IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAYER HEALTHCARE LLC, Plaintiff, v. BAXALTA INCORPORATED, BAXALTA US INC., and NEKTAR THERAPEUTICS, Defendants.	)	C.A. No. 16-1122-RGA

OPENING BRIEF IN SUPPORT DEFENDANTS' MOTION FOR JUDGMENT AS A MATTER OF LAW AND FOR A NEW TRIAL CONCERNING INVALIDITY, NONINFRINGEMENT, AND DAMAGES

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TABLE OF CONTENTS

TABLE OF CONTENTS ii

TABLE OF AUTHORITIES iv

I. Legal Standards 1

A. Motion for Judgment as a Matter of Law Under Rule 50(b) 1

B. Motion for a New Trial Under Rule 59(a) 2

C. Evidentiary Standard 2

II. The Undisputed Record Shows that Non-Random Lysine Conjugation of Factor VIII, as Required by the Court's Claim Construction, Is Not Enabled 3

A. The '520 Patent Inventors Did Not Know How to Achieve "Non-Random" Lysine Conjugation of Factor VIII 4

B. The '520 Patent Is Silent on "Non-Random" Lysine Conjugation of Factor VIII and Teaches Against Conjugation of Factor VIII at Lysines 6

C. Bayer Presented No Evidence To Sustain the Jury's Verdict of Enablement 9

III. The Undisputed Record Shows that Adynovate® Does Not Infringe 10

A. The Record Cannot Support a Finding That Adynovate® Is a Claimed "Isolated" Conjugate Because Its Conjugation Is Undisputedly Random 11

1. Bayer Did Not Rebut Adynovate®'s Random Conjugation Characteristics 14

2. Bayer Did Not Present Evidence that the Conjugation to Make Adynovate® is Not Random, as Required by the Court's Construction 15

3. The Jury's Verdict Rested On Confusion Over the Meaning of "Conjugation That Was Not Random" 18

B. The Undisputed Record Cannot Support a Finding That Adynovate® Meets the "SEQ ID NO:4" Term Because There Is No Evidence of PEGylated Factor VIII With 2,332 Amino Acids Including the Entire B-Domain 19

1. The Doctrine of Equivalents Is Barred 19

C. The Undisputed Record Cannot Support a Finding That Adynovate® Meets the "B-Domain" Term Because Activity Is Lost Resulting From Conjugation 20

IV. The Record Supports That the '520 Patent Is Invalid for Obviousness 21

A. Knowledge in the Art Would Have Motivated a POSA to Conjugate at the B-Domain of Factor VIII 22

B. The Bossard Work Provided a Reasonable Expectation of Success in Conjugation at the B-Domain and Retaining Activity 23

C. Bayer's Alleged Secondary Considerations Do Not Support a Finding of Non-Obviousness 24

V. The Evidence Presented by Bayer and Dr. Addanki Cannot Support the Jury's Damages Award 25

A. After Having Its One and Only Damages Theory Stricken, Bayer Repeatedly Invited the Jury to Improperly Speculate as to an Appropriate Royalty 26

B. Before Trial, Neither Bayer Nor Dr. Addanki Had Ever Opined That 5.1% to 42.4% Constituted a Range of Reasonable Royalties or That Bayer Would Have Had Greater Bargaining Power in a Hypothetical Negotiation 28

C. Royalties From 5.1% to 42.4% Are Not, as a Matter of Law, Plausible Outcomes of the "Hypothetical Negotiation" 31

1. The High End of Dr. Addanki's Range (42.4%) Represents All of Baxalta's Alleged Profit From Selling Adynovate® 31

2. Dr. Addanki's New 5.1% to 42.4% Royalty Range Excludes Substantial Costs Associated with Baxalta's Sale of Adynovate® 32

3. Dr. Addanki's New 5.1% to 42.4% Reasonable Royalty Range Fails to Separate the Value of the Allegedly Infringing and Noninfringing Features of Adynovate® 33

VI. Conclusion 36

TABLE OF AUTHORITIES

Cases

AK Steel Corp. v. Sollac,
344 F.3d 1234 (Fed. Cir. 2003)..... 4, 8, 9

ALZA Corp. v. Andrx Pharms., LLC,
603 F.3d 935 (Fed. Cir. 2010)..... 10

Amazon.com v. Barnesandnoble.com,
239 F.3d 1343 (Fed. Cir. 2001)..... 21

Apple Inc. v. Motorola, Inc.,
757 F.3d 1286 (Fed. Cir. 2014)..... 25

Automotive Techs. Intern., Inc. v. BMW of N. Am.,
501 F.3d 1274 (Fed. Cir. 2007)..... 7

Brooke Grp. Ltd. v. Brown & Williamson Tobacco Corp.,
509 U.S. 209 (1993)..... 2

Commonwealth Sci. & Indus. Research Org. v. Cisco Sys., Inc.,
809 F.3d 1295 (Fed. Cir. 2015)..... 33

Duramed Pharm., Inc. v. Paddock Labs., Inc.,
644 F.3d 1376 (Fed. Cir. 2011)..... 19

Exmark Mfg. Co. v. Briggs & Stratton Power Prods. Grp., LLC,
879 F.3d 1332 (Fed. Cir. 2018)..... 25

Genentech, Inc. v. Novo Nordisk A/S,
108 F.3d 1361 (Fed. Cir. 1997)..... 6, 7, 10

Hughes Tool Co. v. Dresser Indus., Inc.,
816 F.2d 1549 (Fed. Cir. 1987)..... 31

Idenix Pharm. LLC v. Gilead Scis., Inc.,
No. 14-846-LPS, 2018 WL 922125 (D. Del. Feb. 16, 2018)..... 2, 10, 18

Imperium IP Holdings (Cayman), Ltd. v. Samsung Electronics Co., Ltd.,
2019 WL 404570 (Fed. Cir. Jan. 31, 2019) 2, 9, 10

In re Buchner ,
929 F.2d 660 (Fed. Cir. 1991)..... 9

In re Wands,
858 F.2d 731 (Fed. Cir. 1988)..... 3

Johnson & Johnson Assoc. Inc. v. R.E. Serv. Co. Inc.,
285 F.3d 1046 (Fed. Cir. 2002)..... 20

L-3 Commc'ns Corp. v. Sony Corp.,
No. 10-734-RGA, 2014 WL 4674815 (D. Del. Sept. 12, 2014)..... 21

Liebel-Flarsheim Co. v. Medrad, Inc.,
481 F.3d 1371 (Fed. Cir. 2007)..... 5, 8, 9

Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.,
895 F.2d 1403 (Fed. Cir. 1990)..... 25, 32

Lucent Tech., Inc. v. Gateway, Inc.,
580 F.3d 1301 (Fed. Cir. 2009)..... 26, 28

MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.,
687 F.3d 1377 (Fed. Cir. 2012)..... 4

McMillan v. Weeks Marine, Inc.,
478 F. Supp. 2d 651 (D. Del. 2007)..... 2

Millennium Pharm., Inc. v. Sandoz Inc.,
862 F.3d 1356 (Fed. Cir. 2017)..... 8

Nat'l Recovery Techs., Inc. v. Magnetic Sys., Inc.,
166 F.3d 1190 (Fed. Cir. 1999)..... 5

OddzOn Prods. v. Just Toys,
122 F.3d 1396 (Fed. Cir. 1997)..... 23

Ormco Corp. v. Align Tech., Inc.,
498 F.3d 1307 (Fed. Cir. 2007)..... 4

Philip v. Nock,
84 U.S. 460 (1873)..... 27

Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.,
904 F.3d 965 (Fed. Cir. 2018)..... 34

Promega Corp. v. Life Techs. Corp.,
875 F.3d 651 (Fed. Cir. 2017)..... 25, 27, 35

Reeves v. Sanderson Plumbing Prods.,
530 U.S. 133 (2000)..... 2, 9

Rembrandt Vision Tech, L.P. v., Johnson & Johnson Vision Care, Inc.,
725 F.3d 1377 (Fed. Cir. 2013)..... 30

Riles v. Shell Exploration & Prod. Co.,
298 F.3d 1302 (Fed. Cir. 2002) 27

Sitrick v. Dreamworks, LLC,
516 F.3d 993 (Fed. Cir. 2008) 4

Sprint Commc'n Co. L.P. v. Comcast IP Holdings, LLC,
No. 12-1013-RGA, 2015 WL 4720576 (D. Del. Aug. 7, 2017) 2

Weisgram v. Marley Co.,
528 U.S. 440 (2000) 30

Whitserve, LLC v. Computer Packages, Inc.,
694 F.3d 10 (Fed. Cir. 2012) 27, 35

Wordtech Sys. v. Integrated Networks Sols., Inc.,
609 F.3d 1308 (Fed. Cir. 2010) 32

Statutes

35 U.S.C. § 102(f) 23

35 U.S.C. § 103(a) 21, 23

35 U.S.C. § 112 ..... 3, 9

Rules

Fed. R. Civ. P. 26(a)(2)(B) 30

Fed. R. Civ. P. 37 30

Fed. R. Civ. P. 50(a) 1

Fed. R. Civ. P. 50(b) 1, 2, 25, 35

Fed. R. Civ. P. 59(a) 1, 2, 35

Defendants move under Fed. R. Civ. P. 50(b) for judgment as a matter of law.[1] After a 5-day trial, the jury returned a verdict that the '520 patent is not invalid and literally infringed by Defendants' Adynovate® product. The jury further awarded damages on that basis. (Tr. 1588:18-1591:7).) But the evidence at trial cannot sustain this verdict. Asserted claims 1, 2, 3, and 8 of the '520 patent require, as construed by the Court, "isolated" conjugates of PEG attached to Factor VIII where conjugation was "not random." (Tr. 1449:7-8; D.I. 200.) The '520 patent is invalid particularly for lack of enablement because it is undisputed that there is no teaching anywhere in the patent of "non-random" lysine conjugation of Factor VIII (which Bayer asserts is encompassed within the claims), and Bayer offered no evidence that such conjugation was known in the art. The '520 patent is not infringed because Bayer's experts and inventors of the '520 patent conceded that Adynovate® is made by random lysine conjugation, consistent with testing and analysis by Baxalta's scientists which Bayer did not rebut.

Bayer's proffered evidence was also legally insufficient to prove any damages, much less the specific "reasonable royalty" of 17.78% awarded by the jury. There is no substantial evidence to support this award. Bayer improperly and repeatedly asked the jury to speculate on damages—up to and beyond Baxalta's profits from Adynovate®—and presented a damages opinion and theory that was not set forth in any of its expert's damages reports.

Alternatively, a new trial should be granted under Fed. R. Civ. P. 59(a) because the jury's verdict was against the clear weight of the evidence.

I. Legal Standards

A. Motion for Judgment as a Matter of Law Under Rule 50(b)

"To prevail on a renewed motion for JMOL following a jury trial, a party must show that the jury's findings, presumed or express, are not supported by substantial evidence or, if they

[1] Defendants' renewed Rule 50(a) motion before the jury's verdict was not ruled on. (D.I. 389.)

were, that the legal conclusion(s) implied [by] the jury's verdict cannot in law be supported by those findings." *Sprint Commc'n Co. L.P. v. Comcast IP Holdings, LLC*, No. 12-1013, 2015 WL 4720576, at *2 (D. Del. Aug. 7, 2017). "'Substantial' evidence is such relevant evidence from the record taken as a whole as might be accepted by a reasonable mind as adequate to support the finding under review." *Id.*

B. Motion for a New Trial Under Rule 59(a)

A new trial may be granted "on all or some of the issues … after a jury trial . . . ." Fed. R. Civ. P. 59(a). "New trials are commonly granted where 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 . . . ." *Idenix Pharm. LLC v. Gilead Scis., Inc.*, No. 14-846-LPS, 2018 WL 922125, at *4 (D. Del. Feb. 16, 2018) (quotation omitted). In considering a Rule 59 motion, the "court need not view the evidence in the light most favorable to the verdict winner, a distinction from similar motions under Rule 50." *McMillan v. Weeks Marine, Inc.*, 478 F. Supp. 2d 651, 655 (D. Del. 2007).

C. Evidentiary Standard

"'[W]hen an expert opinion is not supported by sufficient facts to validate it in the eyes of the law, or when indisputable record facts contradict or otherwise render the opinion unreasonable, it cannot support a jury's verdict.'" *Sprint*, 2015 WL 4720576, at *5 (quoting *Brooke Grp. Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 242 (1993)). "[T]he Court should give credence to the evidence favoring the nonmovant as well as that evidence supporting the moving party that is uncontradicted and unimpeached, at least to the extent that evidence comes from disinterested witnesses." *Imperium IP Holdings (Cayman), Ltd. v. Samsung Electronics Co., Ltd.*, 2019 WL 404570, *5 (Fed. Cir. Jan. 31, 2019) (quoting *Reeves v. Sanderson Plumbing Prods.*, 530 U.S. 133, 151 (2000)).

II. The Undisputed Record Shows that Non-Random Lysine Conjugation of Factor VIII, as Required by the Court's Claim Construction, Is Not Enabled

In seeking to exclude others from practicing the conjugates encompassed by the '520 patent claims, Bayer was required to teach the public how to make and use the full scope of the claims. Bayer seeks to exclude others from practicing "non-random" lysine, as well as cysteine, conjugation of Factor VIII. But there is no support whatsoever in the patent for non-random lysine conjugation of Factor VIII. Inventors who testified at trial admitted they did not know how to achieve it. The '520 patent claims cannot, as a matter of law, be so broad so as to encompass what it does not teach and the inventors did not know how to achieve.

The enablement requirement of 35 U.S.C. § 112 requires that a patent's specification "teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Trs. of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1362 (Fed. Cir. 2018) (citations omitted). Enablement is a question of law with underlying questions of fact. *Id.* at 1361. "The inquiry is whether the patent's specification taught one of skill in the art how to make [the invention] without undue experimentation as of the patent's effective filing date." *Id.* at 1363. Informative factors ("*Wands* factors") are: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

The record cannot support the jury's verdict of enablement. The nature of the '520 patent's alleged invention is "non-random" conjugation of Factor VIII (*Wands* factor 4). Bayer asserts a claim scope that is broad enough to encompass "non-random" lysine conjugation on Factor VIII (*Wands* factor 8). But the '520 patent does not disclose—and the inventors conceded

they did not know how to achieve—"non-random" conjugation at lysines on Factor VIII (*Wands* factors 1, 2, and 3). The '520 patent is not only silent on "non-random" lysine conjugation of Factor VIII, but teaches against it as a way to achieve the purportedly novel aspects of its invention (*Wands* factor 5, 6, and 7). Bayer presented no evidence that knowledge in the art may substitute for the inadequacy of the '520 patent's disclosure. The only conclusion supported by this record is that the '520 patent is invalid for lack of enablement.

A. The '520 Patent Inventors Did Not Know How to Achieve "Non-Random" Lysine Conjugation of Factor VIII

"[A]s part of the *quid pro quo* of the patent bargain, the applicant's specification must enable one of ordinary skill in the art to practice the full scope of the claimed invention." *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). Claim scope "'must be less than or equal to the scope of the enablement' to 'ensure[] that the public knowledge is enriched by the patent specification … .'" *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008). "This important doctrine prevents both inadequate disclosure of an invention and overbroad claiming that might otherwise attempt to cover more than was actually invented." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012).

Bayer "created its own enablement problem" here by asserting a claim scope that is broader than what its inventors knew how to achieve. *See Boston Univ.*, 896 F.3d at 1365. "If an inventor attempts but fails to enable his invention in a commercial product that purports to be an embodiment of the patented invention, that is strong evidence that the patent specification lacks enablement." *Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1319 (Fed. Cir. 2007). An inventor's "failures to make and use the later claimed invention at the time of the application," including because "he did not know how to achieve" it, is evidence of non-enablement. *AK Steel*, 344 F.3d at 1244; *MagSil Corp.*, 687 F.3d at 1382; *see also Liebel-Flarsheim Co. v.*

Medrad, Inc., 481 F.3d 1371, 1379-80 (Fed. Cir. 2007) (affirming non-enablement where the inventors deemed a later-claimed embodiment "too risky" to pursue); *Nat'l Recovery Techs., Inc. v. Magnetic Sys., Inc.*, 166 F.3d 1190, 1197-98 (Fed. Cir. 1999) (affirming non-enablement where the inventors "did not know particularly how to do" the later-claimed embodiment).

The '520 patent inventors only achieved "non-random" conjugation of Factor VIII by PEGylating at a cysteine (but not at a lysine). Inventor Pan testified that he used a method that conjugated PEG at a single cysteine site on Factor VIII. (Tr. 965:19-967:18; 983:22-984:21; DTX 565.50; Tr. 988:5-18; DTX 3.38.) Inventor Murphy confirmed that "all of the examples refer to using cysteine" for conjugation. (Tr. 379:19-22; *see also* Tr. 994:17-20 (Pan).) The inventors' testimony is borne out by the patent's specification, which teaches conjugation at a single cysteine site that is either: (1) native to Factor VIII (JTX 1 col.22 ll.51-55; Tr. 983:22-984:21 (Pan)); or (2) introduced by mutation. (JTX 1 col.11 ll.15-45, Table 1).

Neither Bayer nor the inventors knew how to achieve "non-random" conjugation by PEGylating Factor VIII at lysines. According to the patent, the "conjugates of the invention are advantageous over the prior art conjugates that had random polymer attachments to FVIII." (JTX 1 col.8 ll.21-23.) Specifically, the conjugates of the invention "maintain substantial FVIII activity" and "allow[] for a uniform product rather than the heterogeneous conjugates produced in the art by random polymer coupling." (JTX 1 col.8 ll.23-30.). Bayer had undertaken some effort in the 1990's to PEGylate Factor VIII at lysines, but that effort failed to produce the "advantageous" characteristics of the '520 patent's conjugates.[2] (Tr. 208:19-209:23; DTX 745.2; Tr. 274:14-275:9, 957:1-958:1, 958:24-959:2.)

[2] In an October 2005 memo, Dr. Pan explained that "[a]ll previous attempts at PEGylating Factor VIII" disclosed in the literature for lysine PEGylation were "random PEGylation and not controlled." (Tr. 989:2-990:18 (citing DTX 745.2).)

Lead inventor Pan confirmed that the '520 patent inventors did not know how to achieve lysine conjugation as a way to "non-randomly" PEGylate Factor VIII. In early 2004, Dr. Pan was added to the "KGN project" team at Bayer, based on his previous PEGylation experience. (Tr. 958:24-959:7.) In March 2004, Dr. Pan proposed a "site-specific" strategy for PEGylation of Factor VIII that did not involve lysine conjugation. (Tr. 965:19-967:18; DTX 724). This strategy conjugated at cysteines and ultimately resulted in the '520 patent. (Tr. 993:13-994:23; JTX 1.) When asked about lysine PEGylation of Factor VIII, Dr. Pan testified:

> Q: Did you ever consider lysine PEGylation as an option for meeting the goals of the KG-N project?
> A: ***I didn't think it was possible.***
>
> * * *
>
> Q: Why is it you never used lysine PEGylation?
> A: Well, if you look at a lot of what I wrote in the proposal background and also a lot of that in the patent application, I really thought especially for Factor VIII, such a complex protein with so many ***lysines, it would not be a feasible way to make that work***.

(Tr. 972:11-13, 973:3-8 (emphasis added), 957:1-19.) Accordingly, the "non-random" lysine conjugation that Bayer now claims was deemed not feasible by the patent's lead inventor.

B. The '520 Patent Is Silent on "Non-Random" Lysine Conjugation of Factor VIII and Teaches Against Conjugation of Factor VIII at Lysines

Bayer should not be permitted to exclude others from practicing what its inventors did not know how to achieve and what its patent fails to disclose. The '520 patent does ***not*** mention "non-random" lysine conjugation of Factor VIII in ***any*** way. "[W]hen there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). The patent refers to lysine conjugation of Factor VIII only in the "Background" section, which teaches that it is "random" and "problematic." (JTX 1 col.3 l.50-col.4 l.20.) Knowledge of "random" lysine conjugation cannot "substitute for a basic enabling

disclosure" of "non-random" lysine conjugation. *See Genentech*, 108 F.3d at 1366. If Bayer "wanted to exclude others from ["non-random" lysine conjugation of Factor VIII], its patent needed to teach the public how to make and use that invention." *Boston Univ.*, 896 F.3d at 1365.

The '520 patent provides no direction, no guidance, and no examples whatsoever of non-random lysine conjugation of Factor VIII. Inventors Murphy and Pan conceded that there is no information anywhere in the patent about non-random lysine conjugation of Factor VIII:

> Q: Isn't it also true, Dr. Murphy, that the patent does not provide any examples about using lysines for site-specific or non-random conjugation?
> A: Yes, that's true.
>
> * * *
>
> Q: Is there anything in this patent that you're aware of that talks about PEGylating lysines in a non-random way?
> A: Not in this patent.

(Tr. 379:8-11, 379:25-380:3 (Murphy); Tr. 994:17-20 (Pan).) Inventor testimony is unanimous: non-random lysine conjugation of Factor VIII is not taught by the patent.

Testimony by Bayer's expert highlights the inadequacy of the '520 patent's disclosure. A specification's detailed disclosure for only one of two "distinctly different" claimed embodiments supports a conclusion of non-enablement. *See Automotive Techs. Intern., Inc. v. BMW of N. Am.*, 501 F.3d 1274, 1285 (Fed. Cir. 2007). The '520 patent teaches a process to "non-randomly" conjugate Factor VIII at one type of amino acid (cysteine) and not any others (particularly, lysine). As Dr. Ravetch explained, "[n]ot all amino acids behave the same way and different amino acids have different reactivities under different conditions so some amino acids are more amenable than other amino acids for modification." (Tr. 1343:1-15.) The '520 patent's silence on any way to "non-randomly" conjugate Factor VIII at an amino acid other than cysteine further evidences non-enablement.

The ’520 patent is not only silent on “non-random” lysine conjugation of Factor VIII, but specifically teaches against lysine conjugation as a way to achieve the “non-random” conjugates of the invention. “A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017). “[W]here the specification teaches against a purported aspect of an invention, such a teaching is ‘itself evidence that at least a significant amount of experimentation would have been necessary to practice the claimed invention.’” *Liebel-Flarsheim*, 481 F.3d at 1379; *see also AK Steel*, 344 F.3d at 1244-45.

Here, the patent’s only teaching of lysine conjugation of Factor VIII is that it produces what the invention seeks to avoid. The conjugates of the invention are conjugated “non-randomly,” thereby avoiding: (1) loss in activity; and (2) heterogeneity. (JTX-1 col.8 ll.21-30.) But the patent’s ***only*** description of lysine conjugation of Factor VIII is that it produces: (1) loss in activity; and (2) “enormous heterogeneity.” (JTX 1 col.3 l.50-col.4 l.1; *see also* Tr. 377:11-379:7 (Murphy).) In fact, examples “change[d]” the conjugation site from lysine (K) to cysteine (C) as a way to achieve the purported invention. (JTX 1 col.11 ll.39-45, Table 1.) That the patent teaches lysine conjugation of Factor VIII only as a method to be avoided in order to achieve the “non-random” conjugates of the invention is itself evidence of non-enablement.

Testimony by the ’520 patent’s inventors is consistent in associating lysine PEGylation of Factor VIII with the problems of “random” conjugation. According to inventor Murphy, lysine PEGylation of Factor VIII “results in random PEGylation since there are generally multiple potential attachment sites.” (Tr. 380:4-382:19 (DTX 1347).) Lead inventor Pan agreed that, because the location of lysines on Factor VIII presents “several hundreds of possibilities, you

can't really control where the PEG goes." (Tr. 966:23-967:2.) As a result, lysine PEGylation of Factor VIII "invariably" results in "enormous heterogeneity" and loss of activity. (Tr. 983:4-21, 989:24-990:10, 992:4-14; JTX 1 col.4 ll.7-16.)

C. Bayer Presented No Evidence To Sustain the Jury's Verdict of Enablement

There can be no enablement where, as here, claim scope extends to embodiments that the inventors did not know how to achieve, and that the patent teaches against. "The specification's reference that teaches away… combined with testimonial evidence that [it] could not have been produced at the time of filing, supports [a] conclusion that the specification fails to fulfill the enablement requirement of § 112." *Liebel-Flarsheim*, 481 F.3d at 1380; *see also AK Steel*, 344 F.3d at 1244-45. The undisputed record showed that none of the *Wands* factors weigh in favor of enablement, and Bayer's experts identified none.

Bayer's rebuttal witness on non-enablement, Dr. Ravetch, ***never*** actually opined that ***non-random*** lysine conjugation of Factor VIII is enabled. (Tr. 1341:25-1343:23.) He did not dispute Defendants' expert Dr. Zalipsky's testimony that the '520 patent is not enabled because "there is no such description" in it for non-randomly conjugating lysines on Factor VIII and, based on 30 years of PEGylation experience, to his knowledge "there is no such methodology." (Tr. 1211:3-1212:11; 1190:18-1192:19.) Defendants' invalidity evidence is "'uncontradicted and unimpeached.'" *See Imperium*, 2019 WL 404570, *5 (quoting *Reeves*, 530 U.S. at 151).

Dr. Ravetch presented no evidence that knowledge in the art may substitute for the inadequacy of the '520 patent's disclosure. Section "112 requires that, unless the information is well known in the art, the application ***must*** contain this information; it is not sufficient to provide it only through an expert … ." *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991) (emphasis added). Here, Dr. Ravetch provided ***no*** opinion on whether ***non-random*** lysine conjugation of Factor VIII was known (much less "well known") or any experimentation was needed to achieve

it. He pointed only to the '520 patent's "mention" of lysine PEGylation (Tr. 1342:20-21)—ignoring that such "mention" is only in the "Background" section, which describes it as "random" for Factor VIII. (JTX 1 col.3 l.50-col.4 l.20.) There is no evidence whatsoever that "non-random" lysine conjugation of Factor VIII was known in any way at the time.

Dr. Ravetch testified merely that lysine PEGylation was generally known in the art. (Tr. 1342:17-21.) But "[a] patent 'cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification." *Idenix*, 2018 WL 922125, at *10 (quoting *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010)) (granting JMOL of non-enablement). In *Genentech*, where Dr. Ravetch was also an expert, his reliance on only what was known in the art "ignore[d] the essence of the enablement requirement." 108 F.3d at 1365-66. While "'a specification need not disclose what is well known in the art,'" such "gap-filling is merely supplemental; it cannot substitute for a basic enabling disclosure." *Boston Univ.*, 896 F.3d at 1364 (citing *Genentech*, 108 F.3d at 1366).

If the '520 patent intended to claim "non-random" lysine conjugation of Factor VIII, "it would have been expressly disclosed in the specification and in the usual detail." *See Genentech*, 108 F.3d at 1367. It is undisputed that there is no such disclosure, nor was it known in the art. The evidence at trial, "was not enough to take the question to the jury," and the '520 patent is not enabled as a matter of law. *See Imperium*, 2019 WL 404570, at *11 (reversing post-verdict JMOL denial, and finding invalidity based on uncontradicted evidence).

III. The Undisputed Record Shows that Adynovate® Does Not Infringe

Infringement of the asserted claims requires a conjugate that (1) is "isolated" ("conjugation was not random"), (2) has Factor VIII with "SEQ ID NO:4" (2,332 amino acids including the entire B-domain) and (3) has PEG "attachment at the B-domain" ("such that the

resulting conjugate retains [] activity"). (D.I. 200.) The evidence shows none of these limitations are met, and the jury's infringement verdict cannot be sustained.

A. The Record Cannot Support a Finding That Adynovate® Is a Claimed "Isolated" Conjugate Because Its Conjugation Is Undisputedly Random

The '520 patent, its inventors, and Bayer's own experts agree that random conjugation is a type of conjugation that involves multiple potential amino acid sites for attachment. There is no dispute that, in Adynovate®, PEG attaches to Factor VIII at multiple (at least 55) potential amino acid sites. This undisputed evidence contradicts the jury's verdict of infringement.

The '520 patent and its inventors equate random conjugation with conjugation that occurs at multiple amino acid sites on Factor VIII. It describes lysine conjugation of Factor VIII as a "random approach" because there are multiple lysine sites on Factor VIII. (JTX 1 col.3 l.50-col.4 l.1.) Inventor Murphy described lysine conjugation of Factor VIII as resulting in "random PEGylation since there are generally multiple potential attachment sites," and therefore "PEG is likely to be attached to different sites." (Tr. 380:4-382:19 (citing DTX 1347); *see also* Tr. 966:23-967:2, 983:4-21 (Pan).) In contrast, inventor Pan described that his invention of "site-specific" conjugation of Factor VIII has only a single amino acid site for attachment. (Tr. 965:19-967:18 (DTX 724); Tr. 983:22-984:21 (DTX 565).)

The undisputed record shows that Adynovate®'s conjugates have PEG attached at multiple amino acid sites. Based on the "Site Analysis Report" that Baxalta submitted to the FDA, samples of the lysine-targeting conjugation to make Adynovate® show attachment of PEG to at least 55 sites throughout Factor VIII: of the 55 sites, 20 could not be identified to a specific amino acid site, and 2 amino acid sites are not even lysines. (Tr. 895:4-896:6 (Mitterer), 1043:16-1045:6 (Walensky).) And Bayer's expert, Dr. Ploegh, conceded that not all of the PEGylation sites have even been identified. (Tr. 467:12-18.) Peptide mapping of Adynovate®

also shows conjugation over multiple sites with no preference for any particular site. (Tr. 1200:23-1202:14 (citing DTX 50) (Zalipsky).) Bayer's expert Dr. Ravetch conceded that peptide mapping of Adynovate® shows the conjugation is "random." (Trial. Tr. 625:12-626:8 (citing DTX 43).) The undisputed multiple potential attachment sites in Adynovate®, some of which have yet to be identified and are not the intended sites, evidences its random conjugation.

Bayer's experts do not dispute that where—as in Adynovate®—conjugation occurs at multiple amino acid sites, such conjugation is random. Dr. Ravetch conceded that conjugation (the "chemical[] attach[ment]" of PEG to Factor VIII (Tr. 529:5-8)) in Adynovate® is random based on the attachment of PEG at multiple lysine sites in the B-domain of Factor VIII:

> A: They're referring to the random PEGylation that goes within the B-domain. They're saying not every lysine could be identified through their [peptide] mapping approach. They couldn't define each specific lysine that was PEGylated in the B-domain, but they knew it was ***random*** within the B-domain.
> Q: It says random PEGylation, right?
> A: Within the B-Domain.
>
> * * *
>
> Q: … So you at least agree within the B-Domain, the PEGylation is random, right?
> A: ***Well, that's what they're saying. They couldn't identify each PEG attached to lysines within the B-Domain.***
>
> * * *
>
> Q: … A Bayer scientist … [wrote] Baxter, which is Baxalta, their random PEGylation particularly on the B-domain. … Did you consider that in forming your opinion?
> A: It's consistent with my opinions.
> Q: What, that the PEGylation is ***random*** at least in the B-Domain?
> A: ***Correct***.

(Tr. 619:23-620:6, 626:5-8, 652:7-18 (emphasis added) (DTX 1338).) Dr. Ploegh conceded that Adynovate® is made by random conjugation[3] (Tr. 469:1-5):

[3] He also conceded that the specific PEG used in Adynovate® is a standard random PEGylation reagent. (Tr. 457:10-12.)

> Q: So another way of saying a definition [of random] is that PEG may attach at any available site of reaction throughout the protein. We just said a moment ago that in the case of two PEGs attaching to 55 sites in Factor VIII [in Adynovate®], do you recall that you answered that the PEGs may attach at any available site of reaction? Do you recall that?
> A: I do.

(Tr. 469:6-12, 468:4-8.) And Dr. Young's own publication and expert report conceded that Adynovate® is made by "random" conjugation. (Tr. 141:14-143:13 (DTX 870.3), 656:11-657:4; *see also* Tr. 151:7-11.)

The '520 patent's inventors also understood the conjugation in Adynovate® to be random. Dr. Pan wrote that it is made using "non-specific lysine conjugation," which he explained means "random lysine PEGylation." (Tr. 1027:1-16 (DTX 959).) And Dr. Murphy wrote that Baxalta was "doing random [conjugation] at lysines." (DTX 738.)

Bayer's representations to the FDA and Bayer's internal documents further support that Adynovate® is made by random conjugation. In a 2017 filing concerning Bayer's Jivi® product, Bayer represented to the FDA[4] that "[a]ll marketed PEGylated products are derived from PEGylation targeting amine [groups], either randomly distributed on the surface [if] the target is the ε-amino on the lysine side-chain. . . .", i.e., Adynovate®. (Tr. 655:2-23 (quoting DTX 1332A.10 (JIVIBAYER0016988)), 141:14-25.) And Bayer's VP of Marketing Ms. Restivo conceded that, after a Bayer legal review process, Adynovate® is described made using "random" conjugation. (Tr. 199:2-201:16 (Restivo) (citing DTX 1336.17), 201:21-202:15.) These concessions by Bayer's experts, the inventors, and Bayer scientists all contradict Bayer's positions in this litigation, as well as the jury's verdict of infringement.

[4] Dr. Ravetch asserted that statements to the FDA must be accurate and true to the best of a company's knowledge. (Tr. 527:17-528:3.)

1. Bayer Did Not Rebut Adynovate®'s Random Conjugation Characteristics

The '520 patent describes hallmark characteristics of random PEGylation: heterogeneity and loss of activity. (JTX 1 col.3 l.50-col.4 l.20.) As a consequence of having multiple conjugation sites, random conjugation "invariably produce[s] large amounts of multiply PEGylated products" resulting in "enormous heterogeneity." (JTX 1 col.4 ll.14-20; *see also* col.8 ll.28-30.) By contrast, the '520 patent's non-random conjugation "covalently attach[s] [PEG] at a predefined site" that allows for a "uniform product rather than the heterogeneous conjugates produced in the art by random polymer coupling." (JTX 1 col.8 ll.15-19, ll.28-30.) The '520 patent also describes a substantial loss in activity as a result of "random" conjugation. (JTX 1 col.3 ll.54-57; *see also* Tr. 608:12-18, 645:3-646:4 (Ravetch), 1203:19-24 (Zalipsky).) By contrast, the '520 patent's non-random conjugation "avoid[s] the regions required for biological activity" and, consequently, retains about 100% activity. (JTX 1 col.8 ll.24-26, col.25 ll.38-41, Table 4; Tr. 348:16-25 (Murphy), 1202:20-1203:11 (Zalipsky), 645:13-646:4 (Ravetch).) Inventor Pan confirmed that heterogeneity and loss of activity are characteristics of random PEGylation. (Tr. 968:9-969:11 (citing DTX 724.9), 989:19-990:10 (citing DTX 745.2).)

Adynovate® undisputedly exhibits the characteristics of random conjugation as described in the '520 patent. First, Adynovate® has enormous heterogeneity based on (i) between 2.0 and 3.2 PEGs per molecule of Factor VIII (for an average of 2.6 PEGs), and (ii) PEGs are attached to at least 55 known sites throughout Factor VIII—resulting in tens of thousands of different combinations of PEGylated Factor VIII in each batch. (Tr. 891:19-892:1 (Mitterer), 1200:2-22 (Zalipsky); *see also* Tr. 465:22-468:8 (Ploegh).) This enormous heterogeneity is characteristic

of random conjugation. (Tr. 1198:14-1200:22 (Zalipsky).) Bayer did not dispute that there is such heterogeneity among Adynovate®'s conjugates, and provided no quantitative rebuttal.[5]

The conjugation in Adynovate® also results in a loss of about 50% activity (two-fold loss). (Tr. 889:15-22 (Mitterer), 1203:19-1204:25 (Zalipsky).) Bayer's expert Dr. Ravetch conceded that such activity loss is evidence of random PEGylation:

> Q: How much activity do you lose when you PEGylate a Factor VIII with a random process?
> A: In the '520 patent, they cite that they get a two-fold loss of activity. So half the activity is gone.

(Tr. 608:12-18 (Ravetch).) There is no dispute that Adynovate® exhibits the loss in activity and heterogeneity that—according to the '520 patent—are characteristic of random conjugation.

Finally, Bayer provided no quantitative rebuttal to the calculation of Defendants' expert Dr. Walensky, who calculated the frequency of B-domain versus non-B-domain PEGylation in Adynovate® to be 50/50 and, like a coin toss, further evidences random conjugation.[6] (Tr. 1050:21-1051:6, 1055:12-1057:20.) Dr. Ploegh conceded that he did not know how often the B-domain of the Factor VIII is PEGylated. (Tr. 469:16-25).

2. Bayer Did Not Present Evidence that the Conjugation to Make Adynovate® is Not Random, as Required by the Court's Construction

The evidence presented by Bayer cannot sustain the jury's verdict of infringement. In order to satisfy the "isolated" limitation, Bayer was required to prove that conjugation in Adynovate® is "not random." Instead, Bayer's evidence was based on selective reading from the Adynovate® Site Analysis Report that B-domain PEGylation in Adynovate® is "preferential[]"

[5] The formula used by Defendant's expert was endorsed by a Bayer scientist. (Tr. 920:1-12 (Salzberg), 1167-25-1169:8 (Bossard) (PTX 934 at 1, 2).)

[6] Bayer's expert Dr. Russell testified that a "Western Blot Analysis" supported his opinions regarding Dr. Walenksy's calculation, but such an analysis from Adynovate®'s BLA confirms that "PEGylation of all domains, reflecting the random PEGylation of Factor VIII." (Tr. 1317:12-1318:11 (DTX 48.15).)

and "targeted," based on the percentage of conjugation sites in the B-domain.[7] (Tr. 554:4-555:13 (Ravetch).) But Dr. Ploegh conceded that this is not how often the B-domain is conjugated:

> Q: Does the site analysis report tell you how often the B-Domain is PEGylated in a given vial of Adynovate?
> A: No.

(Tr. 469:13-25 (Ploegh).) Thus, this information cannot support the jury's verdict.

Bayer's evidence that Adynovate®'s manufacturing process is controlled, consistent or reproducible cannot—and does not—prove that its conjugation is "not random." Dr. Ravetch explained that conjugation is simply the chemical attachment of PEG to Factor VIII. (Tr. 529:5-8 (Ravetch).) Bayer's experts Drs. Ploegh and Ravetch agreed that all marketed drugs must be controlled and consistent. (Tr. 470:7-17 (Ploegh), 637:9-14 (Ravetch).) Ploegh conceded that a drug may be FDA approved and still be randomly PEGylated. (Tr. 461:13-17; *see also* JTX 1 col.3 ll.59-62 ("Randomly PEGylated proteins . . . have been approved as therapeutics in the past.").) A controlled and consistent process is not proof of "non-random" conjugation.[8]

Bayer's selective reliance on representations made in Adynovate®'s BLA materials cannot sustain the jury's verdict of infringement. Importantly, ***none*** of them describe the conjugation in Adynovate® as "not random." To the contrary, Baxalta's FDA filing, which Dr. Ravetch "[a]bsolutely" believed to contain true and accurate statements (Tr. 632:10-12) consistently characterize Adynovate® (BAX 855) as made with random conjugation:

[7] The Adynovate® BLA explains that "lysines in the B-domain are preferentially PEGylated" because the B-domain is "more surface exposed" and thus "more accessible." (DTX 38.3.) Dr. Ravetch conceded that the B-domain is "more exposed, in general." (Tr. 636:23-637:2.)

[8] Bayer's argument is further contradicted by the Bossard patent. Bayer's expert Dr. Russell characterized it as teaching random conjugation, yet it teaches ***"[c]ontrol"*** of the conjugation reaction. (Tr. 1295:3-12; DTX 6 col.37 ll.26-34, col.37 l.67-col.38 l.5 (emphasis added).)

- "BAX 855 is manufactured by conjugating rFVIII [Factor VIII] with PEG via a random PEGylation procedure using N-hydroxy-succinimide (NHS) chemistry, which is specific for modification of primary amino groups." (DTX 55.17.)

- "The NHS ester enables the random coupling to accessible lysine residues of the protein backbone." (DTX 38.3; *see also* PTX 446 at 6.)

- BAX 855 "was investigated using a peptide mapping approach. . . . No relevant decrease of peptide intensity was observed for a single peptide upon PEGylation, likely due to the random PEGylation approach." (PTX 441 at 5; *see also* DTX26.5 (same), 43.1.)

- "Results show that the B-domain was modified by PEG and confirm the random PEGylation of BAX 855." (DTX 45.40.)

See also DTX 47.44; 140.13. These statements contradict the jury's verdict of infringement.

Bayer's reliance on Dr. Bossard's statements regarding the control of an undisputably random conjugation cannot support the jury's verdict. (Tr. 538:4-19 (Ravetch).) Discussing a marketing document, Dr. Bossard explained that by controlling conditions, "we don't want them [PEGs] going to all 160 [sic 158] lysines … ." (Tr. 418:25-419:1 (PTX 489).) The term "random" was not used in this document to avoid the "impl[ication], well, [that PEGs] are just going everywhere" to all 158 lysines in Factor VIII. (Tr. 419:6-8 (referencing PTX 489).) But PEG is randomly conjugated over 55 sites, just not all 158 lysines. Dr. Bossard did not testify that Adynovate® is made by non-random conjugation. Thus, this marketing document and related testimony cannot support the jury's verdict.[9] *PharmaStem*, 491 F.3d at 1351.

Nor can the use of particular process conditions, and control thereof, support the jury's verdict. Bayer's expert Dr. Ploegh relied on the use of calcium and other conditions for his opinion that Adynovate®'s process is "targeted." (Tr. 435:15-438:22, 442:8-23.) Dr. Ploegh's

[9] Bayer's counsel also relied on a Baxalta presentation during closing argument. (Tr. 1476:4-22 (PTX 1233 at 11).) Dr. Pan testified about receiving an e-mail with it attached, but neither he nor any witness testified about it. (Tr. 1020:7-18.) Bayer's attorney argument relied on an alleged juxtaposition of "random" and a "controlled" process—not the random conjugation (chemical attachment (Tr. 529:5-8 (Ravetch)) of PEG to 55 sites throughout Factor VIII.

opinions are contradicted by the evidence since the very conditions he relied on resulted in an undisputed 50% loss of activity resulting from conjugation, which is evidence of random conjugation (*supra*). (Tr. 1204:5-1207:1 (DTX 325.16, 325.23).)

Bayer did no testing, and has no evidence that the conjugation in Adynovate® is anything other than random conjugation. Bayer has no evidence that would serve as a baseline of random conjugation for comparison. (Tr. 485:1-5 (Ploegh), 601:23-602:10 (Ravetch).) Adynovate® has the characteristics of the patent's guideposts for the result of random conjugation—heterogeneity and activity loss. Bayer's lack of evidence to the contrary, and mere conclusory assertions cannot sustain the jury's verdict.

3. The Jury's Verdict Rested On Confusion Over the Meaning of "Conjugation That Was Not Random"

If Defendants' Rule 50 motion is not granted, at a minimum, a new trial is necessary based on confusion over the Court's claim construction. The parties tried different understandings of what "not random" means. Bayer's case confused the Court's construction requiring non-random *conjugation* (chemical attachment of PEG) (Tr. 529:5-8 (Ravetch)). Bayer argued that it can be met with a "controlled" and "targeted" process not limited to the actual conjugation (*see* Tr. 1472-1476). As a result, the jury was misled as to what "not random" conjugation means or, at best, was forced to conduct claim construction itself in the face of competing arguments by the parties. This contributed to the jury's verdict being against the evidence. Thus, a new trial with a definition of "not random" conjugation would be warranted to "prevent a miscarriage of justice." *Idenix*, 2018 WL 922125, at *4.

B. The Undisputed Record Cannot Support a Finding That Adynovate® Meets the "SEQ ID NO:4" Term Because There Is No Evidence of PEGylated Factor VIII With 2,332 Amino Acids Including the Entire B-Domain

The '520 patent claims require a "conjugate," where PEG is attached to a Factor VIII that contains "the amino acid sequence of SEQ ID NO:4." As Dr. Ravetch conceded, "SEQ ID NO:4" is a 2,332 amino acid sequence that "contains the entire B-domain." (Tr. 638:14-639:10; JTX 1 col.39-51.) Bayer did not establish that ***conjugates*** in Adynovate® include Factor VIII with 2,332 amino acids, including the entire B-domain. The undisputed evidence shows that less than 10 percent of the Factor VIII starting material (Advate®) (***unconjugated***, i.e., ***without*** PEG attached) has the full 2,332 amino acid sequence including the entire B-domain—but there was ***no*** evidence presented as to whether (and, if so, to what extent) this form of Factor VIII is then ***conjugated*** (i.e., ***with*** PEG attached) and purified, and is ultimately present in Adynovate®. (Tr. 1219:9-1220:3, 1233:9-20 (Zalipsky).) Indeed, Dr. Ploegh conceded that "[t]he major variant" of Factor VIII in Adynovate®'s conjugates is not 2,332 amino acids and is "lacking the B-domain region 1313 to 1648." (PTX 607 at 7; Tr. 476:1- 477:10 (Ploegh).) Bayer's mere reliance on the Adynovate® label is insufficient. (Tr. 1233:4-8 (citing PTX 905 at 3).) "[A]dvertising and other materials [do] not provide a sufficient basis for a finding of infringement," particularly in light of the aforementioned BLA description. *See PharmaStem*, 491 F.3d at 1351. Bayer failed to offer sufficient evidence that Adynovate® contains conjugates with PEG attached at Factor VIII with 2,332 amino acids including the entire B-domain. Therefore, a reasonable jury could not have found "the amino acid sequence of SEQ ID NO:4" element would have been infringed.

1. The Doctrine of Equivalents Is Barred

The jury found literal infringement. Nevertheless, a reasonable jury could not have found equivalence as a matter of law. First, prosecution history estoppel applies because the "SEQ ID NO:4" limitation was added to the claim for patentability. *Duramed Pharm., Inc. v. Paddock*

Labs., Inc., 644 F.3d 1376, 1380 (Fed. Cir. 2011). Original claim 48 did not recite the term; original claim 49 depended from claim 48 and recited "the amino acid sequence of SEQ ID NO:4." (D.I. 62-6 at 31.) Bayer responded to rejections by cancelling original claims 48 and 49, and adding original claim 58 (issued claim 1) that incorporated the limitations of both claims. (D.I. 62-8 at 58-69, 62-11 at 11.) Prosecution history estoppel applies because "SEQ ID NO:4" was added for patentability to overcome a rejection. Second, equivalence is barred under the disclosure-dedication rule. The '520 patent discloses processing variants of Factor VIII that are less than 2,332 amino acids. (JTX 1 col.9 ll.43-46.) But Bayer chose not to draft the claims to cover such processing variants. Instead, Bayer drafted the claims as expressly requiring "SEQ ID NO:4." "[W]hen a patent drafter discloses but declines to claim subject matter . . . this action dedicates that unclaimed subject matter to the public." *Johnson & Johnson Assoc. Inc. v. R.E. Serv. Co. Inc.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002) (en banc). Bayer dedicated conjugates with Factor VIII processing variants to the public, and cannot recapture them now.

C. The Undisputed Record Cannot Support a Finding That Adynovate® Meets the "B-Domain" Term Because Activity Is Lost Resulting From Conjugation

The "at the B-domain" limitation requires "attachment at the B-domain ***such that the resulting*** conjugate retains functional factor VIII activity." (D.I. 200 (emphasis added).) The '520 patent defines a "[f]unctional factor VIII polypeptide" as requiring that the "functional activity ***remains unaffected in kind***." (JTX 1 col.9 ll.50-55 (emphasis added).) It says that the invention "maintain[s] ***substantial***" activity. (JTX 1 col.8 ll.23-26 (emphasis added).) Table 4 shows that the activity of non-randomly PEGylated Factor VIII compared to unPEGylated Factor VIII was about 100%. (JTX 1 col.25 ll.38-41, Table 4; Tr. 1202:20-1203:11 (Zalipsky).) In other words, the result of the conjugation (chemical attachment of PEG) is that activity is unaffected. Inventor Murphy explained that the patent resulted in 100% of the activity being

retained after non-random conjugation. (Tr. 348:16-25 (Murphy).) Dr. Ravetch conceded that, in the context of the '520 patent, "retaining activity means that there's ***no substantial difference*** between unPEGylated and PEGylated Factor VIII when it's done at the B-Domain in terms of activity." (Tr. 645:13-646:4 (Ravetch) (emphasis added).) In contrast, Dr. Ravetch conceded that 50% activity loss is evidence of random PEGylation. (Tr. 608:12-18.)

The undisputed evidence is that Adynovate® loses about 50% activity as a result of conjugation and, thus, does not "remain unaffected." (Tr. 889:15-22 (Mitterer), 1203:19-1204:25 (Zalipsky).) Bayer relies on requests for admission that Adynovate® retains functional factor VIII activity. (Tr. 899:9-900:11.) There is no dispute that Adynovate® has activity and can treat patients. But the "resulting conjugate" after PEGylation in making Adynovate® has a substantial difference in activity (about 50% loss), and does not "remain[] unaffected," as required by the '520 patent. (JTX 1 col.9 ll.50-55.) Thus, a reasonable jury could not have found that Adynovate® infringes the "at the B-domain" limitation.

IV. The Record Supports That the '520 Patent Is Invalid for Obviousness

Obviousness under 35 U.S.C. § 103(a) is a legal determination that depends on "factual questions relating to the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations." *PharmaStem*, 491 F.3d at 1359. "District courts cannot accept a jury's finding that motivation is lacking when the motivation is evident in the prior art references themselves or a matter of common sense." *L-3 Commc'ns Corp. v. Sony Corp.*, No. 10-734, 2014 WL 4674815, at *3 (D. Del. Sept. 12, 2014).

The '520 patent's claims must be interpreted the same way for validity as for infringement. *Amazon.com v. Barnesandnoble.com*, 239 F.3d 1343, 1351 (Fed. Cir. 2001). If the jury's finding of infringement is sustained, then the '520 patent claims are no different from

the Factor VIII conjugates taught by Bossard and/or communicated to the '520 patent inventors by Dr. Bossard prior to the date of invention. (Tr. 1212:12-1217:21 (Zalipsky).) Therefore, judgment that the '520 patent is invalid as obvious is proper.

A. Knowledge in the Art Would Have Motivated a POSA to Conjugate at the B-Domain of Factor VIII

As the '520 patent acknowledges, one of ordinary skill would have been motivated to avoid the "problematic" loss of activity that resulted from "random" conjugation. (*See* JTX 1 col.3 l.4-col.4 l.20.) "Admissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness." *PharmaStem*, 491 F.3d at 1362. It was known that the inability to control the conjugation "site" on Factor VIII resulted in activity loss. (*See* JTX 1 col.3 l.4-col.4 l.20; *see also* DTX 6 col.3 ll.34-38.) It was also known that the B-domain of Factor VIII was "dispensable" in retaining activity. (JTX 1 col.1 ll.41-44.) Finally, it was known that the B-domain consisted of over 800 amino acids and multiple potential sites for conjugation, including more than half of the 158 lysine sites. (*See* JTX 1 col.3 ll.63-65.)

A POSA would have been motivated to apply the teachings of the Bossard patent (DTX 6) to conjugate at the B-domain of full-length Factor VIII. Bossard teaches conjugation at "desired" sites on Factor VIII, including lysine and cysteine sites. Bossard discloses the amino acid sequence for full-length Factor VIII (SEQ. ID. NO:2),[10] including the number and location of native lysines and cysteines. (DTX 6 col.49-71.) For the native full-length Factor VIII, Bossard identifies "158 amine-containing lysine residues" and methods for conjugation at those sites. (DTX 6 col.16 ll.41-46, Example 6.) Bossard also identifies thiol-containing cysteine residues and methods for conjugation at those sites. (DTX 6 col.28 ll.41-45, Example 7.)

[10] Bossard discloses a Factor VIII with 2,332 amino acids ("SEQ ID NO:2" in Bossard), which is the same as the 2,332 amino acid SEQ ID NO:4 or an allelic variant thereof claimed by the '520 patent. (*Compare* DTX 6.38 (SEQ ID NO:2) *with* JTX 1 at 63 (SEQ ID NO:4).)

Finally, Bossard teaches that the activity of its conjugates is in a range of 50% and 100% relative to unmodified Factor VIII. (DTX 6 col.15 ll.56-61, col.16 ll.6-17.)

B. The Bossard Work Provided a Reasonable Expectation of Success in Conjugation at the B-Domain and Retaining Activity

Prior to November 14, 2005, the '520 patent inventors had received Factor VIII conjugates and information about those conjugates from Dr. Mary Bossard and others at Nektar (the "Bossard Work") under a Research Agreement that was executed on December 11, 2003. The Bossard Work is prior art under 35 U.S.C. § 102(f). "[S]ubject matter derived from another not only is itself unpatentable to the party who derived it under § 102(f), but, when combined with other prior art, may make a resulting obvious invention unpatentable to that party under a combination of §§ 102(f) and 103." *OddzOn Prods. v. Just Toys*, 122 F.3d 1396, 1403-04 (Fed. Cir. 1997). The Bossard Work gave the '520 patent inventors a reasonable expectation of success in conjugating the B-domain of Factor VIII and retaining its activity.

The '520 patent inventors received the Bossard Work in installments. (Tr. 224:3-25, 269:2-270:9; JTX 3.) Inventor Pan was Bayer's point of contact under the Agreement. (Tr. 961:7-12.) After receiving samples from Dr. Bossard and others at Nektar, he circulated them to the other '520 patent inventors. (Tr. 963:10-964:2, 975:2-10; DTX 723.1; DTX 1001.1.)

By March 24, 2004, the Bossard Work included Factor VIII PEGylated at the B-domain. Inventor Pan received the first set of results from Nektar's PEGylation reactions on B-domain deleted Factor VIII from Dr. Bossard in February 2004. (Tr. 961:13-963:9; DTX 705.) They showed "very little, if any" PEGylation at cysteines on B-domain deleted Factor VIII. (Tr. 962:25-963:6; DTX 705.7.) By March 24, 2004, Dr. Bossard had sent the next set of results, this time from Nektar's PEGylation reactions on full-length Factor VIII. (Tr. 973:13-975:1; DTX 787.) Inventor Pan deduced from the Bossard Work that "because we did see PEGylation with

full length and not with the B-domain [deleted], PEGylation must be happening in one of four cysteines or some of the four cysteines in the B-domain." (Tr. 975:2-976:19; DTX 1001.4; *see also* Tr. 976:20-977:5; DTX 756.4.)

By April 23, 2004, the Bossard Work included Factor VIII PEGylated at the B-domain with retained activity. After receiving samples from Nektar's lysine-PEGylation and cysteine-PEGylation reactions on Factor VIII (both B-domain deleted and full-length versions), inventor Pan analyzed "functional activity assays" conducted on the samples. (Tr. 960:16-961:1.) These results showed that the conjugates retained activity, and that PEGylation at lysines was "likely in the B-domain," due to a relatively higher retention of activity.[11] (DTX 666-4; DTX 1001.4.) The Bossard Work therefore gave the '520 patent inventors a reasonable expectation of success in site-specific PEGylation at the B-domain of Factor VIII with retained activity.

C. Bayer's Alleged Secondary Considerations Do Not Support a Finding of Non-Obviousness

The evidence does not support Bayer's assertion that PEGylating the B-domain led to the "surprising" result that activity was retained. As discussed *supra*, it was known that the B-domain has no functional role. It would have come as no surprise, then, that PEGylation at the B-domain does not interfere with activity. Indeed, inventor Pan testified "that's actually not so surprising." (Tr. 1009:2-17.) And Dr. Zalipsky agreed. (Tr. 1217:22-1218:5.)

The evidence does not support Bayer's assertion that the claimed conjugates show an increase in half-life. (JTX 1, col.28 ll.5-6, Fig. 20; Tr. 1092:21-1093:22, 1095:25-1097:24, 1099:15-1101:7, 1218:6-17.) Bayer's pharmacokinetic scientist Dr. Newgren concluded, based on the same data as in the '520 patent (and Defendants' experts Drs. Thakker and Zalipsky

[11] Dr. Ravetch conceded that the B-domain is "more exposed, in general." (Tr. 636:23-637:2.)

agreed) that they show "no significant differences" in half-life. (DTX 740 (*compare* with JTX 1, Fig. 20); Tr. 1092:21-1093:22, 1095:25-1097:24, 1099:15-1101:7, 1218:6-17.)

V. The Evidence Presented by Bayer and Dr. Addanki Cannot Support the Jury's Damages Award

Bayer's damages expert, Dr. Sumanth Addanki, pressed a ***single*** reasonable royalty rate throughout discovery—23.75%, or the midpoint between 5.1% and 42.4%. (D.I. 252.1, Addanki Op. ¶¶ 12, 69-70.) The Court precluded Dr. Addanki from presenting his one-and-only reasonable-royalty rate to the jury because he failed "to tie the 50/50 split to the facts of this case." (D.I. 372 at 15-16.) The Court's *Daubert* ruling prohibited Dr. Addanki from presenting any proposed royalty rate and left Bayer with no legally cognizable royalty opinion to offer, let alone an opinion sufficient to satisfy Bayer's burden of proof on damages. *See Exmark Mfg. Co. v. Briggs & Stratton Power Prods. Grp., LLC*, 879 F.3d 1332, 1350 (Fed. Cir. 2018) ("When performing a Georgia-Pacific analysis, damages experts must not only analyze the applicable factors, but also carefully tie those factors to ***the proposed royalty rate***.") (emphasis added).

Dr. Addanki did not opine in his expert reports on any reasonable royalty other than the excluded 23.75%. But at trial, he offered a ***new*** opinion that a reasonable royalty could be anything between 5.1% and 42.4%. Bayer waived its right to pursue alternative royalty rates by deliberately advancing Dr. Addanki's single legally invalid theory during discovery. *Promega Corp. v. Life Techs. Corp.*, 875 F.3d 651, 666 (Fed. Cir. 2017) ("A patent owner may waive its right to a damages award when it deliberately abandons valid theories of recovery in a singular pursuit of an ultimately invalid damages theory."). The Court should enter judgment as a matter of law under Rule 50(b) that Bayer is entitled to at most nominal damages because Bayer's only damages witness was precluded from providing any reasonable royalty evidence upon which the jury could base an award. *See Apple Inc. v. Motorola, Inc.*, 757 F.3d 1286, 1328 (Fed. Cir. 2014)

(citing *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 895 F.2d 1403, 1407-08 (Fed. Cir. 1990) (affirming nominal $10,000 reasonable royalty because patentee failed to provide sufficient evidence to support a greater award). Alternatively, a new trial is warranted as the evidence does not support more than a 1% royalty.

A. After Having Its One and Only Damages Theory Stricken, Bayer Repeatedly Invited the Jury to Improperly Speculate as to an Appropriate Royalty

"The burden of proving damages falls on the patentee." *Lucent Tech., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1324 (Fed. Cir. 2009). Bayer neglected its burden by repeatedly telling the jury that it could choose any royalty up to 42.4% of Baxalta's sales revenue—which represents 100% of the profit that Bayer asserts Baxalta realized by selling Adynovate® (*infra* § VI.C.1.).

For example, Bayer explicitly advised the jury to pick any rate up to 42.4%:

> Now, what you're going to hear from Dr. Addanki – and this decision is up to you, he's going to tell you that ***you can pick a reasonable royalty rate in a range up to 42 percent*** of their revenues – up to 42.4 percent of their revenues.

(Tr. 66:14-18 (emphasis added).) Dr. Addanki followed counsel's lead and told the jury that "***anything*** between those two points [5.1% and 42.4%] is a number that's at least a feasible royalty rate." (Tr. 747:22-25 (emphasis added).) And just before concluding Dr. Addanki's direct examination, Bayer presented an animated demonstrative exhibit with an arrow moving back and forth between 5.1% and 42.4%—again misleadingly suggesting to the jury that it could arbitrarily pick any royalty in that range. (Tr. 797:16-20; PDX 7.22; *see* PDX 10.112.) Although the Court told Bayer to take down the exhibit because it was "unrelated to what he's testifying about," (Tr. 798:15-17) the jury was left with the indelible impression that it could assess damages by, in Bayer's own words, "pick[ing] a reasonable royalty rate in a range up to 42 percent" (Tr. 66:14-18). During its closing, Bayer repeated the same prejudicial directive and displayed a similar misleading demonstrative:

> What I'm asking you for is to award Bayer the highest amount that you conclude is reasonable up to 42.4 percent.

(Tr. 1578:21-23; PDX 10.112; *see also* Tr. 1517:15-23, 1507:16-25.)

Dr. Addanki's cursory reference to the *Georgia-Pacific* factors cannot cure Bayer's failure of proof. *See Whitserve, LLC v. Computer Packages, Inc.*, 694 F.3d 10, 31 (Fed. Cir. 2012) ("[S]ome explanation of both why and generally ***to what extent*** the particular factor impacts the royalty calculation is needed." (emphasis added)). Dr. Addanki failed to explain how and to what extent the *Georgia-Pacific* factors would affect the royalty. (*See* Tr. 793:13-797:15.) Nor could he. *First*, he could not tie the *Georgia-Pacific* factors to a proposed rate because he was precluded from presenting a proposed rate. *Second*, Dr. Addanki conceded during discovery that none of the *Georgia-Pacific* factors would raise or lower his royalty opinion. (Tr. 6:9-18; D.I. 252.6, Addanki Dep. 175:10-22.)

In sum, the jury's 17.78% royalty was not supported by any evidence. It was not proposed, referenced, or alluded to by anyone. After having its only royalty value excluded by the Court's *Daubert* ruling, Dr. Addanki could not provide the jury with any specific royalty value or explain how the jury should use the information presented by the parties to arrive at a specific royalty value. Instead, Bayer presented an unsubstantiated range of royalties and—without any specific guidance—told the jury to "pick a reasonable royalty rate" from within that range. (Tr. 66:14-18.) This alone entitles Baxalta to judgment as a matter of law or a new trial on damages because "[d]amages must not be left to conjecture by the jury. ***They must be proved, and not guessed at***." *Promega*, 875 F.3d at 660 (emphasis added); *Philip v. Nock*, 84 U.S. 460, 462 (1873) (superseded on other grounds); *Riles v. Shell Exploration & Prod. C*o., 298 F.3d 1302, 1311 (Fed. Cir. 2002) ("To prevent the hypothetical from lapsing into pure

speculation, [the Federal Circuit] requires sound economic proof of the nature of the market and ***likely outcomes*** with infringement factored out of the economic picture." (emphasis added)).

B. Before Trial, Neither Bayer Nor Dr. Addanki Had Ever Opined That 5.1% to 42.4% Constituted a Range of Reasonable Royalties or That Bayer Would Have Had Greater Bargaining Power in a Hypothetical Negotiation

The "hypothetical negotiation" approach for calculating a reasonable royalty—the only damages theory pursued by Bayer—"attempts to ascertain the royalty upon which the parties would have agreed had they successfully negotiated an agreement just before infringement began." *Lucent*, 580 F.3d at 1324. Bayer and Dr. Addanki irreparably biased the jury's damages analysis by presenting what Dr. Addanki incorrectly calls "the end points of the bargaining range" as viable royalty options. Bayer's 5.1% and 42.4% "end points," however, are not, as a matter of law, reasonable royalties, and were never identified as such during expert discovery.

Dr. Addanki's expert reports disclose only ***one reasonable royalty*** (23.75%):

> I conclude that a reasonable royalty for Baxalta's and Nektar's alleged infringement of the '520 patent through the trial in this case is 23.75 percent of the net revenues that Baxalta earns from its sales of Adynovate.

(*See, e.g.*, D.I. 252.1, Addanki Op. ¶ 12.)

His reports make clear that 5.1–42.4% are not "reasonable royalties," but rather "***end points*** of the bargaining range" for the hypothetical negotiation, while the reasonable royalty is an outcome "***within that range***." (D.I. 252.6, Addanki Reply ¶ 23 (emphasis added).) Prior to trial, Dr. Addanki never opined that anything other than 23.75% was a reasonable royalty.

At trial, however, Bayer and Dr. Addanki argued for the first time that any value within the ***entire bargaining range*** may constitute a reasonable royalty and specifically invited the jury to pick any number within the range. (*See, e.g.*, Tr. 66:14-18; PDX 7.20; Tr. 792:20-25, 797:7.) And in the last answer of his direct examination, Dr. Addanki ignored the Court's order not to offer a specific royalty and testified that 42.4% would be reasonable:

> Even at the actual upper end of this range, 42.4 percent, Baxalta still has 40 percent profit left over. Obviously if you conclude that the reasonable royalty would be lower than that, than [sic] Baxalta's profits left over after paying the royalty would be slightly higher.

(Tr. 798:21-799:5; *see* Tr. 748:7-749:15.) By recasting the entire alleged bargaining range as a range of "reasonable royalties," Bayer misleadingly implied that it would be appropriate for the jury to "pick" any number in that range. Further, Baxalta could not correct Bayer's false representation because it was precluded from cross examining Dr. Addanki regarding his original opinion that 23.75% is the ***only*** likely outcome of the hypothetical negotiation. (Tr. 11:21-12:15). As a result, the jurors were never informed that Dr. Addanki had previously opined that there was only one reasonable royalty—instead, they were led to believe by Bayer and Dr. Addanki that they could select a royalty even higher than 23.75%.

With respect to relative bargaining power, Dr. Addanki maintained throughout discovery that the parties would have had equal leverage in a hypothetical negotiation:

> I am aware of no evidence that would provide either party more bargaining power than the other in the hypothetical negotiation.

(D.I. 252.1, Addanki Op. ¶ 70; *see* D.I. 372 at 13-14.) At trial, however, Bayer elicited testimony from Dr. Addanki (Tr. 749:18-759:2) that had no purpose other than to communicate to the jury that Bayer had greater bargaining power. For example, Dr. Addanki testified that in the hypothetical negotiation, Bayer would not be motivated to license the '520 patent because "Bayer was not, in fact, in the business of licensing out its intellectual property [] to competitors

in particular." (Tr. 750:11-751:2.) He then explicitly testified that "[i]t was very important to Baxalta to get into this license agreement on the '520 patent." (Tr. 751:6-9.) Notably, while Dr. Addanki testified that Bayer had a policy against licensing its patents to competitors (Tr. 750:11-751:2), he previously acknowledged that he had ***no knowledge and made no inquiry into Bayer's licensing policies***. (D.I. 252.2, Addanki Dep. 87:13-89:2 (emphasis added).)

Bayer violated Rules 26(a)(2)(B) and 37(c) by suggesting for the first time at trial that: (i) any royalty up to and including 42.4% would be reasonable; and (ii) Bayer would have had greater bargaining power than Baxalta in a hypothetical negotiation. Fed. R. Civ. P. 26(a)(2)(B); Fed. R. Civ. P. 37 ("If a party fails to provide information . . . as required by Rule 26(a) or (e), the party is not allowed to use that information or witness to supply evidence on a motion, at a hearing, or at a trial, unless the failure was substantially justified or is harmless.").

The prejudice to Baxalta was compounded by the fact that Baxalta was not permitted to impeach Dr. Addanki by reference to his excluded opinions. (Tr. 11:21-12:15.) In other words, Baxalta was effectively penalized for filing a meritorious *Daubert* motion seeking to exclude Dr. Addanki's baseless damages theory because Bayer was ultimately permitted—over objection (D.I. 373; Tr. 2:18-12:15, 748:4-749:16, 784:17-787:7)—to argue for a substantially higher damage award (42.4%) than Dr. Addanki presented during discovery (23.75%).

The Court should strike Dr. Addanki's new opinions and either grant Baxalta's motion for judgment as a matter of law or order a new trial on damages.[12] *See Rembrandt Vision Tech, L.P. v. Johnson & Johnson Vision Care, Inc.*, 725 F.3d 1377, 1381 (Fed. Cir. 2013) (finding that, on a JMOL motion, it was proper for a court to exclude undisclosed expert testimony and grant

[12] Judges in this District have promulgated individual rules dictating that where, as here, a party proffers expert testimony "beyond the scope of previous expert disclosures," the costs of the new trial are charged "entirely to the party whose trial conduct necessitates a new trial." Chief Judge Stark's "Revised Procedures for Managing Patent Cases" (June 18, 2014) at 9.

the motion); *Weisgram v. Marley Co.*, 528 U.S. 440, 457 (2000) (courts of appeals can "direct the entry of judgment as a matter of law" when, "on excision of testimony erroneously admitted, there remains insufficient evidence to support the jury's verdict.").

C. Royalties From 5.1% to 42.4% Are Not, as a Matter of Law, Plausible Outcomes of the "Hypothetical Negotiation"

Even if Dr. Addanki's new theory was timely, royalties from 5.1–42.4% are not plausible outcomes of a hypothetical negotiation because: (i) a 42.4% royalty would consume all of Adynovate®'s alleged profits (a legally impermissible disgorgement); (ii) Dr. Addanki ignored significant costs that inflated his royalty range; and (iii) Dr. Addanki failed to apportion the value of the allegedly infringing and noninfringing features. Bayer should not be unjustly enriched from its presentation of a baseless royalty range. *See ZF Meritor LLC*, 769 F. Supp. 2d at 690.

1. The High End of Dr. Addanki's Range (42.4%) Represents All of Baxalta's Alleged Profit From Selling Adynovate®

Bayer and Dr. Addanki irreparably skewed the jury's analysis by suggesting that the hypothetical negotiation could plausibly result in Baxalta agreeing to disgorge 100% of its Adynovate® profit. For example, Dr. Addanki told the jury that any royalty up to 42.4% would be "feasible" despite the fact that he believed only one rate (23.75%) was "reasonable."

> ***Anything*** between those two points [5.1% and 42.4%] is a number that's at least a feasible royalty rate.

(Tr. 747:22-25 (emphasis added).) By Dr. Addanki's own express admission, however, the upper end of his so-called "bargaining range," represents "the full benefit" that Baxalta realized:

> [T]he highest royalty rate that Baxalta would paper was 42.4 percent, that was the full benefit that Baxalta got out of being able to sell Adynovate, 42.4 percent of the selling price of Adynovate.

(Tr. 780:23-781:2; *see also* Tr. 759:24-760:8; D.I. 252.1, Addanki Opening ¶ 61.)

Bayer's invitation for the jury to speculate as to an appropriate royalty up to and including 100% of Baxalta's alleged Adynovate® profits cannot satisfy its burden on damages. *Hughes Tool Co. v. Dresser Indus., Inc.*, 816 F.2d 1549, 1558 (Fed. Cir. 1987) (agreeing that a royalty that would "leave no profit" was excessive).

2. Dr. Addanki's New 5.1% to 42.4% Royalty Range Excludes Substantial Costs Associated with Baxalta's Sale of Adynovate®

Dr. Addanki's failure to account for the costs associated with the parties' respective products also improperly inflated his alleged "bargaining range." *See Wordtech Sys. v. Integrated Networks Sols., Inc.*, 609 F.3d 1308, 1321-22 (Fed. Cir. 2010) (granting a new trial after finding that a damages calculation that assumed the defendant "incurred zero costs" was "clearly not supported by the evidence and based only on speculation or guesswork").

Dr. Addanki inflated the high end of his alleged "bargaining range" by improperly assuming that Baxalta had ***zero*** costs associated with, among other things: (i) undisputed royalties paid by Baxalta to Nektar; (ii) sales and marketing activities, including product launches that were "ongoing" in "multiple countries;" (iii) global medical affairs; and (iv) ongoing research and development. (Tr. 940:21-941:12; DTX 471A; DTX 339A; Tr. 815:9-817:8, 1182:24-1186:8.) In total, Dr. Addanki excluded costs that were expected to reach hundreds of millions of dollars annually. (DTX 471A; DTX 339A.) Dr. Addanki similarly inflated the low end of his alleged "bargaining range" by excluding all costs related to Bayer's Factor VIII products. (PTX 987; Tr. 871:12-872:14.)

Baxalta's economist, Dr. Rausser, replicated Dr. Addanki's calculations and proved that when the improperly excluded costs are accounted for, the alleged bargaining range of 5.1% to 42.4% reduces to ***0.15% to 5.6%***. (*See* Tr. 1272:2-10; *see also* DTX 471A; DTX 339A.) Dr. Addanki did not dispute Dr. Rausser's calculations. (Tr. 817:21-23 ("Q. Well, the math, you

didn't correct any of the math that he did; is that correct? A. I'm not aware that he made calculation errors.").) No reasonable jury could find that the parties would agree to a 17.78% royalty when the upper end of the bargaining range—representing all of Baxalta's profit from selling Adynovate®—is 5.6%. *See Lindemann*, 895 F.2d at 1408 ("Enlow's opinion that AmHoist 'would agree to pay a royalty in excess of what it expected to make in profit' was, in light of all the evidence in this case, absurd.").

3. Dr. Addanki's New 5.1% to 42.4% Reasonable Royalty Range Fails to Separate the Value of the Allegedly Infringing and Noninfringing Features of Adynovate®

"[D]amages awarded for patent infringement must reflect the value attributable to the infringing features of the product, and no more." *Commonwealth Sci. & Indus. Research Org. v. Cisco Sys., Inc.*, 809 F.3d 1295, 1301 (Fed. Cir. 2015). In accordance with this principle of apportionment, the Federal Circuit requires damages experts to "separate the value of the allegedly infringing features from the value of all other features." *Id.*

Bayer and Dr. Addanki failed to separate the damages for Adynovate® conjugates that allegedly meet the claimed amino-acid sequence from those that indisputably do not. Specifically, the asserted claims require that the Adynovate® conjugates have "the amino acid sequence of SEQ ID NO:4." (JTX-1 at 74.) As explained supra, Baxalta's Adynovate® includes process variants that do not meet the SEQ ID NO:4 claim limitation literally or under the doctrine of equivalents. Dr. Zalipsky provided unrebutted testimony and analysis proving that some undetermined amount less than ***ten percent*** of the conjugates in Adynovate® (if any) contain the claimed SEQ ID NO:4. (Tr. 1219:9-1220:3.)

Dr. Addanki also argued that the only benefit of the '520 patent is extended half-life, i.e., less frequent dosing. (Tr. 751:11-752:7.) But as discussed *supra* Sec. V.C., the evidence indisputably proves that the claimed B-domain PEGylation shows "no significant differences" in

half-life. Thus, to the extent that sales of Baxalta's Adynovate® were driven by its extended half-life, that benefit did not arise from the '520 patent. In other words, the evidence proves that Baxalta would ***not*** pay anything more than a nominal amount in a hypothetical negotiation because there is no half-life benefit to the claimed invention.

Even if the '520 patent did extend half-life, Dr. Addanki failed to apportion damages between that alleged benefit and the other unpatented features of Adynovate®. Market studies demonstrated that half-life accounts for no more than 20% of the market demand for Adynovate®. (Tr. 1255:17-1257:11.) When combined with the fact that no more than 10% of Adynovate® conjugates meet the claimed SEQ ID NO:4, the patent can be apportioned no more than 2% (i.e., 10% multiplied by 20%) of the value of Adynovate® sales. (Tr. 1262:25-1263:10.)

Dr. Addanki attempted to excuse his failure to apportion the patented and non-patented features of Adynovate® by arguing that Baxalta cannot "separate out the 90 percent that isn't infringing" from a vial of Adynovate® (the smallest saleable unit). (Tr. 782:2-25.) But Dr. Addanki is not a technical expert qualified to opine on the separation of conjugates. And Federal Circuit precedent requires that "[e]ven when a damages theory relies on the smallest salable unit as the basis for calculating the royalty, the patentee must estimate what portion of that smallest salable unit is attributable to the patented technology when the smallest salable unit itself contains several non-infringing features." *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 904 F.3d 965, 977 (Fed. Cir. 2018). A party may forego apportionment only if it proves that "the patented feature is the sole driver of customer demand." *Id*. at 979. Here, Bayer and Dr. Addanki failed to argue, let alone prove, that all of Adynovate®'s market demand stems from B-domain PEGylation of a Factor VIII with SEQ ID NO:4. Bayer's failure to apportion damages mandates judgment as a matter of law or a new trial on damages. *Id*. at 980.

* * *

As recounted above, Bayer's damages case proceeded as follows:

1. the presentation of an unsubstantiated "bargaining range" of 5.1% to 42.4% that fails to account for the parties' costs or the noninfringing features of Adynovate®;

2. an implication that Bayer would have had greater bargaining power in a hypothetical negotiation, even though Dr. Addanki maintained throughout discovery that the parties had equal bargaining power; and

3. an express instruction for the jury to simply "pick a reasonable royalty rate in a range up to 42 percent," a percentage that exceeds the total profit that Baxalta could potentially realize from selling Adynovate®.

Permitting the jury's damage award to stand based on this record would set a remarkable new precedent for proving reasonably royalty damages—a precedent that would directly conflict with the Federal Circuit's admonition that "[d]amages must not be left to conjecture by the jury." *Promega*, 875 F.3d at 660; *see also Whitserve*, 694 F.3d at 31.

Accordingly, the Court should enter judgment as a matter of law that Bayer is entitled to at most nominal damages. Alternatively, Baxalta is entitled to a new trial because the record supports no more than Dr. Rausser's 1% royalty—the only reasonable-royalty opinion offered at trial. (Tr. 1264:19-1265:3.) In contrast to Dr. Addanki, Dr. Rausser performed a proper reasonable-royalty analysis by:

1. using market studies to determine that the patent's alleged half-life benefit could account for no more than 20% of demand (Tr. 1255:17-1257:11);

2. reducing the royalty from 20% to 2% by apportioning the allegedly patented conjugates from the unpatented conjugates in Adynovate® (Tr. 1262:25-1263:10); and

3. applying the remaining *Georgia-Pacific* factors (Tr. 1264:19-1265:3, 1263:11-1264:18.)

VI. Conclusion

Judgment as a matter of law under Rule 50(b) should be granted against Bayer. A reasonable jury did not have a legally sufficient evidentiary basis to find for Bayer on any of the issues of enablement, infringement, obviousness, and damages. Alternatively, a new trial should be granted under Rule 59(a) because the jury's verdict was against the clear weight of the evidence presented at trial, and a new trial must be granted to prevent a miscarriage of justice.

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