2019-1067, 1102

United States Court of Appeals for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING, LIMITED,

Plaintiffs-Cross-Appellants,

– v. –

HOSPIRA, INC.,

Defendant-Appellant.

On Appeal from the United States District Court for the District of Delaware in No. 1:15-cv-00839-RGA
The Honorable Richard G. Andrews

HOSPIRA, INC.'S PETITION FOR REHEARING EN BANC

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CERTIFICATE OF INTEREST

Counsel for the Defendant-Appellant certifies the following information in compliance with Federal Circuit Rule 47.4:

1. The full name of every party or amicus represented by me is:

   Hospira, Inc.

2. The names of the real parties in interest (if the parties named in the caption are not the real parties in interest) represented by me are:

   None; the parties named in the caption are the real parties in interest.

3. All parent corporations and publicly held companies that own 10 percent or more of the stock of the parties represented by me are:

   Pfizer Inc.

4. The names of all law firms and the partners or associates that appeared for the parties now represented by me in the trial court or are expected to appear in this Court are:

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5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal. *See* Fed. Cir. R. 47.4(a)(5) and 47.5(b).

None.

Dated: January 15, 2020 /s/ Thomas J. Meloro

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FEDERAL CIRCUIT RULE 35(b) STATEMENT

In my professional judgment, en banc review is necessary because the appeal requires an answer to the following precedent-setting question of exceptional importance:

1. Whether 35 U.S.C. § 271(e)(1) provides a safe harbor against infringement of patents claiming a method of manufacture, when the product manufactured is used to generate information for submission to the Food and Drug Administration ("FDA") in order to seek approval of a biosimilar drug.

En banc review also is appropriate because the panel decision is contrary to the following Safe Harbor decision of the Supreme Court of the United States and precedents of the Federal Circuit: *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005); and *AbTox, Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997), *opinion amended on reh'g*, 131 F.3d 1009 (Fed. Cir. 1997).

En banc review also is appropriate because the panel decision is contrary to the following claim construction decisions of the Supreme Court of the United States and precedents of this court: *Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*, 520 U.S. 17 (1997); *United States v. Adams*, 383 U.S. 39 (1966); *Gen. Elec. Co. v. Int'l Trade Comm'n*, 685 F.3d 1034 (Fed. Cir. 2012); *Chef*

America,. Inc. v. Lamb-Weston, Inc., 358 F.3d 1371 (Fed. Cir. 2004); and *Unique Concepts, Inc. v. Brown*, 939 F.2d 1558 (Fed. Cir. 1991).

/s/ Thomas J. Meloro

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INTRODUCTION

This case requires en banc review because the panel misapplied the statutory Safe Harbor provided by 35 U.S.C. § 271(e)(1) as well as Supreme Court and binding precedent of this Court, in a case involving one of the first Biologics License Applications ("BLA") submitted under the Biologics Price Competition and Innovation Act ("BPCIA").

The District Court judgment was affirmed despite a legally erroneous jury instruction which rendered the verdict wholly without merit. The Safe Harbor statute and binding precedent mandate that making an otherwise infringing product is protected if the product is put to uses that are objectively related to development and submission of data for FDA approval. Despite this law, the jury instead was instructed to determine whether Hospira's underlying purpose for the manufacture of its erythropoietin ("EPO") product batches was for FDA approval purposes. Because of the erroneous instruction, the jury found that EPO product batches used for biosimilarity testing, setting required product release specifications, and generating data to respond to a Complete Response Letter ("CRL") from the FDA—all in support of a request for FDA approval—were not covered by the Safe Harbor, even though such uses not only were "reasonably related" to, but actually were required for, FDA approval.

The panel endorsed this erroneous focus on Hospira's underlying purposes for making batches, and ruled that, because the patents-in-suit claim methods of manufacture, subsequent uses that are objectively related to obtaining FDA approval cannot bring the making of the EPO within the Safe Harbor if the manufacture itself was not "required," at the time of manufacture, for seeking FDA approval. *See* Panel Op. at 17. This ruling calls into question the continuing viability of the Safe Harbor, particularly in the context of BPCIA litigation, since the BPCIA permits assertion of method of manufacturing patents. If an act of manufacture infringes regardless of how the product batches produced by the patented method are used, then the statutory protection for "making" a drug is rendered illusory for a large subset of the patents available to be asserted under the BPCIA.

The jury also was instructed to consider whether Hospira infringed claim 27 of United States Patent No. 5,856,298 ("the '298 patent"), using a construction which read out a claim limitation. Claim 27 explicitly incorporates claim 1. But the District Court's claim construction, as put to the jury, ignored the limitation of claim 1 that the individual isoforms be "isolated." The panel endorsed the District Court's flawed construction, and in doing so contravened precedent prohibiting reading limitations out of patent claims.

FACTUAL AND PROCEDURAL BACKGROUND

Hospira filed its BLA in 2014 for a biosimilar to Amgen's Epogen product. Amgen sued on two manufacturing process patents, both of which had expired by the time of trial. The jury found that seven batches of EPO made by Hospira were protected by the Safe Harbor of 35 U.S.C. § 271(e)(1), and that fourteen batches were not. The jury found that claims 24 and 27 of the '298 patent were not invalid and were infringed. Appx117. The jury also found that Hospira did not infringe United States Patent No. 5,756,349 ("the '349 patent"). *Id.* The District Court denied Hospira's renewed motion for judgment as a matter of law ("JMOL"), Hospira filed the instant appeal, and Amgen filed a cross-appeal regarding the '349 patent. A panel of this Court affirmed the District Court judgment, ruling that substantial evidence supported the jury's findings and finding no error in the District Court's application of § 271(e)(1) or its construction of claim 27. Panel Op. at 23–24. Because claim 27 was sufficient to sustain the judgment on the '298 patent, the panel did not address claim 24. *Id.* at 12.

Hospira was one of the first pharmaceutical companies to file a BLA for a biosimilar, and the regulatory landscape was highly uncertain. EPO was Hospira's first biosimilar project and only the second biosimilar application submitted to the FDA. Appx1095(783:9-11). The FDA had not finalized guidance

for the industry (and still has not) and, after repeated meetings with FDA, Hospira was unsure of the amount of testing that would be required. Appx1075(702:7-17).

Amgen asserted infringement against twenty-one batches of EPO. Hospira made and tested all of those batches prior to receiving FDA approval and, as of patent expiry and through trial, none of those batches had been offered for sale or sold. Appx788(648:18-649:22). In fact, Hospira had not even obtained FDA approval as of patent expiry and trial. Appx1079(720:15-18).

Instead, the batches had been used to generate data to support Hospira's BLA submission regarding Process Performance Qualification ("PPQ"), Clinical Trials ("CLIN"), Biosimilarity Testing ("BIO"), Stability Testing ("STAB"), Continued Process Verification ("CPV"), Pre-Approval Inspection ("PAI"), and Revised Release Specifications in response to the CRL ("REV").

The following chart illustrates Hospira's uses of the batches, where shaded batches were found by the jury to be protected by the Safe Harbor:

Batch No.	Mfg. Date	PPQ	CLIN	BIO	STAB	CPV	PAI	REV
410733	Oct. 13, 2013	✓	✓	✓	✓	✓		✓
410740	Nov. 25, 2013	✓		✓	✓	✓		✓
410744	Dec. 9, 2013			✓	✓	✓		✓
410751	Dec. 23, 2013			✓	✓	✓		✓
410753	Feb. 18, 2014					✓		✓
410754	Mar. 17, 2014					✓		✓
410759	Mar. 31, 2014					✓		✓
410762	Apr. 14, 2014					✓		✓
410765	Apr. 28, 2014					✓		✓
410768	May 16, 2014				✓	✓		✓
Hospira BLA Submitted December 16, 2014								
Expiration of the '349 Patent May 26, 2015								
410840	June 25, 2015				✓	✓		✓
410844	July 15, 2015					✓		✓
410845	July 23, 2015					✓	✓	✓
410846	July 29, 2015					✓	✓	✓
410847	Aug. 3, 2015					✓	✓	✓
410848	Aug. 11, 2015					✓	✓	✓
410849	Aug. 19, 2015					✓	✓	✓
410850	Aug. 25, 2015					✓		✓
410851	Sept. 1, 2015					✓		✓
410852	Sept. 7, 2015					✓		✓
410853P	Sept. 15, 2015				✓	✓		✓
Hospira Response to CRL Submitted December 22, 2016								
Expiration of the '298 Patent January 5, 2016								

Op. Br. at 13.

Amgen's FDA expert, Dr. Martin-Moe, admitted that Hospira used data from all of its EPO batches to respond to the CRL, including revising the required product specifications. Appx1840(1478:8-1479:16). She also confirmed that Hospira could not receive approval if the FDA did not approve Hospira's product specifications. Appx1840(1477:5-1478:7).

Hospira's Director of Global Regulatory Affairs testified that if Hospira did not already have the accused batches, Hospira would have had to make them to respond to the FDA's demand for additional information and data in the CRL. Appx1078-1079(716:14-717:6).

Rather than focusing on Hospira's actual uses of the product, the District Court and Amgen focused the jury on Hospira's purported underlying purposes in making the batches. The jury was instructed that "[i]f 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." Appx139. Amgen asserted that many of the batches of EPO were made for "Commercial Inventory," as shown in a table in Hospira's original BLA submission, although that same table listed additional uses, such as biosimilarity testing, for some of these batches. Hospira eventually used all of the accused batches to generate information which was required to support its application for FDA approval. Op. Br. at 13.

The '298 patent is directed to preparing "an isolated . . . isoform" of EPO and using that *isolated* isoform alone or in a mixture with other isolated isoforms to produce an EPO product with a specific activity. Appx2162(3:15-20).

The District Court construed "isoform" 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)." Appx159-160. The District Court further construed "*an isolated . . . isoform*" in claim 1 to mean "only one isoform" because a construction that encompassed mixtures "would render the word 'isolated' superfluous." Appx190. Nevertheless, it instructed the jury that "[c]laim 27 does not require the individual isoforms of Claim 1 to be separately prepared prior to making the mixture." Appx163. That sentence contravened the requirement that each isoform be "isolated" as required in claim 1.

ARGUMENT

I. THE PANEL'S FOCUS ON THE UNDERLYING PURPOSE FOR MANUFACTURING CERTAIN BATCHES, RATHER THAN THE USES OF THE PRODUCT THAT WERE OBJECTIVELY RELATED TO SEEKING FDA APPROVAL, CONTRADICTED CONTROLLING CASE LAW.

This appeal is from the first jury trial to assess the Safe Harbor for a proposed biosimilar drug under the BPCIA. Because Hospira's BLA was one of the first submitted under this new framework, Hospira's EPO project took place against a backdrop of significant regulatory uncertainty.

A. Precedent Mandates that the Safe Harbor Provides Broad Protection to Make a Product if its Uses Are Objectively Related to FDA Submissions.

The panel erred by ignoring the broad, objective nature of the Safe Harbor. The Supreme Court has held that:

> [Congress] exempted from infringement *all* uses of patented compounds 'reasonably related' to the process of developing information for submission under *any* federal law regulating the manufacture, use, or distribution of drugs.

Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193, 206 (2005) (emphasis in original). It further stated that "the use of patented compounds . . . is protected under § 271(e)(1) as long as there is a reasonable basis for believing that [such use] will produce 'the types of information that are relevant to an IND or NDA,'" regardless of whether such data is ultimately submitted to the FDA. *Id.* at 208 (quoting *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), *aff'd* 991 F.2d 808 (Fed. Cir. 1993)). This is especially true because "it will not always be clear to parties setting out to seek FDA approval for their new product exactly which kinds of information, and in what quantities, it will take to win that agency's approval." *Id.* at 207.

Even before *Merck*, this Court has long recognized the objective nature of the inquiry under § 271(e)(1), holding that:

> The statute, therefore, does not look to the *underlying purposes* or attendant consequences of the activity . . . as

> long as the *use* is reasonably related to FDA approval . . . . As long as the activity is reasonably related to obtaining FDA approval, [the accused infringer's] *intent or alternative uses are irrelevant* to its qualification to invoke the section 271(e)(1) shield.

AbTox, Inc. v. Exitron Corp., 122 F.3d 1019, 1030 (Fed. Cir. 1997), *opinion amended on reh'g*, 131 F.3d 1009 (Fed. Cir. 1997) (emphasis added). *AbTox* eschews underlying purposes for activities in favor of determining whether the uses were reasonably related to the submission of information to the FDA, and has been followed for over two decades in both this Court and District Courts. *See, e.g.*, *Integra Lifesciences I, Ltd. v. Merck KGaA*, 496 F.3d 1334, 1347 (Fed. Cir. 2007); *Med. Diagnostic Labs., L.L.C. v. Protagonist Therapeutics, Inc.*, 298 F. Supp. 3d 1241, 1250-51 (N.D. Cal. 2018); *Nexell Therapeutics, Inc. v. AmCell Corp.*, 143 F. Supp. 2d 407, 421 (D. Del. 2001); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 107 (D. Mass. 1998).

B. The Panel Ignored this Binding Precedent and Focused Instead on Hospira's Underlying Purpose for Manufacturing the Accused Batches.

The panel's decision upends this settled precedent by asserting that "[t]he 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." Panel Op. at 14-15 (emphasis in original); *contra Merck*, 545 U.S. at 206-08; *AbTox*, 122 F.3d at 1030.

The panel's focus on Hospira's underlying purposes for each act of manufacture ignores the Supreme Court's admonition that "all uses" reasonably related to FDA approval are exempted, particularly because applicants will not always know the precise kind or quantity of information that will be needed for FDA approval. *Merck*, 545 U.S. at 207. This is especially true here because this was one of the first cases litigated under the BPCIA and the FDA had only issued limited draft guidance for the requirements for approval of a BLA. Appx1092(770:21-771:8); Appx1095(783:9-11). The regulatory uncertainty only increased after Hospira received a CRL. Even by the time of trial in this matter, Hospira still did not have FDA approval. Appx1079(720:15-18).

Merck makes clear that the Safe Harbor is much broader than information *required* for approval, "exempt[ing] from infringement *all* uses of patented compounds 'reasonably related' to the process of developing information for submission under *any* federal law regulating the manufacture, use, or distribution of drugs," 545 U.S. at 206 (emphasis in original), "as long as there is a reasonable basis for believing that the [activities] will produce the types of information that are relevant to an" FDA submission, *id.* at 208. This broad scope acknowledges that it is not reasonable to expect an FDA applicant to submit the minimum amount of data required. Forcing a BLA applicant to cut it too close lest it risk losing Safe Harbor protections frustrates the regulatory system by risking

either giving the FDA less information than it deserves and/or needlessly prolonging the review process if FDA finds the initially submitted data to be insufficient. Constricting the Safe Harbor irrationally promotes such undesired results.

Here, the facts are much stronger than the attenuated activities endorsed by *Merck* as falling within the Safe Harbor. The accused batches actually were all used to generate data submitted to the FDA that was required for FDA approval. Appx1840(1477:5-1479:16). Under a correct jury instruction, properly focused on Hospira's uses of its product, no reasonable jury could have found that any of the accused batches fell outside the Safe Harbor. For example, data from testing of two batches that were found to be outside the Safe Harbor were part of Hospira's biosimilarity testing program, and data from every accused batch was used to revise release specifications in response to the CRL. Op. Br. at 13. Not only were these uses "reasonably related" to submission of data to the FDA, Amgen's own expert admitted that the FDA would not approve Hospira's BLA without such data. Appx1840(1477:5-1479:16).

II. THE COURT SHOULD GRANT REHEARING EN BANC TO DECIDE AN EXCEPTIONALLY IMPORTANT QUESTION OF FIRST IMPRESSION REGARDING THE SCOPE OF THE § 271(e)(1) SAFE HARBOR AS APPLIED TO METHOD OF MANUFACTURE PATENTS UNDER THE BPCIA.

Crucially, this appears to be the first litigation in which this Court specifically has considered the applicability of the Safe Harbor to patents claiming a method of manufacture.

The Safe Harbor provision of 35 U.S.C. § 271(e)(1) states:

> 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 . . . 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).

The Safe Harbor was introduced in the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Act"). *See* Hatch-Waxman Act, § 202, 98 Stat. 1585 (1984). The FDA's Hatch-Waxman regulations, applicable to so-called "small molecule" drug products, require New Drug Application ("NDA") holders to list any patents claiming the drug's active ingredient or uses thereof in the FDA's list of Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), 21 C.F.R. § 214.53(b)(1). These same regulations, however, explicitly state that "[p]rocess

patents . . . and information on these patents must not be submitted to FDA." *Id.* Thus, there appear to have been no Hatch-Waxman cases testing the applicability of the Safe Harbor to patents claiming methods of manufacture.

Unlike Hatch-Waxman, the BPCIA permits the inclusion of process patents in biosimilar patent litigation brought under that act. *See* 42 U.S.C. § 262(*l*)(3)(A)(i). In fact, in addition to being the only "type" of patent asserted in this litigation, manufacturing process patents have constituted a significant proportion of the patents asserted in BPCIA cases to date. For example, over 60 percent of the patents asserted by Genentech, Inc. in its BPCIA cases related to its bevacizumab and trastuzumab biologic products are manufacturing process patents. *See, e.g.*, Complaint at 15-19, *Genentech, Inc. v. Amgen Inc.*, No. 18-cv-924 (D. Del. June 21, 2018), ECF No. 2; Complaint at 9-10, *Genentech, Inc. v. Amgen Inc.*, No. 17-cv-1407 (D. Del. Oct. 17, 2017), ECF No. 19.

The panel here erred in a manner which threatens to eviscerate the protections Congress intended to provide under the Safe Harbor, particularly in the BPCIA context. By stating that for manufacturing process patents "[t]he 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," Panel Op. at 14-15 (emphasis in original), the panel has replaced the well-established test regarding uses of a patented product with an inquiry into the

underlying purposes for why each batch was manufactured. There is no justification for this departure.

There should not be different rules for the Safe Harbor depending on the format of the patent claim. This Court should resolve this issue en banc to provide certainty, particularly given the proliferation of manufacturing process patent disputes already occurring under the BPCIA.

III. THE PANEL DECISION READS A CLAIM LIMITATION OUT OF CLAIM 27 IN CONTRAVENTION OF BEDROCK PRINCIPLES OF PATENT LAW.

The Supreme Court has made clear that "[e]ach element contained in a patent claim is deemed material in defining the scope of the patented invention." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29 (1997). This Court has similarly held that "[a]ll the limitations of a claim must be considered meaningful." *Unique Concepts, Inc. v. Brown*, 939 F.2d 1558, 1562 (Fed. Cir. 1991) (citing *Perkin-Elmer Corp. v. Westinghouse Elec. Corp.*, 822 F.2d 1528, 1532-33 (Fed. Cir. 1987)).

Similarly, the Supreme Court has held that while "claims are to be construed in the light of the specifications," it is "the claims . . . [that] limit the invention, and specifications cannot be utilized to expand the patent monopoly." *United States v. Adams*, 383 U.S. 39, 48-49 (1966); *see also SanDisk Corp. v. Kingston Tech. Co.*, 695 F.3d 1348, 1368 (Fed. Cir. 2012) (Reyna, J., dissenting)

(faulting majority's claim construction that "improperly ignores express limitations of the claims and uses the specification to broaden the patent"). This Court has also held that "a possibly broader disclosure accompanied by an explicit narrow claim shows the inventor's selection of the narrow claim." *Gen. Elec. Co. v. Int'l Trade Comm'n*, 685 F.3d 1034, 1041 (Fed. Cir. 2012).

Finally, this Court "repeatedly and consistently has recognized that courts may not redraft claims," and must "construe the claim as written, not as the patentees wish they had written it." *Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004). The panel's decision in this appeal must be reversed because its construction of claim 27 of the '298 patent violates all three of these principles.

First, claim 27 requires preparing mixtures of "two or more isoforms of claim 1," and the District Court construed "an isolated . . .isoform" in claim 1 to mean "only one isoform" because a construction that encompassed mixtures "would render the word 'isolated' superfluous." Appx190. The "isoforms of claim 1" referenced in claim 27 therefore *must* be "isolated . . . isoform[s]," which in turn must be singular.

The panel, however, read the element "isolated" out of the claim entirely by stating that "[n]othing in the claim language or the specification suggests that it would be proper to limit claim 27" to mixing together the isolated

isoforms of claim 1. Panel Op. at 7. It reaches this conclusion based solely on two brief references in the specification to "isolating selected erythropoietin isoforms simultaneously" and preparing mixtures of isoforms "by techniques such as ion exchange chromatography." *Id.* at 8.

This approach flouts the precedent cited above. In reaching this conclusion, the panel has not only read the singular "an isolated . . . isoform" out of claim 1 (and by reference out of claim 27), but it has done so by using the specification to expand Amgen's patent exclusivity and ignoring this Court's admonition that a broader disclosure paired with a narrow claim shows the inventor's selection of the narrow claim. *Gen. Elec. Co.*, 685 F.3d at 1041. The panel has therefore done what precedent explicitly forbids: redrafted claim 27 "as the patentees wish they had written it" rather than as it was actually written. *Chef America, Inc.*, 358 F.3d at 1374.

CONCLUSION

For the foregoing reasons, Hospira respectfully requests that this Court grant this petition for rehearing en banc.

Dated: January 15, 2020

Respectfully submitted,

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ADDENDUM

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 noninfringement 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/μg. 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.

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[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.

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[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 preapproval 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

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[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 μg/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 μg/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.

CERTIFICATE OF COMPLIANCE

This petition complies with the type-volume limitation of Federal Rule of Appellate Procedure 35(b)(2)(A). This petition contains 3733 words, excluding the parts of the petition exempted by Federal Circuit Rule 35(c)(2).

This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2013 in 14-point Times New Roman font.

_____/s/ Thomas J. Meloro_____
Thomas J. Meloro

PROOF OF SERVICE

I hereby certify that I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the appellate CM/ECF system on January 15, 2020.

I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the appellate CM/ECF system.

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