United States Court of Appeals for the Federal Circuit

2009-1020, -1096

AMGEN INC.,

Plaintiff-Cross Appellant,

v.

F. HOFFMANN-LA ROCHE LTD, ROCHE DIAGNOSTICS GMBH, and HOFFMANN-LA ROCHE INC.,

Defendants-Appellants.

Lloyd R. Day, Jr., Day Casebeer Madrid & Batchelder LLP, of Cupertino, California, argued for plaintiff-cross appellant. With him on the brief were David M. Madrid, Linda A. Sasaki-Baxley and Jonathan D. Loeb. Of counsel on the brief were Stuart L. Watt, Wendy A. Whiteford and Erica S. Olson, Amgen Inc., of Thousand Oaks, California; Cecilia H. Gonzalez and Margaret D. MacDonald, Howrey LLP, of Washington, DC. Of counsel was Christian E. Mammen, Day Casebeer Madrid & Batchelder LLP, of Cupertino, California.

Leora Ben-Ami, Kaye Scholer LLP, of New York, New York, argued for defendants-appellants. With her on the brief were Thomas F. Fleming, Patricia A. Carson, Christopher T. Jagoe, Sr. and Howard S. Suh. Of counsel on the brief were Lee Carl Bromberg, Timothy M. Murphy and Julia Huston, Bromberg & Sunstein LLP, of Boston, Massachusetts. Of counsel were Daniel Forchheimer, Matthew McFarlane, and Krista M. Rycroft, Kaye Scholer LLP, of New York, New York; and Kimberly J. Seluga, Nicole Rizzo Smith and Keith E. Toms, Bromberg & Sunstein LLP, of Boston, Massachusetts.

Appealed from: United States District Court for the District of Massachusetts

Judge William G. Young

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F. HOFFMAN-LA ROCHE LTD, ROCHE DIAGNOSTICS GMBH, and HOFFMAN-LA ROCHE INC.,

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Appeals from the United States District Court for the District of Massachusetts in case no. 05-CV-12237, Judge William G. Young.

DECIDED: September 15, 2009

Before MAYER, CLEVENGER, and SCHALL, Circuit Judges.

SCHALL, Circuit Judge.

This is a patent case. Amgen Inc. ("Amgen") is the owner of U.S. Patent Nos. 5,441,868 ("the '868 patent"), 5,547,933 ("the '933 patent"), 5,618,698 ("the '698 patent"), 5,756,349 ("the '349 patent"), and 5,955,422 ("the '422 patent"). The patents relate to the production of the protein erythropoietin ("EPO") using recombinant deoxyribonucleic acid ("DNA") technology. All five patents share a common specification and descend from Application No. 06/675,298 ("the '298 application"), which issued as now-expired U.S. Patent No. 4,703,008 ("the '008 patent").

In November of 2005, Amgen brought a declaratory judgment action against F. Hoffman-La Roche Ltd, Roche Diagnostics GMBH, and Hoffman-La Roche Inc. ("Roche") in the United States District Court for the District of Massachusetts, alleging that Roche's product, MIRCERA®, would infringe Amgen's five patents if imported into the United States. Roche responded with affirmative defenses and counterclaims that Amgen's asserted patents were invalid and not infringed. In October of 2008, following rulings of summary judgment and judgment as a matter of law ("JMOL"), and a jury trial, the court entered judgment that the '868, '933, '698, and '422 patents were infringed and not invalid, and that the '349 patent was neither invalid nor infringed. Amgen, Inc. v. F. Hoffman-La Roche Ltd., No. 05-12237-WGY, slip op. at 1–2 (D. Mass. Oct. 17, 2008) ("Final Judgment"). Accordingly, the court granted Amgen declaratory relief and permanently enjoined Roche from marketing MIRCERA® in the United States. Id.

Roche appeals from several rulings of the court. Specifically, Roche challenges the court's rulings that none of the claims-in-suit were invalid for obviousness-type double patenting, Amgen, Inc. v. F. Hoffman-La Roche Ltd., 581 F. Supp. 2d 160, 173, 186, 192 (D. Mass. 2008); and that claim 1 of the '422 patent was neither anticipated nor indefinite and infringed, id. at 194, 198, 204. Roche also challenges the court's rulings sustaining the jury's verdict that claims 3, 7, and 8 of the '933 patent were neither anticipated nor indefinite; and that claims 3, 7, and 8 of the '933 patent, claims 1 and 2 of the '868 patent, and claims 6–9 of the '698 patent were literally infringed.

Amgen cross-appeals from the court's rulings that claim 7 of the '349 patent and claims 9, 11, and 14 of the '933 patent were not infringed. Amgen also cross-appeals

from the court's ruling vacating the jury's verdict that claim 12 of the '933 patent was infringed under the doctrine of equivalents ("DOE"). Id. at 205.

We vacate the court's grant of summary judgment and of JMOL to Amgen of no invalidity for obviousness-type double patenting of claims 3, 7, and 8 of the '933 patent; claim 1 of the '422 patent; and claim 7 of the '349 patent. We therefore remand to the district court for an obviousness-type double patenting analysis of those claims in light of this opinion. We also vacate the court's grant of JMOL to Roche of non-infringement of claim 7 of the '349 patent and remand to the district for a new trial on infringement of that claim. We affirm the court's judgment in all other respects.

BACKGROUND

I

As noted, the patents at issue relate to the production of EPO using recombinant DNA technology. EPO, which is a naturally occurring protein (or polypeptide), stimulates the production of red blood cells through a process called erythropoiesis. Amgen, 581 F. Supp. 2d at 168. The production of EPO is useful in treating blood disorders characterized by a low hematocrit, which is a low ratio of red blood cells to total blood cells. Id. One such blood disorder is anemia. In a clinical study performed in 1979–80, Dr. Eugene Goldwasser attempted to treat anemic patients with EPO isolated from human urine. Id. at 168. He had limited success, however, because the EPO recovered from urine was low-yield, of high impurity, and unstable. Id. at 168–69.

Rather than attempting to obtain EPO from natural sources such as human urine, a team of Amgen researchers led by Dr. Fu-Kuen Lin identified a means of producing usable amounts of EPO via recombinant DNA technology. Id. at 169. The common

specification of Amgen's patents describes the production of recombinant EPO. To produce EPO, Dr. Lin made an expression vector carrying the human EPO DNA sequence he had discovered. See '422 patent col.11 ll.1–10. An expression vector is a circular piece of DNA that is inserted into a host cell to produce a protein. Id. col.2 ll.36–54; figs.2 & 3. He then injected, or transfected, host Chinese hamster ovary ("CHO") cells with the expression vector. Id. col.11 ll.5–10

The transfected CHO cells use the EPO DNA sequence to form a protein with the 166 amino acid sequence of EPO shown in Figure 6 of the common specification of the patents. Id. fig.6. Prior to secretion of EPO from the cell, the final amino acid, or the C-terminal amino acid, of the 166 amino acid sequence is cleaved off, leaving a 165 amino acid protein. Amgen, 581 F. Supp. 2d at 170. Also prior to secretion, carbohydrates are attached to certain sites on EPO in a process called glycosylation, which results in a glycoprotein. Id. Thus, Dr. Lin's transfected CHO cells ultimately yield a glycoprotein with the 165 amino acid sequence of human EPO. Id. Recombinant EPO produced in this manner can bind to the EPO receptor and stimulate erythropoiesis. Id. at 169.

On November 30, 1984, Amgen submitted to the United States Patent and Trademark Office ("PTO") the '298 application, from which Amgen's five patents descend. Id. at 180. The '298 application originally contained claims drawn to, inter alia, DNA sequences, host cells, processes of producing polypeptides, polypeptides, and pharmaceutical compositions. Id. In 1986, the PTO subjected Amgen's '298 application to a restriction requirement, which identified claims drawn to DNA, cells, polypeptides, and pharmaceutical compositions as each directed to patentably distinct

subject matter. Id. The PTO examiner stated that, under 35 U.S.C. § 121, restriction to one of the following inventions was required:

> I. Claims 1–13, 16, 39–41, 47–54, and 59, drawn to polypeptide, classified in Class 260, subclass 112.
>
> II. Claims 14, 15, 17–36, 58, and 61–72, drawn to DNA, classified in Class 536, subclass 27.
>
> III. Claims 37–38, drawn to plasmid, classified in Class 435, subclass 317.
>
> IV. Claims 42–46, drawn to cells, classified in Class 435, subclass 240.
>
> V. Claims 55–57, drawn to pharmaceutical composition, classified in Class 435, subclass 177.
>
> VI. Claim 60, drawn to assay, classified in Class 435, subclass 6.[1]

Id. In response, Amgen elected to prosecute Group II claims in the '298 application, which were drawn to DNA and host cells. Id. Ultimately, the '298 application issued on October 27, 1987, as the now-expired '008 patent entitled "DNA Sequences Encoding Erythropoietin." The '008 patent claimed DNA sequences encoding EPO and host cells transformed or transfected with those DNA sequences. '008 patent col.40 ll.17–68.

On October 23, 1987, subsequent to the restriction requirement but before the '008 patent issued, Amgen prosecuted the claims withdrawn from the '298 application in continuation application 07/113,178 ("the '178 application") and continuation application 07/113,179 ("the '179 application"). Amgen, 581 F. Supp. 2d at 180. After a series of

[1] The PTO maintains the United States Patent Classification System ("USPC") for organizing patent documents by common subject matter. Each subject matter division in the USPC includes a major component called a class and a minor component called a subclass. A class generally delineates one technology from another. Subclasses delineate processes, structural features, and functional features of the subject matter encompassed within the scope of a class. Every class has a unique alphanumeric identifier, as do most subclasses. See generally Manual of Patent Examining Procedure ("MPEP") § 902.01 (8th ed., July 2008 rev.) (describing the Manual of Classification).

intervening continuation applications and interferences, the ’933 patent eventually emerged from the ’178 application, while the ’422, ’349, ’868, and ’698 patents eventually emerged from the ’179 application. As a result, all five patents-in-suit (’933, ’422, ’349, ’868, and ’698) claim priority to the ’298 application, share a common specification, and have the title “Production of Erythropoietin” or “Production of Recombinant Erythropoietin.”

In broad strokes, the ’933 patent claims recombinant EPO, a pharmaceutical composition comprising recombinant EPO, and methods of treating kidney dialysis patients by administering pharmaceutical compositions comprising recombinant EPO. ’933 patent col.38 l.17–col.40 l.11. The ’422 patent claims a pharmaceutical composition comprising recombinant EPO. ’422 patent col.38 l.37–41. Because the ’933 and ’422 patents both cover recombinant EPO and pharmaceutical compositions thereof, the parties refer to them collectively as the “product patents.” The ’349 patent claims the process of producing recombinant EPO in vertebrate cells capable of producing EPO at a specific rate. ’349 patent col.38 ll.34–36. The ’868 patent claims the process of producing recombinant EPO in mammalian cells, ’868 patent col.38 ll.24–37, while the ’698 patent claims the process of producing recombinant EPO in cells comprised of amplified DNA encoding EPO, ’698 patent col.38 ll.50–65. Because the ’868 and ’698 patents both cover processes of producing recombinant EPO, the parties refer to them collectively as the “process patents.”

Based on these patents, Amgen has developed two erythropoiesis-stimulating agent (“ESA”) drugs, EPOGEN® and Aranesp®, to treat anemia and anemia-related diseases. Amgen, 581 F. Supp. 2d at 171. The key difference between these drugs is

how frequently patients must take them. Id. The Food and Drug Administration ("FDA") has approved EPOGEN for weekly dosing and Aranesp for bi-weekly dosing to anemic patients. Id.

Roche sought to introduce into the United States market its own ESA drug, MIRCERA®, which it manufactures overseas. Id. at 172. The active ingredient of MIRCERA® is continuous erythropoietin receptor activator ("CERA"). CERA is formed via a chemical reaction that bonds polyethylene glycol ("PEG") to recombinant EPO produced by CHO cells. Id. The attachment of one PEG molecule to EPO, also known as pegylation of EPO, results in the displacement of a single hydrogen atom from the amino acid lysine or from the beginning amino acid (i.e., the N-terminus) of EPO. Id. Pegylation of a therapeutic protein, such as EPO, can expand the drug's life in the body and reduce levels of toxicity, allowing for extended dosing intervals. Id. As a result, MIRCERA® has received FDA approval for once-monthly dosing to anemic patients. Id.

II

Amgen sought a declaratory judgment that, if imported into the United States, MIRCERA® would infringe the '933, '422, '868, '698, and '349 patents. Specifically, Amgen alleged infringement of claims 3, 7–9, 11, 12, and 14 of the '933 patent, claim 1 of the '422 patent, claim 7 of the '349 patent, claims 1–2 of the '868 patent, and claims 6–9 of the '698 patent. Roche responded with affirmative defenses and counterclaims that Amgen's asserted patents were invalid and not infringed.

After discovery, the district court granted Amgen summary judgment of no obviousness-type double patenting of any of the asserted claims in the '933, '422, and '349 patents over the claims in the '008 patent based on the protection from such

challenge afforded by 35 U.S.C. § 121. Amgen, 581 F. Supp. 2d at 173. Over cross-motions for summary judgment, the district court also granted Amgen summary judgment that claim 1 of the '422 patent was infringed. Id. at 167, 204. The parties tried the remaining infringement and invalidity claims to a jury. After Roche presented its case-in-chief to the jury, the court granted Amgen JMOL that claim 1 of the '422 patent was not anticipated. Id. at 198. After conducting hearings outside the presence of the jury and reviewing the trial record, the court granted Amgen JMOL of no obviousness-type double patenting of (1) the asserted claims in the '933, '422, and '349 patents over the claims in the '868 and '698 patents, id. at 192, and (2) the asserted claims in the '868 and '698 patents over the claims in the '008 patent, id. at 186. The court also granted Roche JMOL that claims 9, 11, and 14 of the '933 patent and claim 7 of the '349 patent were not infringed.

On October 23, 2007, the jury rendered a verdict in favor of Amgen, upholding the validity of all the claims-in-suit. The jury found that Roche literally infringed claims 3, 7, and 8 of the '933 patent; claims 1 and 2 of the '868 patent; and claims 6–9 of the '698 patent. Over Roche's motions for renewed JMOL and a new trial, the court sustained these jury findings. The jury also found that claim 12 of the '933 patent was infringed under the DOE. Granting Roche's motion for renewed JMOL relating to claim 12 of the '933 patent, the court vacated the jury verdict of infringement and entered judgment of non-infringement as to that claim. Id. at 205. Subsequently, the court granted Amgen a declaratory judgment and a permanent injunction, enjoining Roche from marketing MIRCERA® in the United States. Final Judgment, slip op. at 1–2. Roche appeals the described rulings and findings in favor of Amgen, while Amgen cross-appeals the

described rulings in favor of Roche. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

In this appeal, we are presented with issues involving obviousness-type double patenting, anticipation, indefiniteness, and infringement relating to the '933, '422, '349, '868, and '698 patents.

I

Obviousness-Type Double Patenting

For purposes of explaining its rulings relating to obviousness-type double patenting, the district court grouped the '933, '422, and '349 patents, and the '868 and '698 patents separately. We shall do the same.

A

The court granted Amgen summary judgment of no obviousness-type double patenting of the asserted claims of the '933, '422, and '349 patents over the claims of the '008 patent.[2] Amgen, 581 F. Supp. 2d at 179. The court also granted Amgen JMOL of no obviousness-type double patenting of the asserted claims of the '933, '422, and '349 patents over the claims of the '868 and '698 patents.[3] Id. at 192. The court

[2] Before the district court, Roche asserted that claims 3, 7, and 8 of the '933 patent; claim 1 of the '422 patent; and claim 7 of the '349 patent are invalid for obviousness-type double patenting over claim 27 of the '008 patent. Generally, as noted, claims 3, 7, and 8 of the '933 patent are drawn to recombinant EPO; claim 1 of the '422 patent is drawn to a pharmaceutical composition comprising recombinant EPO; and claim 7 of the '349 patent is drawn to a process of producing recombinant EPO. Claim 27 of the '008 patent is drawn to CHO cells comprising DNA encoding EPO.

[3] Before the district court, Roche asserted that claims 3, 7, and 8 of the '933 patent; claim 1 of the '422 patent; and claim 7 of the '349 patent are invalid for obviousness-type double patenting over claims 1 and 2 of the '868 patent and claims 6–

arrived at these rulings after concluding that the '933, '422, and '349 patents were shielded from double patenting by 35 U.S.C. § 121. Id.

Section 121, entitled "Divisional applications," provides in its third sentence:

> A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.

35 U.S.C. § 121. The third sentence of § 121 is a safe harbor provision that protects a divisional application, the original application, or any patent issued on either of them from validity challenges based on a patent issuing on an application subjected to a restriction requirement or on an application filed as a result of a restriction requirement. In effect, the third sentence of § 121 shields patents that issue on applications filed as a result of a restriction requirement from double patenting invalidation. See Applied Materials, Inc. v. Advanced Semiconductor Materials America, Inc., 98 F.3d 1563, 1568 (Fed. Cir. 1996) ("[W]hen two or more patents result from a PTO restriction requirement, whereby aspects of the original application must be divided into separate applications, § 121 insulates the ensuing patents from the charge of double patenting.").

The court concluded that the '933, '422, and '349 patents were entitled to the § 121 safe harbor because they had descended from the '178 and '179 applications, both of which had been filed in response to a PTO-imposed restriction requirement. The court observed that "[a]fter the PTO imposed the 1986 restriction requirement," Amgen "filed two divisional applications, the '178 and '179, which ultimately issued as

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9 of the '698 patent. Generally, as noted, claims 1 and 2 of the '868 patent and claims 6–9 of the '698 patent are drawn to processes of producing recombinant EPO.

the ’933, ’422, and ’349 patents.” Amgen, 581 F. Supp. 2d at 179. The court found that the “undisputed evidence show[ed] that both the ’178 and ’179 applications were filed as a result of the PTO’s 1986 restriction requirement.” Id. Thus, the court deemed the ’933, ’422, and ’349 patents immune from a charge of obviousness-type double patenting over the ’008, ’868, and ’698 patents. Id. at 182, 192.

On appeal, Roche contends that the district court erroneously determined that § 121’s safe harbor insulates the ’933 and ’422 patents from obviousness-type double patenting invalidation over the ’008, ’868, and ’698 patents. Roche’s Br. 34. Roche’s main contention is that § 121 cannot shield the ’933 and ’422 patents because they issued from solely continuation applications to which § 121 is inapplicable. Id. Roche contends that § 121 applies exclusively to divisional applications and patents issuing therefrom. Roche emphasizes that the statute, entitled “Divisional applications,” requires on its face that the later patent must issue from “a divisional application” or the “original application.” Id. at 35. Because the ’933 and ’422 patents issued from the ’178 and ’179 continuation applications, Roche contends they are not entitled to the § 121 safe harbor. Id. at 36.

Amgen argues that the district court correctly held that § 121 protects the asserted claims of the ’933 and ’422 patents from obviousness-type double patenting invalidation over the claims of the ’008, ’868, and ’698 patents. Amgen’s Br. 39. Amgen relies on our decisions in Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc., 98 F.3d 1563, 1568 (Fed. Cir. 1996), and Symbol Technologies, Inc. v. Opticon, Inc., 935 F.2d 1569 (Fed. Cir. 1991), for the proposition that patents that issue directly from continuation applications, as the ’933 and ’422 patents did, are

eligible for § 121 protection so long as the other requirements of § 121 are met. Id. at 41. In Amgen's view, the only § 121 requirement at issue is the "divisional application" requirement, and Amgen contends that the '178 and '179 applications meet that requirement. Id. Amgen urges the court to look to an application's substance—not its designation—to determine whether it qualifies as a divisional application under § 121's safe harbor. Id. at 42. In support of this approach, Amgen relies on the definition of "divisional application" in § 201.06 of the Manual of Patent Examining Procedure ("MPEP"), which provides:

> A later application for an independent or distinct invention, carved out of a pending application and disclosing and claiming only subject matter disclosed in the earlier or parent application, is known as a divisional application or "division."

MPEP § 201.06 (8th ed., July 2008 rev.). According to Amgen, the '178 and '179 applications were later applications, which were (1) carved out of a pending application (the '298 application), (2) contained claims to distinct and independent inventions, and (3) disclosed and claimed only subject matter disclosed in the earlier or parent application. Amgen's Br. 41. Thus, Amgen argues, because the '178 and '179 applications, from which the '933 and '422 patents descend, conform to the PTO's definition of a "divisional application" in MPEP § 201.06, the '933 and '422 patents are entitled to the § 121 safe harbor. Id.

Amgen also noted at oral argument that Roche did not contest the no obviousness-type double patenting ruling relating to the '349 patent in its reply brief, even though Amgen cross-appealed the court's ruling that the '349 patent was not infringed by MIRCERA®. See Oral Arg. 33:10–35, June 4, 2009, available at

http://oralarguments.cafc.uscourts.gov/searchscript.asp (search case no. 2009-1020). Amgen urges us to treat Roche's omission as waiver. Id.

We address this last point of Amgen's first. Amgen correctly points out that Roche did not challenge the § 121 protection afforded to the '349 patent in its reply brief. When questioned at oral argument about this omission, counsel for Roche stated, "We won on non-infringement, so you can't appeal when you win." Oral Arg. 37:00–27. While a challenge to the no invalidity ruling of the '349 patent would have been a proper response to Amgen's cross-appeal of the non-infringement ruling of the '349 patent, we do not deem Roche's failure to raise this alternative ground for affirmance as waiver in this case. See Independence Park Apartments v. United States, 449 F.3d 1235, 1240 (Fed. Cir. 2006) (explaining that appellees are in the position of defending a favorable judgment and, under certain circumstances, may not be "required to raise all possible alternative grounds for affirmance to avoid waiving any of those grounds"); cf. Harris Corp. v. Ericsson Inc., 417 F.3d 1241, 1251 (Fed. Cir. 2005) ("An appellate court retains case-by-case discretion over whether to apply waiver."). Therefore, given our ruling on infringement of the '349 patent, see infra Part V.B, we will rule on whether the '349 patent is entitled to the § 121 safe harbor.

B

We review a district court's grant of summary judgment without deference. See In re Metoprolol Succinate Patent Litig., 494 F.3d 1011, 1015 (Fed. Cir. 2007). Summary judgment is appropriate if there are no genuine issues of material fact so that the moving party is entitled to judgment as a matter of law. See Fed. R. Civ. P. 56(c). In other words, the court properly grants summary judgment if no reasonable jury could

return a verdict for the non-moving party. See Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248 (1986). In assessing the evidence, we draw all reasonable inferences in favor of the non-moving party. BMC Res., Inc. v. Paymentech, L.P., 498 F.3d 1373, 1378 (Fed. Cir. 2007).

We apply the standard of review for JMOL rulings used in the relevant regional circuit. DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1329 (Fed. Cir. 2009). In this case, that is the First Circuit. In the First Circuit, a district court's grant of JMOL is reviewed without deference. Id. (applying First Circuit law). Under First Circuit law, JMOL is warranted when, viewing the evidence in the light most favorable to the non-moving party, "there is no legally sufficient evidentiary basis for a reasonable jury to find for the [non-moving] party." Guilloty Perez v. Pierluisi, 339 F.3d 43, 50 (1st Cir. 2003) (quotation marks omitted).

We review a court's conclusion on double patenting without deference because "double patenting is a matter of what is claimed, and therefore is treated like claim construction upon appellate review." Georgia-Pacific Corp. v. U.S. Gypsum Co., 195 F.3d 1322, 1326 (Fed. Cir. 1999). "[Obviousness-type] double patenting is a judicially created doctrine adopted to prevent claims in separate applications or patents that do not recite the 'same' invention, but nonetheless claim inventions so alike that granting both exclusive rights would effectively extend the life of patent protection." Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1373 (Fed. Cir. 2005).

We conclude that, because the '178 and '179 applications were filed as continuation—rather than divisional—applications, the '933, '422, and '349 patents do not receive the benefit of § 121. We reach this conclusion in light of our opinion in

Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc., 518 F.3d 1353 (Fed. Cir. 2008). The Pfizer decision addressed whether a patent that issued from a continuation-in-part application—rather than a divisional application—could receive the protection of the § 121 safe harbor. 518 F.3d at 1358–62. Looking first to the statute, the court observed that § 121 on its face refers to "divisional application[s]." Id. at 1360. Turning to the legislative history, the court observed that a House Report also referred specifically to "divisional application[s]." Id. Notably absent from the legislative history, in the court's view, was a suggestion "that the safe-harbor provision was, or needed to be, directed at anything but divisional applications." Id. at 1361. From there, the court "conclude[d] that the protection afforded by section 121 to applications (or patents issued therefrom) filed as a result of a restriction requirement is limited to divisional applications." Id. at 1362. Accordingly, the court decided that the § 121 safe harbor did not apply to the patent before it, which issued from a continuation-in-part application. Id.

We are persuaded by the reasoning in Pfizer that the § 121 safe harbor provision does not protect continuation applications or patents descending from only continuation applications. The statute on its face applies only to divisional applications,[4] and a

[4] The statute is entitled "Divisional applications" and refers specifically to "divisional applications" in its text:

> § 121. Divisional applications
>
> If two or more independent and distinct inventions are claimed in one application, the Director may require the application to be restricted to one of the inventions. If the other invention is made the subject of a divisional application which complies with the requirements of section 120 of this title it shall be entitled to the benefit of the filing date of the original application. A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as

continuation application, like a continuation-in-part application, is not a divisional application. See Gerber Garment Tech., Inc. v. Lectra Sys., Inc., 916 F.2d 683, 688 (Fed. Cir. 1990) ("To gain the benefits of Section 121 there outlined, [the patentee] must have brought its case within the purview of the statute, i.e., it must have limited the claims in its divisional application to the non-elected invention or inventions." (emphasis added)). We recognize that, unlike a continuation-in-part application, a continuation application can satisfy the definition of a "divisional application" in MPEP § 201.06. That is because a continuation-in-part application adds subject matter not disclosed in the earlier application, see MPEP § 201.08, whereas continuation and divisional applications are limited to subject matter disclosed in the earlier application, see MPEP §§ 201.06, 201.07. This distinction, however, does not justify departing from a strict application of the plain language of § 121, which affords its benefits to "divisional application[s]." See 35 U.S.C. § 121 (sheltering from attack "a divisional application or . . . the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application" (emphases added)); see also Geneva Pharm., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1382

> a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application. If a divisional application is directed solely to subject matter described and claimed in the original application as filed, the Director may dispense with signing and execution by the inventor. The validity of a patent shall not be questioned for failure of the Director to require the application to be restricted to one invention.

35 U.S.C. § 121 (emphases added).

(Fed. Cir. 2003) ("Given the potential windfall [a] patent term extension could provide to a patentee, this court applies a strict test for application of § 121." (footnote omitted)).

Our conclusion that the § 121 safe harbor protects patents descending from divisional applications, but not from continuation applications exclusively, is consistent with our decisions in Applied Materials and in Symbol Technologies. In both of those cases, we affirmed § 121 protection of patents which issued directly from continuation applications. See Applied Materials, 98 F.3d at 1568–69; Symbol Technologies, 935 F.2d at 1579–81. In both cases, however, the continuation applications, from which the protected patents issued, descended from divisional applications that were filed as a result of restriction requirements. See Applied Materials, 98 F.3d at 1568; Symbol Technologies, 935 F.2d at 1580. Our decisions in Applied Materials and Symbol Technologies thus establish that a patent need not have issued directly from a divisional application to receive § 121 protection. In other words, intervening continuation applications do not render a patent ineligible for § 121 protection so long as they descended from a divisional application filed as a result of a restriction requirement. Unlike the patents at issue in Applied Materials and Symbol Technologies, the '933, '422, and '349 patents issued from continuation applications, which descended from continuation applications exclusively, and not from divisional applications. Thus, Applied Materials and Symbol Technologies are of no help to Amgen's position that the '933, '422, and '349 patents deserve § 121 protection.

Furthermore, Amgen has not presented us with any persuasive reason as to why we should deem the '178 and '179 continuation applications divisional applications for purposes of § 121. Amgen does not dispute that it denominated the '178 and '179

applications continuations, that it checked the continuation application box on the submitted form, or that its applications met the PTO's definition of a continuation application in MPEP § 201.07. See Amgen's Br. 38, 42. Instead, Amgen argues that, because the '178 and '179 continuation applications could have been filed as divisional applications, we should treat them as such for purposes of § 121. While this argument convinced the district court to regard the '178 and '179 continuation applications as divisional applications, we are not likewise convinced. We decline to construe "divisional application" in § 121 to encompass Amgen's properly filed, properly designated continuation applications.

Because the '178 and '179 applications were filed as continuation applications instead of divisional applications, we hold that the '933, '422, and '349 patents do not receive the protections afforded by § 121's safe harbor. As a result, we vacate the grant of summary judgment and of JMOL of no obviousness-type double patenting of the '933, '422, and '349 patents and remand to the district court the question of whether the asserted claims of those patents are invalid for obviousness-type double patenting over the claims of the '008, '868, and '698 patents.[5]

In this context, we now address Roche's contention that a new time frame for obviousness-type double patenting should apply in the district court on remand when it considers the validity of the '933, '422, and '349 patents, and in our review of the district

[5] We note that, because the '933 patent issued on August 20, 1996, which was before the issuance of the '698 patent on April 8, 1997, the '698 patent presumably cannot be used as an obviousness-type double patenting reference against the '933 patent on remand. See Georgia-Pacific, 195 F.3d at 1326 ("Under obviousness-type double patenting, a patent is invalid when it is merely an obvious variation of an invention disclosed and claimed in an earlier patent by the same inventor." (emphasis added)).

court's decision on the validity of the '868 and '698 patents. Roche finds support for the new time frame in our recent decision in Takeda Pharmaceutical Co. v. Doll, 561 F.3d 1372 (Fed. Cir. 2009), which post-dates the district court's decision in this case.

C

Takeda presented the situation where a patent applicant sought to overcome a double patenting rejection of a process patent over a product patent by presenting post-invention evidence of alternative processes of making the product. 561 F.3d at 1375–76. In 1974, Takeda Pharmaceutical Co. ("Takeda") filed a Japanese patent application disclosing a product (cephem compounds) and the process for making the product. Id. at 1373. Takeda obtained a patent on the product in 1981, and a patent on the process in 1996, both of which claimed priority to the 1974 application. Id. at 1373–74. During reexamination of the process patent, the PTO examiner rejected the claims of the process patent as patentably indistinct over the claims of the product patent, and, therefore, invalid for double patenting, a ruling which the Board of Patent Appeals and Interferences affirmed. Id. at 1374. The District Court for the District of Columbia disagreed, however, based primarily on MPEP § 806.05(f), which provides that process and product claims are patentably distinct if "the product as claimed can be made by another materially different process." Takeda Pharm. Co. v. Dudas, 511 F. Supp. 2d 81, 96 (D.D.C. 2007), vacated, Takeda, 561 F.3d at 1378. The district court held that, because viable, alternative processes for making the product existed in 2002 and 2005, the process and product were patentably distinct, and, therefore, not invalid for obviousness-type double patenting. Takeda, 511 F. Supp. 2d at 97.

The question on appeal to this court in Takeda was whether, when an issued patent claims a product and discloses, but does not claim, a process for making that product, the patentee, when later seeking a patent on the disclosed process, may present evidence of post-invention, alternative processes that produce the patented product, in order to show that the process and product are patentably distinct. 561 F.3d at 1375–76.[6] The answer was a qualified yes. We concluded that "the relevant time frame for determining whether a product and process are 'patentably distinct' should be at the filing date of the secondary application," which is the later application for the process. Id. at 1377. We reasoned that "[t]he secondary application . . . actually triggers the potential of an 'unjustified extension of patent term,'" which is one of the "policies underlying the double patenting doctrine." Id. That is because the patentee "essentially avers that the product and process are 'patentably distinct'" upon filing of the secondary application. Id. Accordingly, Takeda could "rely on subsequent developments in the art up to January 8, 1990, the filing date of the secondary application, in order to show a patentable distinction between the [product and process for making the product]." Id. at 1378. We thus held that Takeda could rely on alternative processes that were in existence prior to January 8, 1990, the date of the application for the process patent. Id. It could not, however, rely on processes that came into existence after January 8, 1990, which eliminated processes existing in 2002

[6] Takeda could overcome a double patenting rejection by presenting evidence that the product could be produced by alternative processes because "double patenting is not sustainable when the product can be fabricated by processes other than that secured by the issued process patent," In re Cady, 77 F.2d 106, 109 (CCPA 1935) (quotation marks omitted). This principle is embodied in MPEP § 806.05(f), which states that a product is patentably distinct from the process for making the product if "the product as claimed can be made by another materially different process."

and 2005, which did not exist before January 8, 1990. Id. Since the parties disputed whether alternative processes existed prior to the filing of the process patent, we remanded to the district court for a final obviousness-type double patenting decision. Id.

Roche contends that Takeda changed the time frame for an obviousness-type double patenting analysis. Roche's Resp. Ct. Req. 1. Roche hones in on the language in the Takeda opinion stating that "the relevant time frame for determining whether a product and process are 'patentably distinct' should be at the filing date of the secondary application." Id. at 2 (quoting Takeda, 561 F.3d at 1377). Given this language, Roche argues that it should be able to rely on evidence up to the filing date of "secondary application[s]" to show a lack of patentable distinctiveness in this case. Id. Roche contends that interpreting Takeda's holding so that only patentees can take advantage of post-invention developments to show a patentable distinction is manifestly unfair. Id. at 4. In Roche's view, if the patentee is to benefit from art that arises after the invention date, then an accused infringer is likewise benefitted. Id. In other words, Roche contends, Takeda must be a two-way street, benefitting the patentee and patent challenger alike. Thus, Roche argues that evidence arising up to the time of filing of the "secondary application[s]" (June 7, 1995, for the '933 patent; August 2, 1993, for the '422 patent; and June 6, 1995, for the '349 patent) should be considered (1) by the district court on remand in its obviousness-type double patenting analysis of the claims of the '933, '422, and '349 patents over the claims of the '008, '868, and '698 patents, and (2) by this court in its review of the obviousness-type double patenting analysis of the '868 and '698 patents over the '008 patent.

Amgen responds that Takeda did not change the time frame of the obviousness-type double patenting inquiry in all cases. Amgen's Resp. Ct. Req. 1. Amgen reads Takeda to only allow the patentee an opportunity to rely on post-invention evidence. Id. Under this reading, Takeda permits Amgen to show post-invention developments in the art that confirm patentable distinctiveness. Id. at 2. Amgen contends that, if § 121 does not shield the '933, '422, and '349 patents from obviousness-type double patenting invalidation, then Takeda permits Amgen to present evidence of alternative processes for making the products claimed in the '933, '422, and '349 patents up to the filing dates of those patents. Id. at 5. In short, Amgen contends, Takeda is a one-way street, benefitting only the patentee.

Roche's view that Takeda changed the time frame of the obviousness-type double patenting inquiry in all cases collides with 35 U.S.C. § 120. Section 120, entitled "Benefit of earlier filing date in the United States," recites in pertinent part:

> An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, . . . which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.

35 U.S.C. § 120 (emphases added). In short, § 120 provides that a qualifying "application for patent for an invention . . . shall have the same effect . . . as though filed on the date of the prior application." This court has "repeatedly recognized [the] principle" that the "plain and unambiguous meaning of section 120 is that any application fulfilling the requirements therein 'shall have the same effect' as if filed on

the date of the application upon which it claims priority." Transco Prods. Inc. v. Performance Contracting, Inc., 38 F.3d 551, 556 (Fed. Cir. 1994). "The 'effect' described in section 120 is the benefit of the earlier filing date—i.e., the benefit for purposes of priority and section 112 . . . ." Cooper Techs. Co. v. Dudas, 536 F.3d 1330, 1342 (Fed. Cir. 2008). Thus, § 120 requires continuation applications to receive, at the very least, the benefits provided by the earlier filing date.

We cannot read Takeda in the manner for which Roche advocates without violating the plain language of 35 U.S.C. § 120. Section 120 requires that all five of Amgen's asserted patents ('933, '422, '349, '868, and '698) benefit from the effect of having been filed on the filing date of the '298 application, which is November 30, 1984. That means that Amgen's patents cannot be invalidated based on art arising after November 30, 1984. Consequently, we must reject Roche's contention that it should be able to show patentable indistinctiveness by relying on evidence up to the filing date of "secondary application[s]." Therefore, on remand, Roche may not rely on developments in the art subsequent to November 30, 1984, but prior to the filing dates of the '933 patent (June 7, 1995), '422 patent (August 2, 1993), and '349 patent (June 6, 1995), to show that that the '933, '422, and '349 patents are patentably indistinct over the '008 patent.

The question of impairment of a patentee's rights under § 120, as applied to foreign applicants via 35 U.S.C. § 119, did not arise in Takeda.[7] Rather, the Takeda

[7] Because the patents-at-issue in Takeda claimed priority to a Japanese patent application, they received the benefit of the earlier filing date under 35 U.S.C. § 119. Section 119 provides in relevant part: "An application for patent for an invention filed in this country by any person who has . . . previously regularly filed an application for a patent for the same invention in a foreign country . . . , shall have the same effect

decision conferred upon the patentee an additional benefit outside the mandate of § 120. Nevertheless, the Takeda court understood the interrelationship between § 120 and the timing rule it created. It recognized that the rule it crafted could "provide the patentee with the best of both worlds: the applicant can use the filing date as a shield, enjoying the earlier priority date in order to avoid prior art, and rely on later-developed alternative processes as a sword to defeat double patenting challenges." Takeda, 561 F.3d at 1377. Because of § 120, we read Takeda to stand for the limited proposition that an applicant can only rely on subsequent developments in the art up to the filing date of the "secondary application" in order to show that alternative processes to make the product render the product and the process for making that product patentably distinct.

The claims of the '933 and '422 product patents, which we hold are not protected by the § 121 safe harbor, are related to the claims of the '868 and '698 process patents, although not in precisely the same way the claims of the product and process patents were related in Takeda. That is to say, the '933 and '422 patents claim products which are made by processes claimed in the '868 and '698 patents. The '349 patent differs, however, from the '933 and '422 patents in its relationship to the '868 and '698 patents because it, like the '868 and '698 patents, claims a process of producing recombinant EPO. The relationship between the '933 and '422, but not the '349, claims and the '868 and '698 claims implicates the principle applied in Takeda, 561 F.3d at 1375, that "double patenting is not sustainable when the product can be fabricated by processes other than that secured by the issued process patent." In re Cady, 77 F.2d 106, 109

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as the same application would have if filed in this country on the date on which the application for patent for the same invention was first filed in such foreign country." 35 U.S.C. § 119. We also note that divisional applications filed in accordance with the requirements of § 120 benefit from an earlier filing date under 35 U.S.C. § 121.

(CCPA 1935) (quotation marks omitted); see also MPEP § 806.05(f). On remand, Takeda will permit Amgen, if it wishes to do so, to rely on alternative processes for making the products claimed in the '933 and '422 patents up to their filing dates to prove that the claims of those patents and the claims of the '868 and '698 patents are patentably distinct.[8] If Amgen pursues that course, Roche will be free to rely on subsequent developments in the art up to the filing dates of the '933 and '422 patents to prove that any alternative processes put forth by Amgen do not render the claims of the '933 and '422 patents and the claims of the '868 and '698 patents patentably distinct. In other words, Takeda is a two-way street within its own confines.

D

Turning now to the process patents, the court granted Amgen JMOL that claims 1 and 2 of the '868 patent and claims 6–9 of the '698 patent are not invalid for obviousness-type double patenting over claim 27 of the '008 patent. Amgen, 581 F. Supp. 2d at 186. Since the parties had agreed that the § 121 safe harbor did not apply to these claims, the court engaged in an obviousness-type double patenting analysis. Id. at 182–83. The court first construed the claims in the '008, '868, and '698 patents and then determined that there were patentable differences. Id.

The relevant claim of the '008 reference patent is claim 27, which depends from claims 7, 8, 11, and 23–25. Those claims recite as follows:

> 7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the

[8] We note that, because claim 27 of the '008 patent recites host cells, the principle articulated in In re Cady, and embodied in MPEP § 806.05(f), does not apply to the obviousness-type double patenting analysis of the claims of the '933, '422, and '349 patents over claim 27 of the '008 patent.

> biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.
>
> 8. A cDNA sequence according to claim 7.
>
> 11. A genomic DNA sequence according to claim 7.
>
> 23. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 7, 8, or 11 in a manner allowing the host cell to express said polypeptide.
>
> 24. A transformed or transfected host cell according to claim 23 which host cell is capable of glycosylating said polypeptide.
>
> 25. A transformed or transfected mammalian host cell according to claim 24.
>
> 27. A transformed or transfected CHO cell according to claim 25.

'008 patent col.40 ll.18–25, 30, 56–64, 67–68. In short, claim 27 recites a CHO cell—a mammalian cell capable of glycosylating EPO—transfected with a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of EPO to allow possession of the stated biological properties.

The asserted claims of the '868 patent are independent claim 1 and dependent claim 2, which recite as follows:

> 1. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> (a) growing, under suitable nutrient conditions, mammalian host cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin; and
>
> (b) isolating said glycosylated erythropoietin polypeptide therefrom.
>
> 2. The process according to claim 1 wherein said host cells are CHO cells.

’868 patent col.40 ll.24–37. In short, claims 1 and 2 cover a process of producing EPO that involves (a) growing mammalian (CHO in claim 2) cells transfected with DNA encoding EPO and (b) isolating from those cells glycosylated EPO having the stated biological properties in vivo (i.e., in live animals).

The asserted claims of the ’698 patent are independent claim 6 and dependent claims 7–9, which recite as follows:

> 6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and
>
> b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.
>
> 7. The process of claim 6 wherein said vertebrate cells further comprise amplified marker gene DNA.
>
> 8. The process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA.
>
> 9. The process according to claims 2, 4 and 6 wherein said cells are mammalian cells.

’698 patent col.38 ll.50–64. Claims 6–9 of the ’698 patent are similar to claims 1 and 2 of the ’868 patent, but with an additional limitation that the host cells comprise amplified DNA (which includes a marker gene in claim 7 that is DHFR in claim 8).

The district court determined that the asserted claims in the ’868 and ’698 patents were patentably distinct from claim 27 of the ’008 patent. The court identified the following differences between the asserted claims of the ’868 and ’008 patents:

> “Unlike the asserted claims of the ’868 patent, none of the ’008 claims require: (1) that the recited host cell actually express any EPO polypeptide; (2) that the recited host cell actually express a glycosylated

> EPO polypeptide; (3) that the host cell be capable of producing an isolatable amount of a glycosylated EPO polypeptide; and (4) that any glycosylated EPO isolated from cells grown in culture have the stated in vivo function."

Amgen, 581 F. Supp. 2d at 184 (quoting Pl's Mem. Supp. No Obviousness-Type Double Patenting [Doc. 1310] at 41). Citing the declaration testimony of Amgen's expert, Dr. Harvey F. Lodish, the court deduced that "[s]imply having the starting material (which is reflected in the '008 patent) and knowing that, in theory, it can be used to create proteins is not the equivalent of having an actual process that successfully does so." Amgen, 581 F. Supp. 2d at 184. For similar reasons, the court concluded that claims 6–9 of the '698 patent were also patentably distinct over the claims of the '008 patent. Id. at 186. It determined that "[t]o be able to produce [a glycosylated, in vivo biologically active EPO product] from cells containing multiple copies of EPO DNA would have been novel to one skilled in the art at the time of the invention (even if the skilled artisan had possession of the product claimed in the '008 patent)." Id. The court also noted that the "PTO found the '868 and '698 claims patentably distinct from those in the '008 patent." Id. From there, the court concluded: "The credible evidence shows, and the Court so finds, that each invention claimed in the '868 and '698 asserted claims is patentably distinct from each invention claimed in the '008 patent." Id.

On appeal, Roche contends that claims 1 and 2 of the '868 patent and claims 6–9 of the '698 patent are obvious over claim 27 of the '008 patent. Roche's Br. 28. Roche characterizes claim 27 of the '008 patent as drawn to host cells capable of expressing a glycosylated EPO polypeptide that "allow[s] possession" of in vivo biological EPO activity. Id. In turn, it characterizes claims 1 and 2 of the '868 patent and claims 6–9 of the '698 patent as drawn to processes for producing in host cells

EPO "having" that stated activity. Id. Roche argues that this difference—"having" rather than "allow[ing] possession" of the stated activity—is not a patentable distinction. Id. In Roche's view, "having" in vivo activity is obvious if the originally claimed host cells "allow possession" of such activity. Id.

Roche also argues that claim 27 of the '008 patent created a reasonable expectation that an ordinarily skilled artisan could successfully practice the processes described in the asserted claims of the '868 and '698 patents. Id. at 31. Claim 27 of the '008 patent evidences on its face a reasonable expectation of success, according to Roche, because it "allow[s] possession" of biologically active EPO—the invention recited in the asserted claims of the '868 and '698 patents. Roche's Reply Br. 8. In addition, Roche argues that Dr. Lodish's testimony demonstrates that an ordinarily skilled artisan would have had a reasonable expectation of success of producing biologically active EPO in CHO cells. Id. Specifically, Roche highlights Dr. Lodish's testimony that a person of ordinary skill in the art could use claim 27's host cells to express a functional protein "without any difficulty." Id. (quoting Trial Tr. vol. 2, 109, Oct. 4, 2007). Lastly, Roche points to Dr. Lin's admission that he expected that the claim 27 host cells would have in vivo activity. Id. at 9–11 (citing Trial Tr. vol 12, 1884, Sept. 27, 2007).

Amgen responds that claim 27 of the '008 patent does not render obvious claims 1 and 2 of the '868 patent or claims 6–9 of the '698 patent. Amgen's Br. 25. Amgen argues that, contrary to Roche's contention, the host cells recited in claim 27 of the '008 patent do not inevitably produce the biologically active EPO required by the asserted claims of the '868 and '698 patents. Id. Amgen emphasizes that it is not the host cells

that "allow possession of" the stated biological activities; rather, it is the amino acid sequence encoded by the DNA recited in claim 27. Id. at 28. This distinction is critical, in Amgen's view, because there is a vast difference between a CHO cell equipped to produce a polypeptide whose amino acid sequence may permit possession of certain biological activity, and a process that produces a human glycoprotein that actually possesses that activity. Id. at 29. In other words, Amgen argues that while an EPO polypeptide sequence might be necessary, it alone would not be sufficient to produce an EPO product with the stated biological activities. Id.

Amgen also argues that an ordinarily skilled artisan in 1983–84 would not have reasonably expected the host cells in claim 27 of the '008 patent to produce the isolatable, biologically active EPO required by the asserted claims of the '868 and '698 patents. Id. at 32. According to Amgen, before 1984, it was not known whether any recombinant cell—including non-human CHO cells—could be engineered to produce a human EPO glycoprotein with in vivo biological activity. Id. Amgen points out that Dr. Lodish testified at trial that, before 1984, no one had successfully produced any recombinant human glycoprotein where the carbohydrate structures were required for biological activity. Id. at 33 (citing Trial Tr. vol. 2, 83, 102–103, Oct. 4, 2007). As a result, Amgen contends, skilled artisans could not have reasonably expected CHO cells to produce a biologically active EPO glycoprotein. Id.

We agree with the district court that claims 1 and 2 of the '868 patent and claims 6–9 of the '698 patent are not invalid for obviousness-type double patenting over claim 27 of the '008 patent. The obviousness-type double patenting analysis entails two steps: (1) construction of the claims in the earlier patent and the claim in the later

patent to identify any differences, and (2) determination of whether the differences in subject matter between the claims render the claims patentably distinct. See Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 968 (Fed. Cir. 2001). Accordingly, we begin our obviousness-type double patenting analysis, as the district court's analysis began, by construing the claims and identifying any differences. As mentioned, claim 27 of the '008 patent recites a CHO cell—a mammalian cell capable of glycosylating EPO—transfected with a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of EPO to allow possession of the stated biological properties. Claims 1 and 2 of the '868 patent and claims 6–9 of the '698 patent recite processes of producing EPO that involve (a) growing mammalian cells transfected with DNA encoding EPO and (b) isolating from those cells glycosylated EPO having the stated biological properties.

In essence, claim 27 of the '008 patent recites the starting materials necessary to execute the processes recited in the asserted claims of the '868 and '698 patents. The cells described in claim 27 are "capable of glycosylating" EPO and are transfected with DNA encoding a polypeptide "having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession" of the stated biological activities. Neither of these limitations in claim 27, however, requires that the cells actually produce isolatable amounts of glycosylated EPO having the stated in vivo bioactivity. In contrast, the asserted claims of the '868 and '698 patents do require actual production of isolatable amounts of the in vivo biologically active EPO glycoprotein. In addition to possessing the transfected CHO cells recited in claim 27 of the '008 patent, an ordinarily skilled artisan practicing the asserted claims of the '868 and '698 patents would need to grow

those cells and isolate from them glycosylated EPO having the stated in vivo biological properties. Thus, the main difference between claim 27 of the '008 patent and the asserted claims of the '868 and '698 patents is the actual production of isolatable glycosylated EPO having the stated in vivo biological activities.

Next, we must determine whether this difference renders claims 1 and 2 of the '868 patent and claims 6–9 of the '698 patent patentably distinct over claim 27 of the '008 patent. In so doing, we ask whether the identified difference renders the claims of the '868 and '698 patents non-obvious to a person of ordinary skill in the art in light of the prior art. See In re Kaplan, 789 F.2d 1574, 1580 (Fed. Cir. 1986). This part of the obviousness-type double patenting analysis is analogous to an obviousness analysis under 35 U.S.C. § 103, except that the '008 patent is not considered prior art. See In re Longi, 759 F.2d 887, 892 n.4 (Fed. Cir. 1985) ("[A] double patenting of the obviousness type rejection is analogous to [a failure to meet] the non-obviousness requirement of 35 U.S.C. § 103, except that the patent principally underlying the double patenting rejection is not considered prior art." (quotation marks omitted)).

An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art. See In re Kubin, 561 F.3d 1351, 1360 (Fed. Cir. 2009) ("[S]tated in the familiar terms of this court's longstanding case law, the record shows that a skilled artisan would have had a resoundingly 'reasonable expectation of success' in deriving the claimed invention in light of the teachings of the prior art."); In re O'Farrell, 853 F.2d 894, 904 (Fed. Cir. 1988) ("For obviousness under § 103, all that is required is a reasonable expectation of success."); see also Longi, 759 F.2d at 896–97 (holding that a patent

application was properly rejected for obviousness-type double patenting where the prior art references indicated a reasonable expectation of success). At trial, Roche had the burden of showing by clear and convincing evidence that a person of ordinary skill in the art in possession of the transfected CHO cells would have had a reasonable expectation of success in producing a recoverable amount of in vivo biologically active EPO. See Pharmastem Therapeutics, Inc. v. Viacell, Inc., 491 F.3d 1342, 1360 (Fed. Cir. 2007) ("[T]he burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to . . . carry out the claimed process, and would have had a reasonable expectation of success in doing so."). Whether an ordinarily skilled artisan would have reasonably expected success in practicing the asserted claims of the '868 and '698 patents is measured as of the date of the inventions described in those patents.[9] See Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1326 (Fed. Cir. 2000) (measuring reasonable expectation of success from the perspective of a person of ordinary skill in the art at the time the invention was made).

In our view, the identified difference between the asserted claims of the '868 and '698 patents and claim 27 of the '008 patent renders the claims patentably distinct. We conclude that the actual production of glycosylated EPO having the stated in vivo biological activities would not have been obvious to an ordinarily skilled artisan in possession of the transfected CHO cells described in claim 27. That is because one of

[9] As discussed in Part I.C, we reject Roche's contention that, under Takeda, a reasonable expectation of success must be measured at the time of the filing of the '868 patent (August 15, 1995) and '698 patent (April 8, 1997) instead of their effective filing date (November 30, 1984). As explained above, to allow evidence of reasonable expectation of success up to the filing date of the '868 and '698 patents to invalidate Amgen's patents would violate 35 U.S.C. § 120.

ordinary skill in the art would not have reasonably expected to successfully produce isolatable quantities of glycosylated EPO having the stated biological activities in transfected CHO cells. Put most simply, CHO cells transfected with the EPO DNA sequence and the production of recombinant, in vivo biologically active EPO glycoprotein are patentably distinct inventions.

We reach this conclusion in light of Dr. Lodish's declarations and testimony at trial, which demonstrate that an ordinarily skilled artisan would not have reasonably expected success in producing recombinant, in vivo biologically active EPO in CHO cells. According to Dr. Lodish, there are at least two reasons why, prior to Dr. Lin's inventions, a person of ordinary skill in the art would not have had a reasonable expectation of practicing the asserted claims of the '868 and '698 patents: (1) an ordinarily skilled artisan would not have known which, if any, host cells would produce EPO with the carbohydrate structures necessary for its in vivo function; and (2) no one had successfully produced any recombinant glycoprotein with in vivo bioactivity where the carbohydrate structures were important for biological activity.[10] Trial Tr. vol. 2, 83, 102–04, Oct. 4, 2007. As a result, Dr. Lodish testified, an ordinarily skilled artisan would have had "great uncertainty in the ability to make recombinant EPO with carbohydrate chains for in vivo biological activity." Trial Tr. vol. 2, 96, Oct. 4, 2007. According to this testimony and declarations to the same effect, we conclude, like the district court

[10] Dr. Lodish testified that "with the EPO DNA in hand one would have no reasonable expectation of success in generating a recombinant mammalian cell to make an EPO protein with in vivo biological activity." Trial Tr. vol. 2, 83, Oct. 4, 2007. Dr. Lodish then explained the bases for his opinion: "[W]e didn't know any of the post-translational modifications that might have been important for EPO's function. We had no idea which cultured cells, if any, might make these, or introduce these modifications to the EPO. And finally, no one in this 1983 time frame had produced a recombinant glycoprotein with in vivo bioactivity." Id.

concluded, that a person of ordinary skill in the art would not have reasonably expected to successfully isolate from transfected CHO cells recombinant EPO glycoprotein having the stated biological activities.

Roche has pointed to no prior art reference or testimony that demonstrates that an ordinarily skilled artisan would have reasonably expected to successfully produce in CHO cells an in vivo biologically active glycoprotein, much less EPO, where the carbohydrate structures matter for biological activity. Instead, Roche emphasizes Dr. Lin's personal expectation and Dr. Lodish's testimony that claim 27's host cells would and do express glycosylated EPO having the stated biological properties. Neither piece of evidence persuades us that an ordinarily skilled artisan would have reasonably expected such results. First, Dr. Lin's personal expectations are not conclusive of an ordinarily skilled artisan's reasonable expectations. See Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985) ("[O]ne should not go about determining obviousness under § 103 by inquiring into what patentees (i.e., inventors) would have known or would likely have done, faced with the revelations of references."). Second, Dr. Lodish's observation that the transfected CHO cells recited in claim 27 do produce glycosylated EPO having the stated biological activity is one of hindsight, not of reasonable expectation of success at the time of the invention. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007) ("A factfinder should be aware . . . of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning."). Therefore, the district court did not erroneously conclude that no reasonable jury could have found that Roche proved by clear and convincing evidence a reasonable expectation of success.

For these reasons, we affirm the district court's grant of JMOL that claims 1 and 2 of the '868 patent and claims 6–9 of the '698 patent are not invalid for obviousness-type double patenting over claim 27 of the '008 patent.

II

Anticipation

Roche argues that claim 1 of the '422 patent and claims 3, 7, and 8 of the '933 patent are anticipated by EPO purified from urine by Dr. Goldwasser. See, e.g., Takaji Miyake, Charles K.-H Kung, & Eugene Goldwasser, Purification of Human Erythropoietin, 252 J. Biological Chemistry 5558 (1977).

A

The question of anticipation of claim 1 of the '422 patent was presented to the jury. However, after Roche, but before Amgen, presented its case-in-chief, Amgen moved for JMOL of no anticipation of claim 1 of the '422 patent, which the district court granted. Amgen, 581 F. Supp. 2d at 193. Claim 1 of the '422 patent recites:

> A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.

'422 patent col.38 ll.36–41. As a matter of claim construction, the district court determined that claim 1 of the '422 patent required EPO to be "purified from mammalian cells grown in culture" ("the '422 source limitation").[11] Amgen, 581 F. Supp. 2d at 193.

[11] The court construed the source limitation "purified from mammalian cells grown in culture" in claim 1 of the '422 patent as "obtained in substantially homogeneous form from the mammalian cells, using the word from in the sense that it originates in the mammalian cells, without limitation to it only taking it directly out of the interior of the cells, which have been grown in the in vitro culture." Amgen, Inc. v. F. Hoffman-La Roche Ltd., 494 F. Supp. 2d 54, 65 (D. Mass. 2007) ("Markman").

In deciding the JMOL motion, the court found that "[t]he undisputed record revealed that none of the allegedly anticipatory art was 'purified from mammalian cells grown in culture.'" Id. In particular, the court determined that Dr. Goldwasser's study, which involved EPO purified from urine, did not involve EPO purified from mammalian cells grown in culture. Id. at 197. The court rejected Roche's contention that Dr. Goldwasser's urinary EPO anticipated claim 1 of the '422 patent because at least some of the recombinant EPO would be structurally indistinguishable from urinary EPO. Id. The court reasoned that EPO extracted from urine and synthetically engineered EPO differ in glycosylation patterns, specific activity, stability in the human body, and ability to be mass produced. Id. at 194–95. As a result, the court concluded that no reasonable jury could find that Roche had proved by clear and convincing evidence that claim 1 of the '422 patent was anticipated. Id. at 193.

The question of whether claims 3, 7, and 8 of the '933 patent are anticipated by EPO purified from urine by Dr. Goldwasser has a different procedural history than the issue of whether the Goldwasser prior art anticipated claim 1 of the '422 patent. The issue of anticipation of the claims of the '933 patent went to the jury, which returned a verdict of no invalidity. After the verdict was rendered, Roche moved for JMOL of invalidity and for a new trial. Denying Roche's motion for renewed JMOL and its motion for a new trial, the district court sustained the jury verdict of no anticipation of claims 3, 7, and 8 of the '933 patent. Trial Tr. vol. 20, 2981, Oct. 17, 2007. Those claims are as follows:

> 3. A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing the in

> vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.
>
> 7. The glycoprotein product according to claims 3, 4, 5 or 6 wherein the host cell is a non-human mammalian cell.
>
> 8. The glycoprotein product according to claim 7 wherein the non-human mammalian cell is a CHO cell.

'933 patent col.38 ll.26–31, 64–67. Independent claim 3, from which claims 7 and 8 depend, recites the relevant limitation. That limitation is a "product of . . . expression in a mammalian host cell," which is similar to the source limitation present in claim 1 of the '422 patent ("purified from mammalian cells grown in culture"). As a matter of claim construction, the district court determined that claim 3 of the '933 patent required EPO to be "the product of . . . expression in a mammalian host cell" ("the '933 source limitation").[12]

B

On appeal, Roche argues that the district court erred in its determination that Goldwasser's urinary EPO does not anticipate claim 1 of the '422 patent. Roche's Br. 43, 46. In making its anticipation argument, Roche relies on our statement in Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1354 n.20 (Fed. Cir. 2003) ("TKT II"), that "a claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations." Starting from this premise, Roche argues that claim 1 of the '422 patent is not patentable based on the

[12] The court construed the relevant part of independent claim 3 of the '933 patent as follows: "a non-naturally occurring glycoprotein product of the expression in a mammalian host cell" is "a glycoprotein (not occurring in nature) that is the product of the expression in a mammalian host cell," where "expression means that the glycoprotein was produced in a cell and recovered from the cell culture." Markman, 494 F. Supp. 2d at 71–72 (footnote omitted).

addition of the source limitation ("purified from mammalian cells grown in culture") because the EPO recited in claim 1 of the '422 patent is the same as urinary EPO. Roche's Br. 44. In other words, Roche argues that, even though Dr. Goldwasser's EPO is purified from urine, it anticipates claim 1 of the '422 patent because the "purified from mammalian cells grown in culture" source limitation fails to impart novel structure onto EPO. Id. In Roche's view, it demonstrated by clear and convincing evidence that at least some EPO purified from mammalian cells grown in culture is structurally identical to Dr. Goldwasser's urinary EPO. Id. at 44. That evidence included testimony from Roche's expert, Dr. Carolyn Bertozzi, Amgen's publications, and Amgen's submissions to the FDA. Id. Because the source limitation does not impart novel structures onto EPO, Roche argues, the district court erred in concluding that urinary EPO does not anticipate claim 1 of the '422 patent.

Amgen argues that the district court did not err in granting JMOL that Dr. Goldwasser's urinary EPO does not anticipate claim 1 of the '422 patent because it is not "purified from mammalian cells grown in culture." Amgen's Br. 48. Amgen contends that, because the source limitation imparts both novel structure and function onto EPO, and because it is undisputed that Dr. Goldwasser's EPO was purified from urine, urinary EPO does not anticipate claim 1 of the '422 patent. Id. at 48–49. In support of the structural and functional distinctiveness of recombinant EPO, Amgen points to the declarations of its expert, Dr. Ajit Varki, and the specification and prosecution history of the '422 patent. Id. at 50. Amgen notes in particular that the specification shows that, due to different glycosylation patterns, recombinant EPO has a higher molecular weight and a different charge than urinary EPO. See '422 patent col.28 l.48–col.29 l.24.

As far as the ’933 patent is concerned, Roche argues that it is entitled to a new trial because the district court erred in its jury instructions. Roche’s Br. 46. The court, in error according to Roche, refused to deliver Roche’s requested jury instruction that “you can anticipate a product-by-process claim even if the product in the prior art is not made by the same process.” Roche’s Br. 46–47. Instead, the court instructed the jury that anticipation requires the prior art to possess “every single element of a particular claim,” Trial Tr., vol. 20, 3012, Oct. 17, 2007, and that “[a] product-by-process claim is a claim to a product made by the recited process,” Trial Tr. vol 23, 3171, Oct. 22, 2007. Those instructions, in Roche’s view, improperly implied to the jury that a process limitation absent from the prior art sufficed to avoid anticipation. Roche’s Br. 47.

Amgen responds that the district court delivered appropriate jury instructions on anticipation. Amgen’s Br. 57. In Amgen’s view, the court correctly instructed the jury to consider every limitation of the asserted claims of the ’933 patent, which gave effect to the source limitation. Id. Because the source limitation imparts structural and functional distinctiveness onto EPO, Amgen contends, it must define EPO recited in the asserted claims of the ’933 patent. Id. Amgen points out that, at trial, expert testimony, experimental data, and publications demonstrated differences in structure and function between urinary EPO and recombinant EPO. Id. at 50–54. Thus, Amgen contends, the jury instructions were correct as a matter of law. Id. at 57.

C

“A patent is presumed to be valid, and this presumption only can be overcome by clear and convincing evidence to the contrary.” Enzo Biochem, Inc. Gen-Probe Inc., 424 F.3d 1276, 1281 (Fed. Cir. 2005) (citation omitted). A patent claim is invalid by

reason of anticipation if "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a). Anticipation under § 102(a) generally requires the presence in the prior art of each and every limitation of the claimed invention. Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1282 (Fed. Cir. 2000).

It has long been the case that an old product is not patentable even if it is made by a new process. See Gen. Elec. Co. v. Wabash Appliance Corp., 304 U.S. 364, 373 (1938) ("Wabash") ("[A] patentee who does not distinguish his product from what is old except by reference, express or constructive, to the process by which he produced it, cannot secure a monopoly on the product by whatever means produced."); Cochrane v. Badische Anilin & Soda Fabrik, 11 U.S. 293, 311 (1884) ("BASF") ("While a new process for producing [the product] was patentable, the product itself could not be patented even though it was a product made [by an artificial process] for the first time."); SmithKline Beecham Corp. v. Apotex Corp., 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product . . . as produced by a particular process."); In re Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985) ("If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a difference process."); Tri-Wall Containers, Inc. v. United States, 408 F.2d 748, 750 (CCPA 1969) ("It is well established that a product as made by a new process is not patentable unless the product itself is new.").

However, a new product may be patented by reciting source or process limitations so long as the product is new and unobvious. See Wabash, 304 U.S. at 373 ("[I]n some instances a claim may validly describe a new product with some reference to the method of production . . . ."); BASF, 111 U.S. at 311 (determining that "an old article" made by a new process was not patentable); In re Luck, 476 F.2d 650, 653 (CCPA 1973) ("[I]t is well established that product claims may include process steps to wholly or partially define the claimed product."); In re Brown, 459 F.2d 531, 535 (CCPA 1972) ("[I]t is the patentability of the product claimed and not of the recited process steps which must be established."); In re Pilkington, 411 F.2d 1345, 1348 (CCPA 1969) ("[P]atentability of a claim to a product does not rest merely on a difference in the method by which that product is made. Rather, it is the product itself which must be new and unobvious.").

We begin the anticipation analysis with the '422 patent. In that connection, the first question we must answer is whether, as a matter of claim construction, the district court erred in determining that claim 1 of the '422 patent claimed a product reciting a source limitation. Amgen, 581 F. Supp. 2d at 194. We conclude that the court did not err. The reason is that, by its plain terms, claim 1 of the '422 patent claims a product with a source limitation. See TKT II, 314 F.3d at 1329 ("[T]he limitation 'purified from mammalian cells grown in culture' in claim 1 [of the '422 patent] clearly limits the source of the EPO used in the claimed 'pharmaceutical composition.'"). Indeed neither party argues otherwise.

The question we must next address is 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. In other words, does the source limitation "purified from mammalian cells grown in culture" distinguish recombinant EPO from Dr. Goldwasser's urinary EPO? See SmithKline Beecham, 439 F.3d at 1315; In re Luck, 476 F.2d at 653. We see no error in the district court's grant of JMOL in favor of Amgen. The court had before it the specification and prosecution history of the '422 patent, both of which refer to studies indicating that recombinant EPO had a higher molecular weight and different charge than urinary EPO due to differences in carbohydrate composition. '422 patent col.28 l.48–col.29 l.24. The prosecution history also contains a declaration from Amgen's expert, Dr. Richard D. Cummings, explaining that recombinant EPO can be distinguished from urinary EPO based on its carbohydrate content. At trial, Amgen's expert, Dr. Varki, testified at length regarding differences in the carbohydrate composition of recombinant EPO and urinary EPO. Based on this evidence, the presumption of patent validity, and Roche's burden of clear and convincing evidence, we conclude that the court did not err in determining a reasonable jury could only have concluded that EPO "purified from mammalian cells grown in culture" is a new product claimed with reference to its source. Therefore, we affirm the district court's grant of JMOL to Amgen of no anticipation of claim 1 of the '422 patent.

D

We turn now to Roche's claim that an erroneous jury instruction by the district court entitles it to a new trial on the issue of whether Dr. Goldwasser's urinary EPO anticipated claims 3, 7, and 8 of the '933 patent. As mentioned, Roche contends that the jury found no anticipation of the claims of the '933 patent based on the false premise

that the absence of the source limitation from the prior art sufficed to avoid anticipation. We also previously noted that the source limitation "product of . . . expression in a mammalian host cell" recited in independent claim 3, from which claims 7 and 8 depend, is similar to the source limitation present in claim 1 of the '422 patent ("purified from mammalian cells grown in culture").

We review decisions on motions for a new trial under the law of the regional circuit, which is the First Circuit in this case. DePuy Spine, 567 F.3d at 1334. The First Circuit reviews the district court's denial of a motion for a new trial for manifest abuse of discretion. Seahorse Marine Supplies, Inc. v. P.R. Sun Oil Co., 295 F.3d 68, 82 (1st Cir. 2002). We review "the legal sufficiency of jury instructions on an issue of patent law without deference to the district court."[13] Broadcom Corp. v. Qualcomm Inc., 543 F.3d 683, 697 (Fed. Cir. 2008) (quotation marks omitted). "A jury verdict will be set aside, based on erroneous jury instructions, if the party seeking to set aside the verdict can establish that those instructions were legally erroneous, and that the errors had prejudicial effect." NTP, Inc. v. Research In Motion, Ltd., 418 F.3d 1282, 1311 (Fed. Cir. 2005) (quotation marks omitted). Accordingly, "a party seeking to alter a judgment

[13] There may be some question as to whether this court reviews jury instructions relating to patent law under our own law or regional circuit law. Compare, e.g., Broadcom Corp. v. Qualcomm Inc., 543 F.3d 683, 697 (Fed. Cir. 2008) (reviewing a challenge to jury instructions under Federal Circuit law), with Kinetic Concepts, Inc. v. Blue Sky Med. Group, Inc., 554 F.3d 1010, 1021 (Fed. Cir. 2009) ("Challenges to jury instructions are reviewed under the law of the regional circuit where the district court sits." (quotation marks omitted)). Since our review of jury instructions does not seem to substantially differ from that of the First Circuit, we apply our law here. See Seahorse Marine, 295 F.3d at 76 ("We review jury instructions de novo, bearing in mind that the district court's refusal to give a particular instruction constitutes reversible error only if the requested instruction was (1) correct as a matter of substantive law, (2) not substantially incorporated into the charge as rendered, and (3) integral to an important point in the case." (quotation marks omitted)).

based on erroneous jury instructions must establish that (1) it made a proper and timely objection to the jury instructions, (2) those instructions were legally erroneous, (3) the errors had prejudicial effect, and (4) it requested alternative instructions that would have remedied the error." Id. at 1311–12 (quotation marks omitted).

Roche requested the following jury instruction: "You can anticipate a product-by-process claim even if the product in the prior art is not made by the same process." The district court did not give that instruction. Rather, it instructed the jury that "[a] claim is anticipated only if each and every element as set forth in the claim is disclosed either expressly or inherently in a single prior art reference." See Trial Tr. vol. 20, 3011–12, Oct. 17, 2007. In effect, the jury was instructed that Dr. Goldwasser's urinary EPO anticipated the asserted claims of the '933 patent only if it met the source limitation "product of . . . expression in a mammalian host cell."

We recognize that, by omitting Roche's proposed instruction or a similar instruction, the district court effectively took away from the jury the question of whether the asserted claims of the '933 patent recite an old product (urinary EPO) made by a new process (recombinant production). In other words, the court decided as a matter of law that the asserted claims of the '933 patent recite a new product defined by the source limitation "product of . . . expression in a mammalian host cell." It appears that the court did that in view of its grant of JMOL of no anticipation with respect to claim 1 of the '422 patent. As seen, in that ruling, the court determined that no reasonable jury could find that the recombinant EPO described in the asserted claims of the '422 patent was an old product, given the structural distinctions between urinary and recombinant

EPO attributable to recombinant EPO's source. Amgen, 581 F. Supp. 2d at 194–95, 198.

In this case, we do not think the jury verdict should be overturned because the court, and not the jury, decided the question of whether the asserted claims of the '933 patent recite an old product (urinary EPO) made by a new process (recombinant production). The court's instruction was legally correct and not clearly misleading as long as the EPO recited in the asserted claims of the '933 patent is a new product described in terms of its source. That requirement was met. For purposes of the source limitation, which is what is at issue, there essentially is no difference between claim 1 of the '422 patent ("erythropoietin . . . purified from mammalian cells grown in culture") and claim 3 of the '933 patent ("[a] non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin"). At the same time, we hold above that the EPO of claim 1 of the '422 patent is a new product. The same holding necessarily applies to claim 3 of the '933 patent. In short, a reasonable jury could not have found that recombinant EPO described in the asserted claims of the '933 patent was an old product. Under these circumstances, the court's instructions requiring anticipatory prior art to meet the source limitations recited in the asserted claims of the '933 patent were legally sufficient and non-prejudicial.

E

Roche raises one additional argument relating to anticipation of the asserted claims of the '422 and '933 patents. Roche argues that the district court erred in construing the source limitations in the validity context differently than in the

infringement context. Roche's Br. 54. In the context of validity, the district court construed the source limitations as imparting novel structures that distinguish recombinant EPO from urinary EPO. Amgen, 581 F. Supp. 2d at 193–98. As will be seen below, when addressing the issue of whether Roche's MIRCERA® product infringed the '422 and '933 patents, the district court did not require MIRCERA® to possess novel structures that distinguish recombinant EPO from urinary EPO. Id. at 204–05. Quoting Amazon.com, Inc. v. Barnesandnoble.com, Inc., Roche relies on the axiom that "claims must be interpreted and given the same meaning for purposes of both validity and infringement analyses." 239 F.3d 1343, 1351 (Fed. Cir. 2001). Roche contends that, for validity, but not infringement, the court required the source limitations to impart novel structure onto EPO. Roche's Br. 54. According to Roche, because the court did not require Amgen to show for infringement that MIRCERA® possessed novel structures that distinguish it from urinary EPO, the court should not have required Roche to prove for anticipation that the source limitation does not impart novel structure onto EPO. Id. at 55. Roche urges that, without the requirement to prove that recombination imparted novel structures to Amgen's EPO, urinary EPO anticipates recombinant EPO as a matter of law. Id. We are not persuaded by Roche's argument.

In determining validity of a product-by-process claim, the focus is on the product and not on the process of making it. See Atl. Thermoplastics Co. v. Faytex Corp., 970 F.2d 834, 841 (Fed. Cir. 1992) (explaining that, in BASF, the validity rule "focused on the product with less regard for the process limits"); Brown, 459 F.2d at 535 (focusing on the product claimed and not the process); Pilkington, 411 F.2d at 1348 (noting that the product itself must be new). That is because of the already described, long-

standing rule that an old product is not patentable even if it is made by a new process.[14] As a result, a product-by-process claim can be anticipated by a prior art product that does not adhere to the claim's process limitation. In determining infringement of a product-by-process claim, however, the focus is on the process of making the product as much as it is on the product itself. See Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1293 (Fed. Cir. 2009) (en banc). In other words, "process terms in product-by-process claims serve as limitations in determining infringement." Id. (quotation marks omitted). As a result, a product-by-process claim is not infringed by a product made by a process other than the one recited in the claim. Id.

The impact of these different analyses is significant. For product-by-process claims, that which anticipates if earlier does not necessarily infringe if later. That is because a product in the prior art made by a different process can anticipate a product-by-process claim, but an accused product made by a different process cannot infringe a product-by-process claim. Similarly, that which infringes if later does not necessarily anticipate if earlier. That is because an accused product may meet each limitation in a claim, but not possess features imparted by a process limitation that might distinguish the claimed invention from the prior art.

Based on our precedent, the court did not err in conducting its validity and infringement analyses differently. To prove invalidity, Roche had to show that recombinant EPO was the same as urinary EPO, even though urinary EPO was not

[14] Because validity is determined based on the requirements of patentability, a patent is invalid if a product made by the process recited in a product-by-process claim is anticipated by or obvious from prior art products, even if those prior art products are made by different processes. Cf. BASF, 111 U.S. at 311 (assessing the invalidity of an old product recited in a product-by-process claim in terms of patentability).

made recombinantly. The court concluded that Roche did not meet its burden because urinary EPO and recombinant EPO were structurally and functionally different. Those structural and functional differences are not explicitly part of the claim, yet are relevant as evidence of no anticipation because of the source limitation. To prove infringement, Amgen had to show that MIRCERA® comprises EPO made recombinantly, which the court concluded it did. Importantly, Amgen was not required to show that MIRCERA® was also structurally and functionally different from urinary EPO. In other words, for validity, the court correctly required the source limitations to impart novelty onto EPO, but did not require Dr. Goldwasser's EPO to meet the source limitations; for infringement, the court correctly required MIRCERA® to satisfy the source limitations, but did not require MIRCERA® to differ from urinary EPO. For these reasons, the court did not err in conducting distinct validity and infringement analyses of the asserted claims of the '933 and '422 patents.

III

Indefiniteness

Before the jury was charged, Roche moved for JMOL that claim 1 of the '422 patent and claims 3, 7, and 8 of the '933 patent were invalid for indefiniteness. After the district court denied the motion, the jury returned a verdict that the claims were not indefinite. Denying Roche's renewed motion for JMOL and its motion for a new trial, the court sustained the jury verdict that claim 1 of the '422 patent and claims 3, 7, and 9 of the '933 patent were not indefinite. Amgen, 581 F. Supp. 2d at 198–201. On appeal, Roche argues that the court's construction of "human erythropoietin" in claim 1 of the '422 patent and its construction of the source limitation in claim 1 of the '422 patent and

of the source limitation in the asserted claims of the '933 patent render those claims indefinite.

A

Roche contends that the court wrongly construed human EPO in claim 1 of the '422 patent as "[a] protein having the amino acid sequence of human erythropoietin, such as the amino acid sequence of EPO isolated from human urine." Roche's Br. 59 (quoting Markman, 494 F. Supp. 2d at 64). At the time of the invention, Roche contends, no one knew the amino acid sequence of human EPO. Roche's Br. 59. That means, according to Roche, that a skilled artisan confronted with claim 1 of the '422 patent would not have known which amino acid sequence (i.e., the order or number of amino acids) the claim covers. Id. at 60. In Roche's view, this lack of clarity renders the claim indefinite. Id. To make the term human EPO in claim 1 definite, Roche advocates confining its meaning to the specific 166 amino acid sequence disclosed in Figure 6 of the '422 patent specification. Id. at 61.

Amgen responds that the court's construction of human EPO does not render claim 1 of the '422 patent indefinite. Amgen's Br. 61. Amgen points out that the specification defines the claimed product as having the same amino acid sequence as naturally occurring EPO and that it uses human EPO to refer to the product produced according to Example 10 and to urinary EPO. Id. at 62. Amgen also contends that an ordinarily skilled artisan would have understood the parameters of claim 1, and that nothing in the claim or specification requires the court to have limited human EPO to the 166 amino acid sequence disclosed in Figure 6. Id. at 62–63.

Indefiniteness is a question of law. Praxair, Inc. v. ATMI, Inc., 543 F.3d 1306, 1319 (Fed. Cir. 2008). Under 35 U.S.C. § 112, claims must "particularly point[ ] out and distinctly claim[ ] the subject matter which the applicant regards as his invention." If a claim fails to reasonably apprise one skilled in the art of the boundaries of the claim when read in light of the specification, then the claim is invalid under § 112 for indefiniteness. See Miles Labs., Inc. v. Shandon, Inc., 997 F.2d 870, 875 (Fed. Cir. 1993).

We do not think the court's construction of human EPO provides a reason to disturb the jury verdict that claim 1 of the '422 patent is not indefinite. First, the specification of the '422 patent supports the court's construction of human EPO. See In re Marosi, 710 F.2d 799, 803 (Fed. Cir. 1983) (finding claims not indefinite when the specification provided "a general guideline and examples sufficient to enable a person of ordinary skill in the art to determine whether" the claim limitation was satisfied). It defines human EPO as having the same amino acid sequence as naturally occurring EPO and being produced by the process described in Example 10. See '422 patent col.10 ll.12–18; col.15 ll.7–19; col.25 l.27–col.29 l.25. While Figure 6 of the specification discloses a 166 amino acid sequence of human EPO, neither the claim nor the specification defines human EPO in terms of that figure. Therefore, the court correctly construed human EPO as "[a] protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine."

Second, Dr. Lodish's testimony supports a finding that an ordinarily skilled artisan would have understood the boundaries of claim 1 of the '422 patent. Dr. Lodish testified at trial that an ordinarily skilled artisan reading the '422 patent would have understood

what human EPO was. Amgen, 581 F. Supp. 2d at 199. He explained that Figure 6 (i.e., the 166 amino acid sequence of EPO) and Example 10 (describing production of human EPO) in the specification would have reasonably apprised a person of ordinary skill of the scope of human EPO. Id. He also explained that the human EPO produced according to Example 10 would have had 165 amino acids. Id. Based on the specification of the '422 patent and Dr. Lodish's testimony, a jury could have reasonably concluded that claim 1 was not rendered indefinite by the court's construction of human EPO. See Kinetic Concepts, Inc. v. Blue Sky Med. Group, Inc., 554 F.3d 1010, 1022 (Fed. Cir. 2009) (finding a claim not indefinite where the specification provided several examples and the patentee submitted a declaration explaining that the ordinarily skilled artisan would have understood the meaning of the claim).

We are not convinced by Roche's argument that an ordinarily skilled artisan in 1984 could not have known the boundaries of claim 1 of the '422 patent because no one knew the actual amino acid sequence of human EPO. We recognize that an ordinary skilled artisan did not know at the time, and the patent did not explain, that Example 10 would produce, or that urinary EPO possessed, the amino acid sequence disclosed in Figure 6 less the C-terminal amino acid. See Trial Tr. vol. 16, 2339–47 Oct. 3, 2007. That does not mean, however, that an ordinarily skilled artisan at the time of the invention would not have known the scope of human EPO in claim 1. See Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 624 (Fed. Cir. 1985) (explaining that § 112 only requires the claim language to be "as precise as the subject matter permits" (quotation marks omitted)). According to Dr. Lodish's testimony, an ordinarily skilled artisan who possessed urinary EPO or the amino acid disclosed in

Figure 6, or who practiced the invention described in Example 10, would have knowingly been within the scope of claim 1 of the '422 patent, even without knowing that the EPO in hand was actually 165 amino acids in length. Furthermore, Roche has not presented us with any reason as to why the claim is indefinite if human EPO encompasses both the 166 amino acid sequence disclosed in Figure 6 and the 165 amino acid sequence produced by practicing Example 10 and possessed by EPO purified from urine. Therefore, we will not disturb the court's construction of the term human EPO, a construction which we hold does not render claim 1 of the '422 patent indefinite.

B

Roche also argues that the court's construction of the source limitations recited in the asserted claims of the '422 and '933 patents renders the claims indefinite.[15] Roche's Br. 55. In Roche's view, the court concluded that urinary EPO did not anticipate the asserted claims of the '422 and '933 patents because it construed the source limitations to include an implied indefinite term that excludes prior art urinary EPO. Id. According to Roche, the court did not identify which structures distinguish unanticipated recombinant EPO from urinary EPO, and these structures are not defined in the claims. Id. at 56. Moreover, Roche contends, the claims do not avoid indefiniteness based on the glycosylation differences between urinary EPO and recombinant EPO because the carbohydrate structures of urinary EPO were not known. Id. Roche points out that this court has previously stated that "[b]y definition, one must

[15] The source limitation in claim 1 of the '422 patent is "purified from mammalian cells grown in culture," col.38 ll.40–41, while the source limitation in claim 3 of the '933 patent is "product of the expression in a mammalian host cell," col.38 ll.26–27.

know what the glycosylation of uEPO [urinary EPO] is with certainty before one can determine whether the claimed glycoprotein has a glcyosylation different from that of uEPO." Id. (quoting TKT II, 314 F.3d at 1341). The implicit exclusion of urinary EPO from the asserted product claims makes it impossible, in Roche's view, to discern the boundaries of the claims. Id. Accordingly, Roche urges, the implicit term that distinguishes recombinant EPO from urinary EPO renders claim 1 of the '422 patent and claims 3, 7, and 8 of the '933 patent indefinite. Roche's Br. 57.

Amgen responds that the asserted claims of the '422 and '933 patents are not indefinite under the district court's construction of the source limitations. Amgen's Br. 59. The product claims are definite, according to Amgen, because they encompass whatever EPO glycoprotein structures result from the recited process's production. Id. at 61. Amgen contends that it was not required to claim EPO in terms of specific carbohydrate structures. Id.

We conclude that the source limitations do not render the asserted claims of the '422 and '933 patents indefinite. Roche correctly points out that the district court found that the asserted claims were not anticipated by urinary EPO because recombinant EPO and urinary EPO are structurally and functionally distinct. Roche is also correct that those structural and functional distinctions are not stated on the face of the claims. That does not mean, however, that the court implicitly construed the source limitations to include those structural and functional differences. See supra Part II.E (explaining that validity and infringement analyses of product-by-process claims differ). Rather, the court construed the source as a limitation of the asserted claims and found that the source imparted structural and functional features not possessed by EPO purified from

urine. The structural and functional differences were therefore relevant to the court's finding that recombinant EPO was a new product claimed with reference to the source from which it was obtained. See Brown, 459 F.2d at 535 ("[T]he lack of physical description in a product-by process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established."). Contrary to Roche's assertions, findings of fact that go to the question of validity of product-by-process claims do not automatically become part of claim construction.

We note that, if we carried Roche's argument to its logical conclusion, product-by-process claims would be indefinite in instances where the product-by-process format is often preferred. Patentees often use process limitations to distinguish their product from prior art products because their product cannot accurately be discriminated from the prior art except by reference to the process by which it is obtained. See, e.g., Pilkington, 411 F.2d at 1349 ("[T]he differences between the [claimed product] and the [product] of the prior art do not appear to us to be particularly susceptible to definition by the conventional recitation of properties or structures."). In those situations, the product-by-process format allows the patentee to obtain a patent on the product even though the patentee cannot adequately describe the features that distinguish it from prior art products. In effect, the process limitation embodies the difficult-to-describe distinctions that render the product patentable. Thus, to call the process limitation indefinite in this situation would defeat one of the purposes of product-by-process

claims, namely permitting product-by-process claims reciting new products lacking physical description.

We therefore affirm the court's decision to sustain the jury verdict that claim 1 of the '422 patent and claims 3, 7, and 8 of the '933 patent are not invalid for indefiniteness.

IV

Infringement

Roche challenges the findings that MIRCERA® literally infringes claim 1 of the '422 patent; claims 3, 7, and 8 of the '933 patent; claims 1 and 2 of the '868 patent; and claims 6–9 of the '698 patent.

Infringement is a question of fact. Leapfrog Enters., Inc. v. Fisher-Price, Inc., 485 F.3d 1157, 1159 (Fed. Cir. 2007). To prove infringement, the patentee must show that an accused product embodies all limitations of the claim either literally or by the DOE. TIPS Sys., LLC v. Phillips & Brooks/Gladwin, Inc., 529 F.3d 1364, 1379 (Fed. Cir. 2008); see also Tech. Licensing Corp. v. Videotek, Inc., 545 F.3d 1316, 1327 (Fed. Cir. 2008) (stating that, to prove infringement, the patentee has the burden of persuasion by a preponderance of the evidence). If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law. TIPS Sys., 529 F.3d at 1379. We begin our infringement analysis with the product patents.

A

The district court granted Amgen summary judgment of infringement of claim 1 of the '422 patent after finding that MIRCERA® comprised human EPO. 581 F. Supp. 2d at 201. In the court's view, Roche's internal documents and representations to the FDA

confirmed that MIRCERA® contains human EPO, which the court defined by its amino acid sequence. Id. at 202. The court found that Roche's internal documents referred to CERA, the active ingredient in MIRCERA®, as "peg-EPO," and that Roche represented to the FDA that CERA and epoetin beta, the starting material of MIRCERA®, have the same amino acid sequence. Id. Relying on A.B. Dick Co. v. Burroughs Corp., 713 F.2d 700, 703 (Fed. Cir. 1983), for the proposition that "one cannot avoid infringement merely by adding elements," the court rejected Roche's argument that MIRCERA® does not contain EPO because CERA is formed through pegylation. Id. at 203. Thus, the court concluded that MIRCERA® literally infringes claim 1 of the '422 patent. Id. After hearing all of the evidence at trial, the jury similarly concluded that MIRCERA® literally infringed claims 3, 7, and 8 of the '933 patent. The court then denied Roche's motion for JMOL of non-infringement with respect to those claims.

On appeal, Roche argues that MIRCERA® does not infringe the asserted claims of the '422 and '933 patents because MIRCERA® is not produced and purified from mammalian cells. Roche's Br. 48. Roche interprets the source limitations in both patents as requiring that the accused product actually be produced by a mammalian cell. Id. Roche contends that MIRCERA® cannot meet the cell-produced limitations because it is indisputably made in a cell-free reaction. Id. at 50. In addition, Roche argues that, once it is formed, MIRCERA® is a novel, intact molecule that no longer contains human EPO. Id. Although Roche takes issue with the court's analysis of MIRCERA®'s precursor, epoetin beta, it contends that epoetin beta also does not meet the source limitations because epoetin beta loses a hydrogen atom when it reacts with a PEG molecule. Id. at 51. Lastly, Roche argues that the court erred in failing to instruct

the jury that the asserted claims of the '933 patent require a product with a structure capable of being produced in a mammalian host cell. Id. at 52.

Amgen responds that the source limitations do not exclude the attachment of further structure, such as PEG, to human EPO. Amgen's Br. 64. Amgen points to the specification, which describes the chemical attachment of materials, such as detectable markers, to the claimed glycoprotein products. Id. (citing '422 patent col.12 ll.12–16). Amgen contends, as the district court determined, that the source limitations pertain to the source of human EPO, not MIRCERA®, and that they do not preclude the addition of other materials. Id. at 65. Pointing to Roche's internal documents and FDA representations, Amgen disputes Roche's assertion that the attachment of PEG fundamentally transforms MIRCERA® so that MIRCERA® does not contain EPO. Id. at 68. In Amgen's view, the removal of a single hydrogen atom from epoetin beta does not change the fact that MIRCERA® contains the sequence of amino acids that defines human EPO in claim 1 of the '422 patent. Id. at 70.

We see no error in the district court's grant of summary judgment that MIRCERA® literally infringes claim 1 of the '422 patent or its ruling denying Roche's motion for JMOL of non-infringement, which sustained the jury's verdict that MIRCERA® literally infringes claims 3, 7, and 8 of the '933 patent.[16] As a preliminary

[16] Claim 1 of the '422 patent recites "[a] pharmaceutical composition comprising a therapeutically effective amount of human erythropoeitin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture." '422 patent col.38 ll.37–41. Claim 3 of the '933 patent, from which claims 7 and 8 depend, recites "[a] non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoeitin said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells." '933 patent col.38 ll.26–31.

matter, no genuine issues of material fact stand in the way of adjudication by summary judgment of the issue of whether MIRCERA® infringes claim 1 of the '422 patent. The court's determination of infringement followed from its application of its construction of two terms in claim 1 to the undisputed facts of the case. The first term is "human erythropoietin"; the second term is the source limitation "purified from mammalian cells grown in culture." '422 patent col.38 ll.37–41. We conclude that the court correctly construed those terms and that, in view of that claim construction, Amgen was entitled to summary judgment that MIRCERA® infringed claim 1 of the '422 patent.[17] Because the source limitation of claim 1 of the '422 patent is, for purposes of Roche's infringement contentions, the same as the source limitation recited in the asserted claims of the '933 patent, we similarly conclude that a reasonable jury could have found that MIRCERA® infringed claims 3, 7, and 8 of the '933 patent.

MIRCERA® comprises "human erythropoietin" because it contains "[a] protein having the amino acid sequence of human erythropoietin, such as the amino acid sequence of EPO isolated from human urine," Markman, 494 F. Supp. 2d at 64. Roche's internal documents and FDA representations reveal that MIRCERA®, or peg-

[17] As noted, the court construed "human erythropoietin" as "[a] protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine." Markman, 494 F. Supp. 2d at 64. The court construed the source limitation "purified from mammalian cells grown in culture" in claim 1 of the '422 patent as "obtained in substantially homogeneous form from the mammalian cells, using the word from in the sense that it originates in the mammalian cells, without limitation to it only taking it directly out of the interior of the cells, which have been grown in the in vitro culture." Id. at 65. The court construed the relevant part of claim 3 of the '933 patent as follows: "a non-naturally occurring glycoprotein product of the expression in a mammalian host cell" is "a glycoprotein (not occurring in nature) that is the product of the expression in a mammalian host cell," where "expression means that the glycoprotein was produced in a cell and recovered from the cell culture." Id. at 71–72.

EPO, comprises a protein having the amino acid sequence of human erythropoietin. Amgen, 581 F. Supp. 2d at 202; see also id. at 172 ("[T]he resulting glycosylated human EPO polypeptide product [of Roche's manufacturing process] contains the identical amino acid sequence as naturally occurring human EPO." (quotation marks omitted)). Those documents, as well as expert testimony, also indicate that the loss of a hydrogen atom, either from a lysine side chain or from the N-terminus of the protein, does not mean that the protein lacks the amino acid sequence of EPO. See id. at 172; see also id. at 207 ("Roche concedes that Amgen's experts provided testimony that pegylation does not change the amino acid sequence of epoetin beta.").

Furthermore, nothing in the claim construction of human EPO excludes the attachment of a PEG molecule, and the common specification to the '422 and '933 patents contemplates the attachment of additional molecules. See, e.g., '422 patent col.12 ll.12–16. Roche's argument that human EPO no longer exists "as a matter of chemistry" once it reacts with a PEG molecule is unpersuasive because the record shows that the human EPO component exists in the final product and confers its structural and functional properties onto MIRCERA®. The record therefore supports the court's conclusion, and the jury's implicit conclusion,[18] that the attachment of a PEG molecule is the addition of an element, which cannot negate infringement, as opposed to a fundamental chemical transformation, which might save MIRCERA® from infringement. Amgen, 581 F. Supp. 2d at 203–04; see also Amstar Corp. v. Envirotech Corp., 730 F.2d 1476, 1482 (Fed. Cir. 1984) ("Modification by mere addition of elements

[18] The court instructed the jury regarding Roche's theory that MIRCERA® is a single molecule, which no longer contains human EPO: "Roche people say that the very fact of the pegylation, the combination, changes it. It's not the same thing. It's something new and different." Trial Tr., vol. 20, 3021, Oct. 17, 2007.

. . . cannot negate infringement, without disregard of . . . long-established, hornbook law . . . .").

MIRCERA® also comprises EPO produced in and purified from mammalian cells, thereby satisfying the source limitations of the asserted claims. Roche's FDA filings and other admissions show that epoetin beta, the starting ingredient for CERA, is produced in and purified from mammalian cells grown in culture. See Amgen, 581 F. Supp. 2d at 172 ("Like Amgen's EPO, epoetin beta is a recombinant EPO formed by injecting DNA encoding human EPO into a CHO cell." (quotation marks omitted)). Roche fundamentally misreads the asserted claims to require that MIRCERA® be produced in, and purified from, mammalian cells and have a cell-produced structure.[19] Yet, all that these claims require is that MIRCERA® comprise EPO produced in and purified from mammalian cells. See '422 patent col.38 ll.40–41 ("wherein said erythropoietin is purified from mammalian cells grown in culture"); '933 patent col.38 ll.26–29 ("product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoetin"). That MIRCERA® itself can only be produced outside a cell is irrelevant to the source limitations. Consequently, the court properly declined to instruct the jury that the source limitation requires MIRCERA® to be cell-produced.

Because MIRCERA® embodies the human EPO and source limitations of the asserted claims, we affirm the district court's grant of summary judgment to Amgen of

[19] Roche's interpretation of the source limitations stems from its contention that, because structures and functions imparted by the source limitations were relevant for anticipation, they too should be relevant for infringement. We have already explained that the anticipation and infringement analyses differ for product-by-process claims. See supra Part II.E.

infringement of claim 1 of the ’422 patent and its denial of JMOL to Roche of non-infringement of claims 3, 7, and 8 of the ’933 patent.

B

Turning to the two process patents, the jury found claims 1 and 2 of the ’868 patent and claims 6–9 of the ’698 patent literally infringed by MIRCERA®. The district court then denied Roche’s motions for JMOL of non-infringement and for a new trial.

Because Roche manufactures MIRCERA® overseas, the jury’s finding of literal infringement of the ’868 and ’698 patents was based on 35 U.S.C. § 271(g), which provides, in relevant part:

> Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. . . . A product which is made by a patented process will, for purposes of this title, not be considered to be so made after—
>
> (1) it is materially changed by subsequent processes . . . .

Section 271(g) makes the importation into the United States of a product made by a process patented in the United States an act of infringement. If, however, the product made by the patented process is “materially changed by subsequent processes” prior to importation, then importation of that product does not constitute infringement. Id. § 271(g)(1). In short, the question before the district court was whether the MIRCERA® product to be imported into the United States by Roche is “materially changed by subsequent processes” so that it is materially different from the product produced by the processes of claims 1 and 2 of the ’868 patent and claims 6–9 of the ’698 patent. See Eli Lilly & Co. v. Am. Cyanamid Co., 82 F.3d 1568, 1575–77 (Fed. Cir. 1996).

On appeal, Roche argues that MIRCERA® did not infringe the '868 and '698 patents under § 271(g) as a matter of law. Roche's Br. 62. That is because the evidence conclusively demonstrates, according to Roche, that MIRCERA® is materially changed prior to importation. Id. at 63. In Roche's view, to determine whether MIRCERA® has been "materially changed," the drug must be compared to the crude product resulting from the claimed processes, and not the FDA-approved Amgen drugs. Id. Comparing unadministerable crude EPO to FDA-approved MIRCERA® evidences a "material change," according to Roche. Id. In addition, Roche observes that, due to the attached PEG molecule, MIRCERA® possesses different structures and properties than Amgen's EPO. Id. at 64. Roche points out that MIRCERA® has thousands more atoms, hundreds of new bonds, a significantly higher molecular weight, a different charge, and improved pharmacokinetic properties. Id. at 64–65. Those changes are material, according to Roche, because MIRCERA® has improved pharmacokinetic characteristics and requires less-frequent dosing than Amgen's products. Id. at 65. Roche contends that the district court should not have allowed the jury's verdict to stand because no reasonable jury could have concluded that purification and pegylation did not materially change the EPO in MIRCERA®. Id.

Roche separately argues, as it did below, that, even if a factual issue existed for the jury to decide, it is entitled to a new trial because the district court erroneously instructed the jury on § 271(g). Id. at 66. The court instructed the jury to "look at the product that would be produced by that [patented] process" and then "look at the product that's produced by the lawful in Europe, but infringing here in the United States, Roche process." Id. That charge was incorrect as a matter of law, Roche contends,

because § 271(g) requires comparison of the products produced by the patented process to the product imported into the United States, and not to the immediate product Roche produces by employing the patented process. Id. According to Roche, the court erred when it instructed the jury that it could "consider whether [MIRCERA®] would work without Amgen's patented process. Would it do what it's supposed to do absent Amgen's patented process." Id. at 66 (quoting Trial Tr., vol. 20, 3026, Oct. 17, 2007). Roche contends that this "but for" test for material change is inconsistent with § 271(g), which refers to a material change and not different processes. Id.

Amgen responds that there was sufficient evidence for a reasonable jury to find that Roche's imported product is not materially changed from the EPO recited in the asserted claims of the '868 and '698 patents. Amgen's Br. 75. According to Amgen, Roche's own documents show that the human EPO in MIRCERA® has the same structure and function as EPO recited in the claims of the '868 and '698 patents. Id. at 75–76. Amgen emphasizes that MIRCERA®'s biological activity depends on EPO. Id. at 76. Amgen disputes whether the claims are limited to crude isolates unsuitable for human use, but argues that, even if they were, Roche's purification process does not materially change the EPO product recited in the asserted claims. Id. at 78.

As for the jury instructions, Amgen contends that the court properly instructed the jury to determine whether Roche's imported product was materially changed from the product of the claimed processes. Amgen argues that the court correctly delivered the following instruction: "If the Roche product is materially changed from the product of the claimed process, Amgen has lost. That product can be imported into the United States and it does not infringe." Id. at 74–75. Amgen also argues that Eli Lilly, 82 F.3d at

1575–77, supports the instruction that the jury was "entitled to consider whether the item would work without Amgen's patented process." Amgen's Br. 74.

We do not think that Roche was entitled to JMOL that MIRCERA® does not infringe the asserted claims of the '868 and '698 patents, because the record supports a determination that the human EPO in MIRCERA® is not "materially changed" by pegylation. Unlike Roche, we do not read the scope of the asserted claims as limited to production of crude EPO. That being said, the record reveals that MIRCERA®, unlike crude EPO, is suitable for administration to patients. The record also reveals structural and functional differences (e.g., size, molecular weight, half-life, atomic composition) between MIRCERA® and EPO produced by the processes recited in the asserted claims. The question that remains for infringement under § 271(g) is whether these differences are material.

Materiality is context-dependent. See Biotech Biologische Naturverpackungen GmbH & Co. v. Biocorp, Inc., 249 F.3d 1341, 1352 (Fed. Cir. 2001) ("Whether a change in a product is material is a factual determination, and is properly for the trier of fact."). In the biotechnology context, a significant change in a protein's structure and/or properties would constitute a material change. Cf. Eli Lilly, 82 F.3d at 1573 ("In the chemical context, a 'material' change in a compound is most naturally viewed as a significant change in the compound's structure and properties."). A good source for determining whether a change in a product of a process is material under § 271(g) is the patent. Where the specification or asserted claims recite a structure or function for the product of the processes, then significant variations from the recited structure and

function are material. What makes a variation significant enough to be a "material change," however, is a question of degree.

In this case, Amgen presented evidence that the structural and functional differences were not material because MIRCERA® still contains EPO, the structure of EPO remains intact, MIRCERA® binds to the EPO receptor, and MIRCERA® retains its claimed ability to increase the production of reticulocytes and red blood cells. See, e.g., Trial Tr., vol. 17, 2495–98, Oct. 4, 2007. The in vivo biological properties of EPO are recited in the claims of the '868 and '698 patents, so significant variations therefrom (e.g., a significant increase in the production of red blood cells) would constitute material changes. See '868 patent col.40 ll.27–29; '698 patent col.38 ll.51–53. The record reflects, however, that MIRCERA® and human EPO stimulate erythropoiesis similarly. See Trial Tr., vol. 17, 2488–91, Oct. 4, 2007. Roche did not argue to the contrary. Instead, Roche presented evidence that the identified structural and functional changes confer pharmacokinetic properties onto MIRCERA® that render it superior to EPO made by the claimed processes. In particular, Roche emphasized that MIRCERA®'s active ingredient, CERA, exhibits a longer half-life in the bloodstream, producing MIRCERA®'s longer dosing interval. Based on this record, we think there was sufficient evidence for a jury to conclude that the structural and functional differences between MIRCERA® and EPO recited in the process claims were not material. Therefore, Roche was not entitled to JMOL that MIRCERA® does not infringe the asserted claims of the '868 and '698 patents.

We also conclude that instructions delivered to the jury on "material change" under § 271(g) were legally sufficient. When read as a whole, the "material change"

instructions adequately informed the jury that it was to compare the EPO produced according to the claimed processes with MIRCERA®. See Eli Lilly, 82 F.3d at 1573 ("We look . . . to the substantiality of the change between the product of the patented process and the product that is being imported."). While it is true that the jury was instructed to look at the product produced by Roche's process, Trial Tr., vol. 21, 3078, Oct. 18, 2003, the jury was also instructed that if MIRCERA® was materially changed from the product of the claimed process, it would not infringe, id. In addition, the court instructed the jury to ask "does the Roche approach materially change its product MIRCERA®?" Trial Tr., vol. 20, 3025, Oct. 17, 2003. These "material change" instructions, as a whole, adequately conveyed to the jury that it was required to compare MIRCERA® to the product produced by the processes recited in the asserted claims of the '868 and '698 patents.

We similarly conclude that Roche is not entitled to a new trial even though the court instructed the jury that it could consider whether MIRCERA® would function if not made by Amgen's patented process. The court's instruction—"You are entitled to consider whether [MIRCERA®] would work without Amgen's patented process. Would it do what it's supposed to do absent Amgen's patented process?"—was presumably an attempt to provide the jury with some guidance as to the types of changes that would be material in this case. The court effectively instructed the jury that it could consider whether MIRCERA®'s biological function depends on its EPO component produced according to Amgen's patented processes. We assume that is because the court wanted the jury to ask whether the subsequent processes (i.e., pegylation) confer or enhance the biological properties possessed by MIRCERA®. We view the basis of

MIRCERA®'s biological function as a relevant consideration in assessing whether pegylation is a material change, especially where the asserted claims of the '868 and '698 patents recite the "in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells." See Eli Lilly, 82 F.3d at 1577 (discussing whether the chemical and biological properties and utility of the accused product are material changes). Although this instruction is imperfect, we do not think a jury would have been clearly misled by the "material change" instructions as a whole. Therefore, the "material change" charge does not warrant a new trial.

V

Cross-Appeal

Amgen cross-appeals the district court's rulings vacating the jury verdict of infringement of claim 12 of the '933 patent under the DOE and entering judgment of no infringement of claims 9, 11, 12, and 14 of the '933 patent and claim 7 of the '349 patent.

A.

The question of infringement, literally or by equivalents, of claim 12 of the '933 patent was presented to the jury. Roche moved for JMOL of non-infringement as to that claim, which the court denied. After the jury returned a verdict of infringement under the DOE of claim 12 of the '933 patent, Roche moved for renewed JMOL of non-infringement as to that claim. Vacating the jury verdict of infringement by DOE, the court granted Roche's motion for renewed JMOL with respect to claim 12 of the '933 patent. Amgen, 581 F. Supp. 2d at 205. It did so on the ground that Amgen had failed to identify limitation by limitation the equivalent function-way-result. Id. Claim 12 of the

’933 patent depends from claims 3 and 7, both of which the jury found literally infringed. The three claims recite as follows:

> 3. A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.
>
> 7. The glycoprotein product according to claims 3, 4, 5 or 6 wherein the host cell is a non-human mammalian cell.
>
> 12. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 7 and a pharmaceutically acceptable diluent, adjuvant or carrier.

’933 patent col.38 ll.26–31; col. 38 ll.64–65; col.39 ll.12–col.40 ll.2.

Claims 9, 11, and 14 of the ’933 patent did not reach the jury because the district court granted Roche JMOL of no infringement of those claims. Claims 9, 11, and 14 recite as follows:

> 9. A pharmaceutical composition comprising an effective amount [of] a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.
>
> 11. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 9 in an amount effective to increase the hematocrit level of said patient.
>
> 14. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 12 in an amount effective to increase the hematocrit level of said product.

’933 patent col.39 l.1–4; col.39 l.8–col.40 l.2; col.40 ll.7–11. Claim 9 is similar to claim 12, except that claim 9 depends from claim 3 directly, whereas claim 12 depends from claim 7, which depends from claim 3. Claims 11 and 14 are identical except that claim 11 depends from claim 9 and claim 14 depends from claim 12. For purposes of the

issues on appeal, however, claim 9 is the same as claim 12, and claim 11 is the same as claim 14.[20]

Amgen contends that the jury verdict relating to claim 12 should be reinstated because the jury had before it substantial evidence of literal infringement or infringement by equivalents. Amgen's Br. 82. Amgen contends that Roche's representations to the FDA that its product is a "pharmaceutical composition" containing a pharmaceutically acceptable "diluent" satisfy that limitation of claim 12. Id. at 84. Amgen also contends that Roche's FDA representations, internal documents, and expert testimony all establish that MIRCERA® produces an increase in red blood cell count by stimulating erythropoiesis, thus satisfying the limitation, "amount . . . effective for erythropoietin therapy." Id. at 84–85. Amgen notes that the jury heard testimony that pegylation did not change the function (to stimulate maturation of bone marrow cells into red blood cells), way (binding to the EPO receptor), or result (to make more red blood cells). Id. at 85. The only limitation the jury could have found infringed by DOE, in Amgen's view, was "effective for erythropoietin therapy," and, according to Amgen, there was sufficient evidence of equivalence to support the jury's verdict. Amgen's Reply Br. 9.

Amgen also argues that, if the court reinstates the jury verdict of infringement under the DOE of claim 12, the court should reverse the JMOL of no infringement of

[20] We note that our holding in TKT II that claim 9 of the '933 patent was invalid for indefiniteness does not apply here because claim 9 was only indefinite to the extent that it depended from claim 1 of the '933 patent. 314 F.3d at 1342, 1358. That is because we concluded that the limitation "glycosylation which differs from that of human urinary erythropoietin" in claim 1, from which claim 9 may depend, was indefinite. Id. at 1340–42. In this case, claim 9 was only at issue to the extent it depended from claim 3, which does not contain the previously declared indefinite limitation.

claim 9, because the evidence proving infringement of claim 12 also proves infringement of claim 9. Id. at 14–15. Amgen further argues that, assuming claims 9 and 12 are held to be infringed, we should vacate the JMOL of no infringement of dependent claims 11 and 14, which recite methods of treating kidney dialysis patients with pharmaceutical compositions comprising EPO, and remand for a new trial relating to those claims. Id. at 14–17; Amgen's Br. 86–88.

Roche counters that Amgen failed to perform the limitation-by-limitation analysis required to support the jury's verdict of DOE infringement of claim 12. Roche's Reply Br. 59. Roche contends that its representations to the FDA, its internal documents, and expert testimony do not constitute the particularized testimony and linking argument DOE infringement requires. Id. Roche notes that the district court excluded Amgen's proffered expert testimony on equivalents because it lacked a limitation-by-limitation comparison. Id. As for claim 9, Roche argues that the court correctly granted JMOL of no infringement because Amgen presented no testimony relating to infringement of this claim specifically. Id. at 60. Roche also contends that, because JMOL of no infringement of claims 9 and 12 was warranted, JMOL of dependent claims 11 and 14 also was warranted. Id. at 61–62.

"An accused device that does not literally infringe a claim may still infringe under the doctrine of equivalents if each limitation of the claim is met in the accused device either literally or equivalently." Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1459 (Fed. Cir. 1998) (en banc). An element in the accused product is equivalent to a claim limitation if the differences between the two are "insubstantial" to one of ordinary skill in the art. Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 40 (1997).

Insubstantiality may be determined by whether the accused device performs substantially the same function in substantially the same way to obtain the same result as the claim limitation. Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 608 (1950).

To support a finding of infringement under DOE, Amgen must have presented, on a limitation-by-limitation basis, "particularized testimony and linking argument as to the 'insubstantiality of the differences' between [the pharmaceutical composition in claim 12] and [MIRCERA®], or with respect to the function, way, result test." Tex. Instruments v. Cypress Semiconductor Corp., 90 F.3d 1558, 1567 (Fed. Cir. 1996). "[E]vidence and argument on the doctrine of equivalents cannot merely be subsumed in plaintiff's case of literal infringement." Lear Siegler, Inc. v. Sealy Mattress Co., 873 F.2d 1422, 1425 (Fed. Cir. 1989); see also Texas Instruments, 90 F.3d at 1567 ("Generalized testimony as to the overall similarity between the claims and the accused infringer's product or process will not suffice."). But see Paice LLC v. Toyota Motor Corp., 504 F.3d 1293, 1305 (Fed. Cir. 2007) ("Our 'particularized testimony' standard does not require [the expert] to re-start his testimony at square one when transitioning to a doctrine of equivalents analysis."). These requirements "ensure that a jury is provided with the proper evidentiary foundation from which it may permissibly conclude that a claim limitation has been met by an equivalent." Comark Commc'ns, Inc. v. Harris Corp., 156 F.3d 1182, 1188 (Fed. Cir. 1998).

Reviewing the record in the light most favorable to Amgen, we agree with the district court that a reasonable jury could not have concluded that claim 12 was infringed by DOE. In this case, the jury found claim 12 of the '933 patent infringed

under DOE, but we have no way of knowing which limitations were met literally or by DOE. In the absence of a special jury interrogatory informing the court of how the jury found each claim limitation was met by MIRCERA®, we must determine if Roche demonstrated either (1) that there was no substantial evidence from which the jury could have found that a particular identified limitation was met literally or by equivalents or (2) that there was no substantial evidence in the record that would have permitted the jury to find that any limitation had been met by equivalents. Id. at 1190. We hold the latter to be the case.

The record does not contain sufficient evidence that any limitation in claim 12 of the '933 patent was met by DOE. Amgen argues that it provided equivalents evidence pertaining to the "amount . . . effective for erythropoietin therapy" limitation in claim 12. We, however, do not view the evidence that pegylation does not change the biological properties of human EPO contained in MIRCERA® as equivalents evidence of the therapeutic efficacy limitation. Rather, Amgen presented that evidence to demonstrate that pegylation was not a "material change" to the human EPO contained in MIRCERA®.[21] See Trial Tr., vol. 17, 2486–87, Oct. 4, 2007. We fail to see how Dr.

[21] Amgen cites the following testimony from Dr. Lodish as evidence of infringement by equivalents of the therapeutic efficacy limitation:

> Q: Dr. Lodish, if I were to suggest to you that Roche says that attaching peg to EPO materially changes the product of Dr. Lin's processes, would you agree?
>
> * * * *
>
> A. Well, simply put, changing or adding peg to EPO does not change either the structure of EPO or perhaps . . . attaching peg to EPO neither changes the three-dimensional structure of EPO, nor, more importantly, perhaps, its biological function of binding to the erythropoietin receptors on bone marrow cells, stimulating them to produce red blood cells to make more red blood cells. It's the same function in substantially the same way.

Lodish's statements relating to literal infringement of Amgen's process claims under § 271(g) are particularized testimony of equivalents of the therapeutic efficacy limitation in Amgen's pharmaceutical composition claim, and Amgen has not pointed to any argument at trial linking the two. See Lear Siegler, 873 F.2d at 1425–26 (requiring particularized DOE testimony); Texas Instruments, 90 F.3d at 1567 (same). Indeed, the district court excluded Amgen's proffered testimony from Dr. Lodish that MIRCERA® was equivalent to the product recited in the claims of the '933 patent because Dr. Lodish's expert report lacked the limitation-by-limitation analysis required by our case law.[22] See Trial Tr. vol. 17, 2483–86, Oct. 4, 2007. The absence of an expert opinion regarding DOE infringement distinguishes this case from Paice, 504 F.3d at 1305, in which the patentee's proferred expert provided an opinion regarding DOE infringement. Therefore, the court did not err in vacating the jury verdict that claim 12 of the '933 patent was infringed under the DOE and in entering judgment as to non-infringement of that claim.

Because we are affirming judgment of no infringement of claim 12 of the '933 patent, we do not reach Amgen's arguments relating to claims 9, 11, and 14 of the '933 patent, which were contingent on a reinstatement of the jury verdict of infringement of claim 12.

See Trial Tr., vol. 17, 2486–87, Oct. 4, 2007 (emphasis added).

[22] When Amgen asked Dr. Lodish if he had "an opinion whether or not peg-EPO would be equivalent to the product of '933, claim 3," Trial Tr. vol. 17, 2483, Oct. 4, 2007, Roche objected that Dr. Lodish was taking a "generalized doctrine of equivalents approach," id. at 2484. The court sustained Roche's objection, stating that he "didn't think [Amgen was] going to be able to meet the [F]ederal [C]ircuit test." Id. at 2486.

B

At the close of Amgen's case, the court granted JMOL of non-infringement of claim 7 of the '349 patent. See Trial Tr., vol.19, 2787–88, Oct. 16, 2007. Amgen then moved for a new trial on infringement of claim 7, which the court denied. Claim 7 depends from claims 1–6. Claim 1, which is representative of claims 2–6, and claim 7 recite as follows:

> 1. Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin.
>
> 7. A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5 or 6.

'349 patent col.38 ll.8–14, ll.34–36. In short, claim 7 covers a process of producing EPO from cultured vertebrate cells that produce human EPO in excess of 100 U of EPO per 10^6 cells in 48 hours as determined by radioimmunoassay ("RIA").

On appeal, Amgen contends that a new trial is warranted because a reasonable jury could have found claim 7 of the '349 patent infringed. Amgen's Br. 88. Amgen argues that Roche's FDA representations and Dr. Lodish's testimony provide substantial evidence that Roche's actual production process involves cells that meet the production-rate limitation ("vertebrate cells that produce human EPO in excess of 100 U of EPO per 10^6 cells in 48 hours as determined by radioimmunoassay"). Id. Dr. Lodish relied on enzyme-linked immunoabsorbent assay ("ELISA") data in Roche's FDA submissions to arrive at his conclusion that MIRCERA® was made by vertebrate cells that produce approximately 1,500 units of EPO per 10^6 cells in 48 hours. Trial Tr., vol.

17, 2450, Oct. 4, 2007. Dr. Lodish testified that the results would be very similar, if not identical, if Roche's measurements had used RIA instead of ELISA. Id. at 2451. In addition, Dr. Lodish testified that RIA tests performed by another Amgen expert, Dr. Ronald W. McLawhon, confirmed his opinion that Roche's vertebrate cells were capable of producing EPO in excess of 100 units per 10^6 cells in 48 hours. Id. at 2453. In Amgen's view, a reasonable jury could credit Dr. Lodish's expert opinion as showing it is more likely than not that Roche's cells satisfy claim 7 of the '349 patent. Amgen's Br. 89.

Amgen also contends that it presented sufficient evidence demonstrating that Roche's assay, ELISA, satisfied the function-way-result test to prove infringement under DOE. Id. at 90. Dr. Lodish testified that both RIA and ELISA perform the same function (to measure how much EPO is in culture fluids) in a similar way (using an antibody), to obtain very similar, if not identical results. Id. (citing Trial Tr., vol. 17, 2451, Oct. 4, 2007). Amgen notes that the same issue was considered in Amgen, Inc. v. Hoechst Marion Roussel, Inc., 126 F. Supp. 2d 69, 119–20 (D. Mass. 2001) ("TKT"), aff'd in relevant part by TKT II, 314 F.3d at 1358. In TKT, Amgen offered ELISA data to prove infringement of claims in the '349 patent from which claim 7 depends. 126 F. Supp. 2d at 119–20. The court concluded "even if the Court were to hold that radioimmunoassays were required . . . , Amgen's evidence regarding the comparability of ELISA and RIA measurements would more than support the Court's finding of infringement under the doctrine of equivalents." 126 F. Supp. 2d 119–20. Amgen therefore contends it is entitled to a jury trial on infringement by equivalents of claim 7 of the '349 patent. Amgen's Br. 91.

Roche replies that the district court did not err in granting JMOL of non-infringement of claim 7 of the '349 patent. Roche's Reply Br. 62. Roche contends that Dr. Lodish's failure to actually assess Roche's production process made Amgen's proof deficient. Id. Roche argues that its FDA representations are inadequate evidence of infringement of claim 7, because they relate to production of purified clinical-grade material, which is different than the production of EPO in the "medium of their growth." Id. at 62–63. Roche also explains that claim 7 requires RIA measurements, and Roche generated its FDA data using ELISA. Id. at 63. Arguing that the RIA tests performed by Dr. McLawhon were inadmissible, Roche avers that the record does not establish the qualifications of those performing the tests, how the tests were conducted and the protocol used, or the reliability of the results. Id. As for infringement by DOE, Roche contends that Amgen provided neither the limitation-by-limitation analysis proof that DOE infringement requires nor substantial evidence to support DOE infringement. Id.

Reviewing the evidence in the light most favorable to Amgen, we hold that the district court erred in granting Roche JMOL of non-infringement of claim 7 of the '349 patent. Roche's FDA submissions and Dr. Lodish's testimony provided sufficient evidence from which a reasonable jury could have concluded that MIRCERA® infringes claim 7 of the '349 patent. In its FDA submissions, Roche identified, in the case of MIRCERA®, the type of cells used, the growth conditions of the cells, and the specific rate of EPO production. Although Roche used ELISA to measure the amount of EPO in the culture, Dr. Lodish testified that RIA and ELISA yield "very similar, if not identical" results. Trial Tr., vol. 17, 2451, Oct. 4, 2007. Also in evidence was Dr. Lodish's testimony that, in making MIRCERA®'s precursor, Roche essentially practices Example

10 in the asserted patents, see id. at 2404–2410, and Example 10 describes production-rates of EPO-producing cells, see '349 patent col.26 ll.50–52. Lastly, Dr. Lodish relied on data from RIA experiments performed by Dr. McLawhon to confirm that production of MIRCERA® meets the production-rate limitation. Trial Tr., vol. 17, 2452–53, Oct. 4, 2007. From this evidence, a reasonable jury could have concluded that the production-rate limitation of claim 7 of the '349 patent was met literally or by equivalents.

Contrary to Roche's assertions, Amgen was not required to have duplicated Roche's actual production process in order to prove infringement. See Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1349–50, 1356 (Fed. Cir. 1998) (affirming infringement where patentee did not test the accused product, but relied on documents produced by accused infringer). Neither was Amgen required to establish infringement by offering RIA data into evidence. See Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co., 425 F.3d 1366, 1374–75 (Fed. Cir. 2005) (affirming infringement where patentee proved infringement of a limitation measured by the "comparison test" with measurements from a different, but comparable test); cf. Genentech, Inc. v. Wellcome Found. Ltd., 29 F.3d 1555, 1566 (Fed. Cir. 1994) (affirming non-infringement where patentee relied on test different from that specified in the claims without establishing tests were comparable). Indeed, Amgen could have relied on the FDA submissions and Dr. Lodish's opinion that RIA and ELISA tests serve the same function, way, and result to show that the production-rate limitation was met by equivalents. Cf. TKT, 126 F. Supp. 2d at 120 ("Amgen's evidence regarding the comparability of ELISA and RIA

measurements would more than support the Court's finding of infringement under the doctrine of equivalents.").

We are not persuaded that Amgen's evidence was insufficient because Roche's FDA submissions were based on measurements Roche had taken from producing purified MIRCERA®, because Roche's measurements were made using ELISA, or because the record lacks evidence of how Dr. McLawhon's RIA tests were conducted. At trial, Roche was free to challenge the credibility of Dr. Lodish and his reliance on the FDA submissions and RIA tests performed by Dr. McLawhon. Indeed, in its cross-examination of Dr. Lodish, Roche established that ELISA and RIA tests were not identical, and Dr. McLawhon's tests were not admitted into evidence. Without more, however, Roche was not entitled to JMOL of non-infringement. Therefore, we hold that, on this record, the court erred in taking the question of infringement of claim 7 of the '349 patent away from the jury.

CONCLUSION

For the reasons set forth above, we vacate the judgment that the claims of the '008, '868, and '698 patents do not invalidate for obviousness-type double patenting claims 3, 7, and 8 of the '933 patent; claim 1 of the '422 patent; and claim 7 of the '349 patent. We remand to the district court for an obviousness-type double patenting analysis of those claims in light of this opinion. We also vacate the judgment of non-infringement of claim 7 of the '349 patent and remand to the district court for a new trial on infringement of that claim. We affirm the judgments of no invalidity of claims 1 and 2 of the '868 patent and claims 6–9 of the '698 patent. We also affirm the judgments of infringement of claims 3, 7, and 8 of the '933 patent and claim 1 of the '422 patent. In

addition, we affirm the judgments of infringement of claims 1 and 2 of the ’868 patent; claims 6–9 of the ’698 patent; and the judgment of non-infringement of claims 9, 11, 12, and 14 of the ’933 patent. Finally, because we leave certain infringement rulings in place, while vacating and remanding others, the district court is of course free to reconsider the scope of its permanent injunction if it wishes. We do not disturb the court’s injunction.

AFFIRMED-IN-PART, VACATED-IN-PART, and REMANDED.

COSTS

Each party shall bear its own costs.