled rea-

son to disturb the district court's assessment as to the credibility of Biogen's expert testimony. *See Salve Regina Coll. v. Russell*, 499 U.S. 225, 233 (1991) (describing the "unchallenged superiority" of a district court as to the assessment of witness credibility and making findings of fact); *Highmark, Inc. v. Allcare Health Mgmt. Sys., Inc.*, 701 F.3d 1351, 1366 (Fed. Cir. 2012) (Reyna, J., dissenting from the denial of the petition for rehearing en banc) (noting that intervention as to issues of fact finding should be limited to instances of clear error, especially given that "an appellate court cannot adequately, if at all, assess credibility of [expert] testimony because the witness is not before [the appellate panel] in person.").

Viewing the record before us in its totality, we discern no clear error in the district court's judgment that Mylan established its burden of showing, by clear and convincing evidence, that the asserted '514 Patent claims are invalid for lack of written description under 35 U.S.C. § 112.

* * *

Biogen raises several ancillary issues in an effort to reverse the district court decision. For example, Biogen claims that the district court "misinterpret[ed] this [c]ourt's 'blaze[-]marks' jurisprudence; fail[ed] to consider the specification as a whole; erroneously appl[ied] judicial estoppel; disregard[ed] the specification's express disclosure of the claimed dose because it was not described as the most preferred; and confus[ed] the written-description requirement with principles of obviousness and unexpected results." Appellant's Br. 2. But our conclusion that the district court did not clearly err in finding the '514 Patent invalid for lack of written

description under § 112 renders all these arguments superfluous.

Notably, the Dissent claims that the district court legally erred by conflating therapeutic and clinical efficacy. *See* Dissent Op. at 6, 8. However, when viewed through the lens of the '514 Patent, this is not a legal issue, but a factual one. The district court, as the finder of fact, did not find it necessary or appropriate to distinguish between therapeutic effects and clinical efficacy based on the specification's definition of "therapeutically effective dose" and the record before it, and such a determination was not clearly erroneous.

Most notably, the specification's definition of "therapeutically effective dose" indisputably features both clinical and therapeutic insignia. For example, the specification defines a "therapeutically effective dose" as an "*amount* of a compound" that results in the "prevention or delay of onset or amelioration of *symptoms of a neurological disorder in a subject*," namely, clinical insignia, "or an attainment of a *desired biological outcome*, such as reduced neurodegeneration (e.g., demyelination, axonal loss, and neuronal death) or reduced inflammation of the cells of the CNS," which constitute therapeutic insignia. '514 Patent col. 5 ll. 52–59 (emphases added).

On redirect examination, Biogen's expert attempted to characterize the specification's definition as solely describing therapeutic effects—"demyelination, axonal loss, and neuronal death" as well as "fewer [brain] scars"—that once could "see on [an] MRI scan, for example." J.A. 1553–54.

He distinguished these from clinical endpoints, such as "a person hav[ing] less episodes" or "no[ ] progression" of *symptoms*, including "weakness, numb-

ness, loss of bladder or bowel control, [sight deterioration], [and] less relapses." J.A. 1553. But Biogen's expert did not explain why these improved clinical outcomes would not qualify under the first half of the specification's definition, which focuses on preventing, delaying the onset of, or ameliorating "*symptoms of a neurological disorder*" in patients. '514 Patent col. 5 ll. 52–55 (emphasis added).

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.

Accordingly, we conclude that the district court did not clearly err in determining that the original 2007 disclosure, which focused exclusively on screening compounds for activation of the Nrf2 biological pathway, did not disclose a method to administer a therapeutically effective dose of DMF480 for the treatment of MS. Nor did the district court clearly err in finding that "O'Neill's hypothesis, that a [DMF480 dose] would be efficacious in treating MS, evolved from his review" of confidential information, which a skilled artisan would not have been privy to in 2007 and was never included in the original disclosure. *See* J.A. 35, 42, 1586–87.

Because we hold that the '514 Patent is invalid under the written-description doctrine, we need not reach the merits of the parties' arguments in the companion IPR case.

IV. CONCLUSION

For the reasons set forth in this opinion, we affirm the district court's decision that Mylan satisfied its burden of showing, by clear and convincing evidence, that the asserted '514 Patent claims are invalid for lack of written description under 35 U.S.C. § 112. Viewed in its totality, the record shows that the inventors were not in possession of a method of administering a therapeutically effective dose of DMF480 to treat MS on or before the February 8, 2007 priority date. We have considered the parties' remaining arguments and find them unavailing or do not reach them.

AFFIRMED

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

No. 2020-1933

BIOGEN INTERNATIONAL GMBH,
BIOGEN MA, INC.,
Plaintiffs-Appellants,
v.

MYLAN PHARMACEUTICALS INC.,
Defendant-Appellee.

Appeal from the United States District Court for the Northern District of West Virginia in No. 1:17-cv-00116-IMK-JPM, Judge Irene M. Keeley.

O'MALLEY, *Circuit Judge*, dissenting.

While I am loath to reverse district court determinations that rely heavily on credibility findings, I must respectfully dissent. There is no dispute over whether the district court erred in finding that Biogen was judicially estopped from drawing a distinction between clinical and therapeutic effects: it did. Mylan calls the error harmless and the majority finds it "ancillary" to its analysis. I, on the other hand, believe this threshold error impacted the district court's entire written description analysis. I would therefore reverse and remand for reconsideration in light of a proper understanding of the distinction between the two effects and the written descriptions needed for each.

I.

A. The district court erred in applying judicial estoppel

As it had tried to do throughout the trial, Biogen explained the distinction between *clinical efficacy* and *therapeutic effects* in its post-trial briefs before the district court. Clinical 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®. *See* J.A. 8066. Therapeutic effects, by contrast, "do not require efficacy on clinical endpoints or superior efficacy to existing drugs." *Id.* 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. '514 patent, col. 5, ll. 52–55.

Based on this distinction, Biogen took issue in its posttrial brief with Mylan's contention 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." J.A. 8064 (citing Mylan's post-trial brief, which quoted Dr. Dawson's testimony). Biogen pointed out that, in addition to mixing up written description and obviousness inquiries (which I will discuss *infra*), Mylan's argument erroneously assumed that the claims required *clinical* efficacy when they only covered *therapeutic* effects. J.A. 8063–66.

In a two-sentence footnote, the district court concluded that Biogen was judicially estopped from pointing out the distinction between clinical and therapeutic efficacy. *Biogen Int'l GmbH v. Mylan Pharms. Inc.*, 2020 WL 3317105, at *8 n.15 (N.D.W. Va. June 18,

2020). Citing *New Hampshire v. Maine*, 532 U.S. 742 (2001), the district court reasoned that Biogen could not "deliberately chang[e] positions according to the exigencies of the moment." *Id.*

I need not detail why the court's footnote ruling on judicial estoppel constituted an abuse of discretion under Fourth Circuit law. *See Martineau v. Wier*, 934 F.3d 385, 393 (4th Cir. 2019) (setting out a multi-factor test for the judicial estoppel inquiry, which the district court wholly failed to apply in this case). Biogen's briefs explain this error in detail and neither Mylan nor the majority defends the district court's ruling under that governing law.

I will, however, provide detail on how the erroneous judicial estoppel ruling led the district court to legally err in its interpretation of Federal Circuit written description precedent. In my view, the district court's refusal to acknowledge the difference between *therapeutic* and *clinical* effects evinces a fundamental misunderstanding of what is claimed—and, thus, what requires written description support—in the '514 patent.

The '514 patent explains that neurodegenerative disorders like MS are "characterized by inflammation in parts of the [central nervous system (CNS)], leading to the loss of the myelin sheathing around neuronal axons (demyelination), loss of axons, and the eventual death of neurons, oligodendrocytes and glial cells." '514 patent, col. 1, ll. 17–20. The '514 patent discusses the promise of treating MS using DMF, "a member of a large group of anti-oxidant molecules known for their cytoprotective and anti-inflammatory properties." '514 patent, col. 5, ll. 16–18. The '514 patent claims a "therapeutically effective amount" of DMF480, which the specification defines as

> 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., demyelination, axonal loss, and neuronal death) or reduced inflammation of the cells of the CNS.

'514 patent, col. 5, ll. 52–59.

Notably, the '514 patent explains that the inventors measured DMF's *therapeutic* efficacy in terms of its ability to enhance the expression levels of Nrf2—a transcription factor that activates the expression of genes responsible for protecting cells from the neurodegeneration commonly associated with MS. *See* '514 patent, col. 5, ll. 16–24; *see also* '514 patent, col. 1, ll. 35–62. Figures 3 and 4 of the '514 patent provide *in vivo* data showing an increase in Nrf2 expression following DMF treatment. '514 patent, Figures 3 and 4; *see also* '514 patent, col. 22, ll. 1–13. And, the '514 patent states: "the finding that *DMF activates the Nrf2 pathway* … offers a rationale for identification of structurally and/or mechanistically related molecules that would be expected to be *therapeutically effective* for the treatment of neurological disorders, such as, e.g., MS." '514 patent, col. 5, ll. 19–24 (emphasis added). Taken together, it is clear on the face of the '514 patent that the claimed "*therapeutically* effective amount" refers to DMF's ability to mitigate MS symptoms vis-à-vis its modulation of Nrf2 expression; it has nothing to do with whether DMF480 outperforms the standard of care for MS (Rebif®) in a Phase III clinical trial setting.

It is no wonder, then, why Biogen—in response to Mylan's repeated contentions that the '514 patent fails

the written description requirement because it lacks Phase III *clinical* efficacy data—sought in its post-trial briefing to remind the district court that the written description inquiry should focus on *therapeutic* efficacy.[1] Far from deliberately changing positions as the district court accused it of, Biogen was simply attempting to direct the district court's attention to the claim language at issue. Judicially estopping Biogen from doing so was not just legally erroneous under Fourth Circuit law, it misapplied our written description precedents by ignoring the claims at a time when they should have been given primacy. *Cf. Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) ("It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude.") (citations omitted) (internal quotation marks omitted).[2]

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[1] To be sure, Mylan continues its erroneous conflation of therapeutic and clinical efficacy before our court. *See, e.g.*, Appellee's Resp. Br. at 48–49.

[2] The majority's argument that there is no ascertainable difference between clinical and therapeutic efficacy is wrong for several reasons. *See* Maj. Op. at 20–21. As I have detailed above, the '514 patent makes clear that "therapeutically effective amount" does not involve comparing the claimed DMF480 dosage to the standard of care for MS like a clinical trial would. And, neither party ever argued this—either to the district court or on appeal. Biogen, instead, advocated distinguishing the two while Mylan and the district court blithely proceeded as though there were no difference without ever providing any explanation. To make up for this deficiency in the trial record, the majority provides its own explanation: "clinical insignia" is somehow encompassed by the '514 patent's definition of "therapeutically effective dose." *Id.* (citing '514 patent, col. 5, ll. 52–59). The majority appears to forget our role in this appeal: we are a court of review, not the primary factfinder. To the extent the majority fashions its own explanation

As discussed further below, the impact of the district court's errant refusal to acknowledge the difference between *therapeutic* and *clinical* efficacy is evident throughout the rest of the opinion.

B. The district court's conflation of therapeutic and clinical efficacy caused it to erroneously require clinical data, rather than therapeutic effects

The district court's failure to distinguish therapeutic effects and clinical efficacy also led it to conflate concepts of obviousness and written description. This conflation, in my view, caused the district court to erroneously require a showing of clinical data akin to what would be gathered in Phase III clinical trials in its written description analysis.

Somewhat circularly, after acknowledging that clinical data demonstrating effectiveness is not required to satisfy written description, the district court went on to find that the '514 patent does not demonstrate possession because it lacks clinical efficacy data. *Biogen*, 2020 WL 3317105, at *15. To arrive at this conclusion, the district court relied on its interpretation of our precedent in *Nuvo*. According to the district court, the patentees in *Nuvo* could not establish possession because a POSA "would not have expected [the claimed drug] to be effective, and nothing in the specification would teach a [POSA] otherwise." *Id.* (quoting *Nuvo Pharms. (Ireland) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc.*, 923 F.3d 1368, 1377, 1381 (Fed. Cir. 2019) (alteration in original). The district court reasoned that the same set of facts are at issue in this case: because Biogen had defended against Mylan's obviousness challenges in this case and a related *inter partes* review

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of why therapeutic and clinical efficacy are one in the same, it crosses that line.

proceeding by contending that a POSA would not have expected the DMF480 dose to *clinically* treat MS, the '514 patent's failure to teach a POSA otherwise with clinical data dooms Biogen's written description arguments. *Id.* (citing *Nuvo*, 923 F.3d at 1381).

This cannot be right. Whether a claim satisfies the written description requirement of § 112 is a question of fact that we review for clear error. *Ariad Pharms. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). We provide de novo review, however, of a district court's interpretation of Federal Circuit precedent. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1337 (Fed. Cir. 2003). Our court has long held that "the hallmark of written description is disclosure," meaning that a patent must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad*, 598 F.3d at 1351.

Here, the district court's reading of *Nuvo* does not accurately describe what we actually held in that case. The patent at issue in *Nuvo* claimed an acid inhibitor that was *uncoated* and *effective* at raising pH levels. *Nuvo*, 923 F.3d at 1373–1374, 1378. The patent specification in *Nuvo*, however, specifically discussed a known problem in the prior art involving *uncoated* acid inhibitors' *ineffectiveness* at raising pH levels. *See id.* at 1375 (reversing the district court for "not explain[ing] why the mere disclosure of [uncoated acid inhibitors], coupled with the known disadvantages of coated [acid inhibitors], is relevant to the therapeutic effectiveness of uncoated [acid inhibitors], *which the patent recognized as problematic for efficacy due to its potential for destruction by stomach acid*") (emphasis added). Since the patentees in *Nuvo* did nothing to explain how the invention purported to overcome the commonly known

problem with *uncoated* formulations that the patent specification explicitly discussed, our court invalidated the patent for lack of written description. *Id.* at 1381. Nowhere in *Nuvo* did we overlay a POSA's reasonable expectation of success from the obviousness context onto the written description inquiry. To the extent *Nuvo* mentioned a POSA's expectations, it cabined this discussion to what a POSA would have expected based on the explicit teachings of the patent specification—not of the prior art. *See id.* at 1381 ("In light of the fact that the specification provides nothing more than the mere claim that uncoated [acid inhibitors] might work, even though persons of ordinary skill in the art would not have thought it would work, the specification is fatally flawed.").

The 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. What a POSA would expect regarding clinical efficacy based on the prior art is a distinct question from whether a POSA would understand that the inventor possessed the *claimed* invention—i.e., a therapeutically effective dose—based on the patent's written description. Since the district court never engaged in a proper written description inquiry, I would reverse and remand for further proceedings consistent with a proper written description analysis that minds the gaps between obviousness and written description, as well as therapeutic and clinical efficacy.[1]

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[1] To the extent the majority accuses the dissent of reweighing the district court's credibility determinations, I disagree. *See* Maj. Op. at 19–20. Because I believe the district court's misguided interpretation of *Nuvo* led it to erroneously require clinical efficacy

C. The district court's conflation of therapeutic and clinical efficacy caused it to erroneously apply our "blaze marks" precedent

The majority relieves me of the need to discuss the district court's erroneous conclusion that the '514 patent does not contain enough "blaze marks" to direct a POSA toward MS treatment. *See Biogen*, 2020 WL 3317105, at *10 ("Method 4 broadly describes treating neurological diseases with a therapeutically effective amount of DMF; MS is merely one such disease 'among a slew of competing possibilities.'") (citing *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013)). The majority opinion—appearing to recognize this obvious error—says it operates under the assumption that the '514 patent satisfies written description in this regard. Maj. Op. at 15–16. Given the specification's repeated references to MS, that is a wise decision on the majority's part.

I do, however, need to discuss the district court's finding (an erroneous one, in my view) that the '514 patent does not contain enough "blaze marks" to "'link' a therapeutically effective amount of DMF to a dose of 480mg/day." *Biogen*, 2020 WL 3317105, at *10. The district court cites our precedent in *Ariad*, as well as Dr. Greenberg's trial testimony, to justify its application of our "blaze marks" precedent to this case. *Id.* I do not believe our case law required these patentees to include "blaze marks" in the '514 patent, however. And, the district court's reliance on Dr. Greenberg's testimony to conclude that the patentees should have included "blaze marks" only perpetuated its legally er-

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data for the written description inquiry, any expert witness testimony on which the district court relied to bolster that requirement is also legally unsound.

roneous interpretation of our case law. *See* J.A. 1447–49.

It is axiomatic that, to satisfy the written description requirement, a patent specification must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad*, 598 F.3d at 1351 (citations omitted) (alteration in original). This fundamental concept gets tested, however, whenever a patent's specification discloses a broad genus and claims a particular species contained within that genus. In cases such as these, our court has crafted a subgenre within our written description jurisprudence that requires patents containing laundry list-type disclosures "to provide sufficient 'blaze marks' to guide a reader through the forest of disclosed possibilities toward the claimed compound." *Novozymes*, 723 F.3d at 1346; *see also In re Ruschig*, 379 F.2d 990, 994–995 (C.C.P.A. 1967) ("It is an old custom in the woods to mark trails by making blaze marks on the trees. It is no help in finding a trail or in finding one's way through the woods where the trails have disappeared … to be confronted simply by a large number of unmarked trees."). Notably, our "blaze marks" jurisprudence does not apply in *every* case concerning written description; it, instead, provides a useful framework to analyze whether written description has been met in cases involving patents containing laundry list disclosures. *See, e.g.*, *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996) ("In the absence of such blazemarks, simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or subgenuses.").

On my reading of the '514 patent, the district court erred as a matter of law by requiring Column 18 to con-

tain sufficient "blaze marks" regarding the claimed DMF480 therapeutically effective dose. Method 4 of the '514 patent provides a general discussion of treating neurological diseases, such as MS, with therapeutically effective amounts of DMF compounds. *See* '514 patent, col. 8, ll. 35–53. Column 18 picks up where Method 4 left off by indicating which specific DMF doses the patentees considered therapeutically effective. *See id.*, col. 18, ll. 52–64. Column 18 does this by providing ranges of DMF doses—some large, *see id.* at col. 18, ll. 58–60 ("0.1 g to 1 g per [d]ay"), and some small, *see id.*, col. 18, l. 61 ("240 mg to about 720 mg per day"). Notably, Column 18 contains an express disclosure of the claimed DMF480 dose[1]; this reference also comes in the form of a range. *See id.* at col. 18, l. 62 ("480 mg to about 720 mg per day.").

I do not believe our "blaze marks" precedent applies to the claimed DMF480 dose because Column 18 does not provide a laundry list disclosure of therapeutically effective doses. Despite providing a varying degree of ranges, Column 18 begins one such range with the exact DMF480 dose that is claimed. *See id.* Had the patentees instead listed this range as, e.g., "*100 mg* to about 720 mg per day" and expected a POSA to figure out that a 480 mg per day dose was therapeutically effective, I would agree that "blaze marks" would be

[1] The majority's decision affirming the district court partially rests on the fact that the '514 patent only mentions the claimed DMF480 dose once. Maj. Op. at 16. 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.

necessary to "single out particular trees." *In re Ruschig*, 379 F.2d at 995. But, because the range provided in Column 18 particularly points out the claimed DMF480 dose, I believe the claim satisfies Section 112 and our corresponding written description jurisprudence. The district court's application of our "blaze marks" precedent and corresponding reliance on Dr. Greenberg's testimony thus are erroneous as a matter of law for two reasons. First, as discussed above, our "blaze marks" precedent is not applicable to this case because Column 18 lacks a laundry list disclosure. And, second, even if this precedent were to apply here, Column 18 provides a sufficient "blaze mark" by explicitly mentioning the claimed DMF480 dose. How much brighter need a disclosure blaze?

The district court's inability to "link" method 4 and Column 18, moreover, emanates from its original sin of judicially estopping Biogen from distinguishing between therapeutic and clinical effects. With a proper understanding of this distinction, the written description analysis in this case is straightforward: method 4 provides a general description of treating MS using a therapeutically effective DMF dose and column 18 demonstrates the patentees' possession of the claimed DMF480 dose for that purpose.

II.

Because I believe the entire course of the district court's analysis might well change if the court were to adjust the lens through which it considers the evidence and testimony, I would remand for reconsideration of the record with the understanding that the patent is not about clinical efficacy—it is about therapeutic effect—and that the written description and obviousness inquiries are not the same.

APPENDIX B

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

No. 2020-1933

BIOGEN INTERNATIONAL GMBH,
BIOGEN MA, INC.,
Plaintiffs-Appellants,
v.

MYLAN PHARMACEUTICALS INC.,
Defendant-Appellee.

Appeal from the United States District Court for the Northern District of West Virginia in No. 1:17-cv-00116-IMK-JPM, Judge Irene M. Keeley.

Filed: March 16, 2022

ON PETITION FOR PANEL REHEARING AND REHEARING EN BANC

Before MOORE, *Chief Judge*, NEWMAN, LOURIE, DYK, PROST, O'MALLEY,[1] REYNA, TARANTO, CHEN, and HUGHES, *Circuit Judges*.[*]

LOURIE, *Circuit Judge*, with whom MOORE, *Chief Judge*, and NEWMAN, *Circuit Judge*, join, dissents from the denial of the petition for rehearing en banc.

[1] Circuit Judge O'Malley retired on March 11, 2022, and participated only in the decision on the petition for panel rehearing.

[*] Circuit Judge Stoll and Circuit Judge Cunningham did not participate.

PER CURIAM.

ORDER

Biogen International BmbH and Biogen MA, Inc. filed a combined petition for panel rehearing and rehearing en banc. A response to the petition was invited by the court and filed by Mylan Pharmaceuticals Inc. The court also accepted amicus briefs filed by Biotechnology Innovation Organization, Chemistry and The Law Division of the American Chemical Society, and Pharmaceutical Research and Manufacturers of America. The petition was referred to the panel that heard the appeal, and thereafter the petition was referred to the circuit judges who are in regular active service. The court conducted a poll on request, and the poll failed.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue on March 23, 2022.

FOR THE COURT

March 16, 2022
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

No. 2020-1933

BIOGEN INTERNATIONAL GMBH,
BIOGEN MA, INC.,
Plaintiffs-Appellants,
v.

MYLAN PHARMACEUTICALS INC.,
Defendant-Appellee.

Appeal from the United States District Court for the Northern District of West Virginia in No. 1:17-cv-00116-IMK-JPM, Judge Irene M. Keeley.

LOURIE, *Circuit Judge*, with whom MOORE, *Chief Judge*, and NEWMAN, *Circuit Judge*, join, dissenting from the denial of the petition for rehearing en banc.

On March 2, 2010, this court sitting en banc in *Ariad Pharms., Inc. v. Eli Lilly & Co.*, reaffirmed the proposition that "written description" is a requirement that exists in the patent statute separate and apart from any other requirements for patentability. 598 F.3d 1336, 1351 (Fed. Cir. 2010). We stated very clearly that "the hallmark of written description is disclosure." *Id.* The test for written description "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.* "Based on that inquiry"—and not based on other considerations—"the specification must describe an invention understandable to that skilled arti-

san and show that the inventor actually invented the invention claimed." *Id.*

We have found lack of written description in a variety of contexts and circumstances. For example, we found a lack of written description when a patent specification described only rat insulin-encoding cDNA but the claimed microorganism encompassed human insulin-encoding CDNA. *See Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). We found a lack of written description when a patent specification identified only one possible location for controls on a reclining sofa but the claim recited the controls in a different location. *See Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479–80 (Fed. Cir. 1998). In another case, we found a lack of written description when claims were directed to a method comprising administering a compound to achieve a particular result but the specification failed to disclose any compounds that could be used in the claimed method. *See Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927 (Fed. Cir. 2004). We also found a lack of written description when a specification disclosed small numbers of species of antibodies that did not reasonably represent the breadth of antibodies encompassed by the claimed genus. *See Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300–01 (Fed. Cir. 2014).

These decisions, and many more like them, are supported by case law dating back to before this court existed. *See, e.g.*, *In re Ruschig*, 379 F.2d 990, 995 (C.C.P.A. 1967) (finding that the claimed compound was not described in the specification). Indeed, these decisions are supported by Supreme Court precedent dating back almost two centuries when the Court found that Samuel Morse's eighth patent claim was invalid because "he claims an exclusive right to use a manner

and process which he has not described and indeed had not invented, and therefore could not describe when he obtained his patent." *See O'Reilly v. Morse*, 56 U.S. 62, 113 (1853).

But in all that history, this case, in which every claim limitation is expressly described in the disclosure of the patent specification, is at the farthest end of the spectrum of cases where written description has not been found. It is an outlier.

Today, by denying rehearing en banc, the judges of this court have let a panel majority opinion stand that imports extraneous considerations into the written description analysis and blurs the boundaries between the written description requirement and the other statutory requirements for patentability. In doing so, the court has contributed to the muddying of the written description requirement. Accordingly, I respectfully dissent from that denial.

I

Biogen International GmbH ("Biogen") owns U.S. Patent 8,399,514 ("the '514 patent"). Mylan Pharmaceuticals Inc. ("Mylan") contended that the claims of the '514 patent are invalid for lack of written description support in the specification. In asserting that challenge, Mylan bore the burden of proving by clear and convincing evidence that the disclosure of the '514 patent specification failed to demonstrate to a person of ordinary skill in the art that the inventors invented what is claimed. The district court found that Mylan met its burden. *Biogen Int'l GmbH v. Mylan Pharms. Inc.*, No. 1:17-cv-116, 2020 WL 3317105 (N.D. W. Va. June 18, 2020) ("*District Court Decision*"). The panel majority affirmed. *See Biogen Int'l GMBH v. Mylan Pharms. Inc.*, 18 F.4th 1333 (Fed. Cir. 2021) ("*Panel*

Maj. Op."). I begin by explaining why it should have reversed and why this court should have granted the petition for rehearing en banc.

Claim 1 of the '514 patent recites:

> 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,[1] 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.

'514 patent at col. 27 ll. 59–67.

In evaluating whether the written description requirement has been met with respect to claim 1, we must look to what is disclosed in the patent specification. *See, e.g.*, *D Three Enters., LLC v. SunModo Corp.*, 890 F.3d 1042, 1052 (Fed. Cir. 2018) ("[A]dequate written description … asks what is disclosed."); *Ariad*, 598 F.3d at 1351 ("[T]he hallmark of written description is disclosure."). The '514 patent sets forth a number of embodiments, including five methods. Most relevant here, "method 4" includes "methods of treating a neurological disease." '514 patent at col. 8 ll. 35–36. And, pointedly, the title of the patent is "Treatment for Multiple Sclerosis."

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[1] Dimethyl fumarate and monomethyl fumarate are often abbreviated as "DMF" and "MMF."

Accordingly, the specification explicitly states that the neurological disease in method 4 "can [] be multiple sclerosis (MS)." *See id.* at col. 16 ll. 18–22. This disclosure is consistent with the background section of the patent, which begins with a specific discussion of multiple sclerosis. The first sentence of the disclosure states:

> Provided are certain compounds for treating neurological diseases, including demyelinating neurological diseases, such as, e.g., multiple sclerosis.

Id. at col. 1 ll. 12–14. The specification then proceeds to describe the pathology, symptoms, and available treatments for multiple sclerosis. *Id.* at col. 1 ll. 15–52. Viewed from any perspective, including that of a person of ordinary skill in the art, the '514 patent describes the invention of a method for treating multiple sclerosis.

Included within method 4 of the specification are methods that comprise "administering to the subject in need thereof at least one compound that is [] structurally similar to DMF and/or MMF." *Id.* at col. 8 ll. 36–38. The patent notes that the methods comprise administering "a therapeutically effective amount of at least one neuroprotective compound which has Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g., DMF or MMF)." *Id.* at col. 8 ll. 42–44. And the specification provides details about what constitutes an effective amount of DMF or MMF, noting that effective doses may vary depending on a number of factors, and providing examples of effective doses:

> 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 day, 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).

Id. at col. 18 ll. 58–62 (emphasis added).

To summarize, claim 1 is directed to a method of treating a particular disease (multiple sclerosis) by administering particular compounds (DMF or MMF) at a particular dose (480 mg per day). And that is precisely what the specification discloses—treatment of multiple sclerosis with a 480 mg per day dose of DMF or MMF. Thus, the specification provides sufficient written description under 35 U.S.C. § 112. Whatever shortcomings exist in this unfocused patent specification, failure of written description with respect to claim 1 is not one of them.

II

Both the panel majority and the district court began their analyses by correctly recognizing that "it is the specification itself that must demonstrate possession" of the claimed invention. *See Panel Maj. Op.*, 18 F.4th at 1342 (quoting the district court). Yet, despite the clear written description support in the specification itself, neither the panel majority nor the district court resolved the written description inquiry in favor of the patentee, Biogen. It is thus important to explain what I believe are the errors made by the panel majority and the district court.

As a general matter, the panel majority and the district court erred by analyzing factual and legal considerations that are not properly contained within the written description analysis. More specifically, I identify four individual points of error that the en banc court

should have corrected. First, the panel majority and the district court overly emphasized unclaimed disclosures in the specification. Second, they erroneously imposed a heightened burden on the patentee to show that the specification proves efficacy. Third, they imported legal factors from other patentability requirements. And fourth, they were influenced by irrelevant extrinsic evidence. I will address each of these points of error in turn.

A

The first point of error is the undue emphasis that the panel majority and the district court placed on unclaimed disclosures in the specification. Although they acknowledged that the subject matter of the claims—treatment of multiple sclerosis with 480 mg per day of DMF or MMF—was, in fact, disclosed in the patent specification, the panel majority and the district court engaged in irrelevant comparisons between the amount of disclosure of the claimed subject matter versus the unclaimed subject matter.

For example, while conceding that "MS may arguably constitute an important element of the disclosure from the start," the panel majority focused on the fact that the specification "covers a broad array of nearly three dozen neurological disorders." *Panel Maj. Op.*, 18 F.4th at 1342; *see also District Court Decision*, 2020 WL 3317105, at *10 ("MS is merely one such disease 'among a slew of competing possibilities.'"). As another example, the panel majority emphasized that the 480 mg per day dose "is listed only once in the entire specification," finding this to be "a significant fact that cuts against Biogen's case." *Panel Maj. Op.*, 18 F.4th at 1343; *see also District Court Decision*, 2020 WL 3317105, at *10 (noting that column 18 is "the only part

of the specification that mentions 480 mg/day of DMF"). The panel majority contrasted this one express disclosure of 480 mg per day with the "series of ranges" disclosed in the specification, noting that the 480 mg dose "appears at the end of one range." *Panel Maj. Op.* 18 F.4th at 1343.

As Judge O'Malley's panel dissent noted, the district court justified its focus on unclaimed subject matter by looking to our precedent requiring that a specification contain "blaze marks" that point a person of ordinary skill to the claimed species of a disclosed genus. *See* 18 F.4th at 1350–51 (O'Malley, J., dissenting). Blaze mark analysis originated in *In re Ruschig*, where, unlike here, the specification failed to disclose a claimed species within a disclosed genus. *See* 379 F.2d 990, 994–95 (C.C.P.A. 1967). Although Biogen argued that the district court misapplied that blaze mark precedent, the panel majority dismissed that concern as "superfluous." *Panel Maj. Op.*, 18 F.4th at 1345.

This court has developed a body of precedent to govern the genus/species relationship in the context of the written description requirement of 35 U.S.C. § 112. In cases involving claims to a genus, "a sufficient description of a genus [] requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350 (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568–69 (Fed. Cir. 1997)). On the other hand, "[i]n cases where the specification describes a broad genus and the claims are directed to a single species or a narrow subgenus, we have held that the specification must contain '"blaze marks" that would lead an ordinarily skilled investiga-

tor toward such a species among a slew of competing possibilities.'" *Novartis Pharms. Corp. v. Accord Healthcare, Inc.*, 21 F.4th 1362, 1370 (Fed. Cir. 2022) (quoting *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013)).

As we recently clarified in *Novartis*, however, "'[b]laze marks' are not necessary where the claimed species is expressly described in the specification." *Id.* Such is the case here. The '514 patent does not merely disclose the genus "neurological diseases" without reference to the claimed species "multiple sclerosis." Rather, the patent expressly states that the neurological disease in method 4 can be "multiple sclerosis." '514 patent at col. 16 ll. 18–21; *see also id.* at col. 16 l. 44 (listing additional neurological diseases "in addition to MS"). Similarly, with respect to doses, the patent explicitly includes "480 mg per day" as an end point of a limited number of dose ranges. *Id.* at col. 18 ll. 52–64.

In this case, where the claimed species—*i.e.*, "multiple sclerosis" within the genus "neurological diseases"—is expressly described in the specification, the written description requirement is satisfied regardless of the specification's additional disclosure of other unclaimed neurological diseases. *See Scriptpro, LLC v. Innovation Assocs., Inc.*, 762 F.3d 1355, 1359 (Fed. Cir. 2014) ("It is common, and often permissible, for particular claims to pick out a subset of the full range of described features, omitting others."). Moreover, written description support for the claimed 480 mg per day dose is not undermined by the fact that it only appears one time in the specification or by the fact that the patent also discloses unclaimed dose ranges. *See Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1137 (Fed. Cir. 2018) ("The disclosure of a dose outside of the claimed range does not compel a finding

that the asserted claims lack adequate written description."). Once is enough.

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

B

The second point of error is the panel majority's erroneous imposition of a burden of proof on the patentee to show that the specification proves the efficacy of the claimed pharmaceutical composition. Under our precedent, "it is unnecessary to prove that a claimed pharmaceutical compound actually achieves a certain result." *Nuvo Pharms. (Ir.) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc.*, 923 F.3d 1368, 1384 (Fed. Cir. 2019). That is the province of the United States Food and Drug Administration. *See In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995) (delineating between "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption"); *see also Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of

Patent and Trademark Office (PTO) proceedings."). Yet the panel majority affirmed the district court's decision that the patent fails the written description requirement because "nothing in [the specification] teaches a [person of ordinary skill in the art] that a 480 mg/day dose of DMF [] is therapeutically effective for treating MS." *District Court Decision*, 2020 WL 3317105, at *11; *see also Panel Maj. Op.*, 18 F.4th at 1343–44 ("What matters for purposes of the inquiry in this case is whether, at the time of filing the disclosure, … a skilled artisan could deduce simply from reading the specification that DMF480 would be a therapeutically effective treatment for MS.").

The claims specify precisely the amount that they claim would be "therapeutically effective," namely, "480 mg per day." '514 patent col. 27 ll. 65–67. And the patent specification leaves nothing for the skilled artisan to deduce; it expressly states that 480 mg per day is an effective amount.

C

The third point of error is the panel majority's importation of extraneous legal considerations into the written description analysis. In *Ariad*, we stated that the first paragraph of 35 U.S.C. § 112 "contains two separate description requirements: a 'written description [i] of the invention, *and* [ii] of the manner and process of making and using [the invention]." *Ariad*, 598 F.3d at 1344 (quoting 35 U.S.C. § 112, emphasis and brackets original). The panel majority's focus on the efficacy of the claimed pharmaceutical composition runs afoul of that precedent.

Questions about the operability of a claimed invention—*i.e.*, whether or not the claimed invention actually works—can be relevant to patentability. "But written

description is about whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to what was described; it is not about whether the patentee has proven to the skilled reader that the invention works, or how to make it work, which is an enablement issue." *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1191 (Fed. Cir. 2014); *see also Miles Lab'ys, Inc. v. Shandon Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993) (noting that operability is relevant "to the enablement requirement of § 112"). The enablement requirement has its own legal test and its own substantial body of precedent separate and apart from the written description requirement. *See, e.g., In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).[2] By focusing on whether the patentee ***proved*** that 480 mg per day is an effective amount to treat multiple sclerosis—as distinct from whether the '514 patent specification ***discloses*** that 480 mg per day is an effective amount to treat multiple sclerosis—the panel majority and the district court erroneously imported operability considerations into the written description analysis.

In addition to blurring the lines between written description and enablement, the panel majority and the district court also considered factors relevant to the inventorship of the '514 patent. For example, the district court went into detail about the inventors' "respective roles" in developing the patented technology. *District Court Decision*, 2020 WL 3317105, at *12. Similarly, the panel majority focused on what could be extrapolated from each inventor's research as of the time the

[2] Operability is also relevant for the utility requirement of 35 U.S.C. § 101. *See, e.g., Newman v. Quigg*, 877 F.2d 1575, 1581 (Fed. Cir. 1989) (holding that under the utility requirement of 35 U.S.C. § 101, a claimed invention must "operate to produce what [the patentee] claims it does").

patent application was filed. *See Panel Maj. Op.*, 18 F.4th at 1339–40 (citing testimony from inventor Lukashev about whether clinical doses of DMF was the focus of his work); *id.* at 1344 (discussing when inventor O'Neill may have conceived the idea for the invention). But again, the specification itself discloses that 480 mg per day of DMF is an effective dose in a method for treating multiple sclerosis. To the extent Mylan argued, or could have argued, that there was an inventorship problem with the '514 patent, that is a separate issue from written description under 35 U.S.C. § 112.

The district court also imported aspects of a "best mode" requirement into the written description analysis. The district court stated that "on reading the specification, a POSA would be ***drawn to***, if anything, the 720mg/day dose of DMF included in each dosing example." *District Court Decision*, 2020 WL 3317105, at *11 (emphasis added). The court then relied on testimony that a person of ordinary skill reading the specification "would not know which dose provided in Column 18 would be ***most effective*** for treating MS." *Id.* (emphasis added). But there is no requirement that the written description be sufficient to "draw" a person of ordinary skill toward the claimed embodiment and away from unclaimed embodiments. And there is certainly no requirement that patent claims be limited to only the "most effective" embodiment disclosed in the specification. *See ScriptPro LLC v. Innovation Assocs., Inc.*, 833 F.3d 1336, 1341 (Fed. Cir. 2016) ("[A] specification's focus on one particular embodiment or purpose cannot limit the described invention where that specification expressly contemplates other embodiments or purposes.").

By incorporating extraneous legal standards into the analysis, the panel majority opinion creates confu-

sion for future patent applicants and litigants regarding what is required to meet the written description requirement of 35 U.S.C. § 112. The en banc court should have corrected the panel majority's errors and restored the proper and established boundaries of the written description inquiry.

D

The fourth point of error is the consideration of extrinsic evidence. The test for written description "requires an objective inquiry into the four corners of the specification." *Ariad*, 598 F.3d at 1351. Yet, the panel majority affirmed a district court decision that is replete with reasoning that extends far beyond the confines of the disclosure contained in the patent specification.

To be fair, because the written description inquiry is conducted from the perspective of a person of ordinary skill in the art, extrinsic evidence regarding how a person of ordinary skill would understand what is disclosed in the patent specification can, at times, be relevant. *See, e.g.*, *Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 937–38 (Fed. Cir. 2019) (affirming sufficient written description based on expert testimony about how a specification's disclosure would have been understood in view of what was known in the art); *Space Sys./Loral, Inc. v. Lockheed Martin Corp.*, 405 F.3d 985, 988–90 (Fed. Cir. 2005) (considering expert testimony regarding how the disclosure of the patent specification would have been interpreted by a skilled artisan). But, importantly, such extrinsic evidence should be used only as part of an objective inquiry into what is meant by the disclosure in the patent specification. Where the disclosure in a patent's specification plainly corresponds to what is claimed, extrin-

sic evidence should not be used to cast doubt on the meaning of what is disclosed.

Meaning is not in question in this case. The '514 patent contains a disclosure that corresponds to what is claimed—treatment of multiple sclerosis with 480 mg per day of DMF. In my view, the extrinsic evidence does not render that disclosure inadequate to support what is claimed.

The district court, however, went far beyond limiting its use of extrinsic evidence to interpreting what is disclosed in the patent. Under the guise of considering what a person of ordinary skill in the art would have known as of the claimed priority date, the district court placed considerable weight on whether Biogen's clinical trials before the filing date would have been sufficient to show the efficacy of particular doses of DMF to treat multiple sclerosis. *See District Court Decision*, 2020 WL 3317105, at *11 ("Based on the results of Biogen's Phase II study, … a POSA would have known that 720mg/day of DMF [] is a therapeutically effective dose for treating MS, and that lower doses, such as 360mg/day of DMF [] and 120mg/day of DMF [], are not."). The court also considered the disclosures contained in later-filed Biogen patent applications and compared them to the disclosures of the '514 patent. *Id.* at *13–14. The court went so far as to posit explanations for why the disclosures differed between the patent applications, including speculating about Biogen's motivations for its patent prosecution decisions based on the timing of Biogen's clinical trials and possible desires to avoid prior art. *Id.* at *14. And the court concluded its decision by considering the arguments Biogen made in a Patent Trial and Appeal Board proceeding while defending against Mylan's *inter partes* review petitions. *Id.* at *15.

Simply put, none of that is relevant to the question whether the '514 patent specification contains sufficient written description to support what is claimed. The en banc court should have granted the petition for review to make that clear.

CONCLUSION

I recognize the hesitance to go en banc simply to correct errors in one case. But this case involves more than that. Here, the panel majority has affirmed a district court's erroneous broadening of the written description inquiry. In denying rehearing en banc, the court has lost an opportunity to provide clarity for future litigants by reaffirming the proper boundaries of the written description requirement in 35 U.S.C. § 112.

I therefore dissent from the court's decision not to rehear this case en banc.

APPENDIX C

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

CIVIL ACTION NO. 1:17CV116

BIOGEN INTERNATIONAL GMBH
and BIOGEN MA, INC.,
Plaintiffs,

v.

MYLAN PHARMACEUTICALS INC.,
Defendant.

Filed June 18, 2020
(Judge Keeley)

MEMORANDUM OPINION AND ORDER MAKING FINDINGS OF FACT AND GRANTING JUDGMENT IN FAVOR OF THE DEFENDANT, MYLAN PHARMACEUTICALS INC.

I. BACKGROUND

In this patent infringement action, the plaintiffs, Biogen International GmbH and Biogen MA, Inc. (collectively "Biogen"), and the defendant, Mylan Pharmaceuticals Inc. ("Mylan"), dispute whether claims 1-4, 6, 8-13, and 15-16 ("the asserted claims") of Biogen's U.S. Patent No. 8,399,514 ("the '514 Patent") are valid and enforceable (Dkt. Nos. 1 at 14-17, 288 at 1-2).[1] The '514

[1] All docket and page numbers refer to the numbers assigned by the Court's electronic docket.

Patent is associated with Tecfidera®, Biogen's New Drug Application ("NDA") product approved by the FDA for use in the treatment of multiple sclerosis ("MS") (Dkt. No. 1 at 15). Mylan has filed an Abbreviated New Drug Application ("ANDA"), seeking to market a drug that is bioequivalent to Tecfidera®.

The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (otherwise known as the "Hatch-Waxman Act"), seeks to encourage "pioneering research and development of new drugs," as well as the "production of low-cost, generic copies of those drugs." *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 557 F.3d 1346, 1348 (Fed. Cir. 2009). To that end, a manufacturer may obtain Food and Drug Administration ("FDA") approval to market a generic drug by making a certification regarding patents listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") as covering the NDA drug, and certifying that those patents are "invalid or will not be infringed by the manufacture, use, or sale of the new generic drug for which the ANDA is submitted" ("paragraph IV certification"). *Id.* (citing 21 U.S.C. § 355(j)(2)(A)(vii)(IV)). Upon receiving a paragraph IV certification, a patentee may sue the applicant for patent infringement within 45 days, thus delaying FDA approval of the ANDA. *Id.* (citing § 355(j)(5)(B)(iii)).

In this case, where Biogen has sued Mylan under the Hatch-Waxman Act for infringement of Tecfidera®, the Court is tasked with deciding whether the asserted claims of Biogen's '514 Patent are invalid for lack of written description under 35 U.S.C. § 112.[2] As

[2] Initially, six patents associated with Tecfidera® were at issue in this case (Dkt. No. 1). On February 5, 2019, the parties

discussed below, the Court **FINDS** that Mylan has demonstrated by clear and convincing evidence that the asserted claims of the '514 Patent are invalid for lack of written description.

II. FINDINGS OF FACT[3]

A. The Parties, Jurisdiction, and Venue

Biogen International GmbH is a corporation organized under the laws of Switzerland with its principal place of business at Landis + Gyr-Strasse 3, 6300 Zug, Switzerland. Biogen MA, Inc. is a corporation organized under the laws of the Commonwealth of Massachusetts with its principal place of business at 225 Binney Street, Cambridge, Massachusetts 02142. Mylan is a corporation organized under the laws of West Virginia with its principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505. The Court has subject matter and personal jurisdiction, and venue is proper.

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stipulated to the dismissal of all claims, counterclaims, and defenses regarding U.S. Patent Nos. 6,509,376; 7,320,999; 7,803,840; and 8,759,393 (Dkt. No. 196). In advance of trial, the parties further stipulated to stay all remaining claims, counterclaims, and defenses regarding U.S. Patent No. 7,619,001 ("the '001 Patent") until June 20, 2020 (Dkt. Nos. 288, 315 at 12, 336 at 44). After the first day of trial, the parties agreed that, based on an intervening decision from the Patent Trial and Appeal Board ("PTAB") in the related inter partes review ("IPR") proceeding, Mylan was collaterally estopped under 35 U.S.C. § 315(e)(2) from asserting its obviousness case under 35 U.S.C. § 103 (Dkt. No. 357 at 3-6). Thus, based on the parties' various stipulations, the only remaining issue at trial was whether the asserted claims of the '514 Patent are invalid for lack of written description under § 112 (Dkt. Nos. 288, 315 at 12, 357 at 3-6).

[3] Further findings of fact regarding matters in dispute are contained in Part III (Discussion).

B. Factual and Procedural Background

Because the asserted claims of the '514 Patent recite a specific method for treating MS, the Court begins its analysis with a brief discussion of this neurologic disorder, as well as Biogen's clinical development of Tecfidera®, and the relevant prosecution history of Biogen's patent applications related to Tecfidera®.

1. Multiple Sclerosis

MS is a neurologic disorder and autoimmune disease that causes the immune system to attack myelin, a protective sheathing surrounding nerve cell axons (Dkt. Nos. 356 at 106-07, 359 at 84-85). This sheathing protects nerves in the central nervous system, much like a rubber coating protects wires to a computer or stereo system (Dkt. No. 356 at 106-07). Although the immune system is a self-defense system that combats viruses and bacteria that would harm the human body, MS confuses the immune system into attacking myelin (Dkt. Nos. 356 at 107, 359 at 84-85).[4] This causes inflammation that results in demyelination and leads to axonal loss and death of the nerve cell (Dkt. Nos. 356 at 106-07, 359 at 84-85). Together, this damage results in scarring or lesions on the brain, which can be imaged by

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[4] As described by Mylan's expert witness, Benjamin M. Greenberg, M.D., autoimmune diseases such as MS are much like a confused house cat that mistakes a curtain, or other house-hold objects, for an invading mouse (Dkt. Nos. 356 at 107-09). Instead of attacking the mouse, the confused cat attacks a portion of the house it is meant to protect. *Id.* The cat's breed, and the type of friendly object it attacks, will help identify which autoimmune disease is causing the confusion. *Id.* For example, a Siamese cat (i.e., multiple sclerosis) may be confused and attack one part of the house (i.e., the central nervous system), and a Tabby cat (i.e., psoriasis) may be confused and attack another part of the house (i.e., the skin). *Id.* at 107-10.

magnetic resonance imaging (i.e., an MRI) (Dkt. No. 356 at 112, 359 at 86-87). Those images, in turn, are used to monitor disease progress in patients. *Id.*

2. Biogen's Due Diligence of Fumapharm AG

Gilmore O'Neill, M.D. ("Dr. O'Neill") is a neurologist specializing in neuromuscular diseases such as MS (Dkt. No. 362 at 109-10). In 2003, while Biogen was negotiating a prospective licensing agreement with Fumapharm AG ("Fumapharm"), a company studying fumarates, Dr. O'Neill participated in a confidential due diligence of Fumapharm (Dkt. No. 362 at 27-28, 52-53; JTX 2133 at 3-4).[5] This included reviewing confidential studies of Fumaderm® (a mixture of fumarates, including dimethyl fumarate ("DMF")), a drug developed by Fumapharm to treat psoriasis, another autoimmune disease (Dkt. No. 362 at 27-28, 52-53). *See supra* note 4.

Of significance to the issue at hand, after reviewing these studies and the underlying pharmacology of DMF, Dr. O'Neill hypothesized that the peak level of medication in the blood stream, the "C_{max} of DMF," could be driving the efficacy of DMF (Dkt. No. 362 at 53-54). From this, he conceived the idea that, if the drug's "efficacy might be driven by the maximal exposure of the medicine in the [sic] circulation as opposed to a continuous exposure," a daily dose of 480mg (in two equally divided doses or "BID") of DMF could achieve the correct "maximal exposure" and be efficacious in treating MS (Dkt. No. 362 at 53-54).

[5] "JTX" refers to the parties' joint trial exhibits.

3. Biogen's Phase II Development of Tecfidera®

After obtaining a licensing agreement with Fumapharm, Biogen appointed Dr. O'Neill as Medical Director of its BG-12 Development Program (JTX 2133 at 4-5, 9-10, 14),[6] to design and lead the clinical development of Tecfidera® to treat MS. *Id.* at 4-5, 10-11, 14. As Medical Director, Dr. O'Neill proposed that Biogen incorporate a 480mg/day dose of DMF (BID) as part of its Phase II study of Tecfidera® (Dkt. Nos. 358 at 126-27, 362 at 120-21, 125-26, 140; JTX 2013 at 16-17; JTX 2035 at 14; 2133 at 14-16).[7]

Biogen opted instead to test 120mg/day of DMF (in one single dose or "QD"), 360mg/day of DMF (in three equal doses or "TID"), and 720mg/day of DMF (TID) (Dkt. Nos. 358 at 127-28, 135, 362 at 68-70; JTX 2013 at 17; JTX 2036 at 1; JTX 2133 at 16-17) in its Phase II study (JTX 2013 at 17; JTX 2153B at 8, 12). The results of that study, which were published in May 2006, demonstrated that a 720mg/day dose of DMF (TID) was efficacious in treating MS (JTX 2088 at 3-4; JTX 2153B at 8, 12-18), but doses of 120mg/day (QD) and 360mg/day (TID) were not (JTX 2153B at 8, 12-18).

With these results in hand, Biogen began designing its Phase III study (JTX 2091; JTX 2100; JTX 2101;

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[6] BG-12 was Biogen's internal and external name for Tecfidera® prior to its receipt of FDA approval to market the drug (JTX 2133 at 9-10).

[7] Phase II studies are in vivo clinical trials that test a new drug in a mid-sized group of human patients (Dkt. No. 356 at 27 (noting that Biogen's Phase II study included approximately 250 patients)). "In vivo" means inside the body. In other words, an experiment in vivo is done in a living organism (Dkt. No. 358 at 59 (discussing in vivo test performed in mice)).

JTX 2133 at 25-26; JTX 2142; JTX). Before that study got underway, however, Dr. O'Neill left the BG-12 program and was replaced by Katherine Dawson, M.D. ("Dr. Dawson") (Dkt. No. 362 at 17, 153-54; JTX 2091 at 1; JTX2133 at 26).

4. Biogen's Research Regarding the Nrf2 Pathway

It must be noted that Biogen's BG-12 Development Program was not focused solely on the clinical development of Tecfidera®. Matvey E. Lukashev, Ph.D. ("Dr. Lukashev"), a scientist employed by Biogen, joined the BG-12 program in 2005 (Dkt. No. 358 at 41; JTX 2196), where his work was to "elucidate the mechanism of action"; he "was not involved in clinical decision-making" (Dkt. No. 358 at 40-41, 42).

"Mechanism of action" is a "scientific fact-based description of the molecular and cellular events affected by the … active substance of the drug." *Id.* at 47. Through his research, Dr. Lukashev discovered that DMF, with its key regulator, a protein called KEAP1, activated the Nrf2 pathway. *Id.* at 48-49. Based on this mechanism of action, he looked for other compounds that could do the same. *Id.* at 52.

Dr. Lukashev's scope of work thus extended beyond Biogen's BG-12 testing program because it included screening compounds other than DMF that could activate the Nrf2 pathway. *Id.* at 52-53. When asked to describe his work, he noted that it was "a more exploratory nature. It[was] to explore potential for follow-on compound discovery, perhaps movement into other indications or perhaps not previously explored in the clinic in any therapeutic context, combinations of fumarates with other therapeutics." *Id.* at 53. Significantly, Dr. Lukashev 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]." *Id.* at 53-54, 54.

Although Dr. Lukashev conducted experiments with a range of concentrations of DMF and monomethyl fumarate ("MMF") in vitro and in vivo,[8] those experiments "examine[d] details of the molecular events that could be, in principle, triggered by the active ingredient in a cell." *Id.* at 54, 57-60. Two of these examples were included in Biogen's U.S. Provisional Application No. 60/888,921 ("the '921 Application") (JTX 2182 at 37-39), and a third was included in Biogen's International Patent Application No. PCT/US2008/001602 ("the 0016902 Application") (PTX 401 at 33).[9] Dr. Lukashev is the only inventor named in the '921 and 0016902 Applications, entitled "Nrf2 Screening Assays and Related Methods and Compositions," which recite methods for screening drug compounds for their ability to activate the Nrf2 pathway (JTX 2182 at 4, 40-42; PTX 401 at 1-2).

5. Brief Summary of Prosecution History of '514 Patent

Biogen filed the '921 Application on February 8, 2007 (JTX 2182), before beginning its Phase III study of Tecfidera®.[10] It later filed the 0016902 Application,

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[8] "In vitro" means outside the body. In other words, an experiment in vitro is an artificial experiment performed using a test tube or petri dish (Dkt. No. 359 at 28 (explaining the meaning of in vitro)).

[9] "PTX" refers to Biogen's trial exhibits.

[10] Phase III studies are in vivo clinical trials that test a new drug in a large number of human patients (Dkt. No. 377 at 16 (not-

which added to the specification of the '921 Application, on February 7, 2008 (PTX 401). The 0016902 Application later became U.S. Patent Application No. 12/526,296 ("the '296 Application") on August 7, 2009 (DTX 1016).[11]

Biogen received the results of its Phase III study in April 2011, after which it twice amended the '296 Application to change its title and claims and to add an inventor (DTX 1656; DTX 1657). Notably, it did not change the specification in the '296 Application. *Id.*

Biogen later abandoned the '296 Application in favor of a continuing application, U.S. Patent Application No. 13/326,426 ("the '426 Application"), filed on February 13, 2012 (JTX 2173). Ultimately, the '426 Application resulted in the issuance of the '514 Patent on March 19, 2013 (JTX 2000; JTX 2173). And, it was through its '921 Application that Biogen claimed a February 8, 2007 priority date for its '514 Patent (JTX 2000; JTX 2182).

6. Biogen's Phase III Development of Tecfidera®

After receiving FDA approval for its Phase III study, Biogen commenced its first trial (the DEFINE trial) on March 14, 2007, and its second trial (the CONFIRM trial) on July 28, 2007 (JTX 2108 at 12, 23; JTX 2110 at 28, 38; JTX 2133 at 27-28). Although the parties dispute when and why Biogen decided to test a 480mg/day dose of DMF as part of those trials (Dkt. Nos. 376 at 11-12, 377 at 14-15), it is undisputed that, for whatever reason it did so, Biogen ultimately includ-

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ing that Biogen Phase III study involved over 2600 patients (citing JTX 2088; JTX 2133))).

[11] "DTX" refers to Mylan's trial exhibits.

ed a 480mg/day dose of DMF (BID) as part of its Phase III study.

The Phase III study "showed an unexpected magnitude of efficacy where the 480mg/day dose 'met all primary and secondary endpoints' including both MRI and clinical endpoints, e.g., reduction in annual relapse rate, and did so 'with a high level of statistical significance'" (Dkt. No. 377 at 17 (emphasis omitted) (quoting JTX 2088 at 9-10, 19)). Put simply, the Phase III study demonstrated that the 480mg/day and 720mg/day doses of DMF were equally efficacious in treating MS.

7. Biogen's Prosecution of the '514 Patent

In light of these unexpected results, Biogen needed a patent to protect the 480mg/day dose from competition and quickly filed U.S. Provisional Application No. 14/119,373 ("the '373 Application") in May 2011. This application was entitled "Methods of Treating Multiple Sclerosis and Preserving and/or Increasing Myelin Content" and listed three inventors, Dr. Dawson, Dr. O'Neill, and Alfred Sandrock (another Biogen employee) (DTX 1169). The specification of the '373 Application thoroughly reviewed data from Biogen's Phase III study and asserted 42 claims reciting a method for treating MS with a 480mg/day dose of DMF (BID). *Id.*

A month after filing the '373 Application, in June 2011, Biogen amended its '296 Application, filed on August 7, 2009, to replace the title "Nrf2 Screening Assays and Related Methods and Compositions" with "Treatment for Multiple Sclerosis" (DTX 1656). This amendment also deleted all previously listed claims for methods for screening drug compounds for their ability to activate the Nrf2 pathway and added sixteen new claims reciting methods for treating MS with a 480mg/day dose of DMF (BID). *Id.* In October 2011,

Biogen again amended the '296 Application, this time to add Dr. O'Neill as a co-inventor with Dr. Lukashev and also to include three additional claims reciting methods for treating MS with 480mg/day of DMF (BID) (DTX 1657).

At no time throughout this course of amendments did Biogen amend the "specification" (i.e., the written description) of the '296 Application (DTX 1656; DTX 1657). This enabled it to claim a priority date of February 8, 2007, the date on which Biogen had filed the '921 Application (JTX 2182).[12]

Later, on February 13, 2012, Biogen filed a continuing application of its '296 Application, which ultimately became the '426 Application (JTX 2173). The '426 Application included all amendments to the '296 Application, while maintaining the specification from the '921 Application. *Id.* Biogen then abandoned the '296 Application and focused its efforts before the U.S. Patent and Trademark Office ("PTO") entirely on the '426 Application. *Id.*

During prosecution of the '426 Application, the PTO twice rejected Biogen's asserted claims as obvious over the prior art (JTX 2173 at 382-92, 888-96). In response to each rejection, Biogen reasserted its claim

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[12] *See Auto. Tech Int'l, Inc. v. Delphi Corp.*, 776 F. Supp. 2d 469, 488 (E.D. Mich. 2011) ("[A] patent containing enabled and adequately described claims that issue from a continuation application may claim the benefit of the priority date of its parent application because they share identical specifications; a continuation application may not contain new matter." (citing 35 U.S.C. § 120)). The parties, however, dispute whether Biogen may rely on example three (Dkt. Nos. 376 at 22 n.6, 377 at 25 n.4, 384 at 11-12), which was included only in the 0016902 Application (PTX 401 at 33), not Biogen's earlier '921 Application (JTX 2182 at 37-39). This dispute is discussed in detail *infra* in Part III (Discussion).

that the 480mg/day dose of DMF (BID) had exhibited unexpected efficacy in the treatment of MS. *Id.* at 453-55, 914-17.

The PTO eventually overcame its concerns about obviousness and, on March 19, 2013, issued the '514 Patent (JTX 2000), which is listed in the Orange Book for NDA No. 204063, covering Tecfidera® (Dkt. No. 1 at 15), and claims a priority date of February 8, 2007 (JTX 2000). With the '514 Patent in hand, Biogen abandoned the '373 Application it had filed on May 26, 2011 (DTX 1169).[13]

8. The Asserted Claims of the '514 Patent

The asserted claims in the '514 Patent recite a method for treating a specific disease (MS), with a specific drug (DMF or MMF), at a specific dose (480mg/day (BID)) (Dkt. No. 359 at 89-90, 105):

> 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 [DMF], [MMF], or a combination thereof, and (b) one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount of [DMF], [MMF], or a combination thereof is about 480 mg per day.
>
> 2. The method of claim 1, wherein the pharmaceutical composition is administered in the form of a tablet, a suspension, or a capsule.

[13] An addendum attached to this Memorandum Opinion and Order provides a timeline of this prosecution history.

3. The method of claim 1, wherein the therapeutically effective amount is administered in separate administrations of 2, 3, 4, or 6 equal doses.

4. The method of claim 3, wherein the therapeutically effective amount is administered in separate administrations of 2 equal doses.

. . .

6. The method of claim 1, wherein the pharmaceutical composition consists essentially of [DMF] and one or more pharmaceutically acceptable excipients.

. . .

8. The method of claim 1, wherein the pharmaceutical composition is administered to the subject for at least 12 weeks.

9. The method of claim 6, wherein the therapeutically effective amount is administered to the subject in 2 equal doses.

10. The method of claim 9, wherein the therapeutically effective amount is administered to the subject for at least 12 weeks.

11. A method of treating a subject in need of treatment for multiple sclerosis consisting essentially of orally administering to the subject about 480 mg per day of [DMF], [MMF], or a combination thereof.

12. The method of claim 11, wherein about 480 mg of [DMF] per day is administered to the subject.

13. The method of claim 12, wherein the [DMF] is administered in separate administrations of 2 equal doses.

. . .

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

16. The method of claim 15, wherein the [DMF] is administered in separate administrations of 2 equal doses.

(JTX 2000 at 28-29).

III. DISCUSSION

A. Applicable Law

The first paragraph of 35 U.S.C. § 112 requires a patent's specification to include, among other things, "a written description of the invention … ."[14] This written description requirement "allows a person of skill in the art to recognize that the patentee invented what is claimed." *Synthes USA, LLC v. Spinal Kinetics, Inc.*,

[14] The America Invents Act ("AIA"), Pub. L. No. 112-29, § 4(c), 125 Stat. 284, 296 (2011), added subsection headings to the six paragraphs that made up the pre-AIA version of § 112. Although these amendments have no effect on the question presented, the parties agree that, because the priority date of the '514 Patent is February 8, 2007, the pre-AIA version of § 112 applies to the asserted claims (Dkt. Nos. 376 at 17 n.3, 377 at 21 n. 3).

734 F.3d 1332, 1341 (Fed. Cir. 2013) (citing *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)). "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor ha[d] possession of the claimed subject matter as of the filing date." *Id.* (quoting same).

"That requirement is satisfied only if the inventor 'conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrates that by disclosure in the specification of the patent.'" *Nuvo Pharm. (Ir.) Designated Activity Co. v. Dr. Reddy's Labs. Inc.*, 923 F.3d 1368, 1376 (Fed. Cir. 2019) (cleaned up) (quoting *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011)). "[A]ctual 'possession' or reduction to practice outside of the specification is not enough." *Ariad Pharm. Inc.*, 598 F.3d at 1352. "[I]t is the specification itself that must demonstrate possession." *Id.*

Whether the '514 Patent is invalid for lack of written description is a factual question for Mylan to establish by clear and convincing evidence. *Rivera v. Int'l Trade Comm'n*, 857 F.3d 1315, 1319 (Fed. Cir. 2017).

B. Person of Ordinary Skill in the Art

Determining who constitutes a person of ordinary skill in the art ("POSA") is also a factual question, *see ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010), involving a two-step inquiry: "The first part is determining what exactly is that 'relevant art' at issue, the second is determining who qualifies as a 'person of ordinary skill' in that art." *Seed Research Equip. Solutions, LLC v. Gary W. Clem, Inc.*, No. 09-01282-EFM-KGG, 2011 WL 5024351, at *3 (D. Kan. Oct.

20, 2011) (citing *Arachnid, Inc. v. Merit Indus., Inc.*, 201 F. Supp. 2d 883, 888 (N.D. Ill. 2002)).

"Art" is defined simply as "[a] field of useful endeavor." And "relevant art" is the "[a]rt to which one can reasonably be expected to look for a solution to the problem that a patented device tries to solve." Art, Black's Law Dictionary (11th ed. 2019). "The relevant art is defined by the nature of the problem confronting the would-be inventor." *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 716 (Fed. Cir. 1991) (internal quotation omitted). "Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007) (citation omitted). These factors are illustrations, not exhaustive. *Id.*

In this case, the parties agree that a POSA is someone with "at least a medical degree, at least three years of training in neurology, and at least three years of clinical experience treating multiple sclerosis patients" (Dkt. Nos. 356 at 113; 359 at 9, 81; 387 at 1). Mylan presented the testimony of Benjamin M. Greenberg, M.D. ("Dr. Greenberg"), and Biogen presented the testimony of Daniel R. Wynn, M.D. ("Dr. Wynn") (Dkt. Nos. 356 at 99-228, 359 at 6-73, 74-144). Each is a neurologist who treats patients with MS and meets the parties' definition of a POSA (Dkt. Nos. 356 at 165-66, 359 at 80).

C. The Parties' Contentions

Mylan contends that the '514 Patent is invalid for lack of written description because the specification described in 2007 bears no resemblance to the invention claimed in 2011 (Dkt. No. 376 at 16-17). This is so for two reasons. First, as Biogen insisted throughout its prosecution of the '514 Patent, a POSA would not have expected the claimed invention—a 480mg/day dose of DMF (BID)—to effectively treat MS. *Id.* at 17-24. Mylan asserts that nothing in the specification of the '514 Patent teaches otherwise. *Id.*

Second, Mylan contends 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). *Id.* at 24-29. According to Mylan, "[t]he reason is evident: 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 results demonstrated the effectiveness of the 480[mg/day] dose." *Id.* at 24 (emphasis in original).

In resisting these arguments, Biogen asserts that Mylan faces an "added burden" of demonstrating lack of written description in this case because the PTO previously questioned the sufficiency of the written description in the context of an obviousness rejection (Dkt. No. 377 at 20-21). It also contends that Mylan mistakenly relies on evidence of obviousness, which is irrelevant to the written-description analysis. *Id.* at 22. Turning to the specification, Biogen maintains that

"[t]he '514 Patent links through Method 4 each of the three recited elements of the asserted claims: (1) a method of treating MS with (2) DMF and/or MMF (3) at a dose of 480 mg per day." *Id.* at 23, 23-29. Finally, Biogen argues that Mylan has misapplied the law and failed to satisfy its burden of proof. *Id.* at 29-45. The Court addresses each of these arguments in turn.

D. The Asserted Claims of the '514 Patent Are Invalid for Lack of Written Description Under § 112

1. Mylan Faces No "Added Burden"

As a threshold matter, Biogen's argument that Mylan faces an "added burden" in this case misses the mark. As Mylan correctly notes, "[t]he burden [of proof] does not suddenly change to something higher—'extremely clear and convincing evidence' or 'crystal clear and convincing evidence'—simply because" the PTO previously questioned the sufficiency of the written description in the context of an obviousness rejection. In *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012), the Federal Circuit confirmed the applicable burden of proof for establishing invalidity based on obviousness: "The presumption of validity found in [35 U.S.C.] § 282 is reflected in the standard of proof required to prove invalidity, clear and convincing evidence." *Id.* (citing *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 100-01 (2011)). So too here. "Nothing in § 282's text suggests that Congress meant to … enact a standard of proof that would rise and fall with the facts of each case." *Microsoft Corp.*, 564 U.S. at 109.

2. The Specification Does Not Demonstrate that the Inventors "Possessed" the Claimed Invention

In order to satisfy the written description requirement of § 112, the inventor must "'convey[] with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate[] that by disclosure in the specification of the patent.'" *Nuvo Pharm.*, 923 F.3d at 1376 (cleaned up) (citation omitted). Significantly, "actual 'possession' or reduction to practice outside of the specification is not enough." *Ariad Pharm. Inc.*, 598 F.3d at 1352. "[I]t is the specification itself that must demonstrate possession." *Id.*

Here, Mylan contends that the '514 Patent, when viewed as an integrated whole, fails to satisfy this statutory requirement because it does not demonstrate that, as of February 8, 2007, Dr. Lukashev and Dr. O'Neill "possessed" a method of treating MS with a therapeutically effective amount of DMF, i.e., 480mg/day (BID) (Dkt. Nos. 376, 384).[15]

Spanning 30 columns (JTX 2000 at 15-29), the specification of the '514 Patent begins with a general discussion of MS but quickly turns to a discussion of how "the

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[15] In its post-trial brief, Biogen appears to suggest that the therapeutic efficacy required by the asserted claims differs from clinical efficacy (Dkt. No. 377 at 39-40). But based on the factual and evidentiary record in this case, and in light of Biogen's consistent representations to the PTO during prosecution and before the PTAB in the related IPR proceeding, Biogen is estopped from relying on this distinction. *See, e.g.*, *New Hampshire v. Maine*, 532 U.S. 742, 743 (judicial estoppel applies "to protect the integrity of the judicial process by prohibiting parties from deliberately changing positions according to the exigencies of the moment" (cleaned up)).

Nrf2 pathway may be activated in neurodegenerative and neuroinflammatory diseases as an endogenous protective mechanism," and how "[e]merging evidence suggests that [plant-derived] compounds may exert their neuroprotective effects by activating cellular stress-response pathways, including the Nrf2 pathway, resulting in the upregulation of neuroprotective genes" (JTX 2000 at 15). It then acknowledges that "the exact mechanism of action of these compounds remains poorly understood." *Id.*

The specification provides five methods:

1) methods of screening for at least one new candidate compound for treating a neurological disease;

2) methods of evaluating neuroprotective properties of at least one drug candidate for treating a neurological disease;

3) methods of comparing (e.g., for bioequivalence) at least two pharmaceutical compositions which comprise fumaric acid derivatives;

4) methods of treating a neurological disease by administering to the subject in need thereof at least one compound that is partially structurally similar to DMF or MMF; and

5) methods of treating a neurological disease by a combination therapy that comprises administration of at least one first compound that upregulates the Nrf2 pathway and at least one second compound that does not upregulate the Nrf2 pathway.

Id. at 15-16.

Biogen concedes that "Methods 1-3 are directed to methods of screening for compounds to treat neurological diseases," which are "described, but not claimed, in the '514 Patent" (Dkt. No. 377 at 16, 24). It also concedes that "Method 5 relates to the use of [compounds such as DMF] in combination therapy along with other compounds having different activity." *Id.* at 24. According to Biogen, "[t]he '514 Patent links through Method 4 each of the three recited elements of the asserted claims: (1) a method of treating MS with (2) DMF and/or MMF (3) at a dose of 480 mg per day." *Id.* at 23. This simply is not so. The description of Method 4 is limited in scope and makes no mention of treating MS with a 480mg/day dose of DMF (BID):

> In some embodiments method 4 comprises administering to the mammal a therapeutically effective amount of at least one neuroprotective compound having Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g. , DMF or MMF).
>
> In some embodiments method 4 provides a method of slowing or preventing neurodegeneration in a patient in need thereof, by administering the compound in an amount and for a period of time sufficient to slow or prevent demyelination, axonal loss, and/or neuronal death, e.g., by at least 30% relative to a control.

(JTX 2000 at 16).

> Also provided are methods of treating a neurological disease by administering to the subject in need thereof at least one compound

> that is at least partially structurally similar to DMF and/or MMF.
>
> In some embodiments of method 4, a method of treating a mammal who has or is at risk for a neurological disease is provided. The methods comprises [sic] administering to the mammal a therapeutically effective amount of at least one neuroprotective compound which has Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g., DMF or MMF).
>
> In some embodiments of method 4, a method of slowing or preventing neurodegeneration (more specifically, e.g., demyelination, axonal loss, and/or neuronal death) in a subject in need thereof by administering the at least one compound in an amount and for a period of time sufficient to do at least one of slow or prevent demyelination, slow or prevent axonal loss, and slow or prevent neuronal death, e.g., by at least 30%, 50%, 100% or higher over a control over a period of at least 5, 10, 12, 20, 40, 52, 100, or 200 weeks, or more.

Id. at 18.

Thus, Method 4 broadly describes treating neurological diseases with a therapeutically effective amount of DMF; MS is merely one such disease "among a slew of competing possibilities." *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013). Indeed, in Column 3, the specification explains that, "[i]n some embodiments, the neurological disease is a neurodegenerative disease such as, for example, ALS, Parkinson's disease, Alzheimer's disease, and Huntington's disease" (JTX 2000 at 16). In others,

"the neurological disease is MS or another demyelinating neurological disease." *Id.*

Column 16 then provides an exhaustive list of "diseases suitable for the [five] methods described" in the '514 Patent:

> Examples of neurological diseases suitable for the methods described herein include neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, and Huntington's disease. Other examples include demyelinating neurological disease including, in addition to MS, the following diseases: acute haemorrhagic Ieucoencephalomyelitis, Hurst's disease, acute disseminated encephalomyelitis, optic neuritis, Devic's disease, spinal cord lesions, acute necrotizing myelitis, transverse myelitis, chronic progressive myelopathy, progressive multifocal leukoencephalopathy (PML), radiation myelopathy, HTLV-1 associated myelopathy, monophasic isolated demyelination, central pontine myclinolysis, and leukodystrophy (e.g., adrenoleucodystrophy, metachromatic leucodystrophy, Krabbe's disease, Canavan's disease, Alexander's disease, Pelizaeus-Merbacher disease, vanishing white matter disease, oculodentodigital syndrome, Zellweger's syndrome), chronic inflammatory demyelinating polyneuropathy (CIDP), acute inflammatory demyelinating polyneuropathy (AIDP), Leber's optic atrophy, and Charcot-Marie-Tooth disease.
>
> Additional examples of diseases suitable for the methods described herein include polyneuritis and mitochondrial disorders with de-

> myelination. These disorders may be co-presented with, and possibly aggravated by diabetes, e.g., insulin-dependent diabetes mellitus (IDDM; type I diabetes), or other diseases.

Id. at 22.

Because Methods 1-5 can be used for a plethora of neurological diseases, there are no "blaze marks" in Method 4 that would lead a POSA specifically to MS. *Ariad*, 598 F.3d at 1348. Nor, as Biogen posits, does Method 4 "link" a therapeutically effective amount of DMF to a dose of 480mg/day (BID). *Id.* at 1357.

For this proposition, Biogen directs the Court's attention to Column 18, the only part of the specification that mentions 480mg/day of DMF:

> For example, an effective dose of DMF or MMR to be administered to a subject orally can be from about 0.1 g to 1 g per pay [sic], 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.[16]

(JTX 2000 at 23) (footnote added). This passage, however, neither "links" this "effective dose" to the treatment of MS, nor to a 480mg/day dose of DMF (BID). Mylan's POSA, Dr. Greenberg, credibly testified at trial that nothing in Column 18 ties an effective dose of DMF specifically to the treatment of MS (Dkt. No. 359 at 34-36). The cited passage, moreover, offers only a

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[16] Although this passage reads "an effective dose of DMF or MMR," the parties agree that "MMR" is a typographical error and should read "MMF" (Dkt. Nos. 356 at 90, 358 at 73, 362 at 40).

broad range of what an effective dose "can be": "0.1 g to 1 g per day"[17] or "200 mg to 800 mg per day" (JTX 2000 at 23).

The examples following this broad disclosure also fail to direct a POSA to the conclusion that a therapeutically effective amount of DMF is 480mg/day (BID). Strikingly, 480mg dosing is mentioned only once in three examples: "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" (JTX 2000 at 23 (emphasis added)). Although Biogen and its expert insist that 480mg to 720mg/day is the narrowest and, therefore, the most preferred range, thereby teaching a 480mg/day dose (Dkt. Nos. 359 at 49-50, 102, 143-44; 377 at 27, 29), this reading is neither credible nor persuasive.

Based on the results of Biogen's Phase II study, as of the claimed priority date of February 8, 2007, a POSA would have known that 720mg/day of DMF (TID) is a therapeutically effective dose for treating MS, and that lower doses, such as 360mg/day of DMF (TID) and 120mg/day of DMF (QD), are not (JTX 2153B at 8, 12). *See Zoltek Corp. v. United States*, 815 F.3d 1302, 1308 (Fed. Cir. 2016) (stating that the written-description "requirement is applied in the context of the state of knowledge at the time of the invention" (citation omitted)). Thus, on reading the specification, a POSA would be drawn to, if anything, the 720mg/day dose of DMF included in each dosing example: "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*" (JTX 2000 at 23 (emphasis added)). This understanding is confirmed by the next sentence, which fur-

[17] In other words, 100mg to 1,000mg (Dkt. No. 359 at 34).

ther highlights a 720mg/day dose: "For example, the *720 mg per day* may be administered in separate administrations of 2, 3, 4, or 6 equal doses." *Id.* (emphasis added).

Given the emphasis on 720mg/day of DMF, nothing in this passage teaches a POSA that a 480mg/day dose of DMF (BID) is therapeutically effective for treating MS (Dkt. No. 359 at 34-38). Tellingly, Biogen's expert, Dr. Wynn, conceded as much on cross examination. Based on his reading of the '514 Patent, he testified he would not know which dose provided in Column 18 would be most effective for treating MS:

> Q. So based upon reading the patent alone, you wouldn't know what the preferred dose was for treating MS? Is that what I just heard you say?
>
> A. Which would be the most effective dose.
>
> Q. Okay. You wouldn't know that?
>
> A. Correct.
>
> . . .
>
> Q. Based on the data the artisan would know at the time of the filing of the patent, all three of those ranges include doses which, according to you, they would know would be ineffective, right?
>
> A. A dose of 360 or lower would not be felt to be a preferred dose for treating MS.
>
> Q. Okay. So—but we get to the fourth dose, and suddenly now we're talking about treating MS, right?

A. I don't know that the others were not for treating MS. And, again, from reading this, I don't know that 480 would be the preferred dose for treating MS either.

Q. And that's—I think we agree on that. Reading this patent specification as a person of skill in the art, you wouldn't know that 480 milligrams would be a preferred dose for treating MS. I agreed with you on that, right? We agree on that?

A. Okay.

(Dkt. No. 359 at 135-37).

After Dr. Wynn attempted to disavow this testimony, *id.* at 137-38, Mylan effectively impeached his credibility:

Q. All right, Doctor. I'm looking at the Delaware trial transcript at page 64, lines 13 to 18. Do you see that?

. . .

A. Yes.

Q. And do you see you were asked a question there, "Actually, sir, if you had seen this patent in 2007, you wouldn't know about the 480 milligram dose, would you?" And what was your answer?

A. I answered, "I wouldn't know if it was clinically effective."

Q. And then you were asked, "Because there's no data on it provided in the specification, right?" And what did you answer?

A. "Anywhere that I'm aware of."

> Q. All right. That was the testimony you gave in Delaware, correct, sir?
>
> A. Yes.

Id. at 139.

Biogen's reliance on Example 3 fares no better. To start, Biogen may not rely on this example because it was not in the specification of the '921 Application (JTX 2182 at 37-39) through which the '514 Patent claims priority (JTX 2000). *See Delphi Corp.*, 776 F. Supp. 2d at 488 (noting that "a continuation application may not contain new matter" (citing 35 U.S.C. § 120)). Even had it been included in the '921 Application, Example 3 plainly does not teach a therapeutically effective amount of DMF for treating MS in humans (JTX 2000 at 24-25).

Although it employs Experimental Autoimmune Encephalomyelitis ("EAE"), the animal model of MS, not even Dr. O'Neill, who is a POSA himself and named inventor of the '514 Patent, could explain the relevance of Example 3—or any of the examples in the '514 Patent—to the claimed invention. *Id.* The same holds true of Dr. Wynn. On direct examination, he merely testified that Example 3 is a study of DMF and MMF in conjunction with EAE, an animal model of MS (Dkt. No. 359 at 95, 98). He never explained how that experiment teaches a method of treating MS (in humans, not mice) with a therapeutically effective amount of DMF, i.e., 480 mg/day (BID). *Id.*

One need only recall Dr. Lukashev's trial testimony to discern the reason for this omission. Dr. Lukashev credibly testified that the three examples in the '514 Patent were part of *his* research, which "was separate from preclinical development" and unrelated to the clin-

ical application of DMF (Dkt. No. 358 at 60-61).[18] The examples had "nothing to do with the efficacy [of DMF] in clinical disease" and would not be "helpful in identifying a therapeutically effective amount of [DMF]." *Id.* at 61. Indeed, the results of Example 3 "provide[d] evidence of [MMF] and [DMF] activation of NRF2 in vivo." *Id.* at 59-60, 60. Mylan's POSA, Dr. Greenberg, concurred with Dr. Lukashev's testimony (Dkt. No. 359 at 70).

The disparity between the '514 Patent's specification and the claimed invention of the '921 and the 0016902 Applications (JTX 2182; PTX 401) is not surprising given the stark differences between Dr. Lukashev and Dr. O'Neill's respective roles in the BG-12 Development Program. From the evidence presented at trial, Dr. Lukashev's research regarding the activation of the Nrf2 pathway and screening drug compounds had nothing to do with the clinical development of Tecfidera® (Dkt. No. 358 at 60-61). That task fell to Dr. O'Neill and later Dr. Dawson (Dkt. No. 362 at 17, 153-54;JTX 2091 at 1; JTX2133 at 26). Notably, Dr. O'Neill's hypothesis, that a 480mg/day dose of DMF (BID) would be efficacious in treating MS, evolved from his review of Fumapharm's confidential studies of Fumaderm® (Dkt. No. 362 at 27-28, 52-54), not Dr. Lukashev's unrelated research regarding the mechanism of action.

In 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. The

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[18] Dr. Lukashev, while not a POSA, is a named inventor who supplied the information in the specification (Dkt. No. 358 at 57). Ignoring his credible testimony would be unreasonable.

United States Court of Appeals for the Federal Circuit has squarely rejected this approach. *Nuvo Pharm.*, 923 F.3d at 1380 ("We have expressly rejected the 'argument that the written description requirement … is necessarily met as a matter of law because the claim language appears *in ipsis verbis* in the specification.'" (quoting *Enzo Biochem, Inc. v. Gen–Probe Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002))).[19] The '514 Patent thus must be viewed as an integrated whole rather than a sum of its parts. *Novozymes A/S*, 723 F.3d at 1349 ("Taking each claim … as an integrated whole rather than as a collection of independent limitations … .").

With no support in the text of the specification, Biogen must rely on Dr. O'Neill's repeated insistence that he invented the 480mg/day dose of DMF (BID) to treat MS (Dkt. No. 362 at 17-111). But "inventor testimony cannot establish written description support where none exists in the four corners of the specification … ." *Nuvo Pharm.*, 923 F.3d at 1381. Put simply, Dr. O'Neill's testimony offers no more than "actual possession," which is insufficient to satisfy § 112. *Ariad*, 598 F.3d at 1352 ("[A]ctual 'possession' … is not enough."). "There must be some description, such as a constructive reduction to practice, establishing that the inventor 'was in possession of the … claimed invention, including all of the elements and limitations.'" *Nuvo Pharm.*, 923 F.3d at 1380-81 (quoting *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004)).

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[19] In other words, written description is not satisfied simply because the same words appear in the claims and the specification. *See Ipsissima verba*, *Black's Law Dictionary* (11th ed. 2019) (meaning "the very (same) words").

"The essence of th[is] written description requirement is that patent applicant, as part of the bargain with the public, must describe his or her invention so that the public will know what it is and that he or she has truly made the claimed invention." *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1298 (Fed. Cir. 2014). "Patents are not rewarded for mere searches, but are intended to compensate their successful completion." *Nuvo Pharm.*, 923 F.3d at 1381 (citing *Ariad*, 598 F.3d at 1353). "That is why the written description requirement incentivizes actual invention, and thus a mere wish or plan for obtaining the claimed invention is not adequate written description." *Id.* (cleaned up) (citations omitted).

Because the text of the specification in the '514 Patent does not demonstrate that, as of February 8, 2007, Dr. Lukashev and Dr. O'Neill "possessed" the claimed invention—a method of treating MS with a therapeutically effective amount of DMF, i.e., 480mg/day (BID)—Biogen has failed to satisfy its part of the bargain.

3. Extrinsic Evidence Confirms the Lack of Written Description

If the text were not enough, extrinsic evidence further "illuminates the absence of critical description … ." *Nuvo Pharm.*, 923 F.3d at 1381. In this case, that evidence is substantial.

Turning first to the specification of the '373 Application, it is undisputed that Biogen filed this application one month after receiving the "unexpected" results of its Phase III study establishing the efficacy of a 480mg/day dose of DMF (BID) to treat MS (DTX 1169). Entitled "Methods of Treating Multiple Sclerosis and Preserving and/or Increasing Myelin Content," the application claimed methods for treating MS with a

480mg/day dose of DMF (BID), and listed Dr. Dawson, Dr. O'Neill, and Alfred Sandrock as inventors. *Id.* As one would expect, the specification provided and discussed in detail a wealth of data generated during Biogen's Phase III study. *Id.* In contrast, the specification in the '514 Patent included none of this data or information (*compare* DTX 1169 *with* JTX 2000).

The explanation for this omission is readily apparent from the record. Despite Dr. O'Neill's strong belief that a 480mg/day dose of DMF (BID) would effectively treat MS (Dkt. No. 362 at 61 ("I had this strong belief and hypothesis that 480 milligrams could work in the treatment of MS.")), Biogen did not know that to be true until its receipt of the "unexpected" results of its Phase III study (JTX 2088 at 9-10, 19). Moreover, upon recognizing that it had no patent to protect a 480mg/day dose of DMF (BID) from competition, Biogen quickly filed the '373 Application with a priority date of May 26, 2011 (DTX 1169). Problematically, that application likely would not have protected the 480mg/day dose of DMF (BID) from § 112 invalidity challenges based on the prior art before May 26, 2011. *Id.*

In an attempt to resolve this problem, Biogen amended its '296 Application, sitting idle since August 7, 2009 (DTX 1016), which stemmed from the earlier '921 and 0016902 Applications (JTX 2182; PTX 401). It deleted the original title and claims of the '296 Application, added a new title, new claims, and a new inventor (DTX 1656; DTX 1657). But it left the specification unchanged in an effort to obtain the '921 Application's pri-

ority date of February 8, 2007, and avoid over four years of prior art.[20]

This strategy came with a cost, however, since Biogen was left with a specification written in 2007 that bore no resemblance to the '514 Patent's title and claimed invention—a method of treating MS with a therapeutically effective amount of DMF, i.e., 480mg/day (BID) (*compare* DTX 1169 *with* JTX 2000)—an invention that no one knew would work until April 2011 when Biogen received the results of its Phase III study (JTX 2088 at 9-10, 19). Dr. O'Neill's testimony supports this conclusion: "I believed from the outset that 480 milligrams as two divided doses of 240 milligrams a day would demonstrate efficacy. I was very pleased when we saw the Phase 3 results to see that 480 milligrams was efficacious and actually had a high degree of efficacy" (Dkt. No. 362 at 60). Consequently, "there is nothing in the specification of the patent[]-in-suit showing 'that the inventor[s] actually invented the invention claimed.'" *Nuvo Pharm.*, 923 F.3d at 1380 (emphasis omitted) (quoting *Centocor Orth Biotech Inc.*, 636 F.3d at 1348).

The Court is well aware that the Federal Circuit "does not require experimental data demonstrating effectiveness." *Id.* (citation omitted). Nor does it "require theory or explanation of how or why a claimed composition will be effective." *Id.* (citation omitted). But "the lack of any disclosure of examples may be considered when determining whether the claimed inven-

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[20] To underscore this strategy's importance, one need look no further than the PTAB's decision in the parties' related IPR proceeding, where Biogen successfully defeated Mylan's invalidity challenge based on obviousness over prior art. *Mylan Pharm. Inc.*, 2020 WL 582736.

tion is adequately described." *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011).

Here, the disparities between the specifications—including related examples—of the '373 Application and the '514 Patent are stark (*compare* DTX 1169 *with* JTX 2000). And because a POSA would not have expected a 480mg/day dose of DMF (BID) to be efficacious in 2007 (in fact, according to Biogen's own employee and expert testimony, the efficacy of the 480mg/day dose of DMF (BID) was "unexpected" four years later in April 2011 (Dkt. Nos. 359 at 115 (Dr. Wynn agreeing with Dr. Dawson's declaration)), the '514 Patent's omissions in this regard are particularly telling. To start, the '514 Patent does not include examples discussing efficacy data regarding relapse and disability, lesion loads, quality of life, preserving/increasing myelin content, or clinical trials, all of which was included in Biogen's abandoned '373 Application (*compare* DTX 1169 at 28-29 *with* JTX 2000). There are no graphs or data regarding proportion of relapses, distribution of relapses, risk of relapse, progression of disability, distribution of new or newly enlarging lesions, change in baseline, annualized relapse rate, MRI results, lesion volume, or brain atrophy (*compare* DTX 1169 at 2-19 *with* JTX 2000). Nor are there summaries, brief or detailed, of the claimed invention (*compare* DTX 1169 at 20-28 *with* JTX 2000).

Further, the '514 Patent does not include any Phase I data from the BG-12 Development Program or the confidential data reviewed by Dr. O'Neill during the Fumapharm due diligence (Dkt. No. 362 at 52-55 (discussing what Fumapharm data consisted of); JTX 2000). Nor does it include information about the "C_{max} of DMF," on which he based his entire hypothesis (Dkt. No. 362 at 53-54 ("I believed and I hypothesized was

that the—a frequency of twice a day of a Cmax could be driving efficacy. … That is a Cmax of DMF.)).

This case bears a striking resemblance to *Nuvo Pharmaceuticals*, where the Federal Circuit considered whether the patents-in-suit adequately described the claimed effectiveness of uncoated proton pump inhibitors ("PPIs"). 923 F.3d at 1372, 1376. The generic defendants had argued that the written description was insufficient because a POSA "would not have expected uncoated PPIs to be effective, and nothing in the specification would teach a [POSA] otherwise." *Id.* at 1377. The Federal Circuit agreed:

> In light of the fact that the specification provides nothing more than the mere claim that uncoated PPI might work, even though [POSAs] would not have thought it would work, the specification is fatally flawed. It does not demonstrate that the inventor possessed more than a mere wish or hope that uncoated PPI would work, and thus it does not demonstrate that he actually invented what he claimed … .

Id. at 1381.

So too here. At every stage of this case and the related IPR proceeding, Biogen defended against Mylan's obviousness challenge by insisting that a POSA would not have expected a 480mg/day dose of DMF to be efficacious in treating MS (Dkt. No. 356 at 56 (Biogen's opening statement: "Dr. O'Neill's claimed invention of using 480 milligrams per day of DMF to treat MS exhibited an *unexpected* magnitude of efficacy rendering the claimed method nonobvious on this basis alone." (emphasis added))). *See also Mylan Pharm. Inc.*, 2020 WL 582736, at *16 (stating that Biogen "provides ar-

gument and evidence … that the 480 mg/day dose had an *unexpected magnitude of efficacy* as compared to a much higher 720mg/day dose" (emphasis added)). This statement only underscores the failure of the specification to teach a POSA, who would expect otherwise, that a 480mg/day dose of DMF (BID) is efficacious in treating MS. *See Nuvo Pharm.*, 923 F.3d at 1381.

Biogen cannot successfully distinguish *Nuvo* from the case at hand (Dkt. No. 377 at 34-41). In *Nuvo*, the specification of the patents-in-suit explicitly acknowledged that a POSA would not have expected uncoated PPIs to work. *Id.* (discussing *Nuvo*). Because there is no such acknowledgment in the '514 Patent's specification, Biogen contends that *Nuvo*'s holding is inapposite. *Id.* This is a distinction without a difference, however. Although the specification at issue in *Nuvo* explicitly acknowledged what a POSA would not have expected to work, it is well established (as Biogen's own brief acknowledges (Dkt. No. 377 at 33-34)) that a specification "need not include information that is already known and available to the experienced public." *Space Sys./Loral, Inc. v. Lockheed Martin Corp.*, 405 F.3d 985, 987 (Fed. Cir. 2005) (citation omitted). Thus, the specification of the '514 Patent need not explicitly acknowledge that the experienced public (i.e., a POSA) would not have expected a 480mg/dose of DMF (BID) to be efficacious in treating MS.

IV. CONCLUSION

Mylan has established by clear and convincing evidence that the asserted claims of the '514 Patent are invalid for lack of written description. First, the text of the specification does not reasonably convey to a POSA that Dr. Lukashev and Dr. O'Neill "actually invented" a method of treating MS with a therapeutically effective

amount of DMF, i.e., 480mg/day BID, as of February 8, 2007. This reading of the text is confirmed by the testimony of Dr. Greenberg, Dr. Lukashev, Dr. O'Neill, and Dr. Wynn. Second, the context of the '514 Patent's prosecution history and the significant omissions from the specification further underscore the failure to adequately describe the claimed invention. Biogen's attempt to avoid this conclusion by combining a few selectively-plucked disclosures from the specification of the '514 Patent has been squarely rejected by the Federal Circuit.

Therefore, for the reasons discussed, the Court **FINDS** that Mylan has satisfied its burden of demonstrating, by clear and convincing evidence, that the asserted claims of the '514 Patent are invalid for lack of written description under § 112.

The Court **DIRECTS** the Clerk to transmit copies of this Order to counsel of record.[21]

DATED: June 18, 2020.

/s/ Irene M. Keeley
IRENE M. KEELEY
UNITED STATES DISTRICT JUDGE

[21] Because the parties' remaining claims, counterclaims, and defenses regarding the '001 Patent are stayed until June 20, 2020 (Dkt. Nos. 288, 315 at 12, 336 at 44), the Court's decision regarding the invalidity of the asserted claims of the '514 Patent does not deny all requested relief. Accordingly, absent a request from the parties, the Court declines to enter a separate judgment order pursuant to Federal Rule of Civil Procedure 58.

ADDENDUM
CHRONOLOGY OF RELEVANT DATES

February 8, 2007:	Biogen filed the '921 Application, entitled "Nrf2 Screening Assays and Related Methods and Compositions," which recited methods for screening drug compounds for their ability to activate the Nrf2 pathway and listed Dr. Lukashev as the only inventor (JTX 2182);
February 7, 2008:	Biogen filed the 0016902 Application, which maintained the same title, claims, and inventor as the '921 Application but added to its specification (PTX 401);
March 14, 2007:	Biogen began its first clinical trial of the Phase III study, which tested—for the first time—a 480mg/day dose of DMF (BID);
August 7, 2009:	The 0016902 Application became the '296 Application (DTX 1016);
April 2011:	Biogen received the Phase III test results, which demonstrated the "unexpected" efficacy of treating MS with 480mg/day of DMF (BID);
May 26, 2011:	Biogen filed the '373 Application, entitled "Methods of Treating Multiple Sclerosis and Preserving and/or Increasing Myelin Content," which claimed methods for treating MS with 480mg/day of DMF (BID) and listed Dr. Dawson, Dr. O'Neill, and Alfred Sandrock as inventors (DTX 1169);

June 20, 2011:	Biogen amended the '296 Application, deleting its title and related claims but leaving its specification unchanged (DTX 1656);
October 28, 2011:	Biogen again amended the '296 Application in 2011, adding Dr. O'Neill as an inventor but leaving its specification unchanged (DTX 1657);
February 13, 2012:	Biogen filed the '426 Application, a continuing application of the '296 Application which was then abandoned (JTX 2173) ;
March 19, 2013:	The PTO issues the '514 Patent, which claims priority from the '921 Application filed on February 8, 2007 (JTX 2000; JTX 2182); and
May 2016:	Biogen abandoned the '373 Application with its claimed priority date of May 26, 2011.

APPENDIX D

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

Civil Action No. 1:17CV116

BIOGEN INTERNATIONAL GMBH
and BIOGEN MA, INC.,
Plaintiff(s),

v.

MYLAN PHARMACEUTICALS INC.,
Defendant(s).

Filed June 22, 2020

JUDGMENT IN A CIVIL ACTION

The court has ordered that:

☐ Judgment award ☐ Judgment award ☒ Other

other: As the Court has previously dismissed the remining claims involving U.S. Patent No. 7,619,001, and found that the asserted claims of U.S. Patent No. 8,399,514 are invalid for lack of written description under 35 U.S.C. § 112, the Court GRANTS Defendant Mylan Pharmaceuticals' Motion for Entry of Judgment under Rule 54(b).

This action was:

☐tried by jury ☐ tried by judge ☒ decided by judge

decided by Judge Irene M. Keeley

Date: June 22, 2020

CLERK OF COURT
Cheryl Dean Riley
/s/ W. Riffle
Signature of Clerk or Deputy Clerk