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

CORRECTED BRIEF FOR DEFENDANT-APPELLANT HOSPIRA, INC.

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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: December 13, 2018

/s/ Thomas J. Meloro

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TABLE OF ABBREVIATIONS

Term	Definition
Amgen	Plaintiffs-Cross-Appellants Amgen Inc. and Amgen Manufacturing, Limited
Hospira	Defendant-Appellant Hospira, Inc.
the ’298 patent	U.S. Patent No. 5,856,298 (Appx2146-2172)
the ’349 patent	U.S. Patent No. 5,756,349 (Appx2081-2145)
Lai	U.S. Patent No. 4,667,016 (Appx2491-2496)
BLA	Biologics License Application
BPCIA	Biologics Price Competition and Innovation Act
CRL	Complete Response Letter
ODP	Obviousness-Type Double Patenting
CZE	Capillary Zone Electrophoresis
EPO	erythropoietin
FDA	U.S. Food & Drug Administration
GSK	GlaxoSmithKline
JMOL	Judgment as a Matter of Law
NPV	Net Present Value
Vifor Agreement	Exclusive Distribution and Supply Agreement Between Hospira and Vifor International Ltd.

STATEMENT OF RELATED CASES

Interlocutory Appeal No. 16-2179 was filed by Amgen and dismissed on August 10, 2017 in a decision by Judge Dyk.

JURISDICTIONAL STATEMENT

Subject matter jurisdiction in the District Court was based on 28 U.S.C. §§ 1331 and 1338(a). The District Court issued a Final Judgment on September 11, 2018 that disposed of all claims. Appx26-30.

Hospira filed a Notice of Appeal on October 3, 2018. Appx13633-13634. Amgen filed a Notice of Cross Appeal on October 15, 2018. Appx13635-13636. This appeal is timely pursuant to 28 U.S.C. § 2107 and Federal Rule of Appellate Procedure 4(a). Appellate jurisdiction is proper under 28 U.S.C. § 1295(a)(1), and the judgment appealed from is final.

STATEMENT OF THE ISSUES PRESENTED

I. Whether the district court erred in construing claims 24 and 27 of the ’298 patent in an overly broad way that conflicts with the intrinsic evidence?

II. Whether any reasonable jury could find infringement under the proper construction of claim 24 (which requires only one isoform) and claim 27 (which requires mixtures of isolated isoforms), where Hospira’s EPO product contains multiple isoforms that are never isolated?

III. Whether any reasonable jury could properly find validity of claims 24 and 27 under the district court’s erroneous construction, which is so broad that it encompasses the prior art?

IV. Whether the district court erred in instructing the jury on the Safe Harbor of 35 U.S.C. § 271(e)(1) by improperly focusing on Hospira’s subjective intent for manufacturing batches of EPO, rather than the objectively reasonable uses of the batches for the development and submission of information to support Hospira’s BLA filing?

V. Whether any reasonable jury could find that the 21 batches of EPO made by Hospira were not covered by the Safe Harbor even though they were all used for the development and submission of information in Hospira’s original BLA filing and/or in direct response to an FDA CRL?

VI. Whether the district court erred in allowing the jury to consider a damages position from Plaintiffs' expert that was legally flawed because it goes well beyond what was adequate to compensate for the infringement under 35 U.S.C. § 284 and was not tied to any damages suffered by Amgen, but sought $170 million in damages for two expired patents, although Hospira had made no sales?

VII. Whether, for any or all of the issues above, the district court improperly denied Hospira's motion for JMOL or a new trial, and thus Hospira is entitled to JMOL or a new trial?

STATEMENT OF THE CASE

This case involves one of the first BLAs submitted under the BPCIA. Hospira filed its BLA in 2014 for a biosimilar to Amgen's Epogen product. Epogen has been on the market with patent protection since 1989, and the two patents asserted in this case expired well before Hospira's BLA was approved. The '349 patent related to cells that produce EPO and expired on May 26, 2015; the '298 patent related to isoforms of EPO and expired on January 5, 2016. The jury found that Hospira did not infringe the '349 patent, but that the '298 patent was valid and infringed. Appx117. 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 14 were not. The jury awarded damages of $70 million, which is a pure windfall for Amgen, who suffered no harm from the alleged infringement.

For the '298 patent, the jury was asked to consider whether Hospira infringed claims 24 and 27. Claim 24 suffered from multiple claim construction errors. First, the construction was at odds with the Markush wording of the claim and the prosecution history. Second, the construction read out the term "predetermined" from the claim. Under this erroneous construction, the jury could (and in fact did) find that Hospira infringed so long as it had any mixture of EPO isoforms obtained using ion exchange chromatography. Under the correct construction, no reasonable jury could have found infringement because claim 24

is limited to one isoform that must be predetermined based on the number of sialic acids it contains, whereas Hospira's biosimilar has multiple isoforms that are not predetermined. Even under the district court's construction, there was insufficient evidence to show that Hospira "selectively eluted" isoforms simply because it uses ion exchange chromatography. Also, a claim read so broadly as to encompass eluting any mixture of active EPO isoforms would be anticipated by the very prior art from which the applicant distinguished the '298 patent during prosecution.

The second asserted claim, 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 isoforms be "isolated." In fact, the jury was asked to find that Hospira infringed claim 27 without hearing any evidence of whether the limitations of claim 1 were met by Hospira's process. In addition, under the district court's broad construction, no reasonable jury could find that claim 27 was valid over the prior art.

On the Safe Harbor, the jury was asked to answer the wrong question. Binding precedent says that making, using, or selling an otherwise infringing product is protected if it is put to uses that are objectively related to obtaining FDA approval. Despite this case law, the jury was asked whether the subjective intent behind the manufacture of Hospira's EPO was for FDA approval. Amgen used this as an opportunity to focus the trial on Hospira's alleged commercial purpose

for making the EPO, even though that is statutorily irrelevant. In particular, Amgen repeatedly focused the jury on "Risk Authorization" documents that allegedly showed Hospira's "commercial" intent in manufacturing EPO. Not only is that irrelevant, the author testified that those documents did not designate how the EPO would be used. Although Hospira moved to preclude these documents, they were admitted into evidence. Because of the erroneous Safe Harbor instructions and improper admission of this evidence, the jury found that batches used for biosimilarity testing, updating release specifications, and generating data to respond to a CRL were not covered by the Safe Harbor, even though such uses were not only reasonably related to, but were, in fact, necessary for approval.

Finally, the jury was allowed to hear a damages theory that flouted the statutory requirement that damages be "adequate to compensate for the infringement." 35 U.S.C. § 284. Amgen's expert opined that Hospira could have gained $154 million if it was able to launch as soon as Amgen's patents expired by making EPO during the life of the patents rather than delaying until expiration. Amgen's expert did not consider the contingency that Hospira might not get approval and launch early at all, which is what happened in the real world. By focusing on the potential benefit to Hospira (which never materialized) instead of the harm to Amgen, his framework goes beyond making the patentee whole. Here, Amgen suffered no damages yet obtained an improper windfall of $70 million.

STATEMENT OF FACTS

I. FACTS RELATED TO THE ’298 PATENT.

The ’298 patent is directed to isolating an 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.

Dr. Strickland, named inventor on the ’298 patent, explained that he isolated isoforms so that he could determine their biological activity. Appx717(362:8-15); Appx718(369:16-23). The ’298 patent process allowed Dr. Strickland to separate isoforms and then “recombine” them or “mix those fractions back together” to make EPO compositions with a tailored biological activity. Appx720(375:23-376:2); Appx720(377:12-18).

Dr. Strickland testified that the only “real-world” application of the ’298 patent was the “EPO II” project. Appx720(376:3-10); Appx722(382:21-383:2). The primary goal of this project was to design around another company’s patent by making EPO with a predetermined activity that was lower than the commercial product on the market. Appx723-724(388:13-390:11). EPO II was

going to contain a "subset of the active ingredients present in the currently licensed product," namely isoforms 9 to 11 instead of isoforms 9 to 14. Appx721(379:17-380:11). Amgen never finalized its FDA submission for EPO II. Appx722(383:4-6); Appx724(390:12-20).

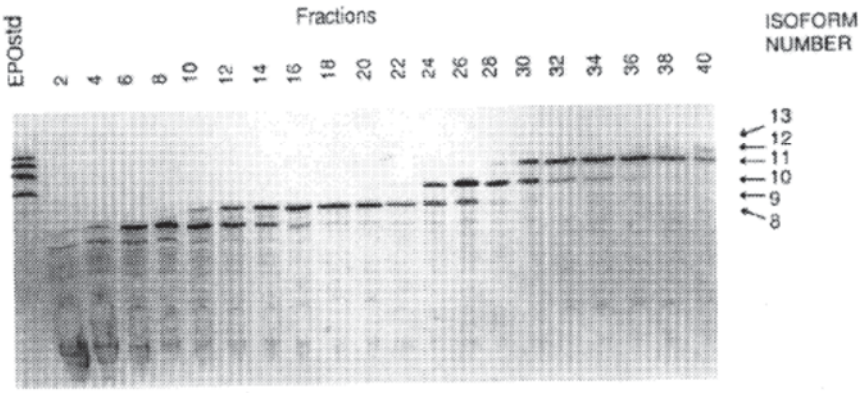
Amgen does not practice the '298 patent for any commercial product. Appx723(386:12-20). In fact, although Epogen has been covered by patents since 1989, Amgen told investors that the last material Epogen patent expired in 2015, with the Lin '349 patent. Appx438-439(220:13-222:12). The purification process for Epogen, the reference product for Hospira's BLA, is based on a purification process disclosed in a prior art patent, Lai. Appx723(386:4-11).

The '298 patent distinguishes its isoform separation process from the process of Lai. Appx722(385:13-386:3). The stated goal of Lai is to use chromatographic procedures that allow for high yields of biologically active EPO. Appx2491; Appx727(403:21-404:7). First, crude EPO material is applied to an ion exchange column. Appx2494(5:20-22); Appx728(406:7-18). A low-pH wash is then applied to the column that removes all materials with a pKa greater than EPO. Appx2494(5:22-31); Appx728(406:19-407:9). Dr. Strickland, a co-inventor of Lai, confirmed that this low-pH wash removes basic isoforms, those below isoform nine, along with other contaminants. Appx728(409:5-13). Next, a high-salt wash elutes the remaining higher-activity EPO. Appx2494(5:34-35); Appx728(409:19-

410:4). It is undisputed that Lai results in a mixture of isoforms, although the term "isoforms" is not used in Lai. Dr. Strickland confirmed that isoforms with 9 to 14 sialic acids are obtained from Example 2 of Lai, and that those are the same isoforms present in Epogen. Appx724(393:14-394:7); Appx729(412:5-13). Varying amounts of those same isoforms are also present in Hospira's product.

The mixture of isoforms resulting from Lai's purification process is used as the comparator in the '298 patent. Appx2164-2165(8:65-9:9); Appx2166(12:55-59); Appx725(396:7-12). For example, in Figure 4, the far left lane shows the "EPOstd" which is "a mixture of isoforms obtained using procedures described in Example 2 of Lai." Appx2162(4:17-22). This is compared to the separation of isoforms 8 through 11 that may be achieved using the methods disclosed in the '298 patent. Appx2168(15:2-4).

FIG. 4



Appx2153.

Amgen alleges that Hospira's purification process infringes claims 24 and 27. However, it is undisputed that Hospira is seeking to make its product biosimilar to Epogen, which, as discussed above, does not practice the '298 patent. Appx1094(778:1-18); Appx724(390:15-20).

Dr. Billingham, Hospira's Director of Manufacturing Science and Technology, testified that Hospira's purification procedure was designed to wash away impurities and collect the EPO that is left. Appx1109(840:1-16); Appx4894; Appx4947-4948. Hospira first applies the crude EPO to an ion exchange column. Appx743(466:13-467:1); Appx750(494:14-21). The column is then washed with an acidic wash to remove impurities and basic isoforms from the column. Appx743(467:5-17). Next, a high-salt wash elutes the more sialylated EPO isoforms. Appx743(467:18-468:6).

Hospira's final EPO drug substance may contain between five and eight isoforms, as shown in Hospira's BLA (Appx4311-4353):

Epoetin Hospira Injection
Module 3: Quality
3.2.S.4.4 Batch Analyses

Hospira

Test	Initial IND 16 Dec 2009 (Serial # 000)	IND Amendment 19 Feb 2010 (Serial # 005)	IND Annual Report 27 Jun 2012 (Serial # 028)	IND Annual Report 30 Jun 2014 (Serial # 089)		IND Amendment Nov 2014 (Serial # 109)	Original BLA Submission 16 Dec 2014 (STN 125545/0)	BLA Amendment 9 Jul 2015 (STN 125545/29)		Proposed Commercial Specification (*Section 3.2.S.4.1, Specification*)
Lots Released Against Each Specification	410340 410344	None	410632 410637 410638	410733 410740 410744 410751 410753	410754 410759 410762 410765 410768	None	None	410844 410845 410840 410846 410847 410848	410849 410850 410851 410852 410853P	No additional lots manufactured
Isoform Distribution (CZE)										
Isoform 1	0 – 2%	No change	No change	No change		No change	0 – 2%	No change		0 – 1%
Isoform 2	0 – 4%						0 – 4%			0 – 3%
Isoform 3	8 – 17%						4 – 19%			6 – 18%
Isoform 4	19 – 34%						16 – 35%			18 – 32%
Isoform 5	24 – 32%						26 – 32%			26 – 32%
Isoform 6	15 – 30%						12 – 33%			16 – 31%
Isoform 7	5 – 12%						3 – 15%			4 – 15%
Isoform 8	0 – 4%						0 – 4%			0 – 3%

Appx4325. As the table shows, Hospira's biosimilar can have varying amounts of what Hospira calls "Isoforms 1 to 8," with Isoform 1 having eight sialic acids, Isoform 2 having nine sialic acids, and so on. Appx4325; Appx748-749(489:20-491:22). Amgen's expert, Dr. Cummings, does not dispute that Hospira's product must always have Isoforms 3 to 7, but may or may not have Isoforms 1, 2, and 8. Appx749(491:23-493:17).

II. FACTS RELATED TO THE SAFE HARBOR.

Hospira was one of the first drug companies to file a BLA, and the regulatory landscape was very uncertain. Dr. Srebalus-Barnes, Hospira's Senior Director of Analytical R&D, stated that EPO was the first biosimilar project at Hospira and only the second application submitted to FDA. Appx1095(783:9-11).

When she started on the project in 2012, FDA had just issued *draft*, not final, guidances for biosimilarity that only contained high-level FDA expectations. Appx1092(770:21-771:8).

Ms. Dianis, Hospira's Director of Regulatory Affairs, confirmed that FDA had established very few rules for the development of biosimilars. Appx1073(694:9-695:1). For example, in her past experience, the introductory information in Section 2.2 of a BLA was usually a couple of pages. Appx1074(697:3-18). However, because Hospira had to pull together the "totality of evidence" for FDA, they put a "roadmap" in Section 2.2. Appx1074(697:19-698:15); Appx4590-4617 at Appx4595. Hospira's Section 2.2, summarizing only the data required under the statute, spanned more than ten pages. Appx1074(700:6-15). A team of fifty scientists performed the testing described in the roadmap. Appx1074(699:4-700:5). Even after repeated meetings with FDA, Hospira was never sure what the rules were going to be or whether FDA would require additional testing. Appx1075(702:7-17).

Hospira filed its BLA on December 16, 2014 and received a CRL on October 16, 2015. Appx2497-2502; Appx4803-4825. Hospira's response to the CRL was filed on December 22, 2016. Appx1079(720:8-14); Appx3705-3780; Appx4826-4885. Hospira's biosimilar did not receive FDA approval until May 2018.

Amgen asserted infringement of twenty-one batches of EPO. All of those batches were manufactured prior to receiving FDA approval and, at the time of trial, none of these 21 batches had been sold. Appx788(649:16-22). Instead, they had been used to generate data to support Hospira's BLA submission. 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								

Appx4315-4316; Appx4319-4347; Appx3721-3722; Appx3725-3728; Appx4475-4589 at Appx4501; Appx4521-4522; Appx4526-4589; Appx1097(792:6-796:14);

Appx1837(1466:7-24); Appx1837-1838(1468:4-1469:1); Appx1840(1477:5-1479:16); Appx1840(1479:17-1482:10).

Process Performance Qualification (PPQ): Hospira used two 2013 batches for PPQ, one for qualifying its process to make the drug product and one to qualify alternate equipment. Appx1130-1131(924:2-925:12). One of those batches was used to make drug product for three clinical trials (CLIN). Appx1110(842:9-843:17). The jury found that the PPQ batches were protected by the Safe Harbor. Appx112-116 at Appx114.

Biosimilarity (BIO): Hospira used all 2013 batches to assess biosimilarity. Appx1128(913:19-914:4); Appx1837(1465:15-24). It is undisputed that biosimilarity testing is necessary for approval. Appx1837(1465:23-1466:14). However, the jury determined that two of the batches were not protected by the Safe Harbor. Appx114.

Stability Testing (STAB): Hospira submitted stability data from all of the 2013 batches in its BLA and three of the 2014-2015 batches in its December 2016 response to the CRL. Appx1097(791:8-792:5). It is undisputed that FDA requires stability testing. Appx1838(1469:6-18). However, the jury determined that five of these seven batches were not protected by the Safe Harbor. Appx114.

Continued Process Verification (CPV): Hospira used all twenty-one EPO batches in its CPV program. Appx1118(873:14-874:5). It is undisputed that FDA requires a CPV program to be in place to get approval. Appx1839(1475:13-23). Hospira committed to manufacture and analyze thirty CPV batches to identify statistically significant sources of variability in the production process. Appx1114(857:8-859:19); Appx1839(1475:1-20). Hospira still had not produced thirty batches as of January 2016. Appx1839-1840(1476:21-1477:1). However, the jury found that none of the CPV batches were protected by the Safe Harbor, except for the batches that were also used for PPQ and PAI. Appx114.

Pre-Approval Inspection (PAI): Hospira engaged in a 2015 manufacturing campaign to ensure that it was in active manufacturing during FDA's PAI of its facilities. Appx1115-1116(864:3-865:10). Hospira had to reserve space at the manufacturer, GSK, twelve months in advance because it did not know when FDA would perform its inspection. Appx1116(866:18-867:22). According to Dr. Billingham, five EPO batches were manufactured during the PAI in July 2015. Appx1115(864:15-22); Appx1118(874:17-23); Appx4315-4316. The jury found that these batches were protected by the Safe Harbor. Appx114.

Revised Release Specifications (REV): Hospira received a CRL on October 16, 2015, in which FDA asked for numerous tests and answers to many questions. Appx4803-4825; Appx1077(712:8-718:2). Hospira updated its release

specifications and submitted other data in response to the CRL. Appx3705-3780; Appx4826-4885. In fact, Hospira specifically responded to FDA's request to tighten its release specifications. Appx3705.

Amgen's FDA expert, Dr. Sheryl Martin-Moe, admitted that Hospira used data from all of its EPO batches to respond to the CRL, including tightening its commercial release and stability specifications. Appx1840(1478:8-1479:16). She also confirmed that Hospira could not receive approval if FDA did not approve its revised release specifications. Appx1840(1477:5-1478:7). Dr. Srebalus-Barnes testified that if Hospira did not have these batches, Hospira would have had to make them to answer the CRL. Appx1078-1079(716:14-717:6). However, the jury found that none of these batches were protected by the Safe Harbor, except for the batches that were also used for PPQ and PAI. Appx114.

Amgen's "Commercial Inventory" Arguments: Rather than focusing on uses, Amgen focused the jury on Hospira's subjective intent in making the batches. 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. At that time, some of the batches labeled "Commercial Inventory" listed other uses, such as PPQ or CLIN. Appx2311. After Hospira submitted an amendment, it changed the use of the batches to CPV to reflect actual uses of the materials. Appx1099-1100(800:7-801:9).

Amgen also introduced Risk Authorization documents that had been signed by Hospira executives allocating the cost to manufacture the EPO. Appx770(575:8-15). As Mr. Noffke, the author of the documents, explained, the Risk Authorization is "a mechanism within Hospira for allocating costs associated with manufacturing before a product is commercially approved." Appx768-769(569:23-570:4). The cost allocation was *not* a designation of how the material would be used. Appx767(562:5-17). Hospira filed a motion *in limine* to preclude these documents, which was improperly denied. Appx196-201 at Appx200-201.

III. FACTS RELATED TO DAMAGES.

Hospira's economic expert, Dr. Bell, addressed a reasonable royalty. If Hospira's product had never been approved or Hospira was never able to sell the EPO it had made, there would be no economic harm to Amgen and no damages. Appx1464(1239:2-6). Also, Hospira could have waited to make EPO until the '298 patent expired in January 2016 and not owed Amgen anything. Appx1465(1244:9-24). He acknowledged that Hospira may benefit from not having to throw its EPO away and make it again. Appx1465(1243:9-1244:8). Taking these factors into account, a reasonable royalty would be $1.5 million per batch, if sold. Appx1463-1464(1237:20-1239:16); Appx1471(1267:11-1268:16).

Amgen's damages expert, Dr. Heeb, opined that a reasonable royalty would be a up-front, lump-sum payment. Appx170. Hospira filed a *Daubert*

motion to preclude his testimony because it sought lost profits in the guise of a reasonable royalty. Appx7856-7858. Although the district court precluded portions of Dr. Heeb's testimony, he was allowed to testify that the royalty should be an up-front, lump-sum of $170.4 million. Appx164-172 at Appx172; Appx161; Appx776(601:10-20).

Dr. Heeb analyzed the hypothetical negotiation by looking at the alleged delay in Hospira's product launch if it did not have a license. Appx777(602:2-24). He testified that the maximum amount Hospira would have been willing to pay for a license was $154 million. Appx784(631:12-22). He calculated this by comparing Hospira's estimated income *with* a license to Hospira's estimated income *without* a license. Appx784(633:4-14). Dr. Heeb then testified that the minimum payment Amgen would have accepted for a license was $170 million. Appx785(636:2-11). This is directly based on the amount of profits Amgen, hypothetically, would have lost. Appx785(636:2-11).

Dr. Heeb then concluded that these two numbers form the bounds of a reasonable royalty. Appx788(646:9-647:7). In other words, Dr. Heeb testified that the bottom end of the reasonable royalty range was his estimate of the *entire value* to Hospira of a hypothetical license. In reality, that is twice the NPV of Hospira's entire EPO project, which was $91.6 million at the time of the hypothetical negotiation. Appx1470(1265:12-1266:19).

Dr. Heeb also testified that Hospira would be willing to pay a large, up-front, lump-sum royalty in 2013, even though FDA approval was uncertain. Appx791(659:18-660:10). He acknowledged that Amgen and Hospira would have known that FDA approval was uncertain, but that he did not factor that into his analysis – rather, he assumed that Hospira would bear all that risk. Appx791(660:4-661:3). Only Dr. Bell accounted for this uncertainty by proposing a running royalty of $1.5 million per infringing batch, if sold. Appx1467(1252:13-1253:9); Appx1471(1267:11-1268:16). As he explained, "there's all of these different possible contingencies that would mean Hospira didn't gain anything, Amgen didn't lose anything. So in that context, from my perspective, the reasonable royalty would be very close to, if not zero." Appx1471(1268:9-16).

Dr. Heeb also testified that an up-front, non-refundable royalty was justified based on the distribution agreement between Hospira and Vifor. Appx787(642:3-22). That was not entered into until December 31, 2015, after Hospira's BLA was filed and years after the hypothetical negotiation. Appx459(301:14-17); Appx779(610:14-18). Vifor agreed to pay Hospira an up-front payment of $30 million, milestone payments, a transfer price, and royalties on sales. Appx460(306:19-307:18). However, that up-front payment could be recovered (or never paid at all) if Hospira failed to obtain FDA approval. Appx791(659:9-17).

SUMMARY OF ARGUMENT

The district court erred in construing claims 24 and 27 of the ’298 patent. Claim 24 claims the selection of EPO molecules with a single, predetermined number of sialic acids (1 to 14) and then selectively eluting those EPO molecules using ion exchange chromatography. Accordingly, this claim covers only one isoform of EPO. The district court adopted an erroneous construction that covered mixtures of isoforms. When construed properly, no reasonable jury could find infringement because Hospira’s product has multiple isoforms. In addition, if the claim were as broad as the district court read it, it would be anticipated by the prior art that was used as a comparator in the ’298 patent examples.

Claim 27 claims a mixture of isoforms of claim 1. The district court’s construction erroneously ignored the limitation of claim 1 that an individual isoform must be “isolated.” When construed properly, no reasonable jury could find infringement because Hospira does not isolate individual isoforms. In addition, the elements of claim 1 were never mentioned at trial. Also, even under the district court’s construction, no reasonable jury could find that claim 27 was both valid and infringed, as the prior art covered mixtures of isoforms that were not isolated.

Next, the district court erred in instructing the jury on the Safe Harbor. The Safe Harbor provides broad protection to make a patented invention that is put to uses that are objectively, reasonably related to the development and submission of information to FDA. Here, the district court improperly let the jury focus on Hospira's subjective purpose for manufacture. Amgen used this opportunity to focus on Hospira's alleged commercial intent—a factor that is irrelevant under the case law. Because of this, the jury (and the district court in denying JMOL) found that batches used to generate data for FDA were not protected by the Safe Harbor. Based on undisputed evidence, no reasonable jury could find that any of Hospira's EPO was not protected by the Safe Harbor.

Finally, the jury was allowed to hear testimony from Amgen's damages expert that contradicted the very heart of the damages statute. Damages are about making someone whole—paying a reasonable royalty "adequate to compensate for the infringement." 35 U.S.C § 284. But here there was no damage to Amgen. Amgen's baseline for damages was the entire alleged value that Hospira might have gained (but did not) if it had launched earlier by manufacturing EPO prior to patent expiration. In the real world, that did not happen, and reasonable parties would have taken that contingency into account. Because the jury was allowed to find damages based on a legally flawed expert opinion, the damages award should be vacated and judgment or a new trial granted to Hospira.

ARGUMENT

I. STANDARD OF REVIEW.

The Federal Circuit reviews a grant or denial of JMOL using the regional circuit standard of review. *Comcast IP Holdings I LLC v. Sprint Commc'ns Co., L.P.*, 850 F.3d 1302, 1309 (Fed. Cir. 2017). In the Third Circuit, the court will "review the record in the light most favorable to the prevailing party unless the record is critically deficient of that minimum quantum of evidence from which a jury might reasonably afford relief." *Id.* (internal quotation marks and citations omitted). Factual findings are reviewed for substantial evidence. *Id.* at 1309-10.

Generally, the Federal Circuit will apply regional circuit law when ruling on challenged jury instructions. *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1359-60 (Fed. Cir. 2004). Jury instructions are reviewed for abuse of discretion, but the court will "exercise plenary review when the question is whether a district court's instructions misstated the law." *Clevenger v. CNH America, LLC*, 340 F. App'x 821, 824 (3d Cir. 2009) (internal quotation marks and citations omitted). However, Federal Circuit law applies to jury instructions involving issues of claim construction. *Arlington Indus., Inc. v. Bridgeport Fittings, Inc.*, 345 F.3d 1318, 1325 (Fed. Cir. 2003). The standard of review is prejudicial legal error. *Tex. Digital Sys., Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 1201 (Fed. Cir.

2002). A district court's error is only harmless if the erroneous jury instruction "could not have changed the result." *Metso Minerals, Inc. v. Powerscreen Int'l Distribution, Ltd.*, 526 F. App'x 988, 995 (Fed. Cir. 2013) (citation omitted).

Claim construction is reviewed *de novo* with subsidiary factual findings reviewed for clear error. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 837-38 (2015). The Federal Circuit may vacate a jury verdict or denial of JMOL because of an erroneous claim construction and direct the lower court to enter judgment in favor of the prevailing party on appeal if "no reasonable jury could have found infringement under the proper claim construction." *SimpleAir, Inc. v. Sony Ericsson Mobile Communications AB*, 820 F.3d 419, 431 (Fed. Cir. 2016); *see also Cave Consulting Group, LLC v. OptumInsight, Inc.*, 725 F. App'x 988 (Fed. Cir. 2018).

The amount of damages is a question of fact reviewed for substantial evidence. *Crystal Semiconductor Corp. v. Tritech Microelectronics Int'l, Inc.*, 246 F.3d 1336, 1346 (Fed. Cir. 2001). The Federal Circuit may overrule a damages award if "the determination was based on an erroneous conclusion of law, clearly erroneous factual findings, or a clear error of judgment amounting to an abuse of discretion." *Rite-Hite Corp. v. Kelley Co.*, 56 F.3d 1538, 1543 (Fed. Cir. 1995) (en banc); *see also Unisplay, S.A. v. American Electronic Sign Co.*, 69 F.3d 512, 520 n.8 (Fed. Cir. 1995).

II. THE DISTRICT COURT ERRED IN CONSTRUING CLAIMS 24 AND 27 OF THE '298 PATENT, AND NO REASONABLE JURY COULD FIND INFRINGEMENT.

A. Judgment Should Be Entered for Hospira on Claim 24.

1. Claim 24 Covers One Isoform, and It Is Undisputed that Hospira's EPO Contains Multiple Isoforms.

Claim 24 in its entirety states:

> A method of preparing erythropoietin molecules having a predetermined number of sialic acids per molecule said number selected from the group consisting of 1-14, comprising applying material containing erythropoietin to an ion exchange column and selectively eluting said molecules from the column.

Claim 24 requires selecting molecules with a predetermined number of sialic acids. Such a group of molecules (e.g., molecules with eleven sialic acids) is one isoform. However, the district court's construction as put to the jury was inconsistent with the claim language, prosecution history, and specification because it encompassed *multiple* isoforms:

> The term "erythropoietin molecules having a predetermined number of sialic acids per molecule selected from the group consisting of 1-14" in Claim 24 essentially describes an isoform, <u>and Claim 24 claims methods of preparing one or more erythropoietin isoforms</u>.

Appx162-163; Appx159-160 (emphasis added).

The district court's construction contradicts the claim language itself, in which the number of sialic acids per molecule is selected from a Markush group

such that a practitioner can select molecules with only 1, 2, or 3, etc., up to 14 sialic acids. A Markush group, by its very nature, excludes multiple selections from the group. It is "a listing of specified alternatives of a group in a patent claim. . . ." *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1280 (Fed. Cir. 2003). "It is well known that 'members of the Markush group are . . . alternatively usable for the purpose of the invention.'" *Id.* (citation omitted). "[M]embers of the Markush group are used singly." *Id.* at 1281 (citation omitted) (emphasis added). Based on the Markush language, the listing of sialic acid numbers in claim 24 is in the alternative and excludes mixtures not recited in the claim. *Id.*

This is bolstered by additional language in claim 24, which recites "a predetermined number." As this Court has explained, "although 'a' without more generally could mean one or more in an open-ended patent claim, 'a' with 'consisting of' in this case indicates only one member of a Markush group. . . . If a patentee desires mixtures or combinations of the members of the Markush group, the patentee would need to add qualifying language while drafting the claim." *Id.* at 1281. The Markush group in claim 24 does not contain any qualifying language, such as "or mixtures thereof."

In fact, claim 24 (original claim 30) initially recited "a mixture of erythropoietin molecules having greater than a predetermined number of sialic

acids per molecule . . . ." Appx5464-5469 at Appx5468. But following indefiniteness, anticipation, and enablement rejections, Amgen removed the terms "a mixture of" and "greater than" from claim 24. Appx5486-5503 at Appx5489; Appx5553-5567 at Appx5556. The prosecution history of claim 24 demonstrates the narrow scope of the claim that was eventually allowed by the Examiner:

Date	**Claim Language**	**Prosecution Notes**
Oct. 12, 1990	30. A method of preparing a **mixture of erythropoietin molecules having greater than a predetermined number** of sialic acids per molecule comprising subjecting material containing erythropoietin to ion exchange chromatography. Appx5468 (emphasis added).	Rejected by Examiner June 20, 1992 for anticipation over Sugimoto, which teaches "the preparation of EPO of the highest purity by use of ion exchange and/or isoelectric point fractionation." Appx5471-5484 at Appx5480.
Dec. 23, 1991	30. (amended) A method of preparing **a mixture of erythropoietin molecules having [greater than] a predetermined number** of sialic acids per molecule comprising subjecting material containing erythropoietin to ion exchange chromatography. Appx5489 (emphasis added).	Rejected by Examiner March 6, 1992 for anticipation over Sugimoto "for reasons of record. The amendment to claim 30 is not deemed to present a method distinguished from the originally presented method because the single process step is the same as that of originally presented claim 30." Appx5505-5516 at Appx5508. Rejected again by Examiner April 1, 1993 because Sugimoto "teaches the single process step of the claimed method: subjecting material containing EPO to ion exchange chromatography, column 3, lines 51-61."

		Appx5533-5551 at Appx5540. **Also rejected for ODP over claims 1-11 of U.S. Patent No. 4,667,016 ("Lai.") "Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent claims the instantly claimed process step."** Appx5548 (emphasis added).
Oct. 4, 1993	30. (twice amended) A method of preparing **[a mixture of] erythropoietin molecules having a predetermined number** of sialic acids per molecule comprising <u>applying</u> [subjecting] material containing erythropoietin to <u>an</u> ion exchange <u>column</u> [chromatography] <u>and selectively eluting said molecules from the column</u>. Appx5556 (emphasis added).	Rejected May 3, 1994 as obviousness over Sugimoto, which teaches "preparation of the highest purity epo by adsorption and desorption with ion exchange chromatography . . . ." Appx5569-5578 at Appx5576. **Also rejected for ODP over Lai for reasons of record.** Appx5577.
May 3, 1994	30. (three times amended) A method of preparing **erythropoietin molecules <u>according to Claim 16</u> having a predetermined number** of sialic acids per molecule comprising applying material containing erythropoietin to an ion exchange column and selectively eluting said molecules from the column. Appx5580-5586 at Appx5581 (emphasis added). 16. (twice amended)	Rejected by Examiner May 5, 1995 for ODP over **Lai**. "Applicants argue that since the claim is amended to recite epo molecules according to claim 16, the claim is patentably distinct. However, the claims recite no positive process steps by which it is distinguished from the method of the patent claims. . . . **Here, the starting material was known, the process of subjecting that known material to ion exchange**

	Erythropoietin consisting essentially of **erythropoietin molecules having an identical number of sialic acids** per molecule, said molecules being the product of the expression of an exogenous DNA sequence in a non-human eukaryotic host cell. Appx5555 (emphasis added).	**chromatography and eluting product was known, and the product isoforms were known in the art, although the art applied does not state that epo was eluted single isoforms."** Appx5588-5598 at Appx5590 (emphasis added).
March 6, 1996	Examiner's Amendment with Examiner's handwriting: 24. A method of preparing **erythropoietin molecules ~~according to Claim 16~~ having a predetermined number of sialic acids per molecule said number selected from the group consisting of 1-14**, comprising applying material containing erythropoietin to an ion exchange column and selectively eluting said molecules from the column. Appx5581 (emphasis added).	Examiner issued a Notice of Allowability including the Examiner's Amendment on March 6, 1996. "Applicants teach the unexpected advantage that the biological activity of compositions of erythropoietin (epo) can be adjusted by formulating epo compositions with single isoforms in combination, varying the number of sialic acids to control the activity. **Single isoforms are not taught by the prior art of record. Although the prior art of record recognized that biological activity varied with number of sialic acids, the prior art does not suggest isolation of single isoforms and does not suggest the instantly claimed combinations of isoforms."** Appx5613-5614 (emphasis added).

As shown above, Amgen was required to narrow claim 24 to avoid Lai, which taught how to obtain purified mixtures of active EPO isoforms through ion exchange chromatography. The Examiner allowed a claim to a specific, predetermined isoform selected from a list of alternatives in a Markush group.

The specification confirms that the listing of sialic acid numbers in claim 24 is in the alternative and excludes mixtures not recited in the claim. In language that mirrors claim 24, the specification explains that: "In a preferred embodiment, the invention relates to an erythropoietin isoform having a specific number (i.e. a fixed number greater than 0) of sialic acids per erythropoietin molecule, said number selected from the group consisting of 1-14." Appx2163(6:32-36) (emphasis added). The district court's claim construction, which allows for multiple isoforms, thus improperly broadens claim 24 to encompass mixtures of isoforms.

Under the correct construction of the claim, based on the Markush group language as viewed through the prosecution history and specification, no reasonable jury could find infringement. There is no question on this record that Hospira elutes all of the isoforms as a single step and, in fact, must always have at least five isoforms. Appx4325; Appx749(492:14-20); Appx743(467:18-468:6); Appx1147(990:24-992:18); Appx2627 (describing how the final protein is eluted from the column). Hospira does not isolate isoforms and cannot infringe.

2. The District Court's Construction Read the Word "Predetermined" Out of Claim 24, and Hospira Does Not Predetermine Isoforms.

Another separate and independent error in the district court's claim construction is the removal of the word "predetermined" from claim 24. Even if this Court were to find that claim 24 could cover multiple isoforms, the claim requires that the isoform(s) must be predetermined.

Hospira proposed the proper construction of claim 24 during claim construction: "erythropoietin molecules having a predetermined number of sialic acids per molecule" means "erythropoietin molecules with an identical, predetermined number of sialic acids per molecule." Appx5309-5365 at Appx5336. The word "predetermined" itself needs no further construction, and it cannot be read out of the claims. Nevertheless, the district court omitted any mention of "predetermined" in the claim construction that was presented to the jury. This omission was clear error, as all limitations in a claim must be considered meaningful. *Randall May Int'l, Inc. v. DEG Music Prods., Inc*., 378 F. App'x 989, 998 (Fed. Cir. 2010) (citation omitted).

In fact, "predetermining" was a key aspect of the alleged invention of the '298 patent and of Dr. Strickland's EPO II project. He obtained single isoforms using ion exchange chromatography and recombined them to form specific mixtures with a lower biological activity than Epogen. Appx720(374:24-

376:19). For example, to obtain a product with a target biological activity of 120,000 units, Dr. Strickland selected specific amounts of isoforms 9, 10 and 11, and remixed them. Appx720(376:24-377:18). That is a clear example of predetermining isoforms, but it is not what Hospira does.

It is undisputed that Hospira's process produces a mixture of five to eight isoforms and allows a range of each isoform. Appx4325. Dr. Cummings admitted that Hospira's process does not always produce the same isoform distribution, and that sometimes one or another isoform may be absent. Appx749(491:23-493:20). It is undisputed that Hospira does not know which isoforms it will get for each batch before it begins its process. *Id.* Thus, under a construction of the claim that does not erroneously omit "predetermined," no reasonable jury could find that Hospira infringes claim 24.

3. Hospira Does Not Selectively Elute Isoforms.

Even if this Court were to find that claim 24 could cover multiple isoforms, those isoforms would not only have to be predetermined but also "selectively eluted." This term was not construed by the district court, and the jury was told that it "shall be given its plain and ordinary meaning to a person of ordinary skill in the art in 1990." Appx160. Under the plain and ordinary meaning, Hospira does not infringe. Hospira's EPO can have anywhere from five to eight different isoforms. Appx4325; Appx3711. The amounts of each isoform

can differ in every batch of product. Appx1110(841:3-17); Appx1145(983:21-984:17); Appx1145(984:23-985:15). Hospira's process demonstrates this variability because, as Dr. Billingham explained, it was designed to remove impurities, not to target specific EPO isoforms. Appx1109(839:13-840:16).

However, Dr. Cummings opined that Hospira selectively eluted "[i]n the sense that basic isoforms of EPO that have less numbers of sialic acid would have already been removed from the column, and then those that have more sialic acid would have been selectively eluted from the column." Appx743(468:18-469:3). That is, he opined that selective elution is simply removing basic isoforms and eluting the remaining ones with more sialic acids and higher biological activity. But there is nothing "selective" about that – rather, that is the simple purification of biologically active EPO known in the art. *See infra*, Sec.II.A.4.

Dr. Cummings also cited Hospira's release specifications as evidence that Hospira "selectively eluted." Appx744(470:13-471:23); Appx3711. But Hospira's release specifications only indicate a broad percentage for each isoform that will be acceptable. Appx3711; Appx4325. A person of skill in the art reviewing Hospira's release specifications could not determine which specific isoforms will be present in Hospira's product. Because Hospira does not "selectively elute" isoforms, no reasonable jury could find infringement.

4. Under the District Court's Erroneous Construction, No Reasonable Jury Could Find Claim 24 Valid over Lai.

Under the district court's erroneous construction, no reasonable jury could have found that claim 24 was valid over Lai. By omitting the "predetermined" element of claim 24 and expanding the Markush group to allow any mixture of isoforms, the district court effectively re-wrote claim 24 to cover the elution of a subset of one or more isoforms separate from any other subset of isoforms using ion exchange chromatography. But Dr. Strickland, a co-inventor of Lai, confirmed that Lai Example 2 did just that—it removed basic isoforms first, those with nine sialic acids or lower, followed by the elution of more biologically active isoforms with higher sialic acid content. Appx728(406:4-407:9; 408:6-408:15; 408:22-409:13); Appx728-729(409:19-410:19); Appx2164(8:67-9:25); Appx2494(5:18-37); Appx2494(5:59-66).

In fact, the goal of Lai was to use chromatographic procedures that allow for high yields of biologically active EPO by targeting molecules having higher sialic acid content. Appx2491; Appx2492(1:5-14); Appx727(403:21-404:7). Dr. Strickland confirmed that isoforms 9 to 14 are obtained from Example 2 of Lai. Appx724(393:14-21); Appx729(412:5-8).

Lai also claimed the "selective elution" of desired EPO using ion exchange chromatography. Claim 10 illustrates this point, as it refers to "selectively eluting" EPO multiple times. Appx2495(7:15-8:18). In fact, prior to

the final amendment during prosecution, the Examiner argued that claim 24 (then claim 30) was invalid for ODP over claims 1 to 11 of Lai. Appx5577. If claim 24 were read as broadly as the district court's construction allows, it would be anticipated by Lai. Appx1150(1003:18-1004:12); *see generally* Appx1412-1414(1032:19-1039:2).

Amgen attempted to obfuscate this issue by arguing that the first low-pH wash of Lai might not necessarily remove lower EPO isoforms and keep higher EPO isoforms because it would depend on the starting material. Appx732(424:12-425:5); Appx740(455:1-456:8). But Amgen does not know the starting material of Hospira's preparation, either. Appx750(495:3-6). If claim 24 is construed to cover a process of eluting EPO isoforms with higher sialic acid using ion exchange chromatography, regardless of the starting material used, then that process was already taught by Lai and no reasonable jury could find that claim 24 was valid.

B. Judgment Should Be Entered for Hospira on Claim 27.

1. The Proper Construction of Claim 27 Requires a Mixture of "Isolated" Isoforms.

Claim 27 in its entirety recites:

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

Appx2171 (emphasis added).

Claim 1 in its entirety 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.

Appx2170 (emphasis added).

Initially, after the Markman hearing, the court construed claim 27 in a way that incorporates claim 1, specifically:

> Claim 27 is an independent claim (D.I. 177, p. 10, ll. 6-7), and the term "mixture of two or more erythropoietin isoforms of Claim 1" in Claim 27 means "a mixture of two or more of the isolated erythropoietin isoforms of Claim 1."

Appx173-175 at Appx174 (emphasis added) (citing Appx176-186 at Appx185).

Also after the Markman hearing, the court held that the term "an isolated . . . isoform" in claim 1 was properly construed as "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)." Appx187-195 at Appx192-193.

The district court's initial constructions of claim 27 and claim 1 were supported by the '298 specification, which states that "[i]t is an object of the present invention to provide separated and isolated isoforms of erythropoietin having a defined sialic acid content and biological activity." Appx2162(3:15-19).

The constructions are also consistent with the Examiner's reasoning in allowing the pending claims to issue, which was that "Applicants teach the unexpected advantage that the biological activity of compositions of erythropoietin (epo) can be adjusted by formulating epo compositions with single isoforms in combination, varying the number of sialic acids to control the activity." Appx5613-5614. The Examiner further noted that the "prior art does not suggest isolation of single isoforms and does not suggest the instantly claimed combination of isoforms." Appx5614.

Hospira does not isolate single isoforms as required by claim 1 which is incorporated in claim 27. Therefore, after the district court entered its initial construction of claim 27, Hospira filed a motion for summary judgment of non-infringement. Appx5738-5741. However, during the summary judgment process, the district court erroneously changed its prior construction. The court added a sentence to its construction of claim 27, and provided the jury this erroneous construction:

> Claim 27 is an independent claim, and the term "mixture of two or more erythropoietin isoforms of Claim 1" in Claim 27 means a mixture of two or more of the <u>isolated erythropoietin isoforms of Claim 1</u>. <u>Claim 27 does not require the individual isoforms of Claim 1 to be separately prepared prior to making the mixture</u>.

Appx163; Appx160 (emphasis added).

This construction is not only inconsistent with claim 1, but is internally inconsistent on its face. It requires the "isolated" isoforms of claim 1, but then immediately reads that phrase out by saying that the isoforms do not need to be separately prepared prior to making the mixture. That contradicts both the intrinsic evidence and the understanding of Dr. Strickland, who testified that the purpose of the '298 patent was to separate isoforms and then "recombine" them or "mix those fractions back together" to make EPO compositions with a specific *in vivo* activity as part of the EPO II project. Appx720(375:12-377:18).

Claim 27 requires the isolated isoforms of claim 1, followed by the subsequent mixture of those isoforms. The district court's later construction should be vacated and the original construction adopted by this Court.

2. Under the Proper Construction of Claim 27, No Reasonable Jury Could Find Infringement Because Hospira Does Not Isolate Isoforms.

Under the proper construction of claim 27, no reasonable jury could find infringement because Hospira does not mix isolated isoforms. It is undisputed that Hospira's product is prepared by a simple purification process that separates the biologically active isoforms from impurities, without targeting specific isoforms. Appx1109(839:13-840:19). Hospira's product must contain at least five isoforms and all of those isoforms elute off the ion exchange column together. Appx750(495:8-497:1). At no point during its purification process does Hospira

prepare single isolated isoforms, or re-mix them to form its product. Appx1109-1110(840:17-841:17).

Because the limitations of claim 1 were read out of claim 27, Amgen never even alleged that Hospira had "isolated" isoforms. In fact, the terms "isolated isoform" or "isolated" alone are never used during the testimony of Amgen's expert Dr. Cummings.

According to Dr. Cummings, claim 27 "describes containing an EPO composition that has a predetermined *in vivo* activity with a mixture of these isoforms that give the correct predetermined activity that you want to achieve." Appx745(476:13-23). He further testified that the isoforms "could be purified as a mixture" under the court's construction. Appx745(476:24-477:4). By looking at the data in Hospira's BLA, he concluded that there was a mixture of isoforms because multiple isoforms are mixed together. Appx3711; Appx746(481:13-16). However, if the limitations of claim 1 would not have been read out of claim 27, Dr. Cummings could not have reached his infringement conclusion, because he pointed to no evidence that the isoforms were "isolated." Under the correct construction, no reasonable jury could find infringement.

3. Under the District Court's Erroneous Construction of Claim 27, Amgen Did Not Establish Every Limitation.

Under the district court's erroneous construction, Hospira does not infringe. No matter what one thinks about the isoforms needing to be "isolated" or

"separately prepared," claim 27 literally references claim 1. Under the district court's claim construction, claim 27 covers "a mixture of two or more of the isolated erythropoietin isoforms of claim 1." Appx160. Amgen never mentioned claim 1 or attempted to prove the limitations of claim 1 at trial. It is well-established law that all elements of a claim must be proven to show infringement. *Mannesmann Demag Corp. v. Engineered Metal Prods. Co., Inc.*, 793 F.2d 1279, 1282 (Fed. Cir. 1986) ("Literal infringement requires that the accused [method] embody every element of the patent claim."). For that reason alone, infringement is legally precluded and JMOL should have been entered for Hospira.

In addition, the evidence is insufficient to establish that Hospira's composition has a predetermined *in vivo* specific activity. Dr. Cummings admitted that Hospira was trying to establish biosimilarity to Epogen. Appx753-754(509:11-511:10). Epogen is not made by the process of the '298 patent. Appx723(386:12-17). Amgen's product has different lots that fall within a 93 to 147 activity range, and Hospira's does the same because it is highly similar. Appx746(479:2-22). Neither of those products is achieved by isolating isoforms and combining them back together as Dr. Strickland did for the '298 patent and EPO II project. Appx720(375:23-377:18). Simply being biosimilar does not prove infringement, particularly when the reference product does not embody the patent.

4. Under the District Court's Erroneous Construction, No Reasonable Jury Could Find Claim 27 Valid over Lai.

Under the district court's erroneous construction, no reasonable jury could have found that claim 27 was valid over Lai. Claim 27 requires a predetermined *in vivo* activity. Under the district court's construction, this can be accomplished by eluting isoforms off the column as a mixture. Appx160; Appx745(476:24-477:3). However, if all it takes to "predetermine" a specific activity is to use ion exchange chromatography to prepare a mixture of active EPO (the EPO with more sialic acids), then that was disclosed by Lai.

Lai's purification method was designed to obtain biologically active EPO. Appx2491. Lai uses ion exchange chromatography to purify EPO, and the purified EPO contains one or more isoforms. Appx727-728(405:18- 406:6). Example 2 used ion exchange chromatography to separate impurities and less biologically active EPO from more biologically active EPO. Appx2494(5:20-37); Appx2494(5:59-68). If predetermining biological activity means eluting biologically active EPO, then Lai anticipates.

In sum, the constructions of claims 24 and 27 were erroneous, the jury verdict should be vacated, and judgment should be entered for Hospira.

III. THE DISTRICT COURT ERRED IN INSTRUCTING THE JURY ON THE SAFE HARBOR, AND NO REASONABLE JURY COULD FIND THAT HOSPIRA'S BATCHES OF EPO ARE NOT PROTECTED.

A. The Safe Harbor Provides Broad Protection to Make a Patented Invention if its Uses Are Reasonably Related to FDA Submissions.

This appeal is from the first jury trial to assess the Safe Harbor for a proposed biosimilar 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 regulatory uncertainty that continues to this day. Under the Safe Harbor statute and case law, all of Hospira's batches used to support its FDA submission should have been protected.

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

> ***It shall not be an act of infringement to <u>make, use, offer to sell, or sell</u> within the United States <u>or import</u> 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 <u>uses</u> 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) (emphasis added).

Under the statute, if the use of an otherwise infringing product is reasonably related to submitting information to FDA, its preliminary making, using, selling, offering to sell, or importing are protected as well.

The Supreme Court has explained that the Safe Harbor "provides a wide berth for the use of patented drugs in activities related to [FDA] approval." *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 202 (2005). If uses are "reasonably related to the development and submission of *any* information" to FDA, they are entitled to protection by the Safe Harbor. *Merck*, 545 U.S. at 202 (emphasis in original). A party asserting the Safe Harbor does *not* have to show that any particular activity was "required" for FDA approval (although, in this case, certain uses by Hospira were, in fact, necessary for approval). *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 110 (D. Mass. 1998).

The standard for establishing the Safe Harbor is broad and objective: the party asserting the defense "must prove by a preponderance of the evidence that it would be objectively reasonable for a party in [its] situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question." *Merck*, 545 U.S. at 200-01. Specifically, the Supreme Court endorsed this language in jury instructions. *Id.* at 208 n.8; *see also Merck KGaA v. Integra*

Lifesciences I, Ltd., Civ. No. 3:96-cv-01307, D.I. 993 at Jury Instruction No. 32 (S.D. Cal. Mar. 16, 2000).

The Safe Harbor exists even if activities have additional purposes or motives beyond FDA approval. "The phrase 'solely for uses reasonably related' is not equivalent to the phrase 'use is solely for purposes reasonably related.'" *Amgen, Inc.*, 3 F. Supp. 2d at 107. "Uses, such as animal testing, human clinical trials, or chemical composition analysis, may be related to FDA approval, and yet be conducted for *purposes* other than, or in addition to, obtaining FDA approval." *Id.* at 107-08 (emphasis in original). The Safe Harbor "does not look to the underlying purposes or attendant consequences of the activity . . . as long as the use is reasonably related to FDA approval." *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).

A commercial intention or business purpose does not extinguish the Safe Harbor. The *Intermedics* decision, affirmed by this Court and cited favorably by the Supreme Court and others, explained this well:

> Moreover, we are confident that Congress understood that in the real world of high-tech medicine, at least, it is "business purposes" that inspire the kinds of infringing activities that the exemption clearly covers. Congress could not have intended the exemption to apply only to those whose purposes were purely scientific, or to those who were motivated simply by a driving curiosity. The

> common law already provided shelter for persons so motivated. *See Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 1984). Rather, Congress surely knew, when it enacted § 271(e) (1), that pursuit of commercial gain ultimately underlies, legitimately, the entire range of activities predictably undertaken by companies in positions like defendants' in this case. We see no reason to conclude that Congress intended to prohibit all product development and testing work (potentially infringing conduct) which was inspired, in part, by a hope that it would someday lead to profitable sales. Again, if a party were to lose the exemption every time a business purpose was detectable in its otherwise infringing activities, the exemption would virtually never be available and thus would fail to achieve Congress' objective.

Intermedics, Inc. v. Ventritex, Inc., 775 F. Supp. 1269, 1279-80 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993) (unpublished).

Furthermore, it is improper for parties and courts to second-guess a company's objectively reasonable activities. Given the regulatory uncertainty at the time of its BLA submission, Hospira had no way of knowing the amount of data it would have to generate. Appx1074(697:8-698:15); Appx1075(701:15-702:17); Appx1076(705:11-24). Courts recognize that "it is unforeseeable how much data FDA will require [a company] to submit during the approval process." *Intermedics, Inc. v. Ventritex Co.*, No. 92-1076, 1993 WL 87405, at *3 (Fed. Cir. Feb. 22, 1993) (unpublished); *see also Amgen, Inc.*, 3 F. Supp. 2d at 110. The objective nature of the Safe Harbor "acknowledges the inherently unpredictable nature of the FDA approval process." *Amgen, Inc.*, 3 F. Supp. 2d at 108.

The Safe Harbor may not protect some routine, post-approval activity. In *Momenta Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc.*, 809 F.3d 610, 620 (Fed. Cir. 2015), this Court found that routine, post-approval use of a patented quality control method was not protected. *Id*. at 620-21. However, there is no indication that *Momenta* applies to pre-approval activities, particularly activities to generate data requested by the FDA in a CRL or commitments made to obtain FDA approval, which are not routine. In sum, the Safe Harbor is broad, objectively reasonable, and is not extinguished by commercial motivation.

B. The Court's Jury Instructions Are Legally Erroneous.

In this case, the jury instructions and verdict form improperly focused the jury on the reasons *why* each batch was manufactured, not *how* each batch was used and whether that use was reasonably related to the development and submission of information to support Hospira's BLA. The jury instructions also failed to specify that Hospira's subjective intent and motives are not relevant. This is reversible error for the reasons discussed below.

The final paragraph of the district court's Safe Harbor jury instruction is shown below (with bracketed numbers for reference):

> [1] You must evaluate each of the accused activities separately to determine whether the Safe Harbor applies. [2] 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. [3] 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.

Appx118-158 at Appx139. This is not the instruction that was proposed by Hospira, which was based on the case law discussed above. Appx10818-10821; Appx139. The first clause of the district court's instruction is generally consistent with the case law and instruction approved in the *Merck* case. 545 U.S. at 208 n.8. The second clause is generally correct, although it is not worded as broadly as articulated in *Merck* (as there only needs to be a "decent prospect" the data will be used). *Id.* at 200-01.

The third clause, however, turned the statute on its head. It told the jury that "Hospira's *additional underlying purposes* for the manufacture and use of that batch *do not remove that batch from the Safe Harbor*" only "[i]f Hospira has proved that *the manufacture of a particular batch was reasonably related* to developing and submitting information to FDA . . . ." Appx139. But under the case law discussed above, underlying purposes never matter; and Hospira only had to prove that the *uses* were reasonably related, not the *manufacture*.

As explained above, if the *use* of a patented invention is covered by the Safe Harbor (as in clause 2), then the *making* must be protected as well. This

instruction forced Hospira to prove that the *manufacture* was reasonably related to approval (clause 3). The instruction confused the jury, who simultaneously had to look at Hospira's objective activities as well as its subjective purpose behind the manufacture, even though the purpose is irrelevant under the statute and case law.

C. The Error in the Jury Instructions Prejudiced Hospira.

The jury instructions' erroneous focus on the purpose for manufacture rather than use was not harmless, and prejudiced Hospira as evidenced by the final verdict. The jury found that PPQ and PAI were protected by the Safe Harbor, but that batches used for all other uses were not. That is because the evidence on the "uses" of PPQ and PAI at trial squarely related to the "making" itself.

For example, Plaintiffs' opening stated that PPQ "allows a company to validate its manufacturing process . . . ." Appx422(156:10-14). Plaintiffs' expert said that PPQ was related to "demonstrat[ing] that you can make your lots reproducibly." Appx1484(1319:15-23). The only point disputed by Amgen's expert was whether Hospira was "required to manufacture" the 2013 PPQ lots after it had already submitted its 2012 batches. Appx1484(1320:3-8). The point of contention between the parties was squarely related to manufacturing.

As to PAI, both parties asserted that it related to manufacturing, and the only debate was whether Hospira had to be in "active manufacturing" at the time of the inspection, as Hospira's witness testified, or whether "it's not required"

and some companies will merely "be polite and try to be in production," as Amgen's expert argued. Appx1116(865:1-10); Appx1492(1352:10-1353:7).

In contrast, when the subjective reason for making a batch was not tied directly to its use, the jury found that the batch was not covered. Biosimilarity, stability, and release specifications all relate to the properties of EPO rather than the manufacturing process. Although CPV relates to process validation, the debate between the parties was whether it was "routine" work or not. These uses are discussed further in the next section.

D. Based on Undisputed Evidence, No Reasonable Jury Could Find that Any of Hospira's Twenty-One Batches Were Not Protected by the Safe Harbor.

1. Biosimilarity (BIO).

The clearest evidence that the erroneous instructions led the jury to the wrong conclusion is that two batches used to demonstrate biosimilarity with the reference product were not protected by the Safe Harbor. It is undisputed that all four 2013 batches of drug substance were used to assess biosimilarity in Hospira's BLA. Appx1096(785:14-786:3); Appx4438-4440. It is also undisputed that biosimilarity testing is required for FDA approval. Appx1837(1465:23-1466:14). Yet the jury found that two of the four batches were not protected. Appx114. This confirms that the jury's analysis included factors beyond whether the accused batches were put to uses reasonably related to FDA approval.

Here, the testimony of both parties establishes that these batches should have been protected by the Safe Harbor. Ms. Dianis testified that biosimilarity is "the fundamental thing you're trying to prove in your application." Appx1073(695:2-9). Dr. Srebalus-Barnes testified that all 2013 batches were used to show that the product was highly similar and there were no clinically meaningful differences. Appx1094(779:13-19); Appx1095(784:8-786:17); Appx4438-4440. Hospira's expert Dr. Levine confirmed that biosimilarity testing is "an absolute requirement," that FDA guidance documents "do not specify the exact tests or the exact number of batches," and that the number of lots tested by Hospira was reasonable. Appx1127(912:9-21); Appx1128(914:19-915:22).

Hospira's evidence on biosimilarity was undisputed. Amgen's expert, Dr. Martin-Moe, *never* discussed "biosimilarity" on direct examination. However, she admitted on cross examination that it is necessary:

> Q. And the requirements for approval for a biosimilar include proving biosimilarity; right?
> A. Yes.
> Q. Hospira must establish that its EPO biosimilar product is, in fact, biosimilar to Epogen; is that right?
> A. Yes.
> Q. And there is something called biosimilar, which is a series of testing that you have to do to get FDA approval; is that right?
> A. Yes.
> Q. And those tests are absolutely necessary to getting FDA approval; right?
> A. Yes.

Appx1837(1465:23-1466:14). Amgen's technical expert, Dr. Cummings, also confirmed that twenty-six lots of Hospira's product (including all twenty-one accused of infringement) were used to establish the quality range that allowed for the conclusion that it was highly similar. Appx754(510:5-23); Appx4606. In fact, his evidence of infringement is the very evidence that Hospira submitted in its application to the FDA for approval. Appx754(510:24-511:10). No reasonable jury could find that all four biosimilarity lots were not covered by the Safe Harbor.

2. Revisions to Release Specifications (REV) in Response to the CRL.

Because of the erroneous jury instructions, the jury found that the Safe Harbor did not protect batches used to update release specifications, even though this update was done in direct response to a CRL from FDA and Hospira submitted a 75-page response addressing this issue. Appx3705-3780; Appx4805.

Amgen does not dispute that this testing was done, but argues that FDA did not tell Hospira to make more batches; in fact, all the batches had been made before the CRL was received. Appx1493(1355:16-1356:22). In addition, Amgen's expert opined that Hospira could have used the 2009-2012 batches. *Id*. But she admitted that she did not know if the batches expired or if there were any drug substance left. Appx1840-1841(1479:17-1482:10).

Hospira's use of those batches in response to the CRL gave them Safe Harbor protection – if a patented invention's "use" is protected by the Safe Harbor,

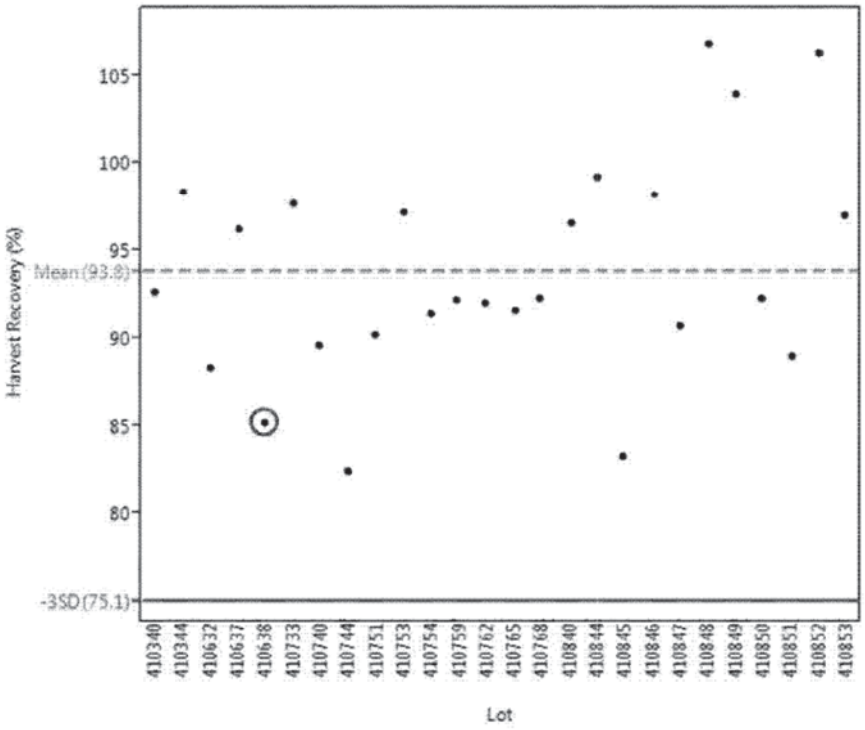
the prerequisite making, using, or selling is as well. Moreover, the CRL highlights the fact that companies never know in advance how much data FDA will need.

Amgen may argue that the batches used to update the release specifications would not have been protected by the Safe Harbor if FDA had never issued the CRL. However, this Court does not need to decide that issue, because that is not the fact pattern here. A satisfactory response to all items listed in a CRL is required for FDA approval. Appx1114(860:10-24); Appx1126(907:18-24). Here, in the CRL, FDA made several comments on the submitted data and required updated and revised release specifications. *See, e.g.*, Appx4805. To provide that information, Hospira needed additional batches to generate the data necessary to revise and update the release specifications, as requested by FDA. Appx4826-4885; Appx1115(861:18-864:2); Appx1100(802:22-804:20); Appx1101(806:24-807:14). If Hospira had not already had batches to use, it would have had to manufacture them to generate the data requested by FDA. Appx1078-1079(716:14-717:6).

The information requested by FDA required significant data for analysis. For example, FDA noted that data generated from the PPQ lots showed that one of the batches had a lower EPO content, which FDA characterized as "a measure of process inconsistency." Appx4842. FDA requested a clarification for the low EPO content and a justification as to why the process was consistent. *Id.*

Dr. Billingham testified that, by using the data generated from all EPO batches, Hospira was able to show FDA that the EPO content of that single PPQ lot was above the exclusion threshold and was not an outlier, thus the manufacturing process was indeed consistent. Appx4842-4845; Appx1115(861:18-864:2). The figure below demonstrates that Hospira used all accused EPO batches to explain this point:

Figure 2. Control chart[1] of Harvest step recoveries for all lots produced to date



[1] As +3SD exceeds 100 %, a one-sided (lower limit) statistical control limit is shown.

Appx4844. As Dr. Billingham explained, it was fortunate that Hospira had the lots from 2013, 2014, and 2015 in order to demonstrate that Hospira had control of its process. Appx1115(862:19-24). As he explained, "we were able to apply

statistical limits to determine if this was truly different from normal, and you needed a reasonable data set in order to apply those mathematical approaches." Appx1115(863:19-864:2).

FDA also requested more information on the presence of the CHO Olfactory-Receptor Related Protein (ORP HCP), the N-linked Glycan levels, and additional purity tests such as SDS-PAGE. Appx4806; Appx4811. Hospira established a revised release specification by testing 21 batches of EPO drug substance manufactured from 2013 to 2015 and provided the results in the updated BLA. Appx4521-4524; Appx4828-4829; Appx4526-4532; Appx4532-4537; Appx4553-4562 at 4559; Appx1100-1101(802:9-807:14). Dr. Srebalus-Barnes confirmed at trial that having the additional drug substance batches allowed Hospira to generate the data necessary to revise the release specifications. Appx1101(805:1-807:3).

Not only were Hospira's EPO batches necessary for the revised release specification, but throughout her testimony Dr. Srebalus-Barnes explained that testing more batches gives better statistical analysis and "a better estimate of what the true value is for the purpose of setting the specs." Appx1101(807:4-14); Appx1104(818:20-819:7); Appx1105(822:15-20). In contrast, Amgen's expert argued that the initial PPQ lots were the "grand finale" and Hospira was not required to make any batches after completing three batches in 2012.

Appx1484(1319:15-1320:8). That is not correct—in fact, Amgen's expert did not even know how much, if any, unexpired EPO was left from those lots. Appx1840-1841(1479:17-1482:10). Hospira could not have properly responded to the CRL with only those batches; that is evident from all of the data that Hospira submitted. From this use alone, no reasonable jury could find that any of Hospira's accused EPO batches were not covered by the Safe Harbor.

3. Stability Testing (STAB).

Another error in the jury instructions is apparent because the jury did not find that all stability batches were protected. Amgen argued to the jury that all of the stability lots were not protected by the Safe Harbor because stability can also be done after FDA approval on an ongoing basis, and is thus routine, post-approval activity that is not covered by the Safe Harbor under *Momenta*.

However, the fact that stability batches can be prepared post-approval is not relevant here, and this Court need not decide whether post-approval stability lots would be protected by the Safe Harbor. Here, *all* of the batches used for stability were submitted to the FDA prior to approval.

Dr. Srebalus-Barnes' undisputed testimony proved that data was generated to support the stability requirements for FDA approval. Appx1097(789:6-791:11). She testified that Hospira submitted stability data from the 2013 batches, 2014 batch 410768, and 2015 batches 410840 and 410853P.

Appx1097(791:8-792:5); Appx4361. Amgen's expert, Dr. Martin-Moe, admitted that stability testing is required. She argued that it only needed to be done on a minimum of three lots, but agreed there was no maximum number of lots set by FDA. Appx1838(1469:19-1470:4). She further admitted that, if more lots are made, stability data must be submitted to FDA. Appx1838(1470:5-15). Thus, no reasonable jury could find that the stability batches were not covered.

4. Continued Process Verification (CPV).

Amgen argued that CPV was not covered by the Safe Harbor because it is a "routine" activity that can continue after FDA approval. Amgen's argument is based on *Momenta*'s holding that routine, post-approval activity is not covered. To the extent *Momenta* only relates to post-approval activity, nothing here was post-approval as *all* of the batches used for CPV were submitted to FDA prior to approval. To the extent *Momenta* focuses on whether uses are routine vs. non-routine, the CPV batches made here are not "routine," because a commitment to make those batches is required for FDA approval.

Hospira's witness, Dr. Billingham, explained that thirty CPV batches were part of Hospira's "process validation master plan" as committed to FDA. Appx1114(857:8-858:15); Appx4206-4207. Amgen's expert, Dr. Martin-Moe, agreed that a CPV program is necessary for FDA approval and that Hospira's commitment to make thirty batches was typical. Appx1839(1475:17-1476:20).

She further admitted that thirty lots are useful because, "when you reach about 30 lots, you have the statistical power to make some very firm determinations about how to adjust the controls and the specification sometimes." Appx1488(1336:14-1337:9). She also admitted that Hospira committed to making these lots, but still had not made them at the end of 2015. Appx1839-1840 (1476:14-1477:1). Thus, CPV should be covered by the Safe Harbor.

5. Amgen's "Commercial Inventory" Argument.

Finally, Amgen argued that Hospira's original BLA listed several batches as "Commercial Inventory" (along with other uses) and that Hospira allegedly used "white-out" to change that to CPV. Appx1088(756:7-11); Appx1869(1593:5-12). This was argued in conjunction with the Risk Authorizations, which allegedly showed the Hospira management had a commercial purpose in making the batches. Appx1489-1490(1342:21-1343:9). As discussed above, Hospira's Motion *in Limine* #3 to preclude the Risk Authorizations was denied. Appx196-201 at Appx200-201.

Once Amgen had the opportunity to introduce these documents, this alleged commercial theme tainted the entire trial. Amgen repeatedly told the jury that Hospira had made nearly a billion dollars' worth of EPO—a fact that was repeated four times in Amgen's opening statement alone. Appx418(137:1); Appx421(152:10); Appx422(155:1); Appx424(161:21). Amgen's counsel

repeatedly referred to Hospira's "stockpile" of "commercial inventory." Appx422(154:9); Appx422(154:24); Appx1871(1604:17). Amgen's Safe Harbor expert referred to the commercial purpose as well. Appx1484(1320:16-17); Appx1487(1332:9-12); Appx1488(1335:11-14; 1336:8-13); Appx1490(1346:3-23). This is legally irrelevant, but was repeatedly put before the jury.

Amgen also made much of the fact that Hospira made a large amount of EPO, as each batch was 20,000 L in size. Appx1093(774:13-24). However, Dr. Srebalus-Barnes testified that this was simply the size of Hospira's commercial reactor, and that FDA required using batches manufactured at commercial scale for all testing that was done. *Id*. If the jury had been properly instructed to focus on the objective uses and not the subjective purpose for manufacture of the batches, the jury would have found that all of Hospira's EPO, regardless of the batch size, was covered by the Safe Harbor because of the undisputed uses described above.

E. The District Court Erred in Denying JMOL on the Safe Harbor.

As shown above, because of the erroneous jury instructions, the jury reached an erroneous verdict on many of the batches Hospira used to support its BLA submission and CRL response. This legal error tainted the district court's JMOL ruling as well. Appx111. The district court stated that the jury was entitled to credit Amgen's witnesses over Hospira's witnesses for three legally irrelevant reasons.

Reason #1. "First, though Hospira argues that it manufactured each of the 2013, 2014, and 2015 drug substance batches for use in obtaining FDA approval, Amgen notes that Ms. Dianis, the regulatory lead for Hospira's EPO product, 'admitted that she did not know why Hospira made its 2015 batches, or why Hospira made as many batches as it did, and that she assumed Hospira's supply team (not the regulatory team) made those decisions.'" Appx73;.

As a factual matter, another Hospira witness, Dr. Sam Billingham, testified that all of the accused batches were made to support the process validation studies, CPV, and PAI. Appx1113(856:9-19); Appx1115(862:17-864:2); Appx1118(873:23-874:5); Appx1118(874:24-875:24). Regardless, it is irrelevant whether one Hospira employee knew why some of the batches were made, because it is the "use" and not the "purpose" that is relevant to the Safe Harbor. As explained in the *Intermedics* decision, the words "purposes" and "uses" are not fungible in this context. *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1274 (N.D. Cal. 1991). "The relevant phraseology is 'solely for uses reasonably related,' not 'solely for purposes reasonably related.' Obviously Congress is familiar with the word 'purposes.' If Congress had wanted courts to focus on 'purposes' it probably would have selected that word instead of the substantially more awkward word 'uses' . . . ." *Id.* at 1278 (emphasis added).

Reason #2. "Second, though Hospira informed the FDA in 2014 that its 2013 and 2014 batches were for 'commercial inventory,' Hospira's 2015 resubmission (after litigation began) designated these batches for use for continued process verification." Appx73.

As a legal matter, a designation in a spreadsheet does not matter—it is the use that matters. Amgen got the jury and the district court to incorrectly focus on the purpose, repeatedly pointing to Hospira's "commercial inventory" document in which Hospira allegedly used "white out" to change the designation to CPV. Appx1122(889:7-15); Appx1088(756:7-11). Amgen tried to make it look like Hospira was a bad actor by focusing on something that (a) is not bad and (b) is legally irrelevant.

A party's intent (commercial or otherwise) is irrelevant, as explained by the *Intermedics* court:

> Plaintiff has urged [that] we put the "intent" of the party that claims to be engaged in activity protected by the exemption at the center of the judicial inquiry.
>
> We are not sure what "intent" means here. One possibility is that plaintiff is suggesting that the ultimate target of the inquiry should be a subjective state of mind. If so, we are troubled by the prospect of having to search for such a thing in a corporate body or other business organization. . . .
>
> We also fail to understand why the subjective state of mind of a party should be significant in this setting. Surely Congress was not concerned about clearing certain "unacceptable" thoughts or hopes or visions out of certain persons' minds.

Intermedics, Inc., 775 F. Supp. at 1274. By focusing on alleged commercial intent, Amgen inappropriately skewed the entire Safe Harbor analysis.

Reason #3. "Third, Dr. Levine admitted that he did not consider whether Hospira made any batches for commercial inventory, and that 'simply submitting data [to the FDA] isn't a justification' for manufacturing a batch of drug substance." Appx73.

Again, the district court should have looked at the evidence of how the batches were used, not the "justification", *i.e.*, purpose, for manufacturing them. Because it is irrelevant whether Hospira made any batches for a commercial purpose, it does not matter whether Dr. Levine considered it. And, most importantly, submitting data to FDA is a core aspect of the Safe Harbor: "It shall not be an act of infringement to make . . . a patented invention . . . solely for uses reasonably related to the development and *submission* of information under a Federal law . . . ." 35 U.S.C. 271(e)(1) (emphasis added). Using something to submit information to FDA—whether it provides a "justification" to manufacture or not—is precisely what the statute protects. In the end, the jury verdict should be vacated and JMOL granted for Hospira.

IV. THE DAMAGES AWARD WAS PREMISED ON LEGAL ERROR.

A. The Purpose of Damages Is To Make the Patentee Whole.

Under 35 U.S.C. § 284, the remedy for patent infringement is "damages adequate to compensate for the infringement, but in no event less than a reasonable royalty for the use made of the invention." The report of the House Committee on Patents (adopted by the Senate), which led to the inclusion of the reasonable-royalty language, was "to make the basis of recovery in patent-

infringement suits general damages, that is, any damages the complainant can prove, not less than a reasonable royalty . . . ." House Report No. 1587 to accompany H.R. 5311 (1946), 35 U.S.C. § 70 (1946) (now 35 U.S.C. § 284).

In interpreting Section 284, the Supreme Court has stated that the measure of damages is "compensation for the pecuniary loss [the patentee] has suffered from the infringement, without regard to the question whether the defendant has gained or lost by his unlawful acts." *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 377 U.S. 476, 507 (1964) (quoting *Coupe v. Royer*, 155 U.S. 565, 582 (1895)). The Federal Circuit has emphasized that infringement damages are only "designed to make whole the injured party," *Del Mar Avionics, Inc. v. Quinton Instrument Co.*, 836 F.2d 1320, 1328 (Fed. Cir. 1987), and that "it is the 'value of what was taken' that measures a 'reasonable royalty' under 35 U.S.C. § 284," *Ericsson, Inc. v. D-Link Sys., Inc.*, 773 F.3d 1201, 1226 (Fed. Cir. 2014) (quoting *Dowagiac Mfg. Co. v. Minn. Moline Plow Co.*, 235 U.S. 641, 648 (1915)).

This Court has recently reaffirmed that, when determining a reasonable royalty, "patent damages are limited to those 'adequate to compensate for the infringement.'" *Enplas Display Device Corp. v. Seoul Semiconductor Co.*, No. 16-2599, slip op. at 22 (Fed. Cir. Nov. 19, 2018). This Court has also held that, "[a]t all times, the damages inquiry must concentrate on compensation for the

economic harm caused by infringement of the claimed invention," and stressed that "the trial court must carefully tie proof of damages to the claimed invention's footprint in the market place." *ResQNet.com, Inc. v. Lansa, Inc.*, 594 F.3d 860, 869 (Fed. Cir. 2010).

Courts have employed a "hypothetical negotiation" to determine a "reasonable royalty." *See, e.g.*, *id.* at 868; *Georgia-Pacific Corp. v. United States Plywood Corp.*, 318 F. Supp. 1116, 1120 (S.D.N.Y. 1970). Three of the factors considered are (i) the assumption of an arm's-length negotiation between a willing licensor and a willing licensee, (ii) "[t]he extent to which the infringer has made use of the invention; and any evidence probative of the value of that use," and (iii) "[t]he utility and advantages of the patent property over the old modes or devices, if any, that had been used for working out similar results." *Id.*

In addition, a fact-finder can consider events after the hypothetical negotiation to determine if a royalty is reasonable. This "book of wisdom" doctrine was set forth by Justice Cardozo in 1933 and endorsed by this Court in 1988. *See Sinclair Refining Co. v. Jenkins Petroleum Process Co.*, 289 U.S. 689 (1933); *Fromson v. Western Litho Plate & Supply Co.*, 853 F.2d 1568 (Fed. Cir. 1988). This Court's *Fromson* decision has been followed extensively. *See, e.g.*, *Maxwell v. J. Baker, Inc.*, 86 F.3d 1098, 1109 (Fed. Cir. 1996); *ResQNet.com, Inc.*, 594 F.3d at 872-73.

B. Amgen Obtained a Windfall That Goes Well Beyond Compensating for any Infringement.

The damages award should be vacated because the district court erred in denying Hospira's *Daubert* motion and allowing Dr. Heeb's testimony, and because the district court erred in denying Hospira's JMOL motion that the damages award should be vacated because both the amount and the lump-sum nature did not reflect a "reasonable royalty" as required by the Patent Act.

Dr. Heeb's opinion is based on a legally flawed methodology that looked to Hospira's potential gain from using the patents, not any harm suffered by Amgen or any economic value of the '298 patent. The core of Dr. Heeb's opinion is based on the "value of delay" to Hospira—namely, how much profit Hospira could earn in the marketplace if it could launch its EPO product as soon as Amgen's patents expired, rather than waiting to make EPO after expiration and delaying launch. Appx784(631:12-632:9). Dr. Heeb set this value, which he calculated to be $154 million, as the baseline for the negotiation. That is, under Dr. Heeb's version of a "willing" negotiation, Hospira would *at minimum* pay the entire amount of its hypothetical value of delay. That is economically nonsensical. But more importantly, from a legal framework, it looks at the (hypothetical) benefit to Hospira, not the harm to Amgen. That approach is squarely inconsistent with the damages principles established in long-standing Supreme Court case law. Damages are meant to be "compensation for the pecuniary loss [the patentee] has

suffered from the infringement, *without regard* to the question whether the defendant has gained or lost by his unlawful acts." *Aro Mfg.*, 377 U.S. at 507 (emphasis added).

In addition, Dr. Heeb testified that Hospira would have been willing to pay a large, up-front, lump-sum royalty in 2013. Appx786(638:13-23). Dr. Heeb opined that Hospira would have accepted all the risk under this arrangement. Appx786(640:1-17); Appx791(660:4-18). Although he admitted that both sides of the hypothetical negotiation would have understood the risk that approval might be delayed, or even denied, he deliberately chose not to adjust his calculations accordingly. Appx791(660:4-20).

Indeed, the only evidence Dr. Heeb identified to justify a lump-sum payment was Hospira's distribution agreement with Vifor. Appx787(642:3-22). But that agreement was entered into years after the hypothetical negotiation, and it accounted for regulatory uncertainty by including a running royalty on batches sold and claw-back provisions tied to FDA approval. *Id.*; Appx789(653:3-16); Appx791(658:22-660:3). A lump-sum payment that cannot be clawed back gives Amgen a windfall because at the time of trial (and long after the patents-in-suit had expired) Hospira had still not received FDA approval or sold any EPO. Appx788(649:16-22). There was no harm to Amgen, particularly not harm that justified an upfront, lump-sum payment with no contingency.

Finally, Dr. Heeb failed to account for the reality that Amgen does not use the ’298 patent to produce Epogen or any commercial product. Appx722-723(385:13-386:20). The “footprint in the market place” is non-existent. As Dr. Bell put it at trial, “no product has ever been commercialized using the ’298 patent, which makes you question a little bit, well, just how much could that actually be worth?” Appx1466(1247:22-1248:5). Amgen practices the Lai prior art. Appx723(386:4-8). Dr. Heeb ignored this and presented a fictional valuation based on sales of Epogen, which is not an embodiment of the ’298 patent. Appx784(633:5-14); Appx785(636:2-11). Amgen should not be able to get lost profits, in the guise of a reasonable royalty, on a patent it does not practice. These flaws resulted in a verdict so grossly disproportionate to any harm suffered by Amgen and the economic value of the ’298 patent that it must be vacated.

CONCLUSION

For the reasons stated above, this Court should reverse or vacate the final judgment on claims 24 and 27 of the ’298 patent, find that all batches were protected by the Safe Harbor, and vacate the damages award.

Dated: December 13, 2018

Respectfully submitted,

/s/ Thomas J. Meloro

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Circuit Rule 28.1. This brief contains 13,990 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

This brief complies with the typeface requirements of Federal Circuit Rule 28.1 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 December 13, 2018.

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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Addendum

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, v. HOSPIRA, INC., Defendant.	)	C.A. No. 1:15-cv-00839-RGA

[PROPOSED] FINAL JUDGMENT

WHEREAS this action between Plaintiffs Amgen Inc. and Amgen Manufacturing, Limited ("Amgen") and Defendant Hospira, Inc. ("Hospira") involves U.S. Patent Nos. 5,756,349 ("the '349 patent") and 5,856,298 ("the '298 patent");

WHEREAS Amgen initially asserted infringement of claims 1 to 7 of the '349 patent and claims 8, 19, 24, and 27 of the '298 patent;

WHEREAS the Court held in its January 23, 2017 Order on Claim Construction (D.I. 180) that claims 8 and 19 of the '298 patent are invalid;

WHEREAS the Court conducted a jury trial beginning on September 18, 2017 on the issues of infringement of claims 1 to 7 of the '349 patent, infringement of claims 24 and 27 of the '298 patent, validity of claims 24 and 27 of the '298 patent, Hospira's safe-harbor defense, and damages;

WHEREAS the Jury returned a Jury Verdict on all issues tried to the jury on September 22, 2017 (D.I. 326);

WHEREAS on September 25, 2017, the Court entered Judgment based on the Jury Verdict (D.I. 327) in the amount of $70,000,000 for Plaintiff Amgen and against Defendant

Hospira on the Third Count of the Second Amended Complaint, further entering judgment for Defendant Hospira and against Plaintiff Amgen on the Fourth Count of the Second Amended Complaint, and further entering judgment for Plaintiff Amgen and against Defendant Hospira on Hospira's Second Counterclaim;

WHEREAS the parties stipulated and the Court ordered on October 12, 2017 that the Judgment entered on September 25, 2017 was not a final judgment under Fed. R. Civ. P. 54(a) or 54(b), was not subject to immediate appeal or execution under Fed. R. Civ. P. 62(a) or 69, and that any execution on the Judgment of September 25, 2017 was stayed pursuant to Fed. R. Civ. P. 62(b) without security until 14 days after the Court entered final judgment or as otherwise ordered by the Court or stipulated by the parties (D.I. 349 and D.I. 350);

WHEREAS the Court, having considered the parties' post-trial motions, issued a Memorandum Opinion (D.I. 386) and Order (D.I. 387) on August 27, 2018 dismissing as moot Hospira's Rule 50(a) Motion for Judgment as a Matter of Law on the Issues of Safe Harbor, Noninfringement, Invalidity, and Damages (D.I. 336); denying Hospira's Motion for Judgment as a Matter of Law Under Rule 50(b) and, in the Alternative, For Remittitur or New Trial Under Rule 59 (D.I. 355), Hospira's Motion to Seal Confidential Exhibits Admitted at Trial (D.I. 361), and Amgen's Renewed Motion for Judgment as a Matter of Law of Infringement of the '349 Patent or, in the Alternative, for a New Trial (D.I. 356); and granting in part Amgen's Motion for Prejudgment and Post-judgment Interest (D.I. 352);

WHEREAS the Court has entered a Stipulation and Order (D.I. 390) dismissing Amgen's First Count of the Second Amended Complaint with prejudice, and dismissing Hospira's Fourth Counterclaim without prejudice, except that Hospira's Fourth Counterclaim will be deemed dismissed with prejudice if Amgen does not appeal the Jury Verdict of non-

infringement of the '349 patent or this Court's denial of Amgen's Renewed Motion for Judgment as a Matter of Law of Infringement of the '349 Patent or, in the Alternative, for a New Trial (D.I. 356), or if the Court of Appeals affirms the Jury Verdict of non-infringement of the '349 patent and this Court's denial of that motion;

IT IS HEREBY ORDERED and **FINAL JUDGMENT IS HEREBY ENTERED** as follows:

IT IS ORDERED AND ADJUDGED that **FINAL JUDGMENT** in the amount of $70,000,000 is entered in favor of Amgen and against Hospira on the Third Count of the Second Amended Complaint (D.I. 139) and Hospira's First Counterclaim (D.I. 151). As set forth in the Jury Verdict (D.I. 326), Hospira infringed claims 24 and 27 of the '298 patent, and Hospira's safe-harbor defense does not apply to fourteen (14) of the twenty-one (21) accused batches of Hospira's EPO drug substance.

IT IS ORDERED AND ADJUDGED that **FINAL JUDGMENT** is entered in favor of Amgen and against Hospira on Hospira's Second Counterclaim (D.I. 151) with respect to claims 24 and 27 of the '298 patent. As set forth in the Jury Verdict (D.I. 326), claims 24 and 27 of the '298 patent are not invalid for anticipation or obviousness.

IT IS ORDERED AND ADJUDGED that **FINAL JUDGMENT** is entered in favor of Hospira and against Amgen on Hospira's Second Counterclaim (D.I. 151) with respect to claims 8 and 19 of the '298 patent. As set forth in this Court's Order on Claim Construction (D.I. 180), claims 8 and 19 of the '298 patent are invalid.

IT IS ORDERED AND ADJUDGED that **FINAL JUDGMENT** is entered in favor of Hospira and against Amgen on the Fourth and Fifth Counts of the Second Amended Complaint

(D.I. 139) and Hospira's Third Counterclaim (D.I. 151). As set forth in the Jury Verdict (D.I. 326), Hospira did not infringe any of claims 1 through 7 of the '349 patent.

IT IS ORDERED that, for the reasons set out in this Court's Memorandum Opinion dated August 27, 2018 (D.I. 386), Amgen is awarded prejudgment interest on the jury's damages award in the amount of $10,018,044.

IT IS ORDERED that, for the reasons set out in this Court's Memorandum Opinion dated August 27, 2018 (D.I. 386), Amgen is awarded post-judgment interest on the $70,000,000 damages award, calculated at the statutory rate specified under 28 U.S.C. § 1961, from September 25, 2017 until such date that Hospira satisfies this Final Judgment, computed daily and compounded annually. The applicable statutory rate for this purpose will be the one in effect for a judgment entered on September 25, 2017, namely, 1.31%.

IT IS ORDERED that, for the reasons set out in this Court's Memorandum Opinion dated August 27, 2018 (D.I. 386), Amgen is awarded post-judgment interest on the $10,018,044 in prejudgment interest calculated at the statutory rate specified under 28 U.S.C. § 1961, from the date of entry of this Final Judgment until such date that Hospira satisfies this Final Judgment, computed daily and compounded annually. The applicable statutory rate for this purpose will be the one in effect for a judgment entered on the date of entry of this Final Judgment, namely, at a rate equal to the weekly average 1-year constant maturity Treasury yield, as published by the Board of Governors of the Federal Reserve System, for the calendar week preceding the date of entry of this Final Judgment.

IT IS ORDERED that Amgen's First and Second Counts of the Second Amended Complaint (D.I. 139) are **DISMISSED** with prejudice.

IT IS ORDERED that Hospira's Fourth Counterclaim (D.I. 151) is **DISMISSED** without prejudice, except that Hospira's Fourth Counterclaim will be deemed dismissed with prejudice if Amgen does not appeal the Jury Verdict of non-infringement of the '349 patent or this Court's denial of Amgen's Renewed Motion for Judgment as a Matter of Law of Infringement of the '349 Patent or, in the Alternative, for a New Trial (D.I. 356), or if the Court of Appeals affirms the Jury Verdict of non-infringement of the '349 patent and this Court's denial of that motion.

SO ORDERED this 11 day of September, 2018.

Richard G. Andrews

THE HONORABLE RICHARD G. ANDREWS
UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, v. HOSPIRA, INC., Defendant.	Civil Action No. 15-cv-839-RGA

MEMORANDUM OPINION

Robert W. Whetzel and Jason J. Rawnsley, RICHARDS, LAYTON & FINGER, P.A., Wilmington, DE; Kevin M. Flowers, Mark H. Izraelewicz, John R. Labbé, Julianne M. Hartzell, Benjamin T. Horton, Tiffany D. Gehrke, and Douglas G. Bolesch, MARSHALL, GERSTEIN & BORUN LLP, Chicago, IL; Nicholas Groombridge, Eric Alan Stone, Jennifer H. Wu, and Stephen A Maniscalco, PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP, New York, NY.

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Attorneys for Defendant.

August 27, 2018

ANDREWS, U.S. DISTRICT JUDGE:

On September 18, 2015, Amgen, Inc. and Amgen Manufacturing, Limited (collectively, "Amgen") sued Hospira, Inc. for infringement of U.S. Patent No. 5,856,298 under 35 U.S.C. §§ 271(a) and 271(e)(2)(C) and for infringement of U.S. Pat. No. 5,756,349 under § 271(a). (D.I. 1). The '298 patent and the '349 patent cover erythropoietin ("epoetin" or "EPO") isoforms and aspects of their production. Hospira submitted Biologic License Application ("BLA") No. 125-545 to the FDA in December 2014, seeking FDA approval for Hospira's epoetin biosimilar product. (D.I. 290-1 at 1). Amgen asserts that Hospira's manufacture of drug substance for its epoetin biosimilar drug product infringes claims 24 and 27 of the '298 patent and claims 1-7 of the '349 patent. (D.I. 290 at 1).

I held a jury trial from September 18-22, 2017. (D.I. 328-332 ("Trial Tr.")).[1] The jury found each of the asserted claims not proved invalid, decided that the asserted claims of the '349 patent were not infringed, and returned a verdict of infringement of all asserted claims of the '298 patent. (D.I. 325 at 2). Of Hospira's twenty-one accused drug substance batches, the jury found seven batches entitled to the safe harbor defense. (*Id.* at 3). The jury awarded Amgen $70 million in damages for Hospira's infringement. (*Id.* at 4).

Presently before the Court are Hospira's Rule 50(a) Motion for Judgment as a Matter of Law on the Issues of Safe Harbor, Noninfringement, Invalidity, and Damages and related briefing (D.I. 336, 337, 348, 351), Hospira's Motion for Judgment as a Matter of Law Under Rule 50(b) and, in the Alternative, For Remittitur or New Trial Under Rule 59 and related briefing (D.I. 355, 357, 374, 381), Hospira's Motion to Seal Confidential Exhibits Admitted at Trial and related briefing (D.I. 361, 369, 370), Amgen's Renewed Motion for Judgment as a Matter of Law of

[1] The trial transcript is consecutively paginated. References to the trial transcript will refer to "Trial Tr." in lieu of the docket item reference number.

Infringement of the '349 Patent or, in the Alternative, for a New Trial and related briefing (D.I. 356, 358, 373, 380), and Amgen's Motion for Prejudgment and Post-judgment Interest and related briefing (D.I. 352, 376, 382).

I. LEGAL STANDARDS

A. Judgment as a Matter of Law

Judgment as a matter of law is appropriate if "the court finds that a reasonable jury would not have a legally sufficient evidentiary basis to find for [a] party" on an issue. FED. R. CIV. P. 50(a)(1). "Entry of judgment as a matter of law is a 'sparingly' invoked remedy, 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 liability." *Marra v. Phila. Hous. Auth.*, 497 F.3d 286, 300 (3d Cir. 2007) (citation omitted).

In assessing the sufficiency of the evidence, the Court must give the nonmovant, "as [the] verdict winner, the benefit of all logical inferences that could be drawn from the evidence presented, resolve all conflicts in the evidence in his favor and, in general, view the record in the light most favorable to him." *Williamson v. Consol. Rail Corp.*, 926 F.2d 1344, 1348 (3d Cir. 1991). The Court may "not determine the credibility of the witnesses [nor] substitute its choice for that of the jury between conflicting elements in the evidence." *Perkin-Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 893 (Fed. Cir. 1984). Rather, the Court must determine whether the evidence reasonably supports the jury's verdict. *See Gomez v. Allegheny Health Servs. Inc.*, 71 F.3d 1079, 1083 (3d Cir. 1995); 9B *Charles Alan Wright & Arthur R. Miller, Federal Practice and Procedure* § 2524 (3d ed. 2008) ("The question is not whether there is literally no evidence supporting the party against whom the motion is directed but whether there is evidence

upon which the jury might reasonably find a verdict for that party.").

Where the movant bears the burden of proof, the Third Circuit applies a stricter standard. *Fireman's Fund Ins. Co. v. Videfreeze Corp.*, 540 F.2d 1171, 1177 (3d Cir. 1976). To grant judgment as a matter of law in favor of a party that bears the burden of proof on an issue, the Court "must be able to say not only that there is sufficient evidence to support the [movant's proposed] finding, even though other evidence could support as well a contrary finding, but additionally that there is insufficient evidence for permitting any different finding." *Id.*

B. New Trial

Federal Rule of Civil Procedure 59(a)(1)(A) provides, in pertinent part: "The court may, on motion, grant a new trial on all or some of the issues—and to any party— . . . after a jury trial, for any reason for which a new trial has heretofore been granted in an action at law in federal court . . . ." Among the most common reasons for granting a new trial are: "(1) when the jury's verdict is against the clear weight of the evidence, and a new trial must be granted to prevent a miscarriage of justice; (2) when newly discovered evidence exists that would likely alter the outcome of the trial; (3) when improper conduct by an attorney or the court unfairly influenced the verdict; or (4) when the jury's verdict was facially inconsistent." *See Zarow-Smith v. N.J. Transit Rail Operations, Inc.*, 953 F. Supp. 581, 584-85 (D.N.J. 1997) (citations omitted).

The decision to grant or deny a new trial is committed to the sound discretion of the district court. *Allied Chem. Corp. v. Daiflon, Inc.*, 449 U.S. 33, 36 (1980); *Olefins Trading, Inc. v. Han Yang Chem Corp.*, 9 F.3d 282, 289 (3d Cir. 1993). Although the standard for granting a new trial is less rigorous than the standard for granting judgment as a matter of law—in that the Court need not view the evidence in the light most favorable to the verdict winner—a new trial should only be granted where "a miscarriage of justice would result if the verdict were to stand" or where the

verdict "cries out to be overturned" or "shocks [the] conscience." *Williamson*, 926 F.2d at 1352-53.

II. HOSPIRA'S 50(a) AND 50(b) MOTIONS

Hospira's Rule 50(a) motion raises the same issues as its Rule 50(b) motion.[2] Having considered and decided the issues in ruling on Hospira's Rule 50(b) motion, I will dismiss Hospira's Rule 50(a) motion as moot.

Hospira seeks judgment as a matter of law on the issues of the applicability of its safe harbor defense, noninfringement and invalidity of the '298 patent, and damages. (D.I. 357, pp. 1-22). Alternatively, Hospira seeks a new trial based on what it characterizes as improper jury instructions on the safe harbor defense and third party liability, improper claim construction, and contradictory infringement and validity verdicts. (*Id.* pp. 22-30). Finally, Hospira argues that it is entitled to a remittitur of the damages award. (*Id.* p. 28).

A. JMOL

1. Safe Harbor

The parties dispute whether any reasonable jury could have found some, but not all, of Hospira's drug substance batches protected by the "safe harbor" defense. (*Id.* p. 1; D.I. 374, p. 2).

The Biologics Price Competition and Innovation Act of 2009 ("BPCIA") "create[s] an artificial 'act of infringement,' similar to that of 35 U.S.C. § 271(e)(2)(A), and [allows] infringement suits to begin based on the filing of a biosimilar application prior to FDA approval and prior to marketing of the biological product." *Amgen Inc. v. Sandoz Inc.*, 877 F.3d 1315, 1321 (Fed. Cir. 2017) (citing 35 U.S.C. § 271(e)(2)(C), (e)(4), (e)(6)). Section 271(e)(1) carves out an

[2] Hospira's Rule 50(a) motion, filed based on information known at the close of Amgen's case-in-chief, raises the issue of noninfringement of the '349 patent. (D.I. 337 at 10). This issue was mooted when Hospira received a verdict of noninfringement of the '349 patent at trial, and Hospira's Rule 50(b) motion does not raise it. (D.I. 325 at 2).

exception to this rule, creating a "safe harbor" defense for defendants when their otherwise-infringing activities are "solely for uses reasonably related" to obtaining FDA approval. 35 U.S.C. § 271(e)(1) ("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."); *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1027 (Fed. Cir. 1997) ("By its terms, this shield from infringement permits use of 'patented invention[s]' to acquire information for regulatory approval of 'drugs or veterinary biological products.'") (brackets in original). "As long as the activity is reasonably related to FDA approval, [a party's] intent or alternative uses are irrelevant to its qualification to invoke the section 271(e)(1) shield." *Abtox*, 122 F.3d at 1030.

Hospira asserts that no reasonable jury could find that the safe harbor defense did not protect each of its twenty-one drug substance batches. (D.I. 357, p. 1). Additionally, Hospira contends that Amgen's arguments improperly limited the applicability of the safe harbor defense to batches required for FDA approval. (*Id.* p. 5). Since each batch was used for one or more of biosimilarity[3] testing, updating product specifications, process validation, stability testing, or continued process verification, Hospira insists that no reasonable jury could have found that each of the batches was not reasonably related to obtaining FDA approval. (*Id.* pp. 4-8). According to Hospira, the jury improperly second-guessed the number of batches that Hospira manufactured,

[3] Hospira cites draft guidance from the FDA, published on September 22, 2017 and distributed for comment purposes only, as further support for its argument that each of the 2013 drug substance batches were reasonably related to FDA approval. (D.I. 357, p. 4). The draft guidance "recommend[s] a minimum of 10 reference product lots be sampled" in order "to establish meaningful similarity acceptance criteria." (D.I. 357-1 at 7).

Hospira seeks to rely on the draft guidance to support its argument that no reasonable jury could have concluded that the safe harbor did not protect each drug substance batch that Hospira used for biosimilarity testing. The draft guidance was not publicly available at the time of trial, let alone at the time Hospira manufactured the drug substance batches at issue. The draft guidance was not presented to the jury. I thus find Hospira's reliance on the draft guidance misplaced.

when "the subjective reason why any batch was made is not relevant" to whether the safe harbor applies. (D.I. 381, pp. 3-4). Essentially, Hospira argues that since Hospira generated test data for each batch prior to FDA approval, each batch could conceivably have been used to respond to inquiries from the FDA, and each batch was reasonably related to FDA approval.

Amgen disagrees and maintains that substantial evidence supports the jury's reasonable conclusion that Hospira failed to prove that the safe harbor defense applies to each of Hospira's drug substance batches. (D.I. 374, p. 2). According to Amgen, the evidence presented at trial gave the jury ample reason to reject Hospira's arguments about biosimilarity, product specifications, process validation, stability, and continued process verification; credit Amgen's witnesses; and conclude that the safe harbor applied to only seven of Hospira's twenty-one drug substance batches. (*Id.* pp. 2-4).

Regarding biosimilarity, even accepting as true that ten reference product lots are required to establish biosimilarity, Amgen points out that Hospira performed biosimilarity testing on drug product batches, not drug substance batches, and that Hospira had previously manufactured twenty-six drug product batches from four drug substance batches. (*Id.* p. 12 (citing Trial Tr. 811:24-812:8; DTX-266 at 3-4)). Therefore, Amgen argues, though Hospira performed biosimilarity testing on nine drug substance batches, "the jury reasonably concluded that the final two of those batches were not made for uses reasonably related to seeking FDA approval where Hospira had made 26 drug product batches from just 4 of those drug substance batches for biosimilarity testing." (*Id.* pp. 12-13).

Amgen also argues, "Hospira's witnesses admitted, and its submissions to the FDA confirmed, that the FDA never required Hospira to manufacture any additional batches of its drug substance to support its narrowed release specifications." (*Id.* p. 10 (citing Trial Tr. 823:4-824:1)).

Regardless, Hospira would be required to perform release testing on all batches manufactured before or after FDA approval to ensure that the batches complied with the release specifications in place at the time of manufacture. (Trial Tr. 819:11-22). Each of the batches at issue in this case "were released against specifications that were in place at the time of manufacture, not against revised specifications," and they remain available to Hospira for future use, since they comply with the release specifications at the time of their manufacture (D.I. 374, p. 10 (citing Trial Tr. 820:24-822:1)). Therefore, Amgen asserts, Hospira's revised product specifications do not justify the conclusion that product specification testing on each of the batches at issue was reasonably related to obtaining FDA approval.

Regarding process validation, Amgen submits that the "Process Validation and/or Evaluation" section of Hospira's BLA does not refer to batches other than those admitted by Amgen or found by the jury to fall within the safe harbor. (*Id.* p. 11 (citing DTX-250)). Amgen points out that even Hospira's updated BLA does not list any of the fourteen batches that the jury found to fall outside the safe harbor defense. (*Id.*). Additionally, Amgen notes, cleaning validation is "the only specific process validation that Hospira raises in its motion," and "Hospira's FDA expert, Dr. Levine, admitted that cleaning validation need not be completed before FDA approval."[4] (*Id.* (citing Trial Tr. 1102:14-24, 1153:16-18); *see also* Trial Tr. 878:5-18 (Dr. Billingham acknowledging same)).

Stability testing would not have required a reasonable jury to conclude that each of Hospira's batches was protected by the safe harbor, Amgen argues, because FDA guidance

[4] Amgen maintains that Hospira relied on a cleaning validation document authored by GSK for Hospira (DTX-252), in lieu of presenting any cleaning validation data submitted to the FDA. (D.I. 374, p. 12). In reply, Hospira responds, "Dr. Billingham clearly testified that all of the 2013, 2014, and some 2015 batches were used in several cleaning validation studies to be completed before FDA inspection," and that the FDA requires that such cleaning validation studies be performed. (D.I. 381, p. 7).

requires only three batches to demonstrate stability before obtaining FDA approval. (D.I. 374, p. 9 (citing PTX-492, p. 3)). Amgen argues that the jury was therefore free to credit Dr. Martin-Moe's testimony that Hospira's five batches from 2009 to 2012 would have provided sufficient stability data. (*Id.* (citing Trial Tr. 1329:6-1331:9)). Additionally, stability testing was required each time a new drug substance batch was made, regardless of the future uses for the batch. (Trial Tr. 1338:2-1339:5). As further support, Amgen cites an internal Hospira Risk Authorization document confirming Hospira's belief that material from drug substance batches manufactured in 2009 and 2012 was sufficient to "support [the drug substance] 'shelf life and commercial saleability of material produced in subsequent campaigns.'" (D.I. 374, pp. 9-10 (quoting PTX-342 at 1)). The Risk Authorization further states, "The balance of the material from the 2013 campaign (approximately 50%) and most of the material from the 2014 and 2015 campaigns will serve as commercial inventory to support single dose vial launch stock."[5] (PTX-342 at 1).

Like stability testing, Amgen's witnesses testified that continued process verification is "an ongoing program . . . during routine commercial production" that sometimes "can take many years to complete." (D.I. 374, p. 8 (citing Trial Tr. 1336:21-1337:9)). Though the FDA requires that applicants have committed to a continued process verification program before approval, completing continued process verification is not required to obtain FDA approval. (Trial Tr. 1337:10-13; *see also* PTX-435, p. 14). Hospira's witnesses confirmed that continued process verification need not be completed before FDA approval, and Hospira made no commitment to manufacture the thirty batches tested for continued process verification prior to FDA approval. (Trial Tr. 752:7-11 (Ms. Dianis), 747:17-748:3 (Ms. Dianis), 883:3-6 (Dr. Billingham), 1095:8-24 (Dr. Levine)).

[5] The remaining 50% of the 2013 drug substance material was to be "allocated to continuing CMC and Clinical development work." (PTX-342 at 1).

Amgen further argues that the jury was free to credit Amgen's witnesses over Hospira's witnesses given the evidence presented. (D.I. 374, pp. 4-5). First, though Hospira argues that it manufactured each of the 2013, 2014, and 2015 drug substance batches for use in obtaining FDA approval, Amgen notes that Ms. Dianis, the regulatory lead for Hospira's EPO product, "admitted that she did not know why Hospira made its 2015 batches, or why Hospira made as many batches as it did, and that she assumed Hospira's supply team (not the regulatory team) made those decisions." (*Id.* (citing Trial Tr. 738:22-740:2)). Second, though Hospira informed the FDA in 2014 that its 2013 and 2014 batches were for "commercial inventory," Hospira's 2015 resubmission (after litigation began) designated these batches for use for continued process verification. (*Id.* at 5 (citing PTX-250 at 4-6; DTX-255 at 5-8); *see also* Trial Tr. 748:9-751:23). Third, Dr. Levine admitted that he did not consider whether Hospira made any batches for commercial inventory, and that "simply submitting data [to the FDA] isn't a justification" for manufacturing a batch of drug substance. (Trial Tr. 1075:18-1076:1, 1098:1-10).

I agree with Amgen and conclude that substantial evidence supports the jury's verdict that not all of Hospira's drug substance batches are protected by the safe harbor. To demonstrate entitlement to judgment as a matter of law on its safe harbor defense, Hospira must demonstrate that "there is insufficient evidence for permitting any other finding." *Fireman's Fund Ins. Co.*, 540F.2d at 1177. Hospira has not met that burden.

A reasonable jury could have concluded that fewer than all of the batches were protected by the safe harbor defense. Testimony by Ms. Dianis and Dr. Levine either called into question or contradicted Hospira's argument that each of the batches at issue fell within the safe harbor defense. Amgen's presentation of FDA guidance documents, admissions in Hospira's internal documents, and post-litigation changes to Hospira's representations to the FDA also challenged

Hospira's assertion that each batch at issue was covered by the safe harbor. Finally, Hospira's argument that the jury impermissibly focused on Hospira's intent in manufacturing the batches does not stand up to further scrutiny. Though all of the 2015 batches were designated for use as "commercial inventory" in Hospira's Risk Authorization, the jury nonetheless found that some of those batches were protected by the safe harbor. (D.I. 325 at 3). This suggests that the jury did not improperly base its verdict on Hospira's intent. I therefore conclude that substantial evidence supports the jury's verdict that only some batches at issue are covered by the safe harbor defense. I will deny Hospira's motion for JMOL on this ground.

2. *Noninfringement of the '298 Patent*

Hospira submits that I should grant its motion for JMOL that it does not infringe claims 24 or 27 of the '298 patent.

Hospira contends that it is entitled to JMOL of noninfringement of claim 24 of the 298 patent because "Amgen failed to prove that Hospira's process 'selectively elutes' isoforms as required by claim 24 and as construed by the Court." (D.I. 357, p. 12). According to Hospira, elution of all biologically active isoforms does not qualify as selective elution. (*Id.*). Specifically, "Hospira's process does not achieve a precise set of isoforms;" instead, it "results in a variable number of different isoforms [i.e., five to eight], and a variable amount of each isoform in the drug substance." (*Id.* (citing Trial Tr. 984:5-989:17 (Dr. Levine))). Dr. Levine opined that such variability is not consistent with selective elution, because one would expect consistent levels of each isoform across batches in a selective elution process. (Trial Tr. 989:3-9, 1580:4-23). Finally, Hospira argues that Amgen failed to prove infringement of the '298 patent because it did not provide any analysis of the starting material that Hospira puts into the chromatography column. (D.I. 381, p. 9).

Amgen maintains that substantial evidence supports the jury's conclusion that Hospira's process "selectively elutes" isoforms as required by claim 24 of the '298 patent. Dr. Cummings testified that Hospira's process "selectively elutes" isoforms because it "first elute[s] more basic isoforms from the chromatography column, then elute[s] the remaining desired isoforms." (D.I. 374, p. 13 (citing Trial Tr. 468:11-469:4)). During trial, Amgen argued that Dr. Levine ignored the first step in the elution process, and that Dr. Levine admitted that he "was intentionally not showing those [more basic isoform elution] steps because [he] had already discussed this" the day before. (Trial Tr. 1156:22-1157:13). Amgen also notes that contrary to Hospira's argument, the Court's claim construction for claim 24 does not "require a 'precise set of predetermined isoforms.'" (D.I. 374, p. 14; *see also* D.I. 180 at 2). Further, Dr. Strickland, the inventor on the '298 patent, testified that the process he invented "select[s] isoforms by—well, specific mixtures of isoforms[,] by selective elution of an ion exchange chromatography column." (Trial Tr. 373:14-20). As further evidence that Hospira's process met the "selectively elute" limitation, Amgen offered Hospira's lot release specifications, which specified five isoforms that must be present, and three additional isoforms that may be present, with specific ranges for each isoform. (DTX-141, p. 7; Trial Tr. 470:13-472:19). Finally, Amgen asserts that Hospira's "starting material" argument is frivolous because "Hospira admitted in its BLA that its ion-exchange chromatography process first removed the 'more basic' isoforms . . . from the column (DTX-116 at 58), a step that would not be necessary if the starting material did not contain isoforms that were 'more basic' than the isoforms required by Hospira's release specification." (D.I. 374, p. 15). Similarly, Hospira's BLA test results reveal that the only isoforms present in the material leaving the column in Hospira's process are the same isoforms present in Hospira's drug substance. (*Id.* (citing DTX-139, p. 102; DTX-141, p. 7; Trial Tr. 474:19-476:11)).

I agree with Amgen that substantial evidence supports the jury's verdict that Hospira infringes claim 24 of the '298 patent. Dr. Strickland's testimony, Hospira's release specifications, and Dr. Cummings' testimony provided the jury substantial evidence to conclude that Hospira's process met the "selectively elute" limitation and infringed claim 24 of the '298 patent. Additionally, I think Dr. Levine's admission that he did not include all steps of the process in his demonstratives for the jury provided a basis for the jury to question the reliability of his conclusions and discount his testimony.

Claim 27 of the '298 patent requires "preparing a mixture of two or more erythropoietin isoforms of claim 1." Though I construed claim 27 as an independent claim, Hospira argues that it is entitled to JMOL because Amgen did not mention claim 1 during trial, nor did it present evidence that "isoforms are isolated during Hospira's manufacturing process." (D.I. 357, p. 13). Amgen responds that since claim 27 is an independent claim, Amgen was not required to present evidence that each of the limitations of claim 1 was met in order to prove infringement of claim 27. (*Id.* p. 15). As to the isolation of isoforms, Amgen notes that the Court's construction of claim 27 "does not require the isoforms of Claim 1 to be separately prepared prior to making the mixture." (D.I. 374, p. 15 (citing D.I. 308 at 2)). Regardless, Amgen urges, "the evidence at trial showed that the limitations of claim 1 were satisfied, that is, that Hospira's product contains 'biologically active' EPO." (*Id.* (citing DTX-270, p. 17; Trial Tr. 394:1-4 (admission by Dr. Strickland that "all EPO isoforms have biological activity."))).

I agree with Amgen. Though Hospira may be correct that Amgen never explicitly mentioned claim 1 at trial, Hospira does not discuss substantively how Amgen failed to prove that the limitations of claim 1 were met. Amgen has also offered citations to Hospira's BLA and to the trial transcript to support the conclusion that the limitations of claim 1 were satisfied.

Claim 27 also has a limitation requiring the creation of an EPO composition with a "predetermined in vivo specific activity." Hospira argues that Amgen failed to prove that Hospira infringed this limitation because "Dr. Cummings did not provide any evidence of the actual in vivo specific activity of Hospira's product," and Hospira's product targets a range of in vivo specific activities, rather than targeting a specific activity. (D.I. 357, p. 14). Hospira also contends, "Dr. Strickland testified that in order to achieve a predetermined specific in vivo activity, one selects individual isoforms and prepares them in such a way to know what biological activity they are going to get."[6] (D.I. 381, pp. 9-10 (citing Trial Tr. 375:12-376:2)). Since there is no evidence that Hospira separates and selects individual isoforms, Hospira argues, there was insufficient evidence for the jury to conclude that Hospira infringed claim 27. (*Id.* p. 10). Amgen responds that Dr. Cummings relied on Hospira's BLA, which stated that 100% of lots fell within an in vivo specific activity of 93-147 U/ μg.[7] (D.I. 374, p. 16 (citing DTX-270, p. 17)).

I agree with Amgen. I do not find Dr. Strickland's testimony, cited by Hospira, inconsistent with Hospira's BLA, which identifies a predetermined in vivo specific activity—93-147 U/μg. (DTX-270, p. 17; *see* Trial Tr. 375:12-376:2). Hospira's BLA provided the jury with substantial evidence to conclude that Hospira's process achieved an EPO composition having a predetermined in vivo specific activity.

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[6] I do not think Dr. Strickland's testimony is as clear as Hospira makes it out to be. The transcript reflects that Dr. Strickand testified as follows:

> Q. And how does that experiment relate to the inventions in claim 24 and 27?
>
> A. Well, it's directly related to both of them in that in claim 24, it's selective elution of isoforms on an ion exchange column, which is what this is an ion exchange column, and it's related to claim 27 in that if we – we can select the fractions from that column to give us a mixture of predetermined biological activity if it was desired since in the background experiments, we determined what the biological activity was of each isoform. Now, since this method separates the isoforms, then we can recombine them and know what biological activity we're going to get.

(Trial Tr. 375:12-376:2 (discussing the '298 patent at 4:12-22)).

[7] EPO is measured in "activity units or international units," represented by "U." (Trial Tr. 208:8-10).

I therefore conclude that substantial evidence supports the jury's verdict that Hospira infringes claims 24 and 27 of the '298 patent. I will deny Hospira's JMOL on this ground.

3. Invalidity of the '298 Patent

Hospira argues that it is entitled to JMOL that the '298 patent is invalid because no reasonable jury could have found that claims 24 and 27 were not anticipated or obvious over U.S. Pat. No. 4,667,016 ("Lai"). (D.I. 357, p. 14). Since it was Hospira's burden to prove invalidity, to prevail on its JMOL, Hospira must demonstrate that "there is insufficient evidence for permitting any different finding" than that the disclosures in Lai render invalid claims 24 and 27 of the '298 patent. *See Fireman's Fund Ins. Co.*, 540F.2d at 1177.

The parties dispute whether Hospira adequately proved that the Lai process inherently anticipates claim 24 of the '298 patent. Specifically, they dispute whether Hospira proved that Lai meets the "selectively eluting" and "predetermined number of sialic acids" limitations of claim 24.

Hospira asserts that Dr. Levine's testimony, Dr. Strickland's testimony, and Dr. Cummings' testimony conclusively established that Lai includes a "selective elution" step. (*Id.* pp. 15-16). Dr. Levine did not dispute that Lai does not refer to the removal of biologically active EPO in ion exchange chromatography. (Trial Tr. 1010:10-16). Based on "the fundamental principles on which ion exchange chromatography works, and the difference in pKa[8] between high sialic and low sialic acid containing isoforms," however, Dr. Levine opined that Lai's step 2 example 2 "low pH, low salt wash will remove proteins that have a pKa greater than the biologically active EPO . . . [which] will include the isoforms of EPO that have a small number of sialic acid[s] and are therefore not biologically active, or less biologically active." (*Id.* 1010:1-16). As further support, Hospira points to Dr. Levine's and Dr. Strickland's discussions of the

[8] pKa is "related to the isoelectric point" of a substance. If a substance "has a low pKa, it's more basic." (Trial Tr. 422:6-22).

'298 patent's disclosure that the starting material for the fourth isoform of EPO is the material removed from the column in Example 2 of Lai, which contains EPO isoforms with less than or equal to nine sialic acids. (*Id.* 1034:5-14, 393:14-21). Dr. Cummings confirmed that when Dr. Strickland replicated the experiment reported in Example 2 of Lai, the result was that EPO isoforms containing nine to fourteen sialic acids were retained on the chromatography column after the first acid wash step. (*Id.* 1508:15-1509:9). Therefore, Hospira argues, Lai inherently discloses selective elution of EPO with less than nine sialic acids. (D.I. 357, p. 16).

Amgen responds that the jury declined to credit Hospira's argument that "practicing Example 2 of Lai 'necessarily and inevitably' resulted in 'selectively eluting' EPO molecules with a 'predetermined' number of sialic acids." (D.I. 374, pp. 16-17). Amgen points to Dr. Cummings, who testified that, contrary to Dr. Levine's assertion, "all EPO is biologically active," and the purpose of Lai was to purify EPO, not to separate EPO isoforms. (Trial Tr. 1494:12-1495:4). Amgen maintains that despite testimony that "some isoforms may be removed in Example 2 of Lai, none of the witnesses "testified that Example 2 in Lai 'necessarily and inevitably' results in" selectively eluting EPO isoforms with a predetermined number of sialic acids, as would be required to prove inherent anticipation. (D.I. 374, p. 18). Amgen argues that Dr. Levine's admission that several factors could affect which isoforms are present in the starting material (including cell culture conditions and the components of the cell culture medium) further supports that the Lai process does not "necessarily and inevitably" meet the limitations of claim 24. (Trial Tr. 1128:19-1130:1). Finally, Amgen notes, Dr. Levine agreed that, "Lai couldn't have selectively eluted isoforms having a predetermined number of sialic acids because Lai eluted all bound isoforms at the same time." (*Id.* 1127:4-9).

Despite the '298 patent disclosures, I think that Dr. Levine's admission that Lai could not

have eluted isoforms having a predetermined number of sialic acids, combined with the absence of testimony from other witnesses that Lai process "necessarily and inevitably" met each of the limitations of claim 24, adequately supports the jury's conclusion that Hospira had failed to prove by clear and convincing evidence that Lai anticipated claim 24.

The issue underlying the parties' dispute over whether Hospira adequately proved that the Lai process inherently anticipates claim 27 of the '298 patent is whether Hospira proved that the Lai process necessarily resulted in an EPO composition "having a predetermined in vivo specific activity." Hospira alleges that testimony by Dr. Levine established that "Lai discloses a composition having a predetermined in vivo specific activity" because Lai "disclosed how to create compositions of the high sialic acid, biologically active EPO." (D.I. 357, p. 18 (citing Trial Tr. 1039:2-1040:16)). Additionally, Hospira asserts that Amgen's witness, Dr. Cummings, essentially conceded that Lai anticipated claim 27 because he opined in the context of infringement that claim 27 may be satisfied by a process that results in a variable amount of the most biologically active isoforms, thus achieving a broad range of in vivo specific activity. (D.I. 381, p. 11). Amgen responds that Dr. Cummings opined that Lai does not disclose a "predetermined in vivo specific activity" because Lai provides no indication of any "finding ahead of time for select mixtures of isoforms." (Trial Tr. 1496:16-1497:16). Amgen also maintains that Lai's disclosure that "biologically active" EPO was eluted does not mean that Lai disclosed an EPO composition with predetermined in vivo specific activity, because all EPO isoforms have some biological activity, and "Lai never refers to a composition with a predetermined in vivo activity." (D.I. 374, p. 19).

The evidence at trial regarding anticipation of claim 27 by Lai consisted primarily of expert testimony. The jury was free to assess the credibility of the experts and weigh their testimony accordingly. Hospira's argument about Dr. Cummings' concession ignores the "predetermined"

portion of the limitation, and does not account for the role of Hospira's BLA to establish an in vivo specific activity in the infringement analysis. It seems to me that a reasonable jury could have credited Dr. Cummings' testimony over that of Dr. Levine, and decided that Lai did not disclose a "predetermined in vivo specific activity," particularly since Hospira was required to prove anticipation by clear and convincing evidence.

Hospira also argues that no reasonable jury could have found that claims 24 and 27 of the '298 patent were non-obvious over Lai in view of Lukowsky. During trial, Dr. Levine offered his opinion that claim 24 would have been obvious because (1) it was known that more sialylated forms of EPO were more biologically active (Trial Tr. 1047:16-23); (2) it was known that sialic acid "add[ed] negative charge to the" EPO molecules to which it was attached (*Id.* 957:3-8); (3) ion exchange chromatography was a well-known method for separating protein molecules by their net charge (*Id.* 967:4-10); and (4) the Beeley reference taught that glycoproteins could be separated by charge using ion exchange chromatography (*Id.* 1052:24-1054:23). Therefore, Hospira argues, a POSA would have been motivated to separate isoforms and create a preparation of EPO with a predetermined in vivo specific activity, and have a reasonable expectation of success in doing so. (D.I. 357, p. 19).

Amgen submits that the Patent Office considered both Lai and Lukowsky during prosecution, and the "PTO examiner acknowledged that the '298 patent taught the unexpected advantage of combinations of isoforms, and the ability to prepare EPO compositions with predetermined EPO isoforms." (D.I. 374, p. 20 (citing PTX-4B, pp. 11-12; Trial Tr. 1500:22-1502:23)). Amgen further points to Dr. Cummings' explanation that Lukowsky does not supply the limitations missing from Lai, because Lukowsky does not disclose EPO "isoforms," a "predetermined mixture of [EPO] isoforms," or "predetermined specific activity" of any EPO

isoforms. (*Id.* (citing Trial Tr. 1489:14-1490:2)).

I think that substantial evidence supports the jury's conclusion that neither claim 24 nor claim 27 of the '298 patent is obvious over Lai in view of Lukowsky and Beeley. Hospira bore the burden by clear and convincing evidence to prove that the asserted claims of the '298 patent were invalid. Since neither Lukowsky nor Lai discloses EPO isoforms, or predetermined mixtures or in vivo specific activities of EPO isoforms, and the PTO acknowledged unexpected results produced by the '298 patent, I cannot say that the jury was unreasonable in deciding that Hospira had not met its burden to prove obviousness. I also note that in the relevant briefing, Hospira's statements of a POSA's motivation to combine these references lack explanation. (D.I. 357, p. 19 ("[A] person of ordinary skill in the art would have been motivated to create a preparation of EPO with a predetermined specific activity, and would have had a reasonable expectation of success in doing so.")).

I therefore conclude that substantial evidence supports the jury's verdict that claims 24 and 27 of the '298 patent are not anticipated by or rendered obvious by Lai. I will deny Hospira's motion for JMOL on this ground.

4. Damages

Hospira also moves for JMOL on the ground that the jury's damages award is not reasonable, challenging both the amount and the lump sum nature of the award. (D.I. 357, p. 20). Based on Dr. Bell's analysis, Hospira asserts, "Dr. Bell's proposed royalty of $1.5 million per batch, when the batch is sold, is the only damages methodology that properly accounts for the expectations of the hypothetical negotiators at the time concerning FDA approval, and the reality of what occurred afterwards." (*Id.* p. 22).

Relying on Dr. Bell's trial testimony, Hospira contends, "Hospira, as a willing licensee,

would not have been willing to pay more than the replacement cost of the batches, which was from $4.1 to $4.6 million per batch." (*Id.* p. 20 (citing Trial Tr. 1241:1-1243:13)). Considering the *Georgia-Pacific* factors, Dr. Bell adjusted this downward to 35% of the replacement cost. (Trial Tr. 1246:12-1248:21). Dr. Bell further opined that due to the uncertainties associated with FDA approval, Hospira would not willingly pay an up-front lump sum royalty. (*Id.* 1252:13-19). According to Dr. Bell, if the FDA never approves Hospira's biosimilar, then Hospira has no opportunity to sell the product and realizes no gain, and Amgen has no losses. (*Id.* 1252:1-9). Hospira further criticizes Amgen's damages theory because it "requires Hospira to bear all the 'risk' of the license," and it reflects an award "more than the twenty-year net present value of the entire EPO project." (D.I. 357, pp. 20-21). According to Hospira, this is inconsistent with a willing licensor and a willing licensee. (*Id.*). Hospira also criticizes Amgen's damages theory as "based entirely on the cost to Hospira of the supposed delay that would have occurred if it had to wait until after patent expiration to manufacture its EPO substance for launch," when "no such delay ever occurred." (D.I. 381, p. 13). Finally, Hospira argues that the Vifor Agreement cited by Amgen "is a non-comparable marketing and distribution agreement with an upfront payment that can be refunded if Hospira does not obtain FDA approval." (D.I. 357, pp. 21-22).

Amgen responds, "Dr. Bell's testimony provides the lowest reasonable royalty that may be supported by the evidence," not the only reasonable royalty. (D.I. 374, p. 21). The jury's award was supported by the evidence, Amgen argues, because "[t]he jury [i]s entitled to choose a damages award within the amounts advocated by the opposing parties."[9] (*Id.* (quoting *Spectralytics, Inc. v. Cordis Corp.*, 649 F.3d 1336, 1347 (Fed. Cir. 2011), *abrogated on other grounds by Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 136 S. Ct. 1923 (2016)) (brackets in original)).

[9] Here, the difference between the parties' positions is $116 million, as Hospira proposed $21 million and Amgen proposed $137 million. (D.I. 374, p. 24).

Amgen presented the Vifor Agreement as an example of a lump sum agreement involving Hospira, asserting that Amgen would not agree to a refund in this case because Amgen and Hospira are competitors. (*Id.* p. 23 (citing Trial Tr. 665:4-666:1)). Additionally, Amgen argues, "Hospira cites no legal support for its contention that economic harm is required for a jury to award a royalty as a lump sum." (*Id.*). "The reasonable royalty determined in a hypothetical negotiation does not compensate for lost sales but rather the lost opportunity of a reasonable royalty before infringement." (*Id.* (citing *AstraZeneca AB v. Apotex Corp.*, 782 F.3d 1324, 1334 (Fed Cir. 2015))).

Amgen maintains that Dr. Heeb "provided numerous bases in addition to the Vifor agreement " to support his damages theory. (*Id.*). Dr. Heeb opined that since Amgen and Hospira are competitors, Amgen would not agree to a running royalty that required Amgen to share any risk associated with Hospira's manufacture of EPO. (Trial Tr. 640:12-641:15). Additionally, Dr. Heeb cited administrative advantages of a lump sum royalty, such as there being no need to track sales. (*Id.* 641:16-23).

Regarding Hospira's arguments that the award does not reflect events occurring after the hypothetical negotiation (i.e., the lack of FDA approval), Amgen notes that the jury was instructed that it could consider such events. (D.I. 374, p. 22). Amgen argues, "It is not error that the jury did not agree with Hospira" about the effect of such events on the reasonable royalty rate. (*Id.*). Contrary to Hospira's argument that Dr. Bell's theory is the only one under which the jury could have found a per-batch royalty (D.I. 357, p. 29), Amgen notes that Dr. Heeb offered testimony on the value of the license if the jury found only some batches to infringe. (D.I. 374, p. 22). For example, if fourteen batches were found to infringe, the value to Hospira of a license would have been $137 million. (*Id.* (citing Trial Tr. 645:22-646:6)). Amgen would have valued a license at

$170 million. (Trial Tr. 636:2-11). Regarding Hospira's criticism that Dr. Heeb's analysis resulted in an award that exceeded the net present value of Hospira's EPO project, Amgen points to testimony by Dr. Bell acknowledging Hospira documents that stated the net present value of its EPO project as up to $297 million. (*Id.* 1273:10-1274:5).

I conclude that substantial evidence supports the jury's $70 million damages award. Regarding the lump sum payment, both parties' experts provided testimony to support their positions on whether a lump sum would be appropriate, and the jury was free to determine the experts' credibility and weigh their testimony accordingly. I decline to substitute my judgment for that of the jury.

Hospira essentially argues that Dr. Heeb's methodology was not supported by substantial evidence because no launch delay ever materialized. Indeed, Hospira's expert Dr. Bell testified that he considered only the hypothetical negotiation scenario in which Hospira does not launch a product prior to mid-2017, "because it's the one that we happen to be in." (Trial Tr. 1293:16-1294:15). In other words, Dr. Bell's analysis focuses solely on a hypothetical negotiation in which the parties have knowledge of all subsequent events. Amgen's analysis appears to amount to a hypothetical negotiation in which the parties do not have the benefit of subsequent knowledge that Hospira did not receive FDA approval.

I cannot say that it was unreasonable for the jury to find neither expert struck the proper balance in considering how post-negotiation events would have affected the reasonable royalty.

> The [reasonable royalty] methodology encompasses fantasy and flexibility; fantasy because it requires [the jury] to imagine what warring parties would have agreed to as willing negotiators; flexibility because it speaks of negotiations as of the time infringement began, yet permits and often requires [the jury] to look to events and facts that occurred thereafter and that could not have been known to or predicted by the hypothesized negotiators.

Fromson v. W. Litho Plate & Supply Co., 853 F.2d 1568, 1575 (Fed. Cir. 1988), *overruled on other*

grounds by Knorr–Bremse Systeme Fuer Nutzfahrzeuge GmbH v. Dana Corp., 383 F.3d 1337 (Fed.Cir.2004) (en banc); *see also Sinclair Ref. Co. v. Jenkins Petroleum Process Co.*, 289 U.S. 689, 698 (1933) ("[A] different situation is presented if years have gone by before the evidence is offered. Experience is then available to correct uncertain prophecy. Here is a book of wisdom that courts may not neglect."). Though the parties would have recognized the possibility, as of the time of the hypothetical negotiation, that Hospira may not receive FDA approval before the expiration of the patents, Hospira did not expect such a result.[10] In essence, Hospira wants me to do what the Federal Circuit has expressly held was error, to "replace[] the hypothetical inquiry into what the parties would have anticipated, looking forward when negotiating, with a backward-looking inquiry into what turned out to have happened." *Aqua Shield v. Inter Pool Cover Team*, 774 F.3d 766, 772 (fed. Cir. 2014). I therefore cannot say that the consideration in Dr. Heeb's analysis of the value to Hospira of avoiding launch delay was not supported by substantial evidence. The parties' experts each provided an endpoint for the range of potential hypothetical reasonable royalties, and as Amgen points out, the jury was free to choose a damages award within the amounts advocated by the opposing parties. Therefore, I will deny Hospira's motion for JMOL on this ground.

B. New Trial

1. Safe Harbor Instruction

Hospira asserts that it is entitled to a new trial because the safe harbor jury instruction was "legally erroneous and prejudicial." (D.I. 357, p. 22).[11] Specifically, Hospira argues that the instructions "confused the 'manufacture' and 'use' of the batches in a way that misrepresents the

[10] Hospira projected that it would obtain FDA approval in the fourth quarter of 2015. (PTX-342, p. 1).
[11] Citing its JMOL arguments, Hospira also argues that the jury's verdict that fourteen batches were not protected by the safe harbor defense is against the clear weight of the evidence. Having already addressed these arguments in Hospira's JMOL, I will not address them again in considering Hospira's motion for a new trial.

statute," and Hospira challenges the instructions' "fail[ure] to instruct the jury that ulterior motives and intent are irrelevant to the Safe Harbor." (*Id.*). Amgen submits that the instructions were adequate, and that any instructional error was "at most harmless error." (D.I. 374, p. 24).

Hospira contends that the verdict form and jury instructions were erroneous because they did not use the terms "make" and "use" consistently with the statute, thus failing to "clarify the difference between 'manufacture' and 'use' under the Safe Harbor." (D.I. 357, pp. 23-24; *see also* Trial Tr. 1404:11-1405:15 (Hospira objecting to the safe harbor jury instruction and stating, "We would urge the broader standard for uses, but focus on the instruction should be on the uses and not the motives or purposes in making [a] batch. The statutory exemption is premised on the use aspect."); Trial Tr. 1445:12-1449:18, 1452:8-23 (Hospira's continuing objections)). The instructions initially refer to Hospira's burden to prove "uses reasonably related to obtaining FDA approval," and Hospira's burden to prove "that the safe harbor defense applies to Hospira's use of Amgen's patented invention," but they subsequently "ask[] the jury to determine whether the manufacture is covered." (D.I. 357 p. 24). According to Hospira, the verdict form "compounded this error[] by asking the jury to find whether the 'Safe Harbor Defense applied to the manufacture of the following batches.'" (*Id.*). Amgen responds that the jury instructions and verdict form track the statute because, "The Court correctly instructed the jury that the alleged infringing activity was Hospira's making of its drug substance, which needed to be 'for uses reasonably related' to seeking FDA approval." (D.I. 374, p. 25 (citing Trial Tr. 1522:5-20, 1553:3-1554:13)).

I agree with Amgen. The safe harbor defense provides,

> 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) . . .) 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 . . . .

35 U.S.C. § 271(e)(1). The safe harbor exempts activity that would ordinarily constitute an act of infringement if that activity is undertaken "solely for uses reasonably related" to obtaining FDA approval. Asserted claims 24 and 27 of the '298 patent are method claims. Hospira is correct in pointing out that the instructions and the safe harbor statute refer to "use" of a patented invention. Here, Hospira's potentially infringing "use" of Amgen's patented invention is Hospira's manufacture of the EPO drug substance referred to in its BLA (i.e., Hospira's performance of the steps of Amgen's method claims), not Hospira's subsequent use of the EPO drug substance (i.e., Hospira's subsequent use of the product obtained by practicing Amgen's method claims). *See Joy Techs, Inc. v. Flakt, Inc.*, 6 F.3d 770, 775 (Fed. Cir. 1993) ("A method claim is directly infringed only by one practicing the patented method." (emphasis omitted)); *Roberts Dairy Co. v. United States*, 530 F.2d 1342, 1354 (Ct. Cl. 1976) ("It is well established that a patent for a method or process is not infringed unless all steps or stages of the claimed process are utilized."). Therefore, the safe harbor defense applies in this case only if Hospira's manufacture of its EPO drug substance is reasonably related to obtaining FDA approval. Though Hospira's subsequent uses of its EPO drug substance are probative in determining whether Hospira's manufacture of its EPO drug substance was reasonably related to obtaining FDA approval, it is the manufacture itself (not Hospira's subsequent uses of EPO drug substance) that is the potentially infringing act which must be evaluated for safe harbor protection. I thus think the jury instructions and the verdict form were proper in asking the jury to determine whether Hospira's potentially infringing act, i.e., its manufacture of the EPO drug substance, was covered by the safe harbor defense.

According to Hospira, "the Court's Safe Harbor instructions were erroneous for a second reason—they omitted any discussion of how intent related to the Safe Harbor analysis." (D.I. 357, p. 23; Trial Tr. 1404:11-1405:15 (Hospira's charge conference objection to the safe harbor jury

instruction); D.I. 318, pp. 30-31 (Hospira's objection to the Court's proposed jury instruction on safe harbor); Trial Tr. 1445:12-1449:18). Though the instructions stated that "Hospira's additional underlying purposes for the manufacture and use of that batch do not remove that batch from the safe harbor defense" (D.I. 323, p. 19), Hospira contends that "this language was ambiguous and did not explicitly state that intent does not matter." (D.I. 357, p. 23). Per Hospira, "This error, coupled with the Court's denial of Hospira's motion *in limine* to preclude Amgen[] from introducing the Risk Authorizations allowed the jury to hear evidence of alleged commercial intent based on the highly prejudicial Risk Authorizations." (*Id.* (citation omitted)). To support its assertion that its internal Risk Authorizations are unduly prejudicial and should not have been admitted into evidence, Hospira repeats its argument that intent is irrelevant to evaluating safe harbor protection. (*Id.*). Essentially, Hospira asserts that I should have used its proposed jury instructions on the safe harbor defense. (*Id.*). Amgen responds, "Hospira's proposed instruction [] also omitted any discussion of 'intent'; it did not even contain that word." (D.I. 374, p. 24 (citing D.I. 304, pp. 3-4). Regardless, Amgen submits that the instructions adequately addressed intent because the court "instruct[ed] the jury that 'Hospira's additional underlying purposes for the manufacture and use of [a] batch do not remove that batch from the safe harbor defense.'" (*Id.* pp. 24-25).

Hospira appears to argue that intent is entirely irrelevant to the safe harbor analysis, but I do not think the cases Hospira cites in its brief stand for such a broad proposition. In *Abtox*, the court found a competitor's limited testing during development of a device "consistent with the collection of data necessary for filing an application with the [FDA]," despite allegations that that the actual purpose of the tests was "to promote the [device] and other equipment to potential customers." 122 F.3d at 1027. Accordingly, the *Abtox* court concluded that the safe harbor defense

"allows [a party] to use its data from the tests for more than FDA approval" and "does not look to the underlying purposes or attendant consequences of the activity (*e.g.*, tests led to the sale of the patent), as long as the use is reasonably related to FDA approval." *Id.* at 1030. Notably, the *Abtox* court did not state that intent was irrelevant in determining whether an activity is reasonably related to obtaining FDA approval.

Hospira's citations to other cases quote language clarifying that the mere existence of some intent, "ulterior motives," or "alternate purposes" to commercialize does not preclude a party from successfully invoking the safe harbor defense. (D.I. 357, pp. 22-23 (citing *Intermedics, Inc. v. Ventritex Co.*, 1993 WL 87405, at *5 (Fed. Cir. Feb. 22, 1993) ("Reliance on section 271(e)(1) is not precluded by manifestation of an intent to commercialize upon FDA approval."); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 108 (D. Mass. 1998) ("[U]lterior motives or alternate purposes do not preclude application of the section 271(e)(1) exemption."); *Intermedics, Inc. v. Ventritext Co.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), *aff'd* 991 F.2d 808 (Fed. Cir. 1993) ("[I]f a party were to lose the exemption every time a business purpose was detectable in its otherwise infringing activities, the exemption would virtually never be available and thus would fail to achieve Congress' objective."))). I think that evidence of intent can be a relevant factor in determining whether an activity is reasonably related to obtaining FDA approval, and that these cases stand for the proposition that evidence of commercial intent is not determinative of the safe harbor inquiry. In my view, they do not support Hospira's assertions that intent is irrelevant to determining whether an activity is reasonably related to obtaining FDA approval and that intent may not be considered at all. But once it is determined that "the activity is reasonably related to obtaining FDA approval, [] intent or alternative uses are irrelevant to its qualification to invoke the section 271(e) shield." *See Abtox*, 122 F.3d at 1030.

Additionally, adopting Hospira's interpretation of the safe harbor defense would expand the defense beyond recognition and create a loophole that would make it virtually impossible to prove infringement in cases involving products regulated by the FDA. Since Hospira's interpretation requires ignoring intent in deciding whether the safe harbor applies, a party could manufacture 200 drug substance batches and earmark them for future use as commercial inventory without infringing, so long as the party used each of those batches for at least one test to generate data of the type used by the FDA in determining whether to approve the drug. In that scenario, each batch would be tested to generate data that could conceivably be used to respond to inquiries from the FDA, making each batch reasonably related to obtaining FDA approval. Essentially, Hospira's interpretation allows a single "token" submission of information derived from a potential infringing act to exempt that act from infringement, without regard to the realities surrounding the potentially infringing act. It seems to me that Hospira's interpretation reads the words "solely" and "reasonably" out of the statute, and that a party's stated intent may be considered as part of whether the manufacture or use of a patented drug was "solely for uses reasonably related to" obtaining FDA approval. I think that the jury instructions properly recited the role of intent in the safe harbor analysis.

Hospira also argues that FDA draft guidance on statistical approaches to evaluate analytical similarity, published on September 22, 2017, constitutes new evidence that "proves the uncertainty of the regulatory landscape" and warrants a new trial. (D.I. 357, p. 24; *see also* D.I. 357-1). Amgen responds that the draft guidance is cumulative of Hospira's other evidence of regulatory uncertainty that would not have changed the outcome at trial. (D.I. 374, p. 26). Setting aside the fact that the draft guidance was distributed for comment purposes only, Amgen points out that the guidance "recommend[s] a minimum of 10 reference product lots be sampled" to "establish

meaningful acceptance similarity criteria." (*Id.* (citing D.I. 357-1 at 2, 7)). The guidance would not have changed the outcome, Amgen maintains, because, "Here, Hospira tested 26 drug product batches to demonstrate biosimilarity, all made using material from 4 drug substance batches on which the jury did not award damages." (*Id.* (citing DTX-266, pp. 3-4)). Finally, Amgen notes that Hospira did not present evidence that the FDA required Hospira to manufacture a certain number of batches to demonstrate biosimilarity. (*Id.*).

I agree with Amgen that the FDA draft guidance does not constitute new evidence that would justify a new trial. Since Hospira submitted test data from twenty-six drug product batches manufactured from four drug substance batches that the jury found not to infringe, the jury could have found the remaining drug substance batches to infringe even if the draft guidelines had constituted a final regulation requiring Hospira to submit data from at least ten drug product batches to prove biosimilarity. Hospira has not shown that the FDA draft guidance would likely alter the outcome of the trial.

Having concluded that neither the safe harbor instructions nor the FDA draft guidance warrants a new trial, I will deny Hospira's motion for a new trial on safe harbor grounds.

2. *Contradictory Verdicts*

Hospira argues that it is entitled to a new trial because the jury's verdicts on infringement of the '298 patent and validity of the '298 patent are inherently contradictory. (D.I. 357, p. 24). Having found each of the jury's infringement and validity verdicts supported by substantial evidence, and having found that Hospira failed to meet its burden of proof that the '298 patent is invalid, I will deny Hospira's motion for a new trial based on contradictory infringement and validity verdicts.

3. *Claim Construction*

Hospira also argues that "the jury received a claim construction order with errors that warrant a new trial." (*Id.* p. 26). Specifically, Hospira argues, "For the reasons advanced by Hospira during claim construction," the Court's construction of claims 24 and 27 of the '298 patent were incorrect. (*Id.*). Amgen responds that Hospira's assertion amounts to an improper request for reconsideration of the Court's claim constructions, since "Hospira raises no new arguments" to support its contention that the Court's claim constructions were improper. (D.I. 374, pp. 27-28).

Hospira frames its claim construction arguments as repetitions of the arguments it made during claim construction. I decline at this late stage to reconsider my constructions based on the same arguments considered and addressed in my previous claim construction opinions. (*See* D.I. 162, 177). Therefore, I will deny Hospira's motion for a new trial based on claim construction.

4. Third Party Liability Instruction

Hospira further submits that it is entitled to a new trial because the jury was erroneously instructed that "Hospira is responsible for the manufacturing activities of GlaxoSmithKline, or GSK, as they relate to Hospira's epoetin drug substance." (D.I. 357, p. 27 (citing Trial Tr. 1552:23-1553:2)). The third party liability jury instruction challenge is proper, Hospira submits, because Hospira "vigorously disputed the jury instruction on third party liability and confirmed that its objections to the jury instructions were preserved." (D.I. 381, p. 15 (citing Trial Tr. 1389:15-1390:11, 1524:11-19)). According to Hospira, the erroneous instruction "allowed Amgen to circumvent the requirements to show induced infringement under 35 U.S.C. § 271(b)[, when] Amgen never pled induced infringement of the '298 patent nor amended its pleadings to do so." (D.I. 357, p. 27).

Amgen asserts that Hospira's motion for a new trial represents an improper vehicle to

challenge the Court's JMOL decision during trial that "Hospira was responsible for GSK's manufacture of Hospira's EPO drug substance for purposes of direct infringement." (D.I. 374, p. 28; *see* Trial Tr. 1391:18-1392:6). According to Amgen, since "Hospira has not sought reconsideration of that ruling and did not object to the jury instruction," Hospira's motion "cannot overturn the Court's decision to grant JMOL on Hospira's responsibility for GSK's activities." (D.I. 374, p. 28).

I will deny Hospira's motion for a new trial based on the third party liability instruction. Hospira acknowledges that I granted JMOL that Hospira was responsible for the activities of GSK. (D.I. 357, p. 27; *see* Trial Tr. 1392:14-24). Assuming JMOL was properly granted,[12] I think it was proper to instruct the jury that, "Hospira is responsible for the manufacturing activities of GlaxoSmithKline, or GSK, as they relate to Hospira's epoetin drug substance." (Trial Tr. 1553:1-4). Though Hospira reserves its right to appeal the grant of JMOL on this issue (D.I. 357, p. 27 n.1), Hospira does not object to the grant of JMOL in its post-trial briefing. (*See id.* pp. 27-28; D.I. 381, p. 15). Regardless, I do not think Hospira's citations to the trial transcript demonstrate a

[12] As I noted at trial, I think the evidence supports the grant of JMOL that Hospira is responsible for the activities of GSK. (Trial Tr. 1392:17-1393:7). As the Federal Circuit stated in *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020, 1023 (Fed. Cir. 2015), it has "held that an actor is liable for infringement under § 271(a) if it acts through an agent (applying traditional agency principles) or contracts with another to perform one or more steps of a claimed method." Under Delaware law, "If the principal assumes the right to control the time, manner and method of executing the work, as distinguished from the right merely to require certain definite results in conformity to the contract, a master/servant type of agency relationship has been created." *Fisher v. Townsends, Inc.*, 695 A.2d 53, 59 (Del. 1997).

Here, Hospira reserves particular time slots with GSK for manufacturing, "sets the overarching specifications for the manufacture of the drug substance" in accordance with Hospira's BLA, and owns the drug substance on completion of manufacturing. (Trial Tr. 296:1-297:12, 554:9-555:14, 886:3-887:6). Additionally, Hospira employees worked with GSK during the manufacturing process and were present at the GSK facility during the FDA's pre-approval inspection. (Trial Tr. 834:3-835:3, 864:3-866:3). I therefore think that Hospira exercises sufficient direction and control over the manufacturing process such that GSK qualifies as Hospira's agent. Accordingly, even if Hospira could not be held liable for direct infringement based on its contract with GSK to perform the steps of the claimed method, Hospira could be held liable for direct infringement based on GSK's actions under an agency theory.

clear objection by Hospira to the third party liability jury instruction. (*See* Trial Tr. 1390:15-1394:24 (discussing third party liability issue, discussing proposed "infringement by agent" instruction ultimately not given, granting JMOL that Hospira is responsible for the activities of GSK, and instructing Amgen to submit a sentence on this issue for the final jury instructions), 1519:9-1524:21 (indicating Hospira's objection to the safe harbor jury instruction; demonstrating no specific objection by Hospira to revised Instruction 5.2, which included a sentence drafted by Amgen stating that Hospira is liable for the activities of GSK; and reflecting both parties' preservation of prior objections)).

5. Remittitur

Finally, Hospira argues that remittitur to $1.5 million per batch, if sold, is appropriate because "the $70 million damages award contradicts the weight of the evidence." (D.I. 357, pp. 28, 30). As support, Hospira restates in part and incorporates by reference its arguments raised in its motion for JMOL regarding damages. (*Id.* pp. 28-30). I will deny Hospira's request for remittitur or a new trial for the same reasons already discussed with respect to Hospira's motion for JMOL regarding damages.

III. HOSPIRA'S MOTION TO SEAL CONFIDENTIAL EXHIBITS

Hospira requests that the Court seal three exhibits admitted at trial which it asserts contain confidential business information. The exhibits are DTX-138 (the Vifor Agreement), DTX-177 (the GlaxoSmithKline ("GSK") Agreement), and DTX-178 (amendments to the GSK Agreement). (D.I. 361 at 2). Amgen opposes Hospira's motion. (D.I. 369).

The Third Circuit recognizes "a strong presumption that material introduced into evidence at trial should be made available for public access." *Littlejohn v. Bic Corp.*, 851 F.2d 673, 678 (3d Cir. 1988) (citation omitted). "It is well established that the release of information in open court

is a publication of that information and, if no effort is made to limit its disclosure, operates as a waiver of any rights a party had to restrict its future use." *Id.* at 680 (citation omitted). "The party seeking the closure of a hearing or the sealing of a transcript bears the burden of showing that the material is the kind of information that courts will protect and that there is good cause for the order to issue. Good cause is established on a showing that disclosure will work a clearly defined and serious injury to the party seeking closure." *Publicker Indus., Inc. v. Cohen*, 733 F.2d 1059, 1069-70 (3d Cir. 1984) (citations omitted).

According to Hospira, it is appropriate to seal these exhibits because they contain "confidential commercial and technical information" that "would damage the competitive standing of the parties and the third parties named in those agreements." (D.I. 361 at 1). Hospira contends that it "took efforts to keep the contents [of these exhibits] confidential" during trial because only limited portions of the exhibits were discussed or shown. (*Id.* at 3). Specifically, Hospira's witnesses discussed these documents only in general terms, and Amgen's witness Dr. Heeb referenced only one page of DTX-178 in live testimony. (*Id.*). Though "[t]he exhibits were discussed in deposition testimony of Mr. Noffke and Mr. Pinnow," they "were only shown on a split screen as the testimony was played," and Hospira had marked the deposition transcripts and exhibits "confidential." (*Id.*). Finally, Hospira argues, "Redaction of the documents is not practicable, as the information discussed at trial was often intertwined with other sensitive information and because the organization and structure of the documents themselves are confidential." (*Id.*).

Amgen submits that the exhibits should not be sealed because "[d]uring trial, the parties introduced exhibits into evidence without restriction." (D.I. 369 at 1). Since "[t]he Court never sealed the courtroom, and Amgen's corporate representative, members of the press, and other

members of the public were present throughout the trial," Amgen maintains that the exhibits are in the public record. (*Id.*). Additionally, Amgen argues that the exhibits should not be sealed because "several witnesses testified about the three agreements, including about specific details in those agreements." (*Id.* at 2 (citing Mr. Noffke's testimony about GSK's reserve capacity in the GSK Agreement (Trial Tr. 565:8-568:5); Dr. Bell's testimony about cost of manufacture information derived from the GSK Agreement (Trial Tr. 1244:6-1245:14); Mr. Pinnow's and Dr. Bell's testimony about payment terms in the Vifor Agreement (Trial Tr. 306:19-22, 309:3-312:2, 1254:1-15))). Finally, Amgen expresses concern that Hospira seeks to seal portions of the GSK Agreement on which Hospira intends to rely in raising the argument that GSK is not an agent of Hospira. (*Id.* at 3-4).

I agree with Amgen that the exhibits should not be sealed. On the first morning of trial I indicated my preference that the parties "redact out [the] portions that aren't relevant," and suggested that the parties ought to think about limiting disclosures of portions of the exhibits to those that are "critical to the testimony" at trial. (Trial Tr. 18:13-19). Though Hospira may have taken some measures to keep the exhibits confidential, Hospira published portions of the exhibits in open court and relied on information from the exhibits in presenting its case. That portions of the exhibits "were only shown on a split screen" does not change the fact that they were published and admitted into evidence without any request by Hospira to seal them at the time. (*Id.* at 317:5-13, 594:16-595:19). Hospira's broad argument about the impracticality of redaction is not sufficient for me to conclude that it would be impractical to redact the exhibits.

Accordingly, I will not seal the exhibits. Since the exhibits were not published in their entirety in open court and contain sensitive information about ongoing commercial agreements, I will allow Hospira to submit proposed redactions within ten days of the date of the order

accompanying this opinion. The parties should meet and confer on the proposed redactions before the submission is made.

IV. AMGEN'S RENEWED JMOL

Amgen seeks judgment as a matter of law that Hospira infringed the '349 patent. (D.I. 358). Alternatively, Amgen seeks a new trial on infringement of the '349 patent because the jury's verdict was against the weight of the evidence, and was based on what Amgen characterizes as Hospira's improper argument to the jury that the '349 claims require RIA evidence for infringement. (*Id.*).

A. JMOL

The only limitations in the '349 patent at issue during trial required cells "capable of producing" EPO at a rate of 100 U, 500 U, and 1000 "U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay." (*Id.* p. 5). It was Amgen's burden at trial to prove by a preponderance of the evidence that Hospira's EPO-producing cells met this limitation. To prevail on its motion, Amgen must demonstrate that "there is insufficient evidence for permitting" a finding that Hospira does not infringe the asserted claims of the '349 patent. *Fireman's Fund Ins. Co.*, 540 F.2d at 1177.

Amgen contends, "The only evidence introduced at trial about the production rate of Hospira's cells established that they were capable of producing EPO at a rate of more than 3500 Units per million cells in 48 hours," because "Hospira's expert, Dr. Hamilton, did not offer any affirmative evidence or an opinion that Hospira's cells were not capable of producing EPO at the rates recited in the '349 claims." (*Id.* pp. 1-2). As further support, Amgen points to a Hospira report submitted to the FDA as part of Hospira's BLA stating that Hospira's cells produce EPO "in the range of 100 μg or higher" per day based on dot-blot analysis. (*Id.* p. 7 (citing PTX-293,

p. 28)). Amgen's expert, Dr. McLawhon, testified that Hospira's 100 μg/mL rate could be converted into the "U" of EPO recited in the '349 patent claims, and that his calculations resulted in a rate of 3,534 U of EPO per 10^6 cells in 48 hours. (*Id.* (citing Trial Tr. 525:1-536:11)). Essentially, since Hospira's expert, Dr. Hamilton, admitted that it was theoretically possible to convert μg/mL EPO production to U of EPO, and since Dr. Hamilton "did not offer any affirmative evidence . . . that Hospira's cells were incapable of producing EPO at the claimed production levels," Amgen asserts that no reasonable jury could have found that Hospira's cells did not infringe. (*Id.* pp. 9-10).

Amgen also argues that no reasonable jury could have found Dr. Hamilton's testimony adequate to rebut Amgen's evidence of infringement. (D.I. 358, pp. 11-14). First, Amgen argues that Dr. Hamilton's criticisms are "inconsistent with the written description of the '349 patent, in which Dr. Lin described using an RIA to assay crude 'culture fluids,' and converted the resulting data to 'U' of EPO using a purified EPO standard." (D.I. 380, p. 3).[13] Amgen's responds to Dr. Hamilton's testimony that the RIA and dot blot testing at issue here are not comparable by arguing that Dr. Hamilton "failed to tie these alleged deficiencies to any limitation recited in the claims: the '349 claims do not require the same standard or antibody used by Dr. Lin when he tested his inventions, nor are the production-rate limitations limited to testing a purified EPO sample." (D.I. 358, pp. 12-13). Amgen further argues that Dr. Hamilton's testimony should not be credited because he "did not interpret the claims, or opine on whether a person of ordinary skill in the art would have understood the claims to require the use of the same EPO standard or anti-EPO antibody preparation that the '349 inventor, Dr. Lin, used." (*Id.* p. 13). Essentially, Amgen argues,

[13] In response, Hospira points to Dr. Hamilton's testimony that "the '349 patent examples use a standard curve," but "that curve was not compared to Hospira's sample in this case." (D.I. 373, p. 13 (citing Trial Tr. 1226:3-23, 1227:21-1228:10)). Therefore, the '349 patent examples further demonstrate a "lack of comparability [that is] another reason that the dot blot from Hospira's BLA does not prove infringement." (*Id.*).

Hospira did not offer any evidence to suggest that the differences identified by Dr. Hamilton actually matter.

Hospira responds that the jury was reasonable in declining to credit Amgen's circumstantial evidence of infringement of the '349 patent. (D.I. 373, p. 1). Hospira maintains that Amgen failed to carry its burden to prove infringement because Amgen never established the comparability of the dot-blot and RIA testing at issue. (*Id.* p. 4). First, Dr. Wall offered no testimony on the comparability of dot-blot and RIA testing. (*Id.* (citing Trial Tr. 271:5-22, 275:19-276:23)). Second, Dr. McLawhon did not "explain[] how the dot blot works or how it compares to an RIA," instead converting mass to units "like a 'currency converter.'" (*Id.* p. 5 (citing Trial Tr. 527:24-530:1)). Third, "Dr. McLawhon d[id] not know whether the same antibody was used in the standard he used for the conversion and the dot blot, although he admit[ted] that should be done if one is going to make a comparison and that he would have known which antibody was used if he had run an experiment." (*Id.* (citing Trial Tr. 545:3-546:2)). Fourth, a former Amgen scientist who conducted RIA testing on Amgen's EPO project testified that the same standard should be used to compare assays, because the standard sets the potency measurement. (*Id.* p. 6 (citing Trial Tr. 1163:5-24)).

Hospira notes that Dr. Hamilton "provided several reasons why [RIA and dot blot] do not yield similar results." (*Id.*). First, "Hospira's BLA contained rough information that some of the vertebrate cells tested could produce 100 μg of EPO per mL of cell-culture medium, [i.e., supernatant]." (*Id.* p. 7; Trial Tr. 540:18-541:3). Second, Hospira argues that Dr. Hamilton "explained that the dot blot was done as a rough measurement of the amount of EPO." (*Id.* p. 8 (citing Trial Tr. 1193:18-1194:8)). Third, as Dr. Hamilton explained, "converting from mass units to biological activity units as measured in the claims is not like converting currency because these

units are not standardized like money." (*Id.* p. 7). Fourth, "a sample taken directly from the supernatant, as done in the dot blot assay, will likely contain biologically inactive impurities and EPO fragments that indiscriminately bind to the antibody, and thus will not be an appropriate sample to use in the conversion calculation." (*Id.* p. 8). Fifth, one "can't rely on a purified standard to give [] an estimate of what's present in the crude mixture of impurities and isoforms as well as active EPO on the dot blot." (Trial Tr. 1198:2-6). Sixth, the standards used in Hospira's BLA and in the '349 patent were not the same. (*Id.* 1198:19-1198:22). In summary,

> [T]he standard was different, the antibodies were different, the assay design was different, the relative degree of quantification was different, and based on all of those variables, one can't accurately assess the level of EPO in a culture supernatant cell preparation, which is really what claims 1 through 6 in the patent are requiring.

(*Id.* 1198:23-1199:6).

I agree with Hospira that substantial evidence supports the jury's verdict that Hospira does not infringe the asserted claims of the '349 patent. That Amgen's calculation was the only one offered at trial did not mean that the jury was obligated to credit it. And the fact that the '349 patent describes using a purified EPO standard to convert RIA assay data obtained from a crude sample to "U" does not compel the conclusion that one could do the same with dot-blot data obtained from a crude sample. Additionally, Amgen's argument that Hospira's BLA documents disclosing dot-blot measured rates of 100 μg/mL constitute an admission that Hospira's cells meet the production limitations is not persuasive. It ignores that the "admission" is explicitly dependent on the measurement technique used, and does not address issues of whether the dot blot testing and RIA testing at issue are comparable. Though Dr. Hamilton acknowledged that one could theoretically convert the dot-blot μg/mL measurement to a measurement in "U," he qualified that statement by saying that the material resulting from Hospira's dot-blot test would need to be purified to get a proper conversion against the pure standard. (Trial Tr. 1214:18-21). Dr. Egrie, a

former Amgen scientist, confirmed that the same standard should be used to compare assays. (*Id.* 1163:21-1164:5). Dr. McLawhon admitted that he did not run any experiments to convert Hospira's dot-blot results to a measurement in "U." (*Id.* 545:3-546:2).

I think that the testimony from Dr. Hamilton and Dr. Egrie provides substantial evidence from which the jury could have concluded that the evidence presented did not establish that Hospira's dot-blot results could be reliably converted to RIA results. Without comparability, the dot-blot production rate in Hospira's BLA would be meaningless to establish infringement, leading the jury to the reasonable conclusion that Amgen had failed to carry its burden. Amgen's assertions that Hospira failed to provide affirmative evidence of noninfringement do not change this result. (*See* D.I. 373, p. 5). Amgen's contention that Dr. Hamilton's comparability testimony should not be credited because he failed to tie it to the claim language also does not change the result. Rather, Amgen's arguments represent an attempt to improperly shift the burden of proving noninfringement to Hospira. To rebut Amgen's infringement argument, Dr. Hamilton need only have presented testimony that called into question Dr. McLawhon's testimony such that a reasonable jury could conclude that Amgen failed to prove infringement by a preponderance of the evidence.[14] Dr. Hamilton's testimony was corroborated in part by Dr. Egrie. (Trial Tr. 1163:21-1164:17). I decline to supplant the jury's determinations of credibility with my own. Thus, I conclude Amgen has failed to show that there is insufficient evidence for the jury's verdict that Hospira did not infringe the asserted claims of the '349 patent.

Accordingly, I will deny Amgen's motion for JMOL that Hospira infringed the asserted claims of the '349 patent.

B. New Trial

[14] Alternatively, if the jury found Dr. Hamilton at least as credible as Dr. McLawhon, Amgen would not have proven that it was more likely than not that Hospira infringed the '349 patent.

First, Amgen asserts that it is entitled to a new trial because, "The great weight of the evidence provided by Amgen established that Hospira's dot blot assays were comparable to an RIA, and that Hospira's cells satisfied every limitation in the '349 claims." (D.I. 358, p. 15). This argument essentially repeats Amgen's JMOL arguments.

Hospira responds that Dr. McLawhon "improperly converted the dot blot assay results into biological activity units without testifying as to why the dot blot assay and the RIA are similar or comparable." (D.I. 373, p. 14). According to Hospira, the jury's verdict is supported by Dr. Hamilton's testimony "present[ing] several reasons why the two tests are not comparable," including that "the dot blot assay used an unpurified sample whereas the standard used in Amgen's calculations was a purified sample of EPO," and the dot blot assay and the RIA in the '349 patent did not use the same standard or the same antibody. (*Id.* (citing Trial Tr. 1197:18-1198:2)).

I conclude that the jury's verdict was not against the great weight of the evidence for the same reasons expressed with respect to Amgen's motion for JMOL of infringement of the '349 patent. Accordingly, I will deny Amgen's motion for a new trial on infringement of the '349 patent on this ground.

Second, Amgen asserts that a new trial is warranted based on Hospira's statements during its closing argument that "based on the evidence [] what is inside the fence is as determined by RIA," while "outside the fence is dot blot." (D.I. 358, p. 15; Trial Tr. 1641:11-1642:8). According to Amgen, these statements were "legally improper, because [they] asked the jury to construe the claims to require evidence produced during an RIA to prove infringement: that is, construing the claims in such a way that they could never be infringed based on evidence from a dot-blot assay." (D.I. 358, p. 15).[15] By contrast, Hospira characterizes its statements as "not ask[ing] the jury to

[15] Amgen also cites *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1385 (Fed. Cir. 2009) as further support for its assertion that Hospira's statements in closing arguments were improper, because that case held that proof of

make a claim construction decision" and "merely point[ing] out, correctly, that 'as determined by radioimmunoassay' is literally recited in the claims." (D.I. 373, p. 15). As support for its "outside the fence" statements, Hospira's counsel pointed to Dr. Hamilton's testimony that Amgen had not adequately established that the dot-blot testing was sufficiently comparable to the RIA testing recited in the '349 claims for the dot-blot results to prove infringement. (*Id.*; Trial Tr. 1641:24-1642:8). Further, "Hospira's counsel never said that dot blot could not be used or that circumstantial evidence was not allowed." (D.I. 373, p. 15).

I agree with Hospira. Taken in context, I do not think that Hospira's "outside the fence" statements request that the jury engage in claim construction. Rather, Hospira used these statements to highlight for the jury Amgen's failure of proof of infringement of the '349 patent. Accordingly, I will deny Amgen's motion for a new trial based on Hospira's counsel's statements during closing argument.

V. AMGEN'S MOTION FOR PREJUDGMENT AND POST-JUDGMENT INTEREST

A. Prejudgment Interest

Asserting "Prejudgment interest on a damages award for patent infringement 'is the rule' under 35 U.S.C. § 284," Amgen moves to amend the judgment under Fed. R. Civ. P. 59(e) to award prejudgment interest to Amgen. (D.I. 352, pp. 1-2 (citing *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1574 (Fed. Cir. 1996); *see also General Motors Corp. v. Devex Corp.*, 461 U.S. 648 (1983))). Hospira requests that I deny Amgen's request for prejudgment interest, arguing that since "Hospira has not received FDA approval or sold its proposed EPO product, and Amgen

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infringement of the '349 patent did not require RIA evidence. (D.I. 358, p. 16). Hospira counters, "The *Roche* case does not provide any support for having a new trial because it merely held that Amgen could present its evidence to a jury—it did not say the jury had to rule in Amgen's favor." (D.I. 373, p. 15). I agree with Hospira. For the reasons stated with respect to Amgen's motion for JMOL of infringement of the '349 patent, substantial evidence supports the jury's conclusion that the dot-blot evidence presented by Amgen was insufficient to prove infringement of the '349 patent.

has suffered no economic harm," a prejudgment interest award would create a windfall for Amgen. (D.I. 376, p. 1). In other words, Hospira appears to argue that since Amgen has suffered no economic harm, prejudgment interest is not required to make Amgen whole. Hospira's argument does not fully account for the purpose of prejudgment interest "to ensure that the patent owner is placed in as good a position as he would have been had the infringer entered into a reasonable royalty agreement." *General Motors*, 461 U.S. at 655-56 ("An award of interest from the time that the royalty payments would have been received merely serves to make the patent owner whole, since his damages consist not only of the value of the royalty payments but also of the foregone use of the money between the time of infringement and the date of the judgment."). To make Amgen whole, I will award Amgen prejudgment interest.

Assuming that prejudgment interest should be awarded, the parties dispute whether interest should be calculated as a lump sum or on a per-batch basis, and the appropriate interest rate.

Hospira asserts that prejudgment interest should be awarded on a per-batch basis, because discrete acts of infringement (i.e., manufacture) occurred on identifiable dates, justifying incremental payments of a reasonable royalty. (D.I. 376, pp. 1-2). According to Hospira, prejudgment interest on a lump sum royalty payment is inappropriate, because it "assume[s] a royalty would have been paid on EPO batches well before they even existed." (*Id.* p. 1). Amgen counters that prejudgment interest on a lump sum royalty is appropriate because, "Based on expert testimony that the lump-sum royalty would have been determined at the time of the hypothetical negotiation in late 2013, the jury awarded Amgen $70 million as lump-sum reasonable-royalty damages." (D.I. 382, p. 1). The jury could not have premised its award on Hospira's per-batch damages theory at trial, Amgen maintains, because Hospira's theory required that sales take place to trigger any damages award, and Hospira has made no sales to date. (*Id.*). I agree with Amgen.

The verdict form reflects that the jury awarded Amgen $70 million in damages, without any mention of batches or indication that the award was calculated on a per-batch basis. (*See* D.I. 325 at 4).

With respect to the applicable interest rate, Amgen submits that an award of prejudgment interest calculated at the prime rate, compounded quarterly is appropriate. (D.I. 352, p. 2). Since Hospira would have needed a license to begin manufacturing EPO batches, Amgen argues that I should award Amgen prejudgment interest starting on November 10, 2013, the date of manufacture of the first infringing batch. (*Id.* pp. 2-3). Hospira asserts that prejudgment interest should be awarded at "Amgen's average debt rate on a per-batch basis," instead of the prime rate. (D.I. 376, pp. 2, 10).[16] According to Hospira, since "Amgen's 10-Ks show loans at rates at significantly below the prime rate," the prime rate "is not supported by evidence and would create a windfall for Amgen." (*Id.* p. 2). Amgen responds that Hospira bases its calculation on "two instances in Amgen's corporate filings, identifying a term loan entered in 2013 and a revolving credit agreement entered in 2014." (D.I. 382, p. 5). This is improper, Amgen submits, because "Hospira is simply speculating that Amgen would have used the awarded royalty, had it been paid when due, to pay off these loans; or, alternatively, that Amgen would have borrowed the money to invest in its business in anticipation that one day Hospira would pay the $70 million owed." (*Id.*). Therefore, Amgen asserts, the prime rate should apply, because "awarding prejudgment interest at the prime rate is one way of compensating Amgen that numerous courts, including this Court, have found to be fair and reasonable." (*Id.* p. 1).

I agree with Amgen. "Courts have recognized that the prime rate best compensate[s] a

[16] Hospira calculates the total prejudgment interest due under its average debt rate theory on a per-batch basis at $4,843,492. (D.I. 376, p. 10). Hospira calculates the total prejudgment interest due under its average debt rate theory on a lump-sum basis at $6,276,396. (*Id.* p. 12).

patentee for lost revenues during the period of infringement because the prime rate represents the cost of borrowing money, which is 'a better measure of the harm suffered as a result of the loss of the use of money over time.'" *IMX, Inc. v. LendingTree, LLC*, 469 F. Supp. 2d 203, 227 (D. Del. 2007). Therefore, I will set prejudgment interest at the prime rate, compounded quarterly. *See, e.g.*, *Ironworks Patents, LLC v. Apple, Inc.*, 2017 WL 2535877, at *14 (D. Del. June 12, 2017); *LG Display Co. v. AU Optronics Corp.*, 722 F. Supp. 2d 466, 475 (D. Del. 2010).

Accordingly, I will award Amgen prejudgment interest using the prime rate compounded quarterly and applied against the $70 million lump-sum reasonable royalty award beginning on November 10, 2013.

B. Post-judgment Interest

The parties agree that post-judgment interest should accrue at the statutory rate as specified in 28 U.S.C. § 1961(a). (D.I. 352, p. 3; D.I. 376, pp. 12-13). They disagree, however, regarding when post-judgment interest begins to accrue on the judgment and when post-judgment interest begins to accrue on the prejudgment interest.

Amgen asserts, "prejudgment interest [should] be awarded through the date of the final judgment and [] post-judgment interest (on the jury award and the prejudgment interest) [should] be awarded after that date." (D.I. 382, p. 6). Hospira argues that post-judgment interest should begin to accrue on the damages award as of September 25, 2017, the date the Court entered judgment on the jury's verdict, and that post-judgment interest should begin to accrue on the prejudgment interest as of the date that the prejudgment interest is quantified. (D.I. 376, p. 14).

Section 1961(a) provides, "Interest shall be allowed on any money judgment in a civil case recovered in a district court. . . . Such interest shall be calculated from the date of the entry of the judgment . . . ." 28 U.S.C. § 1961(a). The Third Circuit addressed the accrual of post-judgment

interest under § 1961(a) in *Eaves v. Cty. of Cape May*, 239 F.3d 527 (3d Cir. 2001). *See Travelers Cas. & Sur. Co. v. Ins. Co. of N. Am.*, 609 F.3d 143, 174-75 (3d Cir. 2010) (declining to limit *Eaves* to the attorneys' fees context). "Given the plain language and structure of the statute, it is clear that 'the judgment' referred to in the third quoted sentence is the 'money judgment' specified in the first." *Eaves*, 239 F.3d at 532. "[T]he phrase 'any money judgment' in § 1961(a) [] requires that the judgment at issue award a fixed amount of fees to the prevailing party in order to trigger the post-judgment interest period." *Id.* at 534. Therefore, "post-judgment interest begins to run on a judgment awarding attorney's fees where that judgment fixes the amount owed to the prevailing party." *Id.* "The statute does not, by its terms, mandate that the judgment from which interest is calculated must be a final judgment." *In re Lower Lake Erie Iron Ore Antitrust Litig.*, 998 F.2d 1144, 1177-78 (3d Cir. 1993); *see also Skretvedt v. E.I. DuPont De Nemours*, 372 F.3d 193, 216 (3d Cir. 2004) ("The fact that the December 13, 2001, judgment was not a final order for purposes of appeal would not otherwise prevent postjudgment interest from running under § 1961 . . . .").

On September 25, 2017, I entered judgment for Amgen and against Hospira on the jury's verdict in the amount of $70 million. (D.I. 327). As of that date, I entered a "money judgment" for Amgen that "include[d] both 'an identification of the parties for and against whom the judgment [wa]s being entered,' and 'a definite and certain designation of the amount . . . owed.'" *See Travelers*, 609 F.3d at 175 (quoting *Eaves*, 239 F.3d at 533) (brackets added). Accordingly, I will award Amgen post-judgment interest on the $70 million damages award beginning on September 25, 2017. Prejudgment interest, however, will not have been quantified in a money judgment until the date of the final judgment accompanying this opinion. Accordingly, I will award Amgen post-judgment interest on the prejudgment interest commencing on the date of entry

of the final judgment quantifying the amount of prejudgment interest owed to Amgen. *See Travelers*, 609 F.3d at 175 (holding that though the district court entered judgment in favor of Travelers on August 14, 2006, "post-judgment interest on Travelers' award of prejudgment interest did not begin to run until the December 5, 2007 order was entered quantifying the amount in prejudgment interest owed to Travelers.").

Amgen cites several cases from this District in which "prejudgment interest has [] been awarded through the date of entry of final judgment, rather than the date of the jury's verdict." (D.I. 382, pp. 6-8 (citing *LG Display Co., Ltd v. AU Optronics Corp.*, 722 F. Supp. 2d 466, 475 (D. Del. 2010); *Telecordia Techs., Inc. v. Cisco Sys., Inc.*, 592 F. Supp. 2d 727, 748-49 (D. Del. 2009), *vacated in part on other grounds*, 612 F.3d 1365, 1379 (Fed. Cir. 2010); *Northeast Controls, Inc. v. Fisher Controls Intern., LLC*, 2008 WL 678701, at *2 (D. Del. Mar. 12, 2008), *rev'd on other grounds*, 373 F. App'x 162 (3d Cir. 2010); *Tristrata Tech., Inc. v. Mary Kay Inc.*, 423 F. Supp. 2d 456, 471 (D. Del. 2006))). Each of these cases, with the exception of *LG Display*, was decided before the Third Circuit's *Travelers* decision. Additionally, none of these cases provide any explanation for their selection of the date through which prejudgment interest was awarded, or any indication that the parties disputed the date through which prejudgment interest would accrue. Amgen also asserts, "The cases that Hospira cites state that post-judgment interest may be awarded on a judgment that sets the amount of the damages, but they do not address the appropriate timing for switching from the prejudgment rate to the post-judgment rate." (D.I. 382, p. 7). Notably, Amgen's discussion of Hospira's cited cases omits any mention of *Travelers*. In fact, *Travelers* is not cited anywhere in Amgen's brief. Therefore, I do not find convincing Amgen's argument that pre-judgment interest should be awarded on the $70 million award through the date of final judgment.

Therefore, I will award Amgen prejudgment interest using the prime rate compounded quarterly and applied against the $70 million lump-sum reasonable royalty award beginning on November 10, 2013. I will award Amgen post-judgment interest on the $70 million award beginning on September 25, 2017, the date judgment was entered on the award. I will award Amgen post-judgment interest on the prejudgment interest beginning on the date of entry of the final judgment quantifying the amount of prejudgment interest owed to Amgen in accordance with this opinion.

VI. CONCLUSION

For the reasons set forth above, Hospira's Rule 50(a) Motion for Judgment as a Matter of Law on the Issues of Safe Harbor, Noninfringement, Invalidity, and Damages (D.I. 336) is dismissed as moot. Hospira's Motion for Judgment as a Matter of Law Under Rule 50(b) and, in the Alternative, For Remittitur or New Trial Under Rule 59 (D.I. 355), Hospira's Motion to Seal Confidential Exhibits Admitted at Trial (D.I. 361), and Amgen's Renewed Motion for Judgment as a Matter of Law of Infringement of the '349 Patent or, in the Alternative, for a New Trial (D.I. 356), are each denied. Amgen's Motion for Prejudgment and Post-judgment Interest (D.I. 352) is granted-in-part.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

AMGEN INC., et al.,	:	
Plaintiffs,	:	
v.	:	Civil Action No. 15-839-RGA
HOSPIRA, INC.,	:	
Defendant.	:	

ORDER

For the reasons set forth in the accompanying memorandum opinion, Hospira's Rule 50(a) Motion for Judgment as a Matter of Law on the Issues of Safe Harbor, Noninfringement, Invalidity, and Damages (D.I. 336) is **DISMISSED** as moot. Hospira's Motion for Judgment as a Matter of Law Under Rule 50(b) and, in the Alternative, For Remittitur or New Trial Under Rule 59 (D.I. 355), Hospira's Motion to Seal Confidential Exhibits Admitted at Trial (D.I. 361), and Amgen's Renewed Motion for Judgment as a Matter of Law of Infringement of the '349 Patent or, in the Alternative, for a New Trial (D.I. 356), are each **DENIED**. Amgen's Motion for Prejudgment and Post-judgment Interest (D.I. 352) is **GRANTED-IN-PART**.

The parties are directed to submit jointly, within two weeks, a proposed final judgment.

IT IS SO ORDERED this 27 date of August 2018.

Richard G. Andrews
United States District Judge

Filed in open court this 22nd September 2017.
MMS

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiffs, v. HOSPIRA, INC., Defendant.	Civil No. 1:15-cv-839-RGA

JURY VERDICT

Instructions: When answering the following questions and completing this Verdict Form, please follow the directions provided throughout the form. Your answer to each question must be unanimous. Please refer to the Jury Instructions for guidance on the law applicable to each question. Throughout this form, "Amgen" refers to the plaintiffs, Amgen Inc. and Amgen Manufacturing Limited, and "Hospira" refers to the defendant, Hospira, Inc.

You should answer all of questions 1 to 5. Question 6, about damages, should only be answered if you find that there is at least one of the accused batches that infringed a valid claim and that was not protected by the Safe Harbor Defense.

QUESTIONS AND ANSWERS

INFRINGEMENT OF U.S. PATENT NO. 5,756,349 (THE '349 PATENT)

1. Do you find that Amgen has proven by a preponderance of the evidence that Hospira infringed any of the following cell or process claims of the '349 patent?

Answer this question for each claim by circling either "Yes" or "No" to the right of the claim number.

"Yes" is a finding for Amgen.
"No" is a finding for Hospira.

Claim 1	Yes	No
Claim 2	Yes	No
Claim 3	Yes	No
Claim 4	Yes	No
Claim 5	Yes	No
Claim 6	Yes	No
Claim 7	Yes	No

INFRINGEMENT OF U.S. PATENT NO. 5,856,298 (THE '298 PATENT)

2. Do you find that Amgen has proven by a preponderance of the evidence that Hospira infringed either of the following process claims of the '298 patent?

Answer this question for each claim by circling either "Yes" or "No" to the right of the claim number.

"Yes" is a finding for Amgen.
"No" is a finding for Hospira.

Claim 24	Yes	No
Claim 27	Yes	No

SAFE HARBOR

3. Do you find that Hospira has proven by a preponderance of the evidence that the Safe Harbor Defense applied to the manufacture of the following batches of Hospira's EPO drug substance?

Answer this question for each lot listed below by marking either "Yes" or "No" to the right of the lot number.

"Yes" is a finding for Hospira.
"No" is a finding for Amgen.

Year of manufacture	Lot Number	Yes	No
2013	410733	✓	
2013	410740	✓	
2013	410744		✓
2013	410751		✓
2014	410753		✓
2014	410754		✓
2014	410759		✓
2014	410762		✓
2014	410765		✓
2014	410768		✓
2015	410840		✓
2015	410844		✓
2015	410845	✓	
2015	410846	✓	
2015	410847	✓	
2015	410848	✓	
2015	410849	✓	
2015	410850		✓
2015	410851		✓
2015	410852		✓
2015	410853		✓

ANTICIPATION

4. Do you find that Hospira has proven by clear and convincing evidence that either of the following claims of the '298 patent is invalid because the claimed method was anticipated by U.S. Patent No. 4,667,016 (Lai)?

Answer this question for each claim by circling either "Yes" or "No" to the right of the claim number.

"Yes" is a finding for Hospira.
"No" is a finding for Amgen.

Claim 24	Yes	No
Claim 27	Yes	No

OBVIOUSNESS

5. Do you find that Hospira has proven by clear and convincing evidence that either of the following claims of the '298 patent is invalid because the claimed method was obvious to a person of ordinary skill in the art at the time of the invention of the '298 patent, based on U.S. Patent No. 4,667,016 (Lai) in combination with the Lukowsky article?

Answer this question for each claim by circling either "Yes" or "No" to the right of the claim number.

"Yes" is a finding for Hospira.
"No" is a finding for Amgen.

Claim 24	Yes	No
Claim 27	Yes	No

DAMAGES

6. What is the amount of damages that Amgen has proven by a preponderance of the evidence?

Damages: $ 70 million

UNANIMOUS VERDICT

UPON REACHING A UNANIMOUS VERDICT ON EACH QUESTION ABOVE, EACH JUROR MUST SIGN BELOW.

We, the jury, unanimously agree to the answers to the above questions and return them under the instructions of this Court as our verdict in this case.

September 22, 2017

REDACTED

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

AMGEN INC., et al.,	:	
Plaintiffs,	:	
v.	:	Civil Action No. 15-839-RGA
HOSPIRA, INC.,	:	
Defendant.	:	

JUDGMENT

This 25 day of September 2017, the Court having held a jury trial, and the jury having rendered a verdict, pursuant to Fed. R. Civ. P. 58(b)(2), IT IS HEREBY ORDERED that:

Judgment in the amount of $70,000,000 is entered for Plaintiffs Amgen Inc. and Amgen Manufacturing Limited and against Defendant Hospira, Inc. on the Third Count of the Second Amended Complaint. (D.I. 139).

Judgment is further entered for Defendant Hospira, Inc. and against Plaintiffs Amgen Inc. and Amgen Manufacturing Limited on the Fourth Count of the Second Amended Complaint. (D.I. 139).

Judgment is further entered for Plaintiffs Amgen Inc. and Amgen Manufacturing Limited and against Defendant Hospira Inc. on Hospira's Second Counterclaim. (D.I. 151).

Richard G. Andrews
United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiffs, v. HOSPIRA, INC., Defendant.	Civil No. 1:15-cv-839-RGA JURY TRIAL DEMAND

FINAL JURY INSTRUCTIONS

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1. GENERAL INSTRUCTIONS

1.1. Introduction

Members of the jury, now it is time for me to instruct you about the law that you must follow in deciding this case.

I will start by explaining your duties and the general rules that apply in every civil case. Then I will explain some rules that you must use in evaluating particular testimony and evidence. Then I will explain the positions of the parties and the law you will apply in this case. Finally, I will explain the rules that you must follow during your deliberations in the jury room, and the possible verdicts that you may return.

Please listen very carefully to everything I say. In following my instructions you must follow all of them and not single out some and ignore others. They are all important.

You will have a written copy of these instructions with you in the jury room for your reference during your deliberations. You will also have a verdict form, which will list the questions that you must answer to decide this case.

1.2. Jurors' Duties

You have two main duties as jurors. The first one is to decide what the facts are from the evidence that you saw and heard here in court. Deciding what the facts are is your job, not mine, and nothing that I have said or done during this trial was meant to influence your decision about the facts in any way.

Your second duty is to take the law that I give you, apply it to the facts, and decide, under the appropriate burden of proof, which party should prevail on each of the issues presented. It is my job to instruct you about the law, and you are bound by the oath that you took at the beginning of the trial to follow the instructions that I give you, even if you personally disagree with them. This includes the instructions that I gave you before and during the trial, and these instructions. All of the instructions are important, and you should consider them together as a whole.

Perform these duties fairly. Do not let any bias, sympathy or prejudice that you may feel toward one side or the other influence your decision in any way.

1.3. Evidence Defined

You must make your decision based only on the evidence that you saw and heard here in court. Do not let rumors, suspicions, or anything else that you may have seen or heard outside of court influence your decision in any way.

The evidence in this case includes only what the witnesses said while they were testifying under oath, deposition testimony that was presented to you, the exhibits that I allowed into evidence and the stipulations that the lawyers agreed to.

Nothing else is evidence. The lawyers' statements and arguments are not evidence. The arguments of the lawyers are offered solely as an aid to help you in your determination of the facts. Their questions and objections are not evidence. My legal rulings are not evidence. My comments and questions are not evidence.

During the trial I may have not let you hear the answers to some of the questions that the lawyers asked. I also may have ruled that you could not see some of the exhibits that the lawyers wanted you to see. And sometimes I may have ordered you to disregard things that you saw or heard, or I struck things from the record. You must completely ignore all of these things. Do not even think about them. Do not speculate about what a witness might have said or what an exhibit might have shown. These things are not evidence, and you are bound by your oath not to let them influence your decision in any way. Sometimes testimony and exhibits are received only for a limited purpose. When I give instructions regarding that limited purpose, you must follow it.

Make your decision based only on the evidence, as I have defined it here, and nothing else.

1.4. Consideration of Evidence

You should use your common sense in weighing the evidence. Consider the evidence in light of your everyday experience with people and events, and give it whatever weight you believe it deserves. If your experience tells you that certain evidence reasonably leads to a conclusion, you are free to reach that conclusion.

1.5. Direct and Circumstantial Evidence

There are two kinds of evidence: direct evidence and circumstantial evidence. Direct evidence is direct proof of a fact, such as the testimony of an eyewitness. For example, if a witness testified that she saw it raining outside, and you believed her, that would be direct evidence that it was raining.

Circumstantial evidence is indirect proof of a fact, that is, proof of facts from which you may infer or conclude that other facts exist. For example, if someone walked into the courtroom wearing a raincoat covered with drops of water and carrying a wet umbrella, that would be circumstantial evidence from which you could conclude that it was raining.

The law makes no distinction between the weight that you should give to either direct or circumstantial evidence, nor does it say that one type of evidence is any better evidence than the other. You should consider all the evidence, both direct and circumstantial, and give it whatever weight you believe it deserves.

1.6. Credibility of Witnesses

You are the sole judges of each witness's credibility. You should consider each witness's means of knowledge; strength of memory; and opportunity to observe; how reasonable or unreasonable the testimony is; whether it is consistent or inconsistent; and whether it has been contradicted; the witness's biases, prejudices, or interests; the witness's manner or demeanor on the witness stand; and all circumstances that, according to the evidence, could affect the credibility of the testimony.

If you find the testimony to be contradictory, you must try to reconcile it, if reasonably possible, so as to make one harmonious story of it all. But if you cannot do this, then it is your duty and privilege to believe the portions of testimony that, in your judgment, are most believable and disregard any testimony that, in your judgment, is not believable.

In determining the weight to give to the testimony of a witness, you should ask yourself whether there was evidence tending to prove that the witness testified falsely about some important fact, or, whether there was evidence that at some other time the witness said or did something, or failed to say or do something, that was different from the testimony he or she gave at the trial. You have the right to distrust such witness's testimony in other particulars and you may reject all or some of the testimony of that witness or give it such credibility as you may think it deserves.

You should remember that a simple mistake by a witness does not necessarily mean that the witness was not telling the truth. People may tend to forget some things or remember other things inaccurately. If a witness has made a misstatement, you must consider whether it was simply an innocent lapse of memory or an intentional falsehood, and that may depend on whether it concerns an important fact or an unimportant detail.

This instruction applies to all witnesses, including expert witnesses and witnesses who provided testimony by deposition.

1.7. Expert Witnesses

During the trial, you heard testimony from expert witnesses. When knowledge of technical subject matter may be helpful to the jury, a person who has special training or experience in that technical field—called an expert witness—is permitted to state his or her opinion on those technical matters. However, you are not required to accept that opinion. As with any other witness, it is up to you to decide whether to rely upon it.

In weighing expert testimony, you may consider the expert's qualifications, the reasons for the expert's opinions, and the reliability of the information supporting the expert's opinions, as well as the factors I have previously mentioned for weighing testimony of any other witness. Expert testimony should receive whatever weight and credit you think appropriate, given all the other evidence in the case. You are free to accept or reject the testimony of experts, just as with any other witness.

1.8. Exhibits and Demonstrative Exhibits

During the course of the trial, you have seen many exhibits. Many of these exhibits were admitted as evidence. Some of these admitted exhibits or portions of them have been displayed for you on a screen and you will have these admitted exhibits, whether displayed on a screen or not, in the jury room for your deliberations.

There are other exhibits (including charts and animations presented by attorneys and witnesses) that were offered to help illustrate the testimony of the various witnesses. These illustrations, called "demonstrative exhibits," have not been admitted as evidence, are not evidence, and should not be considered as evidence. Rather, it is the underlying testimony of the witness that you heard when you saw the demonstrative exhibits that is the evidence in this case.

1.9. Use of Notes

You may use notes taken during trial to assist your memory. However, you should use caution in consulting your notes. There is always a tendency to attach undue importance to matters that you have written down. Some testimony that is considered unimportant at the time presented, and thus not written down, takes on greater importance later on in the trial in light of all the evidence presented. Therefore, you are instructed that your notes are only a tool to aid your own individual memory, and you should not compare notes with other jurors in determining the content of any testimony or in evaluating the importance of any evidence. Your notes are not evidence, and are by no means a complete outline of the proceedings or a list of the highlights of the trial. Above all, your memory should be the greatest asset when it comes time to deliberate and render a decision in this case.

2. THE PARTIES AND THEIR CONTENTIONS

Amgen alleges that Hospira infringed claims 1-7 of the ’349 patent and claims 24 and 27 of the ’298 patent when 21 batches of Hospira’s epoetin drug substance were manufactured over the course of 2013-2015.

Amgen alleges that both the ’349 patent and the ’298 patent were infringed by the manufacture of four batches of Hospira’s epoetin drug substance in 2013, six batches in 2014, and one batch in 2015. Amgen alleges that the `298 patent was also infringed by the manufacture of ten additional batches of Hospira’s epoetin drug substance in 2015.

Hospira denies that it infringed any of Amgen’s patent claims, asserts that its activities are protected under a “safe harbor” provision of the patent laws, and asserts that each of the asserted claims of the ’298 patent is invalid, and denies that it owes Amgen any money damages.

In this case, you must decide the issues according to the instructions I give you. In general, the following are the issues you must decide:

a. Whether Amgen has proven by a preponderance of the evidence that the use of vertebrate cells and manufacturing of Hospira’s epoetin product on or before May 26, 2015 infringed any of claims 1 through 7 of the ’349 patent.

b. Whether Amgen has proven by a preponderance of the evidence that the manufacturing of Hospira’s epoetin product on or before January 5, 2016, infringed either of claims 24 or 27 of the ’298 patent.

c. Whether Hospira has proven by clear and convincing evidence that claim 24 and claim 27 of the ’298 patent are anticipated or obvious, and therefore invalid.

d. Whether Hospira has proven by a preponderance of the evidence that its use of vertebrate cells and manufacturing of its epoetin drug substance are protected by the safe harbor provision of the patent laws.

e. What amount of reasonable-royalty damages that Amgen has proven by a preponderance of the evidence would compensate Amgen for any infringement you determine Hospira has made of Amgen's valid patents.

3. BURDENS OF PROOF

For each issue in this case, either Amgen or Hospira bears the burden of proof, which means that it bears the burden of persuading you to find in its favor. In a patent case such as this, there are two different burdens of proof. The first is called "preponderance of the evidence." The second is called "clear and convincing evidence."

For any issue on which a party bears the burden of proof by a preponderance of the evidence, that party has carried its burden if you find that what the party claims is more likely true than not, when considered in light of all of the evidence. To put it differently, if you were to put each party's evidence on the opposite sides of a scale, the evidence supporting the party with the burden of proof would have to make the scales tip somewhat on the side of that party.

Here, Amgen has the burden of proving by a preponderance of the evidence that the manufacture of Hospira's epoetin drug substance infringed the '349 patent, infringed the '298 patent, and the amount of damages Amgen should receive to compensate it for any infringement. Hospira has the burden of proving by a preponderance of the evidence that the manufacture of Hospira epoetin drug substance is protected from infringement by the safe harbor provision of the patent laws.

For any issue on which a party bears the burden of proof by clear and convincing evidence, that party has carried its burden if you find that the party with the burden has caused you to have an abiding conviction that the truth of that party's factual contention is highly probable, when considered in light of all of the evidence. Proof by clear and convincing evidence is a higher burden than proof by a preponderance of the evidence.

Here, Hospira has the burden of proving by clear and convincing evidence that the claims of the '298 patent are invalid because the claimed method was anticipated or obvious.

4. PATENT CLAIMS

4.1. The Role of Claims in the Patent

Before you can decide the issues in this case, you will need to understand the role of patent "claims." The patent claims are the numbered sentences at the end of each patent. The claims are important because the words of a claim define the scope of the patent right. The figures and text in the rest of the patent provide a description and/or examples of the invention and provide a context for the claims, but the claims define the extent of the patent's coverage. Each claim may cover more or less than another claim. Therefore, what a patent covers depends, in turn, on what each of its claims covers.

4.2. Independent and Dependent Claims

Claims can be stated in two different ways in a patent. The first way a patent claim can be stated is in the form of an "independent" claim. An "independent" claim sets forth all of the requirements that must be met in order for an accused product or method to be covered by that claim, and thus infringe that claim. An independent claim is read alone to determine its scope.

In this case, claims 1 and 4 of the '349 patent and claims 24 and 27 of the '298 patent are each independent claims.

The second way a claim can be stated is in the form of a "dependent" claim. A dependent claim does not itself recite all of the requirements of the claim but instead incorporates the requirements of another claim or claims and adds its own additional requirements. In this way, the claim "depends" on another claim or claims. To determine what a dependent claim covers, it is necessary to look at both the dependent claim and any other claims from which it depends. For example, claim 2 of the '349 patent is a dependent claim of claim 1 and, as a result, claim 2 includes all the requirements of claim 1 and all the additional requirements of claim 2. Claims 2, 3, 5, 6, and 7 of the '349 patent are dependent claims. You are not being asked to consider any dependent claims in the '298 patent.

An accused product or method is only covered by, and therefore infringes, a dependent claim if the accused product or method meets all of the requirements of both the dependent claim and the claims from which the dependent claim depends. Because a dependent claim incorporates all of the features of the independent claims from which it depends, if you find that an independent claim is not infringed, then the claims that depend from that independent claim cannot be infringed.

4.3. Construction of Claims

The law says that it is the Court's duty to define the terms of patent claims. I have already defined the meaning of some of the words of the patent claims that you are considering in this case. These definitions have been provided to you, and they are attached to these jury instructions.

You must accept my definition of these words in the patent claims as correct. You must use the definitions I give you for each claim to make your decisions as to whether the claim is infringed or invalid. You must ignore any different definitions used by the witnesses or the attorneys. You should not take my definition of the language of the patent claims as an indication that I have a view regarding how you should decide the infringement or invalidity issues that you are being asked to decide. These issues are yours to decide.

When I have not defined a term, you should give it its ordinary meaning.

4.4. Open Ended or "Comprising" Claims

Some of the Asserted Claims use the word "comprising."

"Comprising" is interpreted the same way as "including" or "containing." In patent claims, "comprising" means that the claims are open-ended. As such, the accused cells and methods must contain or use everything that is in the claim, but may additionally contain or use other things. Based on this explanation, if you find that Hospira's cells and methods include all of the requirements in a claim, the fact that Hospira's cells and methods may also include an additional component do not mean that the cells and methods does not infringe the claim.

5. INFRINGEMENT

5.1. Infringement Generally

Patent law provides that any person or business entity that makes, uses, sells, or offers to sell, without the patent owner's permission, any product, apparatus, or method covered by at least one claim of a United States patent before the patent expires, infringes the patent.

I will now instruct you how to decide whether Hospira infringed any of the asserted claims in Amgen's patents. Infringement is assessed on a claim-by-claim basis. Therefore, there may be infringement as to one claim but no infringement as to another.

In this case, Amgen asserts that on or before May 26, 2015, in the course of manufacture of Hospira's epoetin drug substance, Hospira infringed claims 1 through 6 of the '349 patent by using the claimed vertebrate cells and infringed claim 7 of the '349 patent by using the claimed process. Amgen also asserts that when Hospira's epoetin drug substance was manufactured on or before January 5, 2016, Hospira infringed claims 24 and 27 of the '298 patent by using the claimed methods. Amgen asserts that Hospira is legally responsible for any infringement by its employees or agents.

In order to prove infringement, Amgen must prove that the requirements of infringement are met by a preponderance of the evidence.

5.2. Infringement

To prove infringement of a patent claim, Amgen must prove by a preponderance of the evidence, that is, that it is more likely than not, that the use of vertebrate cells and manufacture of the Hospira epoetin drug substance met all of the requirements of the patent claim. Infringement requires no more than the unauthorized making, use, sale, offer for sale, or importation of a patented invention during the time when the patent was in force. Thus, Hospira's knowledge of Amgen's patents and Hospira's intent are irrelevant to your determination of direct infringement.

To determine infringement, you must compare the accused product or method with each claim that Amgen asserts is infringed, using my instructions as to the meaning of the patent claims. A patent claim is infringed only if the vertebrate cell or method used in manufacturing Hospira's drug substance includes each and every requirement in that patent claim. If Hospira's cells or methods do not contain one or more requirements or steps recited in a claim, Hospira does not infringe that claim.

Hospira is responsible for the manufacturing activities of GlaxoSmithKline ("GSK") as they relate to Hospira's epoetin drug substance.

6. FDA SAFE HARBOR DEFENSE

Hospira contends that it has not infringed the asserted claims of the patents, based on a statutory provision that you have heard referred to as the "Safe Harbor."

The Safe Harbor is intended to provide protection for the use of patented inventions reasonably related to obtaining FDA approval for a product. Only uses reasonably related to obtaining FDA approval are protected by the Safe Harbor.

Hospira bears the burden of proving that the Safe Harbor defense applies to Hospira's use of Amgen's patented inventions. You must decide whether Hospira has proven that it is more likely than not that the Safe Harbor applies to its use of the vertebrate cells and processes of claims 1-7 of the '349 patent and the use of the claimed processes of claims 24 and 27 of the '298 patent in the manufacture of each lot of Hospira's drug substance.

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.

7. INVALIDITY

In this case, Hospira contends that claims 24 and 27 of the ’298 patent are anticipated by U.S. Patent 4,667,016. Hospira also contends that claims 24 and 27 of the ’298 Patent are obvious over U.S. Patent No. 4,667,016 in view of the prior art. I will explain the legal concepts of anticipation, obviousness, and prior art in a moment.

In making your determination, you must consider each of these patent claims separately and individually.

7.1. Person of Ordinary Skill in the Art

The question of invalidity of a patent claim is determined from the perspective of a person of ordinary skill in the art in the field of the invention at the time the invention was made. In this case, the date of the invention for the ’298 patent is October 12, 1990.

You must determine the level of ordinary skill in the field of the invention. In deciding what the level of ordinary skill is, you should consider all the evidence introduced at trial, including but not limited to: (1) the levels of education and experience of the inventor and other persons actively working in the field; (2) the types of problems encountered in the field; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; and (5) the sophistication of the technology.

7.2. Prior Art

Under the patent laws, a person is granted a patent only if the invention claimed in the patent is new and not obvious in light of what came before. That which came before is referred to as the "prior art." In this case, the following items are prior art to the '298 patent:

- U.S. Patent No. 4,667,016;
- W.A. Lukowsky & R.H. Painter, Studies on the Role of Sialic Acid in the Physical and Biological Properties of Erythropoietin, Canadian Journal of Biochemistry, Vol. 50, 909-917 (1972); and
- Beeley, Laboratory Techniques in Biochemistry and Molecular Biology: Glycoprotein and Proteoglycan Techniques (1985).

The burden of proof on Hospira to prove that the prior art renders a claim invalid never changes regardless of whether the Examiner in the Patent Office considered the prior art reference during the prosecution of the application which matured into the '298 patent. However, if the Patent Office considered a reference, it may be more difficult for Hospira to meet its burden of proof to prove invalidity based on that reference.

7.3. Anticipation

As I have explained, under the patent laws a person is granted a patent only if the invention claimed in the patent is both new and nonobvious in light of what came before. In general, inventions are new when they have not been made, used, or disclosed before. The legal name for this type of challenge to the validity of a patent claim is "anticipation."

In this case, Hospira contends that the inventions of claims 24 and 27 of the '298 patent are anticipated by U.S. Patent No. 4,667,016. Anticipation must be determined on a claim-by-claim basis. Hospira must prove by clear and convincing evidence that each of claims 24 and 27 of the '298 patent was not new based on U.S. Patent No. 4,667,016.

Invalidity by anticipation requires that a single prior art reference disclosed each and every requirement, or limitation, of a claimed invention arranged as in the claim. You may not combine two or more items of prior art to find anticipation. In determining whether every one of the elements of the claimed invention is found in a particular prior art reference, you should take into account what a person of ordinary skill in the art would have understood from his or her review of that reference.

In determining whether a single prior art reference anticipates a patent claim, you should take into consideration not only what is expressly disclosed in that prior art reference but also what is inherently present or disclosed in that reference, or inherently results from its practice. A prior art reference inherently anticipates a patent claim if the element or feature missing from the reference would necessarily result from what that reference teaches to a person of ordinary skill in the art.

A party asserting inherent anticipation must prove that the allegedly inherent element was necessarily present in that reference. The fact that it was likely present is not sufficient. It is not required, however, that a person of ordinary skill actually recognized or appreciated the inherent disclosure at the time the prior art reference was first known or used. Thus, the prior use of the

patented invention that was unrecognized and unappreciated can still be an invalidating anticipating reference, provided the allegedly inherent feature was necessarily and inevitably present in the reference. Evidence outside of the prior art reference itself may be used to show that elements that are not expressly disclosed in the reference are inherent in it.

7.4. Obviousness

As I explained previously, under the patent laws a person is granted a patent only if the invention claimed in the patent is both new and not obvious in light of what came before. Even though an invention has not been identically disclosed or described before it was made by an inventor, in order to be patentable, the invention must also not have been obvious to a person of ordinary skill in the art of the claimed invention at the time the invention was made. Unlike anticipation, which allows consideration of only one item of prior art, obviousness may be proven by considering more than one item of prior art. In this case, Hospira contends that claims 24 and 27 of the ’298 patent are obvious over U.S. Patent No. 4,667,016 in combination with the Lukowsky article and the knowledge of a person of skill in the art.

Hospira must prove by clear and convincing evidence that the inventions of claims 24 and 27 of the ’298 patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. The issue is not whether the claimed inventions would have been obvious to you as a layman, to me as the judge, or to a genius in the field of technology, but whether it would have been obvious to one of ordinary skill in the art at the time the invention was made.

In determining whether a claimed invention would have been obvious, you must avoid using hindsight; that is, you should not consider what is known today or what was learned from the teachings of the ’298 patent. You should not use the patent as a road map for selecting and combining items of prior art. You must put yourself in the place of a person of ordinary skill in the art at the time the invention was made.

In determining whether a claimed invention would have been obvious, you must consider (1) the scope and content of the prior art, (2) the level of ordinary skill in the pertinent art; and (3) the differences between the claimed invention and the prior art.

To determine the scope and content of the prior art, you must determine what prior art is reasonably pertinent to the particular problems the inventor, Dr. Strickland, faced. The person of ordinary skill in the art is presumed to be aware of all of the pertinent prior art.

I have already instructed you on how you are to determine the level of ordinary skill in the art. Once you have made that determination, you are to apply it in your determination whether the asserted claims would have been obvious.

The next factor that you must consider is the differences, if any, between the prior art and the claimed inventions. Importantly, a claim is not proved obvious merely by demonstrating that each of the elements was independently known in the prior art. Most, if not all, inventions rely on building blocks of prior art, and claimed discoveries almost of necessity will likely be combinations of what is already known. Therefore, you should consider whether a reason existed at the time of the invention that would have prompted a person of ordinary skill in the art in the relevant field to combine the known elements in the way the claimed invention does. The motivation to modify the prior art to arrive at the claimed invention need not be the same motivation that the inventor had.

In arriving at your decision on the issue of whether the claimed inventions of the ’298 patent would have been obvious to a person of ordinary skill in the art, you may take into account such factors as: (1) whether the claimed invention was merely the predictable result of using prior art elements according to their known functions; (2) whether the claimed invention provides an obvious solution to a known problem in the relevant field; (3) whether the prior art teaches or suggests the desirability of combining elements claimed in the invention; (4) whether the prior art teaches away from combining elements in the claimed invention; and (5) whether it would have been obvious to try the combinations of elements, such as when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions.

In arriving at your decision on the issue of whether the claimed inventions of the ’298 patent would have been obvious to a person of ordinary skill in the art, you should take into account any “secondary considerations,” also called “objective evidence,” that may have existed at the time of the invention and afterwards that suggest that the claimed invention was not obvious. Such objective evidence may include unexpectedly superior results from the invention.

These factors should be considered along with all the other evidence in the case in determining whether the claimed invention would have been obvious. However, there must be a connection between the secondary consideration and the claimed invention if this evidence is to be given weight by you in arriving at your conclusion on the obviousness issue.

8. DAMAGES

8.1. Damages—Generally

I will now instruct you about the measure of damages. By instructing you on damages, I am not suggesting which party should win this case on any issue.

The damages you award must be adequate to compensate Amgen for any infringement you determine to have occurred. Damages are not meant to punish an infringer. Your damages award, if you reach this issue, should put Amgen in approximately the same financial position that it would have been in if the parties had reached agreement for Hospira to license the patents before the infringement began.

Amgen has the burden to prove the amount of its damages by a preponderance of the evidence. While Amgen is not required to prove the amount of its damages with mathematical precision, it must prove them with reasonable certainty.

If you find that Amgen has established infringement of a valid patent claim of the patents-in-suit, Amgen will be entitled to a reasonable royalty to compensate it for that infringement. A reasonable royalty is defined as the amount of money Amgen and Hospira would have agreed upon as a fee for Hospira using Amgen's invention before the infringement first began.

8.2. Reasonable Royalty as a Measure of Damages

A royalty is a payment made to a patent holder in exchange for the patent holder's permission to make, use, offer to sell, sell, or import the patented invention. A reasonable royalty is the amount of royalty payment that a patent holder and the infringer would have agreed to in a hypothetical negotiation taking place at a time prior to when the infringement first began. In considering this hypothetical negotiation, you should focus on what the expectations of the patent holder (here Amgen) and the accused infringer (here Hospira) would have been had they entered into an agreement at that time, and had they acted reasonably in their negotiations. In determining this, you must assume that both parties believed the patent was valid and infringed and Amgen and Hospira were willing to enter into an agreement.

The relevant date for the hypothetical license negotiation is just before the alleged infringement began. However, you may consider events and facts that occurred after the hypothetical negotiation took place. This is true even of subsequent events that could not have been known or predicted by the hypothetical negotiators, so long as the evidence aids in assessing what royalty would have resulted from the hypothetical negotiation.

The reasonable royalty you determine must be a royalty that would have resulted from the hypothetical negotiation, and not simply a royalty either party would have preferred.

8.3. Factors for Determining a Reasonable Royalty

In determining the reasonable royalty, you should consider all the facts known and available to the parties at the time the infringement began. Some of the kinds of factors that you may consider in making your determination are:

(1) The royalties, if any, received by Amgen for the licensing of the ’349 patent or the ’298 patent.

(2) The nature and scope of the license, such as whether the license is non-exclusive or exclusive.

(3) The utility and advantages of the patented property over the old modes or devices, if any, that had been used for working out similar results.

(4) Amgen’s established policy and program to enforce its patent rights, if any, or license its patents under special conditions to preserve its monopoly.

(5) The portion of the realizable profits that should be credited to the invention as distinguished from non-patented elements, the manufacturing process, or business risks.

(6) The commercial relationship between Amgen and Hospira, such as whether they are competitors in the same territory in the same line of business, or whether they are inventor and promoter.

(7) The duration of the patent and term of the license.

(8) The established profitability of the products made under the patents, its commercial success, and its popularity.

(9) The nature of the patented invention, the character of any commercial example of it, and the benefits to those who have used the invention.

(10) The extent to which Hospira has made use of the invention and any evidence probative of the value of that use.

(11) The opinion testimony of qualified experts.

(12) The amount that a licensor (such as Amgen) and a licensee (such as Hospira) would have agreed upon at the time the infringement began if both had been reasonably and voluntarily trying to reach an agreement; that is, the amount which a prudent licensee—who desired, as a business proposition, to obtain a license to manufacture a particular article embodying the patented invention—would have been willing to pay as a royalty and yet be able to make a reasonable profit and which amount would have been acceptable by a prudent patentee who was willing to grant a license.

No one factor is dispositive, and you can and should consider the evidence that has been presented to you in this case on each of these factors. You may also consider any other factors which in your mind would have increased or decreased the royalty Hospira would have been willing to pay and Amgen would have been willing to accept, acting as normally prudent business people. The final factor establishes the framework which you should use in determining a reasonable royalty, that is, the payment that would have resulted from a negotiation between Amgen and Hospira taking place at a time prior to when the infringement began.

8.4. Availability of Non-Infringing Alternatives

In determining a reasonable royalty, you may also consider evidence concerning the availability and cost of non-infringing alternatives to using the patented invention. A non-infringing alternative must have been available at the time of the infringement, must be acceptable in that it provides the same advantages as the patented invention, and must not infringe the patent.

8.5. Patent Terms

The ’349 patent expired on May 26, 2015. The ’298 patent expired on January 5, 2016. Amgen is only seeking damages for Hospira’s infringement of either patent that occurred before the date each patent expired.

9. DELIBERATION AND VERDICT

9.1. Deliberations and Verdict—Introduction

That concludes the part of my instructions explaining the rules for considering some of the testimony and evidence. Now let me finish by explaining some things about your deliberations in the jury room, and your possible verdicts.

Once you start deliberating, do not talk to the jury officer, or to me, or to anyone else except each other about the case. If you have any questions or messages, you must write them down on a piece of paper, sign them, and then give them to the jury officer. The officer will give them to me, and I will respond as soon as I can. I may have to talk to the lawyers about what you have asked, so it may take me some time to get back to you. Any questions or messages normally should be sent to me through your foreperson, who by custom of this Court is juror No. 1.

One more thing about messages. Do not ever write down or tell anyone outside of the jury how you stand on your votes. For example, do not write down or tell anyone that you are split 4-4, or 6-2, or whatever your vote happens to be. That should stay secret until you are finished.

9.2. Unanimous Verdict

Your verdict must represent the considered judgment of each juror. In order for you as a jury to return a verdict, it is necessary that each juror agree to the verdict. Your verdict must be unanimous.

It is your duty, as jurors, to consult with one another and to deliberate with a view towards reaching an agreement, if you can do so consistent with your individual judgment. Each of you must decide the case for yourself, but do so only after an impartial consideration of the evidence with your fellow jurors. In the course of your deliberations, do not hesitate to reexamine your own views and change your opinion, if convinced it is erroneous. But do not surrender your honest conviction as to the weight or effect of evidence solely because of the opinion of your fellow jurors, or for the purpose of returning a verdict. Remember at all times that you are not partisans. You are judges of the facts. Your sole interest is to seek the truth from the evidence in the case.

A verdict form has been prepared for you. The verdict form asks you a series of questions about the parties' contentions. You will take this form to the jury room and when you have reached unanimous agreement as to your verdict, you will have your foreperson fill in, date, and sign the form. You will then return to the courtroom and your foreperson will give your verdict. Unless you are directed otherwise in the verdict form, you must answer all of the questions posed, and you all must agree on each answer.

9.3. Duty to Deliberate

Now that all the evidence is in and the arguments are completed, you are free to talk about the case in the jury room. In fact, it is your duty to talk with each other about the evidence and to make every reasonable effort you can to reach a unanimous agreement. Talk with each other, listen carefully and respectfully to each other's views, and keep an open mind as you listen to what your fellow jurors have to say. Try your best to work out your differences. Do not hesitate to change your mind if you are convinced that other jurors are right and your original position was wrong.

But do not ever change your mind just because other jurors see things differently, or just to get the case over with. In the end, your vote must be exactly that—your own vote. It is important for you to reach unanimous agreement, but only if you can do so honestly and in good conscience.

No one will be allowed to hear your discussions in the jury room, and no record will be made of what you say. So you should all feel free to speak your minds.

Listen carefully to what the other jurors have to say, and then decide for yourself.

9.4. Social Media

During your deliberations, you must not communicate with or provide any information to anyone by any means about this case. You may not use any electronic device or media, such as the telephone, a cell phone, smart phone, iPhone, blackberry or computer, the internet, any internet service, any text or instant messaging service, any internet chat room, blog, or website such as Facebook, Instagram, Snapchat, MySpace, LinkedIn, YouTube, or Twitter, to communicate to anyone any information about this case or to conduct any research about this case until I accept your verdict. In other words, you cannot talk to anyone on the phone, correspond with anyone, or electronically communicate with anyone about this case. You can only discuss the case in the jury room with your fellow jurors during deliberations.

9.5. Court Has No Opinion

Let me finish up by repeating something that I said to you earlier. Nothing that I have said or done during this trial was meant to influence your decision in any way. You must decide the case yourselves based on the evidence presented.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, vs. HOSPIRA, INC., Defendant.	C.A. No. 15-839 (RGA)

[PROPOSED] ORDER ON CLAIM CONSTRUCTION

This 22 day of September, 2017, IT IS HEREBY ORDERED:

1. With respect to the '298 patent:

   a. The term "an isoform" means 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).

   b. The term "an isolated . . . isoform" in Claim 1 means one and only one isoform, that is, a group of erythropoietin molecules all with the same isoelectric focusing point and the same number of sialic acids per molecule and which appear as a single band on an isoelectric focusing gel, separated from erythropoietin molecules having a different isoelectric focusing point and number of sialic acids per molecule.

   c. The term "erythropoietin molecules having a predetermined number of sialic acids per molecule selected from the group consisting of 1-14" in Claim 24

essentially describes an isoform, and Claim 24 claims methods of preparing one or more erythropoietin isoforms.

d. The term "selectively eluting" in Claim 24 shall be given its plain and ordinary meaning to a person of ordinary skill in the art in 1990.

e. Claim 27 is an independent claim, and the term "mixture of two or more erythropoietin isoforms of Claim 1" in Claim 27 means a mixture of two or more of the isolated erythropoietin isoforms of Claim 1. Claim 27 does not require the individual isoforms of Claim 1 to be separately prepared prior to making the mixture.

2. With respect to the '349 patent:

a. The term "DNA sequences which control transcription" means DNA sequences that initiate and may regulate the processes of transcription.

b. The term "transcription control DNA sequences" means DNA sequences that initiate and may regulate the processes of transcription.

The Honorable Richard G. Andrews

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, vs. HOSPIRA, INC., Defendant.	C.A. No. 15-839 (RGA)

ORDER ON CLAIM CONSTRUCTION

This 15 day of September, 2017, IT IS HEREBY ORDERED:

1. With respect to the '298 patent:

   a. The term "an isoform" means 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).

   b. The term "an isolated . . . isoform" in Claim 1 means one and only one isoform, that is, a group of erythropoietin molecules all with the same isoelectric focusing point and the same number of sialic acids per molecule and which appear as a single band on an isoelectric focusing gel, separated from erythropoietin molecules having a different isoelectric focusing point and number of sialic acids per molecule.

   c. The term "erythropoietin molecules having a predetermined number of sialic acids per molecule selected from the group consisting of 1-14" in Claim 24

essentially describes an isoform, and Claim 24 claims methods of preparing one or more erythropoietin isoforms.

d. Claim 27 is an independent claim, and the term "mixture of two or more erythropoietin isoforms of Claim 1" in Claim 27 means a mixture of two or more of the isolated erythropoietin isoforms of Claim 1. Claim 27 does not require the individual isoforms of Claim 1 to be separately prepared prior to making the mixture.

2. With respect to the '349 patent:

a. The term "DNA sequences which control transcription" means DNA sequences that initiate and may regulate the processes of transcription.

b. The term "transcription control DNA sequences" means DNA sequences that initiate and may regulate the processes of transcription.

United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC., AMGEN MANUFACTURING, LIMITED, Plaintiffs, v. HOSPIRA, INC., Defendant.	Civil Action No. 15-839-RGA

MEMORANDUM ORDER

Presently before me is Defendant Hospira, Inc.'s Motion for Summary Judgment (D.I. 196); Plaintiffs Amgen Inc. and Amgen Manufacturing, Limited's Motion to Exclude Testimony of Dr. Gregory K. Bell (D.I. 204); and Defendant Hospira, Inc.'s Motion to Exclude the Testimony of Randal Heeb, Ph.D. (D.I. 202). I have considered the parties' briefing. (D.I. 197; D.I. 227; D.I. 242; D.I. 206; D.I. 223; D.I. 244; D.I. 203; D.I. 225; D.I. 246). I held oral argument on June 28, 2017.

I. LEGAL STANDARD

A. Summary Judgment

"The court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." FED. R. CIV. P. 56(a). The moving party has the initial burden of proving the absence of a genuinely disputed material fact relative to the claims in question. *Celotex Corp. v. Catrett*, 477 U.S. 317, 330 (1986). Material facts are those "that could affect the outcome" of the proceeding, and "a dispute about a material fact is 'genuine' if the evidence is sufficient to permit a reasonable jury

to return a verdict for the non-moving party." *Lamont v. New Jersey*, 637 F.3d 177, 181 (3d Cir. 2011). The burden on the moving party may be discharged by pointing out to the district court that there is an absence of evidence supporting the non-moving party's case. *Celotex*, 477 U.S. at 323.

The burden then shifts to the non-movant to demonstrate the existence of a genuine issue for trial. *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586–87 (1986); *Williams v. Borough of West Chester, Pa.*, 891 F.2d 458, 460–61 (3d Cir. 1989). A non-moving party asserting that a fact is genuinely disputed must support such an assertion by: "(A) citing to particular parts of materials in the record, including depositions, documents, electronically stored information, affidavits or declarations, stipulations . . . , admissions, interrogatory answers, or other materials; or (B) showing that the materials cited [by the opposing party] do not establish the absence . . . of a genuine dispute . . . ." FED. R. CIV. P. 56(c)(1).

When determining whether a genuine issue of material fact exists, the court must view the evidence in the light most favorable to the non-moving party and draw all reasonable inferences in that party's favor. *Scott v. Harris*, 550 U.S. 372, 380 (2007); *Wishkin v. Potter*, 476 F.3d 180, 184 (3d Cir. 2007). A dispute is "genuine" only if the evidence is such that a reasonable jury could return a verdict for the non-moving party. *Anderson*, 477 U.S. at 247–49. If the non-moving party fails to make a sufficient showing on an essential element of its case with respect to which it has the burden of proof, the moving party is entitled to judgment as a matter of law. *See Celotex Corp.*, 477 U.S. at 322.

B. Federal Rule of Evidence 702

Federal Rule of Evidence 702 sets out the requirements for expert witness testimony, stating that:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if: (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert has reliably applied the principles and methods to the facts of the case.

Fed. R. Evid. 702. The Third Circuit has explained:

> Rule 702 embodies a trilogy of restrictions on expert testimony: qualification, reliability and fit. Qualification refers to the requirement that the witness possess specialized expertise. We have interpreted this requirement liberally, holding that "a broad range of knowledge, skills, and training qualify an expert." Secondly, the testimony must be reliable; it "must be based on the 'methods and procedures of science' rather than on 'subjective belief or unsupported speculation'; the expert must have 'good grounds' for his o[r] her belief. In sum, *Daubert* holds that an inquiry into the reliability of scientific evidence under Rule 702 requires a determination as to its scientific validity." Finally, Rule 702 requires that the expert testimony must fit the issues in the case. In other words, the expert's testimony must be relevant for the purposes of the case and must assist the trier of fact. The Supreme Court explained in *Daubert* that "Rule 702's 'helpfulness' standard requires a valid scientific connection to the pertinent inquiry as a precondition to admissibility."
> By means of a so-called "*Daubert* hearing," the district court acts as a gatekeeper, preventing opinion testimony that does not meet the requirements of qualification, reliability and fit from reaching the jury. *See Daubert* ("Faced with a proffer of expert scientific testimony, then, the trial judge must determine at the outset, pursuant to Rule 104(a) [of the Federal Rules of Evidence] whether the expert is proposing to testify to (1) scientific knowledge that (2) will assist the trier of fact to understand or determine a fact in issue.").

Schneider ex rel. Estate of Schneider v. Fried, 320 F.3d 396, 404–05 (3d Cir. 2003) (footnote and internal citations omitted).[1] The proponent of expert testimony must "demonstrate by a

[1] The Court of Appeals wrote under an earlier version of Rule 702, but subsequent amendments to the rule were not intended to make any substantive change.

preponderance of evidence that the [expert's] opinions are reliable." *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 744 (3d Cir. 1994).

II. DISCUSSION

A. Summary Judgment

1. Safe Harbor

There are genuine disputes of material fact as to whether Hospira's manufacture of twenty one lots of EPO for commercial inventory in 2013 to 2015 was "solely for uses *reasonably* related to the development and submission of information" to the FDA. *See Momenta Pharm., Inc. v. Teva Pharm. USA Inc.*, 809 F.3d 610, 614 (Fed. Cir. 2015) (emphasis added). For example, there is evidence that Hospira manufactured a large quantity (tens of millions of doses) of EPO in its 2013, 2014 and 2015 manufacturing campaigns. (D.I. 228-1 at 21–27 ¶¶ 54–64, 151 n.31). The commercial value of this is in the hundreds of millions. (D.I. 228-1 at 151 n.31). Hospira's own documents and statements to the FDA indicate that the manufacture of some of the lots was for "commercial inventory." (*See, e.g.*, D.I. 228-1 at 184). Thus, although Hospira has evidence that its EPO was manufactured and used to gather information for FDA submission pursuant to FDA guidelines and information requests, that is insufficient to show that there is no genuine of dispute of material fact that the quantity of EPO produced was reasonably related to the development and submission of information to the FDA. (*See* D.I. 197 at 6–9).

I am therefore denying summary judgment because there is a genuine dispute of material fact as to the applicability of the Safe Harbor. *See Integra Lifesciences I, Ltd. v. Merck KGaA*, 496 F.3d 1334, 1347 (Fed. Cir. 2007) ("The variety of experimental activity that may apply to any specific biologic or physiologic investigation reinforces the fact-dependency of the

inquiry."); *Chang v. Biosuccess Biotech Co.*, 76 F. Supp. 3d 1022, 1036 (C.D. Cal. 2014) ("Whether a 'use' falls within the Safe Harbor Exemption is a fact-based issue."); *Isis Pharm., Inc. v. Santaris Pharma A/S Corp.*, 2014 WL 794811, at *13 (S.D. Cal. Feb. 27, 2014) ("The Court finds this question is, as with most questions involving a determination of what is reasonable, best left to the trier of fact.").

2. Claims 24 and 27 of the '298 Patent

i. Claim 24

There is a genuine dispute of material fact as to whether Hospira's process selectively elutes the desired EPO isoforms. Amgen puts forward sufficient evidence that Hospira's "Downstream Manufacturing process" selectively elutes the EPO isoforms. (*See, e.g.*, D.I. 228-2, Exh. 19, HOS13296, Exh. 20 ¶¶ 48–49, 52–56, Exh. 21 ¶¶ 10, 24–26).

Hospira's argument that its method merely practices the "single-step" process of Lai is not persuasive. *See, e.g.*, *Ecolab, Inc. v. Paraclipse, Inc.*, 285 F.3d 1362, 1377 (Fed. Cir. 2002) ("[P]racticing the prior art is not a defense to literal infringement."). For example, there is evidence that Lai does not achieve the same degree of purity of isoforms having nine to fourteen sialic acids as Hospira's mixture. (D.I. 228-2, Exh. 20 ¶¶ 41–42; D.I. 1-1, Exh. A at 9:1–3, 10:39–41). Thus, there is a genuine dispute of material fact as to whether Hospira infringes the "selectively eluting" limitation of claim 24.

ii. Claim 27

Hospira argues that its process does not infringe because the process does not isolate individual isoforms. This is premised on an improper construction of claim 27. Claim 27 provides:

> 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.

(D.I. 1-1, Exh. A, claim 27). Nothing in this language suggests that the individual isoforms of claim 1 have to be separately prepared prior to making the mixture. I have never held that this was the case. Rather the language "preparing a mixture of two or more" of the isoforms of claim 1 naturally allows for the simultaneous preparation of a mixture of the isoforms of claim 1. The specification supports this reading. (D.I. 1-1, Exh. A, 6:61–7:3). Hospira's reading is too limiting. *See also Dow Chem. Co. v. Sumitomo Chem. Co.*, 257 F.3d 1364, 1378 (Fed. Cir. 2001) ("[I]t is [] well established that a claim construction that excludes a preferred embodiment is *rarely, if ever, correct*."). Thus, summary judgment is improper with respect to claim 27.

B. Dr. Bell

Amgen seeks to exclude Dr. Bell's testimony on the following grounds: that (1) his non-infringing alternative theory is improper, (2) his hypothetical-negotiation analysis is improperly tied to what eventually happened, and (3) his "scoring system" is not a generally accepted methodology.

Amgen argues that Hospira's non-infringing alternative is that Hospira could discard the infringing batches before patent expiration and create new ones after patent expiration. (D.I. 206 at 6). Given that Hospira has made no commercial use of the allegedly infringing EPO, reliance on this non-infringing alternative is proper. *See Georgia-Pac. Corp. v. U.S. Plywood Corp.*, 318 F. Supp. 1116, 1120 (S.D.N.Y. 1970) (considering "[t]he extent to which the infringer has made use of the invention; and any evidence probative of the value of that use").

Amgen argues that Dr. Bell's analysis improperly replaces the hypothetical negotiation's inquiry into what the parties would have expected at the time of the negotiation with a

"backward-looking inquiry" into what actually happened later. (D.I. 206 at 7–8). This is not persuasive because consideration of "book of wisdom" evidence is permissible, at least in this context. *See, e.g.*, *Sinclair Ref. Co. v. Jenkins Petroleum Process Co.*, 289 U.S. 689, 698 (1933) ("But a different situation is presented if years have gone by before the evidence is offered. Experience is then available to correct uncertain prophecy. Here is a book of wisdom that courts may not neglect. We find no rule of law that sets a clasp upon its pages, and forbids us to look within.").

Amgen argues that Dr. Bell's three-point "scoring system" is unreliable and, in the alternative, would be unduly prejudicial and misleading to the jury. Addressing the Federal Rule of Evidence 403 issue first, I think his scoring system has minimal probative value and is substantially outweighed by the dangers of undue prejudice and juror confusion. While I do not have a problem with Dr. Bell's underlying analysis, I am concerned with the scoring system. The scoring system makes Dr. Bell's analysis sound like a scientifically-precise analysis, which it is not. *See Apple Inc. v. Motorola, Inc.*, 757 F.3d 1286, 1315 (Fed. Cir. 2014) ("This court has [] recognized that estimating a reasonable royalty is not an exact science."). Because Federal Rule of Evidence 403 decides the matter, it is not necessary to address the *Daubert* issue.

C. Dr. Heeb

Hospira argues for the exclusion of Dr. Heeb's testimony. (*See generally* D.I. 203). One argument that Hospira raises is for the exclusion of Dr. Heeb's MWP-MWA opinion. Hospira argues that Dr. Heeb performs a "Maximum Willingness to Pay" ("MWP") and "Minimum Willingness to Accept" ("MWA") analysis to determine that the reasonable royalty would be a lump-sum payment from $153.9 million (MWP) to $415.3 million (MWA). (D.I. 203 at 4). Hospira argues that the $415.3 million figure is unreliable because it assumes two counterfactual

premises: (1) Hospira would be able to take away Amgen's sales from DaVita, and (2) Amgen's Epogen sales would continue at a fixed rate with respect to Aranesp. I agree that the $415.3 million figure is unreliable because it assumes Hospira would be able to take away Amgen's sales from DaVita.

In determining the MWA, Dr. Heeb assumes that Hospira's EPO product would take Amgen's DaVita sales. The DaVita sales occur in the dialysis market, which is dominated by DaVita and a competing product made by Fresenius. (D.I. 205-3, 86:4–7). At the time of the hypothetical negotiation, Amgen and DaVita were in an exclusive supply contract requiring DaVita to purchase 90% of its EPO from Amgen through at least 2019. The DaVita contract has since been renegotiated. (*See* D.I. 205-5 at 11; D.I. 247-2, 94:12–95:8). Thus, at the time of the hypothetical negotiation, Hospira's EPO could not be freely purchased by DaVita. A damages calculation that assumes otherwise does not fit the facts of the case. Dr. Heeb admits, "If one were to credit a scenario in which Hospira targets primarily Fresenius, Amgen's MWA would have been $170.4 million." (D.I. 247-1 at 45, 81–82). Thus, for this reason alone, the maximum MWA Dr. Heeb can put before the jury would be $170.4 million.

The $415.3 million figure is also challenged on the basis that it assumes that Epogen sales would continue at a fixed proportion in relation to another Amgen product, Aranesp (Amgen's second-generation competitor to Epogen). While certain facts suggest that Amgen is transitioning sales away from Epogen to Aranesp (D.I. 205-3, 138:23–139:5; D.I. 205-5 at 12–13; D.I. 247-2, 144:18–145:4), this is insufficient to render the $415.3 million figure unreliable. To the extent the $170.4 million figure rests on the same assumption, Hospira is free to cross-examination Dr. Heeb on this point.

Thus, I am excluding evidence offered for the purpose of supporting the $415.3 million figure and argument related to the $415.3 million figure. This ruling does not exclude evidence offered for the purpose of supporting the $170.4 million figure and argument related to the $170.4 million figure. Hospira's arguments for excluding other aspects of Dr. Heeb's testimony are better suited for cross-examination and are denied.

III. CONCLUSION

For the foregoing reasons, Defendant's Motion for Summary Judgment (D.I. 196) is **DENIED**. Plaintiffs' Motion to Exclude Testimony of Dr. Gregory K. Bell (D.I. 204) is **GRANTED-IN-PART** and **DENIED-IN-PART**. Defendant's Motion to Exclude the Testimony of Randal Heeb, Ph.D (D.I. 202) is **GRANTED-IN-PART** and **DENIED-IN-PART**.

It is **SO ORDERED** this 7 day of September, 2017.

Richard G. Andrews
United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, vs. HOSPIRA, INC., Defendant.	C.A. No. 15-839 (RGA)

~~PROPOSED~~ ORDER ON CLAIM CONSTRUCTION

This 23 day of January, 2017, the Court, consistent with the findings and conclusions set forth in the Memorandum Opinion dated November 30, 2016 (D.I. 162) and the Memorandum Opinion dated January 12, 2017 (D.I. 177),

IT IS HEREBY ORDERED:

1. With respect to the '298 patent:

   a. The term "an isoform" means "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)" (D.I. 162, p. 6, line 22 to p. 7, line 3; D.I. 177 p. 4, lines 10-12.)

   b. The term "an isolated . . . isoform" in Claim 1 means "one and only one isoform, that is, a group of erythropoietin molecules all with the same isoelectric focusing point and the same number of sialic acids per molecule and which appear as a single band on an isoelectric focusing gel, separated from erythropoietin

molecules having a different isoelectric focusing point and number of sialic acids per molecule." (D.I. 177, p. 4, lines 13-18.)

c. Claim 8 is invalid under 35 U.S.C. Section § 112, ¶ 4 for failure to properly narrow the scope of claim 1, from which it depends.

d. The term "consisting essentially of" in Claim 13 means "the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention." (D.I. 177, p. 8, lines 4-7.)

e. The term "erythropoietin consisting essentially of erythropoietin molecules having a single specific number of sialic acids per molecule" in Claim 13 means "erythropoietin consisting essentially of one and only one isoform." (D.I. 177, p. 8, lines 2-4.)

f. Claim 19 is invalid under 35 U.S.C. Section § 112, ¶ 4 for failure to properly narrow the scope of claim 13, from which it depends.

g. The term "erythropoietin molecules having a predetermined number of sialic acids per molecule selected from the group consisting of 1-14" in Claim 24 essentially describes "an isoform," (D.I. 177, p. 5, lines 14-21), and Claim 24 claims "methods of preparing one or more erythropoietin isoforms." (D.I. 177, p. 7, lines 9-10.)

h. Claim 27 is an independent claim (D.I. 177, p. 10, lines 6-7), and the term "mixture of two or more erythropoietin isoforms of Claim 1" in Claim 27 means "a mixture of two or more of the isolated erythropoietin isoforms of Claim 1."

2. With respect to the '349 patent:

   a. The term "DNA sequences which control transcription" means "DNA sequences that initiate and may regulate the processes of transcription."

   b. The term "transcription control DNA sequences" means "DNA sequences that initiate and may regulate the processes of transcription."

Dated: January 23, 2017

The Honorable Richard G. Andrews

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC., AMGEN MANUFACTURING, LIMITED, Plaintiffs, v. HOSPIRA, INC., Defendant.	Civil Action No. 15-839-RGA

MEMORANDUM OPINION

Jeffrey L. Moyer, Esq., RICHARDS, LAYTON & FINGER, Wilmington, DE; Kevin M. Flowers, Esq. (argued), John R. Labbe, Esq., Amanda K. Antons, Esq., MARSHALL GERSTEIN & BORUN LLP, Chicago, IL.

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Attorneys for Defendant.

January 12, 2017

ANDREWS, U.S. DISTRICT JUDGE:

Presently before me is the issue of claim construction of multiple terms in U.S. Patent No. 5,856,298 ("the '298 patent"). The '298 patent generally relates to erythropoietin ("EPO") isoforms. I have considered the parties' Joint Claim Construction Brief. (D.I. 104). I held a *Markman* hearing on September 21, 2016. I have also considered the parties' supplemental letters submitted after the *Markman*. (D.I. 138; D.I. 144–45). On November 30, 2016, I resolved several threshold issues and invited the parties to submit additional letters if issues remained. (D.I. 162). On December 14, 2016, the parties submitted a lengthy joint letter detailing remaining issues with respect to claim construction. (D.I. 164).

I. LEGAL STANDARD

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to appropriate sources 'in light of the statutes and policies that inform patent law.'" *SoftView LLC v. Apple Inc.*, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (quoting *Phillips*, 415 F.3d at 1324) (alteration in original). When construing patent claims, a court considers the literal language of the claim, the patent specification, and the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977–80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Of these sources, "the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (internal quotation marks omitted).

"[T]he words of a claim are generally given their ordinary and customary meaning. . . . [Which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312–13 (citations and internal quotation marks omitted). "[T]he ordinary meaning of a claim term is its meaning to [an] ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted). "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314.

When a court relies solely upon the intrinsic evidence—the patent claims, the specification, and the prosecution history—the court's construction is a determination of law. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015). The court may also make factual findings based upon consideration of extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317–19. Extrinsic evidence may assist the court in understanding the underlying technology, the meaning of terms to one skilled in the art, and how the invention works. *Id.* Extrinsic evidence, however, is less reliable and less useful in claim construction than the patent and its prosecution history. *Id.*

"A claim construction is persuasive, not because it follows a certain rule, but because it defines terms in the context of the whole patent." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It follows that "a claim interpretation that would exclude the inventor's device is rarely the correct interpretation." *Osram GMBH v. Int'l Trade Comm'n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (citation omitted).

II. BACKGROUND

In my previous opinion (D.I. 162), I construed "an isolated . . . isoform" and "isolated . . . isoform." In particular, I construed "isolated . . . isoform" as "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)." I implicitly construed "an isolated . . . isoform" as "one and only one isolated . . . isoform." I did not separately construe "isoform." In rejecting Plaintiff's proposal, I commented, "Plaintiff's reading would equate the phrase 'an isolated . . . isoform' with 'an isoform.'" The present disputes require that I clarify my earlier constructions.

"An isoform" is "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)."

"An isolated . . . isoform" is "one and only one isoform," meaning that only erythropoietin isoforms, all with the same isoelectric focusing point and the same number of sialic acids per molecule and which appear as a single band on an isoelectric focusing gel, are claimed. Erythropoietin isoforms with different isoelectric focusing points and different numbers of sialic acids per molecule and which appear at other bands on an isoelectric focusing gel are excluded.

Separately, I also found claim 8 invalid because it did not properly depend from claim 1. (D.I. 162 at 7–9). Claim 1 required one and only one isoform. Because claim 8 claimed compositions consisting essentially of two or three isoforms, it contradicted a limitation of claim 1 and thus improperly narrowed claim 1. (*Id.* at 8).

///

III. CONSTRUCTION OF DISPUTED TERMS

A. "erythropoietin molecules having a predetermined number of sialic acids per molecule" ('298 Patent, Claim 24)

The parties dispute whether claim 24 claims one and only one isoform. (D.I. 164 at 3–5, 13–14).

Claim 24 is an independent claim. The complete language of claim 24 is as follows:

> 24. A method of preparing erythropoietin molecules having a predetermined number of sialic acids per molecule said number selected from the group consisting of 1-14, comprising applying material containing erythropoietin to an ion exchange column and selectively eluting said molecules from the column.

('298 patent, claim 24).

The language in claim 24 of "erythropoietin molecules having a predetermined number of sialic acids per molecule said number selected from the group consisting of 1-14" essentially describes "an isoform." "An isoform" is "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)." (D.I. 162 at 6–7). The language of claim 24 is another way of describing the same concept of "an isoform." Thus, I understand claim 24 basically to read: "A method of preparing an isoform . . . ."

Hospira's argument is that claim 24 requires one and only one isoform. (*See* D.I. 164 at 13–14). The language of claim 24, however, does not "evince[] a clear intent" to claim a method of preparing one and only one isoform. *See Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342 (Fed. Cir. 2008). No language in claim 24 would be rendered superfluous by my construction. *See Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006) ("claims are interpreted with an eye toward giving effect to all terms in the claim").

Hospira argues that the *Markush* group language of claim 24 shows that claim 24 seeks to claim one and only one isoform. (D.I. 164 at 13–14). While an isoform of claim 24 must be an isoform with the number of sialic acids per molecule being selected from the *Markush* group of 1-14, it does not necessarily follow that claim 24 prohibits mixtures of such isoforms. *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1353–54, 1362–63 (Fed. Cir. 2016), is inapposite because that case dealt with whether a component could contain combinations of *Markush* members. Here, the component is the isoform which, by my definition, can only have one member of the *Markush* group. If the isoform had more than one member of the *Markush* group, it would no longer appear as a single band on an isoelectric focusing gel and it would no longer be an "isoform" by definition. Thus, *Multiplayer* is not on point. The real issue is whether mixtures of isoforms, where each isoform has one member of the *Markush* group, are allowed, not whether an isoform could be comprised of more than one member of the *Markush* group. *Multilayer* does not speak to this.

Furthermore, the prosecution history does not evince a clear disclaimer of mixtures of isoforms from claim 24. *See Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1095 (Fed. Cir. 2013) ("clear and unmistakable disavowal during prosecution overcomes the heavy presumption that claim terms carry their full ordinary and customary meaning" (internal quotations omitted)). Hospira puts forth evidence that the present language does not encompass mixtures because the original claim language, which expressly provided for mixtures, was eliminated. (D.I. 60-3, Exh. 3 at p. 44; D.I. 60-6, Exh. 9 at p. 4).[1] Amgen puts forth evidence suggesting that the elimination of the original mixture language was not intended to disclaim all

[1] Application claim 30 became issued claim 24. (D.I. 164 at 4, 13).

mixtures, just mixtures generated by techniques of the prior art. (D.I. 60-6, Exh. 9 at p. 10–11). The prior art mixtures were derived from the single-step process of subjecting material containing erythropoietin to ion exchange chromatography. (*Id.*). The present invention derives mixtures through a two-step process of applying material containing erythropoietin to an ion exchange column and selectively eluting the desired isoforms. (*Id.*). The drafting history shows that the patentee intended to disclaim only mixtures derived by prior art techniques and not of mixtures derived from, for example, the "two-step process." Thus, the prosecution history does not clearly disclaim all mixtures.

I therefore reject Hospira's argument, and construe claim 24 to claim methods of preparing one or more "isoforms."

B. "selectively eluting said molecules from the column" ('298 Patent, Claim 24)

The parties initially disputed this phrase. (D.I. 104 at pp. 65–66). In my previous opinion, I requested the parties to inform me if this phrase was still a remaining dispute. (D.I. 162 at 9). Since this phrase was not disputed in the joint letter (D.I. 164), I assume that this phrase is resolved without the need for any construction.

C. "erythropoietin molecules according to claim 13 having two or three specific numbers of sialic acids per erythropoietin molecule" ('298 Patent, Claim 19)

Claim 13 is an independent claim. It provides:

> 13. Erythropoietin consisting essentially of erythropoietin molecules having a single specific number of sialic acids per molecule, said number selected from the group consisting of 1-14, and said molecules being the product of the expression of an exogenous DNA sequence in a non-human eucaryotic host cell.

('298 patent, claim 13). Claim 19 depends from claim 13. Claim 19 provides:

> 19. A composition consisting essentially of erythropoietin molecules according to claim **13** having two or three specific numbers of sialic acids per erythropoietin molecule.

(*Id.*, claim 19).

Beginning with claim 13, I interpret the entire phrase, "Erythropoietin consisting essentially of erythropoietin molecules having a single specific number of sialic acids per molecule," to refer to the concept of "one and only one isoform." I accord the words "consisting essentially of" the meaning usually given to this patent-drafting term of art. It is a phrase where "the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention." *PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998). "A 'consisting essentially of' claim occupies a middle ground between closed claims that are written in a 'consisting of' format and fully open claims that are drafted in a 'comprising' format." *Id.*

Here, Claim 13 claims one and only one isoform. The natural reading, i.e., its plain and ordinary meaning, of the claim suggests that claim 13 is claiming a pure composition of erythropoietin consisting essentially of erythropoietin molecules having a single specific number of sialic acids per molecule. *See Phillips*, 415 F.3d at 1312–13. The first word, erythropoietin, is not further modified to suggest that mixtures of erythropoietin are being claimed. Absent such language, the claim language naturally suggests that it is claiming pure compositions of erythropoietin, or in other words, one and only one isoform. *See id.* at 1314.

With that understanding of claim 13's scope, claim 19 improperly narrows claim 13 because claim 13 permits compositions of one and only one isoform. Claim 19 contradicts a limitation of claim 13 by permitting compositions consisting essentially of two or three isoforms. Thus, for the reasons provided in my previous opinion as to claim 8 (D.I. 162 at 7–9), claim 19 is invalid. *See Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1292 (Fed. Cir. 2006).

D. "mixture of two or more erythropoietin isoforms of Claim 1" ('298 Patent, Claim 27)

Claim 27 provides:

> 27. 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.

('298 patent, claim 27).

The parties dispute whether claim 27 is an independent claim. "To establish whether a claim is dependent upon another," I examine whether "the new claim both refers to an earlier claim and further limits that referent." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1357 (Fed. Cir. 2007). "A claim's status as dependent or independent depends on the substance of the claim in light of the language of § 112, ¶ 4, and not the form alone." *Id.*[2] In *Monsanto*, where both claims were method claims, where the prosecution history showed that one of the claims "was incontestably a dependent claim," the Federal Circuit held that one claim depended from the other. *See id.* at 1357–58.

While the form of claim 27 suggests that it depends from claim 1, the substance of claim 27 does not. First, claim 27 is a method claim, while claim 1 is a composition claim. ('298 patent, claims 1 and 27). This is unlike in *Monsanto*, where both claims were method claims. *See id.* at 1357. Second, the prosecution history tends to show that claim 27 was treated as an independent claim during prosecution. Issued claim 27 corresponded to application claim 35. (D.I. 164 at 8). Application claims 35, 37, and 39 all referred to application claim 1. In the Examiner's Action dated April 29, 1995 (D.I. 60-8, Exh. 12), application claim 1 was rejected

[2] 35 U.S.C. § 112, ¶ 4 provides: "[A] claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers."

(*Id.* at p. 4) and the Examiner objected to application claims 37 and 39 because they were "dependent upon a rejected base claim" (referring to application claim 1) (*Id.* at p. 10). The Examiner did not object to application claim 35 on the same basis as claims 37 and 39, which logically suggests that the Examiner regarded application claim 35 as an independent claim.[3] (*Id.* at pp. 4, 10). Unlike in *Monsanto*, here the prosecution of claim 27 does not show that claim 27 "was incontestably a dependent claim." *See* 503 F.3d at 1358. For these reasons, claim 27 is an independent claim.

Hospira argues that because claim 1 requires one and only one isoform, claim 27, in referring to claim 1, improperly narrows claim 1 because claim 27 teaches mixtures of two or more isoforms. (D.I. 164 at 15). I disagree. Unlike with claim 8, claim 27 is an independent claim. Claim 27 does not have to properly narrow claim 1. Thus, claim 27 can properly claim methods of mixing two or more of the isolated isoforms of claim 1.

Hospira correctly notes that Amgen has materially changed its positions from arguing that claim 27 depended from claim 1 (D.I. 104 at 72) to claim 27 is independent of claim 1 (D.I. 164 at 7–8). More generally, Hospira also correctly notes that Amgen has made statements that could be interpreted as representing that the resolution of terms related to claim 1 and claim 8 would resolve the issues with the other claims (D.I. 164 at 10–11). Hospira's frustrations are reasonable. In the interest of resolution on the merits, however, I decline to hold this against Amgen in connection with claim construction.

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[3] At the time of the April 29, 1996 Action, application claim 35 had the same language as issued claim 27. (*See* D.I. 60-6, Exh. 9 at 4).

IV. CONCLUSION

Within five days the parties shall submit a proposed order consistent with this Memorandum Opinion.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC., AMGEN MANUFACTURING, LIMITED, Plaintiffs, v. HOSPIRA, INC., Defendant.	Civil Action No. 15-839-RGA

MEMORANDUM OPINION

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Attorneys for Defendant.

November 30, 2016

ANDREWS, U.S. DISTRICT JUDGE:

Presently before me is the issue of claim construction of multiple terms in U.S. Patent No. 5,856,298 ("the '298 patent"). The '298 patent generally relates to erythropoietin ("EPO") isoforms. I have considered the parties' Joint Claim Construction Brief. (D.I. 104). I have also considered the parties' supplemental letters. (D.I. 138; D.I. 144–45). Oral argument was held on September 21, 2016.

I. LEGAL STANDARD

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to appropriate sources 'in light of the statutes and policies that inform patent law.'" *SoftView LLC v. Apple Inc.*, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (quoting *Phillips*, 415 F.3d at 1324) (alteration in original). When construing patent claims, a court considers the literal language of the claim, the patent specification, and the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977–80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Of these sources, "the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (internal quotation marks omitted).

"[T]he words of a claim are generally given their ordinary and customary meaning. . . . [Which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312–13 (citations and internal quotation marks omitted). "[T]he ordinary meaning of a

claim term is its meaning to [an] ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted). "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314.

When a court relies solely upon the intrinsic evidence—the patent claims, the specification, and the prosecution history—the court's construction is a determination of law. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015). The court may also make factual findings based upon consideration of extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317–19. Extrinsic evidence may assist the court in understanding the underlying technology, the meaning of terms to one skilled in the art, and how the invention works. *Id.* Extrinsic evidence, however, is less reliable and less useful in claim construction than the patent and its prosecution history. *Id.*

"A claim construction is persuasive, not because it follows a certain rule, but because it defines terms in the context of the whole patent." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It follows that "a claim interpretation that would exclude the inventor's device is rarely the correct interpretation." *Osram GMBH v. Int'l Trade Comm'n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (citation omitted).

II. CONSTRUCTION OF DISPUTED TERMS

The parties dispute various aspects of claim 8, including language in claim 1, which is referenced by claim 8. Claim 8 reads as follows:

8. A composition consisting essentially of two or three erythropoietin isoforms according to claim 1.

('298 Patent, claim 8). Claim 1 in turn reads as follows:

1. 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.

('298 Patent, claim 1).

A. "an isolated . . . isoform" ('298 Patent, Claim 1, 8)

Amgen proposes that "an isolated . . . isoform" allows for mixtures of at least one isoform. (*See* D.I. 138).

Hospira proposes that that language allows for mixtures of only one isoform. (*See* D.I. 144).

I begin with the dispute over "an isolated . . . isoform." "[A]n indefinite article 'a' or 'an' in patent parlance carries the meaning of 'one or more' in open-ended claims containing the transitional phrase 'comprising.'" *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342 (Fed. Cir. 2008). "That 'a' or 'an' can mean 'one or more' is best described as a rule, rather than merely as a presumption or even a convention. The exceptions to this rule are extremely limited: a patentee must 'evince[] a clear intent' to limit 'a' or 'an' to 'one.'" *Id.* "An exception to the general rule that 'a' or 'an' means more than one only arises where the language of the claims themselves, the specification, or the prosecution history necessitate a departure from the rule." *Id.* at 1342–43.

Here, the exception applies because the plain language evinces a clear intent to claim only one isoform. The claim language reads "an isolated . . . isoform." Plaintiff's reading would render the word "isolated" superfluous. Plaintiff's reading would equate the phrase "an isolated . . . isoform" with "an isoform." This violates the principle that "claims are interpreted with an

eye toward giving effect to all terms in the claim." *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006).

Hospira's proposal is consistent with the prosecution history. Claim 1 was initially broadly drafted to read "[a]n . . . isoform." (D.I. 60-4, Exh. 3 at 2). Two rejections were issued to claim 1. Claim 1 was then amended to read "[a]n isolated . . . isoform." (D.I. 60-4, Exh. 7 at 2). The purpose of the amendment was "to further clarify that an erythropoietin isoform represents a homogeneous preparation." (*Id.* at 6). Amgen concedes that the word "isolated" is used to clarify that the isoform in claim 1 is a "homogeneous preparation." (D.I. 138). Consistent with Hospira's interpretation, Amgen appears to concede that each of lanes two through ten in Figure 1 of the '298 patent illustrate isolated homogeneous preparations. (*Id.*). Amgen argues that because two lines appear on lane one multiple isoforms may exist in an "isolated" mixture. (*Id.*). Amgen's argument is in tension with the specification, which explains that degradation of a single isoform could have been the cause. (*See* '298 Patent, 10:65-67).

Hospira's proposal is also consistent with what a person of skill in the art would have understood from the prior art. It appears that the prior art disclosed isoform mixtures of more than one isoform. ('298 Patent, Figure 3 & 3:51–4:11). It would thus make sense for the patentee to "clarify" that claim 1 requires only one isoform to avoid the prior art.

Amgen points to language in the specification that "repeatedly and consistently emphasizes both a single isoform and compositions containing two or more isoforms . . . ." (D.I. 138) (emphasis removed). For example, Amgen points to column 1, lines 9–15 of the specification, which reads: "The present invention relates to erythropoietin isoforms or mixtures thereof, to the methods for the preparation of specific isoforms or mixtures thereof, to pharmaceutical compositions comprising such isoforms or mixtures thereof, and to methods of

treatment utilizing such isoforms and compositions." ('298 Patent, 1:9–15). If claim 1 claimed just one isoform, as Hospira argues, I do not find that that reading would be inconsistent with this portion of the specification because the invention teaches the preparation of single isoforms. *See id.* Thus, Amgen's references to the specification are consistent with Hospira's proposal.

Thus, I adopt Hospira's proposal that "an isolated . . . isoform" means only one isoform.

B. "isolated . . . isoform" ('298 Patent, Claim 1, 8)

As to the phrase, "isolated . . . isoform," Amgen proposes that it means "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)." (D.I. 145).

Hospira proposes that the language refers to "EPO molecules having a specific number of sialic acids per molecule characterized by a single isoelectric point as defined by a single band when EPO is subjected to isoelectric focusing (an example of which is shown in Figure 1 of the '298 patent)." (D.I. 145).

The parties agree that an "isolated . . . isoform" refers to the "single band" that appears on an isoelectric focusing gel, an example of which is reflected by Figure 1 of the '298 patent. The parties agree that this "single band" would reflect molecules with a "single isoelectric point" that have a "specific number of sialic acids per molecule." It appears that Hospira's only objection to Amgen's proposal is that Hospira views Amgen's proposal as an "attempt to eliminate one of the central disputes between the parties[:] whether claim 1 requires an isolated isoform as expressly recited by the claim." (D.I. 145).

Having resolved Hospira's objection above, I adopt Amgen's proposal to construe "isolated . . . isoform," as referred to in claim 1, as "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)."

C. Validity of Claim 8

The parties further dispute whether claim 8 is valid. Here, claim 8 depends on claim 1. ('298 Patent, claim 8). To be valid, claim 8 must properly depend on claim 1.

Section 112 provides, in relevant part:

> [A] claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

35 U.S.C. § 112, ¶ 4. "[A] violation of § 112, ¶ 4 renders a patent invalid just as violations of other paragraphs of § 112 would." *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1292 (Fed. Cir. 2006). A dependent claim that does not properly narrow the scope of the claim from which it depended is invalid under 35 U.S.C. § 112, ¶ 4. *See id.* ("'[R]eading an additional limitation from a dependent claim into an independent claim would not only make that additional limitation superfluous, it might render the dependent claim invalid' for failing to add a limitation to those recited in the independent claim, as required by 35 U.S.C. § 112, ¶ 4."). Although "claims should be construed to sustain their validity," "if the only claim construction that is consistent with the claim's language and the written description renders the claim invalid, then the axiom does not apply and the claim is simply invalid." *Rhine v. Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999). Courts "should not rewrite claims to preserve validity." *Id.* (noting that "claim 6 could have been properly drafted either as dependent from claim 1 or as an independent claim," but declining to do so and holding claim 6 invalid).

Here, claim 1 requires only one isoform. Claim 8 contradicts claim 1's limitation that the isoform is "isolated" by requiring a mixture "consisting essentially of two or three" isoforms. Claim 8 thus improperly narrows claim 1.

Let me illustrate.[1] For example, claim 1 is analogous to a claim that claims "a composition having only one of the substances A, B, C, D, or E." Claim 8 is analogous to a claim of "a composition consisting of two or three of the substances of claim 1." If I had a composition that contained only substances A and B, it might meet the limitations of claim 8, but it would logically fail to meet the limitations of claim 1. In other words, the limitations of claim 8 must contradict and override the limitations of claim 1 in order for claim 8 to work. Where a limitation of a dependent claim is logically inconsistent with that of the independent claim, that is a 35 U.S.C. § 112, ¶ 4 problem.[2]

In contrast, if Claim 8 instead said "a composition of only one of the substances of claim 1, where substance X is present," that might be a proper narrowing. A composition that contained only substances A and X, would meet all the limitations of claim 8. It would also meet the limitations of claim 1, since it could not have any B, C, D, or E, and the presence of X is neither prohibited nor required by claim 1. No limitation in claim 8 needs to contradict or override a limitation of claim 1 in order for claim 8 to work. The dependent claim would be logically consistent with that of the independent claim.

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[1] Among other things, I am not a patent draftsman. The example in the text is for the purpose of explaining my analysis. It is not meant as an example of superior claim drafting.

[2] A different way to identify the problem here is that something that infringes a dependent claim necessarily infringes the independent claim from which the dependent claim depends. *See Kim v. ConAgra Foods, Inc.*, 465 F.3d 1312, 1316 n.1 (Fed. Cir. 2006). When that is not true, there is something wrong with the claim drafting.

Perhaps claim 8 could have been drafted as an independent claim, but the fact is that it was not. *See Pfizer*, 457 F.3d at 1292. I decline to rewrite claim 8 to preserve its validity. *See id.* Claim 8 is thus invalid because it contradicts a limitation of claim 1.

III. CONCLUSION

I understand that the disposition of these issues resolves the remaining *Markman* disputes between the parties. (D.I. 134). To the extent that this is not the case, I request that the parties submit a joint letter laying out the remaining disputes with each parties' respective proposals and rationales within fourteen days.[3] If there are no remaining disputes, the parties are to submit a proposed order consistent with this Memorandum Opinion within fourteen days.

Richard G. Andrews
United States District Judge

[3] I believe this disposition also resolves the "consisting essentially of" dispute. To the extent that is not the case and without prejudice to either side, I was leaning towards adopting the Federal Circuit's construction.

US005856298A

United States Patent [19]

Strickland

[11] **Patent Number: 5,856,298**

[45] **Date of Patent: Jan. 5, 1999**

[54] **ERYTHROPOIETIN ISOFORMS**

[75] Inventor: **Thomas Wayne Strickland**, Moorpark, Calif.

[73] Assignee: **Amgen Inc.**, Thousand Oaks, Calif.

[21] Appl. No.: **334,882**

[22] Filed: **Nov. 3, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 942,126, Sep. 8, 1992, abandoned, which is a continuation of Ser. No. 594,448, Oct. 12, 1990, abandoned, which is a continuation-in-part of Ser. No. 421,444, Oct. 13, 1989, abandoned.

[51] **Int. Cl.**[6] **A61K 38/18**; C07K 14/505; C07K 1/18; C07K 1/28

[52] **U.S. Cl.** **514/8**; 530/395; 530/397; 530/412; 530/416; 435/69.4; 204/182.9

[58] **Field of Search** 530/395, 397, 530/416, 412; 514/8; 435/69.4; 204/182.9

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Primary Examiner—Stephen G. Walsh

Attorney, Agent, or Firm—Robert B. Winter; Steven M. Odre; Ron K. Levy

[57] **ABSTRACT**

Erythropoietin isoforms having a specific number of sialic acids per erythropoietin molecule are disclosed. Also disclosed are mixtures of such isoforms, pharmaceutical compositions containing such isoforms or mixtures thereof and methods of obtaining the erythropoietin isoforms.

31 Claims, 13 Drawing Sheets

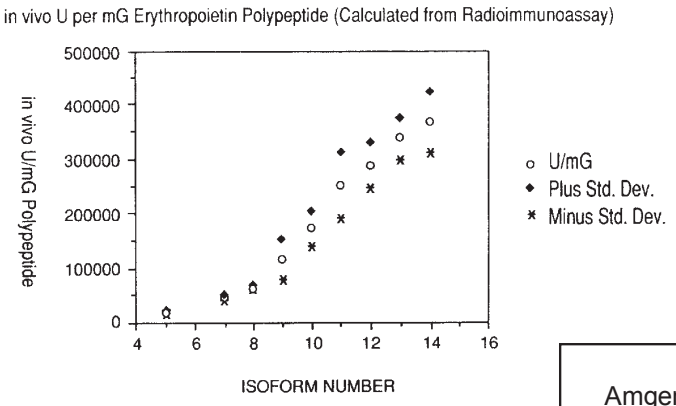

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FIG. 1

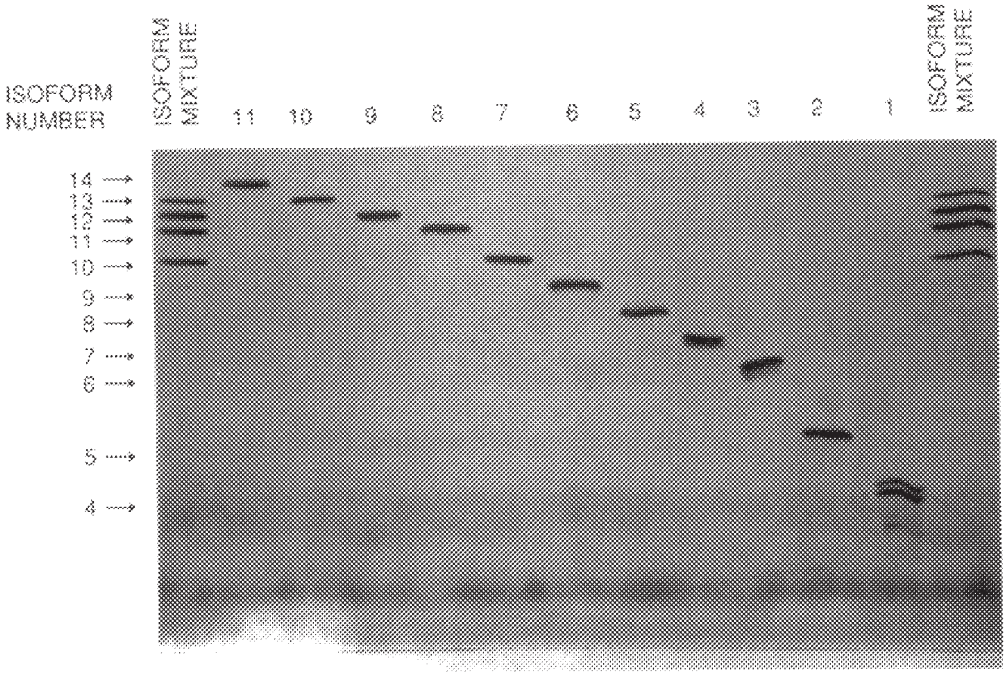
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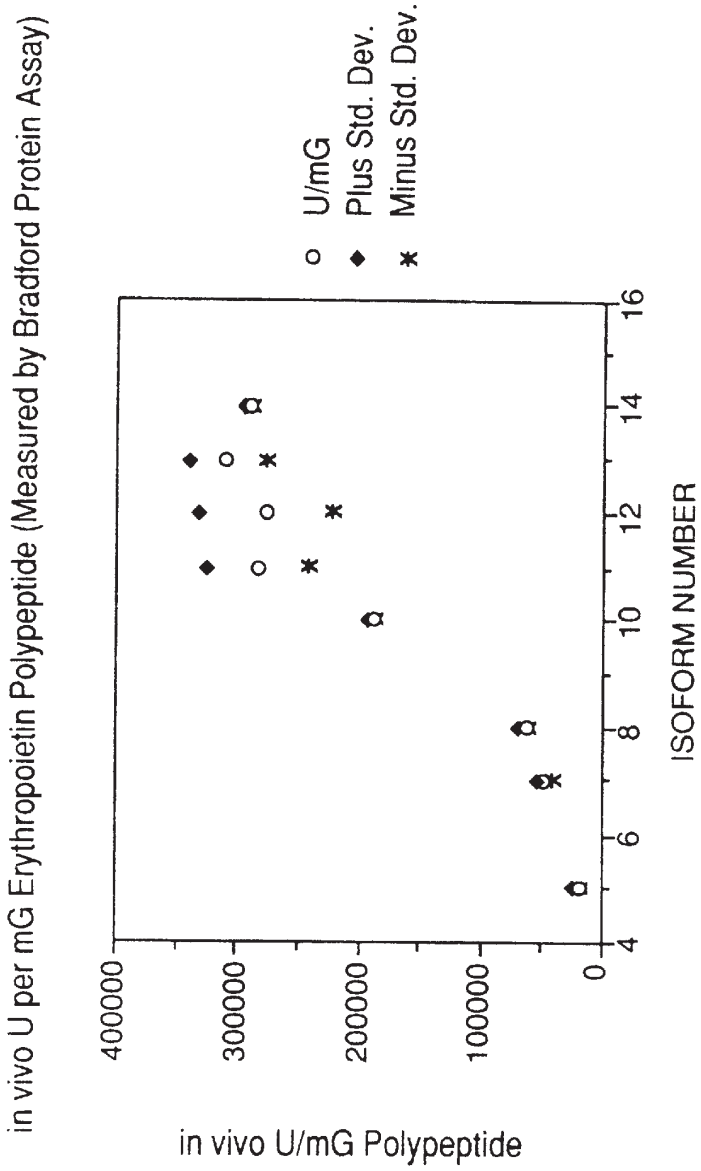
FIG.2A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200000
100000
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6
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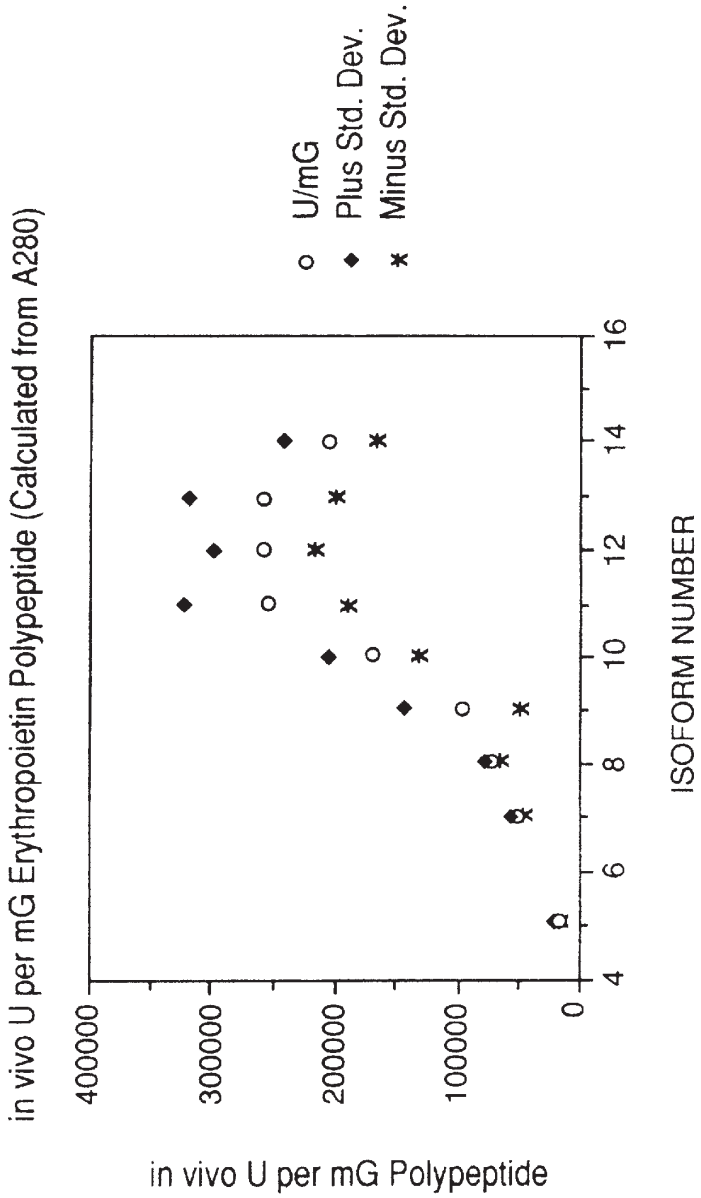
Plus Std. Dev.
Minus Std. Dev.

FIG. 2B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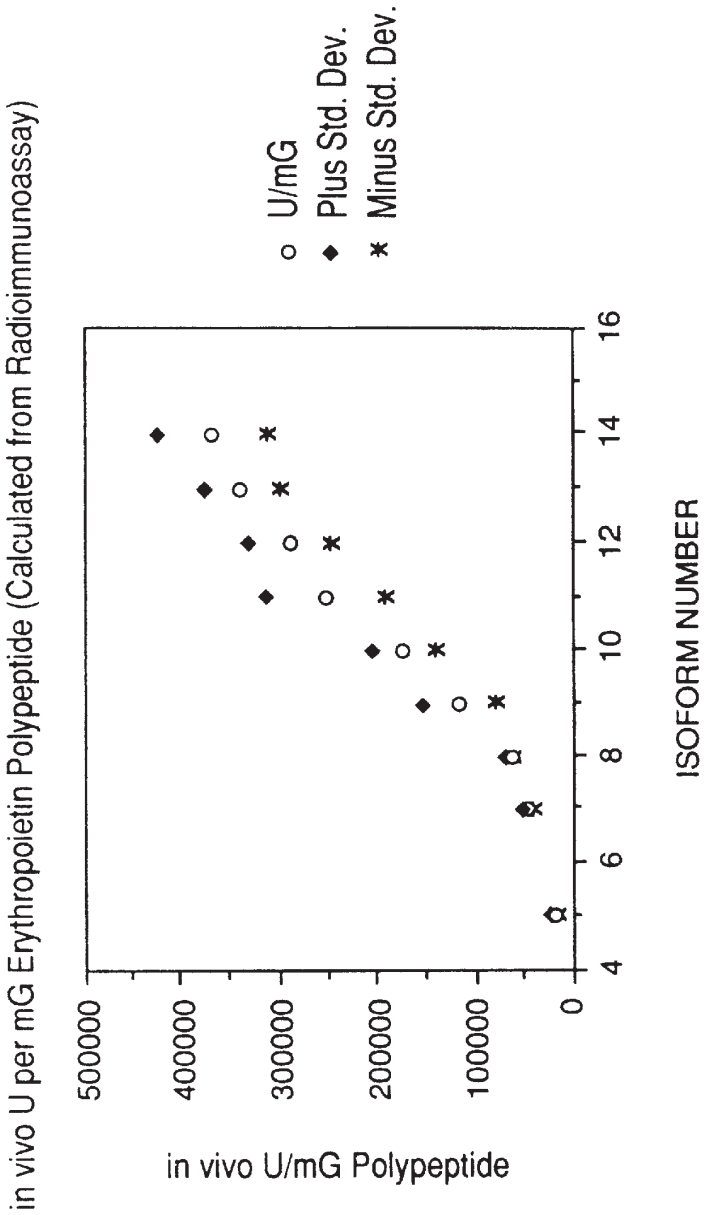
Minus Std. Dev.
in vivo U per mG Polypeptide

FIG. 2C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6
8
10
12
14
16
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Plus Std. Dev.
Minus Std. Dev.

FIG. 3

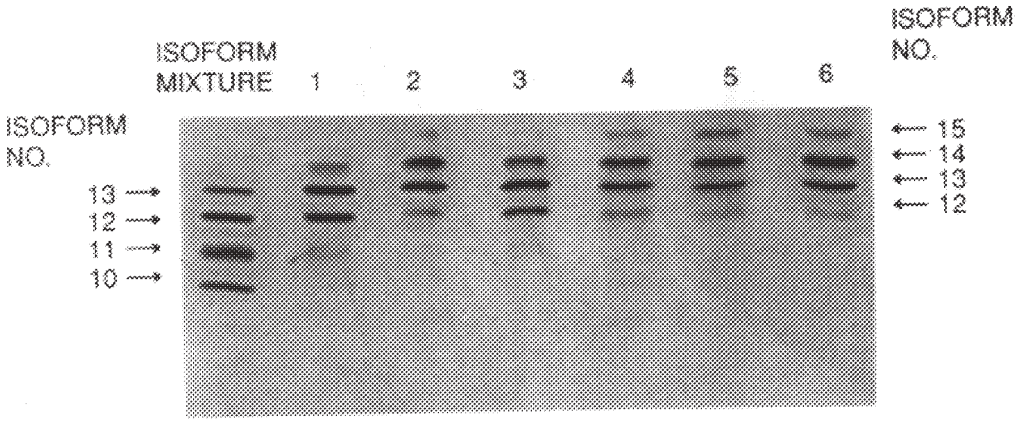

ISOFORM MIXTURE
1
2
3
4
5
6
ISOFORM NO.
13
12
11
10
ISOFORM NO.
15
14
13
12

FIG. 4

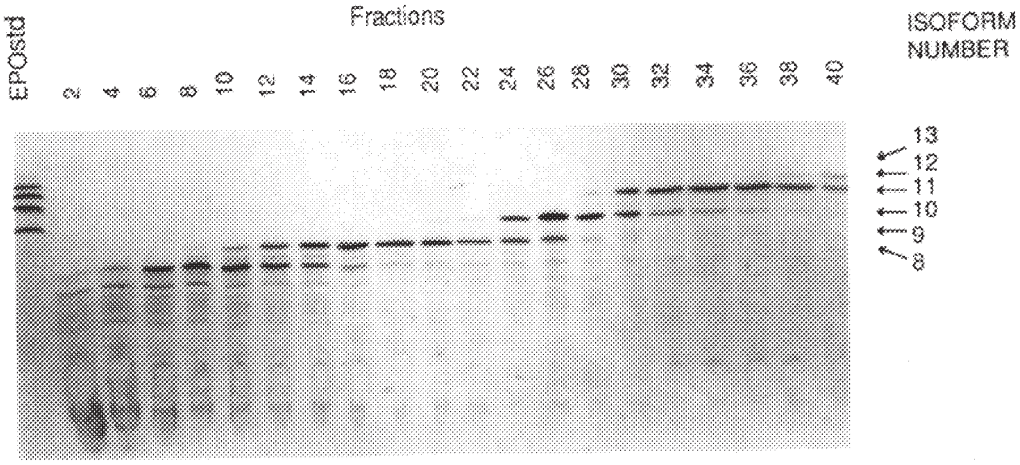
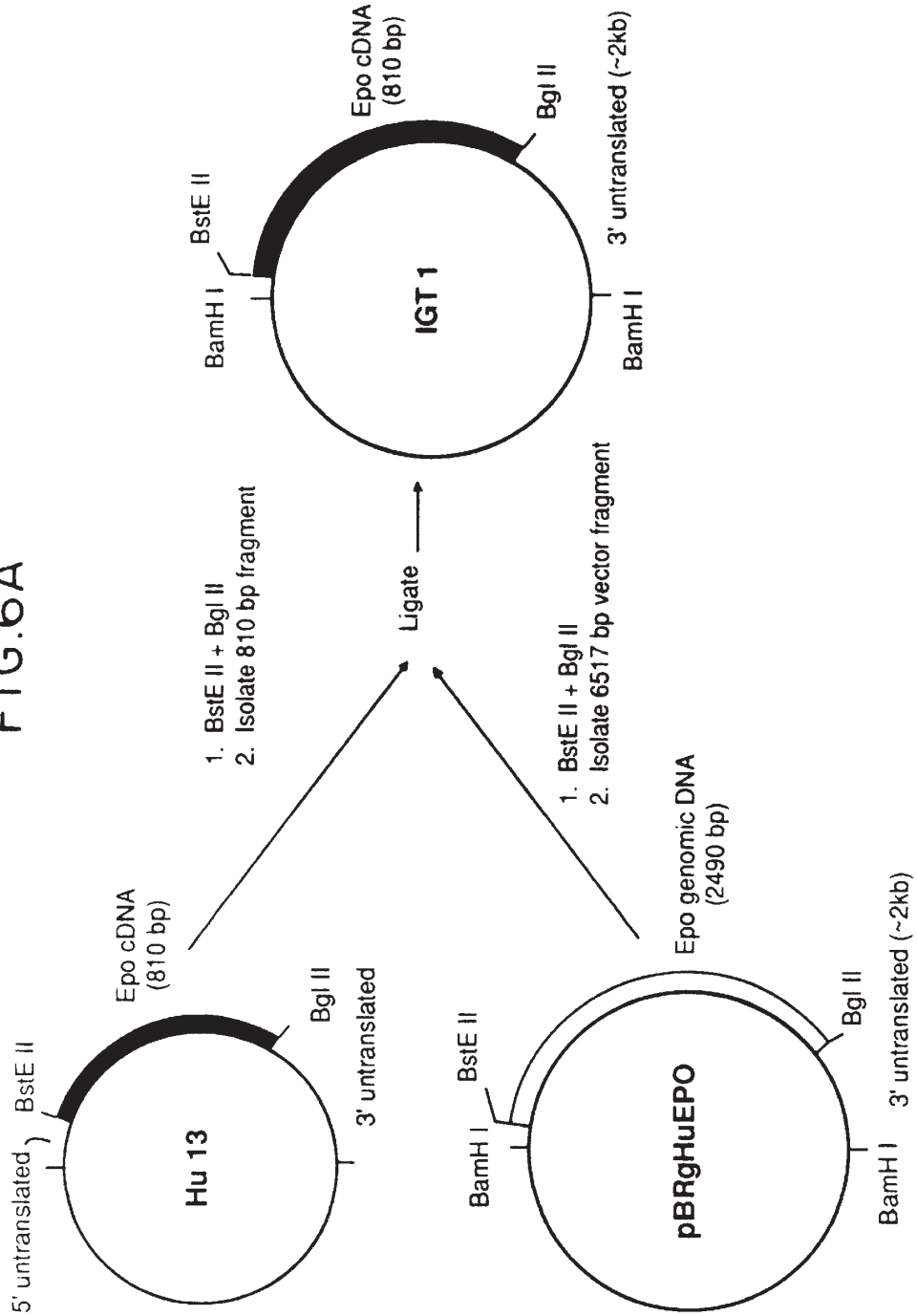

EPOstd
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
Fractions
ISOFORM NUMBER
13
12
11
10
9
8

FIG.5


-27
+1 10 20
MGVHECPAWLWLLLSLLSLPLGLPVLGAPPRLICDSRVLERYLLEAKEAENIT
N S N S
30 40 50 60 70
TGCAEHCSLNENITVPDTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQA
N
*
T
80 90 100 110 120 * 130
LLVNSSQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAASAAPLRT
NN S
140 150 160
ITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
N S
= Site for N-glycosylation
* = Site for O-glycosylation

FIG.6A


5' untranslated
BstE II
Hu 13
Bgl II
3' untranslated
Epo cDNA
(810 bp)
1. BstE II + Bgl II
2. Isolate 810 bp fragment
Ligate
BamH I
BstE II
IGT 1
Epo cDNA
(810 bp)
Bgl II
3' untranslated (~2kb)
BamH I
BamH I
BstE II
pBRgHuEPO
Bgl II
3' untranslated (~2kb)
BamH I
Epo genomic DNA
(2490 bp)
1. BstE II + Bgl II
2. Isolate 6517 bp vector fragment

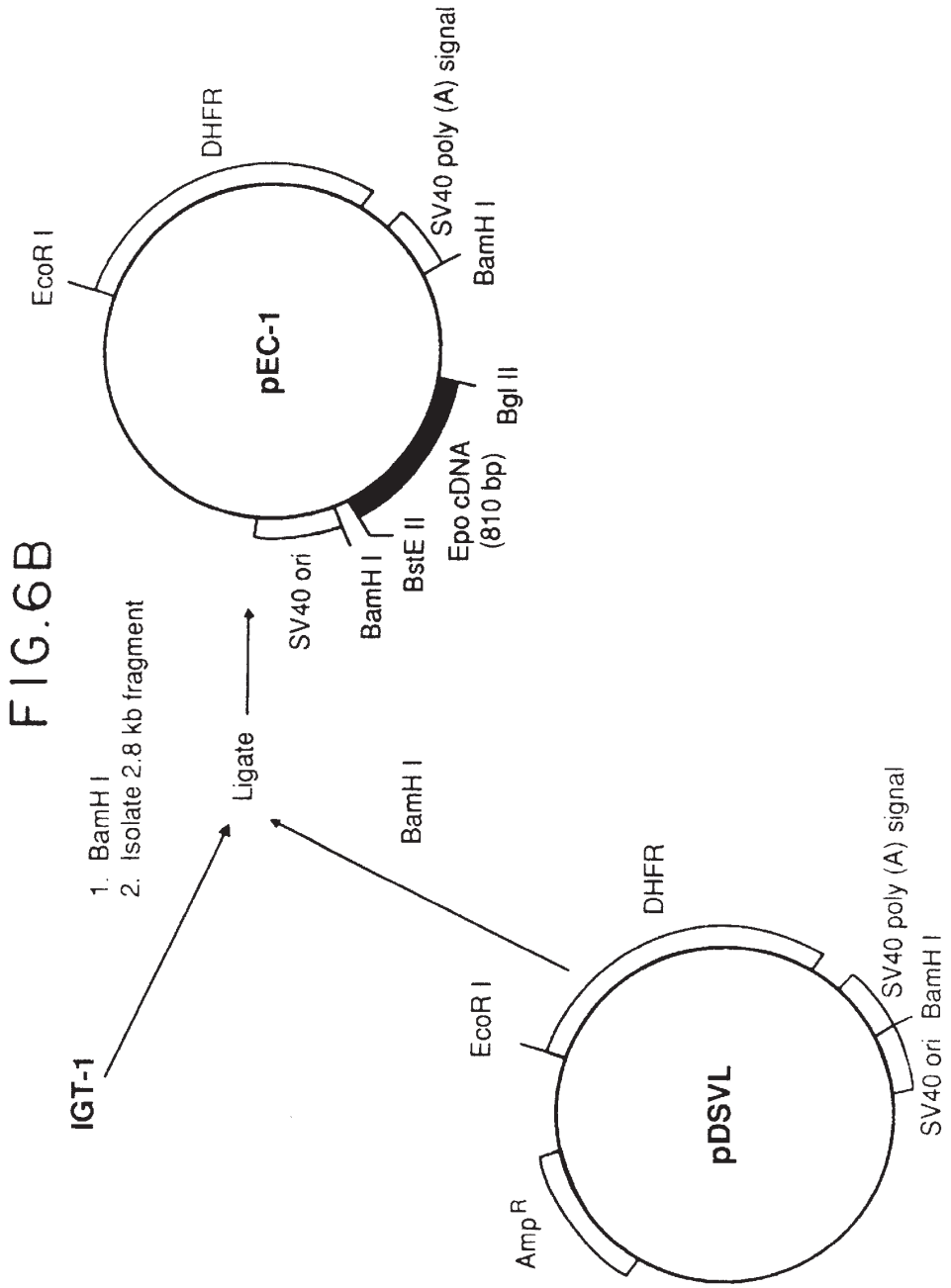

IGT-1
1. BamH I
2. Isolate 2.8 kb fragment
Ligate
BamH I
EcoR I
DHFR
pDSVL
SV40 poly (A) signal
SV40 ori
BamH I
AmpR
EcoR I
DHFR
pEC-1
SV40 poly (A) signal
BamH I
Bgl II
Epo cDNA
(810 bp)
BstE II
BamH I
SV40 ori

FIG.6B

FIG.6C

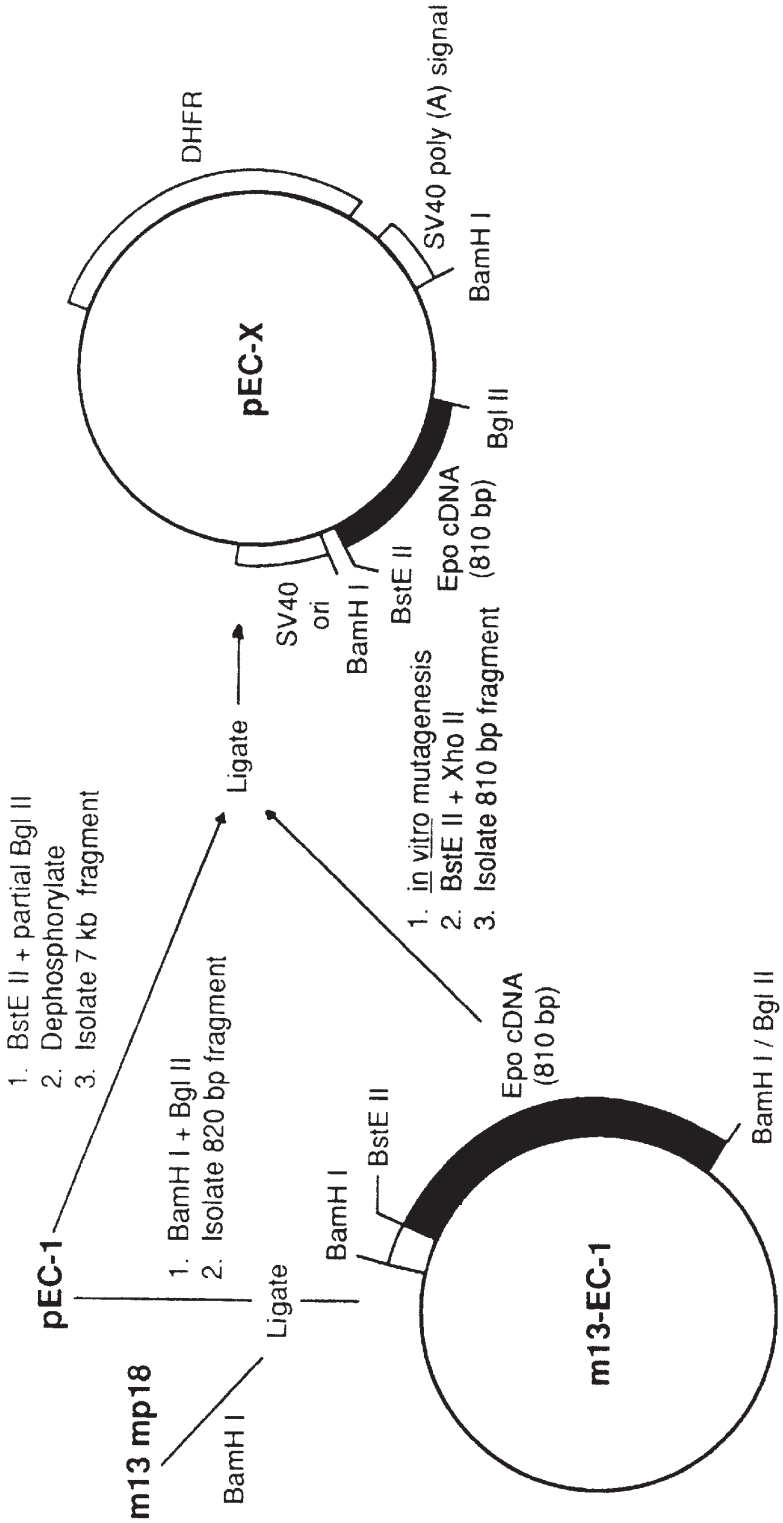
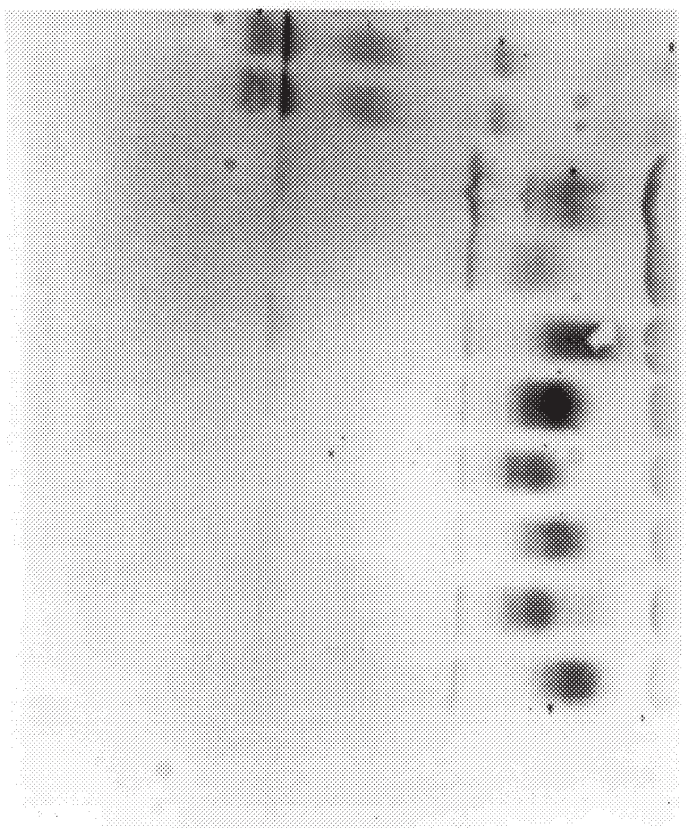

pEC-1
1. BstE II + partial Bgl II
2. Dephosphorylate
3. Isolate 7 kb fragment
m13 mp18
BamH I
Ligate
1. BamH I + Bgl II
2. Isolate 820 bp fragment
Ligate
pEC-X
DHFR
SV40 poly (A) signal
BamH I
Bgl II
Epo cDNA
(810 bp)
BstE II
BamH I
SV40
ori
1. in vitro mutagenesis
2. BstE II + Xho II
3. Isolate 810 bp fragment
BamH I
BstE II
Epo cDNA
(810 bp)
m13-EC-1
BamH I / Bgl II

FIG. 7



Molecular Weight Standards

Human EPO

[Asn^{9}, Ser^{11}] EPO

[Asn^{69}] EPO

[Pro^{125}, Ser^{127}] EPO

[Asn^{126}, Ser^{128}] EPO

[Thr^{125}, Ser^{127}] EPO

[Asn^{125}, Ser^{127}] EPO

[Pro^{124}, Thr^{125}] EPO

FIG. 8

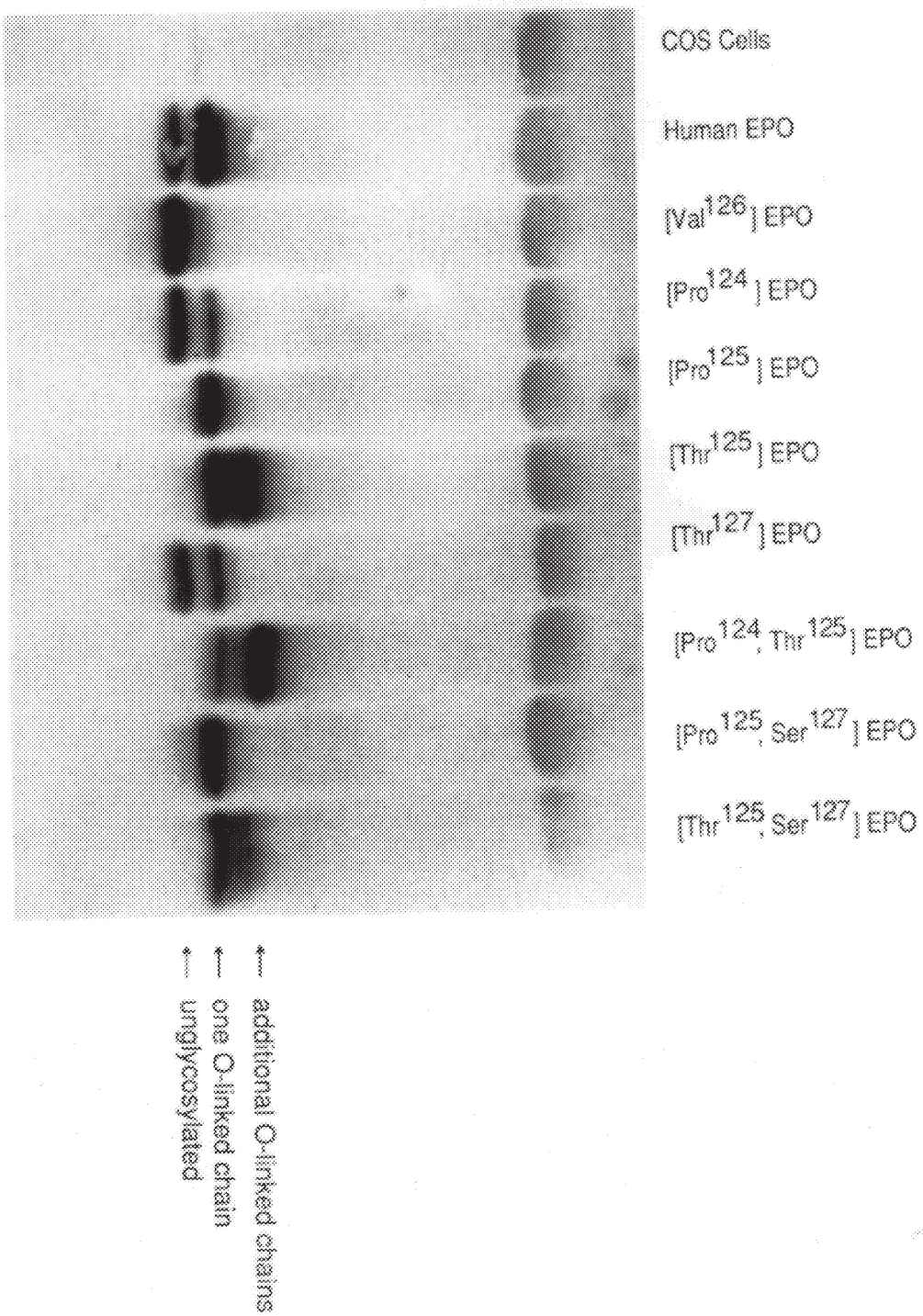
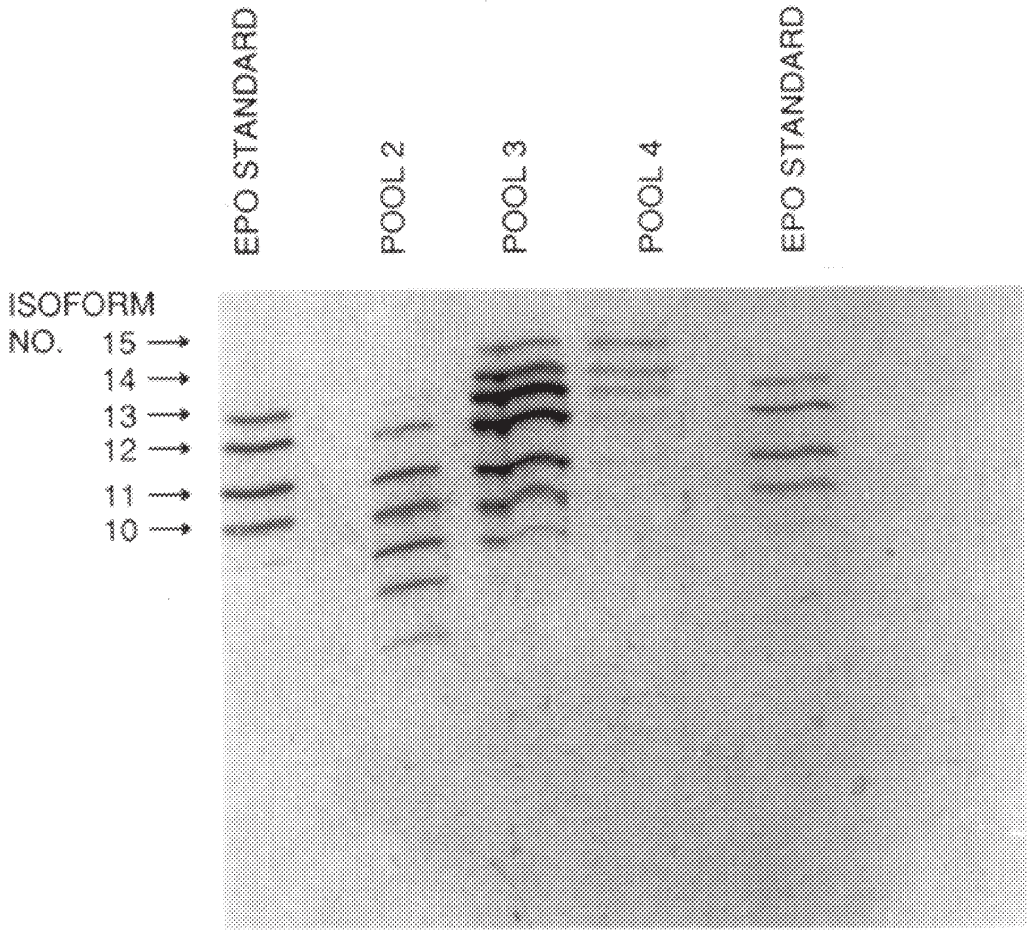

COS Cells
Human EPO
[Val126] EPO
[Pro124] EPO
[Pro125] EPO
[Thr125] EPO
[Thr127] EPO
[Pro124, Thr125] EPO
[Pro125, Ser127] EPO
[Thr125, Ser127] EPO
additional O-linked chains
one O-linked chain
unglycosylated

FIG. 9


EPO STANDARD
POOL 2
POOL 3
POOL 4
EPO STANDARD
ISOFORM NO.
15
14
13
12
11
10

ERYTHROPOIETIN ISOFORMS

This application is a continuation, of application Ser. No. 07/942,126, filed Sep. 8, 1992, now abandoned, which is hereby incorporated by reference, which is a continuation of application Ser. No. 07/594,448 filed on Oct. 12, 1990, now abandoned, which is a continuation-in-part application of U.S. application Ser. No. 421,444, filed Oct. 13, 1989, now abandoned, which is incorporated by reference. The present invention relates to erythropoietin isoforms or mixtures thereof, to the methods for the preparation of specific isoforms or mixtures thereof, to pharmaceutical compositions comprising such isoforms or mixtures thereof, and to methods of treatment utilizing such isoforms and compositions.

BACKGROUND OF THE INVENTION

Erythropoietin is a glycoprotein hormone involved in the maturation of erythroid progenitor cells into erythrocytes. It is essential in regulating levels of red blood cells in circulation. Naturally occurring erythropoietin is produced by the liver during fetal life and by the kidney of adults and circulates in the blood and stimulates the production of red blood cells in bone marrow. Anemia is almost invariably a consequence of renal failure due to decreased production of erythropoietin from the kidney. Recombinant erythropoietin produced by genetic engineering techniques involving the expression of a protein product from a host cell transformed with the gene encoding erythropoietin has been found to be effective when used in the treatment of anemia resulting from chronic renal failure.

Until recently, the availability of erythropoietin has been very limited. Although the protein is present in human urine, excreted levels are too low to make this a practical source of erythropoietin for therapeutic use. Patients suffering from aplastic anemia exhibit elevated levels of urinary erythropoietin relative to healthy individuals, but limited supplies of this urine also make such a source impractical. The purification of human urinary erythropoietin by Miyake et al. in J. Biol. Chem., 252, 5558 (1977), used, as starting material, urine from aplastic anemic individuals.

The identification, cloning, and expression of genes encoding erythropoietin are described in U.S. Pat. No. 4,703,008 to Lin. A description of the purification of recombinant erythropoietin from cell medium that supported the growth of mammalian cells containing recombinant erythropoietin plasmids for example, is included in U.S. Pat. No. 4,667,016 to Lai et al. The expression and recovery of biologically active recombinant erythropoietin from mammalian cell hosts containing the erythropoietin gene on recombinant plasmids has, for the first time, made available quantities of erythropoietin suitable for therapeutic applications. In addition, knowledge of the gene sequence and the availability of larger quantities of purified protein has led to a better understanding of the mode of action of this protein.

The biological activity of a protein is dependent upon its structure. In particular, the primary structure of a protein (i.e., its amino acid sequence) provides information that allows the formation of secondary (e.g, α helix or β-sheet) and tertiary (overall three-dimensional folding) structures by a polypeptide during and after its synthesis. The disruption of proper secondary and tertiary structures by the introduction of mutations or by chemical or enzymatic treatments can result in a reduction in biological activity.

In procaryotic organisms, the biological activities of proteins are largely governed by the structures described above.

Unlike proteins from procaryotic cells, many cell surface and secretory proteins produced by eucaryotic cells are modified with one or more oligosaccharide groups. This modification, referred to as glycosylation, can dramatically affect the physical properties of proteins and can also be important in protein stability, secretion, and subcellular localization. Proper glycosylation can be essential for biological activity. In fact, some genes from eucaryotic organisms, when expressed in bacteria (e.g., *E. coli*) which lack cellular processes for glycosylating proteins, yield proteins that are recovered with little or no activity by virtue of their lack of glycosylation.

Glycosylation occurs at specific locations along the polypeptide backbone and is usually of two types: O-linked oligosaccharides are attached to serine or threonine residues while N-linked oligosaccharides are attached to asparagine residues when they are part of the sequence Asn-X-Ser/Thr, where X can be any amino acid except proline. The structures of N-linked and O-linked oligosaccharides and the sugar residues found in each type are different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (hereafter referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and O-linked oligosaccharides and, by virtue of its negative charge, may confer acidic properties to the glycoprotein.

Both human urinary derived erythropoietin and recombinant erythropoietin (expressed in mammalian cells) having the amino acid sequence 1-165 of human erythropoietin contain three N-linked and one O-linked oligosaccharide chains which together comprise about 40% of the total molecular weight of the glycoprotein. N-linked glycosylation occurs at asparagine residues located at positions 24, 38 and 83 while O-linked glycosylation occurs at a serine residue located at position 126 (Lai et al. J. Biol. Chem. 261, 3116 (1986); Broudy et al. Arch. Biochem. Biophys. 265, 329 (1988)). The oligosaccharide chains have been shown to be modified with terminal sialic acid residues. Enzymatic treatment of glycosylated erythropoietin to remove all sialic acid residues results in a loss of in vivo activity but does not affect in vitro activity (Lowy et al. Nature 185, 102 (1960); Goldwasser et al. J. Biol. Chem. 249, 4202 (1974)). This behavior has been explained by rapid clearance of asialo-erythropoietin from circulation upon interaction with the hepatic asialoglycoprotein binding protein (Morrell et al. J. Biol. Chem. 243, 155 (1968); Briggs, et al. Am. J. Physiol. 227, 1385 (1974); Ashwell et al. Methods Enzymol. 50, 287 (1978)). Thus, erythropoietin possesses in vivo biological activity only when it is sialylated to avoid its binding by the hepatic binding protein.

The role of the other components in the oligosaccharide chains of erythropoietin is not well defined. It has been shown that non-glycosylated erythropoietin has greatly reduced in vivo activity compared to the glycosylated form but does retain in vitro activity (Dordal et al. Endocrinology 116, 2293 (1985); Lin patent, supra). In another study, however, the removal of N-linked or O-linked oligosaccharide chains singly or together by mutagenesis of asparagine or serine residues that are glycosylation sites sharply reduces in vitro activity of the altered erythropoietin that is produced in mammalian cells (Dube et al. J. Biol. Chem. 263, 17516 (1988)).

Glycoproteins such as erythropoietin can be separated into different charged forms using techniques such as isoelectric focusing (IEF). Several parties have reported IEF studies of crude and partially purified erythropoietin preparations (Lukowsky et al., J. Biochem 50, 909 (1972); Shelton et al. Biochem. Med. 12, 45 (1975); Fuhr et al. Biochem.

Biophys. Res. Comm. 98, 930 (1981)). At most, three or four fractions having erythropoietin activity were distinguished by IEF in these studies and none were characterized with respect to carbohydrate content. In addition, no correlation between the isoelectric points of the fractions and their biological activity was made.

During the purification of urinary erythropoietin from human urine discussed in Miyake et. al. supra, two erythropoietin fractions from hydroxylapatite chromatography designated II and IIIA were reported to have the same specific activity. A subsequent carbohydrate analysis of fractions II and IIIA revealed that fraction II had a greater average sialic acid content than fraction IIIA (Dordal et. al. supra).

It is an object of the present invention to provide separated and isolated isoforms of erythropoietin having a defined sialic acid content and biological activity. Pharmaceutical compositions containing such molecules would have therapeutic benefit.

SUMMARY OF THE INVENTION

The subject invention relates to erythropoietin isoforms. Also provided is a method of preparing an erythropoietin isoform comprising the steps of subjecting purified erythropoietin to preparative isoelectric focusing, and eluting a single isoform from the gel. Pharmaceutically acceptable compositions comprising erythropoietin isoforms are also provided. This invention also relates to methods of increasing hematocrit levels in mammals comprising administering a therapeutically acceptable amount of these compositions to increase production of reticulocytes and red blood cells.

The subject invention relates to a method of preparing a mixture of erythropoietin molecules having greater than or alternatively less than a predetermined number of sialic acids per molecule comprising subjecting material containing erythropoietin to ion exchange chromatography. Also comprised by the subject invention is a method of preparing a mixture of erythropoietin molecules having greater than or alternatively less than a predetermined number of sialic acids per molecule comprising subjecting a material containing erythropoietin to chromatofocusing.

The invention also comprises analogs of human erythropoietin having a greater number of sites for carbohydrate chain attachment than human erythropoietin, such as [Asn^{69}] EPO; [Asn^{125}, Ser^{127}] EPO; [Thr^{125}] EPO; and [Pro^{124}, Thr^{125}] EPO.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows an analytical isoelectric focusing gel of the separate recombinant erythropoietin isoforms. Gel lanes 1–11 show isoforms ranging from less acidic (higher pI) in lane 1 to more acidic (lower pI), in lane 11. Purified recombinant erythropoietin containing a mixture of isoforms 9–14 is also shown in the far left and right lanes of the gel.

FIG. **2**A, FIG. **2**B and FIG. **2**C show the relationship between the number of sialic acids per erythropoietin isoform and the in vivo specific activity of each isoform expressed as units per mg of erythropoietin polypeptide. In FIG. **2**A, the concentration of each erythropoietin isoform was determined by the Bradford protein assay; in **2**B, the concentration was determined by absorbance at 280 nm, in **2**C, the concentration was determined by RIA.

FIG. **3** shows an analytical isoelectric focusing gel of defined mixtures of recombinant erythropoietin isoforms prepared by anion exchange chromatography under different conditions. Gel lanes 1–6 represent, respectively, erythropoietin isoforms eluted in a high salt wash after washing the Q-Sepharose fast flow column with 150 mM acetic acid, pH 4.7, 150 mM acetic acid (unbuffered), 200 mM acetic acid, pH 4.7, 250 mM acetic acid, pH 4.7, 300 mM acetic acid, pH 4.7 or 300 mM acetic acid (unbuffered). Purified recombinant erythropoietin containing a mixture of isoforms as obtained using procedures described in Example 2 of Lai et al., supra, except that DEAE-Agarose chromatography is replaced by Q-Sepharose chromatography, is also shown in the far left lane of the gel.

FIG. **4** shows the separation of erythropoietin isoforms 8 to 12 achieved by subjecting cell conditioned medium applied to a column of Q-Sepharose to a gradient of decreasing pH and increasing ionic strength. Aliquots of even numbered fractions from Fraction 2 to Fraction 40 were subjected to analytical isoelectric focusing. Purified recombinant erythropoietin containing a mixture of isoforms obtained using procedures described in Example 2 of Lai et al. supra, except that DEAE-Agarose chromatography is replaced by Q-Sepharose chromatography, is also shown in the far left lane of the gel.

FIG. **5** shows the amino acid sequence of human erythropoietin. Squares indicate asparagine residues to which carbohydrate chains are attached and asterisks indicate threonine and serine residues modified with carbohydrate. Additional glycosylation sites provided in the analogs of Example 6 are indicated by mutations to asparagine serine, and threonine.

FIG. **6**A, FIG. **6**B, and FIG. **6**C show the series of cloning steps used in generating plasmids for the construction and analysis of analogs of human erythropoietin. These analogs have amino acids altered as shown in FIG. **5** which provide additional glycosylation sites.

FIG. **7** shows a Western blot analysis of COS cell supernatants of human sequence erythropoietin and indicated erythropoietin analogs. The analogs [Asn^{9}, Ser^{11}], EPO, [Asn^{69}] EPO, [Asn^{125}, Ser^{127}] EPO, and [Pro^{124}, Thr^{125}] EPO are constructed as described in Example 6. The analogs [$Prol^{125}$, Thr^{127}] EPO, [Asn^{126}, Ser^{128}] EPO and [Thr^{125}, Ser^{127}] EPO which do not contain additional carbohydrate chains are shown for comparison.

FIG. **8** shows a Western blot analysis of COS cell supernatants of human sequences erythropoietin and indicated erythropoietin analogs after treatment with N-glycanase. The analogs [Thr^{125}] EPO and [Pro^{124}, Thr^{125}] EPO are constructed as described in Example 6. The analogs [Val^{126}] EPO, [Pro^{124}] EPO, [Pro^{125}] EPO, [Thr^{127}] EPO, [Pro^{125}, Ser^{127}] EPO and [Thr^{125}, Ser^{127}] EPO are shown for comparison.

FIG. **9** shows an isoelectric focusing gel of pools 2, 3 and 4 obtained by Q-Sepharose and C4 reverse phase chromatography of cell medium that supported the growth of CHO cells transfected with erythropoietin cDNA containing the [Thr^{125}] mutation. Purified recombinant erythropoietin containing a mixture of isoforms are obtained using procedures described in Example 2 of Lai et al., supra, except that DEAE-Agarose chromatography is replaced by Q-Sepharose chromatography, is also shown in the left and right lanes of the gel.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, erythropoietin isoforms are provided. Isoelectric focusing (IEF) separates proteins on the basis of charge. When placed in a pH

gradient and subjected to an electric field, proteins will migrate to the point at which they have no net charge and remain there. This is the isoelectric point (pI) of the protein. Each distinct band observed on IEF represents molecules that have a particular pI and therefore the same overall charge, and is termed an isoform. The term "erythropoietin isoform" as used herein refers to erythropoietin preparations having a single pI, and having the same amino acid sequence.

In a preferred embodiment the erythropoietin is the product of the expression of an exogenous DNA sequence that has been transfected into a non-human eucaryotic host cell, that is, in a preferred embodiment the erythropoietin is "recombinant erythropoietin". Recombinant erythropoietin is advantageously produced according to the procedures described in commonly owned Lin U.S. Pat. No. 4,703,008 hereby incorporated by reference. Recombinant erythropoietin is advantageously purified according to the general procedures described in Example 2 of commonly owned Lai et al. U.S. Pat. No. 4,667,016 hereby incorporated by reference, or alternatively the procedure described in Example 2 wherein DEAE-Agarose chromatography is replaced by Q-Sepharose chromatography. In the Q-Sepharose column modification, 55 mM NaCl replaces 25 mM NaCl in the buffer solution used to bring the column to neutral pH, and 140 mM NaCl replaces 75 mM NaCl in the buffer solution used to elute erythropoietin from the column. This material, when analyzed by sodium dodecyl sulfate polyacrylamide gel electrophoresis, migrates as a single species (i.e. band). When purified erythropoietin is subjected to IEF, multiple bands in the gel are apparent, indicating that different charged forms of the glycoprotein are present.

It has been found that discrete isoforms of recombinant erythropoietin having the amino acid sequence of urinary derived human erythropoietin correspond to erythropoietin molecules having from 1–14 sialic acids, and each isoform present in purified recombinant erythropoietin has an in vivo activity which is related to the number of sialic acids the isoform possesses. The term "erythropoietin", as used herein, includes naturally occurring erythropoietin, urinary derived human erythropoietin as well as non-naturally occurring polypeptides having an amino acid sequence and glycosylation sufficiently duplicative of that of naturally occurring erythropoietin to allow possession of in vivo biological properties of causing bone marrow cells to increase production of reticulocytes and red blood cells.

Crude preparations of erythropoietin have many isoforms but material purified for example, as in the Lai et al. patent supra Example 2, contains predominantly six isoforms when analyzed by IEF. In addition, at least one additional isoform of greater acidity has been detected using the chromatographic procedures described in Example 4. (This more acidic form, migrating at >14 sialic acids on an IEF gel may contain nonsialic acid negative charges as shown by the resistance of some of the charge to sialidase digestion). These isoforms differ from each other by sialic acid content. As shown in the Examples, this is demonstrated by isolating 10 of these isoforms by preparative IEF and determining the sialic acid content of five of them. Of the isoforms assayed for sialic acid content, it is found that the five isoforms contained either 9, 10, 11, 12 or 13 sialic acid residues.

There is a relationship between the relative in vivo specific activity of erythropoietin and number of sialic acid residues per erythropoietin molecule from the isoforms 5 through 11 (each isoform is designated herein by the number of sialic acids per erythropoietin molecule). Isoforms 11 through 14 have approximately the same relative in vivo

specific activity. Isoforms 5–14 are assayed for in vivo activity by the exhypoxic polycythemic mouse bioassay and the amount of each isoform present is determined by Bradford protein assay, absorbance at 280 nm or by radioimmunoassay (RIA) for erythropoietin. RIA determinations (Egrie et al. Immunobiology 172, 213, (1986)), expressed as units/ml, are divided by 212,770 units/mg erythropoietin polypeptide, the average specific activity of purified erythropoietin as determined by RIA, to give protein concentrations of isolated isoforms or isoform mixtures expressed as mg erythropoietin polypeptide/ml. As shown in the Examples, the relative in vivo specific activities increase step-wise from isoform 5 to isoform 11 (see Table 2).

The in vivo specific activities referred to herein are measurements of relative in vivo specific activities and are not measurements of absolute in vivo specific activities. For the purposes of this application, the specific activities are used only to compare relative activities of isoforms that have been assayed using the same assay, using the same conditions including the same internal standard, the same type of animals, having the same analysis of the data used to calculate specific activity, the same assay for determining protein content. It is not intended that any in vivo specific activity value reported for any isoform represents an inherent or absolute value for that isoform.

The subject invention provides erythropoietin isoforms. The specific isoforms of erythropoietin obtained in accordance with the present invention, and their properties, may vary depending upon the source of the starting material. For example, the isoforms of urinary derived human erythropoietin are different than the isoforms of recombinant erythropoietin. In a preferred embodiment, the invention relates to an erythropoietin isoform having a specific number (i.e. a fixed number greater than 0) of sialic acids per erythropoietin molecule, said number selected from the group consisting of 1–14. Advantageously said number is 9, 10, 11, 12, 13, or 14. In another embodiment, said number is greater than 14, advantageously 16–23.

This invention also provides compositions comprising two or more erythropoietin isoforms. In one embodiment the compositions comprise a mixture of isoforms having greater than a predetermined number of sialic acids per erythropoietin molecule, e.g. greater than 11 sialic acids per erythropoietin molecule, or greater than 12 sialic acids per molecule, e.g. a mixture of isoforms 12, 13 and 14. In another embodiment the compositions comprise mixtures of isoforms having a predetermined number of sialic acids per erythropoietin molecule, e.g. less than 12, but greater than 8 sialic acids per molecule as in, for example, a mixture of isoforms 9, 10, and 11. The invention also provides for compositions of erythropoietin isoforms wherein the relative amounts of the isoforms are the same or different. For example, a mixture of isoforms 9, 10 and 11 could have the isoforms present in a variety of ratios such as 1:1:1, 2:3:1 or 20:20:1.

Advantageously, the compositions comprise mixtures of less than four isoforms, for example a mixture of isoforms 11, 12, and 13, or a mixture of 12 and 14, or a mixture of 7 and 13.

In order to produce mixtures of erythropoietin isoforms, this invention also provides methods of isolating selected erythropoietin isoforms simultaneously. These 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. All of these techniques have as their basis the separation of proteins according to charge.

In general, ion exchange chromatography and chromatofocusing involve application of either crude human erythropoietin (cell conditioned media) or purified material to a column resin under conditions that permit binding of some or all of the erythropoietin isoforms to the resin. For crude erythropoietin preparations, it is preferable to apply the protein to the column at about pH 7 while for purified preparations the protein can be applied to the column at pH 7 down to about pH 4. After washing the column with buffer at about pH 4, those erythropoietin isoforms that remain bound on the ion exchange column are eluted by increasing the pH and the salt concentration of the buffer or by applying a gradient of decreasing pH and increasing ionic strength at about pH 4. For chromatofocusing, the isoforms are eluted from the column by a gradient of decreasing pH or by washing the column with a high concentration of salt.

One embodiment the invention relates to mammalian (e.g., Chinese Hamster Ovary, CHO) host cells which preferentially synthesize erythropoietin isoforms having greater than a specific number, e.g. greater than 10 sialic acids per molecule. Erythropoietin molecules have N-linked or O-linked oligosaccharides structures which can limit the sialic acid content of the molecule. For example, tetraantennary (four-branched) N-linked oligosaccharides most commonly provide four possible sites for sialic acid attachment while bi- and triantennary oligosaccharide chains, which can substitute for the tetraantennary form at asparagine-linked sites, commonly have at most only two or three sialic acids attached. O-linked oligosaccharides commonly provide two sites for sialic acid attachment. Thus, erythropoietin molecules can accommodate a total of 14 sialic acid residues provided all three N-linked oligosaccharides are tetraantennary. Mammalian cell cultures are screened for those cells that preferentially add tetraantennary chains to recombinant erythropoietin, thereby maximizing the number of sites for sialic acid attachment.

The N-linked oligosaccharides of urinary erythropoietin contain sialic acid in both an α 2,3 and an α 2,6 linkage to galactose (Takeuchi et al. J. Biol. Chem. 263, 3657(1988)). Typically the sialic acid in the α 2,3 linkage is added to galactose on the mannose α 1,6 branch and the sialic acid in the α 2,6 linkage is added to the galactose on the mannose α 1,3 branch. The enzymes that add these sialic acids (β-galactoside α 2,3 sialyltransferase and β-galactoside α 2,6 sialyltransferase) are most efficient at adding sialic acid to the mannose α 1,6 and mannose α 1,3 branches respectively.

Dihydrofolate reductase (DHFR) deficient Chinese Hamster Ovary (CHO) cells are a commonly used host cell for the production of recombinant glycoproteins including recombinant erythropoietin. These cells do not express the enzyme β-galactoside α 2,6 sialyltransferase and therefore do not add sialic acid in the α 2,6 linkage to N-linked oligosaccharides of glycoproteins produced in these cells. (Mutsaers et al. Eur. J. Biochem. 156, 651 (1986); Takeuchi et al. J. Chromatogr. 400, 207 (1987)). Consequently, recombinant erythropoietin produced in CHO cells lacks sialic acid in the 2,6 linkage to galactose (Sasaki et al. (1987), supra; Takeuchi et al. (1987), supra). In another embodiment of the subject invention, the erythropoietin used to produce the isoforms is made in CHO cells that are transfected with a functional β-galactoside α 2,6 sialyltransferase gene to give incorporation of sialic acid in α 2,6 linkage to galactose. See Lee et al. J. Biol. Chem. 264, 13848 (1989), hereby incorporated by reference, for a disclosure of techniques for creating modified CHO cells or other mammalian host cells.

Also encompassed by the invention are certain analogs of human erythropoietin. As used herein the phrase "analog of human erythropoietin" refers to erythropoietin with one or more changes in the amino acid sequence of human erythropoietin which result in an increase in the number of sites for sialic acid attachment. Analogs are generated by site-directed mutagenesis having additions, deletions, or substitutions of amino acid residues that alter sites that are available for glycosylation. Such analogs have a greater number of carbohydrate chains than human erythropoietin.

Analogs that result in increased biological activity are constructed by increasing the sialic acid content of the erythropoietin molecule. Analogs having levels of sialic acid greater than that found in human erythropoietin are generated by adding glycosylation sites which do not perturb the secondary or tertiary conformation required for biological activity. Advantageously, the analog of human erythropoietin has 1, 2 or 3 additional sites for N-glycosylation or O-glycosylation. For example, a leucine at position 69 is replaced by an asparagine to give the sequence Asn-Leu-Ser, which serves as a fourth site for N-glycosylation. Such a change can commonly provide up to four additional sialic acids per molecule. Examples of other changes that generate additional N- or O-glycosylation sites are alanines at positions 125 and 127 to asparagine and serine, respectively, alanine at position 125 to threonine and alanines at positions 124 and 125 to proline and threonine, respectively. As will be appreciated by those skilled in the art, the subject invention includes many other analogs of human erythropoietin having additional sites for glycosylation.

Also comprehended by the invention are pharmaceutical compositions comprising a therapeutically effective amount of a specific isoform or mixture of isoforms together with a suitable diluent, adjuvant and/or carrier useful in erythropoietin therapy. A "therapeutically effective amount" as used herein refers to that amount which provides therapeutic effect for a given condition and administration regimen. The administration of erythropoietin isoforms is preferably by parental routes. The specific route chosen will depend upon the condition being treated. The administration of erythropoietin isoforms is preferably done as part of a formulation containing a suitable carrier, such as human serum albumin, a suitable diluent, such as a buffered saline solution, and/or a suitable adjuvant. The required dosage will be in amounts sufficient to raise the hematocrit of patients and will vary depending upon the severity of the condition being treated, the method of administration used and the like.

The following examples are offered to more fully illustrate the invention, but are not to be construed as limiting the scope thereof. The erythropoietin standard used in the in vivo bioassays employed in the Examples is a recombinant erythropoietin standard that was standardized against a partially purified urinary erythropoietin standard. Thus, only relative in vivo specific activities are being measured. Also the in vivo specific activities are expressed in "units/ml", "units/mg" and units/A_{280}" and not as "IU/ml", "IU/mg" and IU/A_{280}", because the erythropoietin standard employed has not been directly correlated to any existing international standard.

EXAMPLE 1

Isolation of Recombinant Erythropoietin Isoforms

Recombinant erythropoietin is produced as described in Lin, supra. Recombinant erythropoietin used as starting

material for the first and third isoform isolations is purified according to the procedure described in Example 2 of commonly owned Lai et al., supra. Starting material for the second and fifth isoform isolation is purified according to Lai et al. supra using the modification of Q-Sepharose chromatography. These preparations contain a mixture of isoforms of recombinant erythropoietin having the same amino acid sequence as urinary derived human erythropoietin and contain predominantly isoforms 9 to 14. Starting material for the fourth isoform preparation is the material which elutes during the 5 mM acetic acid/1 mM glycine/6M urea wash of the anion exchange column in Example 2 of Lai et al. This fraction contains isoforms with less than or equal to 9 sialic acids and was further purified by gel filtration chromatography as described in Example 2 of Lai et al. prior to use in the preparative isoelectric focusing procedure. The sixth isoform preparation used as its starting material a purified preparation of recombinant erythropoietin having from 4 to 13 sialic residues. This material was purified as per Example 2 of Lai et al. except for a modification to the ion exchange column (elution of the recombinant erythropoietin with a sodium chloride gradient at pH 8.4 and omission of the acetic acid/urea wash) which results in retention of most of the isoforms present in the starting material.

Six different preparations of individual isoforms are carried out by preparative isoelectric focusing in a granulated gel bed (Ultrodex, LKB) essentially as per LKB Application Note 198. Pharmalyte (Pharmacia) 2.5–5 ampholytes (Pharmacia) are used and the gel bed contains 5M urea.

In the first preparation, approximately 20 mg of recombinant erythropoietin in 6.8 ml of 20 mM sodium citrate/100 mM sodium chloride, pH 7.0 are applied to the gel and focused at 8 watts for approximately 16 hours. After isoelectric focusing, the isoform bands in the gel are visualized by a paper contact print of the gel bed. The print is made and then fixed by soaking in 3 changes (approximately 10 minutes each, room temperature) of fixing solution (40% methanol/10% acetic acid/10% TCA/3.5% sulfosalicylic acid), subjected to one change (approximately 10 minutes) of 40% methanol/10% acetic acid (30°–60° C.), stained for 15 minutes at 60° C. in 0.125% Coomassie Blue R-250/40% methanol/10% acetic acid, and then destained in 7.5% methanol/10% acetic acid in order to visualize the separated isoforms. The region of the granulated gel bed containing the isoforms (~50% of the resin) is removed, water is added (~16 ml), and the slurry is poured into a 5.5×24.5 inch tray and evaporated to ~40 g net weight. This preparation is focused for a second time and a contact print of the gel bed is made as before. The portion of gel containing each of the six discernible isoforms is removed from the gel bed.

In order to elute the isoforms from the gel, a solution containing 10 mM Tris-HCl, pH 7.0/5 mM Chaps is added to each isoform to generate a slurry. The slurries are placed in small columns and washed with the Tris-Chaps buffer. The flow throughs are collected and applied separately to small columns (open column configuration) containing Vydac C4 reversed phase resin equilibrated in 20% ethanol/10 mM Tris-HCl, pH 7.0. The columns are developed stepwise with 20% ethanol/10 mM Tris-HCl, pH 7.0, 35% ethanol/10 mM Tris-HCl, pH 7.0, and 65% ethanol/10 mM Tris-HCl, pH 7.0. The fraction eluting at 65% ethanol/10 mM Tris is diluted 1:1 with 10 mM Tris-HCl, pH 7.0 and subjected to concentration and then buffer exchanged to 10 mM Tris-HCl, pH 7.0 using a Centricon-10 (Amicon) microconcentrator. Analytical isoelectric focusing of this preparation is performed essentially as described in LKB technical note 250 using Servalyte 3–5 ampholines (Serva) in a polyacrylamide gel containing 5M urea.

In a second preparation, approximately 26 mg of recombinant erythropoietin in 6.5 ml of deionized water are applied to the gel and focused at 2.5 watts for 35 minutes and 10 watts for approximately 17 hours. The bands of focused protein, which are visible in the gel bed, are removed as 11 different pools. Each pool is brought to about 7.5 ml with deionized water and 20 ml of each of the resulting pool supernatants is subjected to analytical isoelectric focusing as described above. To each of the pools is added 5 ml of 1.5M Tris-HCl, pH 8.8 and the slurries are each placed in small columns and the liquid phase allowed to flow through. The resin is washed with approximately three volumes of 0.5M Tris-HCl, pH 7 and the rinse solution is combined with the flow through. The eluants are concentrated and buffer exchanged to 20 mM sodium citrate/100 mM sodium chloride, pH 7.0 using Amicon disposable ultrafiltration devices having a 10,000 dalton molecular weight cutoff. The concentrated solutions (approximately 0.5 ml) are then passed through a 0.22 micron cutoff cellulose acetate filter. Based upon analytical isoelectric focusing, five pools are found to contain predominantly the single isoforms 10, 11, 12, 13 and 14.

In a third preparation, approximately 30 mg of recombinant erythropoietin in 21.8 ml of distilled water is applied to the gel and focused at 2 watts for 25 minutes, 10 watts for 20 hours and 15 watts for 15 minutes. Protein bands corresponding to the individual isoforms are observed visually and removed from the gel bed. Distilled water is added to gel-isolated isoforms to generate a slurry and the resulting supernatants are analyzed by analytical isoelectric focusing. An equal volume of 1M Tris-HCl, pH 7.2 is added to each slurry, the suspensions are placed into separate small columns, and the liquid phase is allowed to flow through the column to elute the isoforms. Each flow through is concentrated and buffer exchanged to 20 mM sodium citrate/100 mM sodium chloride, pH 7.0 using Amicon disposable ultrafiltration devices having a 10,000 dalton molecular weight cutoff. An analytical isoelectric focusing gel revealed that pools containing predominantly the single isoforms 9, 10, 11, 12, 13 and 14 were obtained.

A fourth isoform preparation used as its starting material erythropoietin containing isoforms 3–9 (prepared as described above). Prior to preparative isoelectric focusing carried out essentially as described for preparations 1–3 above, the ampholytes (Pharmalyte 2.5–5) were prefractionated in a Rotofor (Bio-Rad, Richmond, Calif.) liquid phase isoelectric focusing cell to yield an ampholyte range more suitable for the lower isoelectric points of the starting material. The prefractionation was carried out by mixing 6.7 mL of Pharmalyte 2.5–5 with 15 g of urea and adding purified water to bring the volume to 50 mL. This mixture was fractionated in the Rotofor at 10 Watts, 1° C., for 5 ½ hours using 0.1M phosphoric acid and 0.1M sodium hydroxide as the anolyte and catholyte, respectively. The ampholyte fractions having measured pHs of between 4.5 and approximately 6 were used in the flat-bed isoelectric focusing.

Ampholytes were removed from the isoforms using a Centrieluter (Amicon, Danvers, Mass.) and a 10,000 MW cutoff Centricon (Amicon) using the following parameters: 0.18 Tris buffer pH 8.8, 100 Volts, 25–30 mA, for 3 hours. The isoforms were then buffer exchanged into 0.1M sodium chloride by gel filtration using Sephadex G-25 (Pharmacia). Analytical isoelectric focusing of the five resulting pools showed them to contain isoforms 4,5,6,7, and 8. Isoform 4 ran as several bands, indicating that it may have undergone some degradation.

The fifth isoform preparation was modified by the addition of a pre-focusing step to the flat bed isoelectric focusing procedure. In this modification, the protein was not added to the ampholyte/urea/gel mixture prior to electrophoresis but was added to the isoelectric focusing apparatus following generation of the pH gradient in the gel bed. Following prefocusing for 75 minutes (1500 volt-hrs) the section of gel bed from 2.25–4.25 cm from the cathode was removed, mixed with the erythropoietin solution, and added back to the gel bed. Following isoelectric focusing, isoforms 10,11, 12,13, and 14 were eluted from the gel bed and separated from the ampholytes by ultrafiltration using Centricon-10 (Amicon) devices.

The pre-focusing modification was undertaken to make the ultraviolet absorbance characteristics of the isoform preparations more similar to that of the starting recombinant erythropoietin. This improvement in spectral characteristics can be seen in the ratio of absorbance at 280 and 260 nm for the isolated isoforms. The average ratio of absorbance at 280 nm to that at 260 nm (A280/A260) for isoforms from preparations 2 and 3 (non-prefocused) is 1.36±0.11 while the average A280/A260 ratio for preparations 5 and 6 (pre-focused) is 1.68±0.20. When isoform #14 is excluded from the calculation, the average A280/A260 ratios are 1.39±0.11 and 1.74±0.09 for preparations 2 & 3 and 5 & 6, respectively. (Isoform 14 may have the most atypical spectrum because it is present in the smallest amounts and is thus more subject to interferences by trace contamination by ampholyte components or because it is nearest to the electrode during the flat bed isoelectric focusing procedure). The average A280/A260 ratio for recombinant erythropoietin prepared according to Example 2 of Lai et al. (modified as described earlier by using Q-Sepharose as the anion exchange resin) is 1.91±0.04.

As described above, the starting material for isoform preparation #6 was a recombinant erythropoietin preparation containing isoforms 4–13. The ampholytes were pre-focused in the Rotofor apparatus as per the fourth preparation. Ampholyte fractions having measured pHs of between 3.7 and 4.8 were used for the flat bed isoelectric focusing. The flat bed was pre-focused as in run #5 and isoforms 9,10,11, 12 and 13 were obtained after ultrafiltration (Centricon-10) to remove carrier ampholytes.

EXAMPLE 2

Sialic Acid Content of Recombinant Erythropoietin Isoforms

The isoforms isolated as described in Example 1 and erythropoietin purified according to procedures described in Lai et al., supra (mixture of isoforms 9 to 14) are buffer exchanged into 0.10–0.15M sodium chloride and analyzed for sialic acid content by a modification of the procedure of Jourdian et al. J. Biol. Chem. 246, 430 (1971). The sialic acid residues are cleaved from the glycoproteins by hydrolysis with 0.35M sulfuric acid at 80° C. for 30 minutes and the solutions are neutralized with sodium hydroxide prior to analysis. In order to estimate the amount of erythropoietin protein present, a Bradford protein assay (Bradford Anal. Biochem. 72, 248 (1976)) using recombinant erythropoietin having the amino acid sequence of human erythropoietin as standard is performed using the assay reagents and the micro-method procedure supplied by Bio-Rad. The results, expressed as moles of sialic acids per mole of erythropoietin, are shown in Table 1. Isoforms are designated according to the number of sialic acids per molecule and range from least acidic (Isoform 9) to most acidic (Isoform 13). Isoforms 9–13 are shown in gel lanes 6–10 of FIG. **1**. Quantities of Isoform 14 are insufficient to accurately measure the sialic acid content. The sialic acid content of this isoform is inferred from its migration on IEF gels relative to other isoforms. The sialic acid content of isoforms 5–8 (preparation #4) has not been measured but is likewise inferred from their migration on IEF gels.

TABLE 1

ERYTHROPOIETIN ISOFORM	MOLES SIALIC ACID/ MOLE ERYTHROPOIETIN
Isoform 13	12.9 ± 0.5
Isoform 12	11.8 ± 0.2
Isoform 11	11.0 ± 0.2
Isoform 10	9.8 ± 0.3
Isoform 9	8.9 ± 0.6
Isoform Mixture (9-14)	11.3 ± 0.2

EXAMPLE 3

Activity of Recombinant Erythropoietin Isoforms

The isoforms isolated as described in Example 1 are assayed by absorbance at 280 nm, by Bradford protein assay and by RIA for erythropoietin to determine the amount of recombinant erythropoietin present. The exhypoxic polycythemic mouse bioassay (Cotes et al. Nature 191, 1065 (1961)) is used to determine the relative in vivo biological activity. Quantitation of the amount of erythropoietin protein present using a radioimmunoassay for erythropoietin produced results having higher relative in vivo specific activity for certain isoforms because of an apparent decreased immunoreactivity of isoforms containing large amounts of sialic acid leading to an underestimation of the erythropoietin concentration and thus an overestimation of the relative in vivo specific activity for the most negative isoforms. Mouse bioassay determinations, expressed as units/ml, are divided by the corresponding protein concentrations to give in vivo specific activities expressed as units/mg erythropoietin polypeptide. These specific activities are shown in Table 2.

In Table 2, "n" is the number of independent isoform preparations which contribute to the specific activity value. In most cases several in vivo assays were performed on each isoform preparation. The same in vivo data contribute to the specific activity calculations for all three columns, units/mg erythropoietin polypeptide was determined by the absorbance at 280 nm, from radioimmunoassay potencies, or from Bradford protein assay results. Purified recombinant erythropoietin containing isoforms 9–14 was used as the standard in the Bradford protein assay. "n" may be less for the calculation made using the Bradford protein assay as some preparations were no longer available at the time the Bradford assays were performed.

Erythropoietin purified according to the procedures described in Lai et al., supra and containing a mixture of isoforms 9 to 14 is used as a standard for the RIAs and in vivo assays.

The relative specific activities expressed as units/mg erythropoietin polypeptide can be converted to units/A_{280} by multiplying by 0.807 mg erythropoietin polypeptide/A_{280}. The conversion factor is derived by multiplying the extinction coefficient of erythropoietin (1.345 mg/A_{280}) by the protein content of the erythropoietin glycoprotein (about 60% by weight, Davis et al. Biochemistry 26, 2633 (1987)) to obtain mg erythropoietin polypeptide/A_{280} (i.e., 1.345 mg erythropoietin/A_{280}×0.60 mg polypeptide/mg

erythropoietin=0.807 mg polypeptide/A_{280}). In addition, specific activities expressed as units/mg erythropoietin polypeptide can be multiplied by the factor 0.60 mg polypeptide/mg erythropoietin glycoprotein to give specific activities expressed as units/mg erythropoietin glycoprotein.

TABLE 2

Isoform	U/mG Polypeptide (Bradford Protein Assay)	n	U/mG Polypeptide (From A280)	n	U/mG Polypeptide (From RIA)	n
14	289,400 ± 3,100	2	205,800 ± 37,700	2	366,700 ± 55,900	2
13	307,600 ± 30,600	4	258,700 ± 59,500	5	337,200 ± 40,200	5
12	275,200 ± 55,600	4	258,400 ± 41,700	5	287,700 ± 42,600	5
11	282,700 ± 41,100	3	255,800 ± 67,300	4	251,400 ± 62,700	4
10	188,000 ± 1,900	1	170,300 ± 34,500	3	171,900 ± 31,600	3
9	—		96,600 ± 46,700	2	113,600 ± 39,600	2
8	65,200 ± 3,800	1	70,600 ± 4,100	1	61,000 ± 3,500	1
7	46,200 ± 5,800	1	50,300 ± 6,300	1	42,800 ± 5,400	1
5	16,600 ± 1,700	1	18,300 ± 1,900	1	15,500 ± 1,600	1

The data in Table 2 are also presented graphically in FIGS. **2**A, **2**B and **2**C. These data show that the relative in vivo activity of erythropoietin increases as a function of sialic acid content up until isoform #11. Isoforms 11–14 have essentially the same relative in vivo bioactivity. (This is most apparent when the concentration of isoform 14 is expressed using the Bradford assay value. The Bradford value may be more accurate for isoform 14 because of the generally low levels obtained and the resulting difficulty in determination by A_{280} and the most apparent decreased reactivity in the RIA of very negative forms discussed previously). The greater relative in vivo specific activity of erythropoietin isoforms having more sialic acid is most likely due to a longer circulating half-life of these forms. Isoforms 9 and 13 were labeled with radioactive iodine (^{125}I) and their rate of clearance in rats was determined. The half-life in circulation was significantly longer for isoform 13 than for isoform 9.

EXAMPLE 4

Selection of Recombinant Erythropoietin Isoform Mixtures by O-Sepharose Chromatography

Cell conditioned media from the production of recombinant erythropoietin according to the procedures described in Lin, supra are concentrated and diafiltered against 10 mM Tris, pH 7.2. Protein concentration is determined by the Bradford microprotein assay using bovine serum albumin as a standard. 19.6 ml of the solution containing 40 mg of total protein is made 20 μM in $CuSO_4$, filtered through a 0.45 micron cutoff filter and loaded onto a 4 ml bed volume (1.05 cm height×2.2 cm diameter) column packed with Q Sepharose Fast Flow (Pharmacia) which has been equilibrated with 10 mM Tris, pH 6.8 to 7.0 at 4° C. After sample application, the column is washed with two column volumes of the same buffer. The column flow rate is about 1 ml/min. Six separate columns are set up using this procedure to select defined erythropoietin isoform mixtures.

Columns are washed with 6 to 9 column volumes of a low pH buffer consisting of: Column #1, 150 mM acetic acid, 1 mM glycine, 20 μM $CuSO_4$, 6M urea adjusted to pH 4.7 with NaOH; Column #2, 200 mM acetic acid, 1 mM glycine, 20 μM $CuSO_4$, 6M urea adjusted to pH 4.7 with NaOH; Column #3, 250 mM acetic acid, 1 mM glycine, 20 μM $CuSO_4$, 6M urea adjusted to pH 4.7 with NaOH; Column #4, 300 mM acetic acid, 1 mM glycine, 20 μM $CuSO_4$, 6M urea adjusted to pH 4.7 with NaOH; Column #5, 150 mM acetic acid, 1 mM glycine, 20 μM $CuSO_4$, 6M urea; Column #6, 300 mM acetic acid, 1 mM glycine, 20 μM $CuSO_4$, 6M urea. The pH of the columns is increased to approximately pH 7 by washing each one with 8 to 11 column volumes of 10 mM Tris-HCl, 55 mM NaCl, 20 μM $CuSO_4$, pH 7. The defined erythropoietin isoform mixtures are eluted from the columns by washing with 10 mM Tris-HCl, 140 mM NaCl, 20 μM $CuSO_4$, pH 7.0.

The eluted isoform pools from each column are concentrated and solvent exchanged into water using an Amicon Centricon-10 microconcentrator. The results of analytical isoelectric focusing of these concentrated pools are shown in FIG. **3**. Gel lanes 1–6 represent defined erythropoietin isoform mixtures eluted from column 1–6, respectively. The "isoform mixture" shown in the far right gel lane of FIG. **3** represents cell media which is applied to a Q-Sepharose column as described above, the column is washed with 5 mM acetic acid, 1 mM glycine, 20 μM $CuSO_4$, 6M urea, and the erythropoietin isoform mixture is eluted from the column using the procedures described above. This eluted mixture of isoforms is further purified according to the procedures described in Lai et al., supra prior to analytical isoelectric focusing.

EXAMPLE 5

Fractionation of Recombinant Erythropoietin Isoforms Using a Low pH Gradient on O-Sepharose

In another procedure, erythropoietin isoforms are separated using a gradient of decreasing pH and increasing ionic strength. The concentrated diafiltered erythropoietin containing media is loaded to a column of Q-Sepharose at a ratio of approximately 40 mg total protein/mL gel. The column is then washed with approximately two column volumes of 10 mM Tris HCl, pH 7.0 and then approximately 10 column volumes of 2 mM acetic acid/1 mM glycine/20 μM $CuSO_4$/6M urea (pH approximately 4.8) to remove contaminating proteins and erythropoietin isoforms containing less than approximately 7 sialic acid residues. Isoforms containing from approximately 8 to approximately 12 sialic acids are eluted from the column using a gradient starting at approximately 2 mM acetic acid in 6M urea/1 mM glycine/20 μM $CuSO_4$ and running to 40 mM acetic acid/6M urea/1 mM glycine/20 μM $CuSO_4$ (pH approximately 4). The total volume of the gradient is approximately 40 column volumes and fractions of approximately one column volume each are collected into vessels containing a volume of Tris buffer sufficient to bring the pH into the range of 6–8.5 so as to avoid long term exposure of the collected fractions to low

pH. Aliquots of the fractions are subjected to analytical isoelectric focusing to monitor the separation. FIG. **4** shows the separation of isoforms 8–11 which may be achieved by this procedure. Isoforms 12–14 which remain bound to the column at the end of the gradient are eluted by washing with a buffer consisting of 10 mM TrisHCl, 140 mM NaCl, 20 μM $CuSO_4$ (pH 7.0). The isoforms (separated during the gradient or eluted by the sodium chloride solution) are freed of contaminating proteins by reverse phase chromatography followed by gel filtration chromatography as described in Example 2 of Lai et al.

EXAMPLE 6

Analogs of Human Erythropoietin Having Additional Glycosylation Sites.

A. Construction of Human Erythropoietin Analogs.

The locations of existing and proposed carbohydrate attachment sites within the erythropoietin amino acid sequence are shown in FIG. **5** and the procedure for generating these additional glycosylation sites is summarized in FIGS. **6**A–C and described below.

The following oligonucleotide primers were synthesized for use in in vitro mutagenesis:

[Asn^4, Ser^6] EPO: 5' CGCCCACCAAACCTC AGCTGTGACAGCCGA 3'

[Asn^9, Ser^{11}] EPO: 5' ATCTGTACAACCGA AGCCTGGAGAGGT 3'

[Asn^{69}]EPO: 5' GGGCCTGGCCAACCTGTCGGAAG 3'

[Asn^{124}] EPO: 5' TCCCCTCCAGAT AATGCCTCAGCTGC 3'

[Asn^{125}, Ser^{127}] EPO: 5' CAGATGCGAACTCA TCTGCTCCAC 3'

[Asn^{163}, Ser^{165}] EPO: 5' AGGCCTGCAGGAATGGG AGCAGATGACCAGGTG 3'

[Thr^{125}] EPO: 5' TCCAGATGCGACCTCAGCTGCTC 3'

[Pro^{124}, Thr^{125}] EPO: 5' CCTCCAGATCCG ACCTCAGCTGC 3'

The underlined codons show the mismatched regions where the amino acids indicated in brackets replace the wild-type amino acids.

[Asn^4, Ser^6] EPO was constructed to add an N-glycosylation site at Asn 4. [Asn^9, Ser^{11}] EPO was constructed to add an N-glycosylation site at Asn 9. [Asn^{69}] EPO was constructed to add an N-glycosylation site at Asn 69. [Asn^{125}, Ser^{127}] EPO was constructed to add an N-glycosylation site at Asn 125. [Thr^{125}] EPO and [Pro^{124}, Thr^{125}] EPO were constructed to add an O-glycosylation site at Thr 125.

The following oligonucleotide primers are synthesized for use in in vitro mutagenesis:

[Asn^{69}, Thr^{71}] EPO: 5' GGGCCTGGCCAACCTGAC AGAAGCTGTC 3'

[Ser^{68}, Asn^{69}, Thr^{71}] EPO: 5' CAGGGCCTG TCCAACCTGACAGAAGCTGTC 3'

[Asn^{125}, Thr^{127}] EPO: 5' CAGATGCGAACTCAA CGGCTCCAC 3'

[Asn^{125}, Thr^{127}, Thr^{131}] EPO: 5'ATGCGAACTCAA CGGCTCCACTCACAACAATCACT 3'

[Pro^{124}, Asn^{125}, Ser^{127}] EPO: 5' CCAGATCCAAATTCA TCTGCTCCACTC 3'

[Pro^{124}, Asn^{125}, Thr^{127}] EPO: 5' CCAGATCCAAATTCA ACAGCTCCACTC 3'

[Thr^{125}, Thr^{126}] EPO: 5' CCAGATGCG ACAACAGCTGCTCCA 3'

[Pro^{124}, Thr^{125}, Thr^{126}, Thr^{131}] EPO:

Starting from [Pro^{124}, Thr^{125}] EPO cDNA, the oligonucleotide primer 5' AGATCCGACCAC CGCTGCTCCAC 3' is used to generate [Pro^{124},Thr^{125}, Thr^{126}] EPO. The oligonucleotide primer 5'TGCTCCACTC ACAACAATCACTG 3' is then used to generate [Pro^{124}, Thr^{125}, Thr^{126}, Thr^{131}] EPO.

[Asn^{69}, Thr^{71}] EPO and [Ser^{68}, Asn^{69}, Thr^{71}] EPO are constructed to add an N-glycosylation site at Asn 69 and to enhance N-glycosylation at that site. [Asn^{125}, Thr^{127}] EPO, [Asn^{125}, Thr^{127}, Thr^{131}] EPO, [Pro^{124}, Asn^{125}, Ser^{127}] EPO and [Pro^{124}, Asn^{125}, Thr^{127}] EPO are constructed to add an N-glycosylation site at Asn 125 and to increase glycosylation at that site. [Thr^{125}, Thr^{126}] EPO and [Pro^{124}, Thr^{125}, Thr^{126}, Ser^{131}] EPO are constructed to add an O-glycosylation site at Thr 125 and to increase glycosylation at that site.

The source of erythropoietin DNA for in vitro mutagenesis was plasmid Hul3, a human erythropoietin cDNA clone in pUC 8 (Law et al. Proc Natl. Acad. Sci. 83, 6920 (1986)). Plasmid DNA derived from Hu13 was digested with BstEII and BglII restriction enzymes, the resulting DNA fragments were subjected to agarose gel electrophoresis, and the **810** base pair (bp) erythropoietin DNA fragment was isolated from the gel using a GeneClean™ kit and procedures supplied by the manufacturer (BIO 101, Inc.). Plasmid pBRgHuEPO contains the erythropoietin genomic gene as a BamHI fragment inserted into a derivative of pBR322, as described in commonly owned Lin patent, supra. pBRgHuEPO was also digested with BstEII and BglII and the 6517 bp vector fragment was recovered. Ligation of the two fragments results in IGT1. To construct pEC-1, pDSVL (described in commonly owned Lin patent, supra, and shown in FIG. **5**B) was digested with BamHI and the isolated 2.8 kilobase (kb) BamHI fragment from IGT1 containing erythropoietin cDNA was ligated into it.

In order to generate single-stranded DNA for in vitro mutagenesis, pEC-1 was digested with BamHI and BglII and the 820 bp erythropoietin cDNA fragment was isolated. It was ligated into the BamHI site of m13mp18 to give m13-EC-1. Single stranded DNA was recovered from supernatants of *E. coli* strain RZ1032 infected by m13-EC-1 as described by Kunkel et al. Methods in Enzymol. 154, 367 (1987) and Messing, Methods in Enzymol. 101, 20 (1983). For in vitro mutagenesis approximately 1 μg of single-stranded DNA and 0.2 pmole of one of the synthetic primers described above were mixed with 6 ml of buffer (250 mM Tris pH 7.8, 50 mM $MgCl_2$, and 50 mM dithiothreitol). For annealing of the primer to the template, the reaction volume was adjusted to 10 μl with water, the mixture was heated to 65° C. for 5 minutes and then allowed to cool to room temperature. For the elongation reaction 2.5 ml of each of dTTP, dATP, dGTP, dCTP and ATP (all at 10 μM) were added, followed by 1 μl (1 unit) of *E. coli* DNA polymerase (Klenow fragment) and 1 μl (1 unit) of T4 DNA ligase. The mixture was then incubated overnight at 14° C. and used to transform *E. coli* JM 109 (Yanisch-Perron et al. Gene 33, 103 (1985)) as described (Messing, supra).

To identify mutant clones by differential hybridization, plaques on nutrient agar were transferred to Gene Screen filters (New England Nuclear). The filters were dried under a heat lamp and then incubated for one hour in 6×SSC containing 1% SDS at 60° C. For the hybridization, the oligonucleotide primer above (8 pmoles) was end-labeled with T4 polynucleotide kinase and γ 32p-labeled ATP and incubated with the filters overnight in 6×SSC, 0.5% SDS and 100 mg/ml salmon sperm DNA at 37° C. for the [Asn^{124}] mutation, 55° C. for the [Asn^4, Ser^6] mutation, 65° C. for the [Thr^{125}] and the [Pro^{124}, Thr^{125}] mutations, and 70° C. for the [Asn^9, Ser^{11}] and [Asn^{163}, Ser^{165}] mutations.

The next day, the filters were washed three times with 6×SSC at room temperature and subjected to autoradiography. If necessary, the filters were then washed with 6×SSC at increasing temperatures until little or no hybridization was detected to plaques having the wild-type erythropoietin CDNA sequence. Clones that gave positive hybridization signals under these conditions were identified and retransfected into JM109 to isolate a pure clone. Dideoxy chain termination sequence analysis indicated that the mutations to asparagine, serine threonine and proline residues were present.

Double stranded m13 EC-1 DNAs carrying the [Asn^4, Ser^6], [Asn^9, Ser^{11}], [Asn^{69}], [Asn^{124}], [Asn^{125}], [Ser^{127}], [Asn^{163}, Ser^{165}] [Thr^{125}], and [Pro^{124}, Thr^{125}] changes were recovered from JM109 transfected cells by the boiling method (Holmes et al. Anal. Biochem 117, 193 (1981)). The DNAs were digested with BstEII and XhoII and the 810 bp erythropoietin DNA fragments were isolated. pEC-1 were digested with BstEII followed by a partial digestion with BglII and the 5' termini of the resulting fragments are dephosphorylated with bacterial alkaline phosphatase in 10 mM Tris, pH 8 at 60° C. for 60 minutes. The 7 kb vector fragment lacking the 810 bp BstEII-BglII fragment was isolated and ligated to the erythropoietin fragments above. The resulting plasmids (designated pEC-X where X identifies the particular mutation) contain human erythropoietin with altered amino acid residues at the indicated positions.

cDNA clones of the human erythropoietin sequence and analogs corresponding to [Asn4, Ser6], [Asn9, Ser11], [Asn^{69}], [Asn^{124}], [Asn^{125}, Ser^{127}], [Asn^{163}, Ser^{165}], [Thr^{125}] and [Pro^{124}, Thr^{125}] erythropoietin cDNA clones were transferred into COS-1 cells (ATCC No. CRL-1650) by electroporation. COS-1 cells were harvested from semi-confluent dishes, washed with medium (Dulbecco's modified essential medium containing 5% fetal calf serum and 1% L-glutamine/penicillin/streptomycin (Irvine Scientific)) and resuspended at 4×10^6 cells/ml. One ml of cells was transferred to an electroporation cuvette (Bio-Rad) and electroporated with a Bio-Rad Gene Pulser™ at 25 μFarads and 1600 volts in the presence of 100 to 200 μg of carrier DNA and 2 to 20 μg of plasmid DNA encoding the erythropoietin analog. The electroporated cells were plated at 2×10^6 cells per 60 mm tissue culture dish in 5 ml of medium. Two to four hours after plating the medium was replaced with 5 ml of fresh medium. The conditioned medium was collected 3 to 5 days after electroporation.

B. Assays for erythropoietin analog activity

RIAs were performed according to Egrie et al., supra. The in vivo biological activity of erythropoietin analogs was determined by the exhypoxic polycythemic mouse bioassay (Cotes et al., supra).

In vitro erythropoietin activity was determined by the erythroid colony forming assay as described by Iscove et al. J. Cell Physiol. 83, 309–320 (1974) with modifications. The mononucleated cells from human bone marrow cells were partially purified on a ficoll-paque cushion and washed in Iscove medium before plating to remove the adherent cells. The culture medium contained 0.9% methyl cellulose and did not include any bovine serum albumin. The erythroid colonies are scored after 8 to 10 days of culture.

The erythropoietin analogs transfected and expressed in COS cells as described in Section A were analyzed in crude COS cell supernatants by RIA and by the erythroid colony forming assay. Human sequence erythropoietin has an in vitro activity that is comparable to the RIA activity as determined by the above-mentioned assays. The analogs [Asn^{69}] EPO, [Asn^{125}, Ser^{127}] EPO, [Thr^{125}] EPO and [Pro^{124}, Thr^{125}] EPO exhibited an in vitro activity that is comparable to the RIA activity and gave evidence of having additional carbohydrate chains (as determined in Section C). These analogs are analyzed further by transfecting a cDNA clone encoding the erythropoietin analog into CHO cells, purifying the erythropoietin analog and measuring the in vivo biological activity of the purified analog.

C. Western Blot Analysis

A volume of supernatant containing 5–20 units from COS cells transfected with erythropoietin analog cDNAs as described in Section A was immunoprecipitated overnight at room temperature with a rabbit anti-erythropoietin polyclonal antibody. 20–80 μl of 1:1 Protein A-Sepharose in phosphate buffered saline (PBS) was added to the immunoprecipitate and allowed to incubate for one hour at room temperature. The samples were centrifuged, washed with PBS and, where indicated, the pellet was treated with N-glycanase to remove N-linked carbohydrate chains. The samples were analyzed by 15% SDS-polyacrylamide gel electrophoresis, transferred to nitrocellulose and subjected to Western analysis as described (Burnette et al. Anal. Biochem. 112, 195–203 (1981); Elliot et al. Gene 79, 167–180 (1989)) using a mixture of mouse anti-erythropoietin monoclonal antibodies. One such antibody, 9G8A, is described in Elliot et al. (1989) Blood 74, Supp. 1, A. 1228.

Analysis of COS cell supernatants transfected with [Asn^{69}] EPO and [Asn^{125}, Ser^{127}] EPO cDNA revealed increased protein size compared to human sequence erythropoietin. This increased size is indicative of an additional N-linked carbohydrate chain (FIG. **7**). Treatment of supernatants from COS cells transfected with [Thr^{125}] EPO and [Pro^{124}, Thr^{125}] EPO cDNA with N-glycanase revealed an increased protein size compared to human sequence erythropoietin. This increased size is indicative of an additional O-linked carbohydrate chain (FIG. **8**).

D. Isolation of Erythropoietin Analog Isoforms

The erythropoietin analog [Thr^{125}] EPO was constructed as described in Section A. An 810 bp. erythropoietin cDNA fragment carrying the [Thr^{125}] mutation was isolated by cleaving the plasmid pEC containing the [Thr^{125}] mutation with BstEII and BglII and ligating the fragment to pDECΔ, a derivative of pDSα2. pDSα2 is generally described in commonly owned U.S. patent application Ser. No. 501,904, now abandoned, hereby incorporated by reference. pDECΔ was derived from pDSα2 by the following steps:

(1) The HindIII site of pDSα2 was deleted by digesting pDSα2 DNA with HindIII, treating the HindIII cohesive ends with *E. coli* DNA Polymerase (Klenow fragment) and dNTPs, and religating the blunt-ended vector. The resulting plasmid was pDSα2ΔH.

(2) pDSα2ΔH was digested with SalI and a synthetic oligonucleotide having an SV40 splice signal with a SalI linker attached to the 3' end of the splice signal was ligated to it. The synthetic oligonucleotide had the following sequence:

5' TCGAGGAACTGAAAAACCAGAAAGT-TAACTGGTAAGTTTAGT CTTTTTGTCTTT-

TATTTCAGGTCCCGGATCCGGTGGTGGT-
G C A A A T C A
AAGAACTGCTCCTCAGTGGATGTTGC-
CTTTACTTCTAGGCCTGTACGG AAGTGT-
TACTTCTGCTCTAAAAGCTGCTGCAA-
CAAGCTGGTCGACC 3'

The resulting plasmid was pDSα2ΔH splice.

3) pDSα2ΔH splice was digested with SalI and blunt-ended by treating the cohesive ends with T4 DNA polymerase and dNTPs. An 820 bp. BamHI-BglII human erythropoietin CDNA fragment was blunt-ended by the same method and ligated to the plasmid. The resulting plasmid was pDEC.

4) pDEC was digested with KpnI and PvuII and blunt-ended by treating the cohesive ends with mung bean nuclease. The plasmid was religated to delete the excised KpnI-PvuII fragment resulting in the plasmid pDECΔ.

Plasmid pDECΔ containing [Thr^{125}] erythropoietin cDNA was transfected into DHFR-deficient CHO cells. 770 ml of CHO cell conditioned medium was concentrated using a 10,000 dalton molecular weight cutoff membrane and diafiltered against 10 mM Tris-HCl, pH 8.6 to a final volume of 34 ml. A 17 ml. aliquot of the concentrate was loaded onto a Q-Sepharose fast flow column (5 ml bed volume) equilibrated in the same buffer and eluted in a linear gradient of 0–250 mM NaCl in 10 mM Tris-HCl, pH 8.6. Aliquots of column fractions, either untreated or digested with N-glycanase, were analyzed by SDS-PAGE or IEF and pools (designated 2, 3 and 4) were made based upon the isoform and/or carbohydrate composition of the fractions. Each pool was loaded onto a Vydac C4 column (214TPB 2030; 1 cm diameter; 1.8–2.5 ml bed volume; 0.34 ml/min) and washed with two column volumes of 20% ethanol in 10 mM Tris-HCl, pH 7.0. The columns were eluted with linear gradients of 20–94% ethanol, 10 mM Tris, pH 7.0. Pools were made, diluted into 10 mM Tris-HCl, pH 7.0, and loaded onto Q-Sepharose fast flow columns. Following a wash in 10 mM Tris-HCl, pH 7.0, the samples were eluted with 20 mM sodium citrate, 250 mM NaCl, pH 7.0. The purified [Thr^{125}] pools were analyzed by IEF and are shown in FIG. **9**. EPO analog is analyzed for in vivo biological activity as described above (Cotes et al., supra).

While the invention has been described in what is considered to be its preferred embodiments, it is not to be limited to the disclosed embodiments, but on the contrary, is intended to cover various modifications and equivalents included within the spirit and scope of the appended claims, which scope is to be accorded the broadest interpretation so as to encompass all such modifications and equivalents.

What is claimed is:

1. 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.

2. An erythropoietin isoform according to claim **1** wherein said isoform comprises erythropoietin having the amino acid sequence of 1-165 or 1-166 human erythropoietin.

3. An erythropoietin isoform according to claim **1** having 14 sialic acids per erythropoietin molecule.

4. An erythropoietin isoform according to claim **1** having 13 sialic acids per erythropoietin molecule.

5. An erythropoietin isoform according to claim **1** having 10 sialic acids per erythropoietin molecule.

6. An erythropoietin isoform according to claim **1** wherein said eucaryotic host cell is a CHO cell.

7. A pharmaceutical composition comprising a therapeutically effective amount of said erythropoietin isoform of claim **1** and a pharmaceutically acceptable diluent, adjuvant or carrier.

8. A composition consisting essentially of two or three erythropoietin isoforms according to claim **1**.

9. A composition according to claim **8** wherein said isoforms have from 1 to 12 sialic acids per erythropoietin molecule.

10. A composition according to claim **9** wherein said isoforms have 9, 10 and 11 sialic acids per erythropoietin molecule.

11. A composition according to claim **8** wherein said isoforms have greater than 11 sialic acids per erythropoietin molecule.

12. A composition according to claim **11** wherein said isoforms have from 13–14 sialic acids per erythropoietin molecule.

13. Erythropoietin consisting essentially of erythropoietin molecules having a single specific number of sialic acids per molecule, said number selected from the group consisting of 1–14, and said molecules being the product of the expression of an exogenous DNA sequence in a non-human eucaryotic host cell.

14. Erythropoietin according to claim **13** having 14 sialic acids per erythropoietin molecule.

15. Erythropoietin according to claim **13** having 13 sialic acids per erythropoietin molecule.

16. Erythropoietin according to claim **13** having 10 sialic acids per erythropoietin molecule.

17. Erythropoietin according to claim **13** wherein said erythropoietin has the amino acid sequence of human erythropoietin.

18. A pharmaceutical composition comprising a therapeutically effective amount of the erythropoietin according to claim **13** and a pharmaceutically acceptable diluent, adjuvant or carrier.

19. A composition consisting essentially of erythropoietin molecules according to claim **13** having two or three specific numbers of sialic acids per erythropoietin molecule.

20. A composition according to claim **19** wherein said molecules have from 1 to 12 sialic acids per erythropoietin molecule.

21. A composition according to claim **19** wherein said molecules have greater than 11 sialic acids per erythropoietin molecule.

22. A composition according to claim **21** wherein said molecules have 13 and 14 sialic acids per erythropoietin molecule.

23. A method of preparing an erythropoietin isoform according to claim **1** comprising the steps of:

subjecting a purified erythropoietin to preparative isoelectric focusing, and

eluting a single isoform.

24. A method of preparing erythropoietin molecules having a predetermined number of sialic acids per molecule said number selected from the group consisting of 1–14, comprising applying material containing erythropoietin to an ion exchange column and selectively eluting said molecules from the column.

25. A method of preparing erythropoietin molecules having a predetermined number of sialic acids per molecule said number selected from the group consisting of 1–14, comprising applying material containing erythropoietin to a chromatofocusing column and selectively eluting said molecules from the column.

26. A method of increasing hematocrit levels in mammals comprising administering a therapeutically effective amount of the composition according to claim **19**.

27. 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**.

28. The method of claim **27** wherein said mixture consists essentially of at least two isoforms having less than 12 sialic acids per molecule.

29. The method of claim **28** wherein said mixture consists essentially of erythropoietin isoforms having 9, 10 and 11 sialic acids per molecule.

30. The method of claim **27** wherein said mixture consists essentially of at least two isoforms having greater than 11 sialic acids per molecule.

31. The method as in claim **28** wherein said mixture consists essentially of erythropoietin isoforms having 13 and 14 sialic acids per molecule.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,856,298

DATED : January 5, 1999

INVENTOR(S) : Strickland, Thomas

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 13, line 43 change "O" to - - Q - -.

Column 14, line 45 change "O" to - - Q - -.

Column 17, line 29 change "[Asn4, Ser6]" to - - [Asn^4, Ser^6] - -.

Column 17, line 29 change "[Asn9, Ser11]" to - - [Asn^9, Ser^{11}] - -.

Signed and Sealed this

Eighteenth Day of May, 1999

Attest:

Attesting Officer

Q. TODD DICKINSON

Acting Commissioner of Patents and Trademarks