AMGEN, INC., Plaintiff,

v.

F. HOFFMANN–LA ROCHE LTD., Roche Diagnostics GmbH, and Hoffmann–La Roche Inc., Defendants.

Civil Action No. 05–12237–WGY.

United States District Court,
D. Massachusetts.

Oct. 2, 2008.

Background: Patentee brought infringement action against competitor alleging infringement of patents related to recombinant erythropoietin (EPO), a naturally occurring protein that stimulates the production of red blood cells. Following jury verdict in favor of patentee, patentee sought entry of injunction to restrain future infringement. The District Court entered preliminary injunction. Competitor appealed. While appeal was pending, patentee sought permanent injunction.

Holdings: The District Court, William G. Young, J., held that:

(1) patent for EPO production was not invalid as anticipated by prior patent;

(2) patentee's defense against obviousness double patenting (ODP) allegations were not barred by judicial estoppel;

(3) competitor was not entitled to new trial based on invalidity of patent;

(4) patent was not invalid based on indefiniteness;

(5) jury's finding that accused product infringed patent claim was supported by sufficient evidence; and

(6) entry of permanent injunction would moot appeal of preliminary injunction.

Ordered accordingly.

1. Patents ⚿120

"Obviousness double patenting" (ODP) is a judicially devised species of obviousness that prevents inventors from over-extending the term of exclusivity by patenting subtle variations of the same device. 35 U.S.C.A. § 102.

See publication Words and Phrases for other judicial constructions and definitions.

2. Patents ⚿120

An obviousness double patenting (ODP) inquiry is comprised of two steps: first, as a matter of law, a court construes the claim in the earlier patent and the claim in the later patent and determines the differences, and second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct. 35 U.S.C.A. § 102.

3. Patents ⚿120

Defendants who seek to invalidate a particular claim via obviousness double patenting (ODP) must prove by clear and convincing evidence that the original claim and the allegedly duplicative claim are not patentably distinct. 35 U.S.C.A. § 102.

4. Patents ⚿120

Where the metes and bounds are discernable from the face of the patent claim, the obviousness double patenting (ODP) inquiry focuses on what is claimed without reference to the disclosure. 35 U.S.C.A. § 102.

5. Patents ⚿120

There are two ways that a court can conduct the obviousness double patenting (ODP) analysis in a patent infringement action; in most cases, courts employ a "one-way" test where the court compares the claims according to the order in which the patents issued.

6. Patents ⚿120

A later patent claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obvious-type double patenting.

7. Patents ⇦120

If the scope of the patent application and the patent claims are not identical, the court must ask whether the later patent's claim defines merely an obvious variation of the earlier patent's claim, when conducting an obviousness double patenting (ODP) analysis.

8. Patents ⇦120

The two-way test to determine obviousness double patenting (ODP) must be used if: (1) the patent applicant could not have filed both claims together in the earlier-filed application, and (2) the applicant did not cause the later filed claim to issue first by delaying examination of the earlier-filed claim during the period when both applications were pending before the Patent and Trademark Office (PTO), the "co-pendency period".

9. Patents ⇦120

Later filed patent for erythropoietin purification disclosed follow-on invention that issued after underlying claims due to restriction order imposed by Patent and Trademark Office (PTO) on application, and thus two-way test to determine obviousness double patenting (ODP) applied in patentee's infringement action; it was impossible for patentee to have filed claim of later patent as part of application, and patentee did not delay examination of earlier filed application during co-pendency period or cause later filed patent to issue before patents in suit. 35 U.S.C.A. §§ 120, 121.

10. Patents ⇦120

Claim in follow-up patent which described specific seven step process for purifying recombinant erythropoietin (EPO) and underlying claims in patent related to recombinant erythropoietin (EPO), were not identical in scope, and thus underlying patent for EPO production was not invalid for obviousness double patenting (ODP); patent was not prior art, applications were not publicly disclosed or available, and as far as ordinarily skilled artisan at the time was concerned, there was no recombinant erythropoietin. 35 U.S.C.A. §§ 102, 121.

11. Patents ⇦120

Obviousness-type double patenting (ODP) rejections are based on the premise that an applicant is claiming no more than an obvious variation, which would be obvious to anyone of ordinary skill in the art, of an invention on which a patent has already been granted.

12. Patents ⇦120

When performing obviousness double patenting (ODP) analysis, patent claims are looked to only to see what has been patented, the subject matter which has been protected, not for something one may find to be disclosed by reading them.

13. Patents ⇦120

Patentee was entitled to protection under safe harbor provision, and thus claims in patent related to recombinant erythropoietin (EPO) were immune from obviousness double patenting (ODP) rejection; follow-up patent applications were filed as result of Patent and Trademark Office (PTO) restriction requirement, and patentee complied with restriction requirements. 35 U.S.C.A. § 121.

14. Patents ⇦120

Claims in a divisional patent application are only immune from an obviousness-type double patenting (ODP) rejection when strict consonance exists between the earlier restriction requirement and the claims later prosecuted. 35 U.S.C.A. § 121.

15. Patents ⇦110

Consonance requires that the line of demarcation between the independent and distinct inventions that prompted the Patent and Trademark Office (PTO) restric-

tion requirement be maintained; where that line is crossed the safe harbor provision does not apply. 35 U.S.C.A. § 121.

16. Patents ⚿110

New or amended claims in a divisional patent application are entitled to the benefit of the safe harbor provision if the claims do not cross the line of demarcation drawn around the invention elected in the restriction requirement. 35 U.S.C.A. § 121.

17. Patents ⚿120

Determining what is patented by correct claim interpretation is essential to the determination of obviousness-type double patenting (ODP) issues.

18. Patents ⚿314(5)

It is the Court's role, not the jury's, to determine the metes and bounds of the claimed inventions in a patent infringement action.

19. Patents ⚿120

When a patent claim is not immunized from allegations of obviousness-type double-patenting (ODP) due to the safe harbor provision, the question becomes whether the defendant has met its burden of proving the ODP defense; as with other affirmative defenses of invalidity, the defendant bears the burden of proving ODP by clear and convincing evidence. 35 U.S.C.A. § 121.

20. Patents ⚿66(1.12)

Patentable differences existed between prior patent for DNA sequences encoding erythropoietin and patent for production of recombinant erythropoietin (EPO), and thus patent for recombinant EPO production was not invalid as anticipated by prior patent; claims in prior patent were directed to purified and isolated DNA sequences and cells into which such DNA sequences had been introduced, while claims in patent at issue were process claims that recited steps required to produce glycosylated polypeptide having specified characteristics. 35 U.S.C.A. § 121.

21. Patents ⚿120

The second step in the obviousness double patenting (ODP) analysis, after identifying the differences between the claims at issue, is to determine whether those differences in subject matter render the later-issued claim patentably distinct from the earlier-issued claim.

22. Patents ⚿120

A later-claimed invention is patentably distinct, and therefore not invalid for obviousness double patenting (ODP), if that invention as a whole would not have been obvious over the earlier-claimed invention to a person of ordinary skill in the art at the time just before the later-claimed invention was made.

23. Estoppel ⚿68(2)

"Judicial estoppel doctrine" prevents a litigant from pressing a claim that is inconsistent with a position taken by that litigant either in a prior legal proceeding or in an earlier phase of the same legal proceeding.

See publication Words and Phrases for other judicial constructions and definitions.

24. Estoppel ⚿68(2)

Primary purpose of the doctrine of judicial estoppel is to safeguard the integrity of the courts by preventing parties from manipulating the machinery of the judicial system.

25. Estoppel ⚿68(2)

Judicial estoppel applies to arguments and positions presented to the Patent and Trademark Office (PTO) from which the patentee gained a benefit.

26. Estoppel ⚿68(2)

Two requirements must be satisfied in order to invoke judicial estoppel: first, the prior position must be directly inconsistent with the present position, and second, the responsible party must have succeeded in persuading a court to accept its prior position.

27. Estoppel ⚿68(2)

Patentee did not take inconsistent position regarding patents related to recombinant erythropoietin (EPO), a naturally occurring protein that stimulates the production of red blood cells, to Patent and Trademark Office (PTO) during prosecution and court during patent infringement action, as required for patentee's defense against obviousness double patenting (ODP) allegations in patent infringement action to be barred by judicial estoppel.

28. Patents ⚿110

Patents related to recombinant erythropoietin (EPO), a naturally occurring protein that stimulates the production of red blood cells, were issued as the result of restriction requirement issued by Patent and Trademark Office (PTO) and maintained consonance with that restriction requirement, and thus patents were protected under safe harbor provision. 35 U.S.C.A. § 121.

29. Patents ⚿120

Previously issued patents related to recombinant erythropoietin (EPO), a naturally occurring protein that stimulates the production of red blood cells, were issued from applications filed as result of restriction requirement issued by Patent and Trademark Office (PTO) and did not share subject matter with later filed patents, and thus prior patents were immunized as prior art, as required for later filed patents to be invalid for obviousness double patenting (ODP). 35 U.S.C.A. § 121.

30. Patents ⚿155

Terminal disclaimers are used to overcome double patenting rejections. 35 U.S.C.A. § 121.

31. Federal Civil Procedure ⚿2608.1

District courts may set aside a jury's verdict only if it is so clearly against the weight of the evidence as to amount to a manifest miscarriage of justice. Fed. Rules Civ.Proc.Rule 50(a)(1), 28 U.S.C.A.

32. Patents ⚿72(1)

A patent claim is anticipated if every limitation is present in a single device in the prior art.

33. Patents ⚿101(6)

The touchstone of the definiteness requirement is whether a person having ordinary skill in the art at the time of the patent application would be able to discern the scope of the claim. 32 U.S.C.A. § 112.

34. Patents ⚿66(1.12)

Claim in patent related to recombinant erythropoietin (EPO), a naturally occurring protein that stimulates production of red blood cell, was not invalid as anticipated by prior art; during claim construction, court determined that term "purified from mammalian cells grown in culture" limited claim, EPO used in prior art study was purified from human urine, source limitation claim was entitled to presumption of validity, and competitor failed to rebut presumption. 35 U.S.C.A. §§ 112, 282; Fed.Rules Evid.Rule 301, 28 U.S.C.A.; Fed.Rules Civ.Proc.Rule 59(a)(1), 28 U.S.C.A.

35. Patents ⚿314(5)

Requiring a patentee to prove to a jury that a source limits a claim inverts the role of judge and fact-finder during trial in patent litigation.

36. Patents ⚿314(5)

Certain issues subsumed in patent claim construction questions resemble questions of fact; but the mere fact the issue requires a court to make credibility determinations does not mean that those questions must be submitted to a jury.

37. Patents ⚿112.1

In patent cases, the respect due to patent, the presumptions that all the preceding steps required by the law had been observed before its issue, the immense importance and necessity of the stability of titles dependent upon these official instruments, demand that the effort to set them aside, to annual them, or to correct mistakes in them, should only be successful when the allegations on which this is attempted are clearly stated, and fully sustained by proof. 35 U.S.C.A. § 282.

38. Patents ⚿72(1)

Invalidity of patent based on anticipation requires that the identical invention was known or its existence would reasonably have been known to a person of ordinary skill in the field. 35 U.S.C.A. § 102.

39. Patents ⚿312(6)

Evidence at patent infringement trial established that patent related to recombinant erythropoietin (EPO), a naturally occurring protein that stimulates the production of red blood cells, was not invalid based on indefiniteness; credible expert testimony suggested that term "human erythropoietin" was as exacting as could have been expected given state of scientific knowledge at time. 35 U.S.C.A. § 112.

40. Patents ⚿101(6), 112.5

Plaintiffs seeking to invalidate a patent for indefiniteness face a difficult burden; not only must they prove their claims by clear and convincing evidence, the degree of definiteness required for a given claim varies depending upon the state of the art.

41. Patents ⚿226.6

In order to prove patent infringement, a plaintiff must demonstrate that an accused device embodies all limitations of the claim either literally or by the doctrine of equivalents.

42. Patents ⚿239

Where a product embodies all patent limitations, merely adding elements to an otherwise infringing device will not enable the infringer to escape liability.

43. Patents ⚿250

Accused product contained erythropoietin (EPO), a naturally occurring protein that stimulates the production of red blood cells, and thus infringed patents relating to recombinant erythropoietin (EPO); claim construction made clear that focus of claim element was amino acid sequence, and competitor failed to produce evidence that pegylation process used in accused product altered EPO's amino acid sequence.

44. Patents ⚿239

It is fundamental that one cannot avoid patent infringement merely by adding elements if each element recited in the claims is found in the accused device.

45. Patents ⚿226.6

A plaintiff alleging patent infringement must prove all elements, including source and process limitations.

46. Federal Civil Procedure ⚿2651.1

The mere fact that a jury verdict could, in theory, appear to be inconsistent with a grant of summary judgment does not require a court to reconsider its pretrial ruling because the determinations are made on different records at different stages of the litigation and according to different legal standards.

47. Patents ⚿312(6)

Jury's finding that accused product containing pegylation erythropoietin (EPO) infringed claim in patent related to recombinant EPO, a naturally occurring protein that stimulates the production of red blood cells, was supported by sufficient evidence and was proper as matter of law; patentee offered evidence that pegylation used in accused product did not alter amino acid sequence of epoetin beta, and patent's focus was glycoprotein's amino acid sequence.

48. Patents ⚿226.6

Infringement liability is found where an accused device falls precisely within the scope of a claim as delineated by the limitations.

49. Patents ⚿317

A party seeking a permanent injunction following a judgment of patent infringement must demonstrate: (1) that it has suffered an irreparable injury, (2) that remedies available at law, such as monetary damages, are inadequate to compensate for injury, (3) that, considering the balance of hardships between the parties, a remedy in equity is warranted, and (4) that the public interest would not be disserved by a permanent injunction.

50. Patents ⚿191

"Patent trolls" are non-practicing entities who do not manufacture products, but instead hold patents, which they license and enforce against alleged infringers.

See publication Words and Phrases for other judicial constructions and definitions.

51. Patents ⚿317

Failure to enter permanent injunction prohibiting competitor's future infringement of patents related to recombinant erythropoietin (EPO), a naturally occurring protein that stimulates the production of red blood cells, would result in irreparable harm to patentee for which monetary damages were inadequate, and balance of hardships favored patentee, as required for permanent injunction; value of patents would be greatly diminished by competitor's entry into market.

52. Patents ⚿317

Public interest would not be disserved by a permanent injunction prohibiting competitor's entry into market for recombinant erythropoietin (EPO), a naturally occurring protein that stimulates the production of red blood cells, as required for permanent injunction in patent infringement action, although some patients might benefit from availability of competitor's product in market; accused product did not offer significant clinical advantages over patented product, competitor's product would not reduce Medicare costs, failure to enter permanent injunction would risk undermining incentives for innovation that have produced medical advances that extend and enhance the value of life.

53. Constitutional Law ⚿2558

Separation of powers considerations dictate that, absent a strong showing that the government is being fleeced, courts should proceed with caution before attempting to intervene on Medicare's behalf.

54. Patents ⚿317

Entry of permanent injunction prohibiting competitor's future infringement of patents related to recombinant erythropoietin (EPO), a naturally occurring protein that stimulates the production of red blood cells, would moot appeal of preliminary injunction to Court of Appeals in patent infringement action, and thus district court would not enter permanent injunction while appeal was pending, although injunction was warranted based on injury to patentee and balance of hardships.

Patents ⇨328(2)

3,623,712, 4,047,496, 4,667,016, 4,703,-008. Cited.

Patents ⇨328(2)

5,441,868, 5,547,933, 5,618,698, 5,756,-349, 5,955,422. Valid and Infringed.

Patents ⇨328(2)

5,621,080. Infringed.

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MEMORANDUM AND ORDER

WILLIAM G. YOUNG, District Judge.

Amgen Inc. ("Amgen") sought declaratory relief to prevent F. Hoffmann–LaRoche Limited, Roche Diagnostics GmbH, and Hoffmann–La Roche Inc. (collectively, "Roche") from marketing a drug that infringes U.S. Patent Nos. 5,441,868, 5,547,-933, 5,618,698, 5,621,080, 5,756,349, and 5,955,422. These patents relate to Amgen's recombinant erythropoietin ("EPO"), a naturally occurring protein that stimulates the production of red blood cells. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F.Supp.2d 104, 106 (D.Mass.1998). The jury found for Amgen across the board, upholding the validity of the claims-in-suit for the '422, '933, '868, '698, and '349 patents and finding that Roche literally infringed all of the claims-in-suit except

for claim 12 of the '933 patent, which it found infringed by the doctrine of equivalents. Jury Verdict [Doc. No. 1542] at 2–3. The Court writes to explain its rulings on various pre-trial motions for summary judgment, specifically its findings and rulings that the Amgen patents survive Roche's obviousness-double patenting contentions, to resolve various post-trial motions, and to explain the decision to grant Amgen's request for a permanent injunction.

Due to the sheer number, the Court will not be able to address every motion.[1] Therefore, all motions not already granted and not resolved herein are denied. After explaining the grant of summary judgment on the issue of obviousness-type double patenting, the Court will address post-trial motions in three groups: validity, infringement, and injunctive relief. Regarding validity, the Court will write to explain three decisions. Primarily, the Court concluded that the source "purified from mammalian cells grown in culture" limits claim 1 of the '422 patent. As shall be discussed, the undisputed record revealed that none of the prior art, including the Goldwasser study, satisfied this limitation. Second, sufficient evidence supported the jury's finding that the term "human erythropoietin," found in claim 1 of the '422 patent and claims 3, 7, and 9 of the '933 patent, is not indefinite, even though the specifications do not specify whether the glycoprotein described therein would be 165 or 166 amino acids in length.

Next, the Court will write to explain its grant of summary judgment to Amgen with respect to infringement of claim 1 of the '422 patent, *see* Electronic Order August 28, 2007, and the decision to uphold the jury's finding that Roche literally infringed claim 3 of the '933 patent. *See* Jury Verdict at 2. As shall be discussed below, Amgen patented recombinant EPO by reference to a specific amino acid sequence. *See Amgen, Inc. v. F. Hoffmann–La Roche Ltd.*, 494 F.Supp.2d 54, 63 (D.Mass.2007) [hereinafter "*Amgen Markman*"]. Pegylation—the chemical reaction that attaches PEG to EPO via a single bond to form CERA, the active ingredient in MIRCERA—does not alter EPO's amino acid sequence. *See* Trial Ex. 53, Roche's Biologic License Application at 00004027 [hereinafter "Roche BLA"]. The attachment of PEG to EPO does not place MIRCERA beyond the boundary of the claims because "the specification expressly contemplates that additional molecules may be attached to 'human erythropoietin.'" *Amgen Markman*, 494 F.Supp.2d at 63 (emphasis omitted). Thus, any minor modification of EPO that does not alter the specific amino acid sequence—such as the displacement of a single hydrogen atom—is immaterial and does not preclude a finding of infringement.

Finally, Amgen has satisfied all four factors necessary for a permanent injunction set forth in *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 126 S.Ct. 1837, 164 L.Ed.2d 641 (2006). Failure to issue a permanent injunction would cause irreparable, immeasurable harm, for which there is no adequate remedy at law. Given that Roche infringes Amgen's valid patents, and in light of the harms that will be discussed, the balance of hardships clearly favors Amgen. Moreover, the Court has concluded that "the public interest would not be disserved by a permanent injunction." *Id.* at 391, 126 S.Ct. 1837. The

1. With well over 1,000 pages of post-trial briefing, responding to every issue would be an inappropriate use of judicial resources. The Court will focus on those issues that the parties raised at the February 28 hearing. All of the parties' remaining contentions have been considered and found wanting. Because the jury's verdict will stand, Roche's anti-trust claims are moot.

record compiled over the course of a four-day evidentiary proceeding reveals no benefit to patient health or the public coffers so great as to outweigh the public's interest in a robust patent system.

I. BACKGROUND

"Erythropoiesis, the production of red blood cells, occurs continuously throughout the human life span to offset cell destruction." '422 Patent col. 5 *ll.* 41–43. "EPO is a protein hormone" that regulates erythropoiesis. Lodish Decl. [Doc. No. 513] ¶ 13. Produced in the kidneys, EPO circulates in the blood stream, *id.* ¶ 15, and, "[l]ike a key in a lock," *id.* ¶ 14, binds with EPO receptors located on erythroid progenitor cells in the bone marrow, *id.* ¶ 17. When EPO binds to the EPO receptor it "initiate[s] the signaling pathway that ultimately leads to red blood cell production." *Id.* ¶ 24. Red blood cells, of course, contain hemoglobin, the body's vehicle for transporting oxygen. *Id.* ¶ 15. "In healthy humans, the amount of EPO in circulation in the bloodstream is exquisitely regulated to produce just the required numbers of red cells." *Id.* Diseases or disorders affecting the kidneys often result in an EPO deficit, which leads to a low level of red blood cells, a condition generally referred to as anemia. *Amgen Inc. v. Hoechst Marion Roussel, Inc.,* 314 F.3d 1313, 1321 (Fed.Cir.2003) [hereinafter "*Amgen II* "].[2]

For some time preceding the 1980s, the medical community believed that the introduction of additional EPO into a patient's bloodstream could combat the effects of anemia by stimulating the production of additional red blood cells. *See id.* Nevertheless, a generation of researchers grappled with how to introduce exogenous EPO into the bloodstream of anemic patients. *Id.* Some of America's most accomplished researchers believed they could isolate and purify EPO that had exited the body in urine. *Id.* Others attempted to obtain EPO from plasma. *Id.* These approaches proved "unsuccessful because such recovery employed techniques that were complicated, yet still resulted in a low-yield, high-impurity, or unstable EPO end product. Similar attempts using antibody techniques failed because of difficulty in providing for the large-scale isolation of quantities of EPO from mammalian sources sufficient for further analysis, clinical testing, or therapeutic use." *Id.* (internal citation omitted). As of 1984, mass production of erythropoietin from recombinant DNA was not possible. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.,* 457 F.3d 1293, 1303–04 (Fed.Cir.2006) (hereinafter "*Amgen IV* ").

In this case, Roche's anticipation defense focused on a clinical study supervised by Dr. Eugene Goldwasser. Dr. Goldwasser's study, which began in 1979–1980, attempted to treat three anemic patients with EPO purified from human urine. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.,* 126 F.Supp.2d 69, 111 (D.Mass.2001) [hereinafter "*Amgen I* "]. The results of the Goldwasser study were mixed and are still a matter of dispute. While experts debate whether and to what extent an increase in reticulocyte count may be attributed to Dr. Goldwasser's urinary EPO, Dr. Goldwasser, who characterized the study as a failure, has admitted

2. *Amgen Inc. v. Hoechst Marion Rousell and Transkaryotic Therapies, Inc.,* No. 97–10814–WGY, a related case in this session of the Court involving the same patents, spawned two written opinions by this Court and two from the Federal Circuit: *Amgen Inc. v. Hoechst Marion Roussel Inc.,* 126 F.Supp.2d 69 (D.Mass.2001) (*"Amgen I"*); *Amgen Inc. v. Hoechst Marion Roussel Inc.,* 314 F.3d 1313 (Fed.Cir.2003) (*"Amgen II"*); *Amgen Inc. v. Hoechst Marion Roussel Inc.,* 339 F.Supp.2d 202 (D.Mass.2004) (*"Amgen III"*); *Amgen Inc. v. Hoechst Marion Roussel Inc.,* 457 F.3d 1293 (Fed.Cir.2006) (*"Amgen IV"*).

that the study did not actually increase patient hematocrit, the primary indicator of health benefits for erythropoiesis-stimulating agents ("ESAs"). *Id.* at 111–12. Moreover, due to a shortage of urine from aplastic anemia patients, the study never expanded beyond the three patients. *Id.* at 112.

In 1983, a team of Amgen researchers led by Dr. Fu–Kuen Lin identified a means of producing recombinant erythropoietin. *Amgen II,* 314 F.3d at 1321. Rather than attempting to obtain EPO from natural sources such as human urine, Lin identified human and monkey EPO and was "able to determine the entire DNA sequence of human EPO and from that, its predicted amino acid sequence." *Id.* at 1321–22. Next, Lin generated an expression vector [3] that he could inject into a host Chinese hamster ovary ("CHO") cell and that would yield a protein with the amino acid sequence of human EPO. *Id.* Because the protein has the requisite amino acid sequence, it performed the key-in-lock function of EPO and stimulated erythropoiesis.

Amgen's recombinant EPO revolutionized the treatment available for anemia and other blood disorders. *See id.* at 1321. To say that the cluster of patents protecting EPO in the United States has been a financial boon to Amgen would be like observing that Standard Oil had done pretty well in the oil business. *See Amgen I,* 126 F.Supp.2d at 77 (noting that EPOGEN, the first commercial embodiment of Amgen's patents, is one of the most successful blockbuster drugs in the history of the American pharmaceutical industry). Of course, Rockefeller never figured out how to produce a limitless supply of his product in a petri dish.

A. Production and Patenting of EPO

Example 10 of the patent's specification [4] discloses the method for producing EPO. The process begins with the:

> transfection (introduction) of exogenous DNA into host [CHO] cells. The CHO host cell, using its own transcription machinery,[5] then expresses human rEPO in abundance, which then accumulates in the host cell cytoplasm or in the culture media. ['933 patent] col. 37, lines 43–49. The rEPO so recovered has the same or similar amino acid sequences and biological properties as naturally occurring human EPO, but differs in its "glycosylation," i.e., in the patterns of branched carbohydrate chains that attach to the protein. [*Id.*] col. 10, lines 34–41.

Amgen II, 314 F.3d at 1321–22 (footnote supplied).

Of utmost importance to this case is the protein this process produces. Graphically depicted, the protein, also referred to as a polymer or a polypeptide, resembles a loosely coiled chain. Pl.'s Stat. Mat. Facts

3. Expression vector refers to a "circular piece of DNA. that is inserted into a host cell to produce (or 'express') a protein." *Amgen II,* 314 F.3d at 1321 n. 2.

4. All of the patents at issue share this identical specification.

5. Transcription is the process wherein the nucleotide sequence of DNA is copied onto ribonucleic acid ("RNA"). Bruce Alberts et al., Molecular biology of the cell 302 (4th ed.2002). RNA "is a polynucleotide comprising adenine, guanine, cytosine and uracil (U), rather than thymine, bound to ribose and a phosphate group." '422 Patent col. 1 *ll.* 50–52. The process of generating a protein begins when "DNA nucleotide sequences (genes) are 'transcribed' into relatively unstable messenger RNA (mRNA) polymers." This mRNA then serves as a template for the formation of the protein. *Id.* col. 1 *ll.* 54–58; *see also* Alberts, *supra,* at 302. Through a process known as "translation," "small RNA strands (tRNA) . . . transport and align individual amino acids along the MRNA strand to allow for formation of polypeptides in proper amino acid sequences." *Id.* col. 1 *ll.* 59–63.

[Doc. No. 512] at 1. Every protein is comprised of a specific amino acid sequence; each amino acid represents a link in the chain. *See id.* at 1–2. The term "amino acid sequence" refers to the order in which each of the particular amino acids are linked to form the protein. *See* BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL 140 (4th ed.2002).

Perhaps the best way to understand the manner in which a specific amino acid sequence represents a particular protein is by analogy. While the English language has an alphabet of 26 letters, there are twenty amino acids. *See* '422 Patent col. 1 *ll.* 63–67. As particular letter combinations in a certain order form a word in the English language, each unique sequence of amino acids forms a different protein. Just as "cat" cannot be spelled c-t-a, the desired protein may only be expressed if the amino acids are in order. Depending upon the type of cell that generates the protein, human EPO consists of 165 or 166 amino acid residues.[6] Pl.'s Stat. Mat. Facts [Doc. No. 512] at 1–2. The precise order of the amino acid sequence is critical because "even a single change in the amino acid sequence of the [EPO protein] or receptor can inhibit binding" and prevent the stimulation of erythropoiesis. Lodish Decl. ¶ 14.

Also critical to this case is the manner in which these amino acids bond. Each amino acid is bookended by a carbon-terminal ("c-terminal") on one end and a nitrogen-terminal ("n-terminal") on the other. The term "n-terminal" refers to a configuration of a nitrogen atom bonded to two or three hydrogen atoms. ALBERTS, *supra*, at 131. In the case of EPO, the nitrogen in the n-terminal is bonded to two hydrogen atoms. *See* Pl.'s Stat. Mat. Facts ¶ 26. A c-terminal is a similar configuration with a carbon atom serving as the base, and, in the case of EPO, oxygen and hydrogen atoms attached. *See id.*

When amino acids bond together to form a protein, the n-terminal of one bonds with the c-terminal of another. *See id.* The bond formed between the carbon from the c-terminal and the nitrogen from the n-terminal of the two amino acids is a peptide bond. ALBERTS, *supra*, at 132. The bonding process results in the displacement of one or two hydrogen atoms from the n-terminal and an oxygen or an oxygen and a hydrogen atom from the c-terminal. See Pl.'s Stat. Mat. Facts ¶ 26. These bonds are replicated at every spot where one amino acid attaches to another along the sequence. At the end, the first amino acid retains an unbonded n-terminal, while the final amino acid has an unbonded c-terminal. *Id.* ¶ 2.

After the protein is produced in the ribosome, it is secreted into the endoplasmic reticulum where it undergoes glycosylation, a process where sugars attach to the polypeptide backbone. ALBERTS, *supra*, at 702. When a protein is formed in a mammalian host cell, it is called a glycoprotein. Lodish Decl. ¶ 20. The EPO protein has four sites where chains of carbohydrates (sugar residues) can be attached, and three of these sites are n-terminals. *Id.*

Glycosylation can affect *inter alia* a protein's three-dimensional structure. *See* ALBERTS, *supra*, at 702. "The three dimensional structure of a protein reflects its primary structure (amino acid sequence), secondary structure (localized folding of parts of the polypeptide chain), and tertiary structure (long-range folding)." Lodish Decl. ¶ 18. Amgen's patents teach EPO by reference to recombinant EPO's primary structure without mentioning the

6. In some mammalian cells, one of the 166 amino acids is removed, leaving 165.

other aspects of structure potentially affected by glycosylation.

B. Amgen Claimed Its Patents By Reference to EPO's Amino Acid Sequence

Amgen obtained a total of seven product and process patents by reference to the amino acid sequence. As the Court noted in claim construction, "[t]he patent itself is silent as to . . . any structural characteristic beyond the required amino acid sequence." *Amgen Markman,* 494 F.Supp.2d at 63. The specification:

> does not define "erythropoietin" by reference to the presence or absence of any attached molecules, such as the carbohydrate that can be attached to EPO proteins for glycosylated EPO. In fact, the specification expressly contemplates that additional molecules *may* be attached to "human erythropoietin." By implication, therefore, those additional molecules are not part of the amino acid structure that comprises the claimed product.

Id. (internal citation omitted). It follows that modifications not affecting the amino acid sequence are immaterial.

C. The Market for Erythropoiesis Stimulating Agents ("ESAs")

Since obtaining its patents, Amgen has developed two drugs to treat anemia and anemia-related diseases, EPOGEN and Aranesp. Anemia can result from excessive loss of blood, from chemotherapy in cancer patients (because some chemotherapeutic agents destroy not only cancer cells, but also the bone marrow where blood cell formation occurs), and from chronic kidney disease ("CKD"), a progressive decline in kidney function leading to the buildup of waste products in the blood. Bernheim Expert Rep. ¶ 25. Patients with 85–95% loss of kidney function are said to experience end-stage kidney failure, commonly called end-stage renal disease ("ESRD"). Chertow Expert Rep. ¶¶ 16–17.

Available in the United States since the 1960s, dialysis removes waste products in the blood of ESRD patients whose kidneys cannot perform that function on their own. *Id.* ¶ 18. Although dialysis cleanses a patient's blood, it does not aid production of erythropoietin. *Id.* While the development of dialysis treatments in the 1960s likely extended the lives of many ESRD patients, the anemia in these people persisted, resulting in symptoms of weakness, fatigue, and lack of energy, requiring either patient acceptance of continued morbidity or some form of treatment. *Id.;* Fishbane Expert Rep. ¶ 20. Recombinant EPO met the previously unmet needs of CKD and ESRD patients for an erythropoiesis stimulating agent.

In 1989, Amgen launched epoetin alfa, or EPOGEN, which served both CKD and ESRD patients. In the mid–1990s, Amgen developed a second-generation ESA, darbepoetin alfa, branded Aranesp. Bernheim Expert Report ¶ 35. The key difference between these drugs is how frequently patients must take them. For patients receiving epoetin alfa (EPOGEN) two to three times per week and switching to Aranesp, the label provides that Aranesp be administered either subcutaneously or intravenously once weekly. For patients initiating treatment for correction of anemia, the recommended dosing is also one administration per week. For maintenance patients who had been receiving EPOGEN once per week, however, the label provides that Aranesp can be administered once every two weeks. Fishbane Expert Rep. ¶ 24. Although the Aranesp label does not provide for less frequent dosing than once every two weeks, for some CKD patients there is off-label usage at once per month. *Id.;* Chertow Expert Rep. ¶ 19.

Anemia drugs are sold in two markets, CKD and ERSD, based upon patient need. In the United States, Amgen markets Aranesp primarily for use in the CKD market segment and markets EPOGEN primarily for use by ESRD patients. Remedy Trial Tr. vol. 1 [Doc. 1737] at 44–46; Berheim Expert Rep. ¶ 37. With the exception of Johnson & Johnson, which obtained limited market entry via a license agreement, Amgen, by virtue of its patents, has a monopoly over both markets. In 2006, annual net sales of Aranesp in the United States were over $2,800,000,000, greater than those of EPOGEN and the Johnson & Johnson drug, Procrit, which each had annual sales of approximately $2,400,000,000. Bernheim Expert Rep. ¶ 37.

D. Production of MIRCERA

Roche sought to break Amgen's monopoly by introducing MIRCERA into the market of ESAs. CERA, the active ingredient in MIRCERA, is an acronym for Continuous Erythropoietin Receptor Activator, referring to the fact that CERA has a longer half-life than either darbepoetin alfa (Aranesp) or epoetin alfa (EPOGEN or Procrit). Fishbane Expert Rep. ¶ 30. While Aranesp has been approved only for dosing every two weeks, MIRCERA received FDA approval to provide correction of anemia with once-every-two-week dosing and to maintain stable hemoglobin levels with once-monthly or once-every-two-week dosing in all CKD patients. As shall be described below, Roche formed MIRCERA by attaching a sugar to EPO in order to extend the protein's half-life in the body.

1. The active ingredient in MIRCERA, CERA, is formed via a chemical reaction that bonds PEG to EPO

MIRCERA is the branded name for methoxy polyethylene glycol-epoetin beta. Epoetin beta, the starting ingredient for CERA, is a protein that is materially indistinguishable from the EPO in EPOGEN or Aranesp. *See* Lodish Decl. ¶ 41 ("Roche's manufacturing process for producing the recombinant EPO in [CERA] closely tracks the teachings of Example 10 of Amgen's [p]atents."). Like Amgen's EPO, epoetin beta is a recombinant EPO formed by injecting DNA encoding human EPO into a CHO cell. *Id.* ¶ 42 (citing Ex. 8 at ITC–R–BLA–000046667). And, like Amgen's EPO, "[t]he resulting glycosylated human EPO polypeptide product contains the identical amino acid sequence as naturally occurring human EPO." *Id.* ¶ 47.

In order to form CERA, Roche subjects epoetin beta to a chemical reaction with a polyethylene glycol polymer ("PEG"), *id.* ¶ 48, attaching PEG to epoetin beta at one of "9 potential pegylation sites on human EPO—the N-terminal amino group [or one of] the 8 epsilon-amino groups of lysines." *Id.* ¶ 52. The net result of the reaction is "a single bond between one carbon atom of [the PEG] molecule and one amino nitrogen of EPO." *Id.* ¶ 50. According to Roche's own analysis, pegylation does not affect epoetin beta's amino acid sequence, glycosylation, or carbohydrate structure. Trial Tr. at 2743; *see also* Lodish Decl. ¶ 53. Prior to marketing or this litigation, Roche referred to CERA as peg-EPO. *See* Trial Tr. at 2738–40.

Pegylation—the attachment of PEG to a protein—is a familiar technique in the pharmaceutical and cosmetic industry. Pl.'s Stat. Undisp. Mat. Facts ¶ 40. In theory, the addition of PEG, an inert polymer, to 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.* ¶¶ 39–40; Lodish Decl. ¶ 31. The technique was first employed as early as 1977, and EPO is only one of a number of human proteins

that have been pegylated. Lodish Decl. ¶ 30.

II. OBVIOUSNESS DOUBLE PATENTING

[1] Since the inception of the Republic, our patent system "has been about the difficult business 'of drawing a line between the things which are worth to the public the embarrassment of an exclusive patent, and those which are not.'" *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.,* 489 U.S. 141, 148, 109 S.Ct. 971, 103 L.Ed.2d 118 (1989)(quoting 13 WRITINGS OF THOMAS JEFFERSON 335 (Memorial ed.1904)). Codified at 35 U.S.C. §§ 102(a)-(b), the novelty requirement reflects Congress's determination that the public will not pay the dear price of a 17–year monopoly for information that is already available to the public. *See id.* "The nonobviousness requirement extends the field of unpatentable material beyond that which is known to the public under § 102, to include that which could readily be deduced from publicly available material by a person of ordinary skill in the pertinent field of endeavor." *Id.* at 150, 109 S.Ct. 971. Obviousness double patenting ("ODP") is a judicially devised species of obviousness that prevents inventors from over-extending the term of exclusivity by patenting subtle variations of the same device. *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.,* 98 F.3d 1563, 1568 (Fed.Cir.1996).

At summary judgment, Roche invoked ODP, averring that the claims-in-suit were obvious over claim 10 of the '016 patent because it contained the term "erythropoietin from a mammalian cell culture supernatant fluid." *See* Mem. Supp. Sum. J. of ODP Over '016 [Doc. No. 491] at 1–2; *see also* Mot. Summ. J. Of ODP Over '016 [Doc. 490]. Amgen then moved for summary judgment of no ODP over both the '016 and '008 patents [Doc. No. 498]. Without explanation, the Court denied Roche's motion for summary judgment but granted Amgen's cross-motions for summary judgment for no obviousness-type double patenting on the eve of trial. The Court now writes to explain that decision.

The Court determined that the two-way test was applicable to the '016 claims because the '016 patent disclosed a follow-on invention that issued after the underlying claims due to a restriction order imposed by the Patent and Trade Office ("PTO"). Applying the two-way test, the claims-in-suit were not obvious over claim 10 of the '016 patent because the metes and bounds of the claim are readily discernable without reference to the specification and are clearly drawn to a seven-step process for purifying EPO. Claim 10 is clearly not drawn to the protein itself or to the process of its production. In addition, because the order in which Amgen's patents issued was a function of a restriction requirement imposed by the PTO, and because the claims at issue are consonant with those restrictions, the claims of the '933, '422, and '349 patents are immune from ODP over the '008 patent under the terms of 35 U.S.C. § 121.

A. THE LEGAL FRAMEWORK

[2–4] An ODP inquiry is comprised of two steps. "First, as a matter of law, a court construes the claim in the earlier patent and the claim in the later patent and determines the differences. Second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct." *Eli Lilly and Co. v. Barr Labs., Inc.,* 251 F.3d 955, 968 (Fed.Cir.2001)(internal citations omitted). Defendants who seek to invalidate a particular claim via ODP must prove by clear and convincing evidence that the original claim and the allegedly duplicative claim are *not* patentably distinct. *Symbol Techs., Inc. v. Opti-*

con, Inc., 935 F.2d 1569, 1580 (Fed.Cir. 1991). It is also important to note that where the metes and bounds are discernable from the face of the claim, the ODP inquiry focuses on what is claimed without reference to the disclosure. *See General Foods Corp. v. Studiengesellschaft Kohle mbH,* 972 F.2d 1272, 1281 (Fed.Cir. 1992)("[T]he *disclosure* of a patent cited in support of a double patenting rejection cannot be used as though it were prior art, *even where the disclosure is found in the claims.*") (emphasis in original).

1. The "One–Way" and "Two–Way" Tests

[5–7] There are two ways that a court can conduct the ODP analysis. In most cases, courts employ a "one-way" test where the court compares the claims according to the order in which the patents issued. "A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obvious-type double patenting." *Eli Lilly,* 251 F.3d at 968. If the scope of the application and the patent claims is not identical, the court must ask whether the later patent's claim defines merely an obvious variation of the earlier patent's claim. *See In re Goodman,* 11 F.3d 1046, 1052 (Fed.Cir. 1993). Although the one-way test applies in the large majority of cases, the Federal Circuit created a "two-way" test that applies in a narrow set of circumstances. *In re Berg,* 140 F.3d 1428, 1432 (Fed.Cir. 1998).

The two-way test is a response to the reality that the Patent Office is perennially underfunded and slow. *See id.* These indisputable facts cause various anomalies, including the issuance of patents in an order other than that which the inventor intended. In rare cases, quirks in the application process may cause a patent covering a subsequently conceived follow-on invention to issue before the patent covering the underlying invention. The two-way test seeks

> to prevent rejections for obviousness-type double patenting when the applicants filed first for a basic invention and later for an improvement, but, through no fault of the applicants, the PTO decided the applications in reverse order of filing, rejecting the basic application although it would have been allowed if the applications had been decided in the order of their filing.

Id. Where patents have issued out of order, the examiner will employ the one-way test, but "the examiner also asks whether the patent claims are obvious over the application claims. If not, the application claims later may be allowed." *Id.* In this case, Amgen asks the Court to apply the two-way test.

[8] The determination of whether the one-way or two-way test applies is matter of law. *Id.* The two-way test must be used if: (1) the applicant could not have filed both claims together in the earlier-filed application; and (2) the applicant did not cause the later filed claim to issue first by delaying examination of the earlier-filed claim during the period when both applications were pending before the PTO (the "co-pendency period"). *See, e.g., In re Emert,* 124 F.3d 1458, 1461 (Fed.Cir.1997); *Engineered Prods. Co. v. Donaldson Co.,* 225 F.Supp.2d 1069, 1111 (N.D.Iowa 2002), *vacated in part on other grounds,* 147 Fed.Appx. 979 (Fed.Cir.2005).

2. The Safe Harbor Provision, 35 U.S.C. § 121

The two-way test is not the only mechanism devised to protect inventors from inadvertent inequities arising from the PTO's application process. Congress enacted a safe harbor, codified at 35 U.S.C. § 121, which provides:

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 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.

B. The Prosecution History Reveals that the PTO, not Amgen, Dictated the Order or Form in which its Patents Issued

Dr. Lin filed U.S. Patent Application No. 06/675,298 on November 30, 1984. *See* Moore Decl. [Doc. No. 501] Ex. H–1, U.S. Patent Application No. 06/675,298, at AM670167625. On June 20, 1985, two other Amgen researchers, Drs. Lai and Strickland, filed U.S. Patent Application No. 06/747,119. Claim 10 of the '119 application is drawn to a specific seven-step process for purifying recombinant EPO. *See* Lodish Decl. [Doc. No. 502] ¶ 48. The claim does not describe a product or teach a process for producing EPO from mammalian cells. Lodish Decl. ¶ 44. It is undisputed that Drs. Lai and Strickland did not conceive of the process described in the '119 application until after Dr. Lin filed the '298 application. *See* Strickland Decl. [Doc. No. 503] ¶¶ 11–16.

On July 3, 1986, shortly after Drs. Lai and Strickland filed the '119 application, the PTO imposed a restriction requirement on the '298 application. Pursuant to 35 U.S.C. § 121, the PTO mandated that Amgen divide the claims in the '298 application into distinct groups based on subject matter: I) polypeptides; II) DNA; III) plasmids; IV) cells; V) pharmaceutical composition; and VI) assay. *See* Lodish Decl. ¶ 17.

As a result of the restriction requirement, Amgen elected to allow its DNA (restriction Group II) claims to proceed to examination in the '298 application. *Id.* ¶ 20. All of the elected claims fit into restriction Group II. *See* Lodish Decl. ¶ 25. In addition, on October 23, 1987, Amgen filed two divisional applications, U.S. Patent Application Nos. 07/113,178 and 07/113,179. All of the claims in the '178 and '179 applications were taken from the '298 application. *See* Pl.'s Stat. Undisp. Mat. Facts [Doc. No. 500] ¶¶ 4–5. The '178 application contained claims drawn to a polypeptide (restriction Group I) and a pharmaceutical composition (restriction Group VI). *See* Moore Decl. Ex. I, U.S. Patent Application No. 07/113,178, at AM–ITC 00941037–45, AM–ITC 00941076–77; Moore Decl. Ex. H–8, Office Action, July 3, 1986, at 2. The '179 application included claim 1 from the '298 application, which was placed in restriction Group I. *See* Moore Decl. Ex. J, U.S. Patent Application No. 07/113,179 at AM–ITC 004539820–90, AM–ITC 00454000–01; Moore Decl. Ex H–8, Office Action, July 3, 1986, at 2.

On May 19, 1987, while Amgen and the PTO were still sorting Amgen's applications into restriction groups, Drs. Lai and Strickland's '119 application issued as U.S. Patent No. 4,667,016. Pl.'s Stat. Undisp. Mat. Facts ¶ 9. The '298 application issued as U.S. Patent No. 4,703,008, but not until October 27, 1987, *see id.* ¶ 1, four days

after Amgen filed the '178 and '179 applications, *see id.* ¶¶ 4–5. The '178 and '179 applications subsequently issued as the '933, '349, and '422 patents. The claims in these patents are not drawn to restriction Group II. *See* Lodish Decl. ¶¶ 26–34.

C. The Court Granted Amgen's Motion for Summary Judgement and Denied Roche's Because There Was No Genuine Issue of Material Fact that the Claims-in-Suit Were Not Invalid for ODP Over the '016 Patent Claims

Roche moved for summary judgment on the ground that claim 10 of Drs. Lai and Strickland's '016 patent rendered the claims-in-suit obvious because claim 10 contains the term "recombinant erythropoietin from a mammalian cell culture supernatant fluid." *See* Def.'s Mem. Supp. Sum. J. at 1–2. As shall be explained, the Court must employ the two-way test in evaluating this claim because the '016 patent was a subsequently conceived follow-on invention that issued before the claims-in-suit due to the PTO's imposition of the 1986 restriction requirement. Under the two-way test, it is clear that claim 10 of the '016 patent and the claims-in-suit are not identical in scope. They are in fact drawn to very different subject matter, and the differences are not merely obvious variations.

As a threshold matter, it is important to note that when deciding a motion for summary judgment, the Court "must view the evidence presented through the prism of the substantive evidentiary burden." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 254, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986). Here, Roche bears the burden of proving ODP by clear and convincing evidence, "a heavy and unshifting burden." *Symbol Techs.*, 935 F.2d at 1580. Moreover, since the PTO—on two separate occasions—rejected Roche's ODP argument and determined that Dr. Lin's claims are patentably distinct from the '016 claims, Roche bears an even heavier burden in proving ODP based on the '016 claims. *See Amgen I*, 126 F.Supp.2d at 105 (Where the asserted grounds for invalidity were reviewed by the PTO, "the challenger has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job.") (internal quotation omitted). Roche cannot overcome that burden.

1. The two-way test applies in evaluating whether the claims-in-suit are invalid over the claim 10 of the '016 patent

[9] While courts generally apply the "one-way" test, the Federal Circuit has recognized special circumstances in which the "two-way" test is to be applied. *Eli Lilly*, 251 F.3d at 968–969. The two-way test should apply where an underlying claim and a follow-on claim issue in reverse order through no fault of the patentee. *See In re Berg*, 140 F.3d at 1432. In order to apply the two-way test, the Court must determine that Amgen (1) could not have filed the '119 application together with the '298 application and (2) did not cause the '016 patent to issue first by delaying examination of the '298 application during the co-pendency period. *See id.; see also In re Emert*, 124 F.3d at 1461; *Engineered Prods.*, 225 F.Supp.2d at 1111. The Court was satisfied that both of these criteria were met.

As noted above, the first filing involved Lin's invention of recombinant EPO as described in the '298 application. *See* Moore Decl. Ex. H–1, U.S. Patent Application No. 06/675,298, at AM670167625. Even though the '016 patent issued prior to the claims in suit, the undisputed record reveals that Lai & Strickland's EPO purification process was a subsequently conceived follow-on invention. *See* Strickland

Decl. ¶¶ 11–16. Thus, it was impossible for Amgen to have filed claim 10 of the '016 patent as part of Lin's November 30, 1984 '298 application that gave rise to the claims-in-suit. Roche does not dispute this fact, but contends that it is sufficient that the '016 claims and Dr. Lin's claims *could* have been combined together in a continuation-in-part application filed some time after Dr. Lin's earlier filed '298 application. *See* Def.'s Mem. Supp. Sum. J. at 14. This argument rests on Roche's contention that the '119 application (from which the '016 patent claims priority) constitutes the "earlier filed application." The undisputed facts, however, are that the claims-in-suit claim priority from the '298 application. Thus, Dr. Lin's '298 application, filed November 30, 1984, is the one deemed "earlier filed" as compared to the '119 application, which was not filed until June 20, 1985. *See* 35 U.S.C. § 120. Therefore, the first requirement of the two-way test is satisfied.

Second, Amgen did not delay examination of Dr. Lin's earlier-filed '298 application during the "co-pendency" period or cause the later-filed '016 patent to issue before Dr. Lin's patents-in-suit. Dr. Lin's '298 application was filed on November 30, 1984. Moore Decl. Ex H–1, U.S. Patent Application No. 06/675,298, at AM67067625. The patents-in-suit issued between 1996 and 1999. *See* U.S. Patent No. 5,547,933 (issued August 20, 1996); U.S. Patent No. 5,756,349 (issued May 26, 1998); U.S. Patent No. 5,955,422 (issued September 21, 1999). The '119 application was filed on June 20, 1985, and the '016 patent issued on May 19, 1987. *See* U.S. Patent No. 4,667,016. Thus, the relevant co-pendency period is from June 20, 1985 (the '016 filing date) to May 19, 1987 (the '016 issuance date). During the co-pendency period, Amgen did not request or receive any extensions of time to prosecute Dr. Lin's '298 application, nor did it delay examination of the '298 application in any other manner to cause the '016 patent to issue first. Instead, the record suggests that Amgen made efforts to accelerate examination of the '298 application. *See, e.g.,* Moore Decl. Ex. H–5, Petition to Make Special. Thus, it was the PTO, not Amgen, that caused the later-filed '016 patent to issue before Dr. Lin's '298 application.

The Court therefore will apply the two-way test.

2. Roche's argument that the '016 patent discloses "purified recombinant EPO" fails because ODP analysis is confined to an examination of the claim

[10] At its essence the ODP inquiry asks: "Is the same invention being claimed twice?" *Gen. Foods,* 972 F.2d at 1278. Claim 10 of the '016 patent is drawn to a seven-step process for recovering a purified recombinant EPO. Claim 10 does not purport to teach the production of recombinant EPO. Lodish Decl. ¶ 44. "Recombinant erythropoietin" is a different invention than the recovery process taught in claim 10. The Court must therefore conclude that the scope of claim 10 is not identical to the scope of the claims-in-suit. *See In re Goodman,* 11 F.3d at 1052. Despite Roche's urging, the Court cannot conclude that these differences are obvious.

[11, 12] Roche's argument that claim 10 is obvious over the claims-in-suit because it contains the term "recombinant erythropoietin" is premised on the fatally flawed assumption that the Court must look to '016 patent specification—including the earlier teachings of Dr. Lin's own patent application as incorporated by reference in the '016 specification—as though they both constituted prior art to Dr. Lin's '298 patent claims. To the contrary, the Federal Circuit has made clear that "[d]ouble patenting is altogether a matter

of what is claimed." *Gen. Foods,* 972 F.2d at 1277. "[T]he *disclosure* ... cannot be used as though it were prior art, *even where the disclosure is found in the claims.*" *Id.* at 1281 (emphasis in original); *see also In re Braat,* 937 F.2d 589, 594 n. 5 (Fed.Cir.1991). As the Court of Customs & Patent Appeals explained in *In re Aldrich,* 55 C.C.P.A. 1431, 398 F.2d 855 (C.C.P.A.1968):

> Obviousness-type double patenting rejections ... are based on the premise that an applicant is claiming no more than an obvious variation—which would be obvious to anyone of ordinary skill in the art—of an invention on which a patent has already been granted.... To that end, patent claims are looked to only to see what has been patented, the subject matter which has been protected, not for something one may find to be disclosed by reading them.

Id. at 859.

Thus, the '016 patent and Dr. Lin's application incorporated therein are not prior art for purposes of the two-way ODP analysis. In fact, Dr. Lin's patent applications were not publicly disclosed or available as prior art as of the date of the Lai & Stickland EPO purification invention reflected in the '016 patent (the legally relevant date for the ODP analysis). As far as the ordinarily skilled artisan at the time was concerned, there was no "recombinant erythropoietin."

Nevertheless, in support of its argument that the Court ought look to the specification, Roche relies on *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC,* 349 F.3d 1373 (Fed.Cir.2003). In *Geneva* the Federal Circuit analyzed the claims' scope and utility by looking not only to the claims themselves but also to the specifications. The Federal Circuit explained:

> [T]his court does not consider the Fleming claim in a vacuum, as a simple compound, without considering the compound's disclosed utility..... *Standing alone, that claim does not adequately disclose the patentable bounds of the invention.* Therefore, this court examines the specifications of both patents to ascertain any overlap in the claim scope for the double patenting comparison. A person of ordinary skill in the art reviewing the disclosure of the Fleming patent would recognize a *single use* for potassium clavulanate, administration to patients to combat bacteria that produce [beta]-lactamase.... The Fleming patent discloses no other use. The '720 patent simply claims that use as a method.

Id. at 1385 (emphasis added)(internal citations omitted).

Geneva is inapposite. Here, unlike *Geneva,* the limitations adequately set forth the metes and bounds of the claim. And it is clear that the claim is drawn to a particular purifying recombinant EPO that has already been produced. The claim does not describe the polypeptide or the process by which it is made. *Geneva* is inapplicable because the sole utility of the '016 patent is purifying EPO for the patents in suit. In fact, even if Roche is right that the '016 and the current patents literally overlap—all mentioning EPO—it does not follow that the patents in suit are the "single use" for EPO.[7]

7. The Federal Circuit's recent decision in *Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc.,* 518 F.3d 1353 (Fed.Cir.2008), does not alter the outcome. In *Pfizer,* the Federal Circuit noted that "[t]here is nothing that prevents us from looking to the specification to determine the proper scope of the claims." *Id.* at 1363 n. 8. The Court reads *Pfizer* as consistent with *Geneva,* which permitted the court to look at the specification where the metes and bounds were not immediately apparent. *See Geneva,* 349 F.3d at 1385. Here, the scope of claim 10 is clear; it claims a seven-step process for purifying recombinant EPO. The claim does

Thus, claim 10 and the claims-in-suit are patentably distinct. On the basis of this conclusion, the Court denied Roche's motion for summary judgment on ODP [Doc. No. 490] with respect to the '016 patent and granted Amgen's [Doc. No. 498].

D. The Court Granted Amgen's Cross Motion for Partial Summary Judgment of No ODP Over the Claims in the '008 Patent because Amgen was Entitled to the Safe Harbor Codified at 35 U.S.C. § 121

The third sentence of 35 U.S.C. § 121 provides:

> 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.

[13] The applicability of this safe harbor provision is matter of law. "In addition to the express requirements of section 121, [the Federal Circuit has] construed the statute to require consonance: the applicant must maintain the line of demarcation between the independent and distinct inventions that prompted the restriction requirement." *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 518 F.3d 1353, 1359 (Fed.Cir.2008). Thus, the Court must determine 1) whether the three applications at issue were in fact filed in response to a PTO imposed restriction requirement; and 2) whether Amgen remained faithful to the restriction requirements. As set forth below, the Court concludes that Amgen has satisfied both the statutes strictures as well as the consonance requirement.

1. Amgen filed the '178 and '179 applications in response to the PTO-imposed restriction requirement

After the PTO imposed the 1986 restriction requirement, Amgen restricted the claims prosecuted in Dr. Lin's '298 application to one invention (Lin's DNA claims), which ultimately issued as the '008 patent. It filed two divisional applications, the '178 and '179, which ultimately issued as the '933, '422, and '349 patents. The undisputed evidence shows that both the '178 and '179 applications were filed as a result of the PTO's 1986 restriction requirement. Thus, Amgen has met its burden with respect to the first part of the safe harbor inquiry. The Court now considers whether Amgen maintained consonance.

2. Amgen satisfied the consonance requirement

[14–16] As noted above, claims in a divisional application are only immune from an obviousness-type double patenting rejection when strict consonance exists between the earlier restriction requirement and the claims later prosecuted. *Bristol–Myers Squibb Co. v. Pharmachemie B.V.*, 361 F.3d 1343, 1348 (Fed.Cir.2004); *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d at 1381; *Gerber Garment Tech., Inc. v. Lectra Sys., Inc.*, 916 F.2d 683, 688 (Fed.Cir.1990). "Consonance requires that the line of demarcation between the 'independent and distinct inventions' that prompted the restriction requirement be maintained.... Where that line is crossed the prohibition of the third sentence of Section 121 does not apply." *Gerber*, 916 F.2d at 688. "[N]ew or amended claims in a divi-

not contemplate the production of recombinant EPO.

sional application are entitled to the benefit of [section] 121 if the claims do not cross the line of demarcation drawn around the invention elected in the restriction requirement." *Symbol Techs.*, 935 F.2d at 1579. In delineating the scope of the groups, the proper point of reference is the actual restriction groupings (i.e., the substance of the claims in each restriction group), not the examiner's written descriptions thereof. *Texas Instruments Inc. v. ITC*, 988 F.2d 1165, 1179 (Fed.Cir. 1993).

Here, the '933, '349 and '422 patent claims are consonant with the PTO's 1986 restriction requirement. *See* Pl.'s Rep. Br. Supp. Sum. J. No ODP [Doc. 676] at 3–12. Under 35 U.S.C. § 121, the 1986 restriction requirement mandated that Amgen confine its inventions to the following groups:

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 240.

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.

Lodish Decl. Ex. E–1, '298 Prosecution, Paper 8 at 2.

Amgen elected claims falling within restriction Group II for further examination in the '298 application. *See* Lodish Decl. ¶ 20. Amgen then filed the '178 and '179 applications by submitting a copy of the '298 application (as originally filed) and canceling certain of the '298 claims so that only subsets of those claims were included in the '178 and '179 applications as filed. *See* Moore Decl. Ex. P–1, PATENT AND TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE § 201.06(a) (5th Ed.1983) (outlining regulations for "[c]ontinuing or divisional application[s] for invention disclosed in a prior application"). In keeping with the 1986 restriction requirement and the election of Group II, Amgen canceled all claims belonging to Group II and selected only claims belonging to the non-elected restriction groups for filing in the '178 and '179 applications. The '178 application as filed contained original claims 1–13, 16, 39–41, 47–49, and 55–57, which the PTO had assigned to restriction Groups I and V. *See* Moore Decl. Ex. I, U.S. Patent Application No. 07/113,178, at AMITC 00941037–45, AMITC 00941076–77; Moore Decl. Ex H–8, Office Action, July 3, 1986, at 2. The '179 application as filed contained original claim 1, which the PTO had assigned to restriction Group I. *See* Moore Decl. Ex. J, U.S. Patent Application No. 07/113,179 at AMITC 004539820–90, AM–ITC 00454000–01; Moore Decl. Ex H–8, Office Action, July 3, 1986, at 2.

The Court is satisfied that Amgen complied with the restriction requirements. To begin, the '298 claims, which issued as the '008 patent, fall within elected Group II. Lodish Decl. ¶ 25. Moreover, the claims-in-suit fall within the scope of the non-elected restriction groups. '933 claims 1–8 (EPO glycoproteins and glycoprotein products) are drawn to "polypeptide"; '933 claims 9–14 and '422 claims 1–2 (pharmaceutical compositions and methods of using same) are drawn to "pharmaceutical composition"; and '349 claims 1–7 (vertebrate cells for producing EPO and processes for using same) fall within the scope of Group IV because they are drawn to "cells." *See id.* ¶¶ 26–34. None of these

claims cross the line of demarcation drawn around the elected Group II. *See id.*

Roche argues that Amgen cannot avail itself of section 121's safe harbor because its prosecutions were not consonant with the restriction requirement. First, Roche contends that Amgen broke consonance by prosecuting claims from Group I and Group V in a single application. Def.'s Mem. Opp. Sum. J. Of No ODP [Doc. No. 568] at 2. Similarly, Roche maintains that during the prosecution of the '422 patent Amgen broke consonance by combining claims from Group V and Group VII in the same application. *Id.* In addition, Roche avers that Amgen vitiated the restriction requirement by claiming a "non-naturally occurring glycoprotein" in claim 7 of the '933 patent. *See id.* Finally, Roche contends that Amgen violated the restriction requirement by converting verbrate cell claims into a process claim during the prosecution of the '349 patent. *Id.* The process claims of the '349 patent, Roche argues, belong in the elected Group II. *See id.*

To begin, Roche's argument that Amgen broke consonance by including claims in multiple restriction groups in the same application lacks legal foundation. Under Roche's theory, Amgen was required to maintain strict consonance by filing a divisional application for claims within each restriction group. Roche cites no case for this proposition. The reason they are unable to do so is that the available Federal Circuit precedent indicates that "new or amended claims in a divisional application are entitled to the benefit of [section] 121 if the claims do not cross the line of demarcation drawn around the invention elected in the restriction requirement." *Symbol Techs.,* 935 F.2d at 1579. Roche does not allege that the '933 or '422 claims blurred the line of demarcation around the elected Group II. Thus, the Court cannot conclude that the '422 and '933 forfeited the shelter provided by section 121.

Roche's claim that the '933 patent broke consonance by claiming a non-naturally occurring glycoprotein is also unpersuasive. Roche argues that the only polypeptides that satisfy the strictures of Group I are those that are isolated from a natural source; the "non-naturally occurring glycoprotein" taught in claim 7, Roche emphasizes, can only be obtained with recombinant DNA. Roche maintains that once Amgen modified gylcoprotein with "non-naturally occurring" the claim was no longer drawn to a polypeptide (Group I), but instead to a DNA sequence (Group II). Were the Court's examination confined solely to the Examiner's written description of the groups, Roche's argument would have considerable force. The relavant line of demarcation, however, is "the grouping restriction actually imposed by the examiner." *Texas Instruments,* 988 F.2d at 1179. Roche does not dispute that the Examiner assigned some claims to Group I that were from non-naturally occurring sources. Thus, the Court cannot conclude that the inclusion of the term "non-naturally occurring" broke consonance.

Finally, Roche contends that Amgen broke consonance by separating the '349 patent into Group IV. Roche maintains that the '349 patent belongs in Group II because Amgen added claim 7, a claim drawn to the recombinant process of using vertebrate cells to produce EPO. Roche is mistaken. As noted above, restriction Group II was comprised of claims drawn to DNA, while Group IV was drawn to cells. Lodish Decl. ¶¶ 23, 29. The mere addition of a process claim does not transform a Group IV claim into a Group II claim. As Amgen notes, "only 4 of the 35 claims assigned to Group II were process claims." Pl.'s Rep. Br. Supp. Sum. J. No

ODP at 9. Moreover, the common feature of the Group II claims is that they "require[ ] a specific, purified, and isolated DNA sequence, encoding either human or monkey erythropoietin or an analog polypeptide related to erythropoietin in both structure and function." Lodish Decl. ¶ 21. Claims 1–3, referenced in the process taught in claim 7, merely require that the EPO DNA in the vertebrate cells "be transcriptionally controlled by 'non-human DNA sequences.' " Lodish Decl. ¶ 30. In short, because the focus remains on the cells, the inclusion of claim 7 does not cause the '349 claim to stray over the line of demarcation into Group II.

Accordingly, on the record before the Court, there were no genuine issues of fact to be decided and, thus, the Court granted Amgen's motion for summary judgment and held that Section 121 "insulates the ensuing patents from the charge of double patenting." *Applied Materials,* 98 F.3d at 1568.

Given these rulings, the Court believed that it had put paid to the ODP issues in this case. The Court was wrong. After extensive argument during the final pretrial conference, Roche convinced the Court that there remained genuine issues of material fact for trial upon what the parties came to call Roche's theories 3 and 4.

E. Findings and Rulings after Trial

And so the trial came. The Court was somewhat surprised (and concerned) that Roche focused heavily in its opening to the jury on double patenting issues, as though this were some sort of equitable defense.

1. Jury or Non-jury?

[17, 18] After careful reflection, the Court ruled on September 7, 2007 that obviousness double patenting ought not be submitted to the jury. "Determining what is patented by correct claim interpretation is essential to [the] determination of obviousness-type double patenting issues." *Gen. Foods,* 972 F.2d at 1279 (capitalization altered). It is the Court's role, not the jury's, to determine the metes and bounds of the claimed inventions. *See Markman v. Westview Instruments, Inc.,* 517 U.S. 370, 384–91, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). Accordingly, because "[d]ouble-patenting is altogether a matter of what is claimed," *Gen. Foods,* 972 F.2d at 1277, obviousness-type double patenting is an issue for the Court. Other district courts have agreed, ruling that decisions regarding the ODP defense should be made by a judge, not a jury. *See, e.g., Engineered Prods.,* 313 F.Supp.2d at 993 ("[T]he double-patenting defense will be tried to the court because it is a question of law."); *Applera Corp. v. MJ Research Inc.,* 363 F.Supp.2d 261, 262 (D.Conn.2005) (explaining that the Court reached "findings of fact and conclusions of law" regarding ODP based upon, inter alia, deposition testimony not introduced at trial as well as evidence submitted at trial). For these reasons, the Court here concluded that the ODP issue presented a matter for the Court.

After conducting hearings outside the presence of the jury, the Court carefully reviewed both ODP arguments that Roche put forward on the basis of the entire trial record. For purposes of simplicity the Court and the parties referred to these arguments as theories number 3 and 4. The Court presents its findings and rulings below.

2. Roche's Theory Number 3

Roche's theory number three argues that the asserted '868 and '698 claims are invalid for ODP over the '008 claims. The parties agree that the safe harbor provision delineated in section 121 does not apply to these claims. *See, e.g.,* Resp. to Roche's Proposed Findings and Conclusions [Doc. 1628] ¶ 5. In order for section

121 to apply, the '868 and '698 patents would have to derive from a patent application that was subject to a restriction requirement; furthermore, the claims of the '868 and the '698 patents would have to address an invention distinct from the elected invention prosecuted by way of the original application. *See, e.g., Gerber,* 916 F.2d at 688. Here, however, both the '008 claims and the asserted claims of the '868 and '698 patents fall within Group II of the PTO's 1986 Restriction Requirement. Therefore, because section 121 does not apply as between patents that contain claims belonging to the same restriction group, no safe harbor protection exists.

[19] When a claim is not immunized from allegations of obviousness-type double-patenting due to section 121, the question becomes whether the defendant has met its burden of proving the ODP defense. As with other affirmative defenses of invalidity, the defendant bears the burden of proving ODP by clear and convincing evidence. *Symbol Techs.,* 935 F.2d at 1580.

As described part III.A, the ODP analysis entails two steps. First, the Court construes the claims and determines whether there are any differences. *Eli Lilly,* 251 F.3d at 968. Second, to the extent that differences exist, the Court must determine whether the distinctions are sufficient to render the claims patentably distinct. *Id.* The Court will consider the '868 patent first:

'008 claims 2, 4, 6, 7, 25, 27	'868 claims 1–2
2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.	1. A process for the production of 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.
4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2 or 3 in a manner allowing the host cell to express erythropoietin.	2. The process according to claim 1 wherein said host cells are CHO cells.
6. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 5.	
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 biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.	

[23. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 7 . . . in a manner allowing the host cell to express 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.

[20] Roche argues that the ′008 claims provided: (1) a "mammalian host cell" (2) that is "transformed or transfected" (3) with "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." Roche further asserts that ′008 claims provide that (4) the cell is transfected in such a way "to allow possession of the biological property" of erythropoietin, which is (5) stimulating red blood cell formation, or "causing bone marrow cells to increase production of reticulocytes and red blood cells." Def.'s Mem. on ODP [Doc. 1550] at 14–15. Roche reasons that claim 1 of the ′868 patent therefore simply tells one skilled in the art to "take the cells that were claimed in the ′008 patent and grow them, let[ting] them do what they normally do." *Id.* at 15 (quoting testimony of Dr. Lowe). Similarly, Roche asserts that claim 2 of the ′868 patent, which specifically contemplates using CHO cells, is obvious given the fact that the ′008 patent also claimed the use of CHO cells. *Id.*

Amgen, on the other hand, argues that the differences between the patents are "several" and "significant." Pl.'s Mem. on No ODP [Doc. 1310] at 40. In particular, Amgen asserts that the ′868 patent claims (1) processes for making (2) isolatable quantities of a glycosylated EPO polypeptide (3) having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, while the claims of the ′008 patent claim only certain DNA molecules and certain cells transformed or transfected with said DNA molecules. *Id.* (asserting that, unlike the ′868 patent, the ′008 patent does not "claim a process for producing anything").

In other words, Amgen explains, "the ′008 claims are directed to purified and isolated DNA sequences and cells into which such DNA sequences have been introduced. In contrast, the ′868 claims 1 and 2 are *process* claims that recite the steps required to produce a glycosylated polypeptide having specified characteristics." *Id.* at 41 (emphasis added). "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." *Id.* These differences, according to Amgen, render the ′868 claims distinct from the ′008 claims.

The Court agrees. Simply 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. *See id.* at 40 (quoting testimony of Dr. Lodish). Roche has failed to meet its burden of demonstrating

by clear and convincing evidence that no patentable difference exists between the '008 and '868 patents. Accordingly, the Court finds that the '868 claims are not anticipated by the '008 patent and rules that the '868 claims are different from the claims of the '008 patent.

The Court now considers the ODP allegations with regard to the '698 patent:

'008 claims 2, 4, 6, 7, 25, 27	'698 claims 6–9
2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.	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 [figure] 6, and (b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.
4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2 or 3 in a manner allowing the host cell to express erythropoietin.	7. The process of claim 6 wherein said vertebrate cells further comprise amplified marker gene DNA.
6. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 5.	8. The process of claim 7 wherein said amplified marker gene DNA is Dihydeofolate reductase (DHFR) gene DNA.
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 biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.	9. The process according to claims 2, 4, and 6 wherein said cells are mammalian cells.
[23. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 7 . . . in a manner allowing the host cell to express 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.	

The parties basically reiterate the arguments made with regard to the '868 patent. *See* Def.'s Mem. on ODP at 17; Pl.'s Mem. on No ODP at 44. The Court's reasoning is likewise similar. Of particular importance to the Court are the two additional limitations included in the '698

claims: (1) the requirement of "amplified DNA encoding the mature erythropoietin sequence of [figure] 6" and (2) the requirement of "amplified marker gene DNA." No such requirements are present in the '008 claims. And, like with the '868 claims, '698 process is designed to produce a glycosylated in vivo biologically active EPO product. To be able to produce such a 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). Accordingly, the Court rules that the '698 is a different process than the product obtained from the '008 patent.

[21, 22] The second step in the ODP analysis, after identifying the differences between the claims at issue, is to determine whether those differences in subject matter render the later-issued claim patentably distinct from the earlier-issued claim. *In re Metoprolol Succinate Patent Litig.*, 494 F.3d 1011, 1016 (Fed.Cir.2007). A later-claimed invention is patentably distinct (and therefore not invalid for ODP) if that invention as a whole would not have been obvious over the earlier-claimed invention to a person of ordinary skill in the art at the time just before the later-claimed invention was made. *See id.* Here, 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. Thus, the Court rejects Roche's Theory Number 3 ODP defense. In other words, Roche's argument that the '008 patent renders the asserted claims of the '868 and '698 patents obvious because, once one skilled in the art had possession of the EPO DNA sequence, growing the cells and culturing them to obtain a protein with the characteristics claimed in the '868 and '698 patents required no inventive effort in 1983 or 1984 is rejected. The PTO found the '868 and '698 claims patentably distinct from those in the '008 patent, and this Court agrees.

The Court also finds unpersuasive Roche's argument that judicial estoppel applies to prevent Amgen from making arguments, when defending against the ODP allegations, that Roche asserts are inconsistent with Amgen's prior representations to the PTO. *See* Def.'s Mem. on ODP at 24. In particular, Roche asserts that because Amgen stated that the '008, '868, and '698 patents are manifestations of a single invention, it is now barred from asserting that the relevant claims are patentably distinct. *Id.* at 24–25.

[23–25] "[T]he doctrine of judicial estoppel prevents a litigant from pressing a claim that is inconsistent with a position taken by that litigant either in a prior legal proceeding or in an earlier phase of the same legal proceeding." *InterGen N.V. v. Grina*, 344 F.3d 134, 144 (1st Cir.2003) (citing *Pegram v. Herdrich*, 530 U.S. 211, 227 n. 8, 120 S.Ct. 2143, 147 L.Ed.2d 164 (2000)). The doctrine's primary purpose is to safeguard the integrity of the courts by preventing parties from manipulating the machinery of the judicial system. *See New Hampshire v. Maine*, 532 U.S. 742, 749–50, 121 S.Ct. 1808, 149 L.Ed.2d 968 (2001); *United States v. Levasseur*, 846 F.2d 786, 792 (1st Cir.1988). Judicial estoppel also applies to arguments and positions presented to the PTO from which the patentee gained a benefit. *See Lampi Corp. v. American Power Prods., Inc.*, 228 F.3d 1365, 1377 (Fed.Cir.2000) (applying judicial estoppel to proceedings before PTO when doing so was dictated by the law of the circuit from which the case originated); *Portela–Gonzalez v. Secretary of the Navy*, 109 F.3d 74, 78 (1st Cir.1997) ("Equitable doctrines of estoppel apply in administrative and judicial fora, and a party cannot take one position in [a] ...

administrative proceeding and then disclaim it in a subsequent suit arising out of the agency proceedings.") (internal citation omitted); *see also Analog Devices, Inc. v. Linear Tech. Corp.,* 479 F.Supp.2d 202, 212 (D.Mass.2007)(Harrington, J.).

[26] Two requirements must be satisfied in order to invoke judicial estoppel. First, the prior position must be directly inconsistent with the present position. *Faigin v. Kelly,* 184 F.3d 67, 82 (1st Cir. 1999); *see also Levasseur,* 846 F.2d at 794. Second, the responsible party must have succeeded in persuading a court to accept its prior position. *See Faigin,* 184 F.3d at 82 (explaining party being estopped must succeed utilizing inconsistent position); *Lydon v. Boston Sand & Gravel Co.,* 175 F.3d 6, 13 (1st Cir.1999) (same). Courts also often inquire as to whether judicial acceptance of a party's initial position conferred a benefit on that party. *See, e.g., Patriot Cinemas, Inc. v. General Cinemas Corp.,* 834 F.2d 208, 213 (1st Cir.1987); *Levasseur,* 846 F.2d at 793.

[27] In this case, Roche fails to satisfy the first requirement. Roche has put forward virtually innumerable arguments in support of the idea that Amgen has taken inconsistent positions. *See* Def.'s Mem. on ODP at 24–33. After careful review of each and every one of these arguments as well as its supporting documents, however, the Court finds that no actual inconsistency exists.

The first alleged contradiction concerns Amgen's statements to the PTO made in the context of the '096 and '097 interferences. *Id.* at 27–30. Roche cites a paragraph entitled "Summary of Lin's Positions" from a brief Amgen filed in connection with the '097 interference, in which Amgen stated:

> While the count is directed to a process for preparing in vivo biologically active EPO using a mammalian host cell transfected or transformed with an isolated DNA sequence encoding human EPO [i.e., the process patent claims], and the litigation was directed to the purified and isolated DNA sequence and host cells transfected or transformed thereby [i.e., the '008 DNA claims], it is evident that these are only different manifestations of the same invention.... Clearly, the whole purpose and intent of the purified and isolated DNA sequence encoding human EPO (and host cells transfected therewith) at issue in the litigation was to express in vivo biologically active human EPO. Stated otherwise, the process language of the Lin patent claims at issue in the litigation ("encoding human EPO") [see '008 patent claims] is, for all intents and purposes, a description of the present count.

Def.'s Mem. on ODP at 27 (quoting Brief for the Senior Party Lin, Interference No. 102,097, dated July 29, 1991, at 25–26). Roche asserts that these statements indicate that Amgen acknowledged that the patents at issue all reflect a single invention, contrary to its representations to this Court. *See id.* at 25.

At first blush, this argument seemed compelling. When the statement is put in the context of the whole interference, however, an entirely different coloration emerges. Roche's quote omits the reference to the adverse party in the interference: Fritsch. A detailed reading of the '097 Lin brief reveals that Amgen was referring to Fritsch's position in order to prove that, even under Fritsch's own theory, Amgen had priority. In other words, Amgen was saying to the Interference Board that (1) given Fritsch's own admissions and (2) taking into account Judge Saris' decision in *Amgen, Inc. v. Chugai Pharm. Co.,* No. 87–2617–Y, 1989 WL 169006 (D.Mass. December 11, 1989), Fritsch would never be able to establish that he had invented the Process Count before Lin. This is not the equivalent of

adopting Frisch's reasoning, as Roche asserts, *see* Def.'s Mem. on ODP at 27; instead, Amgen simply was pointing out that even if Fritsch's arguments were credited Fritsch would still lose.

Roche also asserts that Amgen contradicts itself here because Amgen indicated it did not consider "in vivo biological activity to provide a patentable distinction over the EPO DNA sequence," which is inconsistent with Amgen's arguments to this Court. *See* Def.'s Mem. on ODP at 27–33. Roche again relies upon the theory that Amgen adopted Fritsch's arguments and admitted that, once a skilled artisan had the DNA sequence, the new claims would be obvious. As explained above, however, a detailed reading of the Lin's '097 interference reveals that Amgen was putting forward all the information regarding priority of invention, not adopting this obviousness theory.

Finally, a third alleged contradiction, which initially caught the Court's attention, also ultimately fails. Roche asserts that Amgen's arguments in the '096 and '097 interferences are the basis upon which the Interference Board relied when ruling that Amgen's work "relating to expression of the EPO gene in mammalian host cells and isolation of the resulting glycoprotein product involved [nothing] more than the exercise of ordinary skill by practioners in the field." *Id.* at 32. Roche reasons that the Interference Board's conclusion demonstrates that Amgen itself advocated that there was "nothing novel or inventive in making glycosylated biologically active EPO." *Id.* Nowhere, however, does the Interference Board's decision address the issue of obviousness; rather, its decision appears driven by the issue of priority and Fritsch's concession, not any argument by Amgen.

As mentioned, Roche's memoranda are full of other alleged inconsistencies. For the purposes of this decision, however, the Court is satisfied with mentioning the most compelling ones. As for the rest, the Court has taken them into account but, failing to see factual or legal merit in them, summarily denies them.

3. Roche's Theory Number 4

[28, 29] Roche's last attempt to invalidate the '933, '422, and '349 patents rests on the contention that they would have been obvious to one skilled in the art over the claims of the '868 and '698 patents and that any distinctions between the claims of the former and latter group are not patentable. Def.'s Mem. on ODP at 4. If Amgen is eligible to invoke the safe harbor provision of 35 U.S.C. § 121, Roche would be unable to succeed on this theory. In order to benefit from the protection offered by section 121, it must be true both that (a) the '933, '422, and '349 patents arose from an application that was the result of a PTO restriction requirement, and (b) the claims of those patents are consonant with the restriction requirement. *Gerber,* 916 F.2d at 687–88.

The first of these requirements has already been addressed in this decision. In granting partial summary judgment, this Court ruled that the '933, '422, and '349 patents were filed as a result of the 1986 restriction requirement.

With regard to consonance, in issuing the 1986 restriction requirement, the examiner broke the claims put forth in the '298 application into six groups:

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 240.

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. . . . .

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Lodish Decl. Ex. E–1, ′298 Prosecution, Paper 8 at 2. "Restriction [of the application] to one of the[se six] inventions [was] required under 35 U.S.C. § 121." *Id.* Amgen accordingly selected the Group II claims for continued examination in the ′298 application. Moore Decl. Ex. H–8, Office Action, at AM–ITC 00952502. The other, non-elected claims were cancelled from the application. *Id.* Although Amgen initially elected all of the Group II claims, which included DNA, host cell, and process claims, for further prosecution in the ′298 application, it also later cancelled the process claims after it became apparent that the PTO would not allow issuance of those claims based on *In re Durden*, 763 F.2d 1406 (Fed.Cir.1985). Moore Decl. Ex. H–13, Office Action, at AM–ITC 00952592; *id.* Ex. H–14, Examiner Interview Summary Record, at AM–ITC 00952596; *id.* Ex. H–15, Applicant's Amendment and Reply, at AM–ITC 00952599. On October 27, 1987, Dr. Lin's ′298 application issued as the ′008 patent. Consistent with Amgen's election to have Group II claims examined in the ′298 application, all of the ′008 patent claims fall within the scope of restriction Group II.

On October 23, 1987, Amgen filed two new applications: the ′178 application and the ′179 application. During prosecution of the these applications, as well as subsequent applications leading to the patents-in-suit, Amgen canceled claims, amended claims, and added new claims. As a result, the issued claims in the patents-in-suit are not identical to the original claims filed in the ′178 and ′179 applications. All of the claims of the ′933, ′349, and ′422 patents, however, fall within the scope of the non-elected restriction groups: the ′933 patent claims fall within the scope of restriction Groups I and V, the ′422 patent claims fall within restriction Group V, and the ′349 patent claims fall within restriction Group IV. None of the claims in these patents fall within the scope of restriction Group II, which was prosecuted to issuance in the ′008 patent. In contrast, the issued claims of the ′868 and ′698 patents fall within the scope of restriction Group II.

Roche does not seem to contest these factual findings. In its memoranda, however, Roche argues two propositions. First, in order for section 121 to apply, Roche asserts that each of the patents at issue—the ′933, ′422, and ′349, *as well as* the ′868 and ′698 patents—must have arisen from applications filed as a result of a restriction requirement. Def.'s Mem. on Consonance [Doc. 1548] at 3–5. Second, Roche argues that the ′868 and ′698 patents did not maintain consonance with the restriction requirement, defeating Amgen's ability to invoke section 121. *Id.* at 7–8. The premise underlying both arguments is that the two section 121 prerequisites must be satisfied both by the allegedly invalid patent and by the patent asserted as the ODP reference. *Id.* at 3.

Based on the plain language of section 121, the Court agrees with Roche's first premise: that the prior art, as well as the allegedly invalid patent, must have arisen from applications filed as a result of a restriction requirement. Section 121 states that "a patent issuing on an application with respect to which a requirement for restriction . . . has been made, or [issu-

ing] on an application filed as a result of such a requirement, shall not be used as a reference against" the divisional application, the original application, or any patent issuing therefrom. 35 U.S.C. § 121. In other words, section 121 cannot be invoked to remove a patent as prior art unless that patent issued from an application subject to a restriction requirement or an application as a result of that restriction.

The fact that Roche has correctly identified the limits imposed by section 121 on immunized prior art, however, does not help its cause. This Court concluded at the time it granted summary judgment, as it does now, that the '178 and '179 applications were filed as a result of a restriction requirement. *See supra* part II.D.1. The '868 patent issued from the '179 application; accordingly, it is among those pieces of prior art to which section 121 may apply.

The '698 patent, however, issued from the '381 application, which was a continuation of the '179 application. The scope of prior art immunized by section 121 nonetheless appears to extend to the '698 patent. The Federal Circuit has, when applying section 121 to allegedly invalid patents, permitted its protections to be extended to patents issuing from applications that were continuations of applications filed as a result of a restriction requirement. *See, e.g., Symbol Techs.,* 935 F.2d at 1579–80; [8] *Applied Materials,* 98 F.3d at 1567–69. There is no apparent reason why the same rule should not apply on the other side of the equation.

The Court also rejects Roche's late-arising argument that the '868 and '698 patents must have maintained consonance with the '008 patent in order to be removed as a reference for the '933, '342, and '433 patents. As an initial matter, none of the cases cited by Roche explicitly require this be the case. Indeed, although Roche asserts that "case law makes clear that consonance is relevant to determining whether a patent may be used as a reference," Def.'s Mem. on Consonance at 6, it fails to cite any cases standing for this alleged rule immediately thereafter. *See id.* Instead, it attempts to reach this conclusion in a roundabout way by citing later to three cases—*Applied Materials, Symbol Technologies,* and *Geneva Pharmaceuticals*—that stand for the proposition that consonance is maintained "as long as the amended claims preserved the Examiner's demarcation between claim groups." *Id.* In *Geneva Pharmaceuticals,* however, the court did not analyze consonance with regard to the relevant patents because it concluded that the restriction requirement failed sufficiently to delineate the subject matter such that consonance could be assessed. *See Geneva Pharms.,* 349 F.3d at 1381–82. This case thus does not advance Roche's argument even implicitly.

The Court finds another case relied upon by Roche, *Applied Materials,* quite instructive, but not in the way Roche would hope. In *Applied Materials,* the Federal Circuit analyzed the validity of a patent, the '609 patent, issuing from a divisional application resulting from a restriction requirement by reference to two

8. *Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc.* does not invalidate this precedent. As an initial matter, *Pfizer* did not name *Symbol Technologies* as one of the decisions that was possibly at odds with the *Pfizer* decision. *See Pfizer,* 518 F.3d at 1362 (naming other cases). Furthermore, *Pfizer* addressed the scope of section 121 in the context of a continuation-in-part application filed in lieu of a divisional application when responding directly to a restriction requirement. *Id.* at 1362. It said nothing about what happens if an applicant files a divisional application—which is eligible for section 121's safe harbor—and then files a continuation application to that divisional application.

other patents. One reference patent, the '712 patent, issued from the original parent application upon which the restriction was imposed. *See Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.,* 1994 WL 362005, at *2 (N.D.Cal.1994). The second reference patent, the '496 patent, issued from a second divisional application. *See Applied Materials,* 98 F.3d at 1567. When determining the applicability of section 121, the court focused its consonance analysis on the allegedly invalid patent as opposed to the reference patents, *see id.* at 1568–69, and ultimately concluded that "consonance was not violated, for the process claims [reflected in the challenged '609 patent] remained in the separate patents from the apparatus claims [reflected in the '496 and '712 patents]," *id.* at 1568.

[30] While the *Applied Materials* court looked to the two reference patents to determine whether they covered the same material as the allegedly invalid '609 patent, notably it did *not* ask whether the '496 patent maintained consonance with the '712 patent. This is of particular interest given two facts: (1) the '712 and '496 patent both covered "apparatus" claims and (2) the '496 patent was subject to a terminal disclaimer. *See* U.S. Patent No. 4,047,496. Terminal disclaimers, of course, are used to overcome double patenting rejections. *See, e.g., Eisai Co. v. Dr. Reddy's Laboratories, Ltd.,* 533 F.3d 1353, 1360 (Fed.Cir.2008) (noting patent applicants "routinely overcome" ODP rejections by filing a terminal disclaimer). Indeed, the effective date of the '496 patent's disclaimer, November 30, 1988, indicates that it was designed to resolve double patenting concerns arising from the '712 patent. *See Applied Materials,* 1994 WL 362005, at *1 (noting '712 patent expired in 1988); U.S. Patent No. 3,623,712 (noting issuance date of November 30, 1971). The only reason, meanwhile, that a terminal disclaimer would be required is if section 121 did not immunize the '712 patent as a reference for double patenting, suggesting that the '496 patent did not maintain consonance with the '712 parent.[9]

In any event, the *Applied Materials* court applied section 121 and upheld the district court's determination that the '609 patent was not invalid for double patenting over both the '712 patent *and* the '496 patent. *Applied Materials,* 98 F.3d at 1569. In doing so, it indicated that the relevant inquiry—to the extent that the substance of the reference art determines whether section 121 may apply—is whether the allegedly invalid patent and the reference art adhere to the restriction set forth by the PTO by covering distinct inventions, *not* whether the reference art maintains consonance with the parent it shares with the allegedly invalid patent.[10] *See id.* at 1568 (finding it sufficient that the allegedly invalid patent covered process claims while reference patents covered apparatus claims).

The facts of the instant case, of course, are not so different from *Applied Materi-*

9. For example, because the '868 and '698 patents, like the '008 patent, contain restriction Group II claims, section 121 did not defeat allegations that the '868 and '698 patents were invalid for ODP over the '008 patent. *See* Pl.'s Response to Def.'s ODP Briefs [Doc. 1555] at 41.

10. Nothing about the third case Roche cites, *Symbol Technologies,* alters this conclusion. In *Symbol,* the reference art was a patent issuing from the original application made subject to a restriction requirement. *Symbol Techs.,* 935 F.2d at 1580. The relevant question was ultimately whether the allegedly invalid patent and the reference art covered distinct and separate invention. *See id.* at 1579–81. Of course, because the reference art in *Symbol* was a patent issuing from the original application, *Symbol* has little to say about the question confronting this Court.

als. It is undisputed that the claims of '933, '422, and '349 patents do not cover anything that falls within restriction Group II. Meanwhile, the '868 and '698 patents contain only Group II claims. Accordingly, consonance was not violated, to borrow the phrasing of *Applied Materials,* because the Group II claims remained in separate patents from the claims of other restriction groups.

Because the '933, '422, and '349 patents issued as the result of a restriction requirement and maintain consonance with that restriction requirement, they fall within the protection of section 121. Similarly, because the '868 and '698 patents issued from applications filed as the result of a restriction requirement and do not share subject matter with the '933, '422, and '349 patents, the '868 and '698 patents are immunized as prior art. Accordingly, the Court declines to find the '933, '422 and '349 patents invalid for ODP.

III. POST–TRIAL JUDGMENT AS MATTER OF LAW

A. The Legal Framework

Roche, having lost before the jury, moves for judgment as matter of law ("JMOL") and for a new trial. The JMOL is the modern equivalent of a motion for judgment notwithstanding the verdict. *See Syngenta Seeds, Inc. v. Delta Cotton Co-op., Inc.,* 457 F.3d 1269, 1274 n. 1 (Fed. Cir.2006). "Federal Rule of Civil Procedure 50(a)(1) provides that a court may grant a motion for JMOL only where there is no legally sufficient evidentiary basis for a reasonable jury to find for the nonmovant." *Paice LLC v. Toyota Motor Corp.,* 504 F.3d 1293, 1303 (Fed.Cir.2007) (internal quotation marks omitted).

[31] This Court will apply First Circuit standards in reviewing the motions for a new trial. *See Z4 Techs., Inc. v. Microsoft Corp.,* 507 F.3d 1340, 1347 (Fed.Cir.2007) (reviewing the refusal of a motion for a new trial according to the regional circuit standard). Under Federal Rule of Civil Procedure 59(a)(1), "a 'new trial may be granted ... for any of the reasons for which new trials have ... been granted in actions at law in the courts of the United States.' " *Fernandez v. Leonard,* 963 F.2d 459, 468 n. 13 (1st Cir.1992). "District courts 'may set aside a jury's verdict ... only if [it] is so clearly against the weight of the evidence as to amount to a manifest miscarriage of justice.' " *Rivera Castillo v. Autokirey, Inc.,* 379 F.3d 4, 13 (1st Cir.2004).

B. Validity

Section 282 of the Patent Act, 35 U.S.C., states, "A patent shall be presumed valid." This is far more significant than a true evidentiary presumption, *cf.* Fed.R.Evid. 301; section 282 shifts to the party challenging the patent the burden of proving invalidity by clear and convincing evidence. *Scanner Techs. Corp. v. ICOS Vision Sys. Corp.,* 528 F.3d 1365, 1380 (2d Cir.2008). Under no circumstance is that burden to be borne by the patent holder. *Id.* The presumption of validity codified in section 282 reflects Congress's judgment that the Patent and Trademark Office's decision to issue a patent is entitled to some deference. *See Purdue Pharma L.P. v. Faulding, Inc.,* 230 F.3d 1320, 1329 (Fed.Cir.2000); *see also United States v. Budd,* 144 U.S. 154, 161, 12 S.Ct. 575, 36 L.Ed. 384 (1892). In the instant case, Roche asserted a number of invalidity defenses including anticipation, obviousness, indefiniteness, and non-enablement. Below, the Court focuses on Roche's assertion that claim 1 of the '422 patent was anticipated by the Goldwasser study as well as Roche's contention that the term "human erythropoietin" is fatally indefinite.

[32] A claim is anticipated if every limitation is present in a single device in the prior art. *Finisar Corp. v. DirecTV Group, Inc.,* 523 F.3d 1323, 1334 (Fed.Cir. 2008). As shall be discussed below, Roche's anticipation challenge centered upon its assertion that claim 1 of the '422 patent was anticipated by the Goldwasser study. Roche could not as matter of law meet its burden of proving anticipation because "purified from mammalian cells grown in culture" limits claim 1 while the EPO used in the Goldwasser study was purified from human urine.

[33] The definiteness requirement is derived from section 112, paragraph 2 of the Patent Act, which provides that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112. The touchstone of the definiteness requirement is whether a person having ordinary skill in the art at the time of the application would be able to discern the scope of the claim. *See Exxon Research & Eng'g Co. v. United States,* 265 F.3d 1371, 1375 (Fed.Cir.2001). As the Court shall explain below, the term "human erythropoietin" is sufficiently definite, even though the specification does not specify whether EPO's amino acid sequence was 1 to 165 or 1 to 166.

1. The Court properly concluded that claim 1 of the '422 patent was not anticipated because "purified from mammalian cells grown in culture" limits the claim and the prior art was purified from urine

[34] Roche contends that it is entitled to judgment as matter of law or, in the alternative, a new trial because a reasonable jury would have been forced to conclude that claim 1 of the '422 patent is invalid as anticipated by the prior art. Claim 1 of the '422 patent teaches:

> A [1] pharmaceutical composition comprising a [2] therapeutically effective amount of [3] human erythropoietin and a [4] pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is [5] *purified from mammalian cells grown in culture.*

'422 patent col. 38 *ll.* 36–41 (emphasis supplied). At claim construction, the Court concluded that each of the numbered elements limited the claim, including the product's source, "purified from mammalian cells grown in culture." The undisputed record revealed that none of the allegedly anticipatory prior art was "purified from mammalian cells grown in culture." The Court therefore granted Amgen's motion for a directed verdict on the validity of claim 1 of the '422 patent on the ground that "Roche [ ] failed . . . to prove by clear and convincing evidence as to the '422 patent claim 1 that it was anticipated. . . ." Trial Tr. at 1380.

Roche asserts that "Amgen had the burden at trial to 'convincingly show' that the source limitation imparts novel structure to an otherwise non-novel product." Def.'s Post Tr. Br. at 50. Roche's proffered rule is contrary to the fundamental principle that a defendant must demonstrate "by clear and convincing evidence that each and every element of the claimed invention" was present in the prior art. *Zenon Envtl., Inc. v. U.S. Filter Corp.,* 506 F.3d 1370, 1379 (Fed.Cir.2007). Moreover, it is contrary to *Markman v. Westview Instruments, Inc.,* 517 U.S. 370, 387, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996), which makes clear that issues of claim construction are within the exclusive province of the Court. In addition, the rule contravenes the presumption of validity codified at 35 U.S.C. § 282 by shifting the burden of persuasion to Amgen. While a patentee seeking to have a source or process limit a claim may be required to come forward with evidence during claim construction, once that bur-

den is satisfied, as it was in this case, then the patentee need not re-prove at trial what he has already demonstrated to the patent office and court.

a. "Purified from mammalian cells grown in culture" limits claim 1

At claim construction, the Court noted that "as has long been recognized by the Federal Circuit, source or process limitations can and do serve to define the structure of a claimed product where such limitations are the best means to distinguish a claimed product over prior art." *Amgen Markman,* 494 F.Supp.2d at 65 (citing *In re Luck,* 476 F.2d 650, 653 (C.C.P.A.1973)). As "Dr. Lin has testified[,] at the time, 'the only way [to] characterize [his claimed] product is by the way they were making [it].' Accordingly, the Court deem[ed] it appropriate to include the 'source limitation' in a product claim." *Id.* (internal citation omitted)(first two alterations in original). The Federal Circuit has upheld this construction in a related case. *See Amgen II,* 314 F.3d at 1329 (noting that " 'purified from mammalian cells grown in culture' in claim 1 clearly limits the source of the EPO used in the claimed 'pharmaceutical composition' "). The Court held that "purified from mammalian cells grown in culture" means "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.* The Court's decision that the source limits the claim in this case was consistent with the Court's conclusions in *Amgen I,* where the Court observed distinctions between the claimed recombinant EPO and the urinary EPO employed in the Goldwasser study. *See Amgen I,* 126 F.Supp.2d at 124–27.

One critical distinction between EPO extracted from urine and synthetically engineered EPO is that the urinary EPO has been exposed to enzymes and bodily processes that may hinder its efficacy for future use. In *Amgen I,* the Court noted differences in glycosylation and specific activity, which may also reflect recombinant EPO's resistance to degradation in the human body:

> As disclosed in Column 28 of the patent . . . according to Western blot and SDS–PAGE analyses, "the CHO-produced EPO material had a somewhat higher molecular weight than the COS–1 expression product which, in turn, was slightly larger than the pooled source human urinary extract." [U.S. Patent No. 5,955,422] at [col.] 28 [*ll.*] 38–41. Amgen scientists then treated the proteins with neuraminidase, which removes the sialic acids from the protein. *Id.* at [col.] 28 [*ll.*] 42–43. Following neuraminidase treatment, the COS–1 and CHO recombinant products had approximately equal apparent molecular weights, but were both nonetheless larger than the resulting asialo human urinary extract. *See id.* at [col.] 28 [*ll.*] 42–46. Amgen then treated the CHO and human urinary products with endoglycosidase F, which removes not only sialic acids, but also any other carbohydrate chains attached to the protein. *Id.* at [col.] 28 [*ll.*] 46–48. Amgen scientists discovered that the CHO and urinary products were "substantially homogenous products having essentially identical molecular weight characteristics." *Id.* at [col.] 28 [*ll.*] 49–50. The conclusion to be drawn from this series of tests is that the difference in the apparent molecular weights of recombinant and urinary EPO products on SDS–PAGE and Western blot is explained by differences in glycosylation between the two types of EPO glycoproteins. In light of this data reported in Column 28, one skilled in the art in 1983 would under-

> stand that the recombinant proteins are glycosylated differently than the naturally-occurring protein, and that these differences can be revealed by running an SDS–PAGE and doing a western blot as described here.

Amgen I, 126 F.Supp.2d at 125 (some internal citations and quotation marks omitted).

In addition, evidence suggests that recombinant and urina EPO glycosilate at different rates:

> [i]n the final paragraph of Column 28, Amgen disclosed the results of another set of experiments intended to show differences in glycosylation between recombinant and urinary EPO products. '422 patent at [col.] 28 [*ll.*] 51–67. Amgen performed "carbohydrate analyses" in order to identify the individual monosaccharide sugar residues present on both the EPO derived from CHO cells and derived from urine. *See id.*
>
> [I]n this experiment the glycoprotein is taken and hydrolyzed in the presence of acid . . . and that cleaves the bonds between the amino acids, cleaves the bonds between the individual sugar residues. . . . [A]ll the sugars then are present unlinked to each other as individual monosaccharides. They can be labeled and separated by some chromatographic method. So that, say the sialic acids are separated from the N-acetylglucosamines and Fucose and so forth.
>
> Once all of the sugars are separated and identified, their relative distribution can be calculated. In particular, one type of sugar is designated as one, and the other sugars are compared by their abundance in relation to the standardized sugar. In the nomenclature of the patent specification, one can identify the carbohydrate constitution values expressed as molar ratios of the carbohydrates in the product. *Id.* at [col.] 28 [*l1.*] 56–58. Using this method, the patent reveals that the recombinant EPO product contains a higher ratio of N-acetylneuraminic acid (.998) than the urinary EPO product (.930). *Id.* at [col.] 28 [*ll.*] 56–66. This difference in the carbohydrate constitution values between the recombinant and urinary EPO glycoproteins is "consistent with the Western blot and SDS–PAGE analysis described above." *Id.* at [col.] 28 [*ll.*] 66–67.

Id. (internal indentation of block quote omitted)(footnote omitted)(alterations in second paragraph in original).

It is significant that the source is what enables mass production and commercial viability. If a drug manufacturer sought to produce the naturally occurring EPO in the Goldwasser study, the manufacturer would have to scour the world for aplastic anemia patients whose urine was susceptible to purification according to the Miyake method. Then the producer would have to contract with enough patients willing to provide quantities of urine sufficient to meet the vast demand for anemia drugs, thereby transforming the company into a glorified urine collection agency. Of course, it is unlikely that this ever could have happened because as Dr. Baron informed the FDA "twice, in 1985 and 1987," the requisite type of urine was in such short supply that it prevented even limited three-patient studies like those he had conducted with Dr. Goldwasser. Def.'s Post Tr. Br. at 47. Part of the genius of Amgen's EPO is that it does not depend on a scarce resource.

b. Issues pertaining to claim construction may not be submitted to the jury

[35] Once the Court made its determination at claim construction, there is no precedent that permits courts to treat source limitations differently than other

limitations. *See In re Luck,* 476 F.2d at 653 ("[P]roduct claims may include process steps to wholly or partially define the claimed product. To the extent these process limitations distinguish the *product* over the prior art, they must be given the same consideration as traditional product characteristics.")(internal citation omitted). Requiring a patentee to prove to a jury that a source limits a claim inverts the role of judge and fact-finder during trial in patent litigation. It has long been established that "[q]uestions of construction are questions . . . for the judge, not questions of fact for the jury." *See Markman,* 517 U.S. at 387, 116 S.Ct. 1384 (quoting A. Walker, Patent Laws § 189, at 173 (3d ed. 1895)). Requiring a patentee to prove to a jury that a source limits his claim plainly subverts the longstanding division of responsibility the Supreme Court clarified in *Markman. See id.* at 384–391, 116 S.Ct. 1384.

[36] To be sure, certain issues subsumed in claim construction questions resemble questions of fact. *See id.* at 389–90, 116 S.Ct. 1384. For instance, here, the Court confronted the question of whether and to what extent structural distinctions between urinary and recombinant EPO are attributable to recombinant EPO's source. Resolution of this issue required not only examination of the patent and the prosecution, but also expert opinion. But the mere fact the issue requires a court to make credibility determinations does not mean that those questions must be submitted to a jury. *Id.* at 387, 116 S.Ct. 1384 ("[M]atters of claim construction, even those aided by expert testimony, are questions for the court[.]").

c. Saddling patentees with a burden of proof at trial is contrary to 35 U.S.C. § 282

[37] Section 282 of the Patent Act mandates that the burden of proof shall fall on the "party asserting [ ] invalidity." 35 U.S.C. § 282. Because the source limits Claim 1 of the '422 patent, it is entitled to a presumption of validity that must be overcome with clear and convincing evidence. As the Supreme Court explained in 1892:

> In [patent cases], the respect due to patent, the presumptions that all the preceding steps required by the law had been observed before its issue, the immense importance and necessity of the stability of titles dependent upon these official instruments, demand that the effort to set them aside, to annual them, or to correct mistakes in them, should only be successful when the allegations on which this is attempted are clearly stated, and fully sustained by proof.

United States v. Budd, 144 U.S. 154, 161, 12 S.Ct. 575, 36 L.Ed. 384 (1892)(quoting *United States v. Maxwell Land–Grant Co.,* 121 U.S. 325, 381, 7 S.Ct. 1015, 30 L.Ed. 949 (1887)).

Because the source claim delineates the scope of Amgen's patent, it is entitled to the same presumption of validity due any product limitation. Roche's approach would eviscerate the presumption by forcing Amgen to come forward with evidence to establish novelty. Federal Circuit precedent is to the contrary. *See Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1534 (Fed.Cir.1983). Once applied, the presumption of validity may not be diminished. *Id.*

Neither 35 U.S.C. § 282 nor any precedent provides a basis for shifting the burden to the patent-holder during trial. Nevertheless, Roche insists that "Amgen had the burden at trial to 'convincingly show' that the source limitation imparts novel structure. . . ." Roche has taken the words "convincingly show" from *In re Moeller,* 28 C.C.P.A. 932, 117 F.2d 565, 567 (C.C.P.A.1941), a 1941 opinion of the Court

of Customs and Patent Appeals. *In re Moeller,* however, dealt with an appeal from the Board of Appeals of the United States Patent and Trademark Office. The significance of this fact is that Moeller was a patent applicant and did not enjoy a presumption of validity.

Roche's other cited authority, *SmithKline Beecham Corp. v. Geneva Pharms., Inc.,* No. 99–CV02926, 2002 U.S. Dist. LEXIS 25275 (E.D. Pa Dec. 20, 2002), an unpublished opinion from the District Court for the Eastern District of Pennsylvania, is similarly unpersuasive. Roche avers that *SmithKline* "implicitly recogniz[es] that the patentee bears the burden" of demonstrating that a source limits a claim. Def.'s Post Tr. Br. at 50. The truth is the district court in *SmithKline* did not apply the burden to either party, much less suggest that a patentee must demonstrate that a source limits a claim at trial. *Id.* at *19–21.

In short, there is no reason for this Court to eschew the ordinary presumption of validity. The Court therefore concludes the source limitation in Claim 1 of the '422 patent is entitled to a presumption of validity that Roche failed to rebut.

d. Roche could not prove anticipation of claim 1 of the '422 patent with clear and convincing evidence because the prior art was purified from the urine of aplastic anemia patients

[38] "Invalidity based on 'anticipation,' 35 U.S.C. § 102, requires that the identical invention was known or its existence would reasonably have been known to a person of ordinary skill in the field. . . ." *SmithKline Beecham Corp. v. Apotex. Corp.,* 403 F.3d 1328, 1330 (Fed.Cir.2005). In order to prevail at trial, Roche had to demonstrate a particular piece of prior art anticipated each element of claim 1. *In re Omeprazole Patent Litigation,* 483 F.3d 1364, 1371 (Fed.Cir.2007). It is undisputed that neither "Dr. Goldwasser's study [nor any other allegedly anticipating prior art] involve[d] an EPO purified from mammalian cells grown in culture, which is . . . required by Claim 1 of the '422 patent." *Amgen I,* 126 F.Supp.2d at 140–41. Therefore, the Court will not reverse its directed verdict for Amgen on Roche's defense of anticipation as to claim 1 of the '422 patent.

Nevertheless, Roche contends it is entitled to judgment as matter of law because Amgen failed to meet its "heavy burden" of demonstrating that "purified from mammalian cells grown in culture" imparts novelty. Def.'s Post Tr. Br. at 52. Roche avers this is so because the limitation is so vague that it embraces a myriad of hypothetical EPO structures that might be "structurally indistinguishable . . . from human urinary EPO." *Id.* at 360. Therefore, according to Roche, any distinctions between human and urinary EPO that are caused by differences in purification techniques cannot establish novelty.

As this Court has outlined, Roche bears the burden of proving that Dr. Goldwasser's EPO was in fact identical to the EPO described in claim 1 of the '422 patent. The mere fact that some mammalian cell purified in some manner in some culture *might* produce some glycoprotein structurally similar to Dr. Goldwasser's EPO hardly proves anticipation by clear and convincing evidence.

e. The Court's conclusion is consistent with Federal Circuit's dicta in Amgen IV and the holding of SmithKline

The Court's conclusion that the source limits the claim is consistent with Federal Circuit precedent as well as dicta in the Federal Circuit's opinion in the related TKT litigation. As the Federal Circuit

observed in *Amgen II,* "a claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations." 314 F.3d at 1354 n. 20. It is also true, however, that source and process limitations may impart novel structure to a product claim. *SmithKline,* 439 F.3d at 1319 ("If those product-by-process claims produced a different product than that disclosed in the [prior art], there would be an argument that the [prior art] disclosure did not anticipate."). As discussed above, the source helps to distinguish recombinant EPO from the prior art. The distinctions between urinary and recombinant EPO dictate that the rule articulated in *Amgen II* does not apply.

It is also worth noting that the Court's construction of this term has twice been appealed, and in neither case has the Federal Circuit held that this Court erred in concluding that the source limits the claim. *See Amgen II,* 314 F.3d at 1329–30. In *Amgen II,* the Federal Circuit explained:

> As to the ′422 patent, the limitation "purified from mammalian cells grown in culture" in claim 1 clearly limits the source of the EPO used in the claimed "pharmaceutical composition." The limitation only speaks to the source of the EPO and does not limit the process by which the EPO is expressed. Rather, the claim is broadly drawn to a "pharmaceutical composition" having certain elements, one of those being EPO "purified from mammalian cells in culture." This reading is in line with the district court's construction. . . .

Id. at 1329. The Court expanded on its view in a footnote: "We do not hold that these limitations lack meaning, only that they mean just what they say. Accordingly, they limit only the source from which the EPO is obtained, not the method by which it is produced." *Id.* at 1330 n. 5.

In sum, the Court's grant of summary judgment on the issue of anticipation of claim 1 of the ′422 patent was proper because "purified from mammalian cells grown in culture" limits the claim and because the prior art was derived from human urine.

2. The jury's finding that claim 1 of the ′422 patent and claims 3, 7, and 9 of the ′933 patent are not indefinite is based on sufficient evidence

[39] Roche argues that even if "purified from mammalian cells grown in culture" limits the claim, claim 1 of the ′422 patent as well as claims 3, 7, and 9 of the ′933 patent are indefinite because "the breadth of the claim term 'human erythropoietin' makes it impossible to determine what is and what is not within the claim." Def.'s Post Tr. Br. at 108. Although Roche concedes that Amgen offered expert evidence on this point at trial, Roche contends that Dr. Lodish's opinion was a "tortured explanation," contradicted by Roche's expert, Dr. Flavell. *Id.* Because the Court is not permitted to re-weigh evidence, and because Dr. Lodish's testimony provided a sufficient basis for a reasonable jury to conclude Roche failed to prove indefiniteness by clear and convincing evidence, Roche's motion for judgment as matter of law or a new trial must be denied.

[40] Plaintiffs seeking to invalidate a patent for indefiniteness face a difficult burden. Not only must they prove their claims by clear and convincing evidence, the degree of definiteness required for a given claim varies depending upon the state of the art. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,* 491 F.3d 1342, 1373 (Fed.Cir.2007). The Federal Circuit has recognized that "in fields of new and evolving knowledge, that the claims can be

no more precise than the knowledge in the field permits." *Id.* Simply put, where knowledge is still evolving, a patentee will be held to a lower standard. "[I]f the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, ... [the] claim [is] sufficiently clear to avoid invalidity on indefiniteness grounds." *Exxon Research & Eng'g Co. v. United States,* 265 F.3d 1371, 1375 (Fed.Cir.2001). As will be discussed below, credible expert testimony in this case suggests that the term "human erythropoietin" was as exacting as could have been expected given the state of scientific knowledge at the time.

Amgen presented sufficient evidence from which the jury could have concluded "a skilled artisan could [have] discern[ed] the boundaries of the claim based on the claim language [and] the specification ... as well as her knowledge of the relevant art area." *Halliburton Energy Servs. v. M–I LLC,* 514 F.3d 1244, 1249–50 (Fed. Cir.2008). Amgen presented the testimony of Dr. Lodish who, in addition to being a well-qualified expert, was a person skilled in the art during the relevant time period. Dr. Lodish testified:

> ['Human erythropoietin]' quite certainly is definite. One of skill in the art reading the patent would understand very clearly what human EPO is and what is within the fence of the patent defining human EPO and what would be out.... It was as precise as the subject matter allows.

Trial Tr. at 2324.

Dr. Lodish explained, "human erythropoietin" is "described in many places" in the patent. *Id.* at 2306. For example, "Figure 6 ... describes the deduced amino acid sequence of human erythropoietin; and importantly, Example 10 in the patent describes how using this EPO DNA, introducing it into mammalian cells ... will ... release into their growth medium human EPO." *Id.* at 2306.

According to Dr. Lodish, Example 10 of the specification "inherently demonstrates 165 amino acid EPO." *Id.* at 2314. Example 10 provides instructions for making EPO. "In other words, if a person skilled in the art followed Example 10, they would be in possession of a 165 amino acid human EPO." *Id.* Qualified scientists of the time would know the product was EPO because "[t]he human EPO produced in Example 10 of Dr. Lin's patents has the 1 to 165 amino acid [sequence] recited in Figure 6." *Id.* at 2313.

Using Figure 6 as a demonstrative, Dr. Lodish showed the jury how a skilled worker in 1984 would have understood that portion of the specification to describe human EPO. It is important to note, however, that Dr. Lodish did not explain "human erythropoietin" by reference to a particular number of amino acids:

> Figure 6 describes first of all the DNA sequence of the human EPO gene. And that is this series of A's, G's, and C's just running from left to right in rows. And one skilled in the art at the time, and Dr. Lin did, could deduce from this DNA sequence, the sequence of the EPO protein. And what is indicated above certain of these three base units, these are the triplets or, as it were, codons. Here is a GCC that specifies the first amino acid alanine.
>
> * * *
>
> And then above it in the three letter code, ALA stands for alanine. And the plus 1 above the alanine specifies that it's the first amino acid in this ultimately 166 protein....
>
> And just reading along you can see the sequence, the deduced amino acid sequence from the DNA and the correct

> deduced amino acid sequence of the EPO polypeptide.
>
> * * *
>
> Again, you can see [now referring to Figure 6E] we're talking at the end or the carboxyl-terminus of the EPO protein. Again, the DNA sequence that specifies other amino acids, and it ends in this AGA, which specifies the arginine at 166, which is the one that may or may not be cleaved off when the protein is made.

Id. at 2319–20.

Roche rests its argument on the testimony of its expert, Dr. Flavell, who opined that "[t]he patent specification contemplates dozens of 'polypeptides of the invention' that fall within the scope of 'human erythropoietin,' including mutants, analogs and allelic variants." Def.'s Post Tr. Br. at 68. Thus, Roche contends that, faced with a panoply of possible polypeptides, one skilled in the art would not be able to discern the meets and bounds of "human erythropoietin." *Id.*

Roche is mistaken. As Amgen correctly observes, "none of these polypeptides [to which Dr. Flavell refers] on their face fall within the scope of the claim term 'human erythropoietin.'" Pl.'s Post Tr. Opp. Br. [Doc. 1649] at 127. That the specification may refer to other amino acid sequences is irrelevant. *See* 35 U.S.C. § 112, ¶ 2 ("The specification shall conclude with one or more claims that particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.").

Although Roche's argument seems to be premised on the notion that the Court is required to accept the opinion of its experts and disregard Amgen's testimony, the present procedural posture requires the opposite. *See* Fed.R.Civ.P. 50(a)(1) (stating that the Court may not disturb the jury's verdict unless "a reasonable jury would not have a legally sufficient evidentiary basis to find for the [Amgen]"); *see also Comark Comm., Inc. v. Harris Corp.*, 156 F.3d 1182, 1190 (Fed.Cir.1998) (observing that "it is not the function of the courts to reweigh the evidence presented to the jury."). That Dr. Flavell may have offered a contrary opinion is of little moment because the jury could—and apparently did—believe Dr. Lodish. Thus, Dr. Flavell's disputed testimony does not provide the Court with the authority to set aside the jury's verdict.

a. The fact that Example 10 does not specify that human EPO could consist of 1 to 165 or 1 to 166 amino acids does not render "human erythropoietin" indefinite

In addition to Dr. Flavell's opinion, Roche emphasizes that "the only information available as of November 1984 was that human EPO had 166 amino acids." Def.'s Post Tr. Br. at 68. Thus, according to Roche, the patent does not put those skilled in the art on notice that human EPO could be either be a sequence of 1 to 165 or 1 to 166, "but not sequences of 164 or 167 amino acids." *Id.*

To begin, Roche's focus on the number of amino acids is misplaced. The Court's construction of the term "human erythropoietin" does not require an amino sequence of a precise length. *See Amgen Markman*, 494 F.Supp.2d at 64 (construing "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"). Instead, the Court has held that EPO is best understood by reference to the order in which the particular amino acids are linked. It is perfectly consistent with the claim that Example 10 could produce a protein of either 165 or 166 amino acids. So long as one skilled in the art in 1984 could identify

that protein as human EPO, the term is sufficiently definite.

In explaining how one skilled in the art would have understood "human erythropoietin," Dr. Lodish testified that it was best understood by reference to the sequence of amino acids—the "series of A's, G's, ... and C's just running from left to right in rows." Trial Tr. at 2319. As he explained, whether the EPO amino acid sequence has 165 or 166 amino acids depends on the cell in which it is produced. *See id.* at 2315. Although all mammalian cells produce 166 EPO, "[s]ome cells ... have an enzyme, that is, a kind of machine that cuts off that last amino acid, discards it. So what remains is the first 165...." *Id.* at 2315.

Roche does not dispute that EPO is either 165 or 166 amino acids in length. Nor did it present any evidence that any person skilled in the art now or then actually thought that EPO consisted of 164 or 167 amino acids. Nor does it argue that a person skilled in the art following the instructions in Example 10 would produce anything other than human EPO. At bottom, however, the procedural posture dictates that the Court may only consider whether Amgen presented sufficient evidence to support the jury's conclusion. Dr. Lodish's testimony provides just that.

C. Infringement

[41, 42] In order to prove infringement, a plaintiff must demonstrate that an accused device embodies all limitations of the claim either literally or by the doctrine of equivalents. *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1379 (Fed.Cir.2008). Where, as in this case, a product embodies all limitations, merely adding elements to an otherwise infringing device will not enable the infringer to escape liability. *See A.B. Dick Co. v. Burroughs Corp.*, 713 F.2d 700, 703 (Fed.Cir.1983).

1. The Court's grant of summary judgment of infringement as to claim 1 of the '422 patent was proper because MIRCERA contains EPO

[43] At every stage of the litigation, and now in its post-trial motions, Roche's core theory for evading infringement has been that MIRCERA does not contain EPO because CERA, the active ingredient in MIRCERA, is a solitary and stable molecule with distinct chemical properties. CERA is formed through pegylation, a chemical reaction where methyoxy-polyethylene glycol ("PEG") is connected via a single bond to epoetin beta. *See* Trial Ex. 53, Roche BLA at 00004027. Epoetin beta is made from "EPO-producing [CHO] cells (DN2–3∝3 cells) [that] contain an exogenous DNA sequence encoding the mature erythropoietin amino acid sequence of Figure 6 of Lin's patents spanning from positions +1 through +166." Pl.'s Mem. Supp. Summ. J. Infringe, of '422 Claim 1, '933 Claim 3, and '698 Claim 6 [Doc. No. 510] at 5 ("Pl.'s Mem. Supp. Summ. J."). It is undisputed that epoetin beta fits within the parameters of Amgen's product and process patents. *See* Trial Ex. 53, Roche BLA at 00004027. Roche emphasizes, however, that once pegylation is completed, the resulting product, CERA, does not contain EPO. Roche now seeks to overturn the Court's grant of summary judgment on claim 1 of the '422 patent, *see* Electronic Order, August 28, 2007, based on this single molecule theory.

Roche's single-molecule theory is flawed for two reasons. First, Roche's assertion that MIRCERA does not contain EPO is belied by its internal communications and representations to the FDA. Second, Amgen patented EPO by reference to the glycoprotein's amino acid sequence. Pegylation merely attaches a sugar, via a single carbon bond, to a recombinant glycopro-

tein with the patented amino acid sequence; it does not alter the patented properties of EPO.

a. Roche's internal documents and representations to the FDA confirm that "peg-EPO" contains EPO

Prior to marketing its drug and this litigation, Roche referred to the active ingredient in MIRCERA as "peg-EPO" in internal communications. *See* Trial Tr. at 2738–40. This name reflected Roche's view that not only did peg-EPO contain EPO, but also that pegylation did little if anything to alter the properties of epoetin beta. At trial, Dr. Adrienne Farid, Roche's "project manager for peg-EPO," Trial Tr. at 2738, testified to internal communications describing peg-EPO as "comprised of human erythropoietin which is mono-pegylated," *id.* at 2740. According to a 1999 memo entitled "Description of peg-EPO," Trial Ex. 61, "[b]oth EPO and peg-EPO have identical amino acid sequence and composition." Trial Tr. at 2741. "The only difference in the composition of native and modified proteins is due to the formation of an amide bond between the amino group of EPO and the peg molecule at the point of attachment." *Id.* at 2742. Roche's analysis indicated that pegylation did not affect epoetin beta's amino acid sequence, glycosylation, or carbohydrate structure. *Id.* at 2743.

Roche's internal communications were consistent with its representations to the FDA. In its BLA, which the FDA requires for human testing, Trial Tr. at 2611, Roche emphasized that pegylation did not alter epoetin beta. Roche stated that "[b]oth EPO starting material[, epoetin beta,] and RO0503821[, CERA,] have the identical amino acid sequence and composition of the carbohydrate moiety." *See* Trial Ex. 53, BLA at 00004027.

In short, Roche's internal communications as well as its representations to the FDA are in tension with Roche's assertions that CERA does not contain EPO.

b. Amgen patented recombinant EPO by reference to its amino acid sequence, and pegylation does not alter that sequence

At claim construction, both parties agreed that claim 1's "human erythropoietin" limitation described a particular amino acid sequence that mirrored the amino acid sequence of EPO found in human urine. *See Amgen Markman*, 494 F.Supp.2d at 63. Thus, the Court construed the limitation as follows: "Human erythropoietin: A protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine." *Id.* at 64.

In an effort to avoid summary judgment, Roche pointed to structural differences between EPO and peg-EPO. Roche's argument, for example, that "the Lin specification does not disclose the substitution of hydrogen from human EPO's lysine residues or N-terminal residues" is irrelevant to infringement because the substitution does not affect the amino acid sequence. Def.'s Mem. Opp. Summ. J. Infringe of '422 Claim 1, '933 Claim 3, and '698 Claim 6 [Doc. No. 588] at 4–6. Tellingly, Roche sought to include structural limitations in claim 1 at the claim construction. The Court rejected Roche's request because

> [t]he specification does not define "erythropoietin" by reference to the presence or absence of any attached molecules, such as the carbohydrate that can be attached to EPO proteins for glycosylated EPO. In fact, the specification expressly contemplates that additional molecules *may* be attached to "human erythropoietin." By implication, therefore, those additional molecules are not part of the amino acid structure that comprises the claimed product.

Amgen Markman, 494 F.Supp.2d at 63 (internal citation omitted).

Thus, "[t]he patent itself is silent as to ... any structural characteristic beyond the required amino acid sequence." *Id.* The Court's claim construction makes clear that the focus of this claim element is the amino acid sequence. Roche could not avoid summary judgment because it could not produce evidence from which a reasonable jury could conclude that pegylation altered EPO's amino acid sequence.

Roche asks the Court to enter a judgment in its favor on the basis of its theory that once pegylation has occurred, the process cannot be reversed and the product is a stable, single molecule. Roche's assertion is contested by Amgen expert Dr. Les Benet, who testified that PEG and EPO separate in the body after administration. Trial Tr. at 2610. But even presuming that Roche's assertion about reversibility is correct as a matter of fact, the permanency of the bond does not save Roche.

[44] "It is fundamental that one cannot avoid infringement merely by adding elements if each element recited in the claims is found in the accused device." *A.B. Dick*, 713 F.2d at 703. As the Federal Circuit reasoned by analogy in *A.B. Dick*, an infringer could not avoid liability by incorporating a patented pencil into a complex machine. *See id.* More to the point, just because the pencil cannot be removed from the complex machine, it does not follow that the manufacturer has circumvented infringement. *See id.* Regardless of whether the effects of pegylation can be reversed, Roche is infringing because epoetin beta retains its distinct amino acid sequence through pegylation.

Roche's attempts to distinguish *A.B. Dick* remain as unpersuasive as they were at the time the Court granted summary judgment. In an effort to convince the Court that *A.B. Dick* is not applicable, Roche relied on *Eli Lilly and Co. v. American Cyanamid Co.*, 82 F.3d 1568 (Fed. Cir.1996). In that case, Eli Lilly, the owner of patents describing the popular antibiotic Cefaclor, sought a preliminary injunction to prevent importation of an allegedly infringing drug. *Id.* at 1569–70. The district court denied the injunction based on a factual determination that Cefaclor and the allegedly infringing product "differ significantly in their structure and properties, including their biological activity." *Id.* at 1571. In upholding the district court's decision, the Federal Circuit wrestled with the meaning of "material change" in the context of the Process Patent Amendments Act of 1988. *See id.* at 1571–78. Although it concluded that the district court did not err in holding that Eli Lilly was unlikely to succeed on its infringement claim, its investigation into the meaning of "material change" was inconclusive. *Id.* at 1578.

It is difficult to conceive how *Eli Lilly* could be read to stand for any legal proposition that conflicts with *A.B. Dick*. *A.B. Dick* merely states that the addition of elements will not preclude a finding of infringement so long as all of the elements of the underlying claim are met. *See A.B. Dick*, 713 F.2d at 703. Furthermore, in this case, the Court does not confront the fundamental question addressed—and ultimately left unanswered—in *Eli Lilly*, which is the meaning of "material change." The *Eli Lilly* decision turned on the district court's conclusion that the accused product did not infringe. Here, the facts cut against Roche. To the extent that *Eli Lilly* is applicable here, it merely highlights the principle that questions of infringement raise issues of fact appropriately decided on a case-by-case basis. The Court does not doubt that the substitution of one chemical group for another within a drug, whether in *Eli Lilly* or any hypothetical drug patent case, could provide a basis for a finding of non-infringement.

But that is not the case here. In this case, the addition of PEG to EPO replaces a single hydrogen atom with a single carbon atom. Because the amino acid sequence remains unaltered, this displacement does not enable Roche to avoid infringement.

In short, Roche's argument that CERA constitutes a single molecule that cannot be broken down into smaller parts is untenable because, it is contrary to its own admissions, good science, and common sense. A molecule is merely a group of atoms joined together by covalent bonds, such that the group of atoms is stable and retains a neutral electrical charge. ALBERTS, *supra*, at G:9, G:23. Peg–EPO is a glycosylated protein because the pegylation process adds a sugar to a protein molecule. *See id.* at G:16. The glycosylation process does not alter EPO's patented primary structure, its amino acid sequence. The active ingredient in CERA, EPO, is an expression of the same amino acid sequence taught in Amgen's patents. Therefore, the summary judgment of infringement was proper.

2. The Court's conclusion that "purified from mammalian cells grown in culture" limits claim 1 of the '422 patent does not affect the Court's grant of summary judgment with respect to infringement

Per the preceding discussion, the Court has concluded that "purified from mammalian cells grown in culture" limits claim 1 of the '422 patent. Roche argues that if this is so, then Amgen could not, as matter of law, demonstrate Roche met this limitation for the purposes of literal infringement. Roche argued summary judgment was inappropriate because "CERA is a chemically synthesized product" that cannot be made from mammalian cells. Def.'s Mem. Opp. Summ. J. at 9. This is undoubtedly true because CERA is generated through pegylation. The problem is that Roche relies on the theory that CERA is a single molecule that does not contain EPO. The single-molecule theory reflects Roche's flawed but unwavering belief that it is entitled to judgment as matter of law if it can characterize CERA as a molecule. The theory has no sound basis in law or science, and this Court and the jury have rejected it time and again. As discussed above, EPO is the main ingredient for CERA. Roche did not—and could not—deny that epoetin beta was "made from mammalian cells grown in culture." Therefore, summary judgment was appropriate.

[45] Nevertheless, Roche maintains that "if the source limitation imparts some unique structure, then Amgen had to prove that unique structure existed in MIRCERA." Post Trial Hr'g Tr. [Doc. 1676] at 31. There is no doubt that an infringement plaintiff must prove all elements, including source and process limitations. *See BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed.Cir.2007). But it is quite a different proposition to require patentees to prove not only that the limitation is met, but also that the inclusion of the limitation results in the same expression as the preferred embodiment. Roche has failed to offer any legal support for its contention that Amgen was required to do so in this case.

It is true that certain structural distinctions between recombinant EPO and urinary EPO are attributable to the source. But the structural differences are merely evidence that the source limits the claim; they are not themselves limitations. Once the Court has concluded that the source limits the claim, there is no reason why such a limitation ought not be treated like other limitations. As stated above, epoetin beta satisfied the limitation. Therefore, the Court's grant of summary judgment was appropriate.

3. The Court's grant of summary judgment in favor of Amgen on claim 1 of the '422 patent will stand notwithstanding the jury's verdict regarding claim 12 of the '933 patent

The jury found all of the claims of the patents in suit literally infringed with the exception of claim 12 of the '933 patent, which it found infringed by the doctrine of equivalents. Following the trial, on October 30, 2007, the Court granted Roche's motion for judgment notwithstanding the verdict with respect to this claim because, at trial, Amgen failed to "identify claim by claim the equivalent means-way-result." Scheduling Conference Tr. [Doc. 1736] at 4. Roche alleges that the jury's verdict of infringement by the doctrine of equivalents requires the Court to reverse its grant of summary judgment in favor Amgen on literal infringement of claim 1 of the '422 patent. Assuming *arguendo* that there are theoretical inconsistencies between the court's pre-trial ruling and the jury verdict, there is simply no requirement that this Court reverse its summary judgment determination because Roche's claim that MIRCERA does not contain EPO has no sound basis in the record.

Again, claim 1 of the '422 patent teaches:

> 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.* 36–40.

Claim 12 of the '933 patent describes:

> 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. 39 *l.* 10–col. 40 *l.* 2.

Roche maintains that "for the jury verdict to be internally consistent one must conclude that the jury found that MIRCERA does not have 'an effective amount ... effective for erythropoietin therapy' of the glycoprotein product according to claim 7, and/or that MIRCERA is not 'a pharmaceutical composition comprising ... a pharmaceutically acceptable diluent, adjuvant or carrier.' " Def.'s Post Tr. Br. at 144 (emphasis omitted). Since the Court construed the terms the same way for each patent, Roche contends that the failure to find literal infringement of claim 12 of the '933 patent is inconsistent with the Court's grant of summary judgment in favor of Amgen with regard to infringement of claim 1 of the '422 patent. *Id.* The remedy Roche proposes is that the Court reverse its summary judgment ruling and grant summary judgment for Roche. *Id.* at 145.

[46] Roche's argument rests on a faulty legal premise. The mere fact that a jury verdict could, in theory, appear to be inconsistent with a grant of summary judgment does not require a court to reconsider its pretrial ruling because the determinations are made on different records at different stages of the litigation and according to different legal standards.

The sole case Roche cites in support of its position, *Therma–Tru Corp. v. Peachtree Doors Inc.*, 44 F.3d 988 (Fed.Cir. 1995), is inapplicable. In *Therma–Tru*, the Federal Circuit reversed a district court's post-trial factual finding because it was contrary to facts found by the jury. *Id.* at 994, 996. Although the district court was empowered to make certain findings under its equitable authority, the Federal Circuit reasoned that the district court's findings in *Therma–Tru* deprived the

plaintiff of its right to trial by jury under *Beacon Theatres, Inc. v. Westover,* 359 U.S. 500, 510–11, 79 S.Ct. 948, 3 L.Ed.2d 988 (1959). *See Therma–Tru,* 44 F.3d at 994–95. *Beacon Theatres* explains that "when equitable claims are joined with legal claims and have factual questions in common, the judge's determination of the equitable claims can not deprive the litigants of their right to a jury trial on factual questions." *Therma–Tru,* 44 F.3d at 994–95 (citing *Beacon Theatres,* 359 U.S. at 510–11, 79 S.Ct. 948). Thus, "[w]hen a party has a right to a jury trial on an issue involved in a legal claim, the judge is ... bound by the jury's determination of that issue as it affects his disposition of an accompanying equitable claim." *Id.* at 995 (quoting *Gutzwiller v. Fenik,* 860 F.2d 1317, 1333 (6th Cir.1988))(internal quotation marks omitted).

There is a critical distinction between *Therma–Tru* and the instant case that explains why the reasoning of *Beacon Theatres* does not apply here. The judicial determination in *Therma–Tru* was factual finding that followed a trial. By contrast, the grant of partial summary judgment in this case was a ruling as matter of law made prior to trial. *See IPXL Holdings, L.L.C. v. Amazon.com, Inc.,* 430 F.3d 1377, 1380 (Fed.Cir.2005) (noting that the Federal Circuit "review[s] de novo ... whether the prevailing party is entitled to judgment as a matter of law"). While the district court in *Therma–Tru* made factual findings, "at the summary judgment stage the judge's function is not himself to weigh the evidence and determine the truth of the matter but to determine whether there is a genuine issue for trial." *Anderson v. Liberty Lobby, Inc.,* 477 U.S. 242, 249, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986). This is significant because the determinations were made on records that are different in kind. Here, the Court's grant of summary judgment was based on the undisputed record at the time the parties filed dispositive motions prior to trial, rather than based on evidence adduced at trial and also weighed by a jury. In short, the facts and constitutional concerns that compelled the Federal Circuit's decision in *Therma–Tru* are not present in this case.

More importantly, Roche fails to illuminate any ground for reversal that actually pertains to the Court's grant of summary judgment on claim 1 of the '422 patent. The Court granted summary judgment for Amgen because the Court concluded that a reasonable jury would be forced to conclude that CERA literally infringed all the limitations of the claim. At this stage, Roche has merely repeated its claims that MIRCERA does not contain EPO. This argument has been rejected because it belied by the record.

4. The jury's finding of infringement with respect to claim 3 of the '933 patent was supported by sufficient evidence and was proper as matter of law

[47] In order for the jury's verdict to stand, Amgen must have provided evidence from which a jury could have concluded that Roche's product infringed each of the limitations of claim 3 of the '933 patent. The claim teaches:

> 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.

'933 patent col. 38 *ll.* 26–31.

Roche seeks to overturn the jury's finding of infringement on the '933 patent on two grounds. Primarily, Roche asks for a new trial, contending that the jury's verdict was without support in the record.

Second, Roche claims that it is entitled to judgment as matter of law because the undisputed record reveals that pegylation displaces a hydrogen atom in epoetin beta. *See* Def.'s Post Tr. Br. at 140. Thus, Roche maintains that this minute alteration entitles it to a judgment of non-infringement. As shall be discussed below, however, the jury's verdict finds ample support in the record. Moreover, Roche's request for judgment as matter of law is premised on a misunderstanding of the law with respect to infringement. Amgen need not prove MIRCERA's EPO is identical down to the precise number of hydrogen atoms; rather, the question is whether MIRCERA's EPO deviates from claim 3 of the '933 patent. It does not.

a. The jury's finding of infringement is supported by the record

Roche argues that no reasonable jury could have concluded that MIRCERA is "a product of . . . expression in a mammalian host cell" because "CERA is a chemically synthesized compound that is created in a laboratory" with a "substantially different . . . structure and function from a product of the recited process." Def.'s Post Tr. Br. at 140 (internal quotation marks omitted). According to Roche, the undisputed evidence demonstrates that MIRCERA does not contain "the product of the expression of a DNA sequence encoding human erythropoietin" because pegylation alters the amino acid sequence. *Id.* Even if the amino acid sequence is not altered, Roche contends that the undisputed displacement of a hydrogen atom with a carbon atom results in "differences between the carbohydrates" requiring a finding of non-infringement. Def.'s Post Tr. Rep. Br. at 5–6.

Amgen offered ample evidence that pegylation did not alter the amino acid sequence of epoetin beta. Because claim 3 of the '933 patent describes a product by reference to a specific amino acid sequence, alterations that do not affect the amino acid sequence are immaterial.

I. Amgen offered evidence that pegylation did not alter epoetin beta's amino acid sequence or carbohydrate structures

For all of the reams of paper devoted to overturning the jury's verdict with respect to the '933 patent, Roche concedes that Amgen's experts provided testimony that pegylation does not change the amino acid sequence of epoetin beta. Def.'s Post. Tr. Rep. Br. at 6. This concession is consistent with the record, which reveals ample evidence from which the jury could have concluded that pegylation did not alter the amino acid sequence. For example, Dr. Lodish testified:

> Q. In your opinion, does the removal of [the hydrogen] atom change the amino acid sequence?
>
> A. No.
>
> Q. Why?
>
> A. Because it's the same amino acid before and after and, as I testified, in particular, the linkage between alanine and peg, say, at the beginning of the protein, it's the identical linkage that alanine would have to other amino acids inside the protein. And despite that linkage or not, we still call it an alanine. It's what one skilled in the art calls amino acids. It's the same amino acid. . . .

Trial Tr. at 2528–29. Dr. Torchilin opined that peg-EPO had the "identical amino acid sequence and composition of carbohydrate moiety which relates to the structure. The structure is the same." *Id.* at 2664.

Dr. Torchilin's testimony confirmed what the Court already noted about Roche's representations to the FDA:

> Q. Now, Doctor, based upon your review of [Roche's submission to the FDA], did Roche tell the FDA that the amino acid sequence of EPO was changed by the pegylation?
>
> A. Quite opposite. It exactly say that identical amino acid sequence [sic]. And by the way, this is exactly the way I see it.

Trial Tr. at 2730.

The Court concludes Amgen provided sufficient evidence from which the jury could have concluded that MIRCERA infringed claim 3 of the '933 patent because pegylation does not alter epoetin beta's amino acid sequence. Furthermore, testimony from Amgen's experts indicated that pegylation does not alter the carbohydrate structure. That Roche may have offered evidence to the contrary is beside the point. So long as there is evidence to support the jury's verdict, the Court is not free to reach a different outcome. *See Rivera Castillo,* 379 F.3d at 13.

b. Amgen need not demonstrate infringement to an unclaimed level of specificity

Roche still believes it is entitled to judgment as matter of law even if pegylation does not alter the amino acid sequence or carbohydrate moiety because Amgen cannot prove that the EPO in MIRCERA is identical to the product of the process described in claim 3 of the '933 patent. According to Roche, the fact that pegylation replaces a hydrogen atom with a carbon atom is sufficient to preclude a judgment of infringement. The legal premise of Roche's argument is that plaintiffs seeking to prove infringement of a product-by-process claim must demonstrate that the accused product is identical to the product of the patented process.

[48] Infringement liability is found where an accused device falls precisely within the scope of a claim as delineated by the limitations. *See TIP Sys., LLC,* 529 F.3d at 1379. The law does not require Amgen to prove identity to an unclaimed level of specificity. Thus, variations such as the displacement of a single hydrogen atom, which do not deviate from the scope of at least one claim limitation, are immaterial. To hold otherwise would require inventors to claim their inventions with atomic specificity and would entitle infringers to a patent merely because they were able to make the same product, sans a single atom, via the claimed process.

> Here, the Court construed claim 3 as:
>
> a glycoprotein (not occurring in nature) that is the product of the expression [11] in a mammalian host cell of a DNA sequence that does not originate in the genome of the host, and which contains the genetic instructions (or a DNA sequence) encoding human erythropoietin.

Amgen Markman, 494 F.Supp.2d at 71–72 (footnote in original).

The product of this process described above is, of course, a glycoprotein comprised of the patented sequence of 165 amino acids. The Court's construction makes clear that the patent's focus is the glycoprotein's amino acid sequence. The very reason for this claim is to describe a process for making a product with "genetic instructions." It is not concerned with the particular charge or precise number of carbohydrates, so long as the glycoprotein has a DNA sequence that is exogenous to the mammalian host cell and that "encodes human erythropoietin." It follows that modifications that do not affect the amino acid sequence do not deviate from the claim.

11. Wherein expression means that glycoprotein was produced in a cell and recovered from the cell culture.

I. The cases Roche cites are inapplicable and unpersuasive

There is no precedent requiring the Court to depart from basic patent principles in the context of product-by-process claims. Roche marshals three cases in support of its exact identity theory: *Litton Systems, Inc. v. Honeywell, Inc.,* 140 F.3d 1449 (Fed.Cir.1998), *Southwall Technologies, Inc. v. Cardinal IG. Co.,* 54 F.3d 1570 (Fed.Cir.1995), and *Johnston v. IVAC Corp.,* 885 F.2d 1574 (Fed.Cir.1989). There is simply no way to read any of these cases as departing from the general rule that otherwise immaterial distinctions will not preclude a finding of infringement in the context of a product-by-process claim.

In each case, Roche seizes on the Federal Circuit's use of the word "exactly" to describe the all-elements requirement. *See Litton,* 140 F.3d at 1454 ("Literal infringement requires that the accused device contain each limitation of the claim exactly; any deviation from the claim precludes a finding of literal infringement."); *Southwall Techs.,* 54 F.3d at 1575 ("To establish literal infringement, every limitation set forth in a claim must be found in an accused product, exactly."); *Johnston,* 885 F.2d at 1577 ("To establish infringement of a patent, every limitation set forth in a claim must be found in an accused product or process exactly or by a substantial equivalent.").

Context is everything. Here it is fatal to Roche. These statements Roche quotes are not even in reference to product-by-process claims. That the Federal Circuit has employed "exactly" on approximately three occasions in the context of a boilerplate recitation of the all-elements requirement is by no means illustrative of a transformation in patent law. The '933 patent makes no claim to a specific number of hydrogen atoms, and Amgen's experts opined that Roche's EPO did not deviate from the claim terms despite the hydrogen displacement. Thus, it is entirely plausible, as the jury found, that the EPO in MIRCERA satisfies the requirement that "every limitation set forth in a claim must be found in an accused product, exactly." *Southwall Techs.,* 54 F.3d at 1575.

Having concluded that the jury's findings will stand and that the Court will not reverse its rulings with respect to validity and infringement of claim 1 of the '422 patent, Roche's motion for judgment as matter of law [Doc. No. 1618] and its motion for a new trial [Doc. No. 1618] are DENIED.

IV. INJUNCTIVE RELIEF

[49] As the Supreme Court recently reiterated, a party seeking a permanent injunction following a judgment of infringement must demonstrate:

> (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for injury; (3) that, considering the balance of hardships between the [parties], a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction.

eBay Inc. v. MercExchange, L.L.C., 547 U.S. 388, 391, 126 S.Ct. 1837, 164 L.Ed.2d 641 (2006).

The Supreme Court's decision in *eBay,* which overturned the Federal Circuit's "general rule" that injunctions should issue when a plaintiff has won a judgment of infringement, *see id.* at 393–94, 126 S.Ct. 1837, generated a flurry of speculation about whether district courts would depart from established norms in patent cases.

In the present case, the Court thought initially that the FDA's approval of MIRCERA and the competition it would give Amgen's products indicated rather strong-

ly that the public interest would be served by allowing its introduction, upon terms, into the United States pharmaceutical market. To test this initial impression, the Court held extensive evidentiary hearings, appointed a special master and technical advisor, and carefully weighed the public interest.[12] In fact, the Court's initial impression does not withstand a reflective and detailed analysis.

While *eBay* has allowed courts to decline requests for injunctive relief where the plaintiff is a "patent troll," *eBay* has changed little where a prevailing plaintiff seeks an injunction to keep an infringing competitor out of the market. This case is no exception to that trend. As shall be outlined below, the first three *eBay* factors strongly favor a permanent injunction because Roche's entry into the ESA market would cause immense, immeasurable, irreparable harm, with the balance of the hardships falling on Amgen. In addition, the public interest would not be disserved by an injunction because there is no solid evidence that patients or the public coffers will suffer significant harm if the status quo is maintained. In this case, the public's interest in a robust patent system that maintains incentives for pharmaceutical innovation outweighs the highly speculative, de minimis benefits that might occur as the result of a denial of an injunction.

A. *eBAY* HAS CHANGED LITTLE WHERE FAILURE TO GRANT INJUNCTIVE RELIEF WOULD PERMIT A COMPETITOR TO ENTER THE MARKET

[50] In *eBay,* a jury concluded that eBay, a popular on-line auction site, infringed MercExchange's "business method patent for an electronic market designed to facilitate the sale of goods between private individuals by establishing a central authority to promote trust among participants." 547 U.S. at 390–91, 126 S.Ct. 1837. MercExchange was a company that those familiar with the industry would characterize as a "patent troll." Patent trolls are "nonpracticing entities" who "do not manufacture products, but instead hold ... patents, which they license and enforce against alleged infringers." *Taurus IP v. DaimlerChrysler Corp.,* 519 F.Supp.2d 905, 911 (W.D.Wis.2007). The district court refused the request for an injunction, reasoning that the " 'plaintiff's willingness to license its patents' and 'its lack of commercial activity in practicing the patents' would be sufficient to establish that the patent holder would not suffer irreparable harm if an injunction did not issue.' " *eBay,* 547 U.S. at 393, 126 S.Ct. 1837 (quoting *MercExchange L.L.C. v. eBay, Inc.,* 275 F.Supp.2d. 695, 712 (E.D.Va.2003)). The Federal Circuit reversed, "articulat[ing] a 'general rule,' unique to patent disputes, 'that a permanent injunction will issue once infringement and validity have been adjudged.' " *Id.* at 393–94, 126 S.Ct. 1837 (quoting *MercExchange L.L.C., v. eBay, Inc.,* 401 F.3d 1323, 1338 (Fed.Cir.2005)).

The Supreme Court vacated on the ground that "neither court below correctly applied the traditional four-factor framework that governs the award of injunctive relief." *Id.* at 394, 126 S.Ct. 1837. The Court reiterated that plaintiffs seeking an injunction must satisfy the four-factor in-

12. The Court is not, of course, the only district court to explore the parameters of *eBay*. *See* Lynne Marek, *Juries may take up future damages in patent cases,* NAT'L LAW J. (Aug. 4, 2008) at 7. In fact, Judge Ron Clark of the U.S. District Court for the Eastern District of Texas has entered an order requiring the parties to prepare for jury trial upon the issue of a future royalty since "under some circumstances, the court may award an ongoing royalty for patent infringement in lieu of injunctive relief." *Id.* This technique is not only efficient, it recognizes the vital role of the jury as fact finding partner. *See United States v. Luisi,* 568 F.Supp.2d 106, 2008 WL 2854498, *4–*12 (D.Mass. July 25, 2008).

quiry. *Id.* at 391, 126 S.Ct. 1837. Categorical rules, the Court reasoned, contravened the Patent Act's remedial provision, which "expressly provides that injunctions 'may' issue 'in accordance with the principles of equity.' " *Id.* at 392, 126 S.Ct. 1837 (quoting 35 U.S.C. § 283).

The Supreme Court does not appear to have intended *eBay* to be pathbreaking precedent. The bare-bones majority opinion did little more than remind courts that they must exercise discretion in accordance with the framework Congress approved. *See id.* at 394, 126 S.Ct. 1837. The Court did not even take a "position on whether permanent injunctive relief should or should not issue in [that] particular case." *Id.* The two concurrences emphasized the importance of looking to historical practice when imposing injunctive relief. Chief Justice Roberts, joined by Justices Scalia and Ginsburg, emphasized that the majority opinion "rightly rest[ed] on the proposition that 'a major departure from the long tradition of equity practice should not be lightly implied.' " *Id.* at 395, 126 S.Ct. 1837 (Roberts, C.J., concurring). The Chief Justice explained:

> From at least the early 19th century, courts have granted injunctive relief upon a finding of infringement in the vast majority of patent cases. This "long tradition of equity practice" is not surprising, given the difficulty of protecting a right to *exclude* through monetary remedies that allow an infringer to *use* an invention against the patentee's wishes—a difficulty that often implicates the first two factors of the traditional four-factor test.

Id.

Joined by Justices Stevens, Souter, and Breyer, Justice Kennedy agreed with the Court and the Chief Justice that "historical practice ... is most helpful and instructive when the circumstances of a case bear substantial parallels to litigation the courts have confronted before." *Id.* at 396, 126 S.Ct. 1837 (Kennedy, J., concurring). He suggested, however, that district courts "should bear in mind that in many instances the nature of the patent being enforced and the economic function of the patent holder present considerations quite unlike earlier cases." *Id.* He warned that "[a]n industry has developed in which firms use patents not as a basis for producing and selling goods but, instead, primarily for obtaining licensing fees. For these firms, an injunction ... can be employed as a bargaining tool to charge exorbitant fees to companies that seek to buy licenses to practice the patent." *Id.* at 396, 126 S.Ct. 1837 (internal citation omitted).

History, Justice Kennedy indicated, was not on the side of patent trolls like MercExchange. "[I]njunctive relief may have different consequences for the burgeoning number of patents over business methods, which were not of much economic and legal significance in earlier times. The potential vagueness and suspect validity of some of these patents may affect the calculus under the four-factor test." *Id.* at 397, 126 S.Ct. 1837. He concluded that "equitable discretion over injunctions, granted by the Patent Act, is well suited to allow courts to" take account of such circumstances before issuing an injunction. *Id.*

The Supreme Court's narrow decision and emphasis on history appear to have had their intended effect. Where failure to grant an injunction would allow a competitor to enter the market, district courts have continued to issue injunctions. A recent study reveals that since *eBay,* "with two exceptions, permanent injunctions issued in all twenty-six cases where courts found direct competition between a plaintiff and the infringer." Douglas Ellis et al., *The Economic Implications (and Uncertainties) of Obtaining Permanent Injunctive Relief after eBay v. MercExchange,* 17 FED. CIR. B.J. 437, 442–43

(2008). The two exceptions proved the rule. In "*Innogenetics, N.V. v. Abbott Laboratories,* [512 F.3d 1363 (Fed.Cir. 2008)], the Federal Circuit reversed the district court's grant of a permanent injunction because the damages awarded at trial presumably contemplated a hypothetical license for the life of the patent-at-issue (not just for pre-trial infringement)." *Id.* at 443. In "*Praxair, Inc. v. ATMI, Inc.,* [479 F.Supp.2d 440 (D.Del.2007)] the district court ... did not issue a permanent injunction because the plaintiff did not provide sufficient evidence of lost sales, lost profits, and/or lost market share." *Id.*

B. The first three *eBay* Factors Strongly Favor Permanent Injunctive Relief for Amgen

[51] It is easy to understand why courts have continued to issue injunctions where the infringer will become a direct competitor. Here, were the Court were to deny Amgen's request for a permanent injunction, Roche would enter the ESA market as Amgen's competitor. The vast majority of Roche sales would be to the exclusion of Amgen sales, resulting in lost profits, market share, and good will. Amgen's economic expert, Professor B. Douglas Bernheim, testified that:

> through market share erosion, Amgen would lose considerable revenues. I think that there's a tremendous amount of uncertainty as to exactly what the market share penetration would be, how much revenue ... Amgen would therefore lose. But despite the uncertainty about the specific magnitude, I think that we can be quite confident from the record that the losses would be extremely large.

Remedy Trial Tr. vol. 1 at 103.

Moreover, Roche's entry into the market, despite a judgment of infringement, could encourage other would-be infringers to attempt to gain access, resulting in significant litigation expenses and uncertainty about the value of Amgen's patents. Simply put, the value of the patents at issue, which are admittedly "the foundation of Amgen's business," *see* Pl.'s Mem. Supp. Perm. Inj. [Doc. 1578] at 12, would be greatly diminished. Amgen's stock price would fall along with its ability to attract investment for research and development. In addition, producing and marketing MIRCERA would enable Roche to develop infrastructure that would make Roche a viable competitor not only in the ESA market, but also in markets for future drugs.

In view of these potentially immense and unquantifiable harms, the Court concludes that failure to enter a permanent injunction would result in irreparable harm for which monetary damages are inadequate. Furthermore, because Amgen's patents are valid, enforceable, and infringed, and in light of the potential harms described above, there can be little doubt that the balance of hardships favors Amgen. Thus, the first three *eBay* factors strongly favor an injunction. The Court now turns to the fourth and final *eBay* factor, the public interest.

C. The public interest would not be disserved by a permanent injunction

[52] Entering the remedy phase, the Court identified two aspects of the public interest that might be affected by a decision to keep MIRCERA off the market. Primarily, the Court wanted to be sure that Amgen adequately satisfied the current demand for ESAs. Were it the case that MIRCERA could aid a number of patients not presently served by EPOGEN or Aranesp, then injunctive relief denying them access to the life-altering effects of recombinant EPO would disserve the public interest. Second, it seemed that Amgen's virtual monopoly on the ESA market might be unduly burdensome on Medicare

and the public coffers, and Roche's entry might mitigate the deleterious consequences. Of course, the public derives significant benefits from the innovation generated by the economic incentives in our patent system. Because the first three factors strongly favored an injunction and in light of the public interest in a robust patent system, the Court recognized that the evidence of harm to patients and Medicare would need to be fairly compelling. After a four-day hearing on injunctive relief, the Court was satisfied that the public interest would not be disserved by maintaining the status quo in the ESA market.

Below, the Court will balance three factors: patient health, Medicare savings, and the public's interest in a robust patent system. First, although an additional choice would undoubtedly benefit patients and doctors, it is not clear that MIRCERA offers an advantage so appreciable that it would justify abrogation of Amgen's monopoly privilege. Any conclusions regarding a potential savings to Medicare are too speculative to justify the denial of a permanent injunction. In fact, the warped economic incentives created by Medicare reimbursement and speculation about changes in regulation mean that MIRCERA's presence on the market might actually result in more expensive drugs for consumers. Finally, any marginal health or economic benefits would be outweighed by the potential harm to the incentives for innovation underlying the patent system. In short, the Court cannot conclude that granting a permanent injunction disserves the public interest.

1. Although doctors and patients would probably benefit from additional choice, it is not clear that MIRCERA offers significant clinical advantages over Aranesp

As outlined in the background section, MIRCERA received FDA approval to provide correction of anemia with once-every-two-week dosing and to maintain stable hemoglobin letters with once monthly or once-every-two-week dosing in all CKD patients. Roche's and Amgen's experts debated the effectiveness of MIRCERA when given monthly. In the opinion of Roche's expert, Dr. Steven Fishbane, the data from clinical trials establish non-inferiority of MIRCERA in efficacy when compared to the currently available ESAs, as well as that MIRCERA has a comparable safety profile to the currently available ESAs. Fishbane Expert Rep. ¶¶ 58, 74. In addition to concluding that Roche's studies establish non-inferiority of MIRCERA as compared to currently available ESAs, Dr. Fishbane concluded that "MIRCERA's ability to maintain a safe and stable hemoglobin level over time is not clinically inferior to the hemoglobin stability achieved with presently available ESAs, such as EPOGEN and ARANESP." *Id.* ¶ 75 (using plus/minus 1g/dL criterion).

Amgen's expert John Lubina disputed Fishbane's conclusions regarding hemoglobin stability of MIRCERA and claimed that plots of weekly mean hemoglobin reveal increased hemoglobin variability associated with MIRCERA treatment, particularly during the titration phase of the Phase III trials. Lubina Expert Rep. ¶¶ 87, 93. Moreover, patients treated with peg-EPO (MIRCERA) statistically have a significantly greater likelihood of premature withdrawals from treatment relative to patients treated with reference drugs. *Id.* ¶¶ 91, 100.

The half-life of a medicine is a measure of the amount of time a therapy is available to be used by the body. Dr. Fishbane claims that, for intravenous administration, the half-life of MIRCERA (134 hours) is significantly longer than that for Aranesp (25.3 hours) or EPOGEN (6.8 hours); with

subcutaneous administration, the half-lives are estimated at 139, 48.4, and 19.4 hours for MIRCERA, Aranesp, and EPOGEN, respectively. Unlike Aranesp and EPOGEN, whose half-lives when administered intravenously are considerably shorter than when administered subcutaneously, MIRCERA's half-life is essentially unaffected by route of administration. Fishbane Expert Rep. ¶¶ 30, 130, 132.

While the longer half-life of MIRCERA underlies its FDA approval for once-monthly dosing for CKD maintenance patients, the Roche and Amgen experts differed in how they interpreted and evaluated the less frequent dosing requirement for MIRCERA. According to Amgen's expert Dr. Glenn Chertow, because ESRD patients already typically receive hemodialysis at a dialysis center three times weekly via arteriovenous fistula or graft (native and artificial connections between arteries and veins) or large intravenous catheter, and because these blood lines can also be used efficiently to administer epoetin alfa (EPOGEN) simultaneously three times weekly, there is little benefit to the patient or provider to switching to the less frequent dosing associated with use of MIRCERA. Chertow Expert Rep. ¶¶ 25–26; *see also* Remedy Trial Tr. vol. 2 [Doc. 1738] at 310–11. Moreover, the more frequent administration may in fact be preferable as it can facilitate more rapid and precise titration, which may be particularly important for ESRD patients having comorbidities. Chertow Expert Rep. ¶ 32; *see also id.* ¶¶ 25–26. On the other hand, more frequent dosing involves more time spent ordering, preparing, administering, and recording ESA treatments and thereby creates greater opportunities for making dosing or medication errors. Fishbane Expert Rep. ¶¶ 140, 143, 156. In addition, the less frequent dosing of MIRCERA relative to EPOGEN and Aranesp for patients on dialysis frees up time for dialysis center staff, particularly nurses. Fishbane Expert Rep. ¶ 141; Remedy Trial Tr. vol. 3 [Doc. 1739] at 532; Remedy Trial Tr. vol. 4 [Doc. 1740] at 641–42.

For ESRD patients not going to dialysis centers three times weekly for hemodialysis treatment but instead receiving home dialysis or peritoneal dialysis, any benefits from more intense monitoring associated with thrice-weekly dialysis center visits are not available. Instead, for these patients, there may well be a convenience benefit to less frequent dosing with subcutaneously administered MIRCERA, particularly for those for whom travel times or mobility is an issue. Fishbane Expert Rep. ¶ 138. Similarly, for CKD anemia patients not on dialysis, the less frequent once-every-two-weeks or once-monthly dosing with MIRCERA-as opposed to thrice-weekly dosing with Procrit or once weekly dosing with Aranesp-is likely to provide benefits in the form of increased convenience and less travel time. *See id.* ¶ 153; Remedy Trial Tr. vol. 4 at 616–18. Moreover, for patients receiving an ESA via the subcutaneous route of administration, the less frequent administration with MIRCERA implies less patient discomfort from the fewer number of injections. Fishbane Expert Rep. ¶¶ 139, 150; Remedy Trial Tr. vol. 4 at 656–58. In sum, while for many ESRD patients receiving thrice-weekly dialysis the potential convenience of less frequent dosing on MIRCERA may not be important, for their providers and nurses it would reduce administration efforts and perhaps medication errors. For CKD patients, however, particularly for those patients whose time value and traveling expenses are large, the availability of a more convenient, less frequent dosing regimen could constitute a substantial improvement in quality of life and perhaps even an improved treatment adherence and health outcome.

Other benefits of permitting MIRCERA to enter the market would be expanding the armamentarium with which doctors treat CKD patients with anemia, some of whom exhibit poorly understood idiosyncratic responses, and reducing the vulnerability to manufacturing problems that exists by virtue of the fact that Amgen is the sole manufacturer of all ESAs marketed in the United States: EPOGEN, Procrit, and Aranesp. Fishbane Expert Rep. ¶¶ 164–166; Remedy Trial Tr. vol. 4 at 622–23; *see also* Fishbane Supp. Expert Rep. ¶ 51. As to the first issue, Dr. Rebecca Schmidt testified that it is a common albeit poorly understood phenomenon that some patients respond better with one seemingly similar medication than another. Remedy Trial Tr. at 622–23. While it is impossible to predict with any confidence just how large the overall clinical benefits from entry by MIRCERA into the United States market would be, it is possible they could be considerable.

In contrast, Amgen's expert, Dr. Glenn Chertow argued that:

> The medical need in the case of anemia is to prevent transfusion and to restore the hemoglobin concentration to a level sufficient to maintain adequate energy, strength, and to prevent symptoms such as breathlessness and conditions such as heart failure. And those needs are adequately met by existing ESAs or erythropoiesis stimulating agents.

Remedy Trial Tr. vol. 3 at 421–22. More generally, Dr. Chertow concluded that "Roche's clinical studies, as set forth in its regulatory filings, fail to demonstrate that its peg-EPO product satisfies any unmet medical need in the treatment of anemia associated with chronic kidney disease." Chertow Expert Rep. ¶ 21. In terms of dosing frequency, Chertow notes that although off-label and not approved by the FDA, the established ESAs on the U.S. market are already "clinically used at longer dosing intervals than the intervals that are FDA approved in the labels." Remedy Trial Tr. vol. 3 at 424–26.

Regarding hemoglobin variability, Dr. Chertow testified that "the individuals who were treated with peg-EPO relative to those treated with epoetin alfa and dareopoetin, established ESAs, were, for instance, threefold more likely to experience a hemoglobin excursion above 14 grams per deciliter ... which as I noted earlier are associated with adverse clinical events." Remedy Trial Tr. vol. 3 at 451.[13] Moreover, during the titration phase of the Phase III studies there was a statistically significant greater mortality rate for subjects treated with pegEPO versus those treated with established ESAs, Remedy Trial Tr. vol. 3 at 455, although by the end of the study the likelihood of death was "roughly the same" in peg-EPO treated subjects and subjects treated with the reference ESAs. *Id.* at 455–56. During cross-examination, Dr. Chertow acknowledged that, in approving MIRCERA for the treatment of anemia due to chronic renal failure, the FDA stated that its evaluation of product safety data for MIRCERA "did not reveal particular safety issues that were unexpected for a member of the ESA class when used for this specific indication." *Id.* at 465; *see also* Remedy Trial Tr. vol. 4 at 649 (providing testimony of Dr. Fishbane to same effect).

Dr. Fishbane testified that hemoglobin variability has been quantified in the relevant scientific literature "as large movements of hemoglobin, one and a half to two and half, three grams of hemoglobin." Remedy Trial Tr. at 647. This quantification of variability is considerably larger than that discussed and emphasized by Dr.

13. A hemoglobin excursion is a "hemoglobin concentration that falls outside of the clinically desired target rate." Remedy Trial Tr. vol. 3 at 459.

Chertow, which apparently ranged from 0.3 to 0.5 grams. Fishbane Supplemental Report ¶¶ 56–57. When asked whether he had seen any such variability in the Phase III study patients, Dr. Fishbane responded that "1789 patients studied in the Phase III program, and with this big a primary power analysis, there was no evidence of variability with MIRCERA compared to the comparators." Remedy Trial. Tr. vol. 3 at 647. The implication is that while Chertow's findings on greater hemoglobin variability may be statistically significant, they are not clinically relevant. *See* Fishbane Supp. Rep. ¶¶ 55–58.

Dr. Fishbane notes that because the titration period is a dose-finding exercise designed to find the correct dose of the experimental drug for a particular patient, findings from the titration period are not examined to determine effects of the drug. Rather, the proper period for assessing drug effects is the evaluation phase, which is also known as the assessment phase. *Id.* ¶ 25. Because physicians have more experience with dosing of established ESAs, one should expect that those patients receiving MIRCERA would have greater hemoglobin variations during the titration period. Dr. Fishbane stated:

> As the patients who are continuing on the older drug are not titrating—the correct dose for that patient is already known and the patient is receiving it—any comparisons between results of patients taking the experimental drug with patients taking the older drug is not an equivalent comparison and has no scientific merit.

Id. ¶ 26.

a. Findings with respect to patient health

Obviously, the Roche and Amgen experts differ in their interpretations and evaluations of the clinical, convenience, and quality of life attributes of MIRCERA relative to the currently available ESAs. Nevertheless, one set of facts is clear and warrants particularly strong consideration. Although clinical studies in support of a Biologics License Application at the United States Food and Drug Administration or at the European Medicinal Evaluation Agency frequently involve several thousand patients, it often takes many years before the medical community learns how new therapies are to be used safely and effectively, for what patients and at what doses, and conditions under which their use is not advised. As physician/patient experience accumulates and scientific evidence evolves, the benefit/risk calculation underlying treatment often shifts as well.

For example, while EPOGEN was launched in 1989 and Aranesp in 2001 in the U.S., major changes in treatment guidelines and FDA product labeling for these ESAs were still emerging as late as 2007. These included reducing the hemoglobin treatment upper range target to 12 μg/dL and warning that dosing to achieve target hemoglobin of greater than 12 μg/dL increases the risk for: (1) death and serious cardiovascular events; (2) shortened time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy; (3) increased deaths attributed to disease progression in patients with metastatic breast cancer receiving chemotherapy; and (4) increased risk of death in patients with active malignant disease not under treatment with chemotherapy or radiation therapy. Bernheim Expert Rep. ¶ 39. Some of these new FDA treatment guidelines took the form of product label black box warnings, which are the strongest warnings the FDA can issue short of ordering product withdrawal from the U.S. market. Fishbane Supp. Rep. ¶ 17. In addition, after reviewing data on its ESAs at the request of the FDA, in 2007 Amgen removed a number of quality-of-life claims from its product label.

Id. ¶ 14; Remedy Trial. Tr. vol. 3 at 473–75.

Given that both the FDA and the European Medicines Agency have approved MIRCERA as safe and effective for the treatment of anemia in patients with chronic renal failure, it seems likely that some patients might well benefit from MIRCERA being on the market as an additional element in the physicians' armamentarium due to clinical, convenience, and quality-of-life concerns. Nevertheless, with major changes in recommended treatment modalities still occurring many years after the initial product launch for currently available ESAs, it is also plausible that, were MIRCERA allowed to be marketed in the United States, information and consensus on its risk/benefit profile relative to those of EPOGEN, Procrit, and Aranesp would also evolve and change, perhaps substantially. *See* Remedy Trial Tr. vol. 1 at 157–58. Hence, it is difficult if not impossible to predict with any reasonable level of confidence what the net clinical, convenience, and quality-of-life benefits of Mircera will be relative to those of the existing ESAs.

2. The Court cannot conclude that MIRCERA would reduce Medicare costs[14]

As shall be outlined below, the record does not support a finding that MIRCERA would reduce Medicare costs; indeed, prices may actually rise.

a. A primer on how Medicare calculates its reimbursement rate for ERSD drugs

Medicare is the dominant payor in the ERSD market and plays a very important albeit less dominant role in the CKD market. Because ERSD patients regardless of age are generally eligible for coverage by Medicare Part B beginning in the fourth month of dialysis treatment, Medicare Part B is the dominant payor for EPOGEN. Amgen expert Professor Douglas Bernheim estimates that, in 2006, Medicare Part B accounted for 75% of EPOGEN sales in the United States, while other governmental payors included Medicaid (2%), the Veterans' Administration and Department of Defense (1%), and other public health services (2%). Together, governmental purchasers comprised approximately 80% of EPOGEN sales, while commercial payors accounted for the remaining 20%. Bernheim Expert Rep. ¶ 46, Fig. 4. Medicare is also a large purchaser of Aranesp. In 2006, Medicare accounted for 41% of Aranesp sales. *Id.* ¶ 46, Fig. 5.

Medicare's method of paying for ESRD drugs, which are separately billable under Part B, has changed several times in recent years. Under provisions of the Medicare Prescription Drug, Improvement and Modernization Act of 2003 ("MMA"), the basis on which Medicare Part B reimbursement of most physician-dispensed drugs was changed, effective January 1, 2004, from 95% of the Average Wholesale

14. The Court is indebted in this section of its memorandum to the fine work of Ernest Berndt, an applied economics professor at the Massachusetts Institute of Technology Sloan School of Business, who the court appointed, with the parties' consent, its special master and technical advisor on the economics of the Medicare reimbursement system. *See Amgen I,* 126 F.Supp.2d at 78 n. 3 (discussing the appointment of technical advisors in ''complex technical litigation''); *see also MediaCom Corp. v. Rates Tech., Inc.,* 4 F.Supp.2d 17, 29–30 (D.Mass.1998). While Professor Berndt consulted with and prepared memoranda for the Court, his engagement ended before the writing of this opinion, and he had no participation therein. The analysis and conclusions are, of course, those of the Court alone. Professor Berndt markedly accelerated and deepened the Court's understanding.

Price ("AWP," a list price) to 85% of the April 1, 2003 AWP. Patricia Danzon, Gail R. Wilensky, and Kathleen E. Means, *Alternative Strategies for Medicare Payment of Outpatient Prescription Drugs—Part B and Beyond*, 11 AM. J. MANAGED CARE 173, 173 (2005). Beginning January 1, 2005, Medicare Part B reimbursement for single-source (primarily on-patent originator) drugs became 106% of their two-quarter lagged average sales price ("ASP") or their current wholesale acquisition cost ("WAC"), whichever is lower. *Id.* The ASP is intended to represent the volume-weighted, average manufacturer sales price net of rebates and discounts to all United States purchasers excluding sales that are exempt from the Medicaid best price calculation and those to other federal purchasers. *Id.; see also* Bernheim Expert Rep. ¶ 49.

Rebates and discounts incorporated into the ASP calculation include volume discounts, prompt payment discounts, cash discounts, free goods that are contingent on any purchase requirement, chargebacks, and rebates (other than rebates under the Medicaid drug rebate program). *See* 42 C.F.R. § 414.804(a)(2). Because some discounts and rebates are determined on an annual basis, the manufacturer is instructed to calculate the quarterly ASP by adding up the relevant data for the most recent 12–month period, dividing this by the relevant sales subject to the ASP reporting requirement for the same 12–month period, and applying that percentage to the current quarter sales as the price concession for the quarter for which the ASP is being submitted. *Id.* § 414.804(a).

Rebate payments can also be deferred to time periods after they are earned; specifically, rebates affect ASP calculations by reference to when they are paid, not earned. A consequence of this is the phenomenon known as "rebate overhang," in which rebates are earned in a quarter "t" but are not paid until, say, quarter t + 2. The payment of the rebate increases the price concession for quarter t + 2 (and three subsequent quarters, because ASP is calculated as a four-quarter moving average) but has no impact on the net ASP in quarter t or quarter t + 1. *See* Bernheim Expert Rep. ¶¶ 113–14. As discussed below, this dynamic aspect of rebates and price concessions in ASP calculations has strategic pricing implications for drug manufacturers, including both incumbents and potential entrants.

ASP levels are calculated and then publicly posted each quarter. The published ASP price for quarter t represents the average sales price lagged two quarters, i.e., from quarter t—2. U.S. GOV'T ACCOUNTABILITY OFFICE, END–STAGE RENAL DISEASE: BUNDLING MEDICARE'S PAYMENT FOR DRUGS WITH PAYMENT FOR ALL ESRD SERVICES WOULD PROMOTE EFFICIENCY AND CLINCIAL FLEXIBILITY 12, *available at* http://www.gao.gov/new.items_/d0777.pdf (last visited Sept. 9, 2008). Because the calculation of an average sales price requires a sales history, a different methodology must be employed for new drugs or biologicals. The Centers for Medicare and Medicaid Services ("CMS") has specified that, for new drugs and biologicals approved for marketing in the United States, the payment allowance is 106% of the WAC or, if the WAC is not published, the invoice price. *See, e.g.,* Centers for Medicare and Medicaid Services, Change Request 5646 (June 15, 2007), at 4, *available at* http://www.cms.hhs.gov/Transmittals/downloads R1270CP.pdf (last visited Sept. 2, 2008). Put simply, for the first two quarters for which a new drug is sold, the ASP is computed as 106% of the WAC, or invoice pricing if the WAC is not published. Beginning in the third calendar quarter of its first year of U.S. sales, however, the

drug's published ASP represents the average sales price lagged two quarters.

b. Medicare's current method for calculating reimbursement rates provides an incentive to pharmaceutical companies selling ESAs to keep their prices high

In undertaking an appropriate economic analysis of the effect MIRCERA's entry might have on the ESA market, Professor Bernheim explained that one must "begin with an understanding of the institutional framework within which competition is taking place, an understanding of the incentives that creates, [and] an understanding of how the organizations are intending to respond to those incentives." Remedy Trial Tr. vol. 1 at 106. Bernheim identified three ways in which the market for ESAs, characterized by "ASP-based competition," differs from traditional "plain vanilla competition." *Id.* at 107–08. First, in textbook market competition, end user consumers make choices. In prescription drug markets, however, physicians and providers, not patients, generally make product choices. *Id.* at 108. Second, while in textbook market competition end users pay directly for products they consume, in the ESA market end users pay at most only a relatively small proportional co-payment, and it is Medicare and third-party payors that bear most of the direct burden. *Id.* at 108–09. Third—and perhaps most important—in textbook market competition end users attempt to satisfy their needs at minimum cost. Under ASP-based competition, however, providers are drawn to the drugs that offer the largest difference between the amount a provider is reimbursed per drug unit under Medicare (currently, as discussed above, ASP plus 6%) and what the provider actually paid for the drug. *Id.* at 109. This difference is called the "cost recovery." Bernheim Expert Rep. ¶ 72.

Therefore, unlike in a textbook competitive market where manufacturers compete by reducing prices, vendors in the ESA market instead focus on making their product attractive to physicians by maximizing their cost recovery. Remedy Trial Tr. vol. 1 at 110. This often has the effect of encouraging pharmaceutical companies to avoid reducing their prices.[15] In essence, the Medicare policy of reimbursing providers on a fee-for-service basis at a rate of ASP plus 6% gives those providers incentives to maximize their cost-based billing, subject to acceptable medical practice, a goal that can be best achieved with more expensive drugs.

Given the two-quarter lagged ASP calculation for incumbents and the fact that a new entrant is assigned an ASP equal to its WAC, the above circumstances create an incentive for new entrants to launch at prices that are higher than those of the incumbent and that, accordingly, offer a higher cost recovery to providers, which presumably will gain the new entrant market share. As Professor Bernheim testified, a new entrant can preserve this initial advantage over time:

> [The new entrant] could make this advantage permanent by simply discounting and then maintaining their discounts, or alternatively they could discount and then increase these discounts somewhat through time[.] [T]heir ASP would be declining, but [the entrant] could manage that in a way that would allow them to converge

15. The fact that patients bear little to no burden for the cost of their ESA drugs and that they generally do not pick which drug they will receive remove virtually any need for pharmaceutical companies to reduce their price to gain market share. Instead, the primary factor constraining an upward trend in price is the threat that action by government or other payors will "change the rules of the game." Remedy Trial Tr. vol. 1 at 112.

> to an ASP that's higher than the incumbent's ASP[,] thereby preserving [its] advantage.

Id. at 128.

In general, Professor Bernheim opined that "there's no reason to think that the dynamics of price cutting [present in textbook competition] will apply" in the ESA market. *Id.* at 160. Instead, product pricing will depend on whether the relevant companies are focused on the long or short term. *Id.* at 159–60. Specifically, the ASP-based market creates a "Hobson's choice" for companies choosing a pricing strategy. On one hand, they can choose to discount prices at first to gain market share, which negatively impacts their ASP and thus their future competitiveness. On the other, they can charge high prices to maximize their ASP, losing market share in the present in order to be more competitive in the future. *Id.* at 160. While it is impossible to predict with certainty what will happen, Professor Bernheim testified that some empirical evidence exists as to which of these paths companies might choose.

Professor Bernheim described for the Court the pricing decisions made by drug manufacturers that sell drugs for which Medicare reimbursement is important after the ASP-based Medicare reimbursement system was implemented in 2005. *Id.* at 160–61. A search yielded two such drugs: one for treatment of breast cancer and the other for age-related macular degeneration. *Id.* at 162. In both cases, a new entrant launched at a WAC higher than that of the competitor's ASP. In neither case did the addition of the new competitor to the market lead to decreased prices. Instead, the incumbent manufacturer maintained its ASP while the ASP for the new drug remained above that. *Id.; see also* Bernheim Expert Rep. ¶¶ 107–11. In sum, given the incentives that exist in the ASP-based reimbursement system that represents the core of the ESA market, Professor Bernheim opined that "it [is] likely that you will not get any competition driving prices down." [16] *Id.* at 202–03.

c. Roche is likely to enter the market at a price higher than that of Amgen's products and to maintain high prices over time

The provider preference for drugs that maximize cost recovery was a major factor considered by Roche when formulating its MIRCERA pricing strategy. Barbara Senich, Vice President of Marketing and Sales for Roche, testified that launching MIRCERA with a price that provided phy-

16. Professor Bernheim did admit that there is some degree of uncertainty in predicting the effects on price of a new entrant in the ASP market:

> "THE COURT: You're telling me that under this ASP system you cannot predict the price effects of adding competitors? Stop there.
> THE WITNESS: I think—
> THE COURT: Is that right?
> THE WITNESS: I think it's, I think it's very difficult to do that. We have a limited foundation, a limited amount of evidence that can be brought to bear on that.
> THE COURT: Though in what you're calling vanilla economics, competition is almost the greatest good. If you compete, you know, that's a good almost in and of itself if you can introduce competition. That's generally what economists think, isn't it, generally?
> THE WITNESS: Generally, yes. We think that competition in a free market, and that's the key point, is a good thing. But there are recognitions in the economics literature that competition isn't always beneficial. For example, the phenomenon of the natural monopoly. Competition may lead to very inefficient outcomes . . . ."

Remedy Trial Tr. at 165–66. Ultimately, however, he concluded the incentives present in the ESA-market likely will induce pharmaceutical companies to refrain from reducing their prices. *See id.* 202–03.

sicians with an adequate cost recovery was one of three goals Roche wanted to satisfy with its pricing strategy, the other two being (1) avoiding setting a price so high as to jeopardize Medicare [17] and other coverage and (2) providing a return on Roche's investments. Remedy Trial Tr. vol. 4 at 561–62, 567, 569–71. As explained above, one way that new entrants can provide superior cost recovery to providers is to set their WACs at prices that exceed the ASP of incumbents. Indeed, Professor Bernheim testified that his review of a series of high-level Roche planning documents and his understanding of the institutional peculiarities of the ESA market led him to conclude that Roche is "very likely" to "enter with a WAC that implies a substantial premium on a treatment basis." Remedy Trial Tr. vol. 1 at 130.

This would not be the end of the matter, for as Roche's Vice President of Sales and Marketing testified:

> [I]f you want to maintain the net cost recovery at the provider level you have to then decrease ... the price or increase your discounts to those providers to keep them whole so to speak. But those incremental discounts then are reflected in your ASP two quarters later. So you're constantly stepping down, if you will, to maintain the net cost recovery to the providers. And so by that alone the ASP, if you will, goes down and that's what we call the glide path.

Remedy Trial Tr. vol. 4 at 569. Roche has expressed an intention to do what it can to minimize the decline of its ASP while at the same time maintaining cost recovery for its providers. *See* Remedy Trial Ex. 6, MIRCERA WAC and Pricing Meeting, February 27–28, 2007 ("MIRCERA Pricing Meeting") at slide 47, 197, 206 (stating there is a "[n]eed to carefully monitor rate of ASP decline to avoid race to the bottom—[t]his is the Glide Path concept"). Professor Bernheim opined that, based on his review of Roche documents and his knowledge of the ESA market, Roche would "execute this glide path, this management of its initial advantage [over Amgen], in a way that preserves that advantage through time and maintains a relatively high ASP." Remedy Trial Tr. at 130–31.

Roche's ability to manage its glide path to maintain a high ASP is somewhat dependent on Amgen's pricing decisions. If Amgen fails to reduce the ASP of Aranesp and EPOGEN to increase cost recovery for providers, Roche may be required to implement only minimal decreases to its ASP in order to maintain its advantage, meaning that its price would remain relatively high. On the other hand, if Amgen responded to MIRCERA entry by increasing discounts and rebates substantially—thus increasing Aranesp and EPOGEN's cost recovery and making them more competitive—Roche may be forced to respond in a manner that generates a steeper reduction in its ASP. *See* Remedy Trial Ex. 6, MIRCERA Pricing Meeting at slide 335.

d. Amgen's competitive response to Roche is uncertain, but there is a reasonable likelihood it would either raise prices or maintain the status quo

Professor Bernheim concluded, based on information obtained from Amgen and in part on the evidence gleaned from the

17. Roche analysts recognized that Medicare would be the largest payor for MIRCERA and concluded that "Medicare reimbursement is the foundation of MIRCERA business." Remedy Trial Ex. 6, MIRCERA WAC and Pricing Meeting, February 27–28, 2007, at slide 109. It recognized that an unreasonably high price, although likely to cause MIRCERA to gain market share via a high cost recovery, might trigger unfavorable action. *See id.* at slides 86, 90.

pricing decisions made by incumbents offering breast cancer and macular-degeneration drugs in similar situations in the past, that "the most likely outcome" is that Amgen would not reduce its prices. Remedy Trial Tr. vol. 1 at 178. Similarly, although admitting it was difficult to predict with certainty, Professor Bernheim opined that "the most likely thing is [that there will be] either no price erosion or some degree of price erosion" with regard to Amgen's products. *Id.* at 181.

In fact, Amgen has already taken a significant step toward locking in a high ASP—and with it, a high reimbursement rate—for the life of the patent. On October 13, 2006, Amgen and Fresenius Medical Care Holdings, Inc. entered into a sourcing and supply agreement covering from October 1, 2006 to December 31, 2011. Remedy Trial Ex. 20, Amgen–Fresenius Sourcing and Supply Agreement ("Supply Agreement") ¶¶ 1.11–1.12. Under the terms of the agreement, Amgen is the sole supplier of the erythropoiesis stimulating proteins ("ESPs") that Fresenius uses to treat its patients. *Id.* ¶ 2.1.

Fresenius is a large dialysis organization that, together with another large dialysis organization called DaVita, accounts for about two-thirds of treated ERSD patients in the United States. Because these large dialysis organizations account for such a large percentage of the market, the prices they pay will have a significant affect on ASP. Under the terms of the agreement, Amgen will be able to maximize its ASP and the corresponding Medicare reimbursement rate.

Specifically, the agreement provides for an Annual Incremental Rebate ("AIR") Opportunity to Fresenius if its aggregate Qualified Gross Purchases of EPOGEN meet certain annual volume thresholds. *See id.* ¶¶ 3.1–3.2. Rebates will be calculated on a quarterly basis but will be paid in the year or the year after they are earned. *Id.* ¶ 3.2. The sum of the potential rebates for which Fresenius may qualify during the term of the agreement is $225 million. *Id.* Ex. 3.1, Discount Terms and Conditions, ¶ 8.3.

The rebate scheme, however, is significantly backloaded. Fresenius was eligible to earn just $10,000,000 in rebates in the final quarter of 2006 and just $25,000,000 in rebates in the years 2007, 2008, and 2009. *Id.* The potential rebates increase sharply thereafter to $55,000,000 in 2010 and $85,000,000 in 2011. *Id.* In other words, 62.5% of the rebates are to be paid in the final two years of the agreement—just prior to the point when the first of Amgen's patents is scheduled to expire in 2012.

e. The Court cannot compensate for the peculiarities of the ESA market

MIRCERA's likely market entry at a price higher than that of Amgen products is one reason it seems prices for ESA very well may not decline. While it may seem that the Court could encourage lower prices by directing MIRCERA to set a launch price no higher than the prices of the Amgen products, it is not that simple. As Professor Bernheim testified, one reason for this is the possibility that MIRCERA is less efficient on a dosing basis than EPOGEN; were this true, MIRCERA would still have an advantage. Remedy Trial Tr. vol. 1 at 157. A second reason for this is that the court-ordered parity could be undermined due to the existence of rebate overhang. *Id.* at 188. But perhaps most importantly, putting the companies on equal footing would not eliminate the idiosyncratic dynamics of ASP-based competition, which do not lend themselves to the "usual dynamics of price cutting." *Id.* at 160.

f. Further complicating the inquiry, administrative changes may alter companies' incentives, making it difficult for the Court to predict the effect of MIRCERA on the market

In considering the likely effect of MIRCERA's entry into the ESA market, the Court must bear in mind that the administrative landscape is constantly shifting and, accordingly, altering drug manufacturer incentives. In 2003, Congress instructed CMS to design and assess the feasibility of a payment system that, instead of paying for ERSD drugs under a separate billable rate as is done currently, would bundle payment for these drugs with payment for other ESRD services under a single prospectively set rate. This Medicare policy change has been endorsed by the GAO, the Medicare Payment Advisory Commission, and CMS. U.S. GOV'T ACCOUNTABILITY OFFICE, END–STAGE RENAL FAILURE, *supra,* at 23.

If Congress passed legislation bundling payment for drugs with other items such as clinical laboratory tests, the incentives facing providers of treatment for ESRD would change dramatically. Specifically, if reimbursement came in the form of a predetermined bundled amount, ERSD providers would have an economic incentive to purchase the ESAs and other drugs with the lowest acquisition cost in order to create the maximum cost recovery, which in these circumstances would be the difference between the drug acquisition cost and the fixed bundle reimbursement rate. Bernheim Expert Rep. ¶ 72.

Roche generally assumed, when producing its planning models for the launch of MIRCERA, that CMS would implement ESRD bundling in 2010. Remedy Trial Tr. vol. 4 at 585. Some Roche documents, however, indicated it expected bundling to occur as late as 2011, while Amgen believes it may occur as early as 2009. Bernheim Rebuttal Rep. ¶ 63. One expert indicated he expected bundling polices to be adopted "shortly." Fishbane Expert Rep. ¶ 149. In sum, there is much uncertainty about when the reimbursement scheme will change.

While Roche and Amgen make differing assumptions about when bundling might occur, both agree that the impact of the switch would be substantial. Roche, for example, believes that bundling would produce cost pressures that would reduce ESRD dosing by 25%. Remedy Trial Ex. 8, 2007 MIRCERA Business Plan at slide 25.

g. Ultimately, the Court cannot conclude that MIRCERA's entry into the ESA market would reduce Medicare costs

Professor Bernheim ultimately concluded that MIRCERA's market entry "would probably not lead to reduced Medicare reimbursement costs." Remedy Trial Tr. vol. 1 at 201. He opined that while Amgen "may experience some price erosion," it was "very unlikely that Amgen's prices will go down far enough and fast enough to overcome the higher reimbursements associated with peg-EPO and this high WAC in executing the glide path." *Id.* Accordingly, potentially Medicare might actually end up paying more, were Roche permitted to compete, as providers switched to more-expensive MIRCERA because it offered them a higher cost recovery. *See id.* at 206.

Of course, the future cannot be predicted with certainty, and even Professor Bernheim acknowledged it was "very difficult" to assess the effects of adding a new competitor to ASP-based competition, *id.* at 165–66, in part because it is difficult to anticipate how the companies will decide between short-term versus long-term marketing concerns (and the pricing decisions that will result), *see, e.g., id.* at 176–77. At

bottom, predictions about how Amgen and Roche will compete with regard to price are speculative.

Furthermore, Roche produced their own expert, Professor Einer Elhauge, who opined that "MIRCERA entry would lower prices and spending." Remedy Trial Tr. vol. 4 at 669. Professor Elhauge criticized Professor Bernheim's analysis, arguing it "really assume[s] Medicare is irrational." He explained that, because Bernheim "assumes there's no quality advantage to MIRCERA," there would be "no rational reason" for Medicare to approve reimbursement at higher prices. *Id.* at 676. Professor Elhauge argued that Medicare would rationally approve reimbursement at a rate higher than that charged by Amgen only if (1) MIRCERA is "of higher quality than Amgen's product" or (2) if Medicare "thought, in fact, ... that [MIRCERA's] entry was going to lead to lower prices over time [and] wanted to help fund the entry ... to make sure that happened." *Id.* at 676–77.

Moreover, there is the question of whether Roche will enter into a sole sourcing agreement with DaVita as Amgen has done with Fresenius. It appears to contemplate doing so; its marketing plans assume MIRCERA will capture 100% of DaVita's ESA use by the end of 2009. Remedy Tr. Ex. 8, 2007 MIRCERA Business Plan at slide 17. Under the terms of the Amgen–Fresenius agreement, the majority of rebates Amgen will provide to Fresenius will not be paid until 2010 and 2011. Because the Medicare ASP formula only takes rebates into account when they are paid, these contract provisions will have the effect of delaying considerably the decline of the Medicare-calculated ASP. In addition, were Medicare to switch to a bundled reimbursement system with initial rates based upon contemporaneous ASPs, these provisions would raise the initial reimbursement rate and thus overall Medicare costs. Because DaVita is almost as large as Fresenius, any delayed rebate provisions in a sole-sourcing contract between Roche and DaVita would further delay a reduction in ASP and, accordingly, Medicare savings.

It is simply impossible to predict with certainty the effect that MIRCERA's entry would have on prices and, accordingly, on Medicare expenditures. Making the task even more difficult are several factors. First, historical experiences with ESAs demonstrate it is reasonable to expect that the information about the risk-benefit profile of MIRCERA relative to the incumbent ESAs will evolve and change, perhaps substantially. It is possible that clinical studies or other sources could raise questions about the safety or efficacy of MIRCERA (or indeed, any of the other ESAs), thereby changing CMS treatment guidelines for reimbursement or leading the FDA to issue a black box warning. This latter event, which likely has a substantial impact on the ESA market, has occurred multiple times within the last several years, despite the fact that EPOGEN and Aranesp have been on the market for some time. *See* Bernheim Expert Rep. ¶ 39; Fishbane Supp. Report ¶¶ 14, 17; Remedy Trial Tr. vol. 3 at 473–75.

Second, it is unclear when—or whether—Congress will change the reimbursement policy for ESAs, choosing to reimburse providers on a bundled basis. Third, there is likely a difference between how ESAs are dosed in the "real world" as opposed to in a clinical environment, which affects dose conversion ratios among ESAs and, accordingly, their relative treatment costs. As recognized by Roche's Director for Strategic Pricing in the Renal Segment:

> [Drug companies] can do research or analysis of our clinical studies ... to try and figure out what the appropriate

> dose or dose conversion is going to be. [U]ltimately, the dose conversion that occurs in the marketplace is a function of the provider's experience with the product and what they feel is appropriate for their patients. We can model it all we want[,] and we still may not get it right.

Bernheim Expert Rep. ¶ 63 (quoting deposition of Sonders Beimfohr). Moreover, though it may be possible to pin down the "right" dose conversion ratio for one point in time, new information, changes in reimbursement policies, and the issuance of label warnings may change the dose conversion ratio, with important economic implications for the various ESAs.

In sum, the multiple variables present in the ESA market as well as the incentives provided by ASP-based competition prevent this Court from concluding that MIRCERA's entry into the marketplace would reduce Medicare expenditures.

h. Separation of powers considerations and Federal Circuit precedent suggest that cheaper drugs are not a strong justification for refusing a permanent injunction

[53] Medicare is regulated and administered by the elected branches of government, and it has procedural mechanisms designed to keep drug prices from reaching exorbitant levels. *See* Remedy Trial Ex. 6, MIRCERA Pricing Meeting at slides 83–84, 86, 90. Congress could change the way it calculates reimbursement; as discussed above, for instance, it can choose to reimburse on a bundled basis. It also could simply reduce reimbursement rates. *See, e.g.,* Susan Adler Channick, *The Ongoing Debate Over Medicare: Understanding the Philosophical and Policy Divides,* 36 J. HEALTH L. 59, 70 (2003) (noting that, in response to "runaway cost escalation," "Congress changed [Medicare] inpatient hospital reimbursement in 1983 to a prospective payment system"); Joan H. Krause, *Regulating, Guiding, and Enforcing Health Care Fraud,* 60 N.Y.U. ANN. SURV. AM. L. 241, 268 (2004) (noting Congress's authority to reduce Medicare reimbursement rates). Congress could also pass legislation augmenting or undermining incentives for innovation that affect the value of drug patents. *See, e.g.,* Bayh–Dole Act of 1980, 35 U.S.C. §§ 200–212 (permitting public universities to enter into exclusive license agreements with private companies); Drug Price Competition and Patent Term Restoration Act, Pub.L. No. 98–417, 98 Stat. 1585 (1984) (restructuring regulations for generic drugs). Separation of powers considerations thus dictate that, absent a strong showing that the government is being fleeced, courts should proceed with caution before attempting to intervene on Medicare's behalf. *See United States v. Oakland Cannabis Buyers' Cooperative,* 532 U.S. 483, 497, 121 S.Ct. 1711, 149 L.Ed.2d 722 (2001) (stating that courts fashioning injunctive relief cannot "override Congress' policy choice[s]").[18]

18. As the Honorable Dennis Jacobs, Chief Judge of the Second Circuit Court of Appeals, has explained:

> [A] consequence of biased vision is the assumption that if something is of great importance, it can be safely left to lawyers.... As judges, we tend to assume that adversarial hearings and expert testimony will render the judge omni-competent and fit to decide the great questions, and that a legal mind is the highest and most useful development of mental capacity.... [Yet] depending on the question, the legal mind may be insufficient or may be inferior to the moral imagination; the scientific method; the practical arts of healing, politics, and entrepreneurship; the promptings of loyalty, faith, and patriotism; and the experience and expertise found elsewhere and among others. [J]udges should accept that the legal mind is not the best policy instrument, and that lawyer-driven processes and lawyer-centered solutions can be unwise,

Furthermore, even assuming MIRCERA would reduce Medicare's costs, this is not a sufficiently strong justification for declining Amgen's request for an injunction. The Federal Circuit has concluded that "selling a lower priced product does not justify infringing a patent. Were that to be a justification for patent infringement, most injunctions would be denied because copiers universally price their products lower than innovators." *Payless Shoesource, Inc., v. Reebok Int'l Ltd.,* 998 F.2d 985, 991 (Fed.Cir.1993); *see also Pfizer, Inc. v. Teva Pharm. USA, Inc.,* 429 F.3d 1364, 1382–83 (Fed.Cir.2005) (citing *Payless* when upholding a district court's grant of a preliminary injunction even though a denial would have led to cheaper drugs). Of course, in this case—as explored above—there is no guarantee that allowing MIRCERA to enter the market would lead to lower priced drugs. It is also important to bear in mind that, as much as Medicare may spend on ESAs per year, that amount is a billion-dollar drop in a nearly trillion-dollar bucket. Any savings that might occur as a result of MIRCERA's market entry would be a minute fraction of Medicare's overall expenditures. Hence, Roche's argument that cost savings justify the denial of a permanent injunction simply lacks force. As explored below, while the exclusionary rights conferred with a patent may result in more expensive products, this is part and parcel of the bargain embodied in the Patent and Copyright Clause.

3. Permitting Roche to enter the market would undermine the incentives for innovation embedded in the Patent and Copyright Clause

The Federal Circuit has "long acknowledged the importance of the patent system in encouraging innovation. Indeed, the 'encouragement of investment-based risk is the fundamental purpose of the patent grant, and is based directly on the right to exclude.' Importantly, the patent system provides incentive to the innovative drug companies to continue costly development efforts." *Sanofi–Synthelabo v. Apotex, Inc.,* 470 F.3d 1368, 1383 (Fed.Cir.2006) (quoting *Patlex Corp. v. Mossinghoff,* 758 F.2d 594, 599 (Fed.Cir.1985)).

The evidence in this case confirmed the Federal Circuit's evaluation of the importance of the right to exclude as an incentive for investment. Amgen CEO Kevin Sharer characterized pharmaceutical development as the "riskiest business that I know of in the world." Remedy Trial Tr. vol. 1 at 28. "[I]t can easily take 15 years" and a billion dollars for a company like Amgen to discover and develop a new drug. *Id.* at 27. Sharer's estimate is consistent with the findings of the district court in *Sanofi–Synthelabo,* which concluded that "the average cost of developing a blockbuster drug is $800 million." 470 F.3d at 1383. Of course, most of these enormous investments fail to result in marketable drugs. In his eight years at Amgen, Mr. Sharer has seen a "hundred or more" products "close to or actually in human testing"; only six or seven of those actually made it to market. Remedy Trial Tr. vol. 1 at 35. In order to maintain its business model and its research and development, Amgen must be able "to demonstrate to [its] investors that the full investment they make can be recaptured." *Id.* at 37.

If the Court allowed Roche to introduce MIRCERA into the market, perhaps a few patients would benefit, and maybe Medicare would save a few dollars. These arguments, however, could be made for al-

insufficient, and unjust, even if our friends and colleagues in the legal profession lead us that way.

See Dennis Jacobs, *The Secret Life of Judges,* 75 FORDHAM L.REV. 2855, 2862–63 (2007).

most any infringing drug. Were courts to refuse injunctions on the basis of such speculation, then pharmaceutical patents would be worth far less than they are today because they would no longer include a right to exclude infringers from the market. The diminishing returns would disincentivize research and development for pathbreaking drugs by lowering the expected value of discovery. By contrast, granting injunctions encourages companies to devote their energies toward developing drugs that will satisfy unmet medical needs. Were it possible to obtain market entry by making incremental improvements to existing drugs, it is doubtful that companies designed to generate discoveries could exist.

At bottom, Roche attached a sugar to a patented protein. As the jury concluded, this was not innovation. Of course, Roche's efforts to modify Amgen's patented product will not go entirely unrewarded. As it stands, European companies such as Roche can profit from building upon American discoveries by producing and selling infringing products in Europe and throughout the rest of the world. Nevertheless, the fact that Roche "built up its manufacturing facility in [Europe] and prepared to market its product was simply a risk it took with eyes open to the" possibility that it would not be permitted to market MIRCERA in the United States. *Pfizer*, 429 F.3d at 1382 (internal quotations and alterations omitted).

As Adam Smith observed in 1776, "[i]t is not from the benevolence of the butcher, the brewer, or the baker, that we expect our dinner, but from their regard to their own interest." ADAM SMITH, THE WEALTH OF NATIONS, *Book I, Chapter II: Of the Principle which gives Occasion to the Division of Labour*, *available at* http://www.econlib.org/library/Smith/smWN1.html. The Court has relinquished any notion that the long-suffering or terminally ill among our number may rely upon "the benevolence of" pharmaceutical companies. Companies like Amgen invest in risky research and development to discover drugs like EPO because such drugs are worth tens of billions of dollars, period. If America is to continue to be an engine of medical innovation it will be because we protect the right of inventors to exploit the limited monopoly granted in the Patent Clause.

After taking evidence for four days and entertaining oral argument and extensive briefing, the Court cannot conclude with any certainty that MIRCERA will save lives or money. Failure to enter a permanent injunction, however, would risk undermining the incentives for innovation that have produced, and hopefully will continue to produce, medical advances that extend and enhance the value of life. The Court therefore concludes that the public interest will not be disserved by a permanent injunction.

D. THE PROPOSED MODIFIED INJUNCTION WOULD NOT ADEQUATELY COMPENSATE AMGEN AND WOULD BE INAPPROPRIATE IN VIEW OF THE FINDINGS ABOVE

At a hearing on February 28, after Roche admitted it would no longer voluntarily refrain from entering the ESA market, the Court preliminarily enjoined Roche.[19] The Court, however, indicated

19. Roche's potential presence in the United States required immediate action by the Court, yet the Court was (in February 2008) still conflicted. Notwithstanding the extensive hearing on remedy, the Court then had four large cartons filled with unread depositions. Accordingly, the Court tried to have it both ways. It preliminarily enjoined Roche but apprised the parties of the contours of the permanent injunction it was then considering. The Court figured that if either party appealed it could get some guidance from the Federal Circuit. Since then, of course, the Court has completed its post-trial review and reflection upon the proceedings before it. Its ultimate

that it was considering entering a permanent injunction subject to the following conditions:

> Primarily, Roche must pay a 22.5% royalty. Second, MIRCERA must be introduced in the Medicare field with an ASP at or less that the ASP for EPOGEN, and the ASP must remain at or below EPOGEN's for the remainder of the life of Amgen's patents. Third, Roche must provide evidence of clinical usage and the real world dosage of MIRCERA so that the Court accurately can determine a dose conversion factor for MIRCERA's FDA approved indications. Fourth, Roche must fund an independent agency that will monitor Roche sales and account for the royalty payments. Finally, if Roche decides to enter the market based on these conditions, regardless of the outcome of any future litigation, Roche must agree that it will continue to provide MIRCERA to any patient who requests it, at or below the same price for which it was authorized, so long as the patient requires.

Order and Preliminary Injunction [Doc. No. 1675] at 3.

Although a modified injunction would mitigate the irreparable harm to Amgen, it would still permit Roche to gain profits, market share, and a foothold into the American drug market to which it is simply not entitled. Anything less than a permanent injunction would create uncertainty about the value of Amgen's patents and potentially undermine the incentives for investment and pharmaceutical innovation. In short, the modified injunction could not eradicate the deleterious effects of failing to enter an injunction altogether. As discussed at length above, there is no evidence of medical or economic harm compelling enough to override the public's interest in a robust patent system. Were there evidence of a shortfall in supply, a compulsory license or a modified injunction might be appropriate. If Amgen was unable or unwilling to meet the demand for ESAs, then barring the entry of a company that could supply the public's needs would disserve the public interest. The record, however, reveals that, although EPOGEN and Aranesp are not be perfect, they adequately meet the current demand.

Furthermore, a modified injunction would be difficult to enforce and manage. Before the Court could set and monitor an entry price for MIRCERA, it would have to determine the real world dosing conversion ratio. This is a thorny issue that would require a special master whose conclusions would undoubtedly be disputed and unsatisfying. The Court would almost certainly be called on to monitor pricing and resolve myriad disputes that would occur during the remaining life of the patents. In short, the proposed modified injunction would result in needless, protracted involvement in the affairs of these two companies. Should the parties wish to reach a license agreement, they may do so. If, however, Amgen wishes to exclude Roche from the market, it has earned that right.

findings are set forth in the text of the opinion. There is no reason to delay its issuance.

While the Court entered the preliminary injunction without a complete review of the record, it has no regrets. On the day I first became a judicial officer, Judge Vincent Brogna gave me this sage advice: "Have the courage of your own error." Hon. Vincent Brogna, Justice of the Massachusetts Superior Court, February 24, 1978. "This statement is more profound than it sounds. Of course, we must do our best to get it right and, of course, we must not hesitate to correct our errors. We must, however, *decide*. Failure to act is oft-times as injurious to justice as judicial error." William G. Young, *Vanishing Trials, Vanishing Juries, Vanishing Constitution,* 40 SUFF. U.L.REV. 67, 93 (2006).

V. THE INTERLOCUTORY APPEAL

[54] On April 9, 2008, Roche appealed this Court's entry of a preliminary injunction. *See* Notice of Appeal [Doc. No. 1703]. That appeal is pending. Therefore, with respect to the preliminary injunction, this Court is divested of jurisdiction to act other than in aid of the appeal. *See Gilda Indus., Inc. v. United States,* 511 F.3d 1348, 1350 (Fed.Cir.2008); *Hybritech Inc. v. Abbott Labs.,* 849 F.2d 1446, 1450 (Fed.Cir.1988). Because this an interlocutory appeal, however, this Court retains jurisdiction to enter the necessary findings and rulings on the judge-tried portions of this case and to decide the pending post-trial motions. This memorandum addresses and resolves these matters. Having now fully reviewed and reflected upon the record the Court sets forth its reasoning relative to remedy—i.e. a permanent injunction is not only warranted, but ought be imposed. To enter such a declaratory judgment, however, would moot the appeal of the preliminary injunction—an interlocutory appeal the Court welcomed for appellate guidance. This the Court may not do.

Accordingly, having stated its firm intention to enter such a permanent (for the life of the patents-in-suit) injunction—unless resolution of the interlocutory appeal mandates a different conclusion—the Court will order this case administratively closed. This ought be a sufficiently "final order" to allow any party to appeal at once and seek to consolidate such appeal with that presently pending. The Court seeks to avoid the process of appeal-remand-appeal-remand that unfortunately has characterized the related *Amgen v. TKT/HMR* litigation. *See Amgen IV,* 457 F.3d at 1321–22 (Michel, C.J., dissenting).

VI. CONCLUSION

In sum, the jury's verdict will stand. The Court will not reverse its ruling on validity of claim 1 of the '422 patent because "purified from mammalian cells grown in culture" limits the claim. Moreover, summary judgment of infringement on claim 1 of the '422 patent was appropriate because MIRCERA contains an infringing form of recombinant EPO.

The Court was on the precipice of entering a modified injunction. On a different record, such a decision might have been appropriate. Here, however, the uncertainties inherent in the available clinical evidence and the highly speculative economic projections are simply not enough to override the public's interest in robust patent rights that protect incentives for innovation. Unless the Federal Circuit mandates otherwise in resolving the interlocutory appeal, Roche, its agents, servants, employees, counsel, and all persons and entities acting in concert therewith will be permanently enjoined for the life of the remaining patents-in-suit, as to the claims of the patents-in-suit found to be infringed herein, from infringing those patents in any way within the United States. The case is administratively closed pending resolution of the interlocutory appeal. It may be reopened upon motion of any party thereafter.

SO ORDERED.

Charlene MORRISSEY, Plaintiff,

v.

Elizabeth MANTICA, R.N., Defendant.

Civil Action No. 06–11761–RBC.

United States District Court,
D. Massachusetts.

Oct. 6, 2008.

Background: Patient sued nurse for medical malpractice in connection with physical