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

REPLY 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*

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*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

7/31/2019
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

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FORM 9. Certificate of Interest **Form 9**
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UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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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:

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None

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ARGUMENT

Over the course of a five-week trial, Serono and Pfizer proved that Biogen invented *nothing*. They meticulously established, with clear and convincing documentary and testimonial evidence, that the treatment of viruses with IFN-β was known in the prior art, that others invented biologically active recombinant IFN-β proteins, and that recombinant and native IFN-β polypeptides are *identical*. A properly instructed jury made the *factual finding* that the claimed use of recombinant IFN-β polypeptides to treat viruses was anticipated. The district court erred as a matter of law in substituting its own evaluation of the evidence for the jury's on this quintessentially factual issue.

I. Invalidity

A. Anticipation

The jury was asked whether "the claims of the '755 patent are invalid as anticipated by prior art uses of native human interferon-beta." Appx68292, Appx68295. The jury answered in the affirmative, and the district court had no basis to overturn that factual finding. Accordingly, the verdict of anticipation should be reinstated.

1. Substantial Evidence

"Judgment as a matter of law is 'sparingly invoked' and 'granted only if, viewing the evidence in the light most favorable to the nonmovant and giving it the advantage of every fair and reasonable inference, there is insufficient evidence from

which a jury reasonably could find' for the nonmovant." *E.I. du Pont De Nemours & Co. v. Unifrax I LLC*, 921 F.3d 1060, 1067 (Fed. Cir. 2019) (quoting *Marra v. Phila. Hous. Auth.*, 497 F.3d 286, 300 (3d Cir. 2007)).

Incredibly, nowhere does Biogen even *recite* the applicable standard for JMOL, let alone apply it. Instead, Biogen repeatedly emphasizes the *district court's* "findings" and evidence that might have supported a *different* verdict. *E.g.,* BiogenBr. 15, 19, 23, 25, 29. But this was a jury trial, not a bench trial; the jury was free to "discard or disbelieve" Biogen's evidence and rely instead on the contrary (and overwhelming) evidence in the record that nothing in the claims of the '755 patent is new. *Med. Instrumentation & Diagnostics Corp. v. Elekta AB*, 344 F.3d 1205, 1225 (Fed. Cir. 2003). On JMOL, "although the court should review the record as a whole, it must disregard all evidence favorable to the moving party that the jury is not required to believe." *Reeves v. Sanderson Plumbing Prods.*, 530 U.S. 133, 150-51 (2000).

Biogen does not dispute on appeal that legally sufficient evidence supports the anticipation verdict under the unobjected-to instructions. *See* SeronoBr. 16. "When the jury is supplied with sufficient valid factual information to support the verdict it reaches, that is the end of the matter. In such an instance, the jury's factual conclusion may not be set aside by a JMOL order." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1355 (Fed. Cir. 2001).

The jury was correctly instructed that "to be entitled to a patent, the invention must actually be 'new.'" Appx81262 (109:5-12). Serono and Pfizer proved at trial, and Biogen's witnesses admitted, that the '755 patent contributes *nothing new* to any method of treatment, and that everything concerning treatment in the patent was taught in prior art dating back to the 1970s. *See* SeronoBr. 1, 5, 15. On appeal, Biogen does not contend that it invented any new method of treating any disease; rather, it asserts only that it was "the first to recombinantly express [biologically active] interferon-beta-like proteins." BiogenBr. 7. But even this invention, which is not a method of treatment, was awarded to others over Biogen. *Biogen MA, Inc. v. Japanese Found. for Cancer Research*, 785 F.3d 648 (Fed. Cir. 2015), *cert. denied*, 136 S. Ct. 1450 (2016); Appx61173 (3:12-20).

The jury made the *factual finding* that all claims of the '755 patent were anticipated by prior-art uses of native IFN-β. Appx68295. That finding is supported by clear and convincing evidence. Multiple prior art references disclosed that physicians had successfully treated patients with viral conditions using native IFN-β. *See* SeronoBr. 15; BiogenBr. 9. The jury heard undisputed evidence that the "linear array of amino acids" of recombinant IFN-β (the "polypeptide" of the claims) is *identical* to that of native IFN-β. SeronoBr. 14-15. Biogen does not dispute these facts, nor could it. No more is required to reinstate the verdict of anticipation.

2. JMOL

The JMOL order should be reversed, and the anticipation verdict reinstated, because the district court erred as a matter of law in (a) concluding that the recombinant "source limitation" *alone* suffices to confer novelty, and (b) adopting a post-verdict claim construction that contradicts the agreed jury instruction. *See* SeronoBr. 16-30.

a. Source Limitation

The *sole* point of novelty asserted by Biogen is that the claims are drawn to treating viruses with IFN-β polypeptides made *recombinantly*, whereas the prior art discloses treating viruses with native IFN-β polypeptides. BiogenBr. 15-16. Biogen does not dispute that every other limitation of the claims is in the prior art. The district court's adoption of Biogen's "source limitation" argument (Appx35) was erroneous. *See* SeronoBr. 16-20.

Although this is now Biogen's principal challenge to the anticipation verdict (and its principal defense of the JMOL order), Biogen failed to preserve this argument at trial. Biogen did *not* argue in its Rule 50(a) motion that the source limitation was alone sufficient to confer novelty. On the contrary, Biogen argued—unsuccessfully—that the anticipation question should be taken away from the jury based *only* on alleged differences between recombinant and native IFN-β polypeptides. *See* Appx81206 (53:16-21).

Moreover, Biogen *agreed* that the jury should answer the factual question of whether "the claims of the '755 patent are invalid as anticipated by prior art uses of native human interferon-beta." Appx68295. By doing so Biogen *agreed* that the claimed source limitation itself is *not* sufficient to confer novelty (otherwise, there would be no reason to include the question on the verdict form), and thereby waived the argument that it now advances on appeal. *See Inter Med. Supplies, Ltd. v. EBI Med. Sys., Inc.*, 181 F.3d 446, 463 (3d Cir. 1999); *Whelan v. Teledyne Metalworking Prods.*, 226 F. App'x 141, 146 (3d Cir. 2007). *After* the jury rendered its verdict, Biogen took the contrary position that *regardless* of whether the polypeptides are identical, the recombinant source limitation suffices to confer novelty.

Biogen's reliance on the recombinant source limitation is misplaced. "'[A] claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations.'" *Amgen Inc. v. Hoffman-LaRoche Ltd.*, 580 F.3d 1340, 1365 (Fed. Cir. 2009) (quoting *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 n.20 (Fed. Cir. 2003)). In *Amgen*, the issue of novelty was: "does the source limitation . . . distinguish recombinant EPO from [native] EPO?" *Id.* at 1367. The answer was not an automatic "yes," as Biogen would have it; rather, novelty turned on the factual inquiry "whether the production of EPO by recombinant technology resulted in a *new product*, so that claim 1 was not anticipated by the [native] EPO of [the prior art]." *Id.* (emphasis added).

Amgen applied the well-established principle that applicants cannot sidestep the novelty requirement by claiming an old product—or an old method of using an old product—merely by reciting a source limitation. *See*, *e.g.*, *Leggett v. Standard Oil Co.*, 149 U.S. 287 (1893); *Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345 (Fed. Cir. 2016); *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261 (Fed. Cir. 2012); *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312 (Fed. Cir. 2006). If two products are identical, then a recombinant source limitation does not confer novelty on a claim to the product or a non-novel method of using that product.

Biogen asserts—without authority—that this principle of novelty should apply only to product claims, and not to method claims reciting the use of a product. BiogenBr. 18-19. This argument is foreclosed not only by logic but by *Leggett*, which evaluated whether a claimed *method of using a product made in a particular manner* was novel. *See* BayerBr. 11-12 & n.4. As here, the prior art disclosed the same use for the same product, made in a different manner; and, as the jury did here, the Supreme Court found the method claim invalid as anticipated. *Leggett*, 149 U.S. at 297. Biogen attempts to distinguish *Leggett* as involving obviousness rather than anticipation. *See* BiogenBr. 17-18. But the Court was explicit that the "alleged invention was clearly *anticipated* by the prior *use* . . . of liquid glue," which destroyed "[t]he patentee's claim of *novelty*" because the claimed "*use* of the liquid glue before drying differed in no essential respect from the *use* of the liquid glue

which had been obtained by melting the dried glue of commerce." *Leggett*, 149 U.S. at 295 (emphases added). While there may have been additional bases for invalidity, the Supreme Court squarely held that the old use (coating barrels) of an old product (liquid glue) made in a different way (obtained before drying) is *not novel*.

While *Amgen* and some other precedents were decided in the context of product claims (in particular, product-by-process claims), the reason why source limitations alone do not avoid anticipation is grounded in the statutory requirement of *novelty*—it has nothing to do with claim drafting. "It has long been the case that an old product is not patentable even if it is made by a new process." *Amgen*, 580 F.3d at 1366 (citing *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938)); *see also Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884). An applicant cannot make an end-run around the novelty requirement by the simple expedient of drafting a claim to an *old method* of using an *old product* made by a particular process. *Cf. Providence Rubber Co. v. Goodyear*, 76 U.S. (9 Wall.) 788, 796 (1869) ("Both may be new, or both may be old. In the former case, both would be patentable; in the latter neither.").

According to Biogen, the recombinant source limitation alone is insufficient to make a *product* claim novel, but that *very same* source limitation somehow confers novelty on the non-novel use of the *very same*, non-novel product in a *method* claim. That position has no basis in law or reason, and would exalt the *form* of the

claim over its substance—which is no more acceptable under Section 102 than it is under any other provision of the Patent Act.

"As the Supreme Court has explained, the form of the claims should not trump basic issues of patentability." *Bancorp Servs., L.L.C. v. Sun Life Assurance Co. of Can. (U.S.)*, 687 F.3d 1266, 1277 (Fed. Cir. 2012) (citing *Parker v. Flook*, 437 U.S. 584, 593 (1978)). Biogen cites no case holding that novelty turns on any distinction between method and product claims. The two patent-eligibility cases upon which Biogen relies (BiogenBr. 17) say no such thing, and indeed the Supreme "Court has long warn[ed] . . . against interpreting § 101 in ways that make patent eligibility 'depend simply on the draftsman's art.'" *Alice Corp. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2351 (2014) (alterations in original; some internal quotation marks omitted) (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.,* 566 U.S. 66, 71-72 (2012)); *see also*, *e.g.*, *Quanta Comput., Inc. v. LG Elecs., Inc.*, 553 U.S. 617, 629 (2008) ("Eliminating exhaustion for method patents would seriously undermine the exhaustion doctrine" because "[p]atentees seeking to avoid patent exhaustion could simply draft their patent claims to describe a method rather than an apparatus"); *Dig.-Vending Servs. Int'l, LLC v. Univ. of Phoenix, Inc.*, 672 F.3d 1270, 1276 (Fed. Cir. 2012).

The '755 patent recites method claims, not magic claims. Whether a claim is drawn to a product or a method, it must be drawn to something *new*. Just as "one

cannot avoid anticipation by an earlier product disclosure by claiming . . . the product as produced by a particular process" (*SmithKline Beecham*, 439 F.3d at 1317), neither can Biogen avoid anticipation of an *old method* (treating viruses) by claiming the use of an *old product* (IFN-β) produced by a particular process (recombinant technology).

b. Three-Dimensional Structure

i. The jury was instructed that a "polypeptide" within the meaning of the '755 patent claims is a "linear array of amino acids." Appx47633, Appx47651. That instruction, to which Biogen did not object, was *correct*. The specification defines "polypeptide" *exactly* as the jury was instructed. Appx121 (8:62-64). Patentees are entitled to act as their own lexicographers, and when they do so their explicit definition controls. *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1296 (Fed. Cir. 2010).

The evidence was undisputed that native IFN-β "polypeptides" (amino acid sequences) are *identical* to recombinant IFN-β polypeptides within the scope of the '755 patent claims. SeronoBr. 14-15. Biogen does not deny this. *See* BiogenBr. 19. The jury's anticipation verdict was therefore faithful to the jury charge *and* the record evidence, and should be reinstated for that reason alone. *Lough v. Brunswick Corp.*, 86 F.3d 1113, 1119 (Fed. Cir. 1996) ("When a legal issue is submitted to a jury without an objection, we treat the jury's verdict on the legal issue as a resolution of all genuinely disputed underlying factual issues in favor of the verdict winner").

After the verdict, and at Biogen's invitation, the district court ruled that it was *not sufficient* that the linear arrays of amino acids are identical (as they undisputedly are). Rather, the court ruled that "*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 [*i.e.*, glycosylation]." Appx24 (emphasis added). But Biogen never asked that the jury be instructed to consider *that* analysis; instead, Biogen *agreed* with the explicit definition of "polypeptide" actually given to the jury.

There is a profound difference between a "*linear* array of amino acids" on the one hand, and the "*three-dimensional* structure" of the entire protein on the other. *See* SeronoBr. 21-22. Biogen does not even *try* to reconcile the court's post-verdict construction with the jury charge; rather, Biogen simply asserts, without citation to the jury instructions, that the district court "used the *same claim construction* in . . . its jury instructions, and its JMOL ruling." BiogenBr. 22 (emphasis added). That is false. At Biogen's urging, the court *materially changed* the construction after receiving the jury's verdict. This was reversible error and independently requires reinstating the jury verdict of anticipation. SeronoBr. 20-23.

ii. Even under the district court's erroneous post-verdict claim construction, the court erred in entering judgment for Biogen because the trial record contains

more than substantial evidence that recombinant and native IFN-β *proteins* are structurally and functionally identical. SeronoBr. 25-30. To sustain the JMOL order, Biogen must show that *no* reasonable jury could have reached a verdict of anticipation under the post-verdict construction. *Amgen*, 580 F.3d at 1367. It has not even come close to doing so.

Structural Identity. The InterPharm Study expressly establishes that the "beta RBIF [recombinant IFN-β] molecule is *identical* to HFIF [native IFN-β]," and that "the two protein molecules . . . have the *same three-dimensional structure.*" Appx50549; Appx50541 (emphasis added). The overall conclusion of the InterPharm Study is unequivocal: "RECOMBINANT BETA INTERFERON DERIVED FROM CHO CELLS (RBIF) IS IDENTICAL TO HUMAN FIBROBLAST INTERFERON (HFIF)." Appx50559. This evidence alone requires reversal of the judgment for Biogen.

Biogen argues that the InterPharm Study "acknowledge[s] structural differences" between recombinant IFN-β and native IFN-β. BiogenBr. 24 (emphasis omitted). One of Biogen's citations is to the background section of the study, which addresses protein glycosylation *in general*, but contains no discussion whatsoever of IFN-β. Appx50504. Biogen also cites a section of the study comparing the glycosylation structures of native and recombinant IFN-β, which expressly concludes that "the major structure of [recombinant IFN-β] is constituted by a biantennary glycan

chain *identical in its structure* to that of HFIF [native IFN-β]." Appx50529 (emphasis added). Neither that passage nor anything else in the InterPharm Study compels the finding that Biogen urges.

Biogen suggests that not all native IFN-β molecules are identical (BiogenBr. 25-26), a factual assertion it never made before the jury returned its verdict. As Biogen does not dispute, the parties, their witnesses, and the district court all proceeded on a common understanding that there is only *one* instantiation of the native IFN-β protein. *See* SeronoBr. 27. Indeed, Biogen itself established that "there is only one type of naturally occurring [IFN-β]," and did not suggest otherwise even in response to a question from the jury. *Id.* (internal quotation marks omitted). The jury necessarily found that recombinant and native *polypeptides* are identical, and the evidence does not compel the opposite conclusion with respect to the *proteins*.

Biogen seizes upon Dr. Lodish's testimony that the glycosylation structures are "substantially identical." BiogenBr. 23. As the Kagawa study shows, *populations* of IFN-β —whether made recombinantly or in human cells—include variations in the glycosylation structures of individual protein molecules. Appx51643-51650; SeronoBr. 26-27. Kagawa establishes that the overwhelming majority of glycosylation structures in native and recombinant IFN-β, and thus the proteins themselves, are *atomically identical*. SeronoBr. 26-27; Appx51646 (Table III, Structures I & V). Accordingly, Dr. Lodish testified that these *populations* are "virtually identical"

(Appx79634, Appx79721 (87:3-9)) but differ in their "relative proportion" of particular glycosylation structures. Appx79722 (88:9-25).

Biogen's patent claims a method of treatment with "a therapeutically effective amount of *a composition comprising* . . . a recombinant [IFN-β] polypeptide . . . ." Appx142 (49:61-64) (emphasis added). The term "comprising" means that the claim is open-ended: The composition must include but is *not limited to* the polypeptides of the claims. *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997). Kagawa shows that more than eighty percent of the specific glycosylation structures—hence IFN-β molecules—in native and CHO recombinant IFN-β are *identical*. Appx51643-51650. Accordingly, the patients in the prior art who were treated with native IFN-β *necessarily* received a "therapeutically effective amount of *a composition comprising*"—*i.e.*, including but not limited to—IFN-β that is identical in every respect (including glycosylation) to what is claimed, even under the post-verdict construction. SeronoBr. 3, 26-27. Having chosen to draft "comprising" claims, Biogen cannot avoid anticipation by arguing that the patients in the prior art who were treated with native IFN-β may *also* have received some IFN-β with *non-identical* glycosylation structures.

Functional Identity. Serono introduced substantial evidence that native IFN-β has antiviral activity—the *only* functional characteristic of IFN-β recited anywhere in the '755 patent—as well as substantial evidence of various other ways that native

and recombinant IFN-β are functionally identical. *See* SeronoBr. 28-29. In response, Biogen points to nothing that compels the opposite conclusion.

For example, Biogen argues that recombinant IFN-β differs from native IFN-β because recombinant proteins can be mass-produced. BiogenBr. 29-30. That is a difference in how the proteins are *made*, not how they *function*. The law has long been settled that increased availability of an artificial product does not confer novelty if its properties are identical to the natural product. *See* BayerBr. 15-16.

Biogen also argues that its expert witness, Dr. Kinkel, testified that recombinant IFN-β shows reduced efficacy due to antibodies that neutralize it. BiogenBr. 29. The jury did not have to accept Dr. Kinkel's testimony; regardless, he never testified that native IFN-β does not also induce the production of neutralizing antibodies, and there is no evidence to support Biogen's *ipse dixit* to the contrary. SeronoBr. 29-30.

3. New Trial

Biogen contends that anticipation received "scant attention . . . at trial." BiogenBr. 30. That assertion is belied by the clear and convincing evidence of anticipation summarized above and in the principal brief, on the basis of which the jury made the factual finding that Biogen invented nothing new. In retrospect, Biogen might wish that *it* had spent more time responding to the anticipation challenge; but

since appellants carried *their* burden of proof, that is no basis for repeating an extensive trial to which the parties and the judicial system have already devoted vast resources.

Biogen's rote invocation of the "weight of the evidence" standard (BiogenBr. 31) ignores the overwhelming evidence supporting the verdict. And like the district court, Biogen fails to heed the Third Circuit's admonition "that a district court should grant a new trial on the basis that the verdict was contrary to the weight of the evidence *only where a miscarriage of justice would result* if the verdict were to stand." *Sheridan v. E.I. DuPont de Nemours & Co.*, 100 F.3d 1061, 1076 (3d Cir. 1996) (en banc) (internal quotation omitted; emphasis added); *see also* SeronoBr. 31-32, 53-54. Biogen does not even try to show that reinstatement of the anticipation verdict would work a miscarriage of justice. Reversal of the conditional new trial order is required.

B. Enablement and Written Description

The district court erred in instructing the jury—over appellants' objection, and at Biogen's insistence—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); *see* SeronoBr. 32-37.

1. Biogen's principal argument is that because the '755 patent claims a method, the product or compound used in that method need not be enabled and described. BiogenBr. 32-34. This Court has already rejected that very argument as "a semantic distinction without a difference." *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004); *see also Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1355 (Fed. Cir. 2010) (en banc).

As explained in *Rochester*, "[r]egardless 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*." 358 F.3d at 926 (emphases added). Biogen does not address this holding, or dispute that it requires reversal if applied to this case. *See* SeronoBr. 34.

Biogen seeks to distinguish *Rochester* on the ground that the "essence of the invention" in that case was the compounds rather than the method of using them. BiogenBr. 35 (emphasis omitted). Yet, the district court (at Biogen's urging) found that "the source limitation of claim 1 'lies at the heart of the benefit of the invention.'" Appx35 (citation omitted). In any event, the "essence of the invention" approach finds no support in this Court's decisions. *Cf. Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 344-45 (1961) ("there is no legally recognizable or protected 'essential' element, 'gist' or 'heart' of the invention in a combination patent").

Biogen cites only one appellate decision for its assertion that "the written description requirement is not the same for claims to the use of a class of compounds as for claims to the class of compounds itself." BiogenBr. 32 (citing *In re Herschler*, 591 F.2d 693, 701 (C.C.P.A. 1979)). While *Herschler* indicates that the claimed method of using compounds may affect the *specificity* of the written description required, it does not hold that a method of using a compound need not describe or enable the compound *at all*. Yet that is what the jury was instructed here.

2. Biogen's fallback position is that any instructional error was harmless because there was evidence that the patent discloses the *existence* of many host cells. BiogenBr. 37. But the trial evidence showed that while host cells other than *E. coli* had been used for different purposes, those cells had not been—and could not be—used for recombinant protein expression by a skilled artisan before the asserted priority date. SeronoBr. 35-36. Biogen has no response to this point.

In several recombinant technology cases, this Court has held that inventors who *work* with a limited number of host cells cannot broadly *claim* inventions concerning an expansive range of host cells without describing and enabling those inventions in the full range. SeronoBr. 33. These decisions invalidated *narrower* claims, measured against *later* priority dates—when advancing technology had increased the abilities of skilled artisans. Biogen's response that "[t]he patents in those cases claimed a genus of host cells" (BiogenBr. 33) is both misleading (*see*

Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1368 (Fed. Cir. 1999) (invalidating method claims)) and non-responsive (*see Ariad*, 598 F.3d at 1355) (compounds used must be described)). Since Dr. Fiers worked only with *E. coli*, a properly instructed jury could conclude that the patent is invalid because it neither describes nor enables the making or use of recombinant IFN-β polypeptides produced in "*any* non-human host cell."

3. If the Court were to affirm the JMOL on anticipation, it would also have to declare the patent invalid under Section 112, or at minimum order a new trial on that issue. The district court's post-verdict claim construction materially affects the Section 112 analysis, because the patent does not describe or enable *any* three-dimensional structures. SeronoBr. 36. Biogen's response that this argument was not presented to the jury (BiogenBr. 38) is rich, considering that it arises *only* because of the district court's *post-verdict* construction—which Biogen itself requested. Biogen does not dispute that the same construction must be applied in assessing validity under Sections 102 and 112. *See* SeronoBr. 36.

* * *

At bottom, Biogen argues that the recombinant source limitation alone confers novelty on its claims, yet the way in which the claimed polypeptides are recombinantly made need not be described or enabled. Both statements cannot be correct; in fact, both are wrong.

II. Non-Infringement

A. Direct Infringement

The central claim construction dispute is whether administration is the only step in the method, as the district court concluded, or whether the "produced by" and "transformed by" limitations of the claims are also process steps, as the intrinsic evidence indicates. *See* SeronoBr. 37-42. Biogen maintains that it "never once said that claim 1 comprises more than one step." BiogenBr. 46. In fact, both the Examiner and Biogen referred to the claims now asserted as having "positive process steps" (plural). SeronoBr. 40. According to Biogen, "[t]he Examiner was talking about multiple claims in the aggregate" (BiogenBr. 46); but Biogen itself described a *single* claim (which issued as claim 1 of the '755 patent) as having "positive process steps." Appx47834. While Biogen now calls this "a typographical error" (BiogenBr. 46), at trial its prosecution counsel denied that this was a "mistake." Appx77808-77809 (88:12-89:3).

A skilled artisan, reading the claim language in light of the specification and prosecution history, would understand the claimed method requires the "positive process steps" (Appx53275) of transforming a host cell and producing a recombinant polypeptide in addition to the administering step. Appx78502, Appx78524 (22:16-25); *see also* SeronoBr. 45. Under that construction, there is no direct infringement (and thus no indirect infringement) because Rebif has never been produced in the

United States, let alone from host cells transformed during the term of the '755 patent. SeronoBr. 42.

B. Indirect Infringement

1. Induced Infringement

Inducement liability requires "proof the defendant knew the acts were infringing." *Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1928 (2015). The district court, at Biogen's urging, inferred such knowledge *solely* from the verdict on contributory infringement. Appx47. This was legal error, as the verdict on that separate issue was *not evidence*. SeronoBr. 49-51. This error *alone* is reason enough to reverse the JMOL and reinstate the jury's verdict of no induced infringement. Biogen does not even address this independent ground for reversal.

Instead, Biogen attempts to defend the JMOL by *flipping* the burden of proof, urging that Serono and Pfizer failed to *disprove* the element of specific intent. Thus, Biogen's very first argument is that "*No Evidence Supported a Conclusion That Appellants Did Not Intend That Rebif® Be Used To Treat Multiple Sclerosis Through Immunomodulation*." BiogenBr. 49 (emphasis added). Similarly, Biogen's second argument is that "*The Record Evidence Cannot Support a Conclusion That Either Appellant Lacked Specific Intent Because of a Belief in a Three-Step Claim Construction*." BiogenBr. 53 (emphasis added).

Biogen's effort to saddle appellants with Biogen's own evidentiary shortfalls violates the basic principle that "[t]he burden always is on the patentee to show infringement." *Under Sea Indus., Inc. v. Dacor Corp.*, 833 F.2d 1551, 1557 (Fed. Cir. 1987); *see also*, *e.g.*, *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008) (the "burden to prove infringement . . . [n]ever shifts to" the defendant); *Imhaeuser v. Buerk*, 101 U.S. 647, 662 (1880) (same).

In the district court, Biogen tendered no direct evidence of Serono's or Pfizer's specific intent to cause infringement. Its circumstantial evidence, as summarized by Biogen, showed only that "Pfizer's sales force promoted Rebif® for multiple sclerosis to healthcare professionals, and distributed prescribing information instructing them how to use Rebif®," and that "Serono, too, marketed and sold Rebif® with instructions on how to administer it to treat multiple sclerosis." BiogenBr. 48 (citations omitted). Even assuming the jury credited these facts, they do not even establish knowledge of infringement—much less specific intent to infringe.

"To establish inducement, a patent owner must show that the accused infringer induced the infringing acts and knew or should have known that its actions would induce actual infringement. *It is not enough to simply intend to induce the infringing acts*." *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1331-32 (Fed. Cir.

2010) (emphasis added; citation omitted); *see also Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990) ("It must be established 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 inducement"). The jury was not required to draw from Biogen's evidence the inference that appellants *specifically intended* to cause infringement. Thus, even before considering appellants' contrary evidence, Biogen failed to prove specific intent to infringe.

Although they had no burden to *disprove* culpable intent, both Serono and Pfizer introduced substantial *affirmative* evidence that they lacked any knowledge of infringement or specific intent to infringe, which the jury was entitled to credit. SeronoBr. 43-46.

Immunomodulation. Substantial evidence contradicted Biogen's allegation that appellants "know" that Rebif treats MS through immunomodulation. SeronoBr. 51. Indeed, the FDA-approved label for Rebif—as well as for Avonex, Biogen's IFN-β product—explicitly states that the mechanism of action is "not known." SeronoBr. 51 (citing Appx66993, Appx67003; Appx66763, Appx66787; Appx66775-66776). Although Biogen relies on its *expert's* testimony to dismiss the significance of the labels (BiogenBr. 52-53), the jury was not obligated to credit that testimony. *Med. Instrumentation*, 344 F.3d at 1225. The jury was entitled to rely on the labels

themselves—on which Biogen itself relies as circumstantial evidence of scienter—to conclude that the way Rebif treats MS is "not known" and that, accordingly, neither Serono nor Pfizer "knows" that it works via immunomodulation.

Serono also presented the unequivocal testimony of its Director of Intellectual Property that Serono did *not* understand that Rebif treats MS via immunomodulation. SeronoBr. 52. Biogen does not address this evidence.

Subjective Belief in Non-Infringing Claim Construction. Serono waived privilege and submitted wide-ranging evidence of its subjective, good-faith belief in a non-infringing claim construction. SeronoBr. 43-46. While Biogen asserts that "no reasonable jury could have found that Serono's belief in its noninfringing construction was objectively reasonable" (BiogenBr. 55), Biogen fails to address the extensive evidence of reasonableness—including that two independent biotechnology patent lawyers read the claims exactly the same way as Serono. *See* SeronoBr. 43-46.

Biogen's *only* support for its contention that Serono's belief was unreasonable is an incomplete excerpt of Mr. Einav's trial testimony, from which Biogen argues that *after* the 2016 claim construction order "Serono understood it had been wrong in its belief in non-infringement." BiogenBr. 54-55. Even if Serono abandoned its belief in the proper interpretation of the patent claims in 2016 (it did not, SeronoBr. 47-49)—*fourteen years* after it began selling Rebif in the United States, and *six years* after the filing of this lawsuit—that would not compel a further inference of *specific*

intent to induce infringement at any or all times. Moreover, Biogen *itself* established on cross-examination of Mr. Einav that Serono *continues* to have "a reasonable good faith belief that it doesn't infringe." SeronoBr. 48. Drawing inferences from that testimony was the jury's job, not the court's. *Omega Patents, LLC v. CalAmp Corp.*, 920 F.3d 1337, 1351 n.15 (Fed. Cir. 2019) ("Whatever skepticism the district court had of [defense witnesses] is irrelevant to the issues of inducement and willful infringement as *it was the jury's prerogative as fact-finder whom to credit*") (emphasis added).

Collaboration Agreement. It was Biogen's burden to *prove* that Pfizer had the knowledge and intent required for induced infringement, and the label evidence discussed above applies to Pfizer as well as to Serono. Pfizer introduced evidence that because Serono was indemnifying it under the parties' Collaboration Agreement, the defense of the litigation was left to Serono, and that Pfizer relied entirely on Serono and lacked "any independent knowledge or information regarding" the '755 patent or the litigation—including the proper construction of the asserted claims. SeronoBr. 46; Appx49890.

"Courts grant JMOL for the party bearing the burden of proof only in *extreme cases*, when the party bearing the burden of proof has established its case by evidence that the jury would not be at liberty to disbelieve and the only reasonable conclusion is in its favor." *Mentor H/S Inc. v. Med. Device All., Inc.*, 244 F.3d 1365,

1375 (Fed. Cir. 2001) (emphasis added). This was not an "extreme case," and the evidence warrants neither judgment for Biogen nor a new trial on inducement. The jury found, as a factual matter, that neither Serono nor Pfizer induced infringement of the '755 patent. Appx68293-68294. The district court erred as a matter of law in substituting its view of the evidence for the jury's on this intensely factual inquiry. *Enplas Display Device Corp. v. Seoul Semiconductor Co.*, 909 F.3d 398, 407 (Fed. Cir. 2018) ("Questions of knowledge and intent are factual questions for the jury"); *see* SeronoBr. 47-54.

2. Contributory Infringement

At Biogen's urging, the district court erroneously ruled that a reasonable belief in non-infringement cannot negate the subjective knowledge of infringement required for contributory infringement. *See* SeronoBr. 54. But believing in good faith that one does *not* infringe is the *antithesis* of knowing that one *does* infringe.

The Supreme Court meant what it said in *Commil*: Where a defendant does *not* know of infringement, including when the defendant "reasonabl[y]" "reads the patent's claims differently from the plaintiff," there can be no induced *or* contributory infringement. 135 S. Ct. at 1928. Serono established it has always had—even to this day—a reasonable belief of non-infringement; under *Commil*, that suffices to negate the element of culpable knowledge and a properly instructed jury could have

so found. And Pfizer wholly relied on Serono's evaluation of the patent including this reasonable belief.

The court's ruling that a good-faith belief in non-infringement is irrelevant to contributory infringement, and its consequent refusal to instruct the jury on that issue, cannot be reconciled with *Commil*. Biogen argues that in the pertinent passage (135 S. Ct. at 1928), the Supreme Court was "distinguishing" contributory from induced infringement. BiogenBr. 60-61. In fact, the Supreme Court noted that knowledge is a required element "*both* in inducement *and* contributory infringement cases," and that no liability would attach under either theory "if the defendant reads the patent's claims differently from plaintiff, and that reading is reasonable." 135 S. Ct. at 1928 (emphases added). That is precisely what happened here.

In *Koninklijke Philips N.V. v. Zoll Medical Corp.*, 656 F. App'x 504 (Fed. Cir. 2016), this Court explicitly held that a defendant's "belief in non-infringement, based on its reasonable claim construction argument, *does negate the knowledge requirement of contributory infringement*." *Id.* at 523 (emphasis added). Below, Biogen gave *Zoll* the back of its hand, stating "there is a reason why certain CAFC opinions are not published." Appx80623, Appx80638 (16:18-23); *see also* Appx80637 (15:17). Now, Biogen suggests (BiogenBr. 62) that *Zoll* was superseded by *Lifetime Industries, Inc. v. Trim-Lok, Inc.*, 869 F.3d 1372 (Fed. Cir. 2017), but that case does not address the question presented here.

Although Biogen maintains that "the district court's jury instructions correctly stated the law" (BiogenBr. 58), they were prejudicially incomplete. Appellants requested that the FCBA pattern jury instruction be *supplemented* with an instruction that a reasonable belief in non-infringement defeats the required knowledge for contributory infringement. SeronoBr. 56. That instruction was well-supported by controlling authority and the record evidence. The court gave such an instruction on the inducement claim (Appx47656-47666); the court's refusal to similarly supplement the contributory infringement construction was reversible error as to both Serono and Pfizer. *Cf. Microsoft Corp. v. i4i Ltd.*, 564 U.S. 91, 112 (2011) (jury instruction warranted by the evidence should be given on request).

III. Ineligibility

A. Natural Phenomenon

Biogen maintains that appellants' argument that the asserted claims are directed to the natural phenomenon that IFN-β has antiviral properties "was not asserted in the district court." Biogen Br. 63-64. That is false: Appellants expressly—and repeatedly—argued below that the claims are directed to a "conventional application of" the "known natural phenomenon" that IFN-β has "natural antiviral activity." Appx71110-Appx71143 at Appx71120, Appx71123; Appx75765-75781 at Appx75770; Appx82641-82955, Appx82815-82817 at Appx82816 (175:5-15).

Biogen notes that "[r]ecombinant interferon-beta is a man-made substance, not a natural one." BiogenBr. 64. Biogen does not dispute, however, that the recombinant polypeptides of the claims do not "alter any of the genetic information" in native IFN-β, and that the mere "use of a man-made molecule is not decisive" of eligibility. SeronoBr. 59, 62 (quoting *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116-17 (2013); *Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743, 752 (Fed. Cir. 2019)) (internal quotation marks omitted).

Biogen does not defend the district court's ruling that treatment methods are automatically patent-eligible. *See* Appx70-73. This Court has recognized that *some* method of administration claims are not patent-eligible (*Athena*, 915 F.3d at 752-53 (discussing *Mayo*, 566 U.S. at 75-76)), while other claims—all to *new* methods of treatment—are patent-eligible. *Vanda Pharm. Inc. v. W.-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1135 (Fed. Cir. 2018); *Natural Alts. Int'l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338, 1344-45 (Fed. Cir. 2019); *Endo Pharm. Inc. v. Teva Pharm. USA, Inc.*, 919 F.3d 1347, 1357 (Fed. Cir. 2019).

The treatment method claimed in the '755 patent *is not* new—the claims recite using recombinant IFN-β for antiviral treatment in the *same way* that native IFN-β had long been used. SeronoBr. 61-62. Biogen conceded below that it did *not* "c[o]me up with a *new* way of treating some disease with beta interferon that had

never been known before." SeronoBr. 61 (citing, *e.g.*, Appx81424 (131:8-10) (alteration in original; emphasis added)). Biogen's scientific expert admitted that the claims offer "no new method of treatment" and "no new methods of administration" of IFN-β. SeronoBr. 63-64.

Biogen quibbles with Serono's assertion that the '755 patent claims are directed to the natural phenomenon that IFN-β has antiviral properties. BiogenBr. 65 (citing SeronoBr. 58). But Biogen itself asserts that the '755 patent "is directed to treating a patient by administering a recombinant protein that *has the biological activity of naturally occurring [IFN-β]*." BiogenBr. 6 (emphasis added). Biogen's own recitation confirms that the patent is "directed to" a natural phenomenon.

B. Inventive Concept

Biogen relies on the district court's statement that a skilled artisan would not have expected that recombinant IFN-β would be biologically active. BiogenBr. 66. But Dr. Fiers *admitted* in sworn testimony before this case began that the claimed method involves only well-known, routine, and conventional techniques to express "biologically active, unglycosylated beta interferon" (Appx47749, Appx47829-47830 (¶ 93(d)), that would have been "straightforward" 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." Appx47828-47829 (¶ 93(c)) (emphasis added); *see also* SeronoBr. 63. Biogen is

bound by Dr. Fiers's admissions. SeronoBr. 63 (citing, *e.g.*, *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)). Biogen's only response is to note that "the district court rejected this argument" (BiogenBr. 67); but the premise of this appeal is that the district court was *wrong*.

Biogen's only other argument at Step Two is that the jury found against Serono on its obviousness challenge. BiogenBr. 66-68. But patent eligibility "is a requirement separate from other patentability inquiries"—including obviousness, which involves different considerations, including objective indicia of non-obviousness. *Return Mail, Inc. v. U.S. Postal Serv.*, 868 F.3d 1350, 1370 (Fed. Cir. 2017), *rev'd on other grounds*, 139 S. Ct. 1853 (2019); *see also Amdocs (Isr.) Ltd. v. Openet Telecom, Inc.*, 841 F.3d 1288, 1311 (Fed. Cir. 2016) ("The inventiveness inquiry of §101 should . . . not be confused with the separate novelty inquiry of §102 or the obviousness inquiry of §103"). If the failure to find claims obvious were a proxy for Step Two, then courts would be required to first decide obviousness before reaching patent eligibility. The Supreme Court has rejected that very argument. *Mayo*, 566 U.S. at 88.

In any event, while the jury found that Serono and Pfizer had not carried their burden of proving obviousness (*see Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1429 n.3 (Fed. Cir. 1988)), the jury also found that Serono and Pfizer had carried their burden

of proving anticipation. Thus, if Biogen were correct that the validity verdict should be taken into account at Step Two, the jury's factual finding that Biogen invented nothing new should put an end to the inquiry. In addition to being invalid and not infringed, the claims are not eligible for patenting.

CONCLUSION

The judgment should be reversed.

Respectfully submitted,

/s/ *Mark A. Perry*
Mark A. Perry

Counsel for Defendants-Appellants EMD Serono, Inc. and Pfizer Inc.

CERTIFICATE OF SERVICE

I, Mark A. Perry, hereby certify that that I caused the foregoing to be filed via the Court's CM/ECF system and served on counsel of record who have registered for such service on July 31, 2019.

/s/ *Mark A. Perry*
Mark A. Perry

CERTIFICATE OF COMPLIANCE

The undersigned counsel certifies that this brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a) because this brief contains 6,968 words, excluding parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b). This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman, 14-point.

/s/ *Mark A. Perry*
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