

**United States Court of Appeals
for the Federal Circuit**

**AMGEN INC., AMGEN MANUFACTURING,
LIMITED,**
Plaintiffs-Cross-Appellants

v.

HOSPIRA, INC.,
Defendant-Appellant

2019-1067, 2019-1102

Appeals from the United States District Court for the District of Delaware in No. 1:15-cv-00839-RGA, Judge Richard G. Andrews.

Decided: December 16, 2019

JOHN LABBE, Marshall, Gerstein & Borun LLP, Chicago, IL, argued for plaintiffs-cross-appellants. Also represented by KEVIN M. FLOWERS, JULIANNE M. HARTZELL, MARK HARRY IZRAELEWICZ; THOMAS FRANCIS LAVERY, WENDY A. WHITEFORD, Amgen Inc., Thousand Oaks, CA.

THOMAS J. MELORO, Willkie Farr & Gallagher LLP, New York, NY, argued for defendant-appellant. Also represented by MICHAEL JOHNSON, HEATHER M. SCHNEIDER.

Before MOORE, BRYSON, and CHEN, *Circuit Judges*.

MOORE, *Circuit Judge*.

Hospira, Inc. (Hospira) appeals the District of Delaware's denial of its motion for judgment as a matter of law (JMOL), or alternative motion for new trial, upholding the jury's verdict that: (1) Amgen, Inc. and Amgen Manufacturing, Ltd.'s (Amgen) U.S. Patent No. 5,856,298 (the '298 patent) was infringed and not invalid; (2) fourteen batches of drug substance for Hospira's erythropoietin biosimilar drug product were not covered by the Safe Harbor provision of 35 U.S.C. § 271(e)(1); and (3) Amgen had proven it was entitled to \$70 million in damages. Amgen cross-appeals the district court's denial of its motion for judgment as a matter of law, and alternative motion for new trial, upholding the jury's verdict of noninfringement of U.S. Patent No. 5,756,349 (the '349 patent). For the following reasons, we affirm the district court's decisions as to each.

I. BACKGROUND

A. The Asserted Patents

The patents at issue relate to erythropoietin (EPO) isoforms and aspects of their production. EPO is a glycoprotein hormone that regulates red blood cell maturation and production. Recombinant human EPO is an important therapeutic protein for the treatment of anemia. Human EPO consists of a polypeptide of 165 amino acids and a high content of saccharides (or glycans). It contains various sites for glycosylation, i.e., sites where saccharides can be attached to the protein part of the molecule. Each of these glycosylation sites has the potential for branching and each branch contains a potential terminal sialic acid, a negatively-charged molecule. Thus, each EPO molecule can have different numbers of sialic acids. Amgen manufactures and markets recombinant human EPO as Epogen.

The claims of the '298 patent claim, *inter alia*, methods of producing EPO isoforms having a specific number of

sialic acids per molecule, and methods for obtaining EPO compositions having a predetermined *in vivo* specific activity. According to the '298 patent, each isoform of EPO has an *in vivo* activity which correlates to the number of sialic acids the isoform possesses. '298 patent at 5:33–46, 5:62–64.

Relevant to this case are certain techniques for separating protein molecules. The first, isoelectric focusing, “separates proteins on the basis of charge.” '298 patent at 4:65–67. Proteins placed in a pH gradient and subjected to an electric field will migrate (through attraction toward or repulsion from the negatively- or positively-charged electrode) towards the point at which they have no net charge. *Id.* at 4:67–5:3. This point is known as the isoelectric point, or pI. *Id.* Each band seen on an isoelectric focusing gel represents molecules that have the same overall charge and are termed “isoforms.” *Id.* at 5:4–5:7. The '298 patent describes “erythropoietin isoforms” as EPO preparations “having a single pI, and having the same amino acid sequence.” *Id.* at 5:6–9. A second technique, ion exchange chromatography, involves separation of proteins on the basis of charge by application of material containing the protein “to a column resin under conditions that permit binding of some or all of the [protein of interest] to the resin.” *Id.* at 7:3–8. The resin can be washed with buffers of varying pHs, thereby “elut[ing]” the proteins based on the charge. *Id.* at 7:4–17.

The '349 patent is directed to recombinant cells that are capable of producing EPO at certain rates when grown in culture. The claims of the '349 patent are directed to cells that produce certain units of EPO as determined by a radioimmunoassay, a technique that allows for measuring protein levels using a radioisotope.

B. Procedural History

In 2014, Hospira submitted its Biologics License Application (BLA) No. 125-545 to the FDA, seeking approval for

a biosimilar to Amgen's Epogen product. Amgen sued Hospira for infringement of the '298 patent under 35 U.S.C. §§ 271(a) and 271(e)(2)(C), and for infringement of the '349 patent under 35 U.S.C. § 271(a). Amgen asserted that Hospira's manufacture of twenty-one batches of drug substance for its EPO biosimilar drug product infringes claims 24 and 27 of the '298 patent and claims 1–7 of the '349 patent. A jury trial was held in September 2017. The jury found the asserted claims of the '298 patent not invalid and infringed, and the asserted claims of the '349 patent not invalid and not infringed. Of the twenty-one accused drug substance batches, the jury found seven batches entitled to the Safe Harbor defense. The jury awarded Amgen \$70 million in damages.

The district court denied Hospira's post-trial Rule 50(b) Motion for Judgment as a Matter of Law on issues of non-infringement and invalidity of the '298 patent, Safe Harbor, and damages, or in the alternative, for remittitur or a new trial. The district court also denied Amgen's renewed motion for JMOL for infringement of the '349 patent, or in the alternative, for a new trial.

On appeal, Hospira challenges a myriad of issues, including: (1) the district court's claim construction; (2) the jury instructions regarding the Safe Harbor defense; (3) the jury's findings regarding the Safe Harbor defense and denial of JMOL on the Safe Harbor issue; (4) the evidentiary rulings regarding Amgen's damages expert; and (5) the denial of JMOL of noninfringement and invalidity. On cross-appeal, Amgen challenges: (1) the district court's denial of JMOL of infringement of the '349 patent; and (2) the denial of its motion for a new trial. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

II. DISCUSSION

We review a denial of JMOL under the law of the regional circuit. *Energy Transp. Grp. Inc. v. William Demant Holding A/S*, 697 F.3d 1342, 1350 (Fed. Cir. 2012). "In the

Third Circuit, review of denial of JMOL is plenary.” *Finjan, Inc. v. Secure Computing Corp.*, 626 F.3d 1197, 1202 (Fed. Cir. 2010) (citations omitted). JMOL is “granted only if, viewing the evidence in the light most favorable to the nonmovant and giving it the advantage of every fair and reasonable inference, there is insufficient evidence from which a jury reasonably could find’ for the nonmovant.” *TransWeb, LLC v. 3M Innovative Props. Co.*, 812 F.3d 1295, 1301 (Fed. Cir. 2016) (quoting *Lightning Lube, Inc. v. Witco Corp.*, 4 F.3d 1153, 1166 (3d Cir. 1993)); see also *Pitts v. Delaware*, 646 F.3d 151, 155 (3d Cir. 2011). Moreover, where the movant bore the burden of proof on an issue, JMOL is only granted where “there is insufficient evidence for permitting any different finding.” *Fireman’s Fund Ins. Co. v. Videfreeze Corp.*, 540 F.2d 1171, 1177 (3d Cir. 1976) (citations omitted). The decision to grant or deny a new trial is committed to the discretion of the district court, which grants a new trial only where “a miscarriage of justice would result if the verdict were to stand” or where the verdict “shocks [the] conscience.” *Williamson v. Consol. Rail Corp.*, 926 F.2d 1344, 1352–53 (3d Cir. 1991).

A. Judgment of Infringement and No Invalidity

Hospira contends that it is entitled to a judgment of noninfringement of claim 27 of the ’298 patent because: (1) the district court’s claim construction was erroneous, and no reasonable jury could find infringement under the proper construction; and (2) even under the district court’s construction, Amgen did not establish Hospira’s infringement of every limitation. Hospira also argues that under the district court’s construction, no reasonable jury could find claim 27 not invalid over U.S. Patent No. 4,667,016 (Lai). As discussed below, we find Hospira’s arguments unavailing.

i. Claim Construction

Claim construction is a question of law we review *de novo*, with subsidiary factual findings based on extrinsic

evidence reviewed for clear error. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318 (2015).

Claim 27 recites:

A method for obtaining an erythropoietin composition having a predetermined in vivo specific activity comprising preparing a mixture of two or more erythropoietin isoforms of claim 1.

Claim 1 recites:

An isolated biologically active erythropoietin isoform having a single isoelectric point and having a specific number of sialic acids per molecule, said number selected from the group consisting of 1-14, and said isoform being the product of the expression of an exogenous DNA sequence in a non-human eucaryotic host cell.

On appeal, the parties do not dispute the district court's finding that, although claim 27 refers to claim 1, it is an independent claim. Defendant-Appellant's Resp. Br. 14–15; Plaintiffs-Cross-Appellants' Br. 28. The district court construed the term “[a]n isolated biologically active erythropoietin isoform” in claim 1 to mean “a group of molecules that has a single isoelectric focusing point and a specific number of sialic acids per molecule, and appears as a single band on an isoelectric focusing gel (an example of which is shown in Figure 1 of the '298 patent).” J.A. 192–93. The district court construed the limitation in claim 27, “a mixture of two or more erythropoietin isoforms of claim 1,” to mean “a mixture of two or more of the isolated erythropoietin isoforms of Claim 1.” J.A. 174. In denying Hospira's motion for summary judgment of noninfringement, the district court explained that “[n]othing in [the claim] language suggests that the individual isoforms of claim 1 have to be separately prepared prior to making

the mixture.” J.A.169. Accordingly, the final claim construction provided to the jury included the following sentence: “Claim 27 does not require the individual isoforms of Claim 1 to be separately prepared prior to making the mixture.” J.A. 160.

Hospira challenges this last portion of the construction. According to Hospira, the proper construction of claim 27 requires a mixture of “isolated” isoforms of claim 1, but the district court’s construction reads out the phrase “isolated” by stating that the isoforms do not need to be separately prepared prior to making the mixture. Hospira argues that this construction contradicts the intrinsic evidence and the testimony of the inventor Dr. Strickland, who stated that the purpose of his invention “was to separate isoforms and then ‘recombine’ them or ‘mix those fractions back together’ to make EPO compositions with specific *in vivo* activity.” Defendant-Appellant’s Br. 37 (quoting J.A. 720 at 375:12–377:18). Hospira contends that under the proper construction, no reasonable jury could find infringement because Hospira does not mix isolated isoforms, rather all the isoforms in Hospira’s product elute off the ion exchange column together.

Amgen responds that claim 27 is directed to “preparing a mixture” of isoforms, not “mixing” isoforms. In Amgen’s view, although “‘preparing a mixture’ could be accomplished by preparing isolated isoforms and mixing those isoforms together, claim 27” is not so limited. Construing the claim to require “mixing,” Amgen argues, “would render the term ‘preparing a’ superfluous.” Plaintiffs-Cross-Appellants’ Br. 27.

Nothing in the claim language or the specification suggests that it would be proper to limit claim 27 in the manner Hospira proposes. Claim 27 recites “preparing a mixture of two or more erythropoietin isoforms of claim 1.” Contrary to Hospira’s arguments, this reference to “isoforms of claim 1” does not require that the mixture of

two or more isoforms of claim 1 be prepared in any particular way (i.e., by preparing individual isoforms separately and mixing them together). Indeed, the specification discloses that “mixtures of erythropoietin isoforms” can be produced by “isolating selected erythropoietin isoforms *simultaneously*.” ’298 patent, 6:61–63 (emphasis added). Such “methods include isolation of individual isoforms by techniques such as preparative isoelectric focusing *or* preparation of mixtures of isoforms having a predetermined number of sialic acids per molecule (for example, greater than 11) by techniques such as ion exchange chromatography or chromatofocusing.” ’298 patent, 6:63–7:3 (emphasis added). The specification clearly contemplates the preparation of mixtures of isoforms in more than one way.

The intrinsic evidence suggests that the claim is not limited to methods of preparing individual isoforms separately and mixing them together. It is therefore improper to limit claim 27 to one embodiment based on Dr. Strickland’s testimony. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1318 (Fed. Cir. 2005) (Extrinsic evidence is “less reliable than the patent and its prosecution history in determining how to read claim terms.”). Accordingly, we hold that the district court did not err in construing claim 27 to “not require the individual isoforms of [c]laim 1 to be separately prepared prior to making the mixture.”

ii. Amgen’s Evidence of Infringement

Infringement is a question of fact, “reviewed for substantial evidence when tried to a jury.” *ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1311 (Fed. Cir. 2007). A factual finding is supported by substantial evidence if a reasonable jury could have found in favor of the prevailing party in light of the evidence presented at trial. *See Tec Air, Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1357–58 (Fed. Cir. 1999).

Hospira argues that, even under the district court’s construction, no reasonable jury could have found

infringement of claim 27 for two separate reasons. First, although claim 27 references claim 1, Amgen did not mention claim 1 or attempt to prove the limitations of claim 1 at trial. Second, Hospira contends, Amgen's evidence is insufficient to establish that Hospira's EPO has a "predetermined *in vivo* specific activity," as required by claim 27. In Hospira's view, Amgen's evidence of infringement only demonstrates that Hospira's product is biosimilar to Amgen's Epogen. Hospira contends that this evidence does not prove infringement, particularly when Epogen is not manufactured using the claimed methods of the '298 patent. Defendant-Appellant's Br. 39.

Amgen responds that the evidence at trial showed Hospira prepared a product containing biologically active EPO, establishing that the limitations of claim 1 were satisfied. Amgen further contends that Hospira's statements in its BLA show that its EPO falls within a specified range of *in vivo* specific activity, a range that was, in Amgen's view, "predetermined based on the reference product," Epogen. Plaintiffs-Cross-Appellants' Br. 29.

Substantial evidence supports the jury's infringement verdict. Amgen presented evidence that satisfied the limitations of claim 1. The inventor, Dr. Strickland, testified that "all EPO isoforms have biological activity." J.A. 725 at 394:1-2. Amgen's expert, Dr. Wall, testified that Hospira's product is produced through expression of an exogenous DNA sequence in a non-human eucaryotic host cell. J.A. 453 at 277:7-278:5. Amgen also introduced into evidence portions of Hospira's BLA, which show that Hospira's EPO is a mixture of two or more EPO isoforms, each having a single isoelectric focusing point and a specific number of sialic acids per molecule. J.A. 744-45 at 470:16-475:8 (testimony of Amgen's expert Dr. Cummings, discussing J.A. 3690, J.A. 3693, and J.A. 3711). Thus, the jury heard evidence on whether Hospira's process met the limitations of claim 1. Amgen's failure to mention claim 1 at trial does not negate this evidence. As such, the jury

reasonably found that Hospira's process meets the limitations of claim 1.

As to whether Hospira's process results in EPO that has a predetermined *in vivo* specific activity, Hospira's BLA states that 100% of its EPO batches have a specified range of *in vivo* activity, i.e., 93–147 U/ μ g. J.A. 4606. Amgen's expert, Dr. Cummings, testified that all of Hospira's EPO batches have an *in vivo* specific activity within a specified range, a range predetermined based on Epogen, the reference product. J.A. 746. As such, the jury was presented with substantial evidence that Hospira's process resulted in EPO "having a predetermined *in vivo* specific activity." '298 patent at claim 27.

We conclude that substantial evidence supports the jury's verdict of infringement of claim 27. Accordingly, we affirm the district court's denial of JMOL.

iii. Alleged Anticipation by Lai

"Anticipation is a factual determination that is reviewed for substantial evidence when decided by a jury." *Koito Mfg. Co. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1149 (Fed. Cir. 2004).

Hospira argues that under the district court's erroneous claim construction, no reasonable jury could find claim 27 not invalid over Lai. According to Hospira, if all it takes to "predetermine" a specific activity is to use ion exchange chromatography to prepare a mixture of active EPO, then Lai disclosed exactly such a process in its Example 2. Defendant-Appellants' Br. 40 (citing Lai at 5:20–37, 5:59–68). Hospira argues that Example 2 discloses the use of ion exchange chromatography to separate impurities and less biologically active EPO from more biologically active EPO. *Id.*

Amgen argues that Lai does not expressly disclose EPO isoforms, selectively eluting EPO molecules, or EPO isoforms with a predetermined *in vivo* specific activity. For

this reason, Amgen contends, Hospira resorted to arguing inherency to the jury, but failed to show that Example 2 “necessarily and inevitably” produced EPO with a predetermined *in vivo* specific activity. Plaintiffs-Cross-Appellants’ Br. 30 (citing *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377–78 (Fed. Cir. 2003)).¹

We agree with Amgen and conclude that substantial evidence exists for the jury’s finding that Lai does not anticipate claim 27. Lai is directed to processes of efficient recovery of EPO from a fluid, that is, separating EPO from non-EPO contaminants. *See, e.g.*, Lai at 3:9–15. Lai specifically describes the first step of its Example 2 as removing non-EPO contaminants. *Id.* at 5:29–31. But, Lai does not refer to a composition with a predetermined *in vivo* activity, it discloses only that “[b]iologically active” EPO was eluted. *Id.* at 5:34. Thus, Lai does not expressly disclose EPO isoforms with a predetermined *in vivo* specific activity (or EPO isoforms at all).

Moreover, Amgen’s expert, Dr. Cummings, testified that nothing in Lai “would indicate one to think there’s a predetermined *in vivo* activity.” J.A. 1844–46. Notably, Hospira’s own expert, Dr. Levine, testified that predetermined *in vivo* specific activity means “a specific subset of isoforms” and that Lai does not disclose anything about EPO isoforms. J.A. 1436 at 1128:13–18. Dr. Levine also admitted that the product of Lai’s method depends on what is present in the starting material (*see id.* at 1128:19–24), supporting the finding that the Lai process does not “necessarily and inevitably” meet the limitations of claim 27.

¹ Hospira does not expressly argue inherency on appeal, but instead argues that the district court’s erroneous construction encompasses the prior art and therefore the jury verdict should be vacated. Defendant-Appellant’s Br. 5, 40.

Based on the foregoing, substantial evidence supports the jury's finding that Lai does not anticipate claim 27. Accordingly, we affirm the district court's denial of JMOL as to anticipation.

Because substantial evidence supports the jury's finding that claim 27 is not invalid and Hospira is liable for infringement of claim 27 of the '298 patent, and "[b]ecause the damages calculation at trial was not predicated on the infringement of particular claims," we need not reach the parties' arguments regarding claim 24. *See TiVo, Inc. v. EchoStar Commc'ns Corp.*, 516 F.3d 1290, 1312 (Fed. Cir. 2008).

B. Safe Harbor

35 U.S.C. § 271(e)(1) provides a Safe Harbor defense for defendants for their otherwise infringing activities by stating:

It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

35 U.S.C. § 271(e)(1).

On appeal, Hospira challenges the district court's jury instructions regarding its Safe Harbor defense. Hospira also contends that no reasonable jury could have found that

some, but not all, of Hospira's drug substance batches were protected by the Safe Harbor defense. We address each issue in turn.

i. Jury Instructions

We review *de novo* “[t]he legal sufficiency of jury instructions on an issue of patent law,” such as the Safe Harbor provision of 35 U.S.C. § 271(e)(1). See *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 638 (Fed. Cir. 2011) (citations omitted). A jury verdict based on erroneous instructions is set aside only if “the movant can establish that the instructions were legally erroneous and that the errors had a prejudicial effect.” *Id.* at 639 (citations omitted).

The final paragraph of the Safe Harbor jury instructions states:

You must evaluate each of the accused activities separately to determine whether the Safe Harbor applies. If you find that an accused activity was reasonably related to the development and submission of information to the FDA for the purpose of obtaining FDA approval, then Hospira has proved its Safe Harbor defense as to that activity. If Hospira has proved that the manufacture of a particular batch was reasonably related to developing and submitting information to the FDA in order to obtain FDA approval, Hospira's additional underlying purposes for the manufacture and use of that batch do not remove that batch from the Safe Harbor defense.

J.A. 139.

Hospira argues that the final sentence of the instructions improperly focused on Hospira's intent for manufacturing batches of EPO. In Hospira's view, “the jury instructions and verdict form improperly focused the jury on the reasons *why* each batch of EPO was manufactured,

not *how* each batch was used or whether that use was reasonably related to the development and submission of information to support Hospira's BLA." Defendant-Appellant's Br. 45–46. According to Hospira, it only had to prove that the *use* of the patented invention was reasonably related to submission of information to the FDA, not the *manufacture*.

Amgen responds that Hospira's infringing acts were the use of Amgen's patented methods for making Hospira's EPO drug substance. According to Amgen, the jury instructions "properly focused the jury on Hospira's *use* of the patented invention, that is, the manufacture of [Hospira's EPO] drug substance, and then asked whether each act of manufacture was *for* uses reasonably related to seeking FDA approval." Plaintiffs-Cross-Appellants' Br. 37.

The jury instructions properly articulated the legal principles underlying the Safe Harbor inquiry. Section 271(e)(1)'s exemption from infringement "extends to all uses of patented inventions that are reasonably related to the development and submission of any information under the FDCA." *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 202 (2005) (emphasis removed). The statute does not exclude "certain information from the exemption on the basis of the phase of research in which it is developed or the particular submission in which it could be included." *Id.* The exemption applies "as long as there is a reasonable basis for believing" that the use of the patented invention will produce the types of information that are relevant to an FDA submission. *Id.* at 207–08. Moreover, "[e]ach of the accused activities must be evaluated separately to determine whether the exemption applies." *Id.* at 200.

Here, the patented inventions are Amgen's claimed methods of manufacture. The accused activity is Hospira's use of Amgen's claimed methods of manufacture. The relevant inquiry, therefore, is not *how* Hospira used each

batch it manufactured, but whether each act of manufacture was for uses reasonably related to submitting information to the FDA.² The jury instructions properly asked whether each act of manufacture, that is, each accused activity, was for uses reasonably related to submitting information to the FDA. And, contrary to Hospira's contentions, the instructions struck the appropriate balance by telling the jury that Hospira's additional underlying purposes do not matter as long as Hospira proved that the manufacture of any given batch of drug substance was reasonably related to developing information for FDA submission.

In sum, reading the instructions as a whole, we conclude that it was not legal error to instruct the jury that "[i]f Hospira has proved that the manufacture of a particular batch," that is, Hospira's use of Amgen's patented methods, "was reasonably related to developing and submitting information to the FDA . . . Hospira's additional underlying purposes for the manufacture and use of that batch do not remove that batch from the Safe Harbor defense." J.A. 139. Accordingly, we affirm the district court's denial of Hospira's motion for a new trial on Safe Harbor grounds.

We note that Hospira's arguments regarding the district court's denial of JMOL are also predicated on the jury instructions being erroneous. Defendant-Appellant's Br. 57–60. We have considered these arguments and find them unpersuasive.

² To the extent Hospira suggests that the Safe Harbor exemption *always* applies in the pre-approval context, *see* Defendant-Appellant's Br. 45, we have previously rejected that reading of the statute. It is incorrect to "assume[] that all otherwise infringing activities are exempt if conducted during the period before regulatory approval is granted." *Amgen Inc. v. Int'l Trade Comm'n*, 565 F.3d 846, 852 (Fed. Cir. 2009).

ii. The Jury's Findings

Hospira argues that no reasonable jury could have found that some batches of EPO were not protected by the Safe Harbor where, as here, all twenty-one batches were used for the development and submission of information included in the original BLA filing or in a subsequent filing necessitated by a Complete Response Letter (CRL) from the FDA. We review a jury's factual findings for substantial evidence. *Comcast IP Holdings, LLC v. Sprint Commc'ns Co.*, 850 F.3d 1302, 1309 (Fed. Cir. 2017).

At issue are twenty-one batches of EPO Hospira manufactured in 2013, 2014, and 2015. The jury found seven batches were protected under the Safe Harbor, whereas fourteen were not. The protected batches include two batches used for qualifying Hospira's process to make the drug and for qualifying alternate equipment (manufactured in 2013) and five batches used for a mandatory pre-approval inspection by the FDA (manufactured in 2015). For all other batches, the jury found no Safe Harbor protection.

Hospira used the EPO batches at issue for various types of testing, including biosimilarity, revisions to release specifications, stability testing, and continued process verification (CPV). According to Hospira, each type of testing was conducted as part of its BLA submission or its response to the FDA's CRL. For example, Hospira argues, biosimilarity testing is required for FDA approval, yet the jury found that two of the batches used to demonstrate biosimilarity with the reference product were not protected by the Safe Harbor. Defendant-Appellant's Br. 48. Hospira similarly argues that revised release specification testing was required for it to properly respond to the FDA's CRL, and stability testing was required for FDA approval, as was a commitment to make the CPV batches. Therefore, Hospira argues, no reasonable jury could have found that

certain of these batches were not protected by the Safe Harbor.

Substantial evidence supports the jury's finding that the batches at issue were not manufactured "solely for uses reasonably related to the development and submission of information" to the FDA. For example, Amgen's expert, Dr. Martin-Moe, testified that Hospira was not required to manufacture additional batches after it made its 2012 batches. J.A. 1484. She also explained that stability testing of Hospira's 2013 batches was not required but would be part of a "continuing program for stability that is a post-approval commitment." J.A. 1487 at 1333:9–1334:1. She further explained that CPV is an ongoing process that applies to batches made for commercial use. J.A. 1486–89. Hospira's regulatory witness, Ms. Dianis, admitted that CPV is not required before FDA approval. J.A. 1087–88. Further, Hospira's Senior Director of Analytical R&D, Dr. Srebalus-Barnes, admitted that Hospira did not manufacture any drug substance batches in response to the FDA's CRL and the CRL did not require manufacture of additional batches. J.A. 1105. Accordingly, the jury reasonably found that certain batches at issue were not protected under the Safe Harbor.³

Moreover, documentary evidence shows that Hospira planned for "the balance of the material from the 2013 campaign (approximately 50%) and most of the material from the 2014 and 2015 campaigns [to] serve as commercial

³ We also reject Hospira's suggestion that simply submitting information about a drug substance lot to the FDA brings the manufacture of that lot within the Safe Harbor. We have explained that "routine record retention requirements associated with testing and other aspects of the commercial production process" are not protected by the Safe Harbor. *Momenta Pharms., Inc. v. Teva Pharms. USA, Inc.*, 809 F.3d 610, 620–21 (Fed. Cir. 2015).

inventory to support single dose vial launch stock.” J.A. 2392. When it resubmitted its application in late 2015 after litigation began, Hospira changed the designation of certain batches from “commercial inventory” to “CPV.” *Compare* J.A. 2311–13, *with* J.A. 4314–18. Hospira argues that, in denying its motion *in limine* to exclude this evidence, the district court allowed Amgen to taint the entire trial with its “commercial theme.” Defendant-Appellant’s Br. 56. Hospira contends that this “legally irrelevant” evidence was repeatedly put before the jury. *Id.* at 57. We find no reversible error in the district court’s ruling regarding this evidence. Hospira’s decision to manufacture its EPO drug substance “commercial inventory” was not dispositive of the Safe Harbor defense, but Amgen is correct that this evidence was probative of whether Hospira’s use of Amgen’s patented process was reasonably related to seeking FDA approval. Plaintiffs-Cross-Appellants’ Br. 47–48. The fact that the jury found some of the “commercial inventory” batches nonetheless protected by the Safe Harbor defense supports the conclusion that the jury did not reject the defense simply because Hospira made the batches for commercial inventory.

We conclude that the jury’s finding that certain batches of Hospira’s EPO were not protected by the Safe Harbor is supported by substantial evidence. We therefore affirm the district court’s denial of JMOL on Hospira’s Safe Harbor defense.

C. Damages

Finally, Hospira argues that the jury’s damages award should be vacated because the district court erred in denying Hospira’s *Daubert* motion and allowing Amgen’s expert, Dr. Heeb, to testify. We review the district court’s decision to admit expert testimony for abuse of discretion. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). The jury’s determination of the amount of damages is an issue of fact, which we review for substantial evidence. *Lucent*

Techs., Inc. v. Gateway, Inc., 580 F.3d 1301, 1310 (Fed. Cir. 2009) (citations omitted). A jury's damages award "must be upheld unless the amount is grossly excessive or monstrous, clearly not supported by the evidence, or based only on speculation or guesswork." *Id.* (citations omitted).

According to Hospira, the jury's damages award does not reflect a "reasonable royalty." Hospira takes issue both with the amount of the award and its lump-sum structure. Dr. Heeb's opinions, argues Hospira, are erroneously based on the "value of delay" to Hospira, i.e., the profit Hospira could earn if it were in a place to launch its EPO as soon as the patents expired. Hospira contends that this methodology is flawed because it requires Hospira to accept all the risk of the transaction and considers only the benefit to Hospira, not the harm to Amgen. Further, Hospira argues, a lump-sum payment that cannot be clawed back gives Amgen a windfall because at the time of trial, Hospira still had not received FDA approval or sold any EPO. And, Hospira argues, Dr. Heeb did not account for the reality that Amgen does not use the '298 patent to produce Epogen or any other product. According to Hospira, the "book of wisdom" doctrine allows parties to consider after-the-fact events, like Hospira's lack of FDA approval, Amgen not practicing the '298 patent, and the claw-back provision in the only other lump-sum agreement in the evidence.

Amgen contends that the district court did not abuse its discretion by allowing the jury to hear Dr. Heeb's opinions. According to Amgen, Dr. Heeb determined what Hospira would have expected to gain from obtaining a license to manufacture the volume of batches needed to meet its expected product launch date in 2015, before expiration of the '298 patent, and appropriately concluded that the hypothetical negotiators would have been incentivized to obtain the license needed for Hospira's pre-launch manufacture. Amgen also argues that Dr. Heeb's reliance on a lump-sum royalty structure is supported by the evidence in the record in the context of a method of

manufacture patent, where the infringing act is not tied to the sales of the product. And, Amgen contends, Hospira was permitted to present testimony to the jury that Amgen did not use the '298 patent's inventions. According to Amgen, although Hospira appeals the district court's denial of JMOL, Hospira's damages argument is entirely about its *Daubert* challenges to Dr. Heeb's methodology.

We see no reversible error. The district court permitted Hospira to cross-examine Dr. Heeb and to present the testimony of its own damages expert, Dr. Bell. Hospira was permitted to argue at trial that it had not yet received FDA approval, and that the amount of damages should be based on "replacement cost" because Hospira could simply remake the product. J.A. 1881–82; *see also* J.A. 148–51 (instruction stating that the jury "may consider events and facts that occurred after the hypothetical negotiation took place."). Dr. Heeb testified that he considered the appropriate factors in determining a reasonable royalty and placed the timing of the hypothetical negotiation in late 2013, before the act of first infringement. *See* J.A. 778–79; *see also Georgia-Pacific Corp. v. United Plywood Corp.*, 318 F. Supp. 1116 (S.D.N.Y. 1970). He also explained that he considered the gain to Hospira from obtaining a license to manufacture batches to meet its expected 2015 launch date, and the harm to Amgen if it entered a license. J.A. 779–85. Finally, Dr. Heeb explained his reasoning for proposing a lump-sum structure for the royalties, including the fact that in this case, infringement is tied to manufacture and not directly to the sales of the product. J.A. 786. Accordingly, the district court did not abuse its discretion in permitting Dr. Heeb to testify.

In view of Dr. Heeb's testimony, we also find that substantial evidence supports the jury's damages award and see no reason to vacate it. The jury heard Dr. Heeb testify at length and propose a reasonable royalty in the range of between \$154 and \$170 million. J.A. 788. It also heard the testimony of Hospira's expert, Dr. Bell, who proposed a

reasonable royalty in the range of \$4.1 to \$4.6 million per batch. J.A. 1465. In addition, Dr. Heeb explained his reasoning for proposing a lump-sum structure. J.A. 786. As to his proposal of a lump-sum damages amount without a claw-back provision, Dr. Heeb distinguished the claw-back provision in the only other lump-sum agreement in the evidence as a “mutually profitable arrangement” instead of a license from one competitor to another. J.A. 792 at 664:10–665:13. Dr. Heeb further testified that Amgen would not be incentivized to “refund[] [any] royalty” to Hospira because it would not want to offer license terms that would encourage other competitors to infringe its patent. J.A. 792–93 at 665:15–666:3. It was not unreasonable for the jury to choose a damages award within the amounts proposed by each expert. Accordingly, we affirm the district court’s denial of Hospira’s JMOL motion regarding the jury’s damages award.

D. Amgen’s Cross-Appeal

Amgen also asserted infringement of claims 1–7 of the ’349 patent. Claim 1 is the only independent claim of the ’349 patent. It recites:

Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin.

The only disputed issue at trial was whether Hospira’s cells were capable of producing EPO “in excess of 100 U” (claims 1 and 4), “in excess of 500 U” (claims 2 and 5), or “in excess of 1000 U” (claims 3 and 6) of EPO per 10^6 cells in 48 hours, “as determined by radioimmunoassay.” ’349 patent at claims 1–7. The jury found that Hospira does not infringe the asserted claims. The district court denied

Amgen's motion for JMOL that Hospira infringed claims 1–7 of the '349 patent. Amgen appeals.

Amgen argues that, as part of its BLA submission, Hospira reported to “the FDA that its cells were capable of producing EPO ‘in the range of 100 μg per ml [of culture fluid] or higher’ in a 24-hour period,” as measured by the “dot-blot” immunoassay. Plaintiffs-Cross-Appellants’ Br. 68 (citing J.A. 2372). Amgen’s expert testified that the value obtained from Hospira’s dot-blot assay could be converted from $\mu\text{g}/\text{ml}$ to biological units (expressed as Units or U) and Hospira’s cells were capable of producing 3534 U of EPO per 10^6 cells in 48 hours. *Id.* at 68–69 (citing J.A. 757–760). Amgen contends that, instead of presenting expert testimony refuting this evidence of infringement, Hospira argued that the dot-blot assay results were insufficient proof of infringement because that assay used different standards and antibodies than those described in the '349 patent and because that assay could not be used to calculate the specific activity of the unpurified EPO produced by the cells. According to Amgen, Hospira’s failure to offer competing evidence means that no reasonable jury could have concluded that Amgen failed to meet its burden on infringement.

Hospira responds that its expert, Dr. Hamilton, explained in detail why the dot-blot assay results could not be correlated to EPO production rates as determined by radioimmunoassay (RIA). Defendant-Appellant’s Resp. Br. 38. Hospira contends that Dr. Hamilton provided unrebutted testimony that the two tests were not comparable. *Id.* at 41 (citing J.A. 1452–54). Further, Dr. Hamilton testified that the only way $\mu\text{g}/\text{ml}$ could be converted into U was if the EPO was purified out. Hospira argues that Amgen’s experts did not provide any testimony that the dot-blot assay results are similar or comparable to the RIA results. Thus, according to Hospira, the jury’s verdict is supported by substantial evidence. We agree.

The jury was presented with testimony from both experts. Hospira's expert explained that the dot-blot assay results could be an overestimation and articulated several reasons why those results could not be correlated to EPO production rates as determined by RIA. J.A. 1453–54. Amgen's former employee Dr. Egrie, who conducted RIA testing for Amgen, confirmed the need to use the same standard to compare the two tests. J.A. 1455. Substantial evidence thus supports the jury's finding that Amgen did not meet its burden of proving infringement. Accordingly, the district court did not err in denying Amgen's JMOL motion on this issue.

Amgen also argues that the district court erred in denying it a new trial. According to Amgen, during closing arguments, counsel for Hospira used a demonstrative that showed the '349 claim limitation "as determined by [RIA]" as being within a fence of claimed land, while showing a "dot blot" outside the fence, thereby improperly arguing claim construction and influencing the jury. Plaintiffs-Cross-Appellants' Br. 73 (citing J.A. 13632). Hospira responds that its counsel never argued that a dot blot could not be used as a matter of claim construction. According to Hospira, it was well within the district court's discretion to rule on Amgen's objection to Hospira's demonstrative.

We see no error by the district court, which concluded that Hospira's counsel did not argue claim construction to the jury. J.A. 104–05. It was within the district court's discretion to allow the demonstrative at issue and we do not find any abuse of discretion in the district court's denial of a new trial. This is hardly a situation where "a miscarriage of justice would result if the verdict were to stand." *Consol. Rail Corp.*, 926 F.2d at 1352–53. Accordingly, we affirm the district court's denial of a new trial.

III. CONCLUSION

For the foregoing reasons, we affirm the district court's decision denying the parties' respective JMOL motions and

motions in the alternative for a new trial. We have considered the parties' remaining arguments and find them unpersuasive.

AFFIRMED

COSTS

Each party to bear its own costs.