No. 19-1133

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.

Appeal From The United States District Court For The District of New Jersey,
Case No. 2:10-cv-02734-CCC-MF, Hon. Claire C. Cecchi

CORRECTED PRINCIPAL BRIEF FOR EMD SERONO, INC. AND PFIZER INC.

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

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Biogen Idec 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)

EMD Serono, 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
EMD Serono, Inc.	EMD Serono, Inc.	Merck KGaA

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:

Gibson, Dunn & Crutcher LLP: Joshua Krevitt, Robert A. Vincent, Katherine Q. Dominguez, Blaine H. Evanson, Raymond LaMagna, Minae Yu, Alexander P. Swanson, Michael A. Sitzman, David Glandorf, Tracey B. Davies, Tanya Mazur*, Amanda Tessar*, Megan Fluckiger*, Ellen Lin*, Amelia Marguet*

Gibbons P.C.: David De Lorenzi, Charles H. Chevalier, Christine A. Gaddis, Sheila F. McShane*, Ricardo Solano, Jr.*, Carrie A. Longstaff*, James June-Ho Kang*

*no longer associated with the respective firm

FORM 9. Certificate of Interest **Form 9**
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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).

None

4/15/2019
Date

/s/ Mark A. Perry
Signature of counsel

Please Note: All questions must be answered

Mark A. Perry
Printed name of counsel

cc: All counsel of record via CM/ECF

Reset Fields

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

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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

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CERTIFICATE OF INTEREST

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

Pfizer 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
Pfizer Inc.	Pfizer Inc.	None

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:

Gibson, Dunn & Crutcher LLP: Joshua Krevitt, Robert A. Vincent, Katherine Q. Dominguez, Blaine H. Evanson, Raymond LaMagna, Minae Yu, Alexander P. Swanson, Michael A. Sitzman, David Glandorf, Tracey B. Davies, Tanya Mazur*, Amanda Tessar*, Megan Fluckiger*, Ellen Lin*, Amelia Marguet*

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None

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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, counsel for appellants EMD Serono, Inc. and Pfizer Inc. state that no appeal in or from this same proceeding was previously before this Court or any other court.

The judgment for Biogen MA, Inc. and against EMD Serono, Inc. and Pfizer Inc. (collectively "Serono," unless otherwise specified) should be reversed.

INTRODUCTION

The asserted claims, which recite a method of administering recombinant interferon-beta ("IFN-β") to treat viruses and other conditions, completely lack novelty. Throughout trial, Biogen touted its self-described "treatment" patent, yet explicitly conceded that it adds *nothing new* to the treatment of any condition. Undisputed evidence established that, before the asserted priority date, other scientists discovered native IFN-β, and successfully used IFN-β to treat patients with viruses; moreover, other scientists were the first to invent recombinant IFN-β protein. Having heard this evidence, as well as substantial evidence that native and recombinant IFN-β are "identical," it's not surprising that the jury found the claims anticipated by prior-art uses of IFN-β. What is surprising is that the district court overturned that factual finding—erroneously concluding that a source limitation *alone* is sufficient to confer novelty, and erroneously applying a post-verdict claim construction that was inconsistent with the agreed jury instruction. Correcting the district court's errors requires reinstating the jury's verdict of anticipation.

STATEMENT OF JURISDICTION

The district court, which had jurisdiction under 28 U.S.C. §§ 1331 and 1338(a), entered a partial judgment on October 26, 2018. Appx81698-81700. Serono filed a timely notice of appeal on October 9, 2018. Appx81674-81677. This Court has jurisdiction under 28 U.S.C. § 1292(c)(2).

STATEMENT OF THE ISSUES

I. Whether the asserted claims are invalid because:

A. They were anticipated by the prior art; or

B. They are not enabled and lack sufficient written description.

II. Whether the asserted claims are not infringed because:

A. The steps of the method, properly construed, were not practiced in this country during the patent term; or

B. Serono lacked the scienter required for indirect infringement.

III. Whether the asserted claims are ineligible for patenting.

STATEMENT OF THE CASE

After a jury found U.S. Patent No. 7,588,755 invalid as anticipated, the district court ruled as a matter of law that the claims are not invalid, that Serono is liable for both induced and contributory infringement, and that the patent is eligible under 35 U.S.C. § 101. *See* Appx7-98.

1. The '755 patent claims a method of treating viral and other diseases by administering a therapeutically effective amount of a composition comprising recombinant polypeptides related to human interferon-beta (IFN-β). *See* Appx99-143.

a. IFN-β is made naturally by the human body as part of the immune system's defense against viruses. *See* Appx77849, Appx77872 (23:15-19), Appx77873-77874 (24:3-25:8); Appx118 (1:38-44). Long before the asserted priority date in 1980, clinicians successfully administered "native" IFN-β (harvested from human cells) to treat patients with viral diseases. *See*, *e.g.*, Appx118 (2:53-55); Appx47748, Appx47752, Appx47827, Appx47829; Appx79634, Appx79711-79712 (77:16-78:18); Appx79047, Appx79080-79081 (33:15-34:11), Appx79090-79093 (43:9-46:25), Appx79138-79139 (91:21-92:14), Appx79141 (94:5-9); Appx77874-77875 (25:13-26:25); Appx80874, Appx81047-81049 (173:24-175:22), Appx81050 (176:18-22). Before 1980, Serono (in collaboration with Dr. Michel Revel) developed a native IFN-β product, Frone. Appx 80071, Appx80079-80080 (8:4-9:6), Appx80083 (12:23-25), Appx80086-80087 (15:13-16:19).

Due to clinical successes with native IFN-β, scientists sought to produce greater quantities of IFN-β using known recombinant DNA techniques—specifically, isolating from human cells the particular DNA sequence encoding IFN-β, inserting that DNA into a host cell ("transformation"), and inducing the transformed

host to produce IFN-β ("production"). Appx79532, Appx79580 (49:11-22), Appx79583 (52:11-16).

Before 1980, scientists had transformed *E. coli* bacterial hosts and induced them to produce recombinant human proteins. Appx78613, Appx78648-78649 (35:19-36:20); Appx79693-79694 (59:16-60:9), Appx79695 (61:14-24), Appx79698-79699 (64:19-65:11); Appx47784-47787 (¶¶ 58, 60); Appx48120-48124; Appx51689-51693.

b. In 1980, Dr. Walter Fiers and Biogen filed the first of a series of patent applications that they would prosecute for the next three decades. Biogen sought to patent IFN-β DNA and the IFN-β protein itself, but these inventions were awarded to others. *See Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993) (DNA); *Biogen MA, Inc. v. Japanese Found. for Cancer Research*, 785 F.3d 648 (Fed. Cir. 2015) (protein), *cert. denied*, 136 S. Ct. 1450 (2016).

The '755 patent, which issued on September 15, 2009, claims a method of administering a composition comprising IFN-β-related "polypeptides" produced in non-human hosts transformed by a recombinant DNA molecule. Appx142 (independent claim 1); *see also* Appx142-143 (dependent claims 2 and 3, which specify DNA and amino acid sequences). The specification explicitly defines "polypeptide" as a "linear array of amino acids connected one to the other by peptide bonds." Appx121 (8:62-64). Such "polypeptides" form the backbone of IFN-β proteins,

which fold in various ways. Appx79703-79705 (69:14-71:6), Appx79709 (75:20-21). Biogen claimed the use of IFN-β *polypeptides* (not proteins). It was undisputed that none of the polypeptides Dr. Fiers produced was ever used to treat any condition in any patient. Appx77311, Appx77389-77391 (79:24-81:1); Appx77513, Appx77593 (82:13-23); Appx79831, Appx79853 (22:13-18); Appx81050 (176:8-17). Indeed, Biogen conceded at trial that the '755 patent specification discloses nothing new about treatment using IFN-β that was not already disclosed in the prior art. *See*, *e.g.*, Appx77721, Appx77727-77728 (7:1-8:3); Appx81047-81049 (173:22-175:2), Appx81049-81050 (175:15-176:25); Appx79090 (43:2-8). Rather, the '755 patent focuses on the production of IFN-β polypeptides from transformed host cells. Appx77721, Appx77727-776728 (7:1-8:3); Appx81047-81050 (173:22-176:25); Appx79090 (43:3-8). According to the specification, "[t]his invention allows the *production* of these polypeptides in amounts and by methods hitherto not available." Appx120 (6:57-59) (emphasis added).

c. In the 1980s, Serono's Dr. Revel produced recombinant IFN-β in mammalian Chinese Hamster Ovary ("CHO") cells. Appx80095-80098 (24:15-27:5). In 1984, Dr. Revel applied for a patent that he later received on that cell line, which is used to this day to make Serono's recombinant IFN-β product, Rebif. Appx80098-80100 (27:9-29:10); Appx51624-51636; Appx51601-51604.

In 1993, Rebif became the first recombinant IFN-β product approved anywhere in the world. Appx79369, Appx79379 (10:9-23). Rebif was approved for sale in the United States in 2002. Appx79385 (16:22-25). Serono then entered into a collaboration agreement with Pfizer, under which Pfizer was granted the right to promote (but not sell) Rebif, and Serono agreed to indemnify and defend Pfizer for any liability relating to Rebif. Appx49847, Appx49856-49860.

When the '755 patent issued in 2009, Biogen asked Serono if it intended to take a license pursuant to a pre-existing option agreement. Appx79387-79388 (18:25-19:4), Appx79406-79407 (37:10-38:12). Serono analyzed the patent and its file history to decide whether to do so. Appx79382 (13:9-24), Appx79388-79389 (19:5-20:1). Rebif was Serono's "most important medicine," and Serono knew it was important to get this analysis "right." Appx79406 (37:10-15).

Serono determined that the '755 patent claims require practicing the processes of transforming a host cell and producing IFN-β, which had to be carried out in the United States during the term of the patent to infringe. Appx79389 (20:2-8), Appx79390-79392 (21:25-23:15), Appx79413-79414 (44:24-45:9), Appx79509 (140:15-19); *see also* Appx3537, Appx3572-3573 (358:14-359:17). Because Serono did not perform either process in this country, or ever transform a host cell after the '755 patent issued (Appx79389-79390 (20:19-21:1)), Serono concluded that Rebif does not infringe the '755 patent claims, directly or indirectly, and therefore did

not exercise the option. Appx79419 (50:10-16). Pfizer—having been indemnified by Serono pursuant to its collaboration agreement—wholly relied on Serono's judgment and lacked "any independent knowledge or information regarding" the '755 patent. *See*, *e.g.*, Appx47438-47440 (20:09-15, 28:12-17).

2. On May 28, 2010, Biogen filed this infringement suit. *See* Appx144.

a. During claim construction, the district court rejected Serono's proposed interpretation that the claim limitations "produced by a non-human host" and "transformed by a recombinant DNA molecule" are process steps, adopting instead Biogen's construction that the claims require only a single step of "administering" the recombinant polypeptide. Appx6565, Appx6581.

b. Serono moved for summary judgment that the claims of the '755 patent are invalid under Section 112, and joined another motion for summary judgment that the asserted claims are invalid as anticipated by prior-art treatments using native IFN-β. *See* Appx10576; Appx82526-82529. The district court determined that "genuine factual disputes" remained for both invalidity defenses. Appx46437, Appx46450.

c. During trial, the district court held as a matter of law, over Serono's objection, that although a reasonable belief in non-infringement could negate liability for induced infringement, such a belief is "inapplicable to contributory infringement." Appx81087, Appx81093 (7:11-17); *see also* Appx81089-81096 (3:3-10:14);

Appx38 n.18. The court therefore precluded Serono from presenting evidence of or argument regarding its reasonable belief in non-infringement in response to Biogen's claim of contributory infringement, and refused to instruct the jury on this point. *See* Appx81102-81103 (16:23-17:5), Appx81154, Appx81188-81193 (35:4-40:18).

With respect to anticipation, the jury was asked to decide whether "the claims of the '755 patent are invalid as anticipated by prior art uses of native human interferon-beta." Appx68292, Appx68295. The jury was instructed that a "polypeptide" within the meaning of the '755 patent is "a linear array of amino acids connected one to the other by peptide bonds." Appx47633, Appx47651. Biogen did not object to this (or any other) instruction, or to the verdict form.

As to enablement and written description, over Serono's objection, the jury was instructed that "it is the method of treatment that must be enabled" and described, "not the proteins to be used or the way they are made." Appx81269 (116:10-11), Appx81271 (118:14-16).

After two days of deliberation, the jury returned a verdict that, among other things: the '755 patent claims are all invalid as anticipated; the claims are not invalid for lack of enablement or written description, or for obviousness; claims 1 and 2 of the '755 patent are directly infringed by patients and healthcare professionals taking and prescribing Rebif; and Serono contributed to, but did not induce, this infringement. *See* Appx68292-68297.

3. After trial, the parties filed cross-motions for judgment as a matter of law. The district court ruled in favor of Biogen, and against Serono, on each issue presented in this appeal. *See* Appx7-98.

a. The district court overturned the jury's verdict that the '755 patent is invalid as anticipated on the principal ground that prior-art uses of *native* IFN-β could not anticipate the use of *recombinant* IFN-β for the same purposes. Appx20-22. The court also applied a post-verdict claim construction that materially differed from the one given to the jury. Appx22-33.

The district court sustained the verdict that the patent is not invalid under Section 112 on the basis of its pre-verdict ruling that "it is not the genus of non-human hosts or recombinant polypeptides that must be enabled and described, it is the method of treatment that must be enabled and described." Appx86.

b. The district court overturned the verdict of no induced infringement, relying on the verdict of *contributory infringement* to conclude that "no reasonable jury could have concluded that Serono did not intend that Rebif be used for immunomodulation in the treatment of MS." Appx47.

The court sustained the verdict of contributory infringement by reiterating its trial ruling that "although a good-faith belief in a rejected claim construction can be asserted as a defense to negate the specific intent required to induce infringement,

such a belief is not a defense to negate the lesser knowledge requirement of contributory infringement." Appx38 n.18, Appx90-96.

c. Finally, the district court ruled that the claims of the '755 patent are patent-eligible. Appx68-75.

SUMMARY OF ARGUMENT

Invalidity. Substantial evidence supports the jury's finding that the prior-art use of native IFN-β to treat viral diseases anticipates the '755 patent claims, which cover the administration of recombinant IFN-β for the same therapeutic purpose. On JMOL, the district court overrode this factual finding on two grounds, both erroneous.

First, the court ruled that limiting the claims to IFN-β made by existing recombinant DNA technology—which the court characterized as a "source limitation"—alone sufficed to confer novelty. More than a century of authority, however, confirms that making an old product in a new way confers novelty *only* when it results in something *new*. Substantial evidence established that recombinant IFN-β polypeptides are *identical* to their native counterparts.

Second, the court ruled that the "proper analysis" is not whether the native and recombinant *polypeptides* "share the same linear amino acid sequence" (as the jury was instructed), but rather whether the "three dimensional structure" of the two *proteins* is the same. The court erred by applying a post-verdict construction that is both

wrong and inconsistent with the jury instructions. Even under that construction, however, there is substantial evidence that native and recombinant IFN-β "have the same three-dimensional structure." Appx50541.

Separately, the '755 patent does not adequately describe, or enable a person of ordinary skill to make, recombinant polypeptides in non-human hosts other than the one species of bacteria with which Dr. Fiers worked before the asserted priority date. The court erred in instructing the jury that the genus of non-human hosts need not be enabled or described. The court's post-verdict ruling on anticipation compounded this error, since the patent contains no enabling disclosure or description regarding "three-dimensional structure."

Non-Infringement. The district court failed to give effect to two positive process steps ("produced by" and "transformed by") required to practice the claimed method. Correcting this claim construction error requires reversal of the judgment of infringement, because these steps were not performed in the United States during the patent's term.

Even under the district court's erroneous claim construction, the jury was correctly instructed that Serono's reasonable belief that the use of Rebif does not directly infringe could negate the intent required for induced infringement. Substantial evidence established that Serono held such a belief, and the jury found Serono not

liable for inducement. Yet the district court overturned that factual finding, erroneously ruling that the verdict of *contributory* infringement compels a finding of induced infringement.

During trial, the district court erroneously ruled that, as a matter of law, "a good-faith belief in non-infringement" is "inapplicable to contributory infringement." Appx81093 (7:11-17). The jury was thereby precluded from considering Serono's good-faith belief that it does not infringe in deciding whether Serono had knowledge of the alleged infringement. The resulting verdict of contributory infringement cannot stand.

Ineligibility. The patent claims are directed to the natural phenomenon that IFN-β has antiviral properties, and the district court's ruling that method of treatment claims are categorically eligible is legally erroneous. The court also erred in relying on the verdict of non-obviousness rather than Biogen's admissions that the remaining claim elements were routine and conventional.

STANDARDS OF REVIEW

Anticipation is a question of fact, and the jury's verdict must be reinstated if supported by substantial evidence. *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1068 (Fed. Cir. 2017). Enablement is a question of law reviewed de novo, based on underlying factual inquiries reviewed for clear error. *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013).

Claim construction is a question of law reviewed de novo when based entirely on intrinsic evidence. *Avid Tech., Inc. v. Harmonic, Inc.*, 812 F.3d 1040, 1044-45 (Fed. Cir. 2016). The jury's verdict of no inducement must be reinstated if supported by substantial evidence. *See Kinetic Concepts, Inc. v. Blue Sky Med. Grp., Inc.*, 554 F.3d 1010, 1024 (Fed. Cir. 2009). The jury's verdict of contributory infringement rested on a legal determination that is reviewed de novo. *See Aristocrat Techs. Austl. PTY Ltd. v. Int'l Game Tech.*, 543 F.3d 657, 660 (Fed. Cir. 2008).

Patent eligibility is ultimately a legal question that "may contain underlying issues of fact." *Mortg. Grader, Inc. v. First Choice Loan Servs. Inc.*, 811 F.3d 1314, 1325 (Fed. Cir. 2016).

ARGUMENT

Serono independently developed, patented, received regulatory approval for, and sold its recombinant IFN-β product, Rebif, many years before the '755 patent issued in 2009. Biogen's request for more than $5 billion in damages fails because the asserted claims are not valid, not infringed, and not patent-eligible.

I. Invalidity

A. Anticipation

"[C]ase law from the Supreme Court and this Court has stated for decades that anticipation is a factual question." *Lighting Ballast Control LLC v. Phillips Elecs. N. Am. Corp.*, 790 F.3d 1329, 1340 (Fed. Cir. 2015) ("Anticipation is a question of fact that is ultimately for the jury to decide"). The jury in this case made the *factual*

finding that the claimed use of recombinant IFN-β was anticipated by prior-art uses of native IFN-β. Because that finding is supported by substantial evidence, it must be reinstated. *See Franklin Prescriptions, Inc. v. New York Times Co.*, 424 F.3d 336, 338-39 (3d Cir. 2005); *Lighting Ballast*, 790 F.3d at 1340.

1. Substantial Evidence

All claims of the '755 patent are directed to administering "compositions comprising" recombinant IFN-β "polypeptides." The jury was instructed that a "polypeptide" is "a linear array of amino acids connected one to the other by peptide bonds." Appx47651. This definition of "polypeptide" is set forth explicitly in the patent's specification. *See* Appx121 (8:62-64).

The jury heard undisputed evidence that the "linear array of amino acids" (*i.e.*, the "polypeptide") of native IFN-β is *identical* to recombinant IFN-β, including Serono's accused product, Rebif. Indeed, as part of its infringement case Biogen itself introduced evidence that "the amino acid sequence of Rebif® is identical to that of natural fibroblast derived human interferon beta." Appx66914. Similarly, the jury heard evidence from both parties regarding a "very detailed analytical chemistry" study (Appx80415, Appx80515-80516 (101:11-102:2) (the "InterPharm Study")), that unequivocally concluded that the "amino acid sequence of [recombinant IFN-β] …, when compared to the amino acid sequence of [native IFN-β] …, demonstrates

that *the sequences of both proteins are identical*." Appx50438, Appx50501 (emphasis added).

The jury also heard specific admissions by Biogen that the '755 "treatment" patent contributes *nothing* to any method of treatment with IFN-β, and that *everything* bearing on treatment in the '755 patent specification is from prior art dating as far back as the 1970s. *See*, *e.g.*, Appx77727-77728 (7:1-8:3); Appx81047-81050 (173:22-176:25); Appx79090 (43:2-8); *see also* Appx47826-47829.

Thus, there is substantial evidence that the claimed method is not new, as before the asserted priority date patients were treated for the same viral conditions with native IFN-β, including polypeptides *identical* to the claimed recombinant IFN-β. *See* Appx 81688; Appx52134-52138; Appx51651-51654; Appx51605-51619; Appx78-79 (2:53-4:13).

The jury was correctly instructed that "to be entitled to a patent, the invention must actually be 'new.'" Appx81262 (109:6-12). After receiving the court's charge (including the definition of "polypeptide" as "a linear array of amino acids"), the jury was specifically asked whether Serono had proved by clear and convincing evidence that "the claims of the '755 patent are invalid as anticipated by prior art uses of native human interferon-beta." Appx68295. Biogen did not object to the instructions or the verdict form.

The jury then made the factual finding that all claims of the '755 patent were anticipated by prior-art uses of native IFN-β for the treatment of viruses. Appx68203.

2. JMOL

Although the court stated that there was "insufficient evidence" to support the verdict of anticipation (Appx20), the court did not actually evaluate the sufficiency of the evidence considered by the jury under the unobjected-to instructions. Rather, the JMOL order regarding anticipation ultimately rests on two *legal* rulings—both erroneous.

a. Source Limitation

At trial, Serono introduced four prior-art publications, each of which discloses every element of the '755 patent claims: biologically active, human IFN-β meeting the DNA sequence limitations of claims 1 and 2, and the amino acid sequence limitations of claim 3, administered in therapeutically effective amounts to patients for treatment of viruses and other conditions. Appx51651-51654; Appx52134-52138; Appx51605-51623; Appx51702, Appx52017-52033; *see also* Appx118-119 (2:53-4:13) (discussing prior-art use of IFN-β to treat viruses and cancer); Appx68443, Appx68463-68470.

On JMOL, the court ruled that "[d]efendants failed to present as evidence a single prior-art reference that describes the therapeutic use of a *recombinant* interferon-β polypeptide"; rather, the prior art only "employed native, human interferon-β." Appx20-21 (emphasis added). The court stated that the production of IFN-β polypeptides using known recombinant DNA technology is a "source limitation." Appx33. The court ruled that the presence of this limitation alone suffices—*irrespective* of whether native IFN-β is identical to recombinant IFN-β—to defeat anticipation. This ruling contravenes established law.

The Supreme Court has long recognized that merely specifying that an old product is made by a new process is insufficient to confer novelty. *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884) ("While a new process for producing [an old product] was patentable, the product itself could not be patented, even though it was a product made artificially for the first time"); *Gen. Elec. Co. v. Wabash Appliance Corp*., 304 U.S. 364, 373 (1938) ("[A] patentee who does not distinguish his product from what is old except by reference … to the process by which he produced it, cannot secure a monopoly on the product by whatever means produced"). This longstanding rule of novelty applies to method claims reciting the use of an old product made by a new process. *Leggett v. Standard Oil Co.*, 149 U.S. 287, 289-90 (1893) (method claim directed to lining barrels with an old glue made by a new process "clearly anticipated").

This principle of novelty specifically applies where, as here, a source limitation is asserted to confer novelty in the context of therapeutic human proteins made by recombinant DNA technology. *Amgen Inc. v. Hoffman-La Roche Ltd*., 580 F.3d 1340 (Fed. Cir. 2009). For such a claim to be novel, merely reciting a process limitation (recombinant technology) is *not* sufficient; rather, the claimed product or method must *itself* be new. *Id.* at 1365 ("a claimed product shown to be present in the prior art *cannot be rendered patentable solely by the addition of source or process limitations*") (quoting *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 n.20 (Fed. Cir. 2003) (emphasis added)); *see also*, *e.g.*, *Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1354 (Fed. Cir. 2016); *SmithKline Beecham Corp. v. Apotex Corp.,* 439 F.3d 1312, 1317 (Fed. Cir. 2006); *In re Thorpe*, 777 F.2d 695, 697-98 (Fed. Cir. 1985); *Tri-Wall Containers, Inc. v. United States,* 408 F.2d 748, 750 (Ct. Cl. 1969).

Amgen, which considered whether a claim to recombinant human erythropoietin ("EPO") was anticipated by natural (urinary) EPO, identified the pertinent question as "*whether the production of EPO by recombinant technology resulted in a new product*, so that claim 1 was not anticipated by the urinary EPO of Dr. Goldwasser." 580 F.3d at 1367 (emphasis added); *see also ibid.* ("In other words, does the source limitation 'purified from mammalian cells grown in culture' *distinguish* recombinant EPO from Dr. Goldwasser's urinary EPO?"). *Amgen* held that "[t]o

prove invalidity, [the challenger] had to show that recombinant EPO was the same as urinary EPO, *even though urinary EPO was not made recombinantly*." *Id.* at 1370 (emphasis added). This is a question of *fact*. *See id.* at 1367-70.

The court below noted that, in *Amgen*, "the claims to recombinant EPO were not anticipated by the prior-art native EPO that had been isolated from human urine based on differences in carbohydrate structures between the recombinant protein and the native protein." Appx31. In *Amgen*, those "differences" were established by evidence so unequivocal that no reasonable jury could have found structural or functional identity. *See* 580 F.3d at 1367. For example, although recombinant EPO actually worked to treat anemia, the prior-art urinary EPO did not; indeed, it was a "failure." *Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 581 F. Supp. 2d 160, 168-69 (D. Mass. 2008).

Here, unlike in *Amgen*, it was undisputed that prior-art native IFN-β *is* therapeutically effective; and unlike in *Amgen*, Serono adduced substantial evidence that the recombinant and native products are identical. To be sure, Biogen introduced competing evidence, but this factual dispute was for the jury to resolve. Based on the trial evidence, the jury was asked whether the claimed method of treating viruses by administering IFN-β was a *new* method of treatment because of the manner in which the IFN-β was made (recombinant technology), or whether it was an *old* method of treatment because of the prior-art use of native IFN-β for the identical

therapeutic purpose, and therefore anticipated. *The jury decided that factual question against Biogen*, concluding that the use of recombinant IFN-β to treat viruses was not a new method of treatment, but an old one. And this finding is supported by overwhelming evidence of identicality, as summarized herein.

By providing a framework for evaluating *whether* a claimed recombinant product is anticipated by its native counterpart, *Amgen* makes clear that a recombinant DNA limitation alone is *not* sufficient to confer novelty. The district court's post-verdict ruling that the '755 patent is novel *solely* because it recites a recombinant "source limitation" should therefore be reversed.

b. Three-Dimensional Structure

The district court also ruled that the anticipation inquiry depends not on the "linear array of amino acids" that defines the claimed *polypeptide*, but rather on the "three-dimensional structure," including any carbohydrate groups, of *the entire IFN-β protein*. Appx22-33. This too was erroneous.

First, although the district court relied on a similar argument in denying summary judgment (*see* Appx 46437, Appx46464), Biogen *agreed* to jury instructions defining the "polypeptide" of the claims *not* as a three-dimensional structure, but rather as a "linear array of amino acids." Appx81250. A district court cannot overturn a jury verdict, and grant judgment as a matter of law, on a ground that was not properly preserved pursuant to Rule 51. *Franklin Prescriptions*, 424 F.3d at 339.

Second, the jury was instructed (without objection) that the claim term "polypeptide" is a "linear array of amino acids connected one to the other by peptide bonds"—precisely as that term is defined in the specification. Appx121 (8:62-64); *see also* Appx81246-81247 (93:21-94:7) ("You must accept my definitions of these words in the claims as being correct").

At trial, Serono and Biogen *both* presented evidence confirming that the "linear array of amino acids" of native IFN-β administered in the prior art is *identical* to the "linear array of amino acids" of recombinant IFN-β within the scope of the claims. Indeed, there was no evidence to the contrary, and Biogen itself relied on *precisely* this definition of "polypeptide" to secure a jury verdict of direct infringement. Appx77878-77880 (29:2-31:7) (Biogen's expert applying the agreed construction of "polypeptide" in establishing direct infringement); *see W.L. Gore Assocs., Inc. v. Garlock, Inc.*, 842 F.2d 1275, 1279 (Fed. Cir. 1988) ("Having construed the claims one way for determining their validity, it is axiomatic that the claims must be construed in the same way for infringement").

After the jury found the claims anticipated, the court ruled that the fact "[t]hat the native and recombinant interferon-β proteins share the same linear amino acid sequence is *not enough* for purposes of anticipation." Appx23-24 (emphasis added). "Rather," the court stated, "the *appropriate analysis* is to compare the three-dimensional structure of the prior-art native interferon-β with the recombinant interferon-

β of claim 1, which include the structures of any attached carbohydrate groups." Appx24 (emphasis added). The jury was never instructed on that analysis. On the contrary, the court instructed the jury that a "polypeptide" is a "linear" sequence. The court then overturned the jury's verdict by construing the term "polypeptide" to also include the "three-dimensional structure" of the entire protein of which the "polypeptide" is the backbone, contrary to the jury instruction and the controlling definition in the specification. *See Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1296 (Fed. Cir. 2010) (where patentee acts as his own lexicographer, "definition in the specification controls"). By changing the claim construction after receiving the jury's verdict, the court committed reversible error *regardless* of whether the court's post-verdict redefinition of polypeptide is correct (it is not, as discussed below).

A district court cannot charge the jury with one definition of a claim term, and then overturn a verdict faithful to that definition by using a fundamentally *different* definition on which the jury was never instructed. *Finjan, Inc. v. Blue Coat Sys., Inc.*, 879 F.3d 1299, 1306 (Fed. Cir. 2018) ("*It is too late at the JMOL stage to ... adopt a new and more detailed interpretation of the claim language* and test the jury verdict by that new and more detailed interpretation") (emphasis added) (quoting *Hewlett-Packard Co. v. Mustek Sys., Inc.*, 340 F.3d 1314, 1321 (Fed. Cir. 2003)). "When issues of claim construction have not been properly raised in connection with the jury instructions, *it is improper for the district court to adopt a new or more*

detailed claim construction in connection with the JMOL motion.... The verdict must be tested by the charge actually given." *Hewlett-Packard*, 340 F.3d at 1321 (emphasis added); *Wi-Lan, Inc. v. Apple, Inc.*, 811 F.3d 455, 466 (Fed. Cir. 2016) ("the post-verdict reconstruction altered the scope of the original construction and undermined . . . [the] invalidity case post-verdict").

The *only* relevant question on JMOL was "whether substantial evidence supported the verdict *under the agreed instruction*." *Hewlett-Packard*, 340 F.3d at 1320 (emphasis added). Here, the jury's verdict was supported by substantial evidence showing that native and recombinant IFN-β have "identical" amino acid sequences and are thus identical "polypeptides" under the court's jury charge. The district court therefore erred as a matter of law in adopting a post-verdict construction for JMOL that is not only "more detailed" than the jury charge (*ibid.*), but *inconsistent* with the construction the jury was obligated to follow. That error requires reversal of the JMOL order and reinstatement of the jury verdict.

i. The post-verdict construction is erroneous. The district court reasoned that "for a polypeptide to display [antiviral] activity, it *must be folded into its appropriate three-dimensional structure*." Appx23 (quoting Appx46464) (emphasis added). The court thus compared the three-dimensional structure of native IFN-β

protein to recombinant IFN-β *protein*, concluded that "the *proteins* differ structurally in terms of their attached carbohydrate (or sugar) groups," and overturned the jury verdict. *Ibid.* (emphasis added).

Biogen affirmatively chose to broadly define the claimed method based on the use of a "*polypeptide*," which it specifically defined as a "linear array of amino acids," rather than more narrowly defining its invention based on any three-dimensional structure formed around that amino acid backbone. The claim recites a "recombinant *polypeptide*," not a recombinant *protein*, thus *distinguishing* the "polypeptide" of the claim from the protein of which it is a part. *See* Appx142-143 (49:59-52:7).

The claims *separately* require that the polypeptide display "antiviral activity." Appx142 (50:6-8). Of course, this activity requires *a* three-dimensional structure, but neither the claims nor the specification require any *specific* three-dimensional structure. Biogen's claim construction expert admitted as much, testifying in a pretrial deposition that the '755 patent uses the term "polypeptide" rather than "protein" "to refer to a sequence of amino acids … *with no implication about its three-dimensional conformation*." Appx2537, Appx2538 (emphasis added); Appx82535-82536 (16:6-19:6).

Thus, the district court rewrote the claims, overturning the jury verdict of anticipation on the basis of a construction that was never presented to the jury and is manifestly incorrect.

ii. Even under the post-verdict construction, the claims are invalid. Contrary to the district court's conclusory assertion (Appx22), the record contains substantial evidence that native and recombinant IFN-β proteins are the same. By analogy to product-by-process law, the court separately analyzed "structural" and "functional" identity. Appx22-33. Regardless of whether this was the correct analytical approach, and while either would suffice to establish anticipation (*see Purdue Pharma*, 811 F.3d at 1354), the court was wrong as to both.

Structural Identity. The InterPharm Study, on which both parties relied at trial, explicitly concluded that "RECOMBINANT BETA INTERFERON DERIVED FROM CHO CELLS (RBIF) IS IDENTICAL TO HUMAN FIBROBLAST INTERFERON (HFIF)" (Appx50559), and that "the two protein molecules … have the same three-dimensional structure." Appx50541. This comparative study further concluded that "the antiviral activity of both interferons was neutralized completely by the anti beta antiserum … suggesting that beta RBIF [recombinant IFN-β] molecule is identical to HFIF [native IFN-β]." Appx50549; *see also* Appx50459, Appx50466, Appx50472, Appx50484, Appx50501, Appx50529, Appx50531,

Appx50535, Appx50545, Appx50553, and Appx50558 (each detailing ways in which the two proteins are "identical").

Additional evidence confirmed that "hamster cells glycosylate proteins *identically* to human cells." Appx51578 (9:56-58) (emphasis added); *see also* Appx66993, Appx67003 ("Natural interferon beta and [Rebif] are glycosylated with each containing a single N-linked complex carbohydrate moiety").

A second comparative study ("Kagawa") specifically analyzed the glycosylation patterns of native and recombinant IFN-β proteins, and concluded that each has a population of IFN-β molecules with multiple carbohydrate structures, two of which, I and V, are common to both native and CHO recombinant IFN-β proteins. Appx51643-51650; *see also* Appx79720-79723 (86:2-89:5). These common glycosylation structures account for *more than eighty percent* of native IFN-β molecules. Appx51646.

Accordingly, the patients described in the prior art whose viral conditions were treated with native IFN-β *necessarily* received "a composition *comprising*" native polypeptides that are atomically identical to recombinant polypeptides recited in the '755 patent claims. *Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) ("When a claim covers several structures or compositions . . . the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is

known in the prior art"); *Free Motion Fitness, Inc. v. Cybex Int'l, Inc.*, 423 F.3d 1343, 1353 (Fed. Cir. 2005).

Inexplicably, the district court stated that "there appears to be no evidence or testimony that the native interferon-β proteins used in the prior art are the same as the native proteins studied in [InterPharm and Kagawa]." Appx28. In fact, *Biogen itself* established that there is "*only one type* of naturally occurring interferon beta that we know of." Appx79149 (102:11-13) (emphasis added). There was no contrary evidence, and the parties never suggested that there were different "types" of native IFN-β. Indeed, during deliberations, the jury asked the district court to "[p]lease explain … [the] reference to 'native' human interferon beta as the basis for anticipation." Appx47701. With Biogen's agreement, the court provided the following definition of native IFN-β to the jury: "Interferon beta protein that is produced naturally by human cells." Appx47702.

From this and other evidence (*e.g.*, Appx 54315 ("[s]o far, only one species of human β-interferon has been isolated and described in detail"); Appx51625; Appx51569, Appx51578; Appx51643-51645; Appx50507, Appx50536; Appx52134), a reasonable jury could have concluded *correctly* that there is "only one type" of native IFN-β, it is a "protein that is produced naturally by human cells,"

it was given to patients in the 1970s to treat viruses, it was the subject of the Inter-Pharm and Kagawa comparative studies, and it is "identical" to Serono's accused product, Rebif.

Functional Identity. The jury also heard substantial evidence that native IFN-β functions in the same way as recombinant IFN-β. The '755 patent claims require an IFN-β polypeptide with antiviral activity. Appx142-143. IFN-β harvested from human cells has antiviral activity. *See*, *e.g.*, Appx119 (3:4-14); Appx77872 (23:15-19); Appx48089 (native IFN-β "has potent antiviral activity"). Biogen's expert on infringement explicitly testified that Rebif likewise has antiviral activity. Appx77905 (56:7-24). Moreover, the prescribing information (and product labels) for Rebif (and Biogen's Avonex) establish the antiviral activity of these recombinant IFN-β proteins. *See* Appx66993-67011; Appx66766, Appx66773. This evidence *alone* is sufficient to support functional identity, and there is more.

For example, the evidence showed that recombinant IFN-β has "the same physical properties and specific antiviral activity as the human product." Appx51574 (1:57-62). Additionally, the InterPharm Study concluded that "pure RBIF [recombinant IFN-β] and HFIF bulks [native IFN-β] have *identical antiviral potency*." Appx50556 (emphasis added). Dr. Lodish testified that the InterPharm Study showed "that *the biological function* of [the two proteins is] the same."

Appx79722 (88:5-7) (emphasis added). With respect to the Kagawa study, Dr. Lodish specifically testified that any "small differences" in the relative proportions of identical IFN-β molecules "do not affect the biological activity." Appx79722-79723 (88:18-89:5); Appx51625 (CHO recombinant IFN-β "appears identical in size, activity, and immunospecificity to the native human IFN-β[] glycoprotein").

The jury also heard evidence that an independent researcher (Jacobs) working with the *native* protein discovered that IFN-β could treat MS. *See* Appx78043-78044 (65:15-66:5). The evidence showed that Dr. Jacobs was able to continue his work on the treatment of MS with *recombinant* IFN-β precisely because the recombinant protein was "biologically active like native interferon beta." Appx78064 (86:2-17).

The district court, however, concluded that native and recombinant IFN-β "are not functionally identical." Appx29. The court asserted that the ability to mass produce recombinant IFN-β distinguished it from native IFN-β. Appx30-31. But this pertains to the process of making recombinant IFN-β—not the polypeptide itself—and cannot render either the polypeptide or its administration novel. The jury also heard that Serono was making and selling commercial quantities of its native IFN-β product, Frone. Appx80083 (12:23-25), Appx80086 (15:13-25).

The court also said that the jury heard about "different biological effects" of these two proteins, citing the testimony of Biogen's expert Dr. Kinkel.

Appx29. This is incorrect. Dr. Kinkel's cited testimony only compared the incidence of neutralizing antibodies *among various recombinant IFN-β products*; he never once compared *any* such product to *native* IFN-β, let alone determined any difference whatsoever in the development of neutralizing antibodies as between native and recombinant. Appx77990-77993 (12:16-15:18). Moreover, even if Dr. Kinkel had made such a comparison, it would amount at most to a *conflict* in the evidence—which was resolved in Serono's favor by the jury.

The court had no authority to prefer its understanding of Biogen's expert testimony to the contrary evidence submitted by Serono (or, more generally, to reweigh the evidence submitted at trial and disagree with the jury's assessment of it). *Ambrose v. Twp. of Robinson, Pa.,* 303 F.3d 488, 492 (3d Cir. 2002) (on JMOL, the court must view "the evidence in the light most favorable to the nonmovant [] giving it the advantage of every fair and reasonable inference"); *Lightning Lube, Inc. v. Witco Corp.*, 4 F.3d 1153, 1166 (3d Cir. 1993). This was not a bench trial—it was a jury trial. That the district court might not have reached the same conclusion is no basis for overturning the jury's verdict.

For all of the reasons set forth above, the jury verdict of anticipation should be reinstated.

3. New Trial

The district court also conditionally ordered a new trial on anticipation because the verdict was "against the great weight of the evidence." Appx36.

Under controlling Third Circuit law, however, a district court can grant a new trial on the basis that the verdict is against the weight of the evidence *only* "where a miscarriage of justice would result if the verdict were to stand," or "where the verdict, on the record, cries out to be overturned or shocks [the] conscience." *Williamson v. Consolidated Rail Corp.*, 926 F.2d 1344, 1352-53 (3d Cir. 1991); *Sheridan v. E.I. DuPont de Nemours and Co.*, 100 F.3d 1061, 1076 (3d Cir. 1996). "This limit upon the district court's power to grant a new trial seeks to ensure that a district court does not substitute its judgment of the facts and the credibility of witnesses for that of the jury." *Fineman v. Armstrong World Indus.*, 980 F.2d 171, 211 (3d Cir. 1992) (citations omitted).

Here, the district court did not find that the verdict would result in a "miscarriage of justice" or that it "shock[s] the conscience." *See Sheridan*, 100 F.3d at 1076, 1089 (holding that the district court failed to apply the "complete test for ruling on a new trial motion" where it "merely concluded that the jury's verdict was contrary to the weight of the evidence" without also finding a "miscarriage of justice"). Nor could it have, given the substantial contrary evidence in the record. Tellingly, *not*

once did the district court grapple with the countervailing evidence supporting the jury's verdict.

Rather, the court simply disagreed with the jury's verdict. *See* Appx36. But this was a *jury trial*, and the district court's disagreement with the verdict is no basis for the court to order a new trial, as the Third Circuit has repeatedly held. *See*, *e.g.*, *Lind v. Schenley Indus.*, 278 F.2d 79, 89 (3d Cir. 1960) (district judge "should not set the verdict aside as contrary to the weight of the evidence and order a new trial simply because he would have come to a different conclusion if he were the trier of the facts"); *Williamson*, 926 F.2d at 1353-54. Accordingly, the district court's grant of a new trial should be reversed, and the verdict of invalidity reinstated.

B. Enablement and Written Description

The jury's verdict that the patent is not invalid for lack of enablement or for insufficient written description (*see* Appx68295) was the result of an erroneous jury instruction to which Serono objected. Specifically, the court instructed the jury that "it is the method of treatment that must be enabled [or described], *not the proteins to be used or the way they are made*." Appx47670, Appx47672 (emphasis added). The court repeated this error in denying Serono's JMOL of invalidity under 35 U.S.C. § 112. Appx88. Reversal is required.

1. The claims of the '755 patent broadly encompass the use of recombinant IFN-β polypeptides made in host cells of *any species* except for humans.

Appx79725-79726 (91:15-92:8). But before the asserted priority date, Dr. Fiers worked only in *E. coli* bacteria (*see* Appx79720-79721 (86:22-87:2); Appx79726 (92:9-12)), and the pertinent disclosure in the 1980 specification is limited to such host cells (Appx79720-79721 (86:22-87:2); Appx49007, Appx49037-49092). Had the claims been limited to *E. coli* (or even all bacterial hosts) there would be no infringement, as Rebif is made in a mammalian host.

This Court has rejected under Section 112 claims to the use of host cells that extend beyond the scope of the work actually disclosed by the patent. For example, in *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991), the patent disclosed the inventor's work in a single cyanobacterium. This Court found that claims extending to a genus of host cells including all cyanobacteria were not supported by the inventor's work in a single species of that genus. *Id.* at 496; *see also*, *e.g.*, *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1362 (Fed. Cir. 2007) (claims to use of all plants, including monocots and dicots, as host cells invalid under Section 112 where patent disclosed only work in dicot cells); *Plant Genetic Sys. N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1346 (Fed. Cir. 2003) (same); *In re Goodman*, 11 F.3d 1046, 1052 (Fed. Cir. 1993) (same).

It follows *a fortiori* from these cases that Biogen cannot support claims to the far larger genus of all non-human host cells based on Dr. Fiers' work in a single species of bacteria. The '755 patent's disclosure before the asserted priority date is

limited to work conducted in single bacterial host cell (*E. coli*). The claims, however, extend to host cells from all bacteria, all prokaryotes, and all eukaryotes; in short, all of the approximately six million different (known) species of life on earth—save for *Homo sapiens*.

The '755 patent does not contain written description or enabling disclosure for any host cells other than *E. coli* bacteria, and no *properly* instructed jury could have found otherwise on the basis of the trial record. The jury here, however, was improperly instructed that "it is the method of treatment that must be enabled [or described], *not the proteins to be used or the way they are made*." Appx47670, Appx47672 (emphasis added). That instruction was inconsistent with precedent establishing that when a patent claims methods of using a genus of compounds, the patent must provide written description and enabling disclosure for the compounds that are to be used. *Univ. of Rochester v. GD Searle & Co., Inc.*, 358 F.3d 916, 926 (Fed. Cir. 2004) ("Regardless whether a compound is claimed *per se* or a method is claimed that *entails the use of the compound*, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound") (emphasis added); *see also Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385 (Fed. Cir. 2013); *Ariad Pharm., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1354-55 (Fed. Cir. 2010) (en banc); *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1375 (Fed. Cir. 1999).

The court's instruction was highly prejudicial, as it precluded the jury from considering the fact that the genus of *polypeptides* whose use is claimed is not enabled or described. In addition to preventing the jury from considering the glaring deficiencies in the '755 patent disclosure discussed above, the instruction prevented the jury from considering evidence showing that Biogen vastly overreached by claiming the administration of recombinant polypeptides made in *any* non-human host cells. Specifically, Serono presented evidence that techniques for producing recombinant polypeptides in hosts other than *E. coli*—including cells from yeasts, insects, plants, and non-human animals—simply had not been developed before the application was filed. *See* Appx79726-79728 (92:13-94:20). Indeed, Dr. Fiers declared under oath—and Biogen admitted—that "the *only* hosts that were available [in early 1980] for the expression of cloned DNA sequences were bacterial hosts." Appx47788 (emphasis in original); *compare also* Appx80464 (50:10-25) (recombinant protein expression was "nascent" field), *with Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 2004) (enablement of "[n]ascent technology" requires "'a specific and useful teaching'" of the full scope of the claimed invention) (quoting *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1368 (Fed. Cir. 1997)).

2. Both the jury's verdict and the post-verdict rulings on enablement and written description were based on the construction of "polypeptide" on which the jury

was instructed—*i.e.*, the linear array of amino acids. Appx47651. As discussed above, the district court redefined that term *after* the verdict to include the protein's "three dimensional structure . . . which include[s] the structures of any attached carbohydrate groups." Appx24. If this Court were to affirm the JMOL of no anticipation based on this post-verdict construction, then the same construction would also have to be applied in determining whether the claims are supported and enabled by the disclosure. *See Senmed, Inc. v. Richard-Allan Med. Indus., Inc.*, 888 F.2d 815, 818 n.7 (Fed. Cir. 1989) ("The same interpretation of a claim must be employed in determining all validity and infringement issues in a case") (citation omitted).

The patent contains no enabling disclosure or any written description regarding the three-dimensional structure of the IFN-β polypeptides, including any associated carbohydrate structures. For example, mammalian cells (such as the CHO cells used to produce Rebif) result in glycosylated proteins, whereas bacterial cells (such as the *E. coli* cells disclosed in the patent) do not. Appx79094 (47:12-21); Appx79680-79681 (46:17-47:3), Appx79719-79720 (85:11-86:21); Appx80473 (59:20-24). A correctly instructed jury would (or at least could) have concluded that the '755 patent neither enables nor describes making these IFN-β polypeptides in a wide range of hosts.

Accordingly, Serono is entitled to judgment as a matter of law that the patent is invalid under Section 112. At minimum, a new trial is required to permit a

properly instructed jury to determine whether the production of recombinant polypeptides in non-bacterial host cells was adequately described or enabled—a determination that the jury did not make due to both the erroneous instruction and the post-verdict construction.

II. Non-Infringement

The '755 patent claims a method for administering a composition comprising "a recombinant polypeptide *produced by* a non-human host *transformed by* a recombinant DNA molecule comprising a DNA sequence." Appx142 (49:64-66) (emphases added). A single question of claim construction—whether the "produced by" and "transformed by" limitations are process steps that must be performed to infringe the claims—affects all of the infringement issues in this case.

A. Direct Infringement

1. At the *Markman* stage, the district court concluded that the '755 patent "requires only a single method step" of administration, such that "the 'produced' and 'transformed' limitations … are merely descriptive of the recombinant polypeptide to be administered." Appx6575, Appx6579. That conclusion is wrong as a matter of law.

Claim Language. Claim construction begins with examining the plain meaning of the claim language to a person of ordinary skill in the art. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). Although the claim recites a "step" of

administering a compound, it goes on to describe this compound in process terms. Appx142 (49:61-63). A skilled artisan would understand that the specified polypeptide must be "produced by a non-human host" which has been "transformed by a recombinant DNA molecule," and that the best reading of these phrases is that they state process steps rather than properties of the polypeptide. *See*, *e.g.*, *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1291-95 (Fed. Cir. 2009) ("obtained by" is a "process term[]," which is a "defining limitation[] of the claim").

In *Monsanto*, the claims were similarly directed to a method ("obtaining progeny") of using a particular transgenic corn plant ("obtained by the process of claim 1"). 503 F.3d at 1355. Like Biogen, Monsanto argued that the "obtained by" language need not be performed during the term of the patent for there to be infringement, and instead only described the "starting material" for carrying out a single-step process. *Id.* at 1357-59. This Court disagreed, holding that "obtaining progeny" was one of four steps, the other steps being the process of producing the plant. *Id.* at 1358. Monsanto "might have used express language to clarify that it only invoked the product of the process … as a starting material, but did not do so." *Id.* The same is true here.

Claim terms "are interpreted as structural limitations" rather than process limitations only "when they are used in an adjectiv[al] non-process sense and adequately define a physical characteristic of the product or apparatus." 3 Chisum on Patents

§ 8.05[4] at 8-380 (2010); *see*, *e.g.*, *Gemtron Corp. v. Saint-Gobain Corp.*, 572 F.3d 1371, 1379 (Fed. Cir. 2009). The '755 patent uses "produced" and "transformed" as verbs, not adjectives, and as process steps rather than physical characteristics. *See* Appx142 (49:64-66); Appx1376, Appx1395 (¶32), Appx 1397 (¶34). Biogen's claim construction expert specifically admitted that these limitations define the process by which the recombinant polypeptide is *made* rather than any structural property. Appx82531, Appx82576 (179:5-180-11), Appx82576-82577 (181:18-183:25), Appx82578 (186:16-189:18). Biogen itself explained to the jury that its "invention is about" making "it possible to take this material produced by the body and *make it* artificially, *make it* synthetically…" Appx77232, Appx77244 (12:23-25) (emphases added).

Specification. The claim construction that "most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Phillips*, 415 F.3d at 1316; *see also Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1324 (Fed. Cir. 2008); *Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1316-17 (Fed. Cir. 2007). The '755 patent is entitled "DNA Sequences, Recombinant DNA Molecules and *Processes for Producing* Human Fibroblast Interferon-Like Polypeptides" (Appx118 (1:1-4)), and states that "*[t]his invention allows the production of those polypeptides* in amounts and by methods not hitherto available." Appx120

(6:57-59) (emphases added); *see also* Appx118 (1:15-28). The inventor's description of "the present invention" is strong evidence of the correct construction. *See Regents of Univ. of Minn. v. AGA Med. Corp.*, 717 F.3d 929, 936 (Fed. Cir. 2013); *Pacing Techs., LLC v. Garmin Int'l, Inc.*, 778 F.3d 1021, 1024 (Fed. Cir. 2015).

Prosecution History. During the long prosecution of the '755 patent, the Examiner observed with respect to what would become the asserted claims:

> The *positive process steps* in claims 31-34 of the instant ['755 patent] application and claims 31-34, respectively, of Serial No. 08/448,723 *are identical*. The only difference in the claims is in the preamble, i.e. the intended uses of the two processes. *Since the actual process steps of the two sets of claims are the same, the scope of the two sets of claims is the same*.

Appx53274-53277, Appx53275 (emphases added). Biogen *agreed* with the Examiner's characterization regarding "positive process steps." Appx47831, Appx47833-47834; *see Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1094, 1097 (Fed. Cir. 2013). Biogen amended pending claim 31 (which issued as claim 1 of the '755 patent) and represented that it now recited all of the intended uses "for the *positive process steps* claimed" therein. Appx47834.

Both the Examiner and Biogen read the claims of the '755 patent as reciting multiple "positive process steps," as would a person of skill in the art reviewing the file history. This Court has repeatedly relied on the meaning an applicant ascribes to its claims during prosecution, even when such statements do not rise to the level of clear and unmistakable disavowal required for disclaimer. *See*, *e.g.*, *800 Adept,*

Inc. v. Murex Sec., Ltd., 539 F.3d 1354, 1364-65 (Fed. Cir. 2008); *Schindler Elevator Corp. v. Otis Elevator Co.*, 593 F.3d 1275, 1286 (Fed. Cir. 2010).

Validity. Patents generally should not be construed so as to render them invalid. *Ruckus Wireless, Inc. v. Innovative Wireless Solutions, LLC*, 824 F.3d 999, 1004 (Fed. Cir. 2016); *Whittaker Corp. by Technibilt Div. v. UNR Indus., Inc.*, 911 F.2d 709, 712 (Fed. Cir. 1990). At claim construction, the district court rejected Serono's "argument that the process for making the recombinant polypeptide is the only thing that distinguishes the claim from the prior art," ruling that the argument was "directed to invalidity rather than claim construction." Appx6580 n.6.

Yet, after the jury found the '755 patent claims invalid as anticipated, the court reached the opposite conclusion and "agree[d] with Biogen that since the source limitation of claim 1 '*lies at the heart of the benefit of this invention,*' it should be given 'force and effect in the anticipation analysis.'" Appx35 (emphasis added) (citation omitted). This conclusion cannot be reconciled with the court's claim construction ruling that the producing and transforming limitations are "merely descriptive of the recombinant polypeptide to be administered," and that these steps that, according to the court, are the heart of Biogen's invention need not be performed for there to be infringement. Appx6578-6579. If the patent claims the process of mak-

ing the recombinant polypeptides, it is not infringed; if not, it is invalid as anticipated. Biogen cannot have it one way for infringement and the other way for validity.

2. Under the correct construction, Serono is entitled to judgment of non-infringement. There is no evidence that Serono produced Rebif from a transformed host cell in the United States during the term of the '755 patent. *See NTP, Inc. v. Research in Motion, Ltd.*, 418 F.3d 1282, 1318 (Fed. Cir. 2005); *Meyer Intellectual Props. Ltd. v. Bodum, Inc.*, 690 F.3d 1354, 1371 (Fed. Cir. 2012). The last time Serono transformed a host cell for Rebif was 1984, long before the '755 patent issued in 2009. Appx79369, Appx79389-79399 (20:19-21:1); Appx47525, Appx47528 (170:9-10). Likewise, it is undisputed that Serono has only ever made recombinant IFN-β abroad. *See*, *e.g.*, Appx79390 (21:2-17); Appx79414 (45:10-13); Appx47526-47527 (35:17-36:03); Appx47528 (170:10-15).

Thus, under the correct claim construction, no reasonable jury could find direct infringement by anyone. And without direct infringement, there can be no indirect infringement. *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 572 U.S. 915, 920-21 (2014). Accordingly, correcting the district court's erroneous claim construction requires entering judgment of non-infringement for Serono.

B. Indirect Infringement

While the district court concluded in 2016 that the "produced by" and "transformed by" limitations are not "positive process steps," Serono read the claims differently. Serono waived attorney-client privilege and submitted substantial evidence that it has reasonably believed at all times and in good faith—from the issuance of the patent until the present day—that the use of Rebif does not infringe, and that Pfizer wholly relied on Serono's evaluation. Thus, even if the district court's claim construction were affirmed, the judgment of indirect infringement would have to be reversed or vacated.

Internal Evaluation. Immediately after the '755 patent issued in 2009, Serono's in-house IP professionals studied the patent and its file history and concluded that the claims require not only administering IFN-β, but also transforming a host cell and producing a recombinant IFN-β polypeptide in that cell. *See*, *e.g.*, Appx79382 (13:9-17, 13:21-24); Appx79388-79389 (19:5-20:1); Appx79410-79411 (41:14-42:14); Appx79412 (43:1-7) ("I understood it to mean … that what you were administering first had to be made by a certain process which was transforming the host cell and producing the recombinant protein"); Appx47480-47481 (159:10-16); Appx47528-47529 (169:24-170:15, 173:02-174:05); Appx47483 (267:17-268:8).

Serono's internal analysis was based on the claim language and on statements in the specification indicating that the claims are directed to producing recombinant polypeptides. *See* Appx79388-79394 (21:25-25:21); Appx79395 (26:2-19); Appx79509 (140:15-19). It was also based on the file history, in particular statements by the Examiner *and by Biogen* indicating that the "produced by" and "transformed by" limitations are "positive process steps." Appx79396-79399 (27:22-28:3, 28:9-11, 28:14-21, 29:4-30:10); Appx79400-79402 (31:8-21, 32:17-24, 33:5-23, 33:24-34:4); Appx48678-48681, Appx48680; Appx47831, 47833.

The evidence further showed that Serono had *every incentive* to correctly interpret the '755 patent claims because, under a preexisting agreement with Biogen, Serono had an option to take a license to the patent if it determined one was necessary. Appx79561 (30:1-17); *see also* Appx79403-79404 (34:17-35:14); Appx79482 (113:3-9). The entire purpose of Serono's option right was to avoid future litigation with Biogen (Appx79415 (46:1-5)), and the jury heard that Serono "*would certainly have exercised the option*" had it concluded that it infringed. Appx79415 (46:1-9); Appx79561 (30:14-17) (emphasis added). Moreover, Serono had an indemnification obligation to Pfizer that further required accurate assessment of the infringement issue. Appx67392-67394.

Independent Advice. Serono immediately engaged a U.S. biotechnology patent lawyer, Roger Browdy, who had extensive experience in the field of recombinant IFN-β. Appx79403-79416 (34:17-35:10). Mr. Browdy's written analysis concluded that the claims "contain[] a process step of administering and also define[] the product that is administered by means of *the process steps of making the product, all of which must be conducted in order for there to be infringement*." Appx49996, Appx50022 (emphasis added); Appx79411-79414 (42:15-43:7, 44:10-45:9); *see also* Appx79410 (41:7-20); Appx79490-79491 (121:25-122:9); Appx50021 ("The claims of the '755 patent" are "drawn to a method of use of a product that [first] must be made by a specific process").

Just months later, Serono retained a second U.S. biotechnology patent lawyer, John White, who testified that he independently concluded (and advised Serono) that the claims reflect a combination of both "a method of treatment aspect *and a process of making the substance that was going to be administered*." Appx78502, Appx78524-78525 (22:16-23:7) (emphasis added); Appx78553-78554 (51:21-52:1); Appx79418 (49:13-16); Appx79568 (37:6-21); Appx68112, Appx68115; *see also* Appx78525-78526 (23:23-24:16); Appx78548-78549 (46:11-17, 47:9-13); Appx78553-78553 (51:18, 52:1).

In short, both Mr. Browdy and Mr. White read the '755 patent claims precisely as Serono had (*see*, *e.g.*, Appx79410-79411 (41:14-42:14); Appx79412 (43:1-7)),

and Serono relied on these opinions in concluding that Rebif does not infringe and deciding *not* to exercise its option to license the '755 patent. *See* Appx79414 (45:14-16).

Pfizer. Pursuant to Pfizer's and Serono's collaboration agreement and its contractual indemnification by Serono, Pfizer wholly relied on Serono to defend against Biogen's claims, and thus lacked "any independent knowledge or information regarding" the '755 patent or this litigation apart from Serono. *See*, *e.g.*, Appx47438-47439 (20:09-15); Appx47440 (27:21-28:04). Pfizer's liability thus stands or falls with Serono's—as the jury recognized in its indirect infringement verdicts. Appx68292, Appx68293-68294; c*f.* Appx95-96 (concluding on JMOL that Pfizer's liability for contributory infringement is intertwined with Serono's). With the exception of the "abandonment" theory (which is irrelevant to Pfizer, whose co-marketing activities concluded before the *Markman* ruling, *see* Appx78311, Appx78382 (72:15-18)), the arguments herein apply equally to Serono and Pfizer.

* * *

The district court instructed the jury that it could consider Serono's good-faith belief that it did not infringe in deciding induced infringement, but ruled as a matter of law that the same evidence must not be considered for deciding contributory infringement. Appx47656-47658. The jury thus returned a split verdict—finding no liability for induced infringement, but liability for contributory infringement. *See*

Appx68293-68294. The district court's post-verdict consideration of both claims was erroneous.

1. Induced Infringement

Although the verdict of no inducement is supported by substantial evidence, the district court overturned it on two erroneous grounds.

a. Abandonment

The district court ruled that Serono abandoned its reading of the patent claims after the court's 2016 claim construction decision, and that JMOL of induced infringement was therefore proper because the jury could not have concluded that Serono held a reasonable belief in noninfringement "at all times following the issuance of the '755 patent." Appx48. That conclusion was incorrect.

At trial, Serono's in-house patent counsel Mr. Einav testified that Serono "accepted" the district court's claim construction decision. *See*, *e.g.*, Appx79419 (50:3-9). The court interpreted this testimony to mean that Serono *agreed* with that adverse claim construction and abandoned its previously held view of non-infringement. Appx48 ("Serono no longer believed in its three-step claim construction"). That is *not* what Mr. Einav said, and it is not close. The trial testimony established nothing more than the fact that Serono recognized that the *Markman* ruling was binding on the parties. *See*, *e.g.*, Appx79443 (74:18-21) ("Q. Do you think [the district court's claim construction] is correct? A. This is the decision of the Court.

What I think is of completely no importance. This is the law and *I accept it as such*.") (emphasis added), Appx79445 (76:19-21) ("I will not disrespect this Court and this Jury by saying something different than what the Court has decided. The Court has decided in a certain way, *so I accept this decision*") (emphasis added). A litigant must accept an adverse ruling until it can be challenged on appeal; such acceptance does not, however, constitute agreement.

Serono identified below (*see* Appx72947, Appx72975-72979) additional evidence that Serono has *never* agreed with the district court's construction and *continues* to believe it does not infringe to this day. Mr. Einav specifically 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." Appx79442 (73:11-14 & 73:19-23) (emphases added). In fact, Biogen made precisely this point in its summation. Appx81312 (19:15-20) ("nearly two years after the Court ruled and systematically rejected every single [claim construction] argument advanced by Serono, they still won't admit that they have no reasonable belief in non-infringement"); *see also* Appx81310 (17:2-18). The court did not address any of this in its JMOL order.

The district court was obligated to give Serono "the benefit of all logical inferences that could be drawn from the evidence presented, resolve all conflicts in the evidence in [its] favor, and in general, view the record in the light most favorable to

[Serono]." *Williamson*, 926 F.2d at 1348. The court failed this obligation by unfairly reading only one portion of Mr. Einav's testimony. A reasonable jury could (indeed, would) have understood from all of the trial evidence that Serono *has never* relinquished its belief in the construction it is pursuing to this day. The court's judgment overturning the jury's verdict must accordingly be reversed.

b. Conflation

The court also ruled that, by finding contributory infringement, "the jury necessarily found that Serono 'knew that Rebif was being used by healthcare professionals and/or patients in a manner that infringes a claim of the '755 patent' and that 'Rebif has no substantial, non-infringing use.'" Appx47 (quoting Appx47658). The court then concluded that "[a]ccordingly, JMOL of inducement against Serono is appropriate because no reasonable jury could have concluded that Serono did not intend that Rebif® be used for immunomodulation in the treatment of MS." Appx47.

Although both inducement and contributory infringement require subjective *knowledge* of infringement (*Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2068 (2011)), inducement additionally requires "that the defendant possessed specific intent to encourage another's infringement *and not merely that the defendant had knowledge* of the acts alleged to constitute infringement." *DSU Med. Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1305 (Fed. Cir. 2006) (en banc) (citation omitted) (emphasis added); *see also*, *e.g.*, *Metro-Goldwyn-Mayer Studios Inc. v. Grokster,*

Ltd., 545 U.S. 913, 942 (2005) (Ginsburg, J., concurring) (although "active inducement liability" and "contributory liability" "overlap," they "*capture different culpable behavior*") (emphasis added); *Ricoh Co., Ltd. v. Quanta Computer Inc.*, 550 F.3d 1325, 1340 (Fed. Cir. 2008).

Here, the district court ruled that the jury verdict of contributory infringement mandated overruling the jury's verdict of no inducement, and thus conflated the *knowledge* of infringement required for contributory infringement with the knowledge *and specific intent* additionally required for inducement. This is contrary to the language of the statute and precedent distinguishing the intent requirement from the knowledge requirement.

Moreover, whether substantial evidence supports a jury's verdict must be determined only on the *evidence* adduced at trial. *Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc.*, 344 F.3d 1186, 1192 (Fed. Cir. 2003). The jury's contributory infringement verdict was not part of the "evidence" at trial, and thus it was improper for the district court to rely on it in overturning the jury's verdict of no induced infringement. In deciding JMOL, "a district court's proper analysis is squarely and narrowly focused on the sufficiency of the evidence.... *The jury's findings should be excluded from the decision-making calculus on a Rule 50(b) motion*, other than to ask whether there was sufficient evidence, as a legal matter, from which a reasonable jury could find for the party who prevailed at trial." *Chaney v. City of*

Orlando, Fl., 483 F.3d 1221, 1227-28 (11th Cir. 2007) (emphasis added); Wright & Miller*, Federal Practice & Procedure* § 2524. The infringement verdicts were not inconsistent in light of the different instructions and scienter requirements, but even inconsistency would not suffice to justify JMOL on inducement. *See U.S. v. Uzzolino*, 651 F.2d 207, 213 (3d Cir. 1981); *Chaney*, 483 F.3d at 1227-28.

Further, inducement requires both knowledge and intent that Rebif treats MS by "immunomodulation." On this subject, Serono introduced specific, objective evidence that the mechanism by which Rebif helps people with MS is not known. Specifically, the FDA-approved label for Rebif states that "[t]he mechanism(s) by which REBIF … exerts its therapeutic effects in patients with multiple sclerosis is unknown." Appx66993, Appx67003. The evidence also showed that *Biogen's own label* for its competing IFN-β product, Avonex, similarly states that this mechanism is "not known," and further states that "[t]he way AVONEX works in MS is not known." Appx66763, Appx66787; *see also* Appx66775.

This Court has repeatedly relied on evidence of a product's label in the context of induced infringement claims. *See*, *e.g.*, *Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 630–31 (Fed. Cir. 2015); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364–65 (Fed. Cir. 2003). Here, the product labels constitute substantial evidence supporting the jury's finding that neither Serono nor Pfizer intended to induce infringement.

In addition to the label evidence, Serono introduced expert testimony that "immunomodulation is a very general term" that "does not apply to any particular disease." Appx79120-79121 (73:8-74:3). The evidence also included testimony that Serono "had no evidence that ... selling interferon beta for treating MS that [there] was any correlation with immunomodulation." Appx47537 (248:6-9); Appx47481-47482 (169:13-23) ("Regarding the patent, I think [there is] … no way at that time the person had in mind under the wording immunomodulation to cover multiple sclerosis"); *see also* Appx47482 (174:6-175:7); Appx47582 (359:12-17).

The jury heard all this evidence and determined that Biogen failed to prove that Serono or Pfizer had the requisite knowledge and specific intent to induce infringement. In overruling that factual determination, the district court chose Biogen's evidence over Serono's evidence, concluding that Serono's evidence was "far *outweighed* by" Biogen's competing evidence. Appx42 (emphasis added).

This was a jury trial, and the jury was free to "discard or disbelieve" Biogen's evidence in favor of the substantial evidence that Serono and Pfizer lacked knowledge of the mechanism of action. *Med. Instrumentation & Diagnostics Corp. v. Elekta AB*, 344 F.3d 1205, 1225 (Fed. Cir. 2003) (the jury is free to "discard or disbelieve whatever facts are inconsistent with its conclusion"); *Thomas v. Conemaugh & Black Lick R. Co.*, 234 F.2d 429, 432-433 (3d Cir. 1956). By contrast,

the court was forbidden on JMOL from "weigh[ing] the evidence." *Ambrose*, 303 F.3d at 492.

Indeed, the court incorrectly stated that "there was no contrary testimony or evidence" regarding immunomodulation. Appx43. The court failed to appreciate that Serono's objective label evidence and supporting expert testimony pertains not only to the question of whether Rebif actually treats MS by immunomodulation (direct infringement), but also to whether Serono possessed the requisite *intent* that Rebif be used in an infringing manner (whether Serono *both knew and intended* that Rebif treat MS by immunomodulation).

By substituting its own evaluation of the facts for the jury's, by dismissing Serono's wide-ranging and objective evidence, and by overriding the jury's determination that there was insufficient evidence of knowledge and intent to infringe—a "determination particularly within the province of the trier of fact" (*Water Techs. Corp. v. Calco, Ltd.,* 850 F.2d 660, 669 (Fed. Cir. 1988))—the court improperly usurped the central role of the jury as fact-finder. The jury's verdict on induced infringement must be reinstated accordingly.

The district court also conditionally ordered a new trial on induced infringement because the verdict was "against the clear weight of the evidence." Appx48. For the same reasons discussed in connection with anticipation, the district court failed to apply the correct standard, and failed to make the necessary findings that

the verdict reflects a "miscarriage of justice" or "shocks the conscience," and accordingly the new trial order should be reversed.

2. Contributory Infringement

During trial, the district court ruled that, as a matter of law, "a good-faith belief of non-infringement bears on an accused infringer's specific intent," not knowledge of infringement, "and is therefore *inapplicable to contributory infringement*." Appx81093 (7:11-17) (emphasis added); *see also id.* at Appx81089-81096 (3:3-10:14); Appx38 n.12. That ruling contravenes controlling precedent.

In *Aro Manufacturing Co. v. Convertible Top Replacement Co.*, 377 U.S. 476, 488 (1964) ("*Aro II*") (emphases added), the Supreme Court held that Section 271(c) requires proving that the accused contributory infringer "*knew* that the combination for which his component was especially designed was *both patented and infringing*." The Supreme Court has twice confirmed in recent years that contributory infringement requires subjective, culpable knowledge of infringement. *Global-Tech*, 131 S. Ct. at 2068 ("the 'holding of *Aro II* has become a fixture in the law of contributory infringement under [Section] 271(c)'"); *Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1926 (2015) ("like induced infringement, contributory infringement *requires* knowledge of the patent in suit and *knowledge of patent infringement*") (emphases added); *see also Nalco Co. v. Chem-Mod, LLC*, 883 F.3d 1337, 1356 (Fed. Cir. 2018). Among other things, *Commil* recognized that *both* active inducement

and contributory infringement require "proof the defendant *knew the acts were infringing*," and that "*Global-Tech* was clear in rejecting any lesser mental state as the standard." 135 S. Ct. at 1928 (emphasis added).

Commil 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. *See ibid.* (holding that an accused infringer is not liable for indirect infringement if it "reads the patent's claims differently from the plaintiff," and if "that reading is reasonable"). Likewise, this Court has squarely held that a defendant's "belief in non-infringement, based on its reasonable claim construction argument, does negate the knowledge requirement of contributory infringement," even if the defendant's "claim construction argument" is ultimately held to be "incorrect." *Koninklijke Philips N.V. v. Zoll Med. Corp.*, 656 F. App'x 504, 523 (Fed. Cir. 2016).

Thus, an accused infringer who *subjectively believes that it does not infringe* because it reasonably reads the claims differently than the patentee lacks the culpable knowledge required for contributory infringement liability. *Commil*, 135 S. Ct. at 1928; *Unwired Planet, LLC v. Apple Inc.*, 829 F.3d 1353, 1363-64 (Fed. Cir. 2016) (the "proper focus of indirect infringement analysis is on the subjective knowledge of the accused infringer" for both induced and contributory infringement). Here, the

district court inexplicably ruled that such "subjective knowledge" does *not* include an actual and reasonable belief of non-infringement.

As a direct result of this error, Serono and Pfizer were found liable for a cause of action *requiring subjective knowledge of infringement*, but were precluded at trial from defending themselves by showing that they *lacked* such knowledge. Thus, Serono could not rely on the extensive evidence that it does not believe the sale of Rebif infringes. That evidence included Serono's good faith belief in a non-infringing claim construction as well as the Rebif label—which recites that the means by which Rebif works is "unknown"—and shows that both Serono and Pfizer lacked the knowledge required for contributory infringement. Likewise, Pfizer could not point to its limited role under the collaboration agreement with Serono, its complete reliance on Serono in defending against Biogen's allegations, or its lack of pre-suit knowledge of the '755 patent. Over objection, the district court refused to instruct the jury that it could consider their good-faith belief in non-infringement *at all* in connection with contributory infringement. Appx81093 (7:11-17); *see also* Appx81089-81096 (3:3-10:14); Appx38 n.12. That was reversible error.

The irony here is as palpable as it was consequential: the court *conflated* the scienter requirements of contributory and induced infringement in reversing the induced infringement jury verdict, yet *distinguished* between the two for purposes of

instructing the jury on the relevance of Serono's good faith belief in non-infringement.

Furthermore, while the district court sought (and received) assurance that Serono would adhere to the court's legal ruling and not mention Serono's reasonable belief of non-infringement in connection with the contributory infringement claim (Appx81186-81189 (33:7-36:4); Appx81192-81196 (39:5-43:18)), Biogen was free to tell the jury in summation that the defendants' reasonable belief of non-infringement was *irrelevant* to the claim of contributory infringement. *See* Appx81293, Appx81314 (21:18-23). Had the district court not precluded the jury from considering this evidence in connection with contributory infringement, a reasonable jury could *and would* have found against Biogen on contributory infringement, just as the *actual* jury in this case found against Biogen on induced infringement. To correct this legal error, a new trial on contributory infringement is required.

III. Ineligibility

The asserted claims are not patent-eligible under the two-step framework for applying 35 U.S.C. § 101. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1296-97 (2012); *Alice Corp. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014).

A. Natural Phenomenon

The asserted claims fail Step One of the *Mayo/Alice* framework because they are directed to the natural phenomenon that IFN-β has antiviral properties.

1. Claims that are directed to naturally occurring phenomena are not eligible for patenting. *Funk Bros. Seed Co. v. Kalo Co.*, 333 U.S. 127, 131 (1948) (bacteria that "perform[ed] in their natural way"); *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 761 (Fed. Cir. 2014) (synthetically created primers that "utilize[d] the innate ability of DNA to bind to itself" to form copies, merely "exploited" "this same [natural] function"); *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1375 (Fed. Cir. 2016) (detection method that relied on "a universal, inherent feature of human DNA").

Human cells naturally make IFN-β to protect the body from viruses, and the '755 patent claims the use of recombinant IFN-β for the same purpose. *See*, *e.g.*, Appx51702, Appx51714-51718. The method of administering a compound comprising IFN-β to treat viral diseases thus rests entirely, and exclusively, on the natural phenomenon that IFN-β has antiviral properties. *See Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743, 750 (Fed. Cir. 2019) ("To determine whether a claim is directed to an ineligible concept, we have frequently considered whether the claimed advance improves upon a technological process or merely an ineligible concept").

Although the '755 patent claims are limited to the use of recombinant IFN-β polypeptides, they cover the identical DNA and amino acid sequences of naturally occurring IFN-β. Indeed, claims 2 and 3 recite DNA and amino acid sequences that are made by the human body. Appx64401, Appx64533-64534; Appx77899-77900 (50:24-51:12). The Supreme Court has held ineligible claims to DNA artificially isolated from a human's genome that "did not create or alter any of the genetic information contained therein." *Ass'n for Molecular Pathology v. Myriad*, 133 S. Ct. 2107, 2116-17 (2013). As summarized above, substantial evidence established that the recombinant IFN-β polypeptides encompassed by the '755 claims are identical to native IFN-β.

As this Court recently explained, "the use of a man-made molecule is not decisive" of eligibility. *Athena*, 915 F.3d at 752. For example, this Court has held ineligible claims to man-made clones having no "markedly different characteristics from [the] donor animals," of which the clones were "exact genetic replica" (*In re Roslin Inst.*, 750 F.3d 1333, 1334, 1339 (Fed. Cir. 2014)), as well as claims to "amplifying" certain DNA sequences in a maternal blood sample and "detecting" in that sample the "paternally inherited" sequences, because none of the "genetic information encoded" in the sequences was "created or altered" (*Ariosa Diagnostics, Inc.*

v. Sequenom, Inc., 788 F.3d 1371, 1373-74, 1376 (Fed. Cir. 2015)). Here, the genetic information in the claimed recombinant IFN-β is identical to that of native IFN-β—including, critically, with respect to its antiviral properties.

2. The district court committed legal error in concluding that the claims are patent-eligible simply because Biogen characterizes them as disclosing a "method of treatment." *See* Appx70-73.

In *Mayo*, the Supreme Court held ineligible claims to a "method of optimizing therapeutic efficacy for treatment of a … gastrointestinal disorder" because the claims relied on the natural phenomenon that "concentrations of certain metabolites in the blood" are correlated with "the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." 132 S. Ct. at 1295-96. The Court held that, "[w]hile it takes human action" (administering the drug) "to trigger a manifestation" of that natural phenomenon, the phenomenon "itself exists in principle apart from any human action." *Id.* at 1297. The Court held that the "human action" of administration was not "sufficient to transform the nature of the claim[s]." *Id.* at 1297-98. The Court recognized that a different result might obtain for "a new drug or a new way of using an existing drug." *Id.* at 1302. Here, too, IFN-β's antiviral activity exists "apart" from any human action. Even more, the IFN-β recited in the '755 patent claims performs precisely the same functions for which the human body

makes and uses it, whereas the thiopurine drug recited in the *Mayo* claims performed no such natural function and the claims were still ineligible.

This Court has previously distinguished *Mayo* on the ground (among others) that "the claims in *Mayo* were not directed to a novel method of treating a disease." *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1134 (Fed. Cir. 2018), *cert. pending*, No. 18-807. The *Vanda* majority's eligibility determination ultimately rested on its conclusion that "the claims here are directed to a *specific* method of treatment for *specific* patients using a *specific* compound at *specific* doses to achieve a *specific* outcome." *Id.* at 1136 (emphases added); *see also Athena*, 915 F.3d at 752-53. In *Mayo*'s terms, *Vanda* involved a "new way of using an existing drug." *Vanda*, 887 F.3d at 1302; *see also Natural Alternatives Int'l v. Creative Compounds, LLC*, No. 2018-1295, --- F.3d ---, 2019 WL 1216226, at *4 (Fed. Cir. Mar. 15, 2019) (similar); *Endo Pharms. Inc. v. Teva Pharms. USA, Inc.*, No. 2017-1240 et al., --- F.3d ---, 2019 WL 1387988, at *5, 7 (Fed. Cir. Mar. 28, 2019) (holding patent-eligible claims to "a new treatment for an ailment" requiring "specific steps"). Here, in contrast, Biogen concededly did not "c[o]me up with a new way of treating some disease with beta interferon that had never been known before." Appx81424 (131:8-10). None of the IFN-β that Dr. Fiers made was "ever actually administered to a person for any purpose." Appx77389-77390 (79:24-80:3); Appx77594 (82:13-17); Appx81042-81043 (168:17-169:11).

Method of treatment claims are not categorically eligible (or, for that matter, ineligible). *Cf. Parker v. Flook*, 437 U.S. 584, 594 (1978). Like all claims challenged under Section 101, they must be analyzed under the *Mayo/Alice* framework to determine whether they are directed to a natural phenomenon, and if so whether they add any inventive concept. The claims here are drawn to the natural phenomenon that IFN-β has antiviral properties, and (as in *Mayo*) the human action of administering—without any dosage or other limitations—will not suffice because (unlike *Vanda*) the claims here involve neither a new drug nor a new way of using an existing drug. Thus, the only remaining question is whether the claims also recite an inventive concept.

B. Inventive Concept

The asserted claims fail Step Two of the *Mayo/Alice* framework because the elements, individually and in ordered combination, recite only well-known, routine, and conventional techniques to apply the natural phenomenon that IFN-β has antiviral properties by administering it to treat viral diseases.

There is no inventive concept here. Biogen conceded at trial that it was not the first to discover the DNA sequence of IFN-β, and likewise admitted that it was a third party—not Biogen—who first invented recombinant IFN-β. *See*, *e.g.*, Appx77251 (19:10-23); Appx81051-81053 (177:11-179:10). Although Biogen has maintained that the inventive aspect of the '755 patent is administering recombinant

IFN-β to treat viral diseases (*see*, *e.g.*, Appx81638-81639), this entails nothing but well-known, routine, and conventional techniques—as Biogen itself has admitted.

Dr. Fiers submitted a sworn affidavit to the Canadian Patent Office attesting that native IFN-β was "well known before 1979 and had long been used by that date to treat human tumors and viruses," and that it was "straightforward" for recombinant IFN-β to "be used to prepare compositions for use in treating human tumors and viruses *just as native* [or natural] beta interferon had been used to prepare those compositions for many years." Appx47749, Appx47826-47829 (¶¶ 93(a),(c)) (emphasis added), Appx47830. Biogen is bound by these sworn admissions. *In re Cygnus Telecomms. Tech., LLC, Patent Litig.*, 536 F.3d 1343, 1347, 1354 (Fed. Cir. 2008); *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1374 (Fed. Cir. 2005).

Similarly, the '755 patent acknowledges that native human IFN-β had long been administered to patients in therapeutically effective amounts for treating viral diseases. Appx118-119 (3:4-4:22, 2:53-55). Biogen's own technical expert witness likewise testified that the '755 patent claims "no new method of treatment" and "no new methods of administration" of IFN-β, and that—just as Dr. Fiers had confirmed—"all of the information about treatment, actual treatment, that is in the '755 patent *comes from the understanding of clinicians and scientists* about how *native*

interferon-beta was used in the *1970s*." Appx81048-81049 (174:11-175:14) (emphases added); Appx81050 (176:2-4, 176:18-22); Appx81077 (203:13-15); Appx81078 (204:15-18); *see also id.* Appx81049-81050 (175:15-22, 175:23-176:7).

The district court recognized that the evidence adduced at trial in connection with obviousness "bears on" the post-verdict eligibility determination. Appx73. Yet the court failed even to consider these admissions by Biogen and its representatives, which establish that the asserted claims involve routine and conventional activities that cannot transform the claims—which attempt to monopolize the natural phenomenon that IFN-β has antiviral properties—into patent-eligible inventions. *See Berkheimer v. HP Inc.*, 881 F.3d 1360, 1368-69 (Fed. Cir. 2018), *cert. pending*, No. 18-415. Instead, the court pronounced that its resolution at Step Two would be "guided by the jury's verdict on obviousness." Appx74. That was reversible error. *See Mayo*, 132 S. Ct. at 1298 (emphasizing that eligibility is distinct from obviousness); *Smartflash LLC v. Apple Inc.*, 680 F. App'x 977, 984 (Fed. Cir. 2017) (holding patent ineligible claims following jury verdict of non-obviousness). While the district court failed to discharge its obligation to make an independent determination whether the claim elements supply an inventive concept, this Court may do so on the record developed below, which admits of only one conclusion—the asserted claims are ineligible.

* * *

Because the '755 patent claims are directed to the natural phenomenon that IFN-β has antiviral properties that remedy viral diseases, and are limited to administration of IFN-β for that conventional purpose without disclosing anything else that could remotely be considered an inventive concept, they are not patent-eligible under Section 101.

CONCLUSION

The judgment of the district court should be reversed. The asserted claims are invalid; they are not infringed; and they are ineligible.

Respectfully submitted,

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