2019-1133

United States Court of Appeals for the Federal Circuit

BIOGEN MA INC.,

Plaintiff-Appellee,

– v. –

EMD SERONO, INC., PFIZER INC.,

Defendants-Appellants,

BAYER HEALTHCARE PHARMACEUTICALS INC., NOVARTIS PHARMACEUTICALS CORPORATION,

Defendants.

On Appeal from the United District Court for the District of New Jersey in No. 2:10-cv-02734-CCC-MF Hon. Claire C. Cecchi

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JULY 3, 2019

FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Biogen MA Inc. **v.** EMD Serono, Inc,; Pfizer Inc.

Case No. 19-1133

CERTIFICATE OF INTEREST

Counsel for the:
☐ (petitioner) ☐ (appellant) ■ (respondent) ■ (appellee) ☐ (amicus) ☐ (name of party)

Biogen MA Inc.

certifies the following (use "None" if applicable; use extra sheets if necessary):

1. Full Name of Party Represented by me	2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:	3. Parent corporations and publicly held companies that own 10% or more of stock in the party
Biogen MA Inc.	Biogen MA Inc.	Biogen Inc.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court **(and who have not or will not enter an appearance in this case)** are:

Paul, Weiss, Rifkind, Wharton & Garrison LLP: Julia Tarver-Mason Wood, Catherine Nyarady, Jennifer H. Wu, Jennifer Gordon, Michael Milea, Dexin Deng, Ayelet Evrony, Rebecca Fett (former), Monika Wrobel (former), Nathanial J. McPherson (former), Steven M. Balcof (former), and Eileen Woo (former).

Marino, Tortorella & Boyle, P.C.: John A. Boyle and Erez Joseph Davy.

Weil, Gotshal & Manges LLP: Elizabeth Stotland Weiswasser.

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5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47. 4(a)(5) and 47.5(b). (The parties should attach continuation pages as necessary).

The present case on appeal as between Biogen MA Inc. against EMD Serono, Inc. and Pfizer Inc. was part of a previously consolidated case of Bayer HealthCare Pharmaceuticals Inc. v. Biogen Idec Inc. (Civ. No. 10-cv-02734) and Biogen Idec MA Inc. v. EMD Serono, Inc.; Pfizer Inc.; Bayer Healthcare Pharmaceuticals Inc.; and Novartis Pharmaceuticals Corp. (Civ. No. 10-cv-02760). On October 27, 2017, the case against EMD Serono, Inc. and Pfizer Inc. was severed from the case against Bayer HealthCare Pharmaceuticals Inc. and Novartis Pharmaceuticals Corp. The case against Bayer HealthCare Pharmaceuticals Inc. and Novartis Pharmaceuticals Corp. is currently pending in the District Court for the District of New Jersey before Judge Claire C. Cecchi.

7/3/2019
Date

/s/ Nicholas Groombridge
Signature of counsel

Please Note: All questions must be answered

Nicholas Groombridge
Printed name of counsel

cc: Counsel of Record

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STATEMENT OF RELATED CASES

The case between Biogen MA Inc. ("Biogen") and EMD Serono, Inc. ("Serono") and Pfizer Inc. ("Pfizer") (together, "Appellants") was severed from Biogen's claims against Bayer Healthcare Pharmaceuticals Inc. ("Bayer") and Novartis Pharmaceuticals Corp. ("Novartis"), with which it had previously been consolidated in *Bayer HealthCare Pharmaceuticals Inc. v. Biogen Idec MA Inc.* (Civ. No. 10-cv-02734). Biogen's case against Bayer and Novartis is currently pending in the United States District Court for the District of New Jersey before the Honorable Claire C. Cecchi.

STATEMENT OF JURISDICTION

Biogen agrees with Defendant-Appellants' Statement.

PRELIMINARY STATEMENT

In a series of thorough, well-reasoned decisions—on claim construction, jury instructions, and ultimately a 92-page ruling on post-trial motions—the district court painstakingly analyzed and scrupulously followed controlling precedent of this Court and the Supreme Court. The district court also thoroughly reviewed and analyzed the evidence presented at the five-week jury trial, over which it presided and with which it was deeply familiar. Appellants now contend that the district court erred in virtually everything it decided. They are wrong.

Notably, Appellants' Statement of the Case bears little resemblance to the trial in this case. For nearly five weeks, the jury heard about a worldwide race in 1980 among leading scientists to do what had never been done and might have been impossible: to use recombinant-DNA technology to engineer an analogue of a known human protein, interferon-beta, and to determine whether that recombinant protein had biological activity like the native, human protein and could thus be used to treat disease.

The jury heard that Biogen's Dr. Walter Fiers, the inventor on the patent-in-suit, produced interferon-beta-like polypeptides in E. coli, rigorously tested and re-tested their biological activity to exclude false positives, and filed his patent application before anyone else. The jury heard extensive testimony about the patent's 29-year history in the Patent Office (during much of which time prosecution

was suspended due to multiple interference proceedings). And the jury heard Appellants' refrain that this was all obvious.

Now Appellants have abandoned their obviousness arguments and contest the JMOL rulings regarding anticipation, written description, enablement, direct infringement (based on the district court's claim construction), induced infringement, contributory infringement, and patent eligibility. Despite—and indeed as evidenced by—this multiplicity of issues, Appellants fail to show any error on the part of the district court.

STATEMENT OF THE ISSUES

(1) **Anticipation**: Did the district court correctly grant judgment for Biogen where Appellants identified no prior-art reference disclosing all elements of the '755 Patent claims?

(2) **Section 112**: Did the district court correctly instruct the jury that what must be described and enabled are the claimed methods of treatment using recombinant polypeptides made in non-human host cells, rather than the recombinant polypeptides and the non-human host cells themselves?

(3) **Direct Infringement**: Did the district court correctly construe the claimed method to require only one "step"—the step of administering the composition containing the recombinant polypeptide—and not two additional steps of transforming the host cell and producing the polypeptide?

(5) **Induced Infringement**: Did the district court correctly grant judgment for Biogen where no evidence supported (a) Appellants' professed ignorance about the immunomodulatory effect of their product, or (b) Serono's professed good-faith belief in the three-step claim construction that the district court rejected?

(6) **Contributory Infringement**: Did the district court correctly instruct the jury that a mistaken, good-faith belief in non-infringement is not a defense to contributory infringement?

(7) **Patent-Eligibility**: Did the district court correctly reject Appellants' post-trial theory that claims to methods of treatment with a man-made protein using non-routine, unconventional techniques are not patent-eligible?

STATEMENT OF THE CASE

U.S. Patent No. 7,588,755 is directed to treating a patient by administering a recombinant protein that has the biological activity of naturally occurring interferon-beta. In the case of multiple sclerosis—a disease in which the body's immune system damages the substance that insulates and protects the nerves—the claimed method of action is through immunomodulation, or modulating the immune system. Interferon-beta was the first successful therapy for multiple sclerosis. Biogen and Appellants sell recombinant interferon-beta drugs used to treat multiple sclerosis.

The Unfulfilled Promise of Interferon-Beta, and Dr. Fiers's Solution

To help fend off attacks by viruses, the human immune system makes proteins called "interferons." *See, e.g.*, Appx77873 (24:3–18); Appx77323 (13:10–21). Beginning in the 1950s, doctors sought to isolate human interferons and to use them to treat viral diseases, cancers, and other conditions. Appx118–119 (2:53–4:22);. Appx77874 (25:13–23). By the late 1970's, interferon-beta had great promise as a miracle drug. *See, e.g.*, Appx66140. But interferon-beta is found in only infinitesimal amounts in human cells. *See, e.g.*, Appx119 (4:49–55), Appx66143. The most common source of interferon-beta was fibroblast cells in discarded human foreskin. *See, e.g.*, Appx119–120 (4:49–5:3). That process was inefficient and yielded impure native interferon-beta compositions. *Id.* That scarcity led *Omni* in

1979 to describe interferons as the "miracle cure at $22 billion per pound." Appx66140.

As described in the '755 Patent, which has a priority date of June 6, 1980, then-"recent advances in molecular biology" created the possibility for recombinant expression of desired proteins in non-human cells. Appx120 (5:4–16). Building upon those fundamental techniques, several groups competed to express interferon-beta recombinantly and to determine whether the recombinant protein would have biological activity comparable to native, human interferon-beta. In 1980, *Time* dubbed interferons "the IF drug," raising the question that animated the race at the heart of this lawsuit: Could scientists develop recombinant interferon-beta and prove its biological activity, thereby making it a viable treatment option? Appx66145–66146.

Dr. Fiers was the first to recombinantly express interferon-beta-like proteins and to demonstrate that they do, in fact, have the biological and immunological activity of native, human interferon-beta, and could thus be made in therapeutically effective amounts and used therapeutically. *See* Appx136–140 (37:18–46:37). Dr. Fiers was awarded the '755 Patent, directed to methods of treatment using recombinant interferon-beta.

The Structure of Interferon-Beta

Like all proteins (or "polypeptides"), interferon-beta consists of amino acid building blocks. Appx77878 (29:2–13). Interferon-beta comprises 166 amino acids, connected end-to-end in a linear array. *Id.* (29:19–22). When the amino acid array of interferon-beta is folded into its correct three-dimensional shape, it is biologically active, Appx77880 (31:8–14), modulating the immune system, reducing inflammation, and increasing cells' resistance to viruses. Appx77574 (62:2–9); Appx77872 (23:15–19); Appx47551 (47:14–15).

Native, human interferon-beta is a glycoprotein, which means it has sugars attached to one of its amino acids in a branched structure. Appx77882 (33:11–25). The sugar branches can vary from interferon-beta protein to protein, even when made within the same cell. Thus, in a sample of native interferon-beta taken from a human, each interferon-beta molecule can have one of a variety of sugar branches attached to it. Appx51646 (Kagawa); Appx80514–80515 (100:5–101:2).

While similar proteins can be made by different species, those different species make glycoproteins with different sugar branches, or none at all. E. coli, for example, does not glycosylate proteins. Appx80514 (100:5–20); Appx79094 (47:12–21).

The Claims of the '755 Patent

The '755 Patent disclosed that therapeutic use of native, human interferon-beta was known in the prior art, Appx118–119 (2:53–4:22), and how compositions of native, human interferon-beta had been prepared, Appx119–120 (4:49–5:3). Its claims were limited to a method of treatment with a therapeutically effective amount of recombinant interferon-beta-like polypeptides, made in a non-human host. Claim 1 recites:

> 1. A method for immunomodulation or treating a viral condition[], a viral disease, cancers or tumors comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of a composition comprising:
> a recombinant polypeptide produced by a non-human host transformed by a recombinant DNA molecule comprising a DNA sequence selected from the group consisting of:
> (a) DNA sequences which are capable of hybridizing to any of the DNA inserts of G-pBR322(Pst)/HFIF1, G-pBR322(Pst)/HFIF3 (DSM 1791), G-pBR322(Pst)/HFIF6 (DSM 1792), and G-pBR322(Pst)/HFIF7 (DSM 1793) under hybridizing conditions of 0.75 M NaCl at 68° C. and washing conditions of 0.3 M NaCl at 68° C., and which code for a polypeptide displaying antiviral activity, and
> (b) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences defined in (a);
> said DNA sequence being operatively linked to an expression control sequence in the recombinant DNA molecule.

Appx142 (49:59–50:12). Claim 2 further limited the claimed "DNA sequence" to one of two specified sequences, one of them the sequence for human interferon-beta. Appx142 (50:13–52). Biogen asserted Claims 1 and 2 of the '755 Patent against Appellants.

Appellants' Infringement

The jury found that the use of Appellants' recombinant interferon-beta product, Rebif®, directly infringes claims 1 and 2 of the '755 Patent. One element of that finding is that Rebif® treats multiple sclerosis through immunomodulation. Whether Appellants know and intend that Rebif® be used for immunomodulation was an issue at trial and recurs on appeal, *see* Point IV.A *infra*. The jury heard undisputed testimony from Biogen's expert Dr. Revere Kinkel—who has treated thousands of multiple sclerosis patients with Rebif® and the other interferon-beta treatments—that there is scientific consensus that interferon-beta treats multiple sclerosis through immunomodulation. Appx78011–78012 (33:25–34:7), *see also* Appx78008–78009 (30:25–31:6); Appx77970 (121:11–17); Appx77976 (127:6–9).

The Jury Verdict

The jury found that doctors who administer and patients who self-administer Appellants' Rebif® recombinant interferon-beta product to treat multiple sclerosis infringe claims 1 and 2 of U.S. Patent No. 7,588,755, and that Serono and Pfizer each contributes to the infringement under 35 U.S.C. § 271(c). The jury rejected Appellants' obviousness, written-description, and enablement defenses. The jury found, however, that the claims of the '755 Patent are anticipated by prior-art uses of native, human interferon-beta, and found against Biogen on induced infringement.

The District Court's Post-Trial Decision

All parties sought judgment as a matter of law. The district court denied Appellants' motions on patent eligibility (an issue that had not been presented to the jury) as well as obviousness, written description and enablement. The district court granted Biogen's motions to set aside the verdict of anticipation and to direct a verdict of induced infringement.

SUMMARY OF THE ARGUMENT

I. Anticipation – The '755 Patent claims methods of treatment using recombinant interferon-beta made in a non-human host cell. Appellants' allegedly anticipatory references do not disclose all elements of the claims because—as Appellants admit—they disclose treatments with only native, human interferon-beta harvested from human cells. The district court correctly rejected Appellants' unprecedented attempt to apply a product-by-process framework to method-of-treatment claims, but even under that framework the undisputed record evidence of differences between the native and recombinant proteins supported the district court's entry of judgment for Biogen.

II. Written Description and Enablement – The '755 Patent claims methods of treatment using recombinant interferon-beta-like polypeptides made in non-human host cells. The district court thus correctly instructed the jury that it is the methods of treatment—not the polypeptides themselves or the host cells themselves—that must be described and enabled. Moreover, even under Appellants' version of the law, no reasonable jury would have found the patent invalid by clear and convincing evidence.

III. Direct Infringement – Claim 1 of the '755 Patent has only one method "step": "administering a recombinant interferon-beta polypeptide." The district court correctly rejected Appellants' argument that transforming a host cell and

producing a polypeptide are two additional "steps." They are not steps of the method, but instead source limitations—requirements that the product come from a specific place or be made in a specific way.

IV. Induced Infringement – Both Appellants contended at trial that they do not know how Rebif® works, and thus lack the specific intent that it be used for immunomodulation. There was no evidence to support that conclusion, as the district court found. At trial Serono, but not Pfizer, also argued that it lacked the intent to induce infringement because it believed in good faith in its three-step claim construction, under which there would be no direct infringement. As the district court found, no evidence supported a defense based on that purported belief. And while Pfizer now wants to freeride on Serono's defense, Pfizer waived it by not raising it below.

V. Contributory Infringement – Appellants contend that a good-faith but incorrect belief in a non-infringing claim construction is a defense to contributory infringement. It is not, as the district court correctly instructed the jury. Furthermore, Pfizer presented no evidence that it had a good-faith belief in a non-infringing claim construction.

VI. Patent Eligibility – The '755 Patent claims the administration of a man-made substance to a patient to treat disease. It is not directed to a law of nature, a natural phenomenon, or an abstract idea, and it is patent-eligible.

STANDARD OF REVIEW

This Court applies the law of the regional circuit to both judgment as a matter of law and the conditional grant of a new trial. *See Summit Tech., Inc. v. Nidek Co.*, 363 F.3d 1219, 1223 (Fed. Cir. 2004) (review of JMOL); *Uniloc USA, Inc. v. Microsoft Corp.*, 632 F.3d 1292, 1309 (Fed. Cir. 2011) (new trial). The Third Circuit exercises "plenary review" of a JMOL decision, applying "the same standard as the district court," and reviews a ruling on a motion for a new trial "for abuse of discretion unless the court's denial is based on the application of a legal precept, in which case the standard of review is plenary." *Lightning Lube, Inc. v. Witco Corp.*, 4 F.3d 1153, 1166–67 (3d Cir. 1993). While the Third Circuit "exercises a closer degree of scrutiny when the district court grants a new trial because it believes the jury's verdict is against the weight of the evidence," particularly in a case "involving simple factual determinations well within the comprehension of the jurors," that court "recognize[s] that 'considerable deference remains due to'" the district court. *Wilburn v. Maritrans GP Inc.*, 139 F.3d 350, 363 (3d Cir. 1998) (quoting *Williamson v. Consolidated Rail Corp.*, 926 F.2d 1344, 1353 (3d Cir. 1991)).

ARGUMENT

I. Anticipation: The District Court Correctly Held That No Substantial Evidence Supported the Verdict of Anticipation

The jury found that prior-art treatments using native, human interferon-beta harvested from human cells anticipated the claimed methods of treatment using

recombinant interferon-beta created in a non-human host cell. The district court correctly granted JMOL because that verdict was not supported by the evidence or the law. Appx35–36 (JMOL Op.). This Court should affirm.

A. Appellants Never Identified an Anticipatory Prior-Art Reference

"A claim is anticipated only if each and every element is found within a single prior art reference, arranged as claimed." *Summit 6, LLC v. Samsung Elecs. Co.*, 802 F.3d 1283, 1294 (Fed. Cir. 2015). Anticipation requires "strict identity" between the claimed invention and that single prior-art reference. *Trintec Indus. Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002); *TF3 Ltd. v. Tre Milano, LLC*, 894 F.3d 1366, 1374 (Fed. Cir. 2018) (the "identical invention must be shown" in the prior art). Any differences "between the prior art reference and the claimed invention, however slight, invoke the question of obviousness, not anticipation." *Net MoneyIN, Inc. v. VeriSign, Inc*., 545 F.3d 1359, 1371 (Fed. Cir. 2008).

The district court correctly found that Appellants failed to present an anticipatory prior art reference. Appx22 (JMOL Op.). Appellants never tried to meet that burden. They called no witness to compare the patent claims to the prior art and to demonstrate that all the claimed elements are found in one prior-art reference. Nor could they have done so. The '755 Patent claims methods of treatment using only recombinant interferon-beta that was produced in non-human hosts. Appellants' four prior-art references disclose treatments using only natural,

human interferon harvested from human fibroblast cells. Appx52134 (Sundmacher); Appx51651 (Kingham); Appx51605 (Carter); Appx52017 (Stewart). The prior-art treatments would not infringe the '755 Patent, and therefore cannot anticipate the patent although performed before it. No more is required to affirm.

B. The '755 Patent Claims Are Not Product-By-Process Claims

Appellants seek to recast the '755 Patent claims as product-by-process claims, because such claims are anticipated by the same product in the prior art, even if made by a process other than the one claimed. Br. at 17–20; *see also* Bayer Br. at 4–5. The district court correctly rejected this argument. Appx33–36 (JMOL Op.). The '755 Patent does not claim a product; it claims methods of treatment. Dr. Fiers's invention demonstrated that non-human hosts could recombinantly express interferon-beta-like polypeptides with biological activity like native, human interferon-beta, and that the recombinant polypeptides thus could be used therapeutically. Appx118 (1:15–28).

As the district court correctly noted, "there appears to be no binding precedent supporting [Appellants'] position that the anticipation inquiry of product-by-process claims governs the analysis of method of treatment claims that include source limitations, such as claim 1 of the '755 Patent." Appx33 (JMOL Op.). And Appellants have never cited any case that "would warrant" extending "the framework for assessing novelty of product-by-process claims to method of

treatment claims." Appx34 (JMOL Op.). Product-by-process claiming allows inventors to claim "an otherwise patentable product" that is not easy to define "other than [by] the process by which it is made." Appx34–35 (JMOL Op.) (citing *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) (emphasis added)). The doctrine avoids "foreclosing inventors 'from the benefits of the patent system simply because a product is difficult to define in words, or its structure is insufficiently understood.'" Appx35 (JMOL Op.) (citation omitted).

Here, the product used in the method of treatment is not difficult to define; claim 1 specifies precise structural limitations on the DNA sequence used to make the recombinant polypeptide. *See id.*; Appx142 at 50:1–10. And, as a general matter, the Supreme Court and this Court have cautioned that claims to a product itself and claims to a method of using that product should be analyzed separately. *See Ass'n for Molecular Pathology v. Myriad Genetics, Inc*., 569 U.S. 576, 595 (2013) (Section 101 context); *Vanda Pharm. Inc*. *v. West-Ward Pharm. Int'l Ltd*., 887 F.3d 1117, 1136 (Fed. Cir. 2018) (same).

Appellants suggest that *Leggett v. Standard Oil Co*., 149 U.S. 287 (1893), held that product-by-process law "applies to method claims reciting the use of an old product made by a new process." Br. at 17; *see also* Bayer Br. at 11–12. Appellants are mistaken. In *Leggett*, the Supreme Court specifically differentiated the method claim (original claim 1) from the product-by-process claim (reissue claim 2), noting

that the invalidity of the product-by-process claim "does not impair the validity of the original claim." 149 U.S. at 293. And when the *Leggett* Court turned to the method claim, in the passage that uses the words Appellants tout ("clearly anticipated"), the Court first conducted what today, 126 years later, is an obviousness analysis: Leggett's invention "would have occurred to" skilled artisans and was "a commercial suggestion that would naturally occur to any one engaged largely in the use of glue," and the differences between the claimed invention and the prior art were "merely a question of degree." *Id.* at 295–96. This portion of *Leggett* is of no help to Appellants; they did not appeal the jury's rejection of their obviousness defenses. And when the Supreme Court then addressed what today would be called anticipation, it found that "precisely this same process" had been in use for more than a decade before the purported invention date. *Id.* at 297. What was present in *Leggett* is exactly what is missing here: evidence that all steps of the claim were shown in the prior art.

Next, Appellants rely on *Amgen Inc. v. Hoffman-La Roche Ltd.*, 580 F.3d 1340 (Fed. Cir. 2009). Br. at 18–19; *see also* Bayer Br. at 6–8. But *Amgen* involved claims to a product, recombinant human erythropoietin ("EPO"), and whether that product claim was anticipated by the native EPO protein. *See Amgen*, 580 F.3d at 1365. This Court held that a source limitation alone—that the product be made recombinantly—cannot render the product itself patentable if the recombinant

product is structurally and functionally identical to the prior-art product. *Id.* 1365–70. The Court then affirmed judgment of no anticipation because there were structural differences between recombinant and native erythropoietin. *Id.* at 1367.

C. The Record Evidence Confirmed That a "Polypeptide" Must Be Correctly Formed To Be Biologically Active

As the district court correctly found, the record evidence is also clear that recombinant interferon-beta and native, human interferon-beta are not the same product, making product-by-process law factually irrelevant as well as legally inapplicable. Appx23 (JMOL Op.). To avoid the undisputed evidence of differences between the products (which Biogen addresses below in Point I.D), Appellants argue that what matters in assessing Claim 1 is only the amino acid sequence of the polypeptide. From that premise, Appellants contend that the amino acid sequences of the native, human protein would fall within the scope of Claim 1. Br. at 20–21. But as the district court correctly held in rejecting this argument on summary judgment, Claim 1 requires that the polypeptide have 'antiviral activity' and be administered in a 'therapeutically effective amount,'" which "is not possible from its amino acid sequence" alone. Appx46464.

The '755 Patent notes that a "polypeptide" is a "linear array of amino acids connected one to the other by peptide bonds between the α-amino and carboxy groups of adjacent amino acids." Appx121 (8:62–64); *accord* Appx47651. (Jury Instruction). But the undisputed evidence was that the array of amino acids—

the polypeptide—must be properly folded for the polypeptide to "display[] antiviral activity" and be "therapeutically effective." Appx142 (49:59–50:12); Appx77880 (31:8–14); Appx80476–80477 (62:12–63:5).

For example, natively sourced human interferon-beta is a glycoprotein, which means that it has a branched sugar structure attached to one of its amino acids. Appx118 (1:39–40). The sugar branches of interferon-beta can vary from polypeptide to polypeptide, even when made within the same cell. Appx77883 (34:1–6). A polypeptide's structure, including its attached sugar groups, can determine whether the polypeptide has biological activity. Appx77880 (31:8–14); Appx77881 (32:8–22); Appx80459–80460 (45:3–46:13); Appx80476–80477 (62:14–63:5).

The '755 Patent confirms this. It refers to the recombinant production of "a polypeptide having a biological or immunological activity of" human interferon-beta. Appx125 (15:4–10) (emphasis added). Indeed, while Appellants seek to differentiate polypeptides from proteins, *see, e.g.*, Br. at 24, the patent equates those terms: "[T]he nucleotide sequences or cDNA fragments . . . may include nucleotides which are not part of the actual structural gene for the desired polypeptide or may include only a fragment of the complete structural gene for the desired protein." Appx124–125 (14:66–15:4) (emphases added); *see also* Appx125 (15:11–19)

(regarding factors for selecting an appropriate "host to express polypeptides" including "ease of recovery of the desired protein").

The prosecution history confirms this understanding. For example, during prosecution, Biogen stated that "Applicant's polypeptide is produced in a non-human host, and as such, it is not identical to known IFN-β." Appx23744 ('930 Appl., 3/24/97 Amendment) (emphasis original). During prosecution of a sister application, Biogen repeatedly stated that Dr. Fiers's recombinant polypeptides are not the same as native interferon-beta:

- "None of these polypeptides is identical to human IFN-β." Appx24313 ('843 Appl., 4/8/96 Amendment).

- "As amended, claim expressly recites production in non-human cells. As such, the claims exclude the IFN-β of the three cited documents. Those IFN-βs were produced in human cells. This is not semantics. IFN-β produced in human cells is glycosylated and has a particular type and content of sugar groups. The claimed polypeptides do not have the identical type or content of sugar groups. They cannot have. They are produced in non-human cells whose ability to post-translationally modify proteins is different from that of human cells." Appx24315 (emphasis original).

- "Applicant's polypeptide is produced in a non-human host, and as such, it is not identical to the known IFN-β. Its biological activity, thus, is unpredictable." Appx24319 (emphasis original).

Thus, the trial record makes clear that the polypeptide of claim 1 is not limited to only its amino acid sequence, as Appellants contend, but also includes the three-dimensional structure of the polypeptide, which is different than the three-dimensional structure of human interferon-beta.

Appellants have no answer to this trial evidence. Instead, they rely on an expert report and deposition testimony from Biogen's claim-construction expert, Dr. David Jackson, that the jury never saw. (Dr. Jackson withdrew from the case years before trial for personal reasons). While Appellants cannot rely in this Court on evidence that was not before the jury, Dr. Jackson's testimony, too, would have supported Biogen. He agreed that in general scientific usage, "the two terms 'polypeptide' and 'protein' are used loosely and often interchangeably." Appx2538–2539; *accord* Appx82534 (11:16–17).

Finally, Appellants accuse the district court of failing to apply the parties' agreed-upon construction "post-verdict." Br. at 23, 25. Appellants are wrong: The district court used the same claim construction in its summary judgment decision, its jury instructions, and its JMOL ruling. The court consistently held that while a "polypeptide" is construed as a "linear array of amino acids," the polypeptide of Claim 1 must be analyzed with regard to its three-dimensional structure because only a properly folded protein can have "anti-viral activity" and be therapeutically useful. Appx119 (3:4–16); Appx23 (JMOL Op.). Appellants cannot secure reversal of JMOL by redefining "polypeptide" in a manner contrary to the claims, the specification, the prosecution history, and how one of ordinary skill would understand the term.

D. The Evidence Demonstrates Structural and Functional Differences Between the Claimed Invention and the Prior Art

The district court correctly noted that, even under Appellants' unprecedented extension of product-by-process law to method-of-treatment claims, there was no evidence that the native, human interferon-beta used in the prior-art therapeutic studies was the same as recombinant interferon-beta expressed in non-human host cells. Appx22–33 (JMOL Op.). That is the linchpin of Appellants' argument, and no reasonable jury could have found it by clear and convincing evidence.

Structural Differences. Canvassing the trial evidence, the district court made a finding that "[t]he evidence presented at trial demonstrates that native interferon-β and recombinant interferon-β are not structurally identical" because "the record evidence shows that the proteins differ structurally in terms of their attached carbohydrate (or sugar) groups, also referred to as glycosylation patterns." Appx23 (JMOL Op.). That finding was correct.

No witness testified at trial that the native and recombinant proteins are structurally identical. Indeed, as the district court found, Appellants' own expert, Dr. Harvey Lodish, testified that the native and recombinant proteins are "not identical with respect to their carbohydrate groups" (*i.e.*, their glycosylation), Appx24 (JMOL Op.) (emphasis original), and instead are "at best, 'substantially identical,'" *id.*(citing Appx79581 (50:9–14)), and Biogen's expert Dr. Christopher Garcia testified that with regard to "the glycosylation patterns of the native and

recombinant proteins" "[i]n some cases, they're close, but they're never identical" and "'have some significant differences.'" Appx25 (JMOL Op.) (citing Appx80515–80516 (101:9–102:15)). That would not be enough for anticipation even under Appellants' extension of product-by-process law. "Anticipation is not shown by a prior art disclosure which is only 'substantially the same' as the claimed invention." *Jamesbury Corp. v. Litton Indus. Prods., Inc.*, 756 F.2d 1556, 1560 (Fed. Cir. 1985).

Appellants rely on two post-priority date studies, the InterPharm report and Kagawa, each of which compared the structure of recombinant interferon-beta and native, human interferon-beta. But neither helps Appellants, because both studies acknowledge structural differences between the two. *See* Appx50504 (InterPharm report); Appx50526–50531; Appx51646 (Kagawa). Appellants highlight the summary "Conclusion" section of the InterPharm report's statement that "[b]ased on the above sections, it can be concluded that recombinant beta interferon derived from CHO cells (Rebif) is identical to human fibroblast interferon (HFIF)." Appx50559. However, as the district court correctly noted, the "document as a whole and its more detailed statements and analyses underlying this conclusory statement" show that the molecules in the recombinant-interferon beta material "are structurally different from the molecules of the native material." Appx24 n.11 (JMOL Op.) (emphasis added). Indeed, Appellants' expert Dr. Lodish disagreed

with the InterPharm report's conclusion that the native and recombinant proteins were identical: "I wouldn't call them identical." Appx79721–79722 (87:24–88:7). The body of the report confirms that the recombinant and native forms of interferon-beta differ in exactly the aspect at issue here: glycosylation. Appx50525–50531. And the report recognizes that "[i]t is well established that a single glycoprotein may be glycosylated differently in different cell types." Appx50505. As the district court found, "[a] reasonable jury would not rely solely on that single statement under the 'Conclusion' heading in the InterPharm Study and ignore contrary expert testimony and the detailed analyses throughout the document." Appx24 n.11 (JMOL Op.).

Furthermore, neither the InterPharm report nor the Kagawa paper—neither of which is prior art—analyzes the native, human interferon-beta that was actually used in the supposedly anticipatory prior-art publications. As the district court correctly noted, Appellants presented no evidence of the structure of native interferon-beta used in the prior-art studies, nor is there any evidence "that all native, human interferon-β proteins are structurally identical." Appx28 (JMOL Op.). On the contrary, the InterPharm report and Kagawa both show that the structure of native, human interferon-beta itself can differ depending on how the protein is obtained, Appx50504 (InterPharm report), Appx50526–50531; Appx51646 (Kagawa). Accordingly there is no way to know—and thus was no proof of—what specific structures of native, human interferon-beta were used in the prior-art treatment

references. Appellants thus did not compare the native, human interferon-beta used in those studies with the recombinant protein or demonstrate that they were identical.

In the face of this reality, Appellants resort to misdirection. They argue that "there is '<u>only one type</u>' of naturally occurring interferon beta that we know of." Br. at 27 (emphasis original). What they mean is this: Some interferons, like interferon-alpha, have recognized subtypes (such as interferon-α1, interferon-α2, etc.) that have different amino acid sequences, different glycosylation patterns, and different three-dimensional structures. *See* Appx79148–79149 (101:25–102:19). They are considered subtypes, rather than entirely different proteins, because the genes encoding for them are located on the same chromosome and the proteins are sufficiently similar to have similar biological effect. *See generally* Appx118 (1:49–53), Appx120 (5:30–32); Appx79149 (102:4–7, 16–19). It is undisputed that interferon-beta is isomorphic; it has no recognized subtypes. Appx79149 (102:11–13). But that does not mean that all native, human interferon-beta molecules are identical. On the contrary, the uncontroverted evidence is that there is great variability in sugar structures among interferon-beta molecules. *See, e.g.*, Appx118 (1:63–64) (interferon-beta is "heterogeneous in regard to size presumably because of the carbohydrate moieties").

Finally, Appellants seek to rewrite claim 1 such that there would be anticipation under their novel product-by-process theory if any one recombinant

interferon-beta molecule in a therapeutic composition were structurally identical to any one native, human interferon-beta molecule in the prior art, relying on a misreading of *Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001). Br. at 26–27. *Brown* involved a claimed system that could act on two-, three-, or four-digit-year data, and a prior-art system that acted on two-digit data. The claim was anticipated because it was "written in the alternative, and as written would be literally infringed by a system that offsets year dates only in two-digit formats." *Id*. at 1353. In so holding, *Brown* only reinforces that it is the claim language that matters when assessing anticipation. The '755 Patent claims the administration of a "therapeutically effective amount" of a composition comprising recombinant interferon-beta, not the administration of one individual molecule. Appellants have not presented any evidence that the therapeutically effective amount of native, human interferon-beta administered in the prior-art references precisely and identically matches a therapeutically effective amount of recombinant interferon-beta required by the claims.

Functional Differences. Amicus Bayer emphasizes that these structural differences are not enough to defeat anticipation, and that both structural and functional differences are required to distinguish over the prior art. Bayer Br. at 8–12; Br. at 25. Bayer is wrong. It so happens that in *Amgen*, the Court found both structural and functional differences, while in *Purdue Pharma L.P. v. Epic Pharma,*

LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016), the Court found neither structural nor functional differences. But neither case requires both structural and functional differences. Indeed, the *Amgen* holding was based solely on structural differences. 580 F.3d at 1367. And, although Bayer suggests *Greenliant Sys., Inc. v. Xicor LLC* turned on both structural and functional differences, *see* 692 F.3d 1261, 1269–71 (Fed. Cir. 2012), Bayer misreads the case. While the patentee described its invention in terms of its superiority and its characteristics—which Bayer says refers to function and structure (Bayer Br. at 9)—the Court considered only structural differences, and made no functional comparison. Thus, the Court noted that "Xicor's arguments clearly and unmistakably represented to the examiner and the Board that TEOS was a necessary component of the deposition process that imparted the distinct structural characteristics upon Xicor's claimed tunneling oxide layer." *Id*. at 1271 (emphasis added). The Court affirmed that "the process limitations in product-by-process claims" cannot be used to distinguish prior art "unless the process imparts structural difference to the product," *id*. at 1265, again with no mention of functional differences. Indeed, at least one lower court has found that "structural differences alone may distinguish the prior art." *See, e.g.*, *United Therapeutics Corp. v. Sandoz, Inc*., Nos. 12-CV-01617, 13-CV-316, 2014 WL 4259153, at *52 (D.N.J. Aug. 29, 2014) (citing *Greenliant*, 692 F.3d at 1269–71; Manual of Patent Examining Procedure § 2113 (8th ed. Rev. 9, Aug. 2010)).

In any case, as the district court found, the uncontroverted trial evidence showed functional differences between recombinant interferon-beta and native interferon-beta as well as structural differences. Appx29–30 (JMOL Op.) ("The evidence presented at trial also demonstrates that native, human interferon-β and recombinant interferon-β are not functionally identical."); *accord* Appx119 (4:49–55); Appx77476 (43:15–23), Appx77482–77483 (49:9–50:2); Appx77990–77993 (12:16–15:18). To be sure, there are areas of similarity: Both recombinant interferon-beta and native interferon-beta have similar biological activity and are immunomodulatory such that both can be used to treat disease. But that is not sufficient; anticipation requires strict identity.

The jury heard from Biogen's expert Dr. Kinkel that the efficacy of recombinant interferon-beta can be hampered by the body's immune system recognizing recombinant interferon-beta as "foreign" (which does not happen with the native, human protein) and generating antibodies that neutralize it. Appx77991–77992 (13:1–14:8); *see also* Appx77482 (49:9–19). There was no contrary evidence to rebut this functional difference.

There was also undisputed evidence that recombinant interferon-beta can be manufactured at scales that are not possible with natively sourced human interferon-beta. *See, e.g.*, Appx119–120 (4:10–13, 4:49–61, 6:64–67); *see also* Appx119 (4:11–13) (noting that "antitumor and anticancer applications" had been "severely

hampered by lack of an adequate supply of purified IFN-β"). Appellants now seek to rebut this evidence by citing the development of Frone, Serono's interferon-beta product that is sourced from native, human tissue, but there was no evidence that Frone was ever sold in the United States (it has never been approved here) or that it is prior art or that it can be made as inexpensively or on the same scale as recombinant interferon-beta. That some countries approved a native, human interferon-beta therapeutic does not detract from the undisputed record evidence of functional manufacturing advantages provided by the recombinant protein.

* * * *

Thus, even if Appellants were correct that prior-art methods of treatment with native, human interferon-beta could, as a hypothetical legal matter, anticipate a claim to methods of treatment with recombinant interferon-beta made in a non-human cell, the undisputed record evidence was that the native, human and recombinant proteins are not identical. They are both structurally and functionally different. The jury's verdict of anticipation thus lacked clear and convincing evidentiary support even under Appellants' mistaken view of the law.

E. The District Court Did Not Abuse Its Discretion by Conditionally Granting a New Trial

Noting the scant attention Appellants gave their anticipation argument at trial, the district court held that if its grant of JMOL were reversed, a new trial would be warranted. Appellants assert that the court abused its discretion by ordering a new

trial where it "simply disagreed with the jury verdict." Br. at 32. That did not happen. The district court conditionally granted a new trial because the jury's determination was "against the weight of the evidence" and because of "the overall setting of the trial, the character of the evidence, and the complexity of the legal principles that the jury was asked to apply to the facts. . . ." Appx36 (JMOL Op.). As the district court recognized, the jury spent the vast majority of the five-week trial hearing testimony on issues other than anticipation. *Id*. In fact, Appellants did not even mention anticipation in their closing arguments. *Id*. Because "the five-week trial in this case was 'long and complicated,' required complex factual determinations on multiple infringement, validity, and damages issues, was noticeably focused on issues other than anticipation, and involved scientific concepts that are not the 'subject matter lying within the ordinary knowledge of jurors,'" Appx36 (JMOL Op.) (quoting *Lind v. Schenley Indus., Inc*., 278 F.2d 79, 90–91 (3d Cir. 1960)) (internal quotations omitted), the district court determined that a new trial is warranted. If this Court reaches the issue, it should affirm that exercise of discretion.

II. Section 112: The District Court Correctly Sustained the Jury's Verdicts Rejecting Written Description and Enablement Defenses

A. The District Court's Jury Instruction Was Proper

The '755 Patent claims methods of treatment with recombinant interferon-beta-like polypeptides produced in transformed non-human host cells. The district

court instructed the jury that, in assessing the Section 112 support for the '755 Patent claims, "it is the method of treatment that must be" described and enabled, "not the proteins to be used or the way they are made." Appx47670-47672 (Jury Instruction). Appellants' and Bayer's assertion that the district court should have instead instructed the jury that the '755 Patent needed to describe and enable the host cells in which the polypeptides are made, the polypeptides themselves, and their "associated carbohydrate structures" is contrary to the law. *See* Br. at 32–36; Bayer Br. at 19–24.

It is the claims themselves that must be described and enabled. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). In a case involving methods of treatment using steroidal agents, this Court's predecessor was careful to make clear that the written description requirement is not the same for claims to the use of a class of compounds as for claims to the class of compounds itself. *See In re Herschler*, 591 F.2d 693, 701 (C.C.P.A. 1979). The '755 Patent claims "[a] method for immunomodulation or treating . . . a patient." Appx142 (49:59–50:12). Dr. Fiers demonstrated, and the '755 Patent teaches at length (Appx135–140 (36:1–46:37), that recombinant interferon-beta has biological activity like that of native human interferon-beta, and can thus be used for the medical treatments for which the native protein can be used. Dr. Fiers described and enabled methods to determine that biological activity—which Appellants do not dispute.

The '755 Patent does not claim the polypeptides themselves or the host cells themselves. A scientist may create any of the polypeptides that match the "production and transformation" limitations of Claim 1, and use them for any purpose other than treating a patient in accordance with the patent, without needing a license from Biogen. Likewise, a scientist may transform any non-human host cell with DNA matching those limitations without a license from Biogen. Infringement occurs only when a person therapeutically administers the composition of the patent claims—*i.e.*, practices the method of treatment. That is why the district court held that "produced by a non-human host" is "merely descriptive of the recombinant polypeptide to be administered," and that it is the method of treatment that must be described and enabled. Appx6579.

Appellants and Bayer assert that claims should be rejected under Section 112 if they are directed "to the use of host cells that extend beyond the scope of the work actually disclosed by the patent." Br. at 33; Bayer Br. at 17. But their cases underscore that it is the claimed invention that needs to be enabled and described. The patents in those cases claimed a genus of host cells, or a composition of matter, or expression technology. *See Monsanto Co. v. Syngenta Seeds, Inc*., 503 F.3d 1352 (Fed. Cir. 2007) (gene capable of functioning in plant cells); *Plant Genetic Sys. N.V. v. DeKalb Genetics Corp*., 315 F.3d 1335 (Fed. Cir. 2003) (transformed plant cell); *Adang v. Fischhoff*, 286 F.3d 1346, 1358 (Fed. Cir. 2002) (transformed tomato

plant); *In re Goodman*, 11 F.3d 1046 (Fed. Cir. 1993) (processes for producing proteins in plants); *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) (gene capable of being expressed in Cyanobacteria cells).

Where a patent claims a method of treatment with a genus of compounds, the written description requirement focuses on the method of treatment, and whether the inventor possessed the invention that administering the recited compounds would treat the disease at issue. *Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, No. 2:15-CV-1202-WCB, 2016 WL 6138124, at *16 (E.D. Tex. Oct. 21, 2016), *aff'd*, 739 F. App'x 643 (Fed. Cir. Oct. 10, 2018). In *UroPep*, the claims were directed to methods of treating benign prostatic hyperplasia ("BPH") using a genus of phosphodiesterase ("PDE") V inhibitors. *UroPep*, 2016 WL 6138124, at *1. The court held that "given that at least some PDE V inhibitors were known and were disclosed" in the specification, "the written description issue does not turn on whether the patentees were in possession of the entire genus of PDE V inhibitors." *Id.* at *15. Rather, "[g]iven the nature of the claims," the proper inquiry is "whether the disclosure in the specification shows that the inventors possessed the invention that administering an effective amount of a PDE5 inhibitor would treat BPH." *Id.*

Similarly, in *Regents of University of California v. Dako North America., Inc.*, the court held that, for a claimed method of staining target chromosomal DNA using a genus of probes, "it is not the number of probe species used in the generic method

that must be described in representative number in order to meet the written description requirement." No. C 05-03955 MHP, 2009 WL 1083446, at *9 (N.D. Cal. Apr. 22, 2009). The patentee need not describe a "representative number of species of the broad genera of components used in the claimed method," because the patentee was "not claiming the components as novel compositions themselves." *Id.* at *10; *see also Herschler*, 591 F.2d at 701.

University of Rochester v. G.D. Searle & Co., on which Appellants and Bayer rely, is not to the contrary. *See* 358 F.3d 916 (Fed. Cir. 2004). There, the claims were to "methods for selectively inhibiting PGHS-2 activity in a human host," *UroPep*, 2016 WL 6138124, at *16 (citing *Rochester*, 358 F.3d at 918), using "compounds that would inhibit PGHS-2 activity." *Id*. Thus, "the written description requirement was the same whether the claims were directed to inhibitors of PGHS-2 activity or to methods of inhibiting PGSH-2 activity," precisely because "the essence of the invention was the same in both cases—the identification of compounds that would inhibit PGHS-2 activity." *UroPep*, 2016 WL 6138124, at *16 (emphasis added); *see also Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1370 (Fed. Cir. 1999).

Here, the invention is not the recombinant polypeptides themselves, but rather the proof that those polypeptides have biological activity similar to that of human interferon-beta and thus can be used to treat disease. Bayer seeks to distinguish

UroPep by asserting that "[u]nlike the patent at issue in *UroPep*, the allegedly novel aspect of the '755 Patent was not the method of treatment." Bayer Br. at 22 (emphasis original). Bayer is wrong. The method of treatment was precisely the point of novelty: Dr. Fiers demonstrated that because recombinant interferon-beta-like polypeptides have biological activity like native interferon-beta, they can thus be used to treat patients.

It is that invention for which the district court instructed the jury to assess written description and enablement. The district court's instruction was proper. [1]

B. Any Error in the Jury Instructions Was Harmless Given the Undisputed Trial Evidence

If a corrected jury instruction "would not have changed the result, given the evidence presented," affirmance is required. *See Teleflex, Inc. v. Ficosa N. Am. Corp*., 299 F.3d 1313, 1328 (Fed. Cir. 2002). In making this determination, the Court reviews whether there is sufficient evidence to support a different outcome. *See Ecolab, Inc. v. Paraclipse, Inc*., 285 F.3d 1362, 1374 (Fed. Cir. 2002). Here, Appellants have failed to prove that any alleged error in the jury instruction had any impact on the outcome.

[1] To be clear, there is a patent that claims recombinant interferon-beta polypeptides themselves. *See*, Appx61170–61179 (U.S. Patent No. 9,376,478). The '478 patent claims priority before the priority date of the '755 Patent, when the state of the art of protein expression was certainly no broader or more developed than at Biogen's priority date. Serono has rights to the '478 patent and charges Biogen royalties under it.

1. There Was Undisputed Evidence at Trial That the Full Range of Host Cells Was Enabled

Appellants' principal argument is that the '755 Patent does not adequately describe the host cells in which the therapeutic interferon-beta-like polypeptides can be made. Br. at 32–35. In fact, it does. The '755 Patent discloses numerous "useful hosts" for the expression of recombinant interferon-beta, including numerous species of bacteria (such as Pseudomonas and Bacillus subtilis), yeasts and other fungi, animal or plant hosts, and plant cells in culture. Appx124 (13:54–64). The jury heard evidence from Biogen's expert Dr. Michael Green about these disclosures and about the state of the art at the priority date, which included public disclosure of additional non-human cell lines, as well as expression systems, that would allow the ordinarily skilled artisan to express recombinant interferon-beta in other host cells without undue experimentation. Appx80901 (27:2–8), Appx80980–80985 (106:25–111:13). Appellants tried to counter this by citing the testimony of their expert Dr. Lodish that "techniques for producing recombinant polypeptides in hosts other than E. coli . . . simply had not been developed" at the time of the '755 Patent. Br. at 35. But the jury witnessed Dr. Lodish's striking self-impeachment, which Appellants omit. The jury learned that 14 years before the trial, Dr. Lodish opined in another case that "[b]y February 25, 1980"—some three months before the priority date in this case—"many types of cells had been used as host cells, and workers of ordinary skill in the art had various types of cultured cells that could be

used as host cells in transformation experiments." Appx68243 (emphasis added). He further opined that "[s]everal types of human, mouse, and Chinese hamster cell lines, including Chinese Hamster Ovary cells lines, were in routine use." *Id.* (emphasis added). Biogen's Dr. Green testified that he was "in complete agreement" with Dr. Lodish's prior expert opinion. Appx80984 (110:13–18). Thus, had the jury been instructed that the '755 Patent needed to describe and enable the range of host cells, no reasonable jury could have found that Appellants proved their host-cell written-description and enablement challenges by clear and convincing evidence.

2. Had Appellants Presented Their Three-Dimensional-Structure Argument, a Reasonable Jury Would Have Rejected It

Appellants next argue that the '755 Patent does not describe or enable "the three-dimensional structure" of the interferon-beta polypeptides within the scope of the patent, "including any associated carbohydrate structures." Br. at 36. Appellants did not make this argument to the jury, and any reasonable jury would have rejected it. At trial, Biogen presented evidence that the right three-dimensional structure, or folding, of the protein was necessary for the recombinantly expressed interferon-beta to have biological activity and be used as a therapeutic. Appx77880 (31:8–14); Appx80476–80477 (62:4–63:5). In rejecting Appellants' obviousness defense, the jury agreed with Biogen that prior to Dr. Fiers's work, it was unknown whether recombinantly expressed interferon-beta would fold appropriately and be

biologically active. Appx80472 (58:15–22). Dr. Fiers was able to discern that the sugar groups on the human protein are not necessary for proper folding and biological activity. Appx80546-80547 (132:13–133:9); Appx81049 (175:3–14).

Appellants have not appealed the jury's rejection of their obviousness defense. And in support of this new, three-dimensional-structure-based Section 112 defense, Appellants cite no trial testimony. Had Appellants presented this argument at trial, Biogen would have responded—as it did on summary judgment—that given that human interferon-beta is glycosylated, Dr. Fiers's proof that unglycosylated interferon-beta made in E. coli has biological activity is sufficient to demonstrate that the polypeptides would have biological activity if made in the full range of recombinant hosts. Appx21930–21938; Appx22533–22539. Biogen's expert Dr. Green would have testified at trial, as he did on summary judgment, that Dr. Fiers made interferon-beta in the least hospitable host cell possible, and thus demonstrated that these proteins made in any host cell would have biological activity. Appx22536–22537. Any reasonable jury presented with Appellants' "three-dimensional structure" defense would have rejected it.

3. Bayer's "Polypeptides" Argument Is Not at Issue on This Appeal and Would Not Affect the Outcome of a Retrial Against Appellants

Amicus Bayer argues that the '755 Patent "does not adequately describe the vast number of polypeptides used in the claimed method." Bayer Br. at 24; *see also*

id. at 27–28 (regarding enablement). Bayer relies on evidence that was not even before the jury at trial, to make an argument that Appellants do not make in this Court. Indeed, Bayer concedes the issue is not before this Court and makes clear that the reason for briefing it is "because of its potential impact on Biogen's separate case against Bayer." Bayer Br. at 24. In other words, Bayer is seeking an improper advisory opinion to guide its strategy in separate proceedings in the district court. The Court therefore has no reason to address Bayer's argument.

To be clear, however, Bayer is wrong. Section 112 can be satisfied by the disclosure of (i) the DNA and amino acid sequences of a representative species within a genus of closely related species, and (ii) test data demonstrating that species within the genus have the features claimed in the patent. *See Invitrogen Corp. v. Clonetech Labs., Inc.*, 429 F.3d 1052, 1073 (Fed. Cir. 2005). In *Rochester* this Court explicitly recognized that the "disclosure of a DNA sequence might support a claim to the complementary molecules that can hybridize to it." 358 F.3d at 925.

Bayer cites *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1357–58 (Fed. Cir. 2011) and *Carnegie Mellon University v. Hoffmann-La Roche Inc*., 541 F.3d 1115 (Fed. Cir. 2008), but neither applies here. The patents in *Boston Scientific* did not provide "any 'definitions, examples, or experimental models . . . for determining whether a compound is a structurally similar analog as contemplated by the patentees.'" 647 F.3d at 1360 (citation omitted). There was "no guidance at

all in the specification as to how to properly identify or choose the claimed analogs." *Id*. at 1365. The '755 Patent discloses all three things missing in *Boston Scientific*: (1) specific limitations on the recombinant polypeptide used in the method (it must have antiviral activity and the DNA that encodes it must be similar, *i.e*., capable of hybridizing, to DNA encoding human interferon-beta), *see, e.g.,* Appx142 (50:1–10), (2) specific examples of such recombinant polypeptides, Appx132–135 (29:12–35:67), Appx140–141 (46:10–48:41), and (3) extensive disclosure on how to reliably test for antiviral activity, *see, e.g.,* Appx135–140 (36:1–46:37).

In *Carnegie Mellon*, the patent claimed recombinant plasmids that contain a DNA sequence encoding a bacterial enzyme, DNA polymerase, but there was undisputed evidence that the genus was so broad as to claim "not a single enzyme, but a family of enzymes encoded by a family of genes that varied from one bacterial species to another." 541 F.3d at 1125. In contrast, the '755 Patent does not claim a family of proteins encoded by a family of genes that vary from claimed species to claimed species. It claims a method of treatment with a recombinant protein (interferon-beta) encoded by a single gene from a single source (humans), or with polypeptides having closely related structure. Moreover, the '755 Patent teaches that the claimed recombinant polypeptides must be encoded by DNA that is identical or nearly identical to the DNA that encodes human interferon-beta, and must have

antiviral activity like that of human interferon-beta. Appx121 (7:15–36), Appx142 (49:58–50:12).

Thus, even if the jury should have been instructed that the patent needed to describe and enable the full range of polypeptides that can be administered using the method of claim 1, no reasonable jury would have found a lack of Section 112 support by clear and convincing evidence. And the outcome in this case would be the same in any event, because, as Bayer concedes, Biogen asserted the narrower Claim 2 against Appellants. Bayer Br. at 17–18. Under claim 2, the DNA sequence from which the polypeptide is made must be selected from one of just two alternatives, both of which are identified by their precise DNA sequence, and one of which is the sequence for native, human interferon-beta. Appx142 (50:13–52). Bayer does not contend that, under its proposed jury instruction and polypeptide argument, a jury would have found claim 2 invalid by clear and convincing evidence. Any error in the jury instruction was harmless.

III. Direct Infringement: The District Court Correctly Construed Claim 1 To Cover Only a Single Method "Step"

The jury heard undisputed testimony from three expert witnesses that the use of Rebif® to treat multiple sclerosis meets every limitation of claims 1 and 2 of the '755 Patent. Appx77895–77907 (46:8–58:14); Appx77930 (81:13–22), Appx77938–77942 (89:4–93:6); Appx77998–78016 (20:19–38:8). And the jury found that when doctors administer and patients self-administer Rebif® to treat

multiple sclerosis, they directly infringe claims 1 and 2. Appellants do not challenge the sufficiency of the evidence supporting that verdict; their direct-infringement challenge is limited to one of claim construction. Br. at 37–43.

Appellants' challenge to that construction turns on one question: How many steps are there in the treatment method of Claim 1? The parties all agree on one such step: the step of administering a therapeutically effective amount of a composition comprising recombinant interferon-beta to a patient. The disagreement is whether transforming a host cell with DNA and producing the recombinant interferon-beta in that host cell are two additional steps of the claimed method. Br. at 37. They are not; as Biogen argued and the district court held, the claimed method requires only one step, administering a therapeutically effective amount of the claimed composition. Appx6574–6575.

The Court's analysis begins with the language of the claim. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). Yet Appellants never quote the operative language in their brief. Claim 1 claims a "method for immunomodulation or treating a viral condition[], a viral disease, cancers or tumors comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of a composition comprising," and then goes on to describe the composition to be administered. There is only one "step" in the claim. It says so explicitly.

As the district court found, "a natural reading of the claim supports a construction that requires only a single method step." Appx6575. "The word 'step' in the claim is singular, not plural. The 'step' it describes is written in the present tense—'administering.'" *Id*. In contrast, the limitations requiring that the polypeptide have been produced in a transformed host cell are not called "steps" and are described in the past tense. *Id*. The claim language indicates that the "transformed" and "produced" language "describes the recombinant polypeptide that is administered to practice the claimed invention." *Id.* They are not "two additional affirmative steps that must be performed." *Id.*

Notably, under Appellants' construction claim 1 would never be infringed. Physicians who administer interferon-beta would also have to be molecular biologists with an FDA-approved facility in which to manufacture recombinant interferon-beta. The attorney who drafted these claims testified that Appellants' construction "would be crazy" because "[d]octors aren't going to, or healthcare people or the patients themselves, are not going to be transforming host cells with DNA and culturing them to produce proteins." Appx77767 (47:11–20). Dr. Kinkel testified that in his decades of multiple-sclerosis experience he has never "heard of a neurologist transforming a nonhuman host to produce recombinant human interferon beta and administering it to a patient," and that such a prospect would be "preposterous." Appx78014–78015 (36:11–37:25). This testimony was unrebutted.

None of Appellants' arguments provides any basis to treat claim 1 as anything other than what it says it is: a one-step method-of-treatment claim.

***Monsanto*:** Appellants rely on the fact that the "obtained by" limitation in Claim 4 was a required step in *Monsanto,* 503 F.3d 1352. But claim 4 was a dependent claim. Independent claim 1 recited a three-step method for producing a transgenic corn plant, *id*. at 1357, and dependent claim 4 then added a fourth step: "[a] process comprising obtaining progeny from a fertile transgenic plant obtained by the process of Claim 1 which comprise said DNA." *Id*. at 1355. The Court held that to practice Claim 4 the infringer had to practice the three steps in Claim 1 as well. *Id*. at 1355, 1358. But Claim 1 of the '755 Patent does not depend from a claim requiring transforming a host cell and producing the polypeptide.

The Patent Specification: Appellants note that the '755 Patent is entitled "DNA Sequences, Recombinant DNA Molecule and *Processes for Producing* Human Fibroblast Interferon-Like Polypeptides," and that the specification says that "[t]his invention allows the production of those polypeptides in amounts and by methods not hitherto available" as evidence that the claim encompasses the "produced" and "transformed" steps. Br. at 39 (citing Appx118 (1:1–4); Appx120 (6:57–59)) (emphasis added). That is true; when the patent application was filed, it included claims not only to methods of treatment, but also to methods of production (as well as DNA and protein claims). The Examiner restricted those claims into

separate groups, Appx58180–58185, and the '755 Patent is the method-of-treatment patent. As the district court found, the "fact that the specification also contains a description of the transformation of non-human hosts and the production of the recombinant polypeptide does not detract from the plain language of the claim itself, which refers only to a single-step method." Appx6579. Indeed, the specification explicitly differentiates the therapeutic use of the recombinant polypeptide as "independent of the method for making the recombinant polypeptide." *Id*. (citing Appx118 (1:24-28); Appx120 (6:54–59)) (emphasis added).

Prosecution History: In the 29-year prosecution history, Biogen never once said that claim 1 comprises more than one step. The Examiner and Biogen consistently treated these as claims to a one-step method. To obscure that reality, Appellants resort to out-of-context quotes and a typographical error. Thus, they note that the Examiner referred to the "process steps in claims 31–34 of the instant application" and another then-pending application, and—because then-claim 31 matured into Claim 1—they argue that the Examiner said the claim had multiple "steps." Br. at 40 (citing Appx53275). Not so. The Examiner was talking about multiple claims in the aggregate, and taken together they do recite multiple "steps." Appellants then note that Biogen referred to claim 31 alone as having "'positive process steps.'" Br. at 40 (emphasis original). But that is the very amendment in which Biogen added the language denoting "the step of administering," Appx53283,

without referring to steps of production or transformation. As the district court found, the stray "s" in "steps" is "insufficient to require three separate method steps in Claim 1," especially "given the actual language of the claim, which supports a single-step method." Appx6580.

Validity: Finally, Appellants erect a straw man: They argue that if the production and transformation limitations "need not be performed for there to be infringement," then the prior-art references with native, human interferon-beta would anticipate the '755 Patent. Br. at 41–42 (emphasis added). Certainly the production and transformation limitations must be performed, because the polypeptide has to have been produced in a transformed host cell. But the infringer need not have transformed the host cell or produced the polypeptide. *See* Appx6574.

IV. Induced Infringement: The District Court Correctly Held That No Substantial Evidence Supported the Verdict of No Inducement

For induced infringement, Biogen needed to prove by a preponderance of the evidence that (i) healthcare professionals and patients directly infringe the claims of the '755 Patent when healthcare professionals administer and patients self-administer Serono's and Pfizer's Rebif® recombinant interferon-beta product to treat multiple sclerosis; (ii) Appellants were aware of the '755 Patent; (iii) Appellants knew that the use of Rebif® to treat multiple sclerosis directly infringes the '755 Patent; and (iv) Appellants took action specifically intending to cause healthcare professionals and patients to use Rebif® to treat multiple sclerosis

through immunomodulation. *See, e.g.*, *Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 766 (2011); *Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1926 (2015); *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1304–5 (Fed. Cir. 2006). The jury found the first three elements as part of its direct- and contributory-infringement verdicts, *see* Appx68292–68294; Appx81256–81257 (103:8-104:12), but returned a verdict of no induced infringement because it found that Biogen had not proven the specific intent required for inducement. The district court correctly held that no reasonable jury could have reached that conclusion, granted judgment of induced infringement for Biogen, and conditionally certified a new trial on the issue. Appx42-43, Appx46-48 (JMOL Op.).

The undisputed record evidence showed that Pfizer and Serono took action intending to cause healthcare professionals to use Rebif® to treat multiple sclerosis via immunomodulation. Pfizer's sales force promoted Rebif® for multiple sclerosis to healthcare professionals, and distributed prescribing information instructing them how to so use Rebif®. Appx47438–47439 (17:19–21, 20:09–21:08, 21:17–22:08, 22:10–21 (Moore)). Serono, too, marketed and sold Rebif® with instructions on how to administer it to treat multiple sclerosis. *See, e.g.,* Appx66872–66891 (Rebif 2005 label); Appx66892–66913 (Rebif 2012 label); Appx66914–66944 (Rebif 2013 label). "Evidence of active steps" like these "taken to encourage direct infringement, such as advertising an infringing use or instructing how to engage in an infringing

use, show an affirmative intent that the product be used to infringe." *Metro-Goldwyn-Mayer Studios, Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936 (2005) (internal quotation omitted).

Appellants nevertheless contended at trial and contend now on appeal that they lacked the requisite intent to induce infringement. First, Appellants profess not to know whether Rebif® treats multiple sclerosis through immunomodulation, as the claims require, or through some other, as-yet-still-unidentified method. Br. at 5152. Second, Serono contended at trial (and Pfizer now says for the first time on appeal) that they believed that claim 1 required three steps (administering, transforming, and producing), and that because the transformation and production "steps" happened outside the United States before the '755 Patent issued, they further believed that use of Rebif® did not infringe the claims. Br. at 4348.

The district court did not err in granting JMOL of induced infringement.

A. No Evidence Supported a Conclusion That Appellants Did Not Intend that Rebif® Be Used To Treat Multiple Sclerosis Through Immunomodulation

Appellants' entire argument about immunomodulation is a smokescreen. They claim that they did not intend that Rebif® be used to treat multiple sclerosis through immunomodulation, but there was no evidence at trial about (and Appellants never even suggested) any other mechanism of action.

Biogen's Dr. Kinkel, one of the country's leading multiple sclerosis doctors, testified that while the precise manner in which interferon-beta modulates the immune system to treat multiple sclerosis is still being determined, there is scientific consensus that interferon-beta treats multiple sclerosis through immunomodulation, and he explained to the jury how interferon-beta is thought to modulate the immune system. Appx77966–77976 (117:21–127:12); *see also* Appx78008–78009 (30:25–31:6); Appx78011–78012 (33:25–34:7); Appx66246–66254; Appx68104–68111. Dr. Richard Rudick, the former director of the country's largest multiple sclerosis treatment center, agreed that interferon-beta treats multiple sclerosis through immunomodulation. *See, e.g.*, Appx78047–78049 (69:2–71:11); Appx78053–78055 (75:20–77:2); *see also* Appx66258–66269; Appx66270–66281; Appx66282–66290. Appellants' only physician witness, Dr. Jordan Gutterman, likewise testified that interferon-beta is immunomodulatory, and Dr. Michel Revel, the inventor of Rebif®, agreed. *See* Appx79198–79199 (36:23-37:4), Appx79207–79208 (45:6–13, 46:16–19); Appx80124–80126 (53:16–55:16); Appx68173 (PTX1055).

The jury also saw documents from within Serono's and Pfizer's own files confirming each company's knowledge that Rebif® treats multiple sclerosis through immunomodulation by the same immunomodulatory pathways that Dr.. Kinkel identified. *See* Appx64563 (PTX59); Appx65872–65874 (PTX61); Appx66203–66217 (PTX227); Appx67062; Appx67102 (PTX102); *see also* Appx78001–78007

(23:7–29:11); Appx78010–78011 (32:14–33:24). Thus, an internal Pfizer presentation referred to Rebif® as an "immunomodulatory agent[]," Appx67175, and diagrammed the "MOA"—mechanism of action—of interferon-beta in the treatment of multiple sclerosis as modulating the immune system. Appx67102. And Serono explicitly told the FDA that, in treating multiple sclerosis, Rebif® results in "the modulation of the immune process, which leads to reduction in disease activity." Appx64563. The Rebif® Biologics License Application ("BLA") identified three "proposed mechanisms of action of Interferon beta in influencing MS disease," each of which is immunomodulatory, *id*.; *see also* Appx78001–78002 (23:12–24:18), and—in a section entitled "Immunoregulatory Properties Relevant to Multiple Sclerosis"—stated that interferon-beta "exerts a number of immunoregulatory effects on cells of MS patients" and "seems to act by regulating excessive immune responses in the local inflammation sites in MS . . . ," Appx65872–65873.

Importantly, Appellants adduced no contrary evidence. They did not call a multiple sclerosis physician at all, either as an expert or a fact witness, and did not introduce any evidence of any other, non-immunomodulatory method of treating multiple sclerosis. They never even suggested another method. Nor did they ever suggest that they believed in another method.

Appellants pointed to only the "Mechanism of Action" statement in the prescribing information for Rebif®, which says that "[t]he mechanism(s)" by which Rebif® works on multiple sclerosis "is unknown." Appx66984. The undisputed evidence at trial, however, from leading expert Dr. Kinkel, was that this sentence is entirely consistent with Rebif® treating multiple sclerosis through immunomodulation. He explained that a "mechanism of action" is the "precise way that a particular drug has its effect," Appx77971 (122:21–23), and that even today doctors and researchers do not know exactly how interferon-beta modulates the immune system in treating multiple sclerosis. That is why the BLA for Rebif® lists three possible immunomodulatory pathways to treating multiple sclerosis. There is no dispute, however, that whatever the precise immunomodulatory mechanism, interferon-beta treats multiple sclerosis by modulating the immune system. Appx77975-77976 (126:19-127:9). As the district court correctly found after reviewing the trial evidence, "what is 'unknown' is only the precise mechanisms involved." Appx42 (JMOL Op.) (emphasis original).

Moreover, as the district court found, distinctions between whether the mechanism of action is unknown or the precise mechanism is unknown do not go to an intent to induce infringement. They go "to a different question that the jury resolved against" Appellants, *id.*, as part of its contributory-infringement verdict, namely, whether Appellants know that Rebif® treats multiple sclerosis through

immunomodulation. The jury found that Appellants do know that Rebif® works through immunomodulation, a finding that Appellants do not challenge in this Court. Given that, as the district court found, "[n]o contrary hypothesis was advanced or was supported by the record," the jury "was not free to disregard the evidence" of intent adduced by Biogen. Appx43 (JMOL Op.). The district court properly held that no reasonable jury could have concluded that Appellants lacked the specific intent that doctors use Rebif® to treat multiple sclerosis through immunomodulation. Appx43, Appx47 (JMOL Op.).

B. The Record Evidence Cannot Support a Conclusion That Either Appellant Lacked Specific Intent Because of a Belief in a Three-Step Claim Construction

1. The District Court Correctly Entered JMOL of Induced Infringement Against Serono

Serono's second defense to liability for inducing infringement was that its mistaken good-faith belief in its rejected three-step claim construction negated intent.

On JMOL, the district court noted that the jury had not answered the verdict form questions regarding Serono's good-faith belief defense and correctly "declined to give credence to non-answers by the jury." Appx48 (JMOL Op.). The district court also found that Serono's three-step-claim-construction belief would not afford it a complete defense for the entirety of the liability period, because "the jury heard evidence that as of March 2016, when the Court issued its claim construction

decision construing claim 1 as a one-step method, Serono no longer believed in its three-step claim construction." *Id*. (citing Appx79442–79443 (73:11–74:21); Appx79546 (15:4–21)).

Serono now claims that the district court misunderstood the evidence because Serono "has never relinquished its belief" in its rejected three-step claim construction. Br. at 49. But Serono misstates the record in support of that argument. Thus, Serono quotes its corporate representative Mr. Henry Einav as having testified that "Serono 'has a reasonable good faith belief that it doesn't infringe'" and that "Serono believes it doesn't infringe because it believes that the patent entails a three-step method." Br. at 48 (citing Appx79442 (73:11–14, 19–23)). Those were the questions asked of Mr. Einav, not his answers. And in the very next question and answer, which Serono omits, Mr. Einav made clear that Serono no longer holds that view:

> Q. And that continues to be your view today. Right?
>
> A. No.

Appx79442 (73:24–25). Mr. Einav testified that Serono accepted the district court's claim construction:

> Q: Was that significant to Serono, that the Court had reached a different conclusion [regarding claim construction]?
>
> A: Of course it was significant. We had believed from 2009 up to that decision that our interpretation of the claims was a reasonable and correct interpretation. The Court handed down a

> decision in March 2016 telling us that we were wrong. So of course we accept that decision and we respect that decision of course.

Appx79419 (50:3–9) (emphases added); *accord* Appx79507 (138:5–10) ("we respect that we were wrong in our interpretation between 2009 and 2016").

Serono now tries to differentiate "accepting" the district court's claim-construction decision from agreeing with it. Br. at 47–49. There is no such distinction. The point of Mr. Einav's testimony was that after the district court's claim construction, Serono understood it had been wrong in its belief in non-infringement. He was asked, point blank, whether Serono still believed in that claim construction as of trial, and he answered: "No."

In light of the evidence, no reasonable jury could have found that Serono's belief in its noninfringing construction was objectively reasonable. *See, e.g.*, *Warsaw Orthopedic, Inc. v. NuVasive, Inc.*, 824 F.3d 1344, 1349–50 (Fed. Cir. 2016). Despite the clear language of the claim, which provides for a single step, "the step of administering to a patient in need," Appx142 (49:60–61), Serono relied on a construction of the claim that required three steps: transforming a host cell, producing a recombinant polypeptide, and administering it to a patient. As the jury heard, Serono's three-step construction was rejected as contrary to the plain language, grammar, and natural reading of the claim. Appx79503–79505 (134:13–136:9); *see also* Appx6575–6576, Appx6581

The district court committed no error in granting judgment as a matter of law that Serono's alleged belief in its three-step claim construction did not negate Serono's intent to induce infringement.

2. Pfizer Waived Any Argument About a Belief in the Three-Step Claim Construction

At trial, Pfizer disclaimed any claim-construction-based defense to induced infringement. Before closing arguments, Appellants' counsel conceded that there was no evidence that Pfizer had a good-faith belief in non-infringement based on claim construction, and committed not to argue otherwise. Appx81200–81201 (47:10–48:24). Pfizer offered no such defense in closing arguments. And the district court's instruction to the jury regarding this defense and the Verdict Form questions about it were specific to Serono, Appx47656–47657 (Final Jury Instructions); Appx68293–68294, *compare* Questions 2–5 with Question 6).

On appeal, however, Pfizer argues for the first time that "Pfizer wholly relied on Serono's evaluation" of the patent and was entitled to rely on Serono's supposed good-faith belief in the rejected three-step claim construction. Br. at 43. Appellants cite no evidence for that proposition, because there is none. No witness testified to Pfizer's understanding of the patent claims, that Pfizer believed that it did not infringe the '755 Patent, or that Pfizer relied on Serono's belief. Having not presented this argument in the district court, Pfizer may not raise it for the first time

on appeal. *See, e.g.*, *Singleton v. Wulff*, 428 U.S. 106, 120 (1976); *Golden Bridge Tech., Inc. v. Nokia, Inc.*, 527 F.3d 1318, 1322 (Fed. Cir. 2008).

Appellants contend that "Pfizer's liability . . . stands or falls with Serono's" because Serono must indemnify Pfizer. Br. at 46. That is a non-sequitur. Indemnification means Serono would have to pay any judgment against Pfizer. But Serono's indemnification obligations do not give Pfizer a defense, and Pfizer cannot raise for the first time on appeal the argument that it could, or did, rely on Serono's belief in non-infringement.

C. The District Court Properly Exercised Its Discretion in Conditionally Ordering a New Trial on Inducement

The district court further found that—for the same reason that the jury's verdict of no induced infringement was unsupported by the record evidence—a new trial on induced infringement would be appropriate were this Court to conclude that judgment in Biogen's favor was improper. Appx43, Appx48 (JMOL Op.). Given (a) the jury's finding that recombinant interferon-beta does treat multiple sclerosis through immunomodulation, (b) the overwhelming evidence that both Appellants know and intend it be used for such purpose, and (c) Pfizer's attempt to raise a defense that it did not offer at trial, were this Court to reverse the judgment in Biogen's favor it should nevertheless affirm the grant of a new trial.

V. Contributory Infringement: The District Court Correctly Instructed the Jury Regarding the Mental State for Contributory Infringement

Appellants argue that the district court erred by refusing to instruct the jury that an incorrect but good-faith belief in non-infringement is a defense to contributory infringement. Br. at 54–57. This argument would apply only to Serono, because (as set forth above), Pfizer offered no good-faith defense at trial. But, to be clear, the district court's jury instructions correctly stated the law.

As Appellants agree, Br. at 49, induced and contributory infringement require different mental states. As the district court addressed in a thorough oral ruling, Appx81089–81096, induced infringement requires specific intent to induce others to engage in infringing conduct, whereas contributory infringement requires "only proof of a defendant's knowledge, not intent, that his activity causes infringement." *Lifetime Indus., Inc. v. Trim-Lok, Inc.*, 869 F.3d 1372, 1381 (Fed. Cir. 2017) (citing *Commil,*135 S. Ct. at 1927; *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469 (Fed. Cir. 1990)). For contributory infringement the defendant must be aware of the patent, *see Aro Mfg. Co. v. Convertible Top Replacement Co.*, 377 U.S. 476, 488–89 (1964) (*Aro II*), and know "of patent infringement," *Commil*, 135 S. Ct. at 1927. But once it is established that the defendant, while aware of the patent, sold a product with no substantial non-infringing use, the requisite mental state is presumed from the sale itself: "One who makes and sells articles which are only adapted to be used in a patented combination will be presumed to intend the natural

consequences of his acts; he will be presumed to intend that they shall be used in the combination of the patent.'" *Grokster*, 545 U.S. at 932 (quoting *New York Scaffolding Co. v. Whitney*, 224 F. 452, 459 (8th Cir. 1915)). "[W]hen a manufacturer includes in its product a component that can only infringe, the inference that infringement is intended is unavoidable." *Ricoh Co., Ltd. v. Quanta Computer Inc.*, 550 F.3d 1325, 1338 (Fed. Cir. 2008) (citation omitted) (emphasis original).

Different mental states give rise to different scienter-based defenses. As relevant here, an erroneous-but-good-faith belief in non-infringement can negate the specific intent required for inducement, but it is not a defense to contributory infringement. That is why this Court observed in *Commil* that "a good-faith belief of non-infringement is relevant evidence that tends to show that an accused inducer lacked the intent required to be held liable for induced infringement." *Commil USA, LLC, v. Cisco Sys. Inc.*, 720 F.3d 1361, 1367–68 (Fed. Cir. 2013) (emphasis added). Notably absent from *Commil* and any of the cases it cited was any suggestion that a good-faith belief in non-infringement bears on contributory infringement. *See id.*; *accord DSU*, 471 F.3d at 1307; *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1351 (Fed. Cir. 2009); *Kinetic Concepts, Inc. v. Blue Sky Med. Grp., Inc.*, 554 F.3d 1010, 1025 (Fed. Cir. 2009); *Bettcher Indus. Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 649 (Fed. Cir. 2011).

Appellants contend that the Supreme Court's *Commil* decision overruled *Grokster* and its progeny (without citing them) and "expressly held" that a "good-faith belief in a reasonable, non-infringing claim construction, even if that construction is ultimately rejected, negates the knowledge of infringement required for both induced and contributory infringement." Br. at 55 (emphasis omitted). Appellants misread *Commil*, as is clear from the very passage on which they rely. *Commil* was an induced-infringement case, not a contributory-infringement case. Importantly, so was the Supreme Court's then-recent decision in *Global Tech*, in which the Court held that induced infringement "requires knowledge that the induced acts constitute patent infringement," *Global-Tech*, 563 U.S. at 766. Commil and the Government asked the Court to overrule *Global-Tech* and hold that induced infringement requires only knowledge of the patent's existence and the possibility of infringement, *see Commil*, 135 S. Ct. at 1926, which had long been the requirement for contributory infringement, *see Aro II*, 377 U.S. at 488–89. In rejecting the invitation to overrule *Global-Tech*, the Supreme Court specifically differentiated induced infringement from contributory infringement:

> Qualifying or limiting [*Global-Tech*'s] holding, as the Government and Commil seek to do, would lead to the conclusion, both in inducement and contributory infringement cases, that a person, or entity, could be liable even though he did not know the acts were infringing. In other words, even if the defendant reads the patent's claims differently from plaintiff, and that reading is reasonable, he would still be liable because he knew the acts might infringe. *Global-Tech* requires more. It requires proof the defendant knew the acts were infringing.

Id. at 1928 (emphases added). Critically, contributory infringement was not at issue in *Commil*. Thus, the only reason the Court discussed contributory infringement in this passage was to distinguish the two theories of liability, and to reject the Government's and Commil's invitation to equate them. A defendant who reasonably reads the patent in a way that would be non-infringing, yet knows that the acts might infringe, is liable for contributory infringement, but is not liable for induced infringement.

The district court's jury charge reflects this distinction. Indeed, the court used the pattern charges from the Federal Circuit Bar Association, which were updated after *Commil* and which treat a good-faith but mistaken belief in non-infringement as a defense to induced infringement—instructing the jury that if the alleged infringer "was aware of the patent, but believed that the acts it encouraged did not infringe that patent, [the alleged infringer] cannot be liable for inducement"—but not as a defense to contributory infringement. Appx75952–75954; Appx81094–81095.

As the district court noted, this distinction is corroborated by Section 298, in which Congress addressed the role of advice of counsel in negating specific intent. Congress established that "[t]he failure of an infringer to obtain the advice of counsel with respect to any allegedly infringed patent . . . may not be used to prove . . . that the infringer intended to induce infringement of the patent." 35 U.S.C. § 298

(emphasis added). That Section 298 refers to only induced infringement, and not to contributory infringement, further confirms that a good-faith belief in non-infringement, even if informed by legal advice, is not a defense to contributory infringement. Appx81095.

Next, Appellants contend that this Court "squarely held" in *Zoll* that a good-faith belief in an incorrect, non-infringing claim construction negates the knowledge requirement for contributory infringement. Br. at 55. *See Koninklijke Philips N.V. v. Zoll Med. Corp.*, 656 F. App'x 504, 523 (Fed. Cir. 2016). *Zoll* was a non-precedential opinion, and it treats *Commil* as applying to "indirect infringement" generally, subsuming both induced and contributory infringement. *Id.* at 523. This Court's subsequent, precedential opinion in *Lifetime Industries*, also citing *Commil*, specifically differentiates contributory and induced infringement, noting that only induced infringement requires "the intent to infringe." 869 F.3d at 1381.

Finally, Appellants cite *Unwired Planet, LLC v. Apple Inc.*, 829 F.3d 1353, 1363-64 (Fed. Cir. 2016), for the proposition that "the 'proper focus of indirect infringement analysis is on the subjective knowledge of the accused infringer' for both induced and contributory infringement." Br. at 55. But *Unwired* addressed a district court's grant of summary judgment based on its own assessment of the objective merit of Apple's non-infringement defenses, without regard to Apple's subjective belief. The Court addressed indirect infringement as a category, without

addressing the argument that Appellants make: that a good-faith belief in a mistaken claim construction is a defense to contributory infringement specifically.

Because the district court's jury instructions correctly stated the law of contributory infringement, this Court should reject Appellants' challenge to the jury's finding that both Appellants contribute to direct infringement by selling Rebif®, a product that (all agree on this appeal) has no non-infringing use.

VI. Patent Eligibility: The District Court Correctly Rejected Serono's Section 101 Argument

Appellants relegate patent eligibility to the back of their brief, consonant with their treatment of it at trial. Appellants included Section 101 in the joint pretrial order, but then presented no evidence or argument about it. The district court correctly denied their JMOL motion because the '755 Patent claims a patent-eligible method of treatment.

On appeal, Appellants have changed their Section 101 theory. On JMOL, they rested their argument on assertions that "the '755 Patent claims cover the use of a product of nature" and that "process claims directed to the use of a product of nature like recombinant interferon-beta encompass 'abstract ideas,' which are likewise ineligible for patenting." Appx71120–71123. They now assert instead that the '755 Patent claims are ineligible "because they are directed to the natural phenomenon that IFN-β has antiviral properties." Br. at 58. That argument should

be deemed waived, as it was not asserted in the district court. It is also wrong as a matter of law.

A. Step 1: The '755 Patent Claims Do Not Cover a Natural Product, an Abstract Idea, or a Natural Phenomenon

Appellants' argument rests on the premise that recombinant interferon-beta is identical to native, human interferon-beta, and thus fails for the same reasons discussed above in Point I.D: the undisputed record evidence is that recombinant interferon-beta made in non-human hosts and native, human interferon-beta are both structurally and functionally different. Recombinant interferon-beta is a man-made substance, not a natural one.

Even if the polypeptides were identical, however, the '755 Patent claims would be patent-eligible. The Supreme Court made clear in *Myriad* that while human genes are not themselves patentable, methods of using those genes can be patented. *See* 569 U.S. at 595. And this Court recently held that methods of treatment with a natural substance—the amino acid beta-alanine—are patent-eligible. *Nat. Alts. Int'l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338 (Fed. Cir. 2019). "Administering certain quantities of beta-alanine to a human subject alters that subject's natural state," and the claims at issue required that an "infringer actually administer the dosage form claimed in the manner claimed, altering the athlete's physiology to provide the described benefits." *Id*. at 1344. The claims specifically required administration of "unnatural quantities to alter a patient's

natural state." *Id.* at 1346. Likewise, the '755 Patent claims require the administration of "a therapeutically effective amount" of interferon-beta to a person "in need thereof," explicitly excluding patients whose natural immune systems make enough interferon-beta to treat the disease without exogenous administration. Appx142 (49:60–62).

Appellants' argument also misstates the law. While they assert that the '755 Patent claims "rest[] entirely, and exclusively, on the natural phenomenon that IFN-β has antiviral properties," Br. at 58, resting on, or depending on, the body's natural processes does not mean that the claim is "directed" to that natural ability within the meaning of Step 1 of the Section 101 analysis. *See Nat. Alts.*, 918 F.3d at 1345 (quoting *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1049 (Fed. Cir. 2016)); *Vanda*, 887 F.3d at 1136. The '755 Patent does not claim, and thus monopolize, the fact that native, human interferon-beta has antiviral properties. *See Vanda*, 887 F.3d at 1135.

The '755 Patent claims are not directed to unpatentable subject matter and thus the district court's patent-eligibility decision should be affirmed without any need to reach Step 2. *See id.* at 1334

B. Step 2: The '755 Patent Claims Add an Inventive Step and Were Not Well Understood, Routine, or Conventional

Step 2, in turn, would require Appellants to prove by clear and convincing evidence that the elements of the '755 Patent claims consist only of well-understood,

routine, conventional activity. There is no evidence of that, much less clear and convincing evidence.

On the contrary, the jury determined that the '755 Patent claims are non-obvious, Appx68294 (Verdict at Question 9), and the district court found on post-trial motions that an ordinarily skilled artisan "would not have had a reasonable expectation that recombinantly-produced interferon-β would be biologically active." Appx81 (JMOL Op.) (citing Appx80949 (75:8–19), Appx80950–80951 (76:9–80:2); Appx80475–80478 (61:23–64:13), Appx80481–80485 (67:10–71:21), Appx80486–80487 (72:24–73:23)). The jury heard evidence that prior to the '755 Patent, "no human glycoprotein had ever been expressed in E. coli," Appx80472 (58:1–10), and that it was an "open question"—that is, no one knew—whether E. coli's "primitive simple protein synthesis machinery" would be able to produce interferon-β that folds into the appropriate three-dimensional structure to render it biologically active. Appx80478 (64:4–13). The jury further heard that prior to the '755 Patent, producing biologically active recombinant interferon-beta "would have taken much more than routine experimentation," Appx80950–80951 (76:20–77:19), and that world-leading scientists of far more than ordinary skill tried and failed to do so, Appx80956–80960 (82:3–86:15); *see also* Appx80900 (26:10–20).

Appellants have not even raised obviousness on appeal, and thus the non-obviousness of the claims are law of the case. *Suel v. Sec'y of Health & Human Servs.*, 192 F.3d 981, 986 n.2 (1999). While Appellants make much of statements Dr. Fiers made to the Canadian Patent Office, Br. at 63, the jury heard them and rejected Appellants' arguments. The Appellants make the conclusory assertion that "Biogen is bound by these sworn admissions." Br. at 63. But the district court rejected this argument with a detailed explanation of why the authorities cited by Appellants do not support their premise. Appx46445–46447 (SJ Op.); Appx83 (JMOL Op.). Appellants offer no argument as to why the district court's reasoning is incorrect.

If the claims of the '755 Patent were not obvious it follows that they cannot have involved only well-understood, routine, conventional techniques. While Appellants cite the passage of *Mayo* addressing the interplay of Sections 101 and 103, Br. at 64, they get it backwards: the *Mayo* Court held that claims that involve only routine techniques can be invalid under Section 101 without reaching Section 103; the Court did not suggest that non-obvious steps beyond the reach of ordinarily skilled artisans could be "routine and conventional." Likewise, in *Smartflash*, the defendant asserted both Section 101 and Section 103 on appeal, preserving both issues. *See Smartflash LLC v. Apple Inc.*, 680 F. App'x 977, 984 (Fed. Cir. 2017) (non-precedential).

No case has ever held or suggested that non-obvious claim elements could somehow be routine and conventional. That makes no sense. A jury finding of non-obviousness, unchallenged on appeal, precludes a finding that the elements of a claim are routine and conventional at Step 2 of the *Alice* analysis. Thus, even if this Court were to reach Step 2, the '755 Patent claims would be patent-eligible.

CONCLUSION

For the reasons set forth above, the Court should affirm the district court's judgment that Serono and Pfizer have infringed the asserted claims of the '755 Patent and that the patent is not invalid.

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Respectfully submitted,

/s/ Nicholas Groombridge

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CERTIFICATE OF SERVICE

I, Robyn Cocho, being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

Counsel Press was retained by PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP, Attorneys for Plaintiff-Appellee to print this document. I am an employee of Counsel Press.

On **July 3, 2019**, Counsel for Appellant has authorized me to electronically file the foregoing **Brief of Plaintiff-Appellee** with the Clerk of Court using the CM/ECF System, which will send notice of such filing to the following registered CM/ECF users:

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) and this Court's June 13, 2019 Order permitting Biogen to exceed those limitations by 1,000 words. The brief contains 14,794 words, excluding parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b). The word count includes the words counted by the Microsoft Word 2010 function. This brief also complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6). The brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in 14-point font of Times New Roman.

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