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 DEMAND FOR JURY TRIAL

MEMORANDUM OF LAW IN SUPPORT OF DEFENDANT HOSPIRA, INC.'S RULE 50(A) MOTION FOR JUDGMENT AS A MATTER OF LAW ON THE ISSUES OF SAFE HARBOR, NONINFRINGEMENT, INVALIDITY, AND DAMAGES

HEYMAN ENERIO
GATTUSO & HIRZEL LLP

Dominick T. Gattuso (# 3630)
300 Delaware Avenue, Suite 200
Wilmington, DE 19801
(302) 472-7300
dgattuso@hegh.law

Attorneys for Hospira, Inc.

OF COUNSEL:
WILLKIE FARR & GALLAGHER LLP
Thomas J. Meloro
Michael W. Johnson
Heather M. Schneider
Dan Constantinescu
M. Diana Danca
Tara L. Thieme
Philip F. DiSanto
787 Seventh Avenue
New York, NY 10019
(212) 728-8000

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Pursuant to Federal Rule of Civil Procedure 50(a) and the Court's instruction in court on September 22, 2017,[1] Hospira submits this memorandum of law in support of its motion for judgment as a matter of law ("JMOL") on the issues of safe harbor, noninfringement, invalidity, and damages. JMOL is appropriate when "a party has been fully heard on an issue during a jury trial and the court finds that a reasonable jury would not have a legally sufficient evidentiary basis to find for the party on that issue." Fed. R. Civ. P. 50(a)(1).

Hospira presented evidence sufficient to preclude a reasonable jury from concluding that it is not entitled to the protection of 35 U.S.C. § 271(e)(1) (the "Safe Harbor") for all 21 batches of EPO accused of infringing. Amgen failed to present sufficient evidence at trial from which a reasonable jury could find infringement by Hospira of any asserted patent claim of either U.S. Patent No. 5,756,349 (the "'349 patent") or U.S. Patent No. 5,856,298 (the "'298 patent"). Hospira also presented evidence sufficient to preclude a reasonable jury from concluding that the asserted claims of the '298 patent are not invalid as anticipated or obvious to a person of ordinary skill in the art. Finally, if the jury were to find no Safe Harbor, infringement of both patents, and validity of the '298 patent, Amgen failed to present sufficient evidence at trial from which a reasonable jury could award damages within the range proffered by Amgen.

I. The Court Should Grant JMOL On Hospira's Defense Of Noninfringement Based On The Safe Harbor Provision Of 35 U.S.C. § 271(e)(1).

The "Safe Harbor" provision of 35 U.S.C. § 271(e)(1) provides that "[i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States" a recombinant DNA product "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

[1] *Amgen Inc. v. Hospira, Inc.*, No. 15-839-RGA, Transcript of Proceedings, September 18-22, 2017 ("Trial Tr.") 1520:12-21 (acknowledging Rule 50(a) motions have "been made" and requesting Hospira's counsel "submit them in writing later").

veterinary biological products." 35 U.S.C. § 271(e)(1) (2017). If Hospira proves by a preponderance of the evidence that it used the '349 and '298 patents for uses "reasonably related to the development and submission of *any* information" to the FDA, it is entitled to the Safe Harbor. *See Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 200-02 (2005) (emphasis in original). Hospira's intent or ulterior motives in undertaking allegedly infringing activities are irrelevant to whether Hospira is entitled to Safe Harbor protection. *See, e.g., 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); *see also Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 108 (D. Mass. 1998) ("The Federal Circuit precedents indicate that such ulterior motives or alternate purposes do not preclude application of the section 271(e)(1) exemption.").

Hospira not only proved by a preponderance of evidence that its activities are exempt from infringement under the Safe Harbor, but offered evidence sufficient to preclude a reasonable jury from reaching any other verdict. *Fireman's Fund Ins. Co. v. Videfreeze Corp.*, 540 F.2d 1171, 1177 (3d Cir. 1976).

A. Hospira's Evidence Established The Safe Harbor Protection.

Three witnesses testified that all of Hospira's allegedly infringing drug substance batches were used for purposes reasonably related to obtaining FDA approval, including biosimilarity, clinical, stability, process performance qualification ("PPQ"), process validation, continued process verification ("CPV"), pre-approval inspection ("PAI"), and revising product specifications. Accordingly, any other commercial purpose or motive in making the batches, if any, does not remove the batches from the Safe Harbor protection.

Ms. Tracy Dianis, Hospira's Director of Global Regulatory Affairs for Biosimilar Products, described years of interactions between Hospira and the FDA concerning Hospira's proposed biosimilar. Ms. Dianis testified that Hospira received limited guidance on the FDA's

expectations for its proposed biosimilar EPO because the regulatory landscape for biosimilars was uncertain at the time Hospira submitted its original BLA. (Trial Tr. 694:9-697:2.) Ms. Dianis testified that Hospira has not yet obtained FDA approval for its proposed biosimilar, despite filing an extremely comprehensive application and responding to numerous FDA requests for more data and information. (*Id.*, 705:11-24; 706:9-709:16.)

Dr. Catherine Srebalus-Barnes, Pfizer's Senior Director of Executional Excellence and Biosimilar Strategy, described Hospira's development of analytical methods and data requested by and submitted to the FDA for the purpose of obtaining FDA approval of Hospira's proposed biosimilar. Dr. Srebalus-Barnes testified that Hospira's team of more than fifty analytical researchers tested all twenty one allegedly infringing batches of drug substance to support Hospira's application for FDA approval and respond to an FDA Complete Response Letter that Hospira received in October 2015. (*Id.*, 770:9-13; 771:7-772:1; 801:13-802:8.) Dr. Srebalus-Barnes also testified that the 2013 drug substance lots were manufactured and tested in support of Hospira's biosimilarity assessment, which, as Hospira's expert confirmed, is an "absolute requirement" for obtaining FDA approval. (*Id.*, 785:12-786:1; 912:6-19.) Dr. Srebalus-Barnes testified that the work her team of analytical scientists performed to assess biosimilarity, study stability, and develop product specifications was required to obtain FDA approval. (*Id.*, 767:1-768:20; 781:3-22; 789:3-22.)

Dr. Sam Billingham, Hospira's Director of Manufacturing Science and Technology, testified concerning Hospira's development and validation of its manufacturing process for the purpose of obtaining FDA approval. Dr. Billingham confirmed that all of the allegedly infringing batches were used for process validation, PPQ, CPV, and clinical studies, and that those uses of drug substance were necessary to obtain FDA approval. (*Id.*, 872:16-24; 873:1-

874:13; 874:21-875:16.) Dr. Billingham also testified that the FDA required Hospira to be in active manufacturing of its proposed biosimilar product during its PAI in July 2015. (*Id.*, 874:14-20; 875:11-16.) Five batches were in active manufacturing at that time. (*Id.*, 870:5-10.)

Dr. Howard Levine—an expert in the regulatory requirements for obtaining FDA approval of biological drug products—also opined that all of the drug substance lots Hospira manufactured in 2013, 2014, and 2015 are protected by the Safe Harbor. (*Id.*, 904:9-15; 909:13-23.) Dr. Levine testified that those lots are protected by the Safe Harbor because they were manufactured to collect information and data that is reasonably related to obtaining FDA approval. (*Id.*, 909:13-23.) Dr. Levine confirmed that every single use demonstrated by Hospira—biosimilarity, clinical studies, stability, PPQ, process validation, CPV, PAI, and product specification—are requirements by FDA for approval of a biosimilar product. (*Id.*, 1150:13-1151:10.)

B. Amgen Failed To Rebut Hospira's Evidence Supporting Safe Harbor Protection.

Amgen's experts agreed with the testimony of Drs. Srebalus-Barnes, Billingham, and Levine, confirming that all of Hospira's allegedly infringing activities were for purposes related to obtaining FDA approval. In fact, Amgen's '298 infringement expert, Dr. Cummings, testified that the data he relied on in his infringement opinion was generated using the lots that were tested for FDA approval, including 26 lots that were used to establish that Hospira's product is highly similar to Epogen. (Trial Tr. 489:10-18; 510:4-511:9; DTX-255-0015.)

Dr. Sheryl Martin-Moe, Amgen's own expert on regulatory requirements for biologics, does not provide sufficient evidence to rebut Hospira's position. Dr. Martin-Moe admitted that PPQ testing was "required" to obtain FDA approval. (Trial Tr. 1467:24-1468:6). However, Dr. Martin-Moe presented the implausible opinion that the PPQ lots from 2012 were the "grand finale" and that no further batches would be needed for FDA approval. (*Id.*, 1318:15-1319:8.)

That opinion is in direct contrast with the evidence in the case, which showed that Hospira did work above and beyond the PPQ lots, but that work was still not sufficient for FDA approval and resulted in a Complete Response Letter. (*See, e.g.*, Trial Tr. 710:18-711:14; 714:21-717:4; DTX-502.)

Dr. Martin-Moe's opinion that the 2012 PPQ lots were the "grand finale" (Trial Tr. 1318:15-1319:2) also contradicts other admissions that Dr. Martin-Moe made at trial. For example, Dr. Martin-Moe testified that product specifications are "necessary" for FDA approval, and that Hospira was "required" to perform additional testing to revise its product specifications in response to the FDA's Complete Response Letter. (*Id.*, 1477:2-1479:1.) Dr. Martin-Moe acknowledged that Hospira's "product wouldn't be approvable" if the FDA did not conduct a pre-approval inspection ("PAI"), and that if the FDA asks to see active manufacturing during a PAI, the company will "be polite and try to be in production." (*Id.*, 1351:9-1352:6; 1474:4-1475:3.) In addition, Dr. Martin-Moe agreed that performing a comprehensive biosimilarity assessment is "absolutely necessary to getting FDA approval," that information from stability studies "was required to be submitted to the FDA," and that CPV is "related to FDA approval." (*Id.*, 1465:23-1466:14; 1469:2-1470:20; 1475:13-1476:13.) Dr. Martin-Moe also confirmed that "clinical testing is a requirement for FDA approval[.]" (*Id.*, 1467:21-23.) Thus, none of Dr. Martin-Moe's testimony rebuts the evidence presented by Hospira.

The only evidence Amgen offered at trial to allegedly rebut the testimony of Hospira's fact and expert witnesses (and Amgen's own expert witnesses) consisted of several Hospira commercial documents stating that Hospira allegedly manufactured drug substance for commercial purposes, and Hospira's original submission to the FDA, which included a single table listing "commercial inventory" as a lot use of certain 2013 and 2014 drug substance

batches. Even if a commercial purpose were relevant to the Safe Harbor, which it is not, the internal Hospira documents that Amgen relies on had nothing to do with allocating drug substance for specific purposes. The author of the Risk Authorizations, Mr. Tim Noffke, testified that commercial was only a "potential use" for the 2013 batches, and the objective of the documents was "cost allocation, not necessarily material allocation." (*Id.*, 559:4-16; 575:3-14.) And Dr. Srebalus-Barnes testified that the "Lot Use" of "commercial inventory" submitted with Hospira's BLA meant that the analytical research team had not withdrawn all of the material from those lots for other purposes. (*Id.*, 799:7-800:3.) However, even in the document cited by Plaintiffs, other uses of the "commercial inventory" lots are shown, including stability, PPQ, clinical studies, and CPV. (PTX-250-0004, -0017.) In addition. Dr. Srebalus-Barnes testified that material from all of those lots was later used to support Hospira's application for FDA approval and the "Lot Use" was updated. (Trial Tr. 800:4-13; DTX-255-0005-0006.)

Thus, Hospira offered sufficient evidence at trial to preclude a reasonable jury from concluding that it is not entitled to Safe Harbor protection. And Amgen's experts agreed that all of the uses of Hospira's drug substance were reasonably related to obtaining FDA approval. Based on the evidence at trial, no reasonable jury could conclude that all twenty-one batches of EPO are not protected by the Safe Harbor. Hospira therefore requests judgment as a matter of law that its allegedly infringing activities qualify for Safe Harbor protection.

II. The Court Should Grant JMOL Of Noninfringement On The Asserted Claims Of The '349 Patent.

Amgen has the burden of providing infringement by a preponderance of the evidence. *Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1336 (Fed. Cir. 2015). Amgen's burden of proof never shifts to Hospira. *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008). If Amgen fails to prove that every element of an asserted claim has been met, then

Amgen fails to prove that the allegedly infringing product literally infringes that patent claim. *Cephalon, Inc. v. Watson Pharm.*, Inc., 707 F.3d 1330, 1340 (Fed. Cir. 2013).

Amgen has failed to present legally sufficient evidence from which a reasonable jury could find literal infringement of any of the asserted claims of the ’349 patent. Proving infringement of any of claims 1 to 7 of the ’349 patent requires Amgen to establish that the accused cells meet the claimed EPO production rates “as determined by radioimmunoassay.” (PTX-001, col. 38:8-36.) Amgen has failed to do so because it has introduced no evidence based on radioimmunoassay (“RIA”) testing of the accused cells and, independently, because the dot blot evidence Amgen relied on does not demonstrate that the accused cells are capable of achieving the claimed EPO production rates “as determined by radioimmunoassay.” (*Id.*)

A. Amgen Failed To Demonstrate Infringement Because It Introduced No Evidence Of RIA Testing Of The Accused Cells.

Amgen has only asserted literal infringement of claims 1 to 7 of the ’349 patent. (Pretrial Conf. Tr. at 12:12-15, September 8, 2017.) Amgen must prove that the asserted claims satisfy the RIA limitation of the claims in order to demonstrate literal infringement. But Amgen has introduced no evidence in this trial based on RIA testing of the accused cells. Indeed, Amgen’s two technical experts who testified about infringement of the ’349 patent *admitted* that they did not perform or consider any RIA testing results for the accused cells. (Trial Tr. 283:5-7; 287:24-288:4; 537:2-19.)

Thus, it is undisputed that Amgen has introduced no evidence of infringement based on RIA testing of the accused cells. Because Amgen has failed to introduce any evidence of the EPO production rate based on RIA testing, it has failed to demonstrate that the accused cells infringe any of the asserted claims of the ’349 patent.

B. Amgen Failed To Demonstrate Infringement Because It Did Not Show That Dot Blot And RIA Yield Similar Results.

As explained above, it is Hospira's position that RIA testing is required to demonstrate literal infringement. But if RIA testing of the accused cells were not required to show literal infringement, the limitation "as determined by [RIA]" (PTX-001, col. 38:8-36) nonetheless requires that Amgen show that the accused cells are capable of achieving the recited production rate limitation. Amgen would need to show that EPO production rates determined by dot blot are sufficiently predictive of EPO production rates determined by RIA, such that a reasonable jury could find based on the dot blot results that the accused cells are capable of achieving the recited EPO production rates "as determined by [RIA]." (*Id.*) Amgen attempted to do so by having its technical experts purport to calculate EPO production rates based on the dot blot results in Hospira's BLA, but Amgen introduced *no* evidence for a reasonable jury to conclude that dot blot results are similar to results obtained using RIA.

For example, Dr. Wall provided *no* testimony that RIA and dot blots yield similar results. Rather, he testified that he relied on Dr. McLawhon's opinions regarding RIA. (Trial Tr. 271:5-22; 275:19-276:23.) In turn, Dr. McLawhon, also provided *no* testimony about whether dot blot and RIA yield similar results. In contrast, Hospira's technical expert Dr. Hamilton, provided unrebutted testimony that dot blot and RIA are different assays and that dot blot is a very insensitive and inaccurate assay. (*Id.*, 1193:18-1194:8; 1198:5-12; 1191:5-13.)

Thus, even if Amgen could theoretically show that Hospira's cells meet the claimed production rate using a different assay than RIA, it failed to do so because it introduced no evidence that EPO production rates as determined by dot blot are similar to or representative of EPO production rates as determined by RIA. For these reasons, Amgen has failed to present legally sufficient evidence from which a reasonable jury could find literal infringement of any of

the asserted claims of the ’349 patent. Hospira therefore renews its motion for judgment as a matter of law of no infringement of the ’349 patent.

III. The Court Should Grant JMOL Of Noninfringement On The Asserted Claims Of The ’298 Patent.

The Court has previously granted JMOL that Amgen is not asserting infringement of the ’298 patent under the doctrine of equivalents. (Trial Tr. 675:5-22.) Amgen has failed to present legally sufficient evidence from which a reasonable jury could find Hospira literally infringed claims 24 and 27 the ’298 patent. Amgen’s claim that Hospira infringed claims 24 and 27 of the ’298 patent under 35 U.S.C. § 271(e)(2)(C) is also insufficient as a matter of law.

A. Amgen Failed To Present Sufficient Evidence That Hospira Infringed Claim 24.

Amgen has failed to present evidence demonstrating that Hospira’s accused process “selectively elutes” isoforms as required by claim 24. Relying on a single, generic statement that Hospira’s Source 30Q chromatography column “removes basic isoforms,” Amgen’s expert Dr. Cummings testified that Hospira’s process selectively elutes isoforms. (Trial Tr. 467:4-469:4.) Dr. Cummings opined that this alleged separation of the more basic, less sialylated isoforms, from the less basic, more sialylated biologically active isoforms constituted selective elution. (*Id.*) But Amgen failed to present any evidence that Hospira actually selectively elutes isoforms. In fact, Amgen failed to present any evidence of the isoform composition entering or being eluted from Hospira’s Source 30Q chromatography column. Instead, Dr. Cummings relies on speculation and the isoform distribution that results from Hospira’s 13 step manufacturing process. (*Id*., 495:3-6; 503:12-16.) Rather, as explained by Hospira’s expert Dr. Levine, Hospira simply elutes all of the biologically active isoforms present on the column. (*Id*., 984:2-985:12.) This is not “selectively eluting.” (*Id.*)

The record is especially insufficient to support Amgen's infringement claims because Hospira's process does not elute a predetermined number of isoforms. (*Id.*, 841:8-10.) In fact, Dr. Cummings admitted that Hospira's process can result in anywhere between five and eight different isoforms, and that the exact isoforms and their distribution are not known ahead of time by Hospira. (*Id.*, 491:15-493:16; 496:22-497:1; 506:23-508:16.) This is consistent with the testimony of Drs. Billingham and Levine as well. (*Id.*, 841:8-10; 984:2-14; 987:20-22; 989:7-14.) Based on this record, no reasonable jury could find that Hospira predetermines the isoforms to be selectively eluted as required by claim 24.

B. Amgen Failed To Present Sufficient Evidence That Hospira Infringed Claim 27.

For claim 27, Amgen has also failed to provide sufficient evidence that Hospira prepares a "mixture of two or more erythropoietin isoforms of claim 1," as required by claim 27 and as construed by the Court. The Court has construed this phrase to mean a "mixture of two or more of the *isolated* erythropoietin isoforms of Claim 1." (D.I. 320, [Proposed] Order on Claim Construction dated September 22, 2017) (emphasis added.) Although the Court has stated that individual isoforms need not be separately prepared prior to making the recited mixture, the limitations of claim 1 must still be satisfied. Claim 1 requires "one and only one isoform . . . separated from erythropoietin molecules having a different isoelectric focusing point and number of sialic acids per molecule." *Id.* Thus, although individual isoforms need not be separately prepared according to the Court's construction, an isoform must be isolated at some point to infringe claim 27. Amgen has failed to provide any evidence that isoforms are isolated during the course of Hospira's manufacturing process. Thus, Amgen has failed to prove that Hospira's process involves the mixing of two or more "isolated isoforms of claim 1," as required by Claim 27. Based on this record, no reasonable jury could find that Hospira's process prepares a "mixture of two or more erythropoietin isoforms of claim 1."

In addition, Amgen has failed to provide sufficient evidence that Hospira obtained a "composition having a predetermined in vivo specific activity" as required by claim 27 and as construed by the Court. Dr. Cummings testified that Hospira's product has a predetermined *in vivo* specific activity of 93-147 U/μg. (Trial Tr. 478:3-479:21.) However, Dr. Cummings admitted that this range was not calculated as a result of testing Hospira's product, but rather was based on the average value for *Amgen's product.* (*Id*.) Dr. Cummings was unable to produce any evidence of the actual *in vivo* specific activity of Hospira's product. Indeed, Hospira does not target a specific activity; rather, Hospira's process achieves a broad range of activities. (*Id*., 999:13-1000:15.) Based on this record, no reasonable jury could find that Hospira's process obtains a composition having a predetermined *in vivo* specific activity as required by claim 27.

In sum, no reasonable jury could find that Hospira's accused process literally satisfies all of the elements of claims 24 and 27 as construed by the Court. Hospira therefore renews its motion for judgment as a matter of law of no infringement for the '298 patent.

C. Hospira Cannot As a Matter Of Law Infringe The '298 Patent Under 35 U.S.C. § 271(e)(2)(C).

Amgen cannot as a matter of law prove infringement of claims 24 or 27 of the '298 patent under 35 U.S.C. § 271(e)(2)(C) because the '298 patent expired on January 5, 2016. Section 271(e)(2)(C)(i) provides that "[i]t shall be an act of infringement to submit . . . an application seeking approval of a biological product . . . if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a . . . biological product claimed in a patent or the use of which is claimed in a patent ***before*** the expiration of such patent." (Emphasis added.) Thus, much like in the context of litigation under the Hatch-Waxman Act, Section 271(e)(2)(C) renders the submission of a biologics license application an artificial act of infringement to allow for the adjudication of patent infringement

claims prior to launch. Amgen cannot as a matter of law maintain this claim because the '298 patent has expired. Hospira therefore is entitled to judgment as a matter of law of no infringement for claims 24 and 27 of the '298 patent under 35 U.S.C. § 271(e)(2)(C).

IV. The Court Should Grant JMOL Of Invalidity Of The '298 Patent.

A. Claims 24 And 27 Of The '298 Patent Are Anticipated By U.S. Patent No. 4,667,016.

Hospira has presented evidence that would preclude a reasonable jury from reaching any determination other than that claims 24 and 27 of the '298 patent as construed by the Court are invalid as anticipated by U.S. Patent No. 4,667,016 (the "Lai patent"). A patent claim is invalid if "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). The prior art reference may disclose each limitation either expressly or inherently. *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002) (citation omitted). Additional evidence beyond a single prior art reference may be considered when it is used to explain how one skilled in the art would reasonably understand the meaning of a reference. *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991). "Because the claims of a patent measure the invention at issue, the claims must be interpreted and given the same meaning for purposes of both validity and infringement analyses. . . . A patent may not, like a 'nose of wax,' be twisted one way to avoid anticipation and another to find infringement." *Amazon.com, Inc. v. Barnesandnoble.com, Inc*., 239 F.3d 1343, 1351 (Fed. Cir. 2001) (internal citations omitted).

For claim 24, no reasonable jury could find that the Lai patent does not anticipate. Dr. Strickland, an inventor of both the Lai patent and the '298 patent testified that the Lai patent taught applying erythropoietin containing material to an ion exchange chromatography column to obtain isoforms of EPO. (Trial Tr. 406:10-407:9; 409:5-13; 412:5-8.) Thus, the limitation of

"applying material containing erythropoietin to an ion exchange column" is satisfied by the Lai patent.

The only remaining dispute is whether the Lai patent teaches "selectively eluting" a predetermined number of isoforms from the column. During his testimony on infringement, Dr. Cummings opined that since Hospira allegedly separated the more basic, lower isoforms from the higher, biologically active isoforms, Hospira's process selectively eluted predetermined isoforms. (*Id.*, 467:4-469:4.) But this separation of biologically active isoforms from less active isoforms was already taught in the Lai patent. Dr. Levine explained that in Step 2 of Example 2 of the Lai patent, EPO is applied to an ion exchange column and then washed with a buffer at a low pH. (*Id.*, 1009:6-1011:12.) This low pH wash served to remove materials with a pKa greater than biologically active EPO, including the less sialylated, less active forms of EPO. (*Id.*) The remaining EPO was then selectively eluted and collected for further processing. (*Id.*) Dr. Levine concluded that the Lai patent inherently discloses a method of separating good isoforms from bad isoforms—exactly what Dr. Cummings testified is "selectively eluting." (*Id.*, 1038:13-18.)

Dr. Strickland confirmed that Step 2 of his Lai patent used a low pH wash to remove basic, inactive isoforms before selectively eluting the subset of six biologically active isoforms having between 9 and 14 sialic acids per molecule. (*Id.*, 393:14-21; 406:10-407:9.) This was also confirmed by testing using the Lai patent procedure published in the '298 patent, which found that the low pH wash contained isoforms with 9 or fewer sialic acids, and that the complete Lai process resulted in a mixture of isoforms 9 through 14. (*Id.*, 1012:16-24; 1035:3-9.) Dr. Levine also confirmed that the starting material for both the Lai patent and the Strickland patent was made according to the same procedure set forth in one of the Lin patents. (*Id.*,

1138:3-14.) Based on this record, no reasonable jury could find that the Lai patent does not anticipate claim 24 of the '298 patent.

For claim 27, Dr. Levine testified that the Lai patent taught a person of ordinary skill in the art to obtain a predetermined in vivo specific activity because it disclosed how to create compositions of biologically active EPO. (*Id*., 1039:2-1040:16.) Dr. Strickland confirmed that the compositions created using the Lai patent process were enriched with biologically active EPO. (*Id*., 389:20-390:3; 393:14-394:7; 403:24-404:9; 405:7-13.) Based on this record, no reasonably jury could find that the Lai patent does not anticipate claim 27 of the '298 patent.

In sum, no reasonable jury could find that the Lai patent does not anticipate claims 24 and 27. Hospira therefore requests judgment as a matter of law that claims 24 and 27 of the '298 patent are invalid as anticipated.

B. Claims 24 And 27 Of The '298 Patent Would Have Been Obvious To A Person Of Ordinary Skill In The Art.

Hospira has presented evidence that would preclude a reasonable jury from reaching any determination other than that claims 24 and 27 of the '298 patent as construed by the Court are invalid because they would have been obvious to a person of ordinary skill in the art in 1990 in view of the Lai patent. A patent claim is invalid if "the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Whether a patent claim is obvious is a question of law based on underlying factual determinations including: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences, if any, between the prior art and the claimed invention; and (4) secondary considerations of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

No reasonable jury could find that claim 24 would not have been obvious in light of the teachings of the Lai patent. As discussed above, the only element of claim 24 allegedly not found in the prior art is the step of "selectively eluting" a predetermined number of isoforms from an ion exchange column. However, this step would have been obvious to a person of ordinary skill in the art. Dr. Levine testified that it was known that the more sialylated EPO molecules were more biologically active. (Trial Tr. 1047:14-21.) Drs. Strickland and Levine are also in agreement that sialic acid produced a difference in charge in the EPO molecules to which it was attached. (*Id.*, 360:4-10; 407:17-21; 956:24-957:5.) Drs. Cummings, Strickland, and Levine also confirmed that ion exchange chromatography was a well-known method for separating protein molecules on the basis of their net charge. (*Id.*, 418:14-18; 452:5-454:23; 967:1-7; 1507:2-24.)

Dr. Levine concluded from this that it would have been obvious for a person of ordinary skill in the art to use the ion exchange chromatography process to separate isoforms. (*Id.*, 1050:9-1051:19.) The skilled artisan would have been motivated to do this and would have had a reasonable expectation of success in doing so. (*Id.*, 1054:22-1055:22.) Based on this record, no reasonable jury could find that claim 24 would not have been obvious.

Also, no reasonable jury could find that claim 27 would not have been obvious in light of the Lai patent. For the reasons discussed above, the Lai patent disclosed obtaining compositions having a mixture of two or more isoforms of EPO. Although compositions with exact biological activities were not disclosed explicitly in the Lai patent, Dr. Levine explained that a person of ordinary skill would have known that EPO is a mixture of proteins that vary by sialic acid content, and that this knowledge would have motivated a skilled artisan to separate individual isoforms. (*Id.*, 1056:6-1057:10.) Indeed, Lukowsky taught that sialic acid is crucial to

biological activity and that there is some correlation between activity and sialic acid content. (*Id*., 1050:12-22.) Thus, Dr. Strickland's alleged discovery of the relationship between sialic acid content and activity was completely expected. (*Id*., 1058:1-23.) This would motivate a skilled artisan to separate EPO by sialic acid content into its various isoforms and test the activity of each isoform to obtain the exact relationship. (*Id*., 1056:6-1057:10.) Based on this record, no reasonable jury could find that claim 27 would not have been obvious in view of the Lai patent.

V. The Court Should Grant JMOL Precluding A Damages Verdict Greater Than $1.5 Million Per Batch.

Only if the patents are valid and infringed, and Hospira is not entitled to Safe Harbor protection, Amgen shall be awarded "damages adequate to compensate for the infringement, but in no event less than a reasonable royalty for the use made of the invention by the infringer[.]" 35 U.S.C. § 284 (2017). A reasonable royalty is calculated by considering factors discussed in *Georgia-Pacific Corp. v. United States Plywood Corp.*, 318 F. Supp. 1116, 1120 (S.D.N.Y. 1970). The reasonable royalty must be based on a hypothetical negotiation between a willing licensee and a willing licensor at the time of the alleged infringement. *See id.* at 1120-21. The *Georgia-Pacific* framework requires a "flexible" analysis of relevant factors to calculate a reasonable royalty. *See Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1335 (Fed. Cir. 2009). Consistent with this "flexible" analysis, the factfinder may consider actual events that post-date the hypothetical negotiation to assess the reasonableness of a proposed royalty. *Fromson v. Western Litho Plate & Supply Co.*, 853 F.2d 1568, 1575 (Fed. Cir. 1988).

The jury may resolve factual questions concerning the appropriate reasonable royalty, but the underlying methodology considered by the jury must be sound and its opinion based on substantial evidence. *CSIRO v. Cisco Sys., Inc.*, 809 F.3d 1295, 1302 (Fed. Cir. 2015); *Lucent Techs.*, 580 F.3d at 1335. The jury should not credit expert opinions that rely on licenses that are

"radically different from the hypothetical agreement under consideration to determine a reasonable royalty." *Uniloc USA, Inc. v. Microsoft Corp.*, 632 F.3d 1292, 1316-17 (Fed. Cir. 2011) (citations and internal quotations omitted).

Amgen has failed to present sufficient evidence for a reasonable jury to determine that it is entitled to a damages award of $154 million to $170 million, or to any amount greater than $1.5 million per batch, if sold. The evidence presented by Amgen's expert, Dr. Randal Heeb, does not support a "reasonable" royalty because (1) the amount itself is not reasonable, and (2) the payment of an upfront, lump-sum payment is not reasonable.

As to the amount of the royalty, the evidence at trial from Hospira's expert, Dr. Gregory Bell, established that 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. (Trial Tr. 1242:2-1243:13.) Adjusting that amount based on the *Georgia-Pacific* factors, Dr. Bell opined that Hospira would pay to Amgen 35% of the replacement cost, or $1.5 million per batch, if sold. (*Id.*, 1245:5-1248:12.)

In contrast, Amgen's proffered damages range is "simply not reasonable." (*Id.*, 1239:1-7.) Dr. Heeb suggests that Hospira would have paid $154 to $170 million, which is more than the twenty-year net present value of the entire EPO project at the time of the hypothetical negotiation. (*Id.*, 1263:7-1265:20; DTX-190-0005.) In addition, Dr. Heeb's analysis assumes that Amgen would not want to license its patents to Hospira, a competitor, but that is at most one of the *Georgia-Pacific* factors and cannot be used to flout the hypothetical negotiation framework that requires a "willing licensor." (Trial Tr. 665:4-666:1; 1246:4-1247:17.)

As to the upfront, lump-sum nature of the royalty, Amgen has not presented sufficient evidence that a jury could find such an award to be reasonable. Dr. Bell testified that Hospira

would not have agreed to a lump-sum royalty because of the inherent risks in launching a proposed biosimilar. (*Id.*, 1251:18-1252:14.) Dr. Heeb's analysis requires Hospira to bear all the "risk" of the license. (*Id.*, 639:23-640:15; 660:13-18.) That is inconsistent with the requirement of a "willing" licensor and licensee. Dr. Heeb also acknowledged that the hypothetical negotiators on both sides knew the risk that Hospira might not get approval, but that he did not weigh or adjust his analysis to account for that. (*Id.*, 660:2-12.)

Amgen failed to establish *any* economic harm that justified a large, upfront payment and, as Dr. Bell testified, many patent licenses only account for the royalties to be paid upon sale. (*Id.*, 1237:19-1238:21; 1287:1-1288:1.) Amgen cannot simply leave the jury to calculate damages based "mainly on speculation or guesswork." *Lucent Techs., Inc.*, 580 F.3d at 1335. The Vifor Agreement, which is Dr. Heeb's sole evidence that the parties would have agreed to an up-front lump sum royalty payment, is a non-comparable agreement that was entered after the hypothetical negotiation. (Trial Tr. 642:1-20; 653:1-22; 1253:11-1254:15; DTX-138.) The Vifor Agreement is a marketing and distribution agreement that includes an upfront payment that can be *refunded* if Hospira does not obtain FDA approval. (Trial Tr. 659:7-15.) The Vifor Agreement therefore gives the parties no basis for arguing that the hypothetical negotiators would have agreed to a similar lump-sum payment.

Finally, with respect to both the amount and structure of damages, the jury may look to actual events that post-date the hypothetical negotiation to inform its assessment of the reasonableness of a royalty calculation. *Fromson*, 853 F.2d at 1575. Dr. Heeb attempts to justify the amount of the royalty by saying that Hospira would have paid a significant amount to launch on time in Q4 2015 rather than experience a "delay" until Q3 2017. (Trial Tr. 602:14-23.) But Hospira did not launch at that time and, as Dr. Bell explained, there is no need to

calculate what extra royalties Hospira would have paid to launch then. (Trial Tr. 1255:3-1257:15.) In light of the fact that Hospira does not have FDA approval for its proposed biosimilar, and has therefore made zero commercial sales, no reasonable jury could conclude that Amgen is entitled to a lump-sum damages award of $154 to $170 million. Dr. Bell's calculation of a reasonably royalty of $1.5 million per batch, at the time the batch is sold commercially, 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.

Hospira has presented evidence sufficient to establish that no reasonable jury would return a damages verdict greater than $1.5 million per batch at the time of commercial sale. Hospira therefore renews its motion for judgment as a matter of law under Rule 50(a) that it is not liable for damages greater than $1.5 million per batch at the time of commercial sale.

HEYMAN ENERIO
GATTUSO & HIRZEL LLP

/s/ Dominick T. Gattuso
Dominick T. Gattuso (# 3630)
300 Delaware Avenue, Suite 200
Wilmington, DE 19801
(302) 472-7300
dgattuso@hegh.law

Attorneys for Hospira, Inc.

OF COUNSEL:

WILLKIE FARR & GALLAGHER LLP
Thomas J. Meloro
Michael W. Johnson
Heather M. Schneider
Dan Constantinescu
M. Diana Danca
Tara L. Thieme
Philip F. DiSanto
787 Seventh Avenue
New York, NY 10019
(212) 728-8000

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