Nos. 2018-1804, -1808, -1809

In the
United States Court of Appeals
for the Federal Circuit

SANOFI-AVENTIS U.S., LLC, AVENTIS PHARMA S.A., SANOFI,

Plaintiffs-Appellants,

v.

DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., SANDOZ, INC.,

Defendants-Appellees,

FRESENIUS KABI USA, LLC, ACCORD HEALTHCARE, INC., APOTEX CORP., APOTEX INC., ACTAVIS LLC, ACTAVIS ELIZABETH LLC, MYLAN LABORATORIES LIMITED,

Defendants – Cross-Appellants.

Appeals from the United States District Court
for the District of New Jersey, Case Nos. 3:14-cv-07869-MAS-LHG, 3:14-cv-08079-MAS-LHG, 3:14-cv-08082-MAS-LHG, 3:15-cv-02520-MAS-LHG, 3:15-cv-00287-MAS-LHG, 3:15-cv-01835-MAS-LHG, 3:15-cv-00290-MAS-LHG, 3:15-cv-00776-MAS-LHG, 3:15-cv-03107-MAS-LHG, 3:15-cv-02522-MAS-LHG, 3:16-cv-02259-MAS-LHG, 3:15-cv-03392-MAS-LHG, 3:15-cv-02631-MAS-LHG & 3:16-cv-05678-MAS-LHG,
The Honorable Michael A. Shipp

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CERTIFICATE OF INTEREST FOR APOTEX INC. AND APOTEX CORP.

Sanofi-Aventis U.S., LLC v. Fresenius Kabi USA, LLC

Case Nos. 18-1804, -1808, -1809

Counsel for Defendants – Cross-Appellants Apotex Inc. and Apotex Corp. certifies as follows:

1. The full name of the party represented by me is

   Apotex Inc.

   Apotex Corp.

2. The name of the real party in interest (only including any real party in interest not identified in Question 3) represented by me is:

   None.

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

   Apotex Delaware Holdings Corp. (parent to Apotex Corp.)

   Apotex Pharmaceutical Holdings Inc. (parent to Apotex Inc.)

4. The names of the law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

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   Hill and Wallack, LLP, 21 Roszel Road, Princeton, NJ 08540: Eric I. Abraham, Christina L. Saveriano.

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

   Aventis Pharma S.A., v. Mylan Laboratories Limited, No. 18-1203 (Fed. Cir.)

Dated: August 20, 2018

/s/Andrew M. Alul
Andrew M. Alul, Esq.

Counsel for Defendants – Cross-Appellants Apotex Inc. and Apotex Corp.

CERTIFICATE OF INTEREST FOR FRESENIUS KABI USA, LLC

Sanofi-Aventis U.S., LLC v. Fresenius Kabi USA, LLC

Case Nos. 18-1804, -1808, -1809

Counsel for Defendants – Cross-Appellant Fresenius Kabi USA, LLC certifies as follows:

1. The full name of the party represented by me is

   Fresenius Kabi USA, LLC

2. The name of the real party in interest (only including any real party in interest not identified in Question 3) represented by me is:

   Fresenius Kabi USA, LLC

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

   Fresenius Kabi Pharmaceuticals Holding, Inc.

   Fresenius Kabi AG

   Fresenius SE & Co. KGaA

4. The names of the law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

   Goodwin Procter LLP: John P. Hanish, Ph.D. (no longer with firm) Brian J. Prew (no longer with firm)

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   Patunas Law, LLC: Michael E. Patunas

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

   Aventis Pharma S.A., v. Mylan Laboratories Limited, No. 18-1203 (Fed. Cir.)

Dated: August 20, 2018

/s/Daryl L. Wiesen
Daryl L. Wiesen, Esq.

Counsel for Defendants – Cross-Appellant Fresenius Kabi USA LLC

CERTIFICATE OF INTEREST FOR ACTAVIS AND ACTAVIS ELIZABETH LLC

Sanofi-Aventis U.S., LLC v. Fresenius Kabi USA, LLC

Case Nos. 18-1804, -1808, -1809

Counsel for Defendants – Cross-Appellants Actavis and Actavis Elizabeth LLC certifies as follows:

1. The full name of the party represented by me is

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   Actavis Elizabeth LLC

2. The name of the real party in interest (only including any real party in interest not identified in Question 3) represented by me is:

   Actavis LLC

   Actavis Elizabeth LLC

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

   Teva Pharmaceutical Industries Ltd.

4. The names of the law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

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

   Aventis Pharma S.A., v. Mylan Laboratories Limited, No. 18-1203 (Fed. Cir.)

Dated: August 20, 2018

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CERTIFICATE OF INTEREST FOR ACCORD HEALTHCARE, INC.

Sanofi-Aventis U.S., LLC v. Fresenius Kabi USA, LLC

Case Nos. 18-1804, -1808, -1809

Counsel for Defendants – Cross-Appellant Accord Healthcare, Inc. certifies as follows:

1. The full name of the party represented by me is

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2. The name of the real party in interest (only including any real party in interest not identified in Question 3) represented by me is:

   Accord Healthcare, Inc.

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

   Intas Pharmaceuticals Ltd.

4. The names of the law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

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   Lisa J. Rodriguez of Schnader Harrison Segal & Lewis.

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

   Aventis Pharma S.A., v. Mylan Laboratories Limited, No. 18-1203 (Fed. Cir.)

Dated: August 20, 2018 /s/Imron T. Aly

Imron T. Aly, Esq.

Counsel for Defendant – Cross-Appellant Accord Healthcare, Inc.

CERTIFICATE OF INTEREST FOR MYLAN LABORATORIES LIMITED

Sanofi-Aventis U.S., LLC v. Fresenius Kabi USA, LLC

Case Nos. 18-1804, -1808, -1809

Counsel for Defendants – Cross-Appellant Mylan Laboratories Limited certifies as follows:

1. The full name of the party represented by me is

   Mylan Laboratories Limited

2. The name of the real party in interest (only including any real party in interest not identified in Question 3) represented by me is:

   Mylan Laboratories Limited

   Mylan Pharmaceuticals Inc.

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

   Mylan Laboratories Limited is a wholly owned subsidiary of Mylan Inc. Mylan Inc. is indirectly wholly owned by Mylan N.V., a publicly held company. No publicly held company owns more than 10% of Mylan N.V.'s stock

4. The names of the law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

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5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by

this court's decision in the pending appeal. *See* Fed. Cir. R. 47.4(a)(5) and 47.5(b).

Aventis Pharma S.A., v. Mylan Laboratories Limited, No. 18-1203 (Fed. Cir.)

Dated: August 20, 2018

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TABLE OF ABBREVIATIONS

Abbreviation	**Meaning**
505(b)(2)	New Drug Application pursuant to Section 505(b)(2) of the FDCA, 21 U.S.C. § 355(b)(2)
'170 Patent	U.S. Patent No. 5,847,170 (JTX-1)
'470 patent	U.S. Patent No. 4,814,470 (JTX-119)
'592 Patent	U.S. Patent No. 8,927,592 (JTX-6)
ACS	American Chemical Society
ANDA	Abbreviated New Drug Application pursuant to 505(j) for the FDCA, 21 U.S.C. § 355(j)
Appx_	Page number citation for Joint Appendix
AUC	Area under the plasma drug concentration-time curve
Aventis appeal or IPR appeal	*Aventis Pharma S.A., v. Mylan Laboratories Limited*, No. 18-1203 (Fed. Cir.)
BlueBr_	Page number citation to Confidential Brief for Plaintiffs – Appellants
Commerçon	A. Commerçon *et al.*, *Practical Semisynthesis and Antimitotic Activity of Docetaxel and Side-Chain Analogues*, Ch. 17 in TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS, (G. I. Georg et al., Eds.) ACS Symposium Series American Chemical Society, Washington, DC, 583:233-246 (1994) (JTX-109)
Defendants	Defendants – Cross-Appellants
Defendants – Appellees	Defendants – Appellees Dr. Reddy's Laboratories, Inc., Dr. Reddy's Laboratories, Ltd., Sandoz Inc.

Abbreviation	**Meaning**
Defendants – Cross-Appellants	Defendants – Cross-Appellants Fresenius Kabi USA, LLC, Accord Healthcare, Inc., Apotex Corp. and Apotex Inc., Mylan Laboratories Ltd., Actavis LLC.
Eisenhauer	E. A. Eisenhauer *et al.*, *European-Canadian Randomized Trial of Paclitaxel in Relapsed Ovarian Cancer: High-Dose Versus Low-Dose and Long Versus Short Infusion*, 12 J. CLIN. ONCOL. 2654-2666 (1994) (DTX-2177)
EP '910	European Patent No. EP 0 604 910 A1 (JTX-125)
FDCA	Federal Food, Drug, and Cosmetic Act
FPTO	Final Pretrial Order (D.I. 167)
FWD	Final Written Decision
GCRI Report	Gujarat Cancer & Research Institute Annual Report (2007-2008) (DTX-2209)
Georg	Georg *et al.* (Eds.) *Preface* to TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS, ACS Symposium Series, 583:1-353, American Chemical Society, Washington, D.C. (1994) (JTX-162, DTX-2196I)
Golik (EP '577)	European Patent No. 0 639 577 A1 (JTX-111)
Greenberger	L. M. Greenberger, *et al*., *Photoaffinity Probes for the α_1-Adrenergic Receptor and the Calcium Channel Bind to a Common Domain in P-glycoprotein*, 265 J. BIOL. CHEM. 4394-4401 (1990) (DTX-2203)

Abbreviation	**Meaning**
Greene	T. W. GREENE & P. G. M. WUTS, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, 2d Ed., John Wiley & Sons (1991) (JTX-128)
Hait	W. Hait & D. T. Aftab, *Rational Design and Pre-Clinical Pharmacology of Drugs for Reversing Multidrug Resistance*, 43 BIOCHEM. PHARMACOL. 103-107 (1992) (JTX-102)
HSR	Hypersensitivity Reaction
IPR	*Inter partes* review pursuant to 35 U.S.C. §§ 311-319
IPR appeal	*Aventis Pharma S.A., v. Mylan Labs. Ltd.*, No. 18-1203 (Fed. Cir.)
Kant	J. Kant *et al.*, *A Chemoselective Approach to Functionalize the C-10 Position of 10-Deacetylbaccatin III. Synthesis and Biological Properties of Novel C-10 Taxol Analogues*, 35 Tetrahedron Lett. 5543-5546 (1994) (JTX-114)
Kingston 1994	D. I. Kingston, *Recent Advances in the Chemistry and Structure-Activity Relationships of Paclitaxel*, Ch. 15 in TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS, (G. I. Georg et al., Eds.) ACS Symposium Series American Chemical Society, Washington, DC, 583:203-216 (1994) (JTX-107)
Klein	L. L. Klein *et al.*, *Chemistry and Antitumor Activity of 9(R)-Dihydrotaxanes*, Ch. 20 in TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS, (Georg et al., Eds.) ACS Symposium Series American Chemical Society, Washington, DC, 583:276-287 (1994) (JTX-110)

Abbreviation	**Meaning**
Lampidis	T. J. Lampidis, *Relevance of the Chemical Charge of Rhodamine Dyes to Multiple Drug Resistance*, 38 BIOCHEM. PHARMACOL. 4267-4271 (1989) (DTX-2241)
MDR	Multi Drug Resistance
MMA	Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub.L. No. 108-173, 117 Stat. 2066 (2003)
MTM	Methylthiomethoxy
Ojima 1994	I. Ojima *et al.*, *Synthesis and Structure-Activity Relationships of New Taxoids*, Ch. 19 in TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS, (Georg et al., Eds.) ACS Symposium Series American Chemical Society, Washington, DC, 583:262-275 (1994) (JTX-104)
P-IV certification	Certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) or § 355(j)(2)(A)(iv)(IV)
Pgp	P-Glycoprotein
Phase III Disclosures	Collectively, *Winquist*, *Rodrigues*, and the *GCRI Report*
Plaintiffs - Appellants	Plaintiffs – Appellants Sanofi-Aventis U.S. LLC, Aventis Pharma S.A., and Sanofi, and including predecessor company Rhone-Poulenc Rorer ("RPR")
POSA	Person of ordinary skill in the art
PTAB	Patent Trial and Appeal Board

Abbreviation	**Meaning**
PTO	United States Patent and Trademark Office
Riou	J. F. Riou *et al.*, *Effects of Taxotere On Murine And Human Tumor Cell Lines*, 187 BIOCHEM. BIOPHYS. RES. COMM. 164-170 (1992) (JTX-98)
RPR	Rhône Poulenc Rhorer, *see* Plaintiffs
Rodrigues	G. Rodrigues *et al., Open Clinical Uro-oncology Trials in Canada,* 14 CAN. J. UROL. 3779-3786 (2007) (DTX-2316)
Safa	A. R. Safa *et al.*, *The α-adrenergic photoaffinity probe [^{125}I]arylazidoprazosin binds to a specific peptide of P-glycoprotein in multidrug-resistant cells*, 166 BIOCHEM. BIOPHYS. RES. COMM. 259-266 (1990) (DTX-2320)
Sanofi	*See* Plaintiffs - Appellants
SAR	Structure-activity relationship(s)
Tr.	Trial Transcript
Uziely	B. Uziely *et al.*, *Paclitaxel (Taxol) in Refractology Breast Cancer: Response Correlates With Low Levels of MDR1 Gene Expression*, Abstract 104 in 13 ASCO PROGRAM PROCEEDINGS, DALLAS, TX 75 (Mar. 1994) (DTX-2370)
Verweij	J. Verweij *et al.*, *Paclitaxel (Taxol) and Docetaxel (Taxotere): Not Simply two of a Kind*, 5 ANN. ONCOL. 495-505 (1994) (JTX-29)

Abbreviation	**Meaning**
Wils	P. Wils *et al.*, *Polarized Transport of Docetaxel and Vinblastine Mediated by P-Glycoprotein in Human Intestinal Epithelial Cell Monolayers*, 48 BIOCHEM. PHARMACOL. 1528-1530 (1994) (JTX-31)
Winquist	E. Winquist, *et al., Open Clinical Uro-oncology Trials in Canada,* 15 CAN. J. UROL. 3942-3949 (2008) (DTX-2391)
Wong ('140 patent)	U.S. Patent No. 6,201,140 (JTX-115)

STATEMENT OF RELATED CASES

The instant appeal is from the following cases which were consolidated for discovery and trial:

Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC, No. 3:14-cv-07869(MAS)(LHG) (LEAD)

Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC, No. 3:14-cv-08082(MAS)(LHG)

Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC, No. 3:15-cv-02631(MAS)(LHG)

Sanofi-Aventis U.S. LLC v. Accord Healthcare, Inc., No. 3:14-cv-08079(MAS)(LHG)

Sanofi-Aventis U.S. LLC v. Accord Healthcare, Inc., No. 3:15-cv-02520(MAS)(LGH)

Sanofi-Aventis U.S. LLC v. Apotex Corp., No. 3:15-cv-00287(MAS)(LHG)

Sanofi-Aventis U.S. LLC v. Apotex Corp., No. 3:15-cv-01835(MAS)(LHG)

Sanofi-Aventis U.S. LLC v. Mylan Laboratories Ltd., No. 3:15-cv-00290(MAS)(LHG)

Sanofi-Aventis U.S. LLC v. Mylan Laboratories Ltd., No. 3:15-cv-03392(MAS)(LHG)

Sanofi-Aventis U.S. LLC v. Actavis LLC, No. 3:15-cv-00776(MAS)(LHG)

Sanofi-Aventis U.S. LLC v. Actavis LLC, No. 3:15-cv-03107(MAS)(LHG)

and from the following cases, which were consolidated for discovery with the above-referenced cases:

Sanofi-Aventis U.S. LLC v. Dr. Reddy's Laboratories, Inc., No. 3:15-cv-02522(MAS)(LHG)

Sanofi-Aventis U.S. LLC v. Dr. Reddy's Laboratories, Inc., No. 3:16-cv-02259(MAS)(LHG)

and from the following case:

Sanofi-Aventis U.S. LLC v. Sandoz Inc., No. 3:16-cv-5678(MAS)(LHG).

There have been no other appeals in or from these civil actions previously pending before this Court or any other appellate court.

There is one appeal pending in this Court, *Aventis Pharma S.A., v. Mylan Laboratories Limited*, No. 18-1203 (Fed. Cir.), that may directly affect or may be directly affected by this Court's decision in the instant appeal. The *Aventis* appeal involves the '592 patent, which is one of the two patents involved in the instant appeal.

STATEMENT OF JURISDICTION

This appeal arises from lawsuits Sanofi instituted against Defendants – Cross-Appellants ("Defendants") in the District of New Jersey asserting infringement of the '170 and '592 patents. Defendants counterclaimed seeking declarations of invalidity and non-infringement of the '170 and '592 patents, over which the District Court had subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a) and 2201(a). After a bench trial held in September 2017, on December 17 and 19, 2017, the court issued its Order and Sealed Opinion finding and concluding that: (a) asserted claims 1 and 2 of the '170 patent were infringed and not invalid, and

(2) claims 7, 11, 14-16, 21, 26, and 30 of the '592 patent were infringed but invalid as obvious. Appx15-83. On March 5, 2018, the court entered final judgment for Sanofi on the '170 patent, and for Defendants on the '592 patent. Appx1-14. On April 4, 2018, Sanofi and Defendants filed their notices of appeal. This Court has jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

I. SANOFI'S APPEAL: The '592 Patent.

1. Whether Sanofi is precluded from suing Defendants a second time on the '592 patent as soon as it secures substitute claims it is actively seeking in the copending appeal of a FWD by the PTO denying Sanofi's motion to amend the '592 patent ("IPR appeal") because, during the District Court litigation, Sanofi could have asserted (and, in fact, did previously assert) claims 1 and 27, which are broader in scope than the substitute claims. If so, Defendants do not oppose Sanofi's appeal.

2. If the Court does not find claim preclusion in connection with Issue 1, then whether Defendants' counterclaims with respect to claims 7, 11, 14-16, and 26, which Sanofi disclaimed nearly two months after trial, and on the eve of the District Court's decision ("the disclaimed claims"), were justiciable at the time the court entered judgment.

II. DEFENDANTS' CROSS-APPEAL: The '170 Patent.

Whether the district court erred by disregarding key prior art references and

expert testimony in holding that claims 1 and 2 of the '170 patent, directed to cabazitaxel and formulations thereof, respectively, were not obvious over the prior art.

STATEMENT OF THE CASE

Defendants are drug manufacturers who have filed ANDAs and/or 505(b)(2) NDAs seeking FDA approval to market cabazitaxel products as alternatives to Sanofi's Jevtana® (cabazitaxel) injection, a prostate cancer chemotherapy.

I. SANOFI'S APPEAL: The '592 Patent.

A. Sanofi's Phase III TROPIC Study and the '592 Patent.

Starting in October 2009, Sanofi filed a series of patent applications seeking to cover the results of its Phase III clinical trial ("the TROPIC study") that led to the approval of Jevtana®. Appx21, Appx76, Appx89-90, Appx349. The '592 patent eventually issued on January 6, 2015, with claims directed to the FDA approved use of cabazitaxel to treat prostate cancer that has progressed during or after treatment with docetaxel by administration of 20-25 mg/m^2 of cabazitaxel in combination with a corticoid. Appx91-99, Appx349, Appx368-369, Appx24348. The specification also includes a summary of the TROPIC study results. Appx77-78, Appx353-359, Appx364-368, Appx13891-13895, Appx30714-30715.

Over a year before Sanofi began filing applications for the '592 patent, Sanofi had published the protocol for its Phase III TROPIC study in the *Winquist*,

Rodrigues, and *GCRI Report* references, collectively referred to as the "Phase III Disclosures." Appx89-90. As the District Court found, the Phase III Disclosures expressly disclosed that Sanofi was conducting a Phase III clinical study on the use of 25 mg/m^2 of cabazitaxel in combination with prednisone to treat patients with hormone-refractory metastatic cancer previously treated with docetaxel, with overall survival as an endpoint. *Id*.

B. Sanofi Files Suit—Discovery and Claim Construction.

At the outset of the case, Sanofi asserted infringement of claims 1-30 against Defendants. Appx6929. Claims 1 and 27 are the broadest independent claims and recite methods of treating a patient with prostate cancer (claim 1) or of increasing survival of patient with castration resistant metastatic prostate cancer (claim 27) that has progressed during or after treatment with docetaxel comprising administering 20-25 mg/m2 of cabazitaxel in combination with a corticoid. Recognizing that many of its '592 patent claims were likely anticipated by the Phase III Disclosures, Sanofi argued during discovery and claim construction that the preamble languages "[a] method for treating" and "[a] method of increasing the survival" for claims 1 and 27 were limiting and required efficacy in treating prostate cancer and increasing survival, respectively. Appx4606-4608, Appx6965-6966. Based on its preamble constructions, Sanofi argued early in discovery that that none of the prior art Defendants relied upon anticipated the '592 patent claims because they did not

disclose that cabazitaxel would be effective in treating prostate cancer (or increasing survival), and that Defendants' prior art combinations for obviousness would not provide a POSA with a reasonable expectation of success because there was no data cabazitaxel to be effective. Appx6965-6966, Appx7007-7012.

Before expert reports were served on September 21, 2016, Sanofi informally dropped its assertion of claim 2. Defendants served an opening report from their '592 patent invalidity expert, Dr. Ratain, in which Dr. Ratain opined that asserted claims 1 and 3-30 were anticipated and/or obvious, while Sanofi's '592 patent infringement expert, Dr. Petrylak, opined that Defendants' cabazitaxel products infringed those same claims. Appx6484-6486, Appx12557-12559. On October 7, 2016, the District Court issued its claim construction ruling rejecting Sanofi's position that the preambles were limiting or required efficacy. Appx91, Appx4604-4609. Thereafter, without notifying Defendants that it was dropping its assertion of claims 1, 3-6, 9, 12-13, 17-20, 22-25, and 27-29, Sanofi served a rebuttal report from Dr. Sartor, its invalidity expert for the '592 patent, stating that it was his "understand[ing] that Sanofi is asserting Claims 7-8, 10-11, 14-16, 21, 26, and 30 of the '592 patent." Appx8622. Defendants thereafter sought written confirmation from Sanofi that it was in fact dropping assertion of claims 1, 3-6, 9, 12-13, 17-20, 22-25, and 27-29. Appx14197.

C. Mylan's '592 Patent IPR Petition and Sanofi's Motion to Stay.

On March 15, 2016, while the parties were proceeding through fact discovery, Defendant Mylan filed a petition for IPR of the '592 patent. Appx523-524, Appx15158. The PTO instituted IPR on September 22, 2016 for '592 patent claims 1-5 and 7-30. Appx15162.

On December 23, 2016, after the District Court issued its claim construction ruling, Sanofi filed a contingent motion in the IPR to amend claims 27-30 of the '592 patent with substitute claims that were amended versions of claims 27-30. Appx5144, Appx5174-5175. Independent Claim 27 was amended to make two modifications: (1) to amend the preamble to recite "[a] method of increasing survival comprising administering to a patient in need thereof"; and (2) to add a premedication regimen of an antihistamine, a corticoid, and an H_2 antagonist prior to cabazitaxel administration. Appx10793-10794. Substitute claims 32 and 34 were versions of claims 28 and 30, respectively, amended to reflect dependency from claim 31, and substitute claim 33 was a version of claim 29, amended to include the premedication regimen. *Id*.

The narrowing limitations were intended to accomplish two separate goals. First, having lost its bid in both the District Court litigation and in the IPR to have the preambles of claims 1 and 27 construed as limitations requiring efficacy in order to avoid its own anticipatory prior art in the Phase III Disclosures (Appx10735-

10736), Sanofi sought by amendment to introduce a "limit[ation] as a statement of intentional purpose for how the method is to be performed." Appx10795 (internal quotations omitted). The premedication regimen was added in an attempt to further distinguish the substitute claims from prior art. Appx10800-10801.

Nearly three months after the PTO instituted the '592 patent IPR, and months after the District Court issued its claim construction decision, Sanofi moved to stay the litigation. Appx4978. At no time between March 15, 2016, when Mylan filed its IPR petition, and December 16, 2016, when Sanofi filed its stay motion, did Sanofi inform the court that a stay might be necessary. Appx4970, Appx5109. In support of its motion, Sanofi argued that: (1) it was likely to prevail on the '170 patent, (2) there was no 30-month stay tied to the '592 patent, and (3) a stay would conserve resources, particularly if Sanofi's motion to amend was granted. Appx4983-4985. Defendants opposed, arguing that: (1) a stay would undermine the goal of quick resolution of Hatch-Waxman disputes; (2) the timing of Sanofi's stay motion and motion to amend the '592 patent in the IPR suggested gamesmanship and an attempt to overcome Defendants' claim construction victory, which rendered many '592 patent claims invalid; and (3) a stay would not obviate the need for litigation, in view of defenses Defendants had raised that were not at issue in the IPR. Appx5083-5085, Appx5088. Separately, the non-IPR Defendants (Apotex, Fresenius, Actavis, Accord) argued that a stay would tactically

disadvantage them as it would disincentivize Sanofi from settling with any defendant except Mylan. Appx5191-5192.

On July 20, 2017, the District Court denied Sanofi's motion to stay, agreeing with the non-IPR Defendants that a stay would put them at a tactical disadvantage vis-à-vis Mylan and that a stay would not simplify issues, particularly in view of the additional defenses asserted in the litigation. Appx5694-5695.

D. Trial and the PTO's Decision.

In the Final Pretrial Order, Sanofi asserted infringement of claims 7-8, 10-11, 14-16, 21, 26, and 30. Appx5728. In the days before trial, Sanofi informed Defendants that it was no longer asserting claims 8 and 10. Appx14200, Appx14200. At the start of trial, Sanofi's infringement expert, Dr. Petrylak, asserted that Defendants' cabazitaxel products infringed claims 7, 11, 14-16, 21, 26, and 30. Appx12744-12745, Appx12767-12773, Appx12786. Defendants' invalidity expert, Dr. Ratain, testified that those same claims, and claims 1 and 27 were anticipated and/or obvious. Appx12559, Appx12590-12591.

On September 21, 2017, three days into trial, the PTO issued its FWD in the '592 patent IPR finding all challenged claims (1-5 and 7-30) unpatentable and denying Sanofi's motion to amend.[1] Appx10730. Thereafter, on September 28,

[1] The PTO rejected Sanofi's argument that the preambles of the substitute claims were limitations requiring efficacy, or that the premedication regimen sufficiently distinguished the claims from the prior art. Appx10795-10806.

2017—the night before the last day of trial, when Sanofi's invalidity expert, Dr. Sartor, was set to testify—Sanofi's counsel notified counsel for Defendants by phone that Dr. Sartor would be testifying only about claims 21 and 30. Appx13841. Sanofi reiterated during Dr. Sartor's direct examination the next day that Sanofi was "going to focus Dr. Sartor's direct examination today on two specific claims…Claims 21 and 30." Appx13841. In response, Defendants made clear on the record that they would "continue [to] ask for a judgment of invalidity on all of the claims that have been a part of the case." *Id*. Sanofi did not take any steps before the close of trial to withdraw asserted claims 7, 11, 14-16, and 26.

E. Post-Trial.

In its post-trial brief, Sanofi discussed and defended the validity of only claims 21 and 30, but did not drop its assertion of claims 7, 11, 14-16, and 26. Appx12054, Appx12068. Defendants, addressing the evidence presented during the trial, in their post-trial brief argued that all claims asserted at the outset of trial were invalid. Appx11153.

On November 17, 2017, after completion of post-trial submissions, Sanofi filed a letter advising the District Court that it had not appealed the PTO's determination that claims 7, 11, 14-16, and 26 were unpatentable, that those claims would inevitably be cancelled by the PTO, and that there remained no further controversy between the parties as to those claims. Appx12182. On December 4,

2017, Defendants responded that: (1) cancellation had not yet occurred and it was unclear when it would occur; (2) Defendants presented evidence at trial on all claims Sanofi's originally asserted at trial; and (3) there remained a justiciable controversy between the parties as to claims 7, 11, 14-16 and 26, regardless of their eventual cancellation, because of the substitute claims Sanofi was seeking in the IPR, then on appeal. Appx14131-14132. On December 11, 2017, Sanofi filed a letter enclosing a statutory disclaimer for claims 7, 11, 14-16 and 26. Appx14135.

On December 11, 2017, Defendants submitted a letter arguing that the disclaimer was insufficient to render non-justiciable Defendants' counterclaims with respect to the disclaimed claims, citing this Court's decisions in *Senju Pharmaceutical Co. v. Apotex Inc.*, 746 F.3d 1344 (Fed. Cir. 2014) and *Apotex, Inc. v. Daiichi Sankyo, Inc.,* 781 F.3d 1356 (Fed. Cir. 2015). Appx14138.

Frustrated at the "constantly moving target with respect to the '592 patent," on December 12, 2017, the District Court ordered the parties to submit further briefing on whether Defendants' counterclaims for the disclaimed claims were justiciable. Appx14140-14142. In its brief, Sanofi argued—as it does here on appeal—that the statutory disclaimer mooted any controversy between the parties over the disclaimed claims, that *Apotex* was inapposite because it was limited to situations where a disclaimed patent was holding up regulatory approval of an ANDA, that any claim preclusion justification was too speculative to create an actual

controversy, and that *Senju* was inapposite anyway because the disclaimed claims did not cover in scope the substitute claims. Appx14149-14150. Defendants countered that under this Court's precedent applying the standard for justiciability set forth by the Supreme Court in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007), such as *Teva Pharmaceuticals USA, Inc. v. Novartis Corp.*, 482 F.3d 1330 (Fed. Cir. 2007) and *Apotex*, there remained a justiciable dispute between the Parties concerning patent certainty, and that a statutory disclaimer did not render non-justiciable Defendants' counterclaims for the disclaimed claims, because judgment on those claims would result in collateral consequences. Appx14183-14186.

F. The Court's Sealed Opinion and Final Judgment.

On December 19, 2018, the District Court issued its Sealed Opinion finding Defendants' counterclaims with respect to the disclaimed claims justiciable, and finding those claims invalid. The court relied on the following facts: Defendants had asserted counterclaims, Sanofi had asserted the disclaimed claims at trial, and both sides presented evidence on them. Appx60-62. Sanofi appealed.

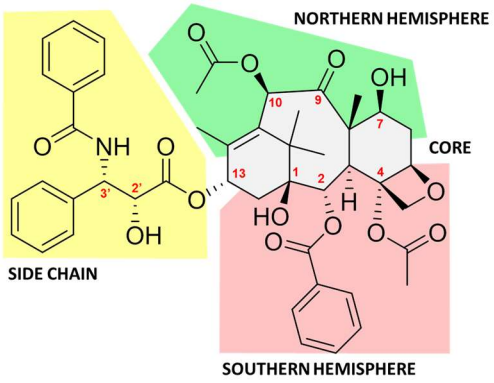
G. The *Aventis* Appeal.

Despite initially informing the District Court that it was appealing the PTO's unpatentability determination for claims 21 and 30 and denial of Sanofi's motion to amend, Sanofi ultimately appealed only the PTO's denial of its motion to amend. BlueBr14.

II. DEFENDANTS' CROSS-APPEAL: The '170 Patent.

A. Background: Taxane Drugs.

Cabazitaxel belongs to a class of compounds called "taxanes." All taxanes share a basic chemical structure consisting of a tricyclic "core" to which various substituents are attached. Appx12304 (Dr. Kingston), Appx13084 (Dr. Heathcock). Chemists refer to three distinct regions in the structure of taxanes: (1) the "northern hemisphere"; (2) the "southern hemisphere"; and (3) the "side chain." Appx12304-12305 (Dr. Kingston), Appx13088-13089 (Dr. Heathcock), Appx25144 (*Kingston 1994*). By convention, the carbon atoms that make-up the core and side chain are numbered (*e.g.* "C-1"), Appx13084-13085 (Dr. Heathcock), Appx13088-13089 (Dr. Heathcock), as illustrated below:



The first chemotherapeutic taxane, paclitaxel (Taxol, depicted above), was originally discovered in the 1960s after being isolated from the bark of the Pacific yew tree (genus *Taxus*), Appx12301-1232 (Dr. Kingston), its structure was published in 1971, and FDA approved it for cancer treatment in 1992. Appx12302,

12305-12306 (Dr. Kingston). The next generation taxane, docetaxel (Taxotere), was discovered in the mid-1980s. Appx12313 (Dr. Kingston). Following its discovery, docetaxel was patented[2] by Rhône Poulenc Sante, a predecessor to both RPR and Sanofi, and was in advanced clinical development as of 1995. Appx12318 (Dr. Kingston), Appx13093-13094 (Dr. Heathcock), Appx13355-13356 (Dr. Bouchard).

Paclitaxel and docetaxel have identical chemical structures except that at the C-3' position of the side chain, paclitaxel has a phenylcarbonyl or "PhCO" group while docetaxel has a *tert*-butoxycarbamate or "Boc" group, and at the C-10 position of the core, paclitaxel has an acetoxy group while docetaxel has a hydroxy or "-OH" group. Appx13092-13093 (Dr. Heathcock).

B. The '170 Patent Claims Elements Taught by the Prior Art.

The '170 patent claims cabazitaxel, formulations thereof, and various related chemical syntheses. Only claims 1 and 2 were asserted. Appx6.

Claim 1 recites: "4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate." Appx336. This compound is cabazitaxel. *Id.*

Claim 2 recites: "A pharmaceutical composition comprising at least the product according to claim 1 in combination with one or more pharmaceutically

[2] Rhône Poulenc Sante filed patent applications covering docetaxel in the 1980s, which eventually issued as the '*470 Patent*. Appx25426.

acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds." *Id.*

1. The District Court Correctly Found That Docetaxel Was a Lead Compound and That the Skilled Artisan Would Have Been Motivated to Modify It to Overcome MDR.

Although the District Court ultimately found the asserted claims of the '170 patent to be non-obvious, the court made several important findings in Defendants' favor.

First, the court held that as of March 26, 1995, the priority date for the '170 patent, the skilled artisan would have selected docetaxel or paclitaxel as a lead compound. Appx45-46. In 1995, docetaxel and paclitaxel were considered "the most promising new chemotherapeutic agents developed for cancer treatment in the past decade." Appx16771 (*Georg*), Appx24288 (Dr. Ojima). As the court correctly found, the skilled artisan would therefore have selected one of these compounds as a lead to begin development of a new chemotherapy agent. Appx45-46.

The District Court also properly found that the skilled artisan would have recognized multi-drug resistance ("MDR") as a significant problem for taxanes in 1995 and would have been motivated to modify docetaxel to mitigate it. Appx52-53. MDR is a type of drug resistance in which cancer cells are simultaneously resistant to a wide variety of diverse chemotherapy drugs. Appx13121-22 (Dr. Heathcock), Appx25038-40 (*Kartner*). Both sides' experts agreed that as of 1995,

the most well-known cause of MDR was P-glycoprotein ("Pgp"). Appx13128-13129 (Dr. Heathcock), Appx24259 (Dr. Ojima[3]).

Pgp is a protein found in the cell membrane that binds to foreign objects inside the cell and pumps them out through the cell membrane. Appx13123-13127 (Dr. Heathcock), Appx24216-24217 (Dr. Ludueña), Appx25038-25041 (*Kartner*). When a cancer cell produces abnormally large amounts of ("overexpresses") Pgp, the increased Pgp enables the cell to expel drugs at a rate high enough to cause drug resistance. *Id.*

As of 1995, the prior art taught that Pgp overexpression caused taxane resistance. Appx52-53. Sanofi itself published prior art papers confirming that docetaxel was susceptible to Pgp-mediated MDR. Appx25034-25036 (*Riou*), Appx24476 (*Wils*). The relevance of Pgp to taxane resistance in humans was confirmed in a 1994 clinical study. Appx17051 (*Uziely*); *see also* Appx24225-24226 (Dr. Ludueña). The district court correctly found that the POSA would have been motivated to modify docetaxel to reduce its susceptibility to Pgp-mediated MDR. Appx52-53.

[3] Dr. Ojima, Sanofi's expert, submitted an expert report and sat for deposition in this case, but did not testify live at trial after being withdrawn by Sanofi. *See* Appx12862-12863. Defendants subsequently offered testimony from Dr. Ojima via deposition designation. Appx24257-24288.

2. The District Court Properly Found That Lipophilicity Was a Known Strategy to Overcome Pgp But Erroneously Dismissed Its Applicability to Taxanes.

Although the court correctly found that the prior art taught "that a strategy for overcoming Pgp-mediated resistance in cancer cells was to increase lipophilicity," Appx42, the court erred in finding that a POSA would not have applied this strategy to taxanes. This critical error led the court to make other, related errors that ultimately resulted in finding the asserted claims of the '170 patent non-obvious.

Lampidis taught that a drug's susceptibility to Pgp could be mitigated by increasing its cell permeability (*i.e.*, ability to pass through the cell membrane) such that it could enter the cell faster than Pgp could pump it out. Appx42, Appx16954 (*Lampidis*). Both Defendants' expert, Dr. Heathcock, and Sanofi's biochemistry expert, Dr. Ludueña,[4] agreed that as a general matter, a drug compound's cell permeability typically increases as it becomes more lipophilic (having affinity for oil), Appx13138-40 (Dr. Heathcock), Appx24243 (Dr. Ludueña). As the compounds disclosed in *Lampidis* became more lipophilic, their ability to accumulate in and kill MDR cells was substantially increased, because more lipophilic drugs could "better overcome the efficiency of the MDR efflux 'pump' system." Appx1695, Appx24243-24245 (Dr. Ludueña). As the District Court correctly found, "a strategy

[4] Dr. Ludueña submitted an expert report and sat for deposition but did not testify live at trial. Defendants offered testimony from Dr. Ludueña via deposition designation. Appx24200-24256.

for overcoming Pgp-mediated resistance in cancer cells was to increase lipophilicity." Appx42. Accordingly, the POSA would have been motivated by *Lampidis* to make docetaxel more lipophilic. Appx13143-13144 (Dr. Heathcock).

Hait taught how specific changes to a drug's chemical structure could impact its ability to bind to Pgp (*i.e.*, its "Pgp affinity"). Appx25093-25094. Specifically, *Hait* disclosed a study conducted on a series of phenothiazine "reversal agents" (*i.e.*, "chemosensitzers" or "Pgp inhibitors") which were specifically designed to bind so tightly to Pgp that they interfered with its pumping activity. *Id*. *Hait* showed that compounds with the highest Pgp affinity had discrete hydrophilic and lipophilic regions. Appx25094. The POSA would therefore have been motivated to modify docetaxel such that its structure did not have discrete hydrophilic and lipophilic regions. Appx13151-13152 (Dr. Heathcock).

a) The District Court Erred in Dismissing the *Lampidis* and *Hait* References.

The court found that *Lampidis* and *Hait* were inapplicable to taxanes because they did not explicitly reference taxanes. Appx50. But an explicit teaching is not required. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1290–91 (Fed. Cir. 2006). There was substantial evidence that *Lampidis's* and *Hait's* teachings applied to taxanes, which the district court erroneously ignored.

The court failed to consider testimony from both sides' experts that the relationship between lipophilicity and cell permeability is generally applicable to all

drug compounds. Appx13138-13140 (Dr. Heathcock), Appx24243 (Dr. Ludueña). This would suggest to the POSA that *Lampidis*'s central teaching—that increased cell permeability results in improved performance against MDR cells—be applied to taxanes as well.

The District Court also erred in its dismissal of *Hait*. The court outright ignored admissions from Dr. Ojima that he was aware of the *Hait* binding model in 1994 and "took account" of this work when designing new taxanes. Appx24284, Appx24286. The court also made no mention of the prior art references that taught that both Pgp inhibitors (like those in *Hait*) and Pgp substrates (like taxanes) bind to the same site on Pgp. Appx16801-16802 (*Greenberger)*, Appx17014-17015 (*Safa*). Moreover, the court erroneously referred to *Hait* as being a binding model for "calmodulin," Appx50, when *Hait* itself makes clear that the model is directed to (and based on data from) Pgp binding. Appx25093-25094. All of this evidence would have provided an implicit connection between *Hait* and taxanes (as demonstrated by Dr. Ojima), and it was clear error for the court to ignore it.

3. The District Court Properly Concluded That the POSA Would Have Focused on Lipophilic Modifications to C-7 and C-10 But Erred in Finding No Specific Motivation to Arrive at Cabazitaxel.

Likewise, while the court properly found that the skilled artisan would have had a general motivation to "make modifications on the C-7 or C-10 position," Appx53, and that lipophilic substitutions at these positions could increase potency

against MDR cells, Appx39-40, Appx42-43, the court erroneously failed to apply the evidence presented that a POSA would have specifically focused on these positions in modifying docetaxel over other positions on the taxane core. The court also failed to analyze the evidence that the smallest, most conservative changes at these positions to improve lipophilicity would have resulted in cabazitaxel.

a) The Prior Art Identified C-7 and C-10 as Preferred Positions for Lipophilic Modification.

In applying the teachings of *Hait* and *Lampidis* to docetaxel, the skilled artisan would have been motivated by the prior art to focus on the C-7 and C-10 positions.

A substantial body of data regarding the Structure-Activity Relationships ("SAR")[5] associated with taxane drugs had been published in the prior art as of 1995 and summarized in a book (*Georg*), co-edited by Dr. Ojima, that "presented the key work in the taxane field at the time." Appx38. *Commerçon*, a chapter in that book by a research group at RPR, reported that while the side chain and southern hemisphere of the core (e.g., C-2, C-4, C-2', C-3') were "crucial" positions, such that substitutions at these sites result in significant losses in anti-cancer activity of the taxane, the northern hemisphere of the core (e.g., C-7, C-9, and C-10) was "flexible," and substitutions there did not carry the same risks. Appx25160-25162.

[5] SAR relates the chemical structure of a drug compound to its biological activity and is the primary basis by which skilled artisans design and evaluate new drug candidates. Appx13108-13109 (Dr. Heathcock), Appx13579-13580 (Dr. Roush), Appx24262-24263 (Dr. Ojima).

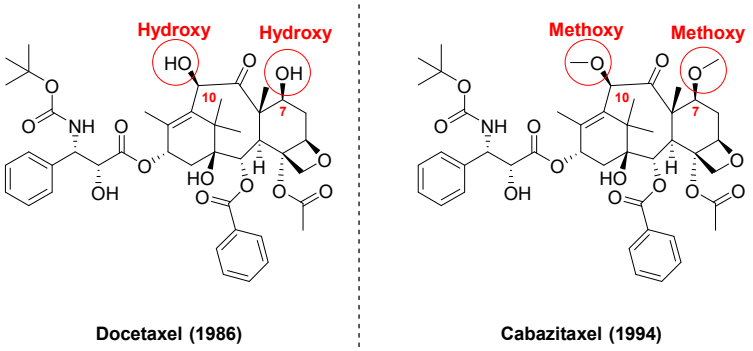
Kingston 1994, authored by Defendants' expert Dr. Kingston, came to a similar conclusion. Appx25148, Appx25155. A POSA seeking to make improvements to docetaxel without risking substantial potency losses would therefore focus on the "flexible" positions in the northern hemisphere. Appx13144 (Dr. Heathcock).

Both Drs. Heathcock and Ojima agreed that the hydroxy groups at C-7 and C-10 of docetaxel were the most hydrophilic region of the molecule. Appx13151-52 (Dr. Heathcock); Appx24266 (Dr. Ojima). The POSA would thus immediately recognize that making the C-7 and C-10 positions more lipophilic would likely satisfy the teachings of both *Lampidis* and *Hait* by increasing the overall lipophilicity of the compound while also removing a hydrophilic region required for Pgp binding. Appx13143-13144, Appx13151-13152 (Dr. Heathcock).

This was confirmed by the prior art, which taught that converting a C-7 hydroxy group to a more lipophilic group increased activity against MDR cells, Appx39-40, Appx25206 (*Golik*), Appx25506 (*EP'910*), and that potency against MDR cells could be improved by converting a C-10 hydroxy group to a small lipophilic group. Appx42-43, Appx25114-25115 (*Ojima 1994*). Indeed, the district court correctly found that the POSA would have had a general motivation to "make modifications on the C-7 or C-10 position", Appx53, and that the prior art taught that lipophilic substitutions at these positions could increase potency against MDR cells. Appx39-40, Appx42-43.

b) Adding Methoxy Groups at C-7 and C-10 Was the Smallest, Most Conservative Change to Increase Lipophilicity at These Positions.

Experts from both sides agreed that POSAs typically make small, incremental changes to a lead compound's structure. Appx13109 (Dr. Heathcock), Appx13579-13581 (Dr. Roush), Appx24262-24263 (Dr. Ojima). The smallest, most conservative change a POSA could make to docetaxel's C-7 and C-10 hydroxy groups to make them more lipophilic would be to convert each into methoxy groups, resulting in cabazitaxel. Appx13144-13146 (Dr. Heathcock).



The POSA would have been confident that this change would not be detrimental to anti-cancer potency because several studies in the prior art indicated that methoxy groups at both the C-7 and C-10 positions preserved potency of the compound. *Klein* and *Wong* taught that the use of a more lipophilic methoxy group at C-7 was well-tolerated and even increased *in vitro* potency against various cell lines and in mouse tumors. Appx25178-25179 (*Klein*), Appx25318, Appx25324 (*Wong*). *Kant* taught that the use of a methoxy group at C-10 maintained or

improved *in vitro* activity. Appx25311-12.

c) The District Court Erred in Finding No Specific Motivation to Make Simultaneous Methoxy Substitutions at C-7 and C-10.

Because the court failed to appreciate the import of *Hait* and *Lampidis*, the court found no specific motivation to modify C-7 and C-10 because "modifications were being made at multiple positions" across the taxane core and side chain. Appx53. This analysis failed to apply the teachings of *Commerçon* and *Kingston 1994* specifically that the C-7 and C-10 positions were "flexible" and could thus be readily modified without losing biological activity. Appx13113-13116 (Dr. Heathcock), Appx25160-25162 (*Commerçon*), Appx38, Appx42.

The District Court also made similar errors regarding the taxane references *EP '910*, *Golik*, and *Ojima 1994*. Although the court properly acknowledged that these references taught that lipophilic substitutions at C-7 and C-10 resulted in improved performance against MDR cells, Appx39-40, Appx42, it failed to apply these teachings in its substantive obviousness analysis. These references explicitly confirm the skilled artisan's motivation to substitute C-7 and C-10 to make them more lipophilic based on *Lampidis* and *Hait*.

The District Court further erred in failing to consider testimony about the POSA's motivation to make small, conservative changes. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.* ("*BMS*"), 752 F.3d 967, 974-75 (Fed. Cir. 2014). The

POSA would perform a simultaneous methoxy substitution at the C-7 and C-10 positions of docetaxel because, as Dr. Heathcock explained, this would have been the smallest, most conservative change to make those positions more lipophilic. Appx13144-13145, Appx13152, Appx13177-13178.

Based on these errors, the court erroneously characterized the testimony of Drs. Heathcock and Kingston regarding the C-7 and C-10 position data from *Kant, Klein,* and *Wong* references as "cherry pick[ing]." Appx52. But the evidence showed that the POSA would have already been focused on making these small conservative changes at these specific positions, and that these references would have served simply as confirmation of this approach in the prior art. In other words, Defendants' experts picked these data because these are precisely the data a POSA would have focused on to confirm that the small conservative changes at these positions they were *already* interested in making would not be detrimental to the compound's potency.

d) The District Court's Findings on Unexpected Results Supports *Prima Facie* Obviousness

Finally, the district court found that cabazitaxel's superior performance was "not entirely unexpected," and as such, the skilled artisan would "expect that cabazitaxel would show improved potency over docetaxel." Appx55-56. These findings laid a strong foundation for *prima facie* obviousness. Despite making these findings, the District Court clearly erred by ignoring critical evidence and expert

testimony in finding the claims non-obvious.

SUMMARY OF THE ARGUMENT

I. SANOFI'S APPEAL: The '592 Patent.

The District Court entered judgment of invalidity on claims 7, 11, 14-16, 21, 26, and 30 of the '592 patent—claims Sanofi asserted against Defendants for nearly three years and took to trial. Sanofi appeals whether the court had subject matter jurisdiction over Defendants' counterclaims with respect to the disclaimed claims (7, 11, 14-16, and 26). While Sanofi does not appeal the judgment of invalidity with respect to claims 21 and 30, Sanofi argues that Defendants' counterclaims for the disclaimed claims became moot: (1) as of November 24, 2017, the date the time for appeal of the PTO's FWD in the '592 patent IPR had passed; or (2) at the latest, December 8, 2017, the date of the statutory disclaimer. BlueBr3, BlueBr12.

At the core of this justiciability dispute is the issue of claim preclusion; specifically, whether Sanofi should be allowed to sue Defendants a second time on the '592 patent if and when it secures substitute claims that it is actively pursuing in the IPR appeal. At the time of the District Court's judgment, Sanofi's intentions were clear, and they remain clear today—as soon as it secures the substitute claims, it intends to sue Defendants a second time on the '592 patent. Defendants respectfully submit that under this Court's claim preclusion precedents—such as *Aspex Eyewear, Inc. v. Marchon Eyewear, Inc.*, 672 F.3d 1335 (Fed. Cir. 2012) and

Senju—Sanofi's intended second suit on the '592 patent is precluded because, during the litigation, Sanofi could have asserted claims 1 and 27 (and in fact did initially assert those claims), which indisputably are broader in scope than the substitute claims. If this Court agrees, Defendants do not oppose Sanofi's appeal seeking vacateur of the District Court's judgment of invalidity for the disclaimed claims.

If, however, this Court disagrees with Defendants that Sanofi's previous assertion of claims 1 and 27 of the '592 patent bar a second suit Sanofi intends to file, then Defendants respectfully submit that Defendants' counterclaims with respect to the disclaimed claims were not moot, and in fact were justiciable, at the time the District Court entered judgment, because: (1) there was a concrete, ripe dispute between the parties with respect to patent certainty that was not mooted by the inevitable cancellation of the disclaimed claims or by Sanofi's statutory disclaimer, in accordance with this Court's decision in *Teva*; and (2) the court's judgment of invalidity for the disclaimed claims presents collateral consequences, namely, collateral estoppel, for certain issues of fact and law that will inevitably arise in Sanofi's second suit. *Minnesota Mining & Mfg. Co. v. Barr Labs., Inc.*, 289 F.3d 775, 780-81 (Fed. Cir. 2002) ("*3M*") (no mootness if collateral consequences are not duly conjectural); *Microsoft Corp. v. ITC*, No. 2012-1445, 2014 WL 10209132, at *1 (Fed. Cir. Jan. 3, 2014) (same). The court's judgment as to the disclaimed claims should thus be affirmed if this Court finds that Sanofi's previous

assertion of claims 1 and 27 do not bar the second suit Sanofi intends to file.

II. DEFENDANTS' CROSS-APPEAL: The '170 Patent.

1. Despite making several findings in Defendants' favor, the District Court committed clear error in ultimately concluding that the asserted claims are non-obvious. The court failed to assess the prior art as a whole, criticizing several references for perceived defects while failing to consider or outright ignoring other highly relevant prior art and implicit teachings in the prior art that vitiated these alleged defects. Moreover, the court failed to consider whether the skilled artisan would have been motivated to make small conservative changes when modifying docetaxel. Furthermore, the court's unexpected results analysis, specifically the finding that a skilled artisan would expect cabazitaxel to have superior properties to docetaxel, directly undermines the court's core holding regarding *prima facie* obviousness.

2. Given the obviousness of the claims on their face, the court's analysis of secondary considerations cannot rescue them. The court afforded minimal weight to Sanofi's unexpected results argument, finding that a skilled artisan would have expected cabazitaxel to have superior biological performance when compared to docetaxel. This holding reinforces an already strong *prima facie* obviousness case, which cannot be overcome by the court's findings in favor of Sanofi regarding failure of others and commercial success.

ARGUMENT

I. SANOFI'S APPEAL: The '592 Patent.

A. Standard of Review.

This Court reviews a district court's decision on whether an actual controversy exists in declaratory judgment actions involving patent infringement or invalidity *de novo*. *Apotex*, 781 F.3d at 1361.

B. Legal Standard for Justiciability.

This Court has held that, "federal courts have subject matter jurisdiction over [declaratory judgment actions brought under the Hatch-Waxman Act] to the extent that [such actions] present an Article III case or controversy." *Caraco Pharm. Labs., Ltd. v. Forest Labs., Inc.*, 527 F.3d 1278, 1290 (Fed. Cir. 2008). In *MedImmune*, the Supreme Court explained that for a dispute to be justiciable it must be:

> "definite and concrete, touching the legal relations of parties having adverse legal interests"; and that it be "real and substantial" and "admi[t] of specific relief through a decree of a conclusive character, as distinguished from an opinion advising what the law would be upon a hypothetical state of facts."

MedImmune, 549 U.S. at 127 (quoting *Aetna Life Ins. Co. v. Haworth*, 300 U.S. 227, 240-241 (1937)). The Court distilled the inquiry into "whether the facts alleged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *Id*. (internal quotation omitted).

In applying "all-the-circumstances," this Court has been guided by the

Supreme Court's three-part framework for determining whether a justiciable Article III controversy exists: (1) the plaintiff has standing; (2) the issues are ripe; and (3) the case is not moot at any stage of the litigation. *Caraco*, 527 F.3d at 1291.

C. Defendants Do Not Oppose Sanofi's Appeal If Its Previous Assertion of Claims 1 and 27 Precludes It from Later Asserting the Substitute Claims.

Sanofi filed its appeal for one reason: to prevent any claim preclusion arising from the District Court's judgment of invalidity for the disclaimed claims, so that it may sue Defendants a second time on the '592 patent once it secures the substitute claims it is seeking through the IPR appeal. BlueBr4-5. But Sanofi is already precluded from asserting the substitute claims by virtue of the fact that, during the litigation, Sanofi could have asserted, (and did initially assert), claims 1 and 27 of the '592 patent. If this Court agrees, then Defendants do not oppose Sanofi's appeal.

1. Principles of Claim Preclusion.

Claim preclusion is a question of law. *Brain Life, LLC v. Elekta Inc.*, 746 F.3d 1045, 1052 (Fed. Cir. 2014). Claim preclusion bars "the relitigation of a claim, or cause of action, or any possible defense to the cause of action which is ended by a judgment of the court." *Id*. at 1053 (internal quotations omitted). "Under Third Circuit law…claim preclusion principles require: '(1) a final judgment on the merits in a prior suit involving[](2) the same parties or their [privies]; and (3) a subsequent suit based on the same cause of action." *Senju*, 746 F.3d at 1348 (quoting *CoreStates*

Bank, N.A. v. Huls Am., Inc., 176 F.3d 187, 194 (3d Cir. 1999)). Whether a cause of action in a patent case is the same as, or different from, another cause of action, is analyzed under Federal Circuit law. *Id*. "[C]laim preclusion bars both claims that were brought as well as those that *could have been* brought." *Brain*, 746 F.3d at 1053 (emphasis in original); *see also*, *C.I.R. v. Sunnen*, 333 U.S. 591, 597 (1948). "Claim preclusion will generally apply when a patentee seeks to assert the same patent against the same party and the same subject matter." *Senju*, 746 F.3d at 1349.

2. Sanofi's Previous Assertion of Claims 1 and 27 Bars It from Later Asserting the Substitute Claims.

Sanofi does not dispute that in the subsequent suit it intends to file against Defendants asserting the '592 patent, the Third Circuit's Factors 1 and 2 for claim preclusion will be met. Sanofi only disputes whether Factor 3 (same cause of action) is met. BlueBr31-39.

This Court has analyzed claim preclusion in the context of amended and new claims for a patent secured through reexamination. In both *Aspex* and *Senju*, this Court held that, where patent claims secured through reexamination[6] are

[6] There is no principled reason why the holdings of *Aspex* and *Senju* should not apply in the IPR context. Congress replaced *inter partes* reexamination with IPR. *Abbott Labs. v. Cordis Corp.*, 710 F.3d 1318, 1326 (Fed. Cir. 2013). As with reexamination, IPR does not result in a new patent—the process ends with the same patent and a certificate incorporating any cancellations or allowed changes. 35 U.S.C. § 318(b). Like reexamination, IPR only permits amendment that does not enlarge the scope of the claims. 35 U.S.C. § 316(d)(3).

insubstantially different, or narrower in scope, than patent claims that were asserted, or could have been asserted, against a defendant in a prior suit involving specific acts of infringement, that went to final judgment, a subsequent suit on those insubstantially different, or narrower claims, against the same defendant involving the same acts of infringement is barred by claim preclusion. *Aspex*, 672 F.3d at 1340-42; *Senju*, 746 F.3d at 1352-54.

In *Aspex*, the patent owner sued Revolution on claims 6, 22, and 34 of the '545 patent. *Aspex*, 672 F.3d 1337-38. The district court granted Revolution's motion for summary judgment of non-infringement of claims 6 and 34, but found that Revolution infringed claim 22, and that it was not invalid. *Id*. at 1338-39. Meanwhile, the '545 patent was reexamined by the PTO at the request of a third party. *Id*. During that process, Aspex amended original claim 23 to narrow it and added new claim 35, which depended from amended claim 23. *Id*. at 1339-40. On appeal from a subsequent suit Aspex filed against Revolution asserting amended claim 23 and new claim 35, this Court rejected Aspex's argument that reexamination created new causes of action. *Id.* at 1341. This Court noted that amended claim 23 and new claim 35 were "insubstantial[y]" different in that they were merely narrower versions of original claim 23, and that, therefore, they did not create any new rights that Aspex did not enjoy in connection with the original '545 patent. *Id*. at 1341-42. The Court also expressly noted that, although original claim 23 was not asserted

against Revolution in the prior action, it could have been, and that, "[t]o allow Aspex to pursue amended claim 23 and new claim 35 in this case would thus present a clear instance of 'claim splitting,' which is forbidden by the principles of res judicata." *Id*. at 1341.

In *Senju*, the brand patent owner Senju sued alleging that Apotex's ANDA for gatifloxacin infringed claims 1-3 and 6-9 of the '045 patent. *Senju*, 746 F.3d at 1347. After a bench trial, the district court found those claims invalid. *Id*. at 1347. After the court issued its opinion, but before entering final judgment, Senju sought reexamination of the '045 patent, where it narrowed claim 6, and added new claims 12-16, which were narrowed versions of claim 1. *Id*. at 1347, 1353 n.2. On appeal of a subsequent suit Senju filed asserting that Apotex's same gatifloxacin ANDA infringed amended claim 6 and new claims 12-16, this Court, following *Aspex*, agreed that Senju's subsequent suit was barred by claim preclusion. *Id*. 1353-54.

Aspex and *Senju* are directly on point here. Sanofi sued Defendants initially asserting infringement of claims 1-30. After the District Court issued its claim construction ruling rejecting Sanofi's argument that the preambles of independent claims 1 and 27 were limitations requiring efficacy, Sanofi dropped its assertion of those claims, as they were clearly anticipated by its Phase III Disclosures. It is indisputable that claims 1 and 27, the only independent claims of the '592 patent, are broader in scope than the substitute claims Sanofi is seeking through the IPR.

BlueBr10. Under *Aspex*, it matters not that Sanofi did not take claims 1 and 27 to trial, as claim preclusion applies to all claims that were or *could have been* asserted. Thus, the fact that Sanofi could have, and in fact, initially did assert claims 1 and 27 bars a second suit on the substitute claims.

3. Sanofi's Attempts to Distinguish *Senju* Should Be Rejected.

Sanofi attempts to distinguish *Senju* by arguing that: (1) as a matter of policy, claim preclusion should not apply because Sanofi has been above-board, is not seeking a "do-over" of a case it lost, and because it would frustrate the purpose of claim amendment in IPR proceedings parallel to Hatch-Waxman litigation; and (2) the substitute claims it is seeking create new causes of action because those claims are not narrowed versions of the disclaimed claims. BlueBr31-39.

First, its arguments notwithstanding, Sanofi engaged in extensive gamesmanship throughout the District Court litigation. As explained in detail, *supra*, Sanofi asserted all 30 claims against Defendants at the outset of the litigation, but after it lost its bid to have the preambles of claims 1 and 27 construed as limitations requiring efficacy to overcome its own Phase III Disclosures, Sanofi began dropping claims—often times without informing either Defendants or the court that it was no longer asserting the claims those claims. Perhaps most egregious are the disclaimed claims, which Sanofi asserted in the pretrial order, litigated at trial, and then, after the Parties' experts testified on infringement and Defendants'

expert testified as to invalidity of those claims, Sanofi notified the court and Defendants that it was "going to focus [its invalidity expert's] direct examination…on two specific claims…Claims 21 and 30." Appx13841. Sanofi never formally notified the court that it was withdrawing its assertion of the disclaimed claims before the close of trial, or even during post-trial briefing, despite being on actual notice that Defendants were pursuing their counterclaims and seeking judgment of invalidity for those claims. It wasn't until nearly two months after trial, after post-trial submissions, and on the eve of the court's decision, that Sanofi finally informed the court that it was not appealing the PTO's unpatentability determination for the disclaimed claims and that, in Sanofi's opinion, there remained no justiciable controversy with respect to those claims. Defendants respectfully submit that Sanofi's failure to timely withdraw its assertion of the disclaimed claims before trial, or even during post-trial briefing, resulted in a waste of court and party resources and was nothing short of gamesmanship.

Second, Sanofi's argument that it was not seeking a "do-over" when it filed its motion to amend because the IPR was filed by Mylan, not Sanofi, and because Sanofi's motion to amend was filed before any decision by the District Court, is disingenuous. Sanofi filed its motion to amend ***after*** it lost its critical battle on claim construction. While Defendants maintained all along that, irrespective of how the '592 patent claims were construed, all 30 claims were invalid, at that point, there

ceased to be any reasonable doubt that a number of the '592 patent claims—especially independent claims 1 and 27—were anticipated by Sanofi's Phase III Disclosures, and that the remaining claims were obvious over the prior art. As explained above, Sanofi's motion to amend was an attempt to circumvent both the District Court's and the PTO's claim construction rulings by re-writing the preamble of claim 27 in a way that Sanofi believed (incorrectly) would transform it into a limitation requiring efficacy.

And Sanofi's motion to stay the District Court litigation was not a genuine attempt to conserve court and party resources (BlueBr33)—it was merely a self-serving attempt to stave off an adverse ruling on the invalidity of the '592 patent until the IPR was resolved. In the nine months after Mylan filed its IPR petition and before Sanofi filed its stay motion, Sanofi never once informed the court that a stay might be necessary, despite Mylan's affirmation to the court that the IPR should not impact the schedule (Appx5109).

Third, Sanofi's policy arguments about why claim preclusion should not apply ignore *Senju*, the purposes behind the long-standing doctrine of claim preclusion, and Sanofi's own malfeasance. *Senju* itself was a Hatch-Waxman case, and the same policy arguments Sanofi makes could have been made by Senju to this Court—namely, that claim preclusion should not apply because it would frustrate claim amendment by brand companies in reexamination during the pendency of

parallel Hatch-Waxman litigation. To accept Sanofi's position, this Court would essentially have to overrule *Senju*, and ignore decades of claim preclusion jurisprudence recognizing the important purpose served: "economy of judicial time and public policy favoring the establishment of certainty in legal relations." *Senju*, 746 F.3d at 1348 (quoting *C.I.R.*, 333 U.S. at 597).

Sanofi could have avoided the present situation had it adopted a more prudent course. It could have filed for the '592 patent ***before*** it published in its Phase III Disclosures the very use of cabazitaxel it claimed in the '592 patent. It could have filed for the substitute claims during original prosecution of the '592 patent, or it could have sought reexamination shortly after the patent issued and sought the claims then. Instead, Sanofi filed for the '592 patent over a year after the Phase III Disclosures published, and waited almost two years after it filed suit on the '592 patent to seek amendment. Sanofi's malfeasance does not justify its policy arguments or its request for this Court to overrule *Senju*.

The *Target Training International, Ltd. v. Extended Disc North America, Inc.*, 645 F. App'x 1018 (Fed. Cir. 2016) case Sanofi relies on is inapposite; in that case there was no final judgment that could give rise to claim preclusion. *Id*. at *1025-*1026. Moreover, Sanofi misconstrues *Target*'s reliance on *Aspex* to incorrectly argue that "amended [patent] claims [that] do not yet exist and could not have been asserted in the district court litigation" cannot be precluded by a prior suit on the

same patent. BlueBr35. The quotation from *Aspex* relied on by *Target* referenced "claims" to refer to "causes of action," not "patent claims," that arise during the pendency of a prior litigation. *Target*, 645 F. App'x at *1018; *Aspex*, 672 F.3d at 1345; *Senju*, 746 F.3d at 1349. In *Aspex*, the potential new causes of action related to new products made/sold during the pendency of the case. *Aspex*, 672 F.3d at 1345. Neither *Aspex* nor *Target* held that ***patent claims*** that issue during the pendency of a case are not barred by claim preclusion, and *Senju* held just the opposite—patent claims secured through reexam/IPR during the pendency of a case that are insubstantially different than claims from the same patent previously adjudicated are barred. *Senju*, 746 F.3d at 1347, 1353.

Finally, Sanofi's argument that *Senju* does not apply because Sanofi's substitute claims are not narrower versions of the disclaimed claims misses the mark. The fact that they are indisputably narrower than claims 1 and 27 is what bars Sanofi from asserting the substitute claims.

D. If Sanofi's Previous Assertion of Claims 1 and 27 Does Not Bar the Substitute Claims, Then There Was a Justiciable Controversy Regarding the Disclaimed Claims.

If this Court disagrees that Sanofi's previous assertion of claims 1 and 27 bars a second suit on the '592 patent, then the disclaimed claims were justiciable at the time the District Court entered final judgment because there was a concrete, ripe, non-moot dispute regarding patent certainty, and because collateral consequences

preclude mootness.

1. There Was a Justiciable Controversy Regarding Patent Certainty.

a) "All-the-Circumstances": *Teva v. Novartis*.

Teva was a pre-MMA case where Novartis, had listed five patents in the Orange Book for Famvir®. *Teva*, 482 F.3d at 1334. In response to Teva's ANDA filing, Novartis sued on only one patent—the '937 patent—but did not "file suit nor threaten Teva" on the remaining four patents ("the unasserted patents"). *Id*. at 1334, 1340. Teva responded with a declaratory judgment action on the unasserted patents to establish patent certainty, which the district court dismissed as non-justiciable, applying this Court's pre-*MedImmune* standard. On appeal, this Court reversed, finding the pre-*MedImmune* standard abrogated, and finding that, under the *MedImmune* "all-the-circumstances" standard, a justiciable controversy existed with respect to the unasserted patents because of: (1) Novartis' listing of the Famvir® patents in the Orange Book; (2) Teva's submission of its ANDA with P-IV certifications for all listed patents; (3) the combination of a) 21 U.S.C. § 355(j)(5)(C) (civil action to obtain patent certainty), b) 35 U.S.C. § 271(e)(5) (ANDA declaratory judgment provision), and c) the purpose of the Hatch-Waxman act; (4) Novartis' pending suit on the '937 patent; and (5) "the possibility of future litigation" on the unasserted patents ("threat of protracted litigation creates a present and real harm"). *Id*. at 1341-46.

All of the *Teva* circumstances exist here with respect to the disclaimed claims. First, Sanofi listed the '592 patent in the Orange Book for Jevtana®, and the patent remains listed. Second, Defendants have submitted regulatory applications seeking approval for cabazitaxel products, and have maintained P-IV certifications for the '592 patent. Third, in 21 U.S.C. § 355(j)(5)(C) (§ 355(c)(3)(D) for 505(b)(2) NDAs), Congress expressly authorized ANDA-filers (and 505(b)(2)NDA-filers) to file declaratory judgment actions seeking patent certainty for unasserted patents. Here, Sanofi has asserted the '592 patent, but is attempting to avoid any finality in order to retain the right to re-assert that same patent after it secures the substitute claims. Fourth, Sanofi sued Defendants on the '592 patent, and expressly telegraphed its intent (with its motion to amend the '592 patent and its appeal of the PTO's denial) to sue Defendants a second time on the '592 patent.

Finally, the threat of future litigation that Sanofi has created, by suing Defendants on the '592 patent and expressing its intent to sue Defendants a second time, creates a present and real harm for Defendants. All of the *Teva* factors are met.

b) The District Court Judgment Provides Certainty.

The District Court's judgment of invalidity for the disclaimed claims bars a second suit. Disclaimed claim 11 depends from claim 10, which in turn depends from claim 1. Appx368-369. As the District Court found, claim 1 covers a method of treating docetaxel-resistant prostate cancer by administering 20-25 mg/m^2 of

cabazitaxel plus a corticoid. Appx74, Appx91. Claim 10 adds the requirement of monitoring blood counts and measuring neutrophil levels, and claim 11 adds discontinuing treatment when neutrophil counts are ≤ 1,500 cells/mm^3. As the court found, "monitoring blood counts and measuring neutrophil levels are part of the standard of care inherent in providing chemotherapy," and the prior art disclosed discontinuing treatment when neutrophils dip below 1,500 cells/mm^3 (Appx96-97), findings not challenged by Sanofi. Thus, claim 11 is insubstantially different from claim 1, and the substitute claims are insubstantially different from, and merely narrower versions of, claims 1 and 11. Under *Aspex* and *Senju*, Sanofi is barred from asserting the substitute claims against Defendants.

Sanofi's argument that *Senju* does not apply because the disclaimed claims individually are not broader in scope than any of the substitute claims, except claim 26 vis-à-vis substitute claim 34 (BlueBr36-39), reflects a misunderstanding of this Court's claim preclusion jurisprudence. *Aspex*, which *Senju* relies on, never required a prior claim broader in scope, only that any new or substitute claims are insubstantially different from the patent claims that were, or could have been, previously asserted. *Aspex*, 672 F.3d at 1341; *Senju*, 746 F.3d at 1350-54. Here, the substitute claims are insubstantially different from at least disclaimed claim 11.

c) "Inevitable Cancellation" and Sanofi's Disclaimer Do Not Moot the Controversy.

Sanofi's argument that Defendants' counterclaims with respect to the

disclaimed claims became moot on November 24, 2017, the deadline for Sanofi to appeal the PTO's unpatentability determination, or at the latest by December 8, 2017, the date of its disclaimer, is incorrect because neither event provided Defendants with the patent certainty to which they are entitled under *Teva*. "A case becomes moot only when it is impossible for a court to grant any effectual relief whatever to the prevailing party." *Knox v. Serv. Emp. Int'l Union, Local 1000*, 132 S. Ct. 2277, 2287 (2012) (internal quotations omitted). "[A]s long as the parties have a concrete interest, however small, in the outcome of the litigation, the case is not moot." *Id*. (internal quotations omitted). As explained above, to the extent Sanofi's previous assertion of claims 1 and 27 does not bar a second suit on the '592 patent, the District Court's judgment of invalidity provides Defendants with the claim preclusion relief to which they are entitled. *Caraco*, 527 F.3d at 1281-82 (holding covenant-not-to-sue insufficient to render declaratory judgment claims moot); *Apotex*, 781 F.3d at 1358 (patent disclaimer insufficient to render ANDA-filer's declaratory judgment claims against disclaimed patent non-justiciable).

d) The Patent Certainty Dispute Is Not Speculative.

Sanofi attempts to distinguish *Teva* by arguing that the unasserted patents there had issued while the substitute claims Sanofi is actively seeking "do not yet exist." BlueBr42-44. But this misleading argument is predicated on the assumption that the substitute claims—which exist, and are specific, defined and cannot be

changed by Sanofi alone (35 U.S.C. § 316(d); 37 C.F.R. § 42.121), but have not yet issued—represent a separate patent that has not yet issued; they do not. Sanofi is merely seeking to amend the '592 patent—an existing, issued patent—to include narrower claims so that it can sue Defendants yet again after it lost its first suit. Sanofi's focus on the substitute claims, as opposed to the existing issued patent it is seeking to amend, is erroneous for purposes of patent certainty under *Teva*. The patent certainty provisions of the MMA—21 U.S.C. § 355(j)(5)(C) (§ 355(c)(3)(D) for (b)(2) NDAs)—authorize a civil action for ***patent*** certainty, not certainty as to some but not all claims. Defendants are entitled to secure a judgment and relief sufficient to preclude a second suit from Sanofi on the same '592 patent.

The cases Sanofi relies on to argue that there is no immediate or real controversy "[w]here the existence of patent claims is uncertain" (BlueBr43)—*Amana Refrigeration, Inc. v. Quadlux, Inc.*, 172 F.3d 852 (Fed. Cir. 1999), *Spectronics Corp. v. H.B. Fuller Co.*, 940 F.2d 631 (Fed. Cir. 1991), and *Visto Corp. v. Sproqit Technologies, Inc.*, No. C-04-0651 EMC, 2006 U.S. Dist. Lexis 96173 (N.D. Cal. Oct. 4, 2006)—all predate *Teva* and are no longer good law. *See Liquid Dynamics Corp. v. Vaughan Co.*, 355 F.3d 1361, 1370-71 (Fed. Cir. 2004) (recognizing *Spectronics*' abrogation); *Vestcom Int'l, Inc. v. Info. Planning and Mgmt. Serv., Inc.*, No. 4-08-CV00276, 2008 WL 11346217, at *8 n.1 (E.D. Ark. Aug. 12, 2008) (recognizing *Amana*'s abrogation); *Visto*, 2006 U.S. Dist. Lexis

96173, at *19-*20 (relying on *Amana* and *Spectronics*). Moreover, *Amana* and *Spectronics* involved alleged controversies based on potential issuance of reissue patents, which this Court has recognized are separate patents ordinarily giving rise to "independent and distinct causes of action." *Senju*, 746 F.3d at 1349, 1352; *Amana*, 172 F.3d at 855-56; *Spectronics*, 940 F.2d at 636-38. By contrast, the substitute claims Sanofi is seeking are for the same '592 patent.

Finally, none of *Amana*, *Spectronics*, or *Visto* involves the *Teva* circumstances present here—Orange Book patent listings, P-IV certifications for those patents, and suit by the brand on one or more of the patents. Under *Teva*, that is all that is needed for justiciability of Defendants' counterclaims for the disclaimed claims. *Teva*, 482 F.3d at 1344 ("The combination of these three circumstances is dispositive in establishing an actual declaratory judgment controversy as to all the [P-IV] certified patents.").

Even if this Court considers the fact that the substitute claims have not yet issued, this does not render speculative the harm they pose to Defendants. BlueBr39-44. "Whether an action is ripe requires an evaluation of both the fitness of the issues for judicial decision and the hardship to the parties of withholding court consideration." *Caraco*, 527 F.3d at 1294-95 (internal quotations omitted). "[A]n action is fit for judicial review where further factual development would not significantly advance a court's ability to deal with the legal issues presented." *Id*.

(internal quotations and brackets omitted). Additional factual development would not advance the District Court's ability to decide Defendants' invalidity counterclaims—Defendants presented unrebutted evidence at trial that the disclaimed claims were invalid, and the court relied on that evidence to find the claims invalid.

"Withholding court consideration…causes hardship to [a party] where the complained-of conduct has an immediate and substantial impact on the [party]." *Id*. at 1295 (internal quotations omitted). Here, the threat of a second suit on the '592 patent "creates a present and real harm." *Teva*, 482 F.3d at 1345. Sanofi is actively seeking issuance of the substitute claims it has sought to add to the '592 patent—it is presently before this Court in a parallel appeal (*Aventis*) seeking reversal of the PTO's denial of its motion to amend. If this Court does reverse, then a second suit on the '592 patent is all but guaranteed. While this Court could remand to the PTO for further findings, that would simply extend the IPR process and forestall Sanofi's second suit by an additional amount of time. But "[t]he immediacy requirement is not concerned in the abstract with the amount of time that will occur between the filing of the declaratory judgment action and the liability-creating event." *Sandoz, Inc. v. Amgen Inc.*, 773 F.3d 1274, 1277 (Fed. Cir. 2014) (noting that "[a]n event that is several years in the future may be an appropriate subject for a declaratory judgment."). "The immediacy requirement is concerned with whether there is an

immediate impact on the [party] and whether the lapse of time creates uncertainty." *Id*.

There is clearly an immediate impact on Defendants—the threat of a second suit on the '592 patent, subjecting Defendants to potential injunctive relief and damages if Defendants have launched their products. Sanofi has taken concrete actions to make this threat a reality, by aggressively pursuing its substitute claims, appealing the PTO's denial of its motion to amend, filing its statutory disclaimer in an attempt to eliminate claim preclusion, and filing this appeal. Under *Teva* that is enough for immediacy. Sanofi's argument that Defendants are not suffering any harm from the threat of a second suit on the '592 patent because they are blocked by the '170 patent (BlueBr43-44) is incorrect—throughout the litigation Defendants have challenged the validity of the '170 patent, and do so here on appeal.

The remaining contingencies Sanofi identifies—whether it will actually sue Defendants a second time on the '592 patent and whether these litigations will settle—are contingencies that existed in *Teva* and were rejected by this Court as rendering the controversy there too speculative.

2. Collateral Consequences Preclude Mootness.

The District Court's judgment of invalidity for the disclaimed claims has collateral consequences that preclude mootness—namely, collateral estoppel relief to Defendants for issues of law and fact decided by the District Court in connection

with the disclaimed claims that will inevitably arise in Sanofi's second suit asserting the substitute claims.[7]

This Court has recognized that collateral consequences that are not unduly speculative preclude mootness. *3M*, 289 F.3d at 780-81; *Microsoft*, 2014 WL 10209132, at *1. In *3M*, a pre-MMA ANDA suit, 3M sued ANDA-filer Barr alleging infringement of an Orange Book patent, and Barr counterclaimed for non-infringement. *3M*, 289 F.3d at 777-78. After discovery, "3M represented that it no longer claimed infringement by Barr," and requested dismissal without prejudice, believing that a dismissal without prejudice would not trigger first-filer Alphapharm's 180-day exclusivity (and would therefore forestall approval of Barr's ANDA until that exclusivity expired). *Id.* at 778-79. The district court denied 3M's dismissal request and granted Barr summary judgment of non-infringement. *Id.* On appeal, 3M argued that its representation stripped the district court of jurisdiction. *Id*. at 780. This Court agreed that, "if this case did not involve the Hatch-Waxman Amendments, [3M] might well be correct" that jurisdiction was lost after 3M's

[7] Sanofi currently also has a continuation application pending, U.S. Pat. App. No 15/627,962, that contains claims that are substantially similar to those of the '592 patent. Sanofi will likely try to assert these claims against Defendants should the application issue as a patent. The factual findings and legal conclusions that the district court made with respect to the disclaimed claims will still be relevant to the claims of the continuation application. A finding of invalidity on the disclaimed claims could support collateral estoppel that would prevent Sanofi from asserting the claims that issue from its continuation application that raise the same legal and factual issues, another potential collateral effect of the district court's decision.

representation. *Id*. But because: (1) it was a Hatch-Waxman case, (2) "the parties strenuously disagree about whether the action should be dismissed with or without prejudice," and (3) 3M argued "that the form of dismissal could have significant consequences in the FDA proceedings," this Court found that, whether or not 3M was correct about such collateral consequences, "these differences are more than sufficient to create subject matter jurisdiction." *Id*. at 780-81.

Here, at the time of the District Court's judgment, the parties had a dispute about patent certainty and the scope of the final judgment. The District Court's judgment for the disclaimed claims provides Defendants with collateral estoppel relief from Sanofi's second suit. "Collateral estoppel protects a party from having to litigate issues that have been fully and fairly tried in a previous action and adversely resolved against a party-opponent." *Ohio Willow Wood Co. v. Alps South, LLC*, 735 F.3d 1333, 1342 (Fed. Cir. 2013). Here, the validity of the disclaimed claims was fully litigated at trial, and issues of fact and law found or concluded by the District Court concerning those claims should not have to be relitigated by the Parties in Sanofi's second suit. For example, the Parties should not have to relitigate the invalidity of substitute claims directed to methods of increasing survival with dosages of cabazitaxel beyond the 20 mg/m^2 dosage recited in non-disclaimed claims 21 and 30 (*e.g.*, substitute claim 31). Appx368-369, Appx10793. In connection with disclaimed claim 11, the District Court found that dosages of

cabazitaxel beyond 20 mg/m^2 were in the prior art and used to treat docetaxel-resistant prostate cancer. Appx91, Appx96-97.

Because the District Court's judgment has collateral consequences in the second '592 patent suit Sanofi intends to bring against Defendants, those consequences preclude mootness.

3. Sanofi's Attempts to Manipulate the District Court's Jurisdiction Should Be Rejected.

Federal courts have an "interest in preventing litigants from attempting to manipulate [their] jurisdiction" to achieve a favorable result, which counsels against mootness. *City of Erie v. Pap's A.M.*, 529 U.S. 277, 288 (2000); *3M*, 289 F.3d at 780. As detailed above, Sanofi engaged in extensive gamesmanship with respect to the claims from the '592 patent it was asserting throughout the litigation, culminating in a statutory disclaimer filed over two months after trial on the eve of the District Court's decision. This calculated strategy was an attempt by Sanofi to preserve its ability to sue Defendants a second time on the '592 patent. For this additional reason, the District Court's judgment should be affirmed.

II. DEFENDANTS' CROSS-APPEAL: The '170 Patent.

A. Standard of Review.

On appeal from a bench trial, this court reviews the trial court's conclusions of law *de novo* and findings of fact for clear error. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). The ultimate conclusion of whether a claimed

invention would have been obvious is a question of law reviewed *de novo* based on underlying findings of fact, which are reviewed for clear error. *Id*. at 1359. Factual findings that rest on a mistaken view of the law are not entitled to deference, however. *Inwood Labs., Inc. v. Ives Labs., Inc.*, 456 U.S. 844, 855 n.15 (1982). A factual finding is clearly erroneous if, despite some supporting evidence, "the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *Pfizer*, 480 F.3d at 1359.

B. The District Court's Decision Was Premised on Both Legal Error and Clearly Erroneous Factual Findings.

Despite crediting and accepting much of Defendants' evidence of obviousness, the District Court's obviousness analysis was based on several legal errors which led the district court to reach clearly erroneous factual findings and legal conclusions. Each error detailed below is independently grounds for remand if not reversal of the court's obviousness determination.

1. The District Court Properly Credited Much of Defendants' Evidence Supporting *Prima Facie* Obviousness.

As discussed above, despite a number of legal and factual errors in its analysis, the court made several key findings that support Defendants' *prima facie* obviousness case.

The court properly found that the skilled artisan would have "selected either docetaxel or paclitaxel as a lead compound," Appx45, and found Defendants'

experts "credible with respect to the fact that a [skilled artisan] might have selected docetaxel as the lead compound." *Id.*[8]

The court also correctly held that a skilled artisan at the relevant time would have recognized the problem of MDR with taxanes, like docetaxel, understood that the resistance was likely the result of the action of Pgp, Appx52, and concluded that for the POSA, "the issue of Pgp overexpression presented an area of interest for research during the relevant time period." Appx53.

Next, the court properly found that *Lampidis* taught that "a strategy for overcoming Pgp-mediated resistance in cancer cells was to increase the lipophilicity and therefore cell permeability of a drug, which would then, in effect, overwhelm the Pgp efflux mechanism." Appx42.

The court also properly found that in modifying docetaxel to overcome MDR, a POSA would have been motivated to "to make modifications on the C-7 or C-10 position" of docetaxel, Appx53, and that lipophilic substitutions at these positions could increase potency against MDR cells. Appx39-40, Appx42-43. But the court qualified this finding by stating that C-7 and C-10 were just two of many positions that were being modified as of the priority date. Appx53.

[8] The court also identified paclitaxel as a viable lead compound, Appx45-46, and there is no requirement that the "prior art must point to only a single lead compound." *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009).

Finally, the court correctly found that cabazitaxel's improved properties when compared to docetaxel were "not entirely unexpected," because the skilled artisan would "expect that cabazitaxel would show improved potency over docetaxel." Appx55-56.

In making the findings discussed above, the court recognized the strong foundation for *prima facie* obviousness of cabazitaxel present in the prior art. In finding the claims to cabazitaxel non-obvious, the district court found that the prior art failed to show only that the skilled artisan would have made "the simultaneous methoxy substitutions at the C-7 and C-10 positions required to form cabazitaxel." Appx53. This conclusion was based on a cascading series of errors described below.

2. The District Court Erred Legally and Factually in Holding That *Lampidis* and *Hait* Were Inapplicable to Taxanes.

As discussed above, the district court found that *Lampidis* taught the skilled artisan that increasing the lipophilicity of a drug compound would overcome the pumping action of Pgp. The evidence also showed that *Hait* taught that binding to Pgp could be disrupted by modifying a compound to avoid discrete hydrophilic and lipophilic regions. *Supra*, p. 18-19. But the District Court rejected the applicability of both of these references to docetaxel by ignoring the complete record, finding that the POSA would disregard *Hait* and *Lampidis* because neither reference explicitly addressed taxanes. Appx50, Appx53.

In considering whether a patent is obvious, courts are required to consider

how a skilled artisan would have interpreted the prior art as a whole; a court cannot simply distinguish isolated individual prior-art references while ignoring other relevant references. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007). This is because prior art references are "perhaps the most reliable" evidence of what the skilled artisan would have known and, unlike trial testimony, are not "litigation generated." *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013).

This Court has reversed decisions that do not consider the prior art as a whole. In *Randall*, this Court reversed the PTAB for focusing only on select references and "ignoring the additional record evidence…cited to demonstrate the knowledge and perspective of one of ordinary skill in the art." *Id*. at 1362. Several of the references ignored by the Board in *Randall* related to the background knowledge in the art and were thus "important evidence" not only "of the state of the art" but also of "the context in which [other references] should be evaluated." *Id.* at 1363. This Court recently reached a similar conclusion in *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1326 (Fed. Cir. 2017), where it repeatedly emphasized the importance of considering the "entire record" of evidence when evaluating the motivation to combine prior art references. *Id.* at 1324-25.

Furthermore, this Court has consistently held that motivation to combine may come from implicit teachings in the art, which are "what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be

solved as a whole would have suggested" to the POSA. *Alza*, 464 F.3d at 1290–91; *see also Allergan, Inc. v. Apotex Inc*., 754 F.3d 952, 964 (Fed. Cir. 2014). The motivation to combine may be found in the general knowledge available to the POSA, and the court may rely on expert testimony to ascertain that knowledge. *Alza*, 464 F.3d at 1294.

Here, the District Court failed to account for the entire record in finding that a POSA would not have applied the teachings of *Lampidis* and *Hait* to taxanes. Appx50-51. The district court based its conclusion for *Lampidis* on the fact that *Lampidis* focused on dye compounds and "does not discuss taxanes." Appx50. The court, however, failed to address or take into account testimony from Dr. Heathcock that the teachings of *Lampidis* were directed to general properties of drugs, and thus would apply equally to taxanes. Appx13142-43. Likewise, the court's finding ignored the testimony of Dr. Ludueña, who admitted that "cellular permeability is generally correlated with increased lipophilicity." Appx24243. Further, *Lampidis* itself does not limit its teachings to dyes, instead reporting the positive correlation between lipophilicity and potency against MDR cells can be explained by the general principle that more lipophilic compounds "would be expected to be transported more rapidly through the cell membrane." Appx16954. Indeed, Dr. Heathcock analyzed the lipophilicity of various taxane compounds disclosed in prior art reference, *Ojima 1994,* and concluded that the more lipophilic compounds tended to perform better in

MDR cells, confirming that *Lampidis* applies to taxanes. Appx13225-13227.

Turning to *Hait*, the court based its conclusion that the POSA would not have applied *Hait* to taxanes on the fact that "Hait was not cited in any prior art taxane references." Appx50. But this ignores contradictory testimony from Sanofi's own taxane expert, Dr. Ojima, indisputably a leader in the field (Appx16771-16772), who admitted that when he was working to design new taxanes in 1994, he was aware of *Hait*'s binding model, Appx24284, and that he "took account" of it in designing taxanes during the relevant time period. Appx24286. Furthermore, Dr. Ojima admitted that as of 1995, he engaged in the design of docetaxel analogs that had reduced susceptibility to MDR. Appx24261-24262.

The District Court also erroneously focused on the fact that *Hait* discussed phenothiazines, "which differ from taxanes in size and chemical structure," and are Pgp "inhibitors," while taxanes are Pgp "substrates" that are actually pumped out of the cell. Appx50. The court completely ignored two key prior art references, *Greenberger* and *Safa*, each of which taught the POSA that both Pgp substrates and Pgp inhibitors bind to a common site on the Pgp protein, confirming the applicability of *Hait* to taxanes. Appx16801-02 (*Greenberger*), 17014-15 (*Safa*). The authors of these references tested distinct, but overlapping, sets of Pgp inhibitors and antitumor drugs (Pgp substrates), including a phenothiazine and paclitaxel. *Id.* Both references reached the same result—"antitumor drugs and [Pgp inhibitors] interact

with a common domain in [Pgp]." *Id.* Both sides' experts acknowledged this teaching of the *Greenberger* and *Safa* references. Appx13259-13260 (Dr. Heathcock), 24227-24229 (Dr. Ludueña).

As Dr. Heathcock explained, the significance of both reversal agents (e.g., phenothiazines) and antitumor drugs (e.g., taxanes) binding to the same site on Pgp is that the POSA could "trust that…Hait's model would also work for anticancer compounds like docetaxel." Appx13260. The teachings of *Greenberger* and *Safa* therefore provide important evidence not only as to the state of the art but also the context in which other prior art (i.e., *Hait*) should be evaluated. *Randall*, 733 F.3d at 1363.

The court's characterization of *Hait* as "provid[ing] only a hypothetical binding model for a protein called calmodulin, which is different from and unrelated to Pgp" (Appx50), reflects a misreading of the reference. *Hait* describes an experiment "to study the structural features required for optimum interference with the function of P-gp," not calmodulin. Appx25093. The only mention of calmodulin in the reference is to construct a visual binding model. Appx25094. The fact that *Hait*'s *visual model* was constructed by analogy to calmodulin does not affect the underlying teaching of the *Hait* reference, which is focused on Pgp. Appx13149-13150 (Dr. Heathcock); Appx25093 (*Hait*).

Finally, the district court's dismissal of *Hait* and *Lampidis* for not explicitly

discussing taxanes was error—such an explicit teaching is not required under this court's precedent. *Alza*, 464 F.3d at 1290-91. There was substantial record evidence that the teachings of *Hait* and *Lampidis* had been extended to taxanes.

3. The District Court Compounded Its Error by Finding No Specific Motivation to Modify C-7 and C-10.

Having erred in finding that the POSA would not have applied either *Hait* or *Lampidis* to docetaxel in seeking to overcome the problem of Pgp-mediated resistance for docetaxel, the court compounded this error in concluding that the POSA would not have applied these teachings to make "the simultaneous methoxy substitutions at the C-7 and C-10 positions required to form cabazitaxel." Appx53. Numerous prior art references pointed the skilled artisan directly to lipophilic modifications at C-7 and C-10, with methoxy being the simplest of these.

a) The District Court Failed to Properly Apply the Teachings of *Kingston 1994* and *Commerçon*.

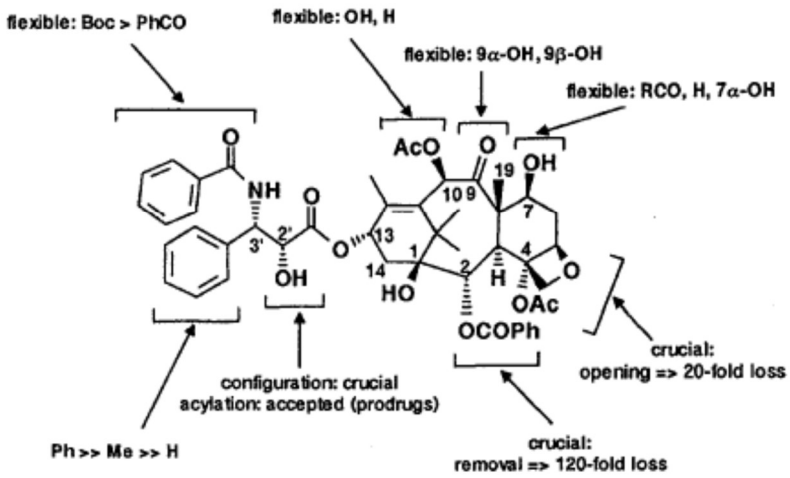
In finding that the POSA would have had no specific motivation to modify C-7 and C-10 over other positions on the taxane core, the court overlooked key prior art that, read in light of *Hait* and *Lampidis*, pointed directly to modifying the northern hemisphere of docetaxel. A POSA applying *Hait* and *Lampidis* to docetaxel would immediately recognize that the compound's susceptibility to Pgp could be reduced by either: (1) increasing cell permeability by making the compound more lipophilic (*Lampidis*); or (2) reducing Pgp affinity by modifying the compound such that it did

not have distinct hydrophilic and lipophilic regions (*Hait*). Appx13143-13144, 13151-13152 (Dr. Heathcock). Guidance as to which positions to modify in order to accomplish these goals was provided by both *Kingston 1994* and *Commerçon*.

Kingston 1994 and *Commerçon* would have been invaluable to the POSA because they provide a concise summary of SAR data collected from hundreds of prior art compounds. Indeed, Sanofi's inventor Dr. Bouchard testified that *Commerçon*'s SAR summary was derived from RPR's own substantial taxane research efforts as of 1994 and reflected RPR's collective knowledge of taxane SAR at that time. Appx38, 13390-92 (Dr. Bouchard). The core teachings of *Kingston 1994* and *Commerçon* identify which positions on the taxane scaffold are "flexible" and can be modified without substantial losses in potency, and which positions are "crucial" such that any modification can have "profound consequences" on bioactivity. Appx25148, Appx25155 (*Kingston 1994*), Appx25160-25162 (*Commerçon*).

Specifically, *Commerçon* identified certain positions on the positions on the side chain and southern hemisphere (e.g., C-2, C-4, C-2', C-3') as "crucial" while identifying positions on the northern hemisphere (e.g., C-7, C-9, C-10) as "flexible."

Figure 2. Modifications influencing the cytotoxicity of paclitaxel.



Appx25161[9]. *Kingston 1994* reached similar conclusions as to each of these positions. Appx25155. Accordingly, the skilled artisan would have been motivated to focus her modification efforts on the "flexible" northern hemisphere. Appx13144 (Dr. Heathcock). The court failed to consider any of these teachings.

The entirety of the court's analysis of *Kingston 1994* and *Commerçon* was provided in two brief prior art summaries preceding the court's substantive obviousness opinion. Appx38, Appx42. Specifically, the court characterized *Kingston 1994* as "provid[ing] a diagram of the taxane core detailing what chemical modifications (if any) are tolerated at each position," Appx42, and *Commerçon* as "disclos[ing] the potency impact of making changes at certain positions on the

[9] Dr. Heathcock noted that of the three "flexible" northern hemisphere positions, C-7 and C-10 were substantially easier to modify that C-9. Appx13116-17. Dr. Kingston similarly testified that modifying the C-7 and C-10 hydroxy groups would be preferred because they were among the easiest positions to modify and doing so would not risk a potency loss. Appx12341-42.

taxane core." Appx38.

Having concluded erroneously that *Hait* and *Lampidis* would not apply to taxanes, the court failed to appreciate how the POSA applying those references would use *Kingston 1994* and *Commerçon* to guide the application of the teachings of *Hait* and *Lampidis* to docetaxel. Dr. Heathcock testified that in applying *Lampidis* to taxanes, the POSA would select the "flexible" northern hemisphere C-7 and C-10 hydroxy groups for modification because the POSA "could afford [to] make changes there without jeopardizing the…biological potency of the drug." Appx13144.

Dr. Bouchard admitted that *Commerçon* summarized the results of all the taxane modification work RPR had done as of March 1994. Appx13390-13392. *Commerçon* represented the *end result* of the modifications made "at multiple positions," that is, of all those modifications, only the northern hemisphere was flexible enough to "tolerate a wide variety of substituents." Appx25161. *Commerçon*'s teachings, when viewed in light of Dr. Bouchard's testimony, and in light of *Hait* and *Lampidis*, therefore directly undercut the court's conclusion that a skilled artisan would not have had a specific motivation to focus on C-7 or C-10. Appx53.

Finally, the court's failure to substantively address *Commerçon* cannot be saved by its decision to credit Dr. Roush's testimony regarding "the modifications that were being made at multiple positions on the taxane molecule." Appx52. Dr.

Roush offered no testimony at all regarding *Commerçon*. It was thus clear error for the court to credit Dr. Roush's testimony regarding *Commerçon*; "a district court cannot, through a credibility determination, ignore the wealth of evidence, especially…where the expert did not even address it." *Bayer Pharma*, 874 F.3d at 1324.

b) The District Court Failed to Properly Apply the Teachings of *EP '910*, *Golik*, and *Ojima 1994*.

Once the POSA was motivated to modify the northern hemisphere of docetaxel to make it more lipophilic, the prior art provided specific guidance in the *Golik*, *EP '910* and *Ojima 1994* references, all of which would have pointed the skilled artisan directly to the C-7 and C-10 positions.

Both *EP '910* and *Golik* disclose that when the C-7 hydroxy group of paclitaxel is converted to a lipophilic methylthiomethyl ("MTM") group to form "Example 1(a)," performance against MDR cells is substantially improved while performance against normal cells is maintained. *Compare* Appx25206 (*Golik*) *with* Appx25506 (*EP '910*).

Both sides' experts agreed that Example 1(a)'s improvement in MDR cell potency was due to the lipophilic MTM group at C-7. Appx12357-12359 (Dr. Kingston); Appx13159-13160 (Dr. Heathcock); Appx13686-13687 (Dr. Roush);

Appx24204 (Dr. Ludueña); Appx24276, Appx24278 (Dr. Ojima).[10] The court reached a similar conclusion, stating in its summary of *EP '910* that the reference discloses that "increasing the lipophilicity of the C-7 hydroxy position of the taxane core could improve the potency of the compound in treating resistant cancer cells." Appx39.

The District Court failed to apply this teaching in its substantive obviousness analysis. Appx46-47. The court focused instead on *Golik*'s lack of disclosure of a specific methoxy substitution at C-7 and did not discuss *EP '910* at all. *Id.* The teachings of both *Golik* and *EP '910* regarding lipophilicity at the C-7 position are directly relevant to what positions on docetaxel a skilled artisan would choose to modify and how she would interpret other prior art references such as *Hait* and *Lampidis*. *See Randall*, 733 F.3d at 1363. Indeed, the teaching that increased lipophilicity at C-7 leads to improvements against MDR cells directly supports Dr. Heathcock's position that *Hait* and *Lampidis* would motivate the skilled artisan to increase the lipophilicity of docetaxel's northern hemisphere. Appx13143-44, Appx13151-52.

Furthermore, the court's suggestion that *Ojima 1994* would not have

[10] Drs. Kingston and Heathcock further testified that the POSA would recognize that the sulfur atom in the C-7 MTM group could present biological complications, and that utilizing a simpler methoxy group there would mitigate this risk while retaining the compound's beneficial MDR properties. Appx12361-12362 (Dr. Kingston), Appx13160 (Dr. Heathcock).

specifically motivated a substitution at C-10, Appx50-51, is inconsistent with the court's own summary of the reference. *Ojima 1994* presents a comparison of two compounds, SB-T-1101 and SB-T-1102, showing that changing a hydrophilic hydroxy group to a more lipophilic methoxy group at C-10 resulted in a significant increase in potency against drug resistant cells. Appx13154-13155 (Dr. Heathcock), Appx25114-25115 (*Ojima 1994*); *see also* Appx2420 (Dr. Ludueña). The court, relying on testimony of Dr. Heathcock and Dr. Ludueña, summarized *Ojima 1994* as teaching that "using small lipophilic groups at C-10 improved performance against resistant cancer cells." Appx43. Thus, the court's ultimate conclusion that "Ojima 1994 does not teach that making the 'northern hemisphere' of docetaxel more lipophilic increases activity in resistant cell lines," Appx50-51, is inconsistent with the court's own summary of the reference itself.

Similarly, the court's suggestion that the improved properties of compound SB-T-1102 as compared to its counterpart SB-T-1101 is due to its modified side chain, Appx51, is clearly erroneous on its face. The two compounds have the *same* side chain and, in fact, are identical in every respect except for the substituent at the C-10 position, where SB-T-1101 has a hydrophilic hydroxy group and SB-T-1102 has a more lipophilic acetoxy group. Appx13154-13155 (Dr. Heathcock), Appx25114-25115 (*Ojima 1994*). Thus, any differences in biological activity of the two compounds can be attributed solely to the substitution at C-10, not the side

chain. *Id.*

If anything, the six side-chain analogues discussed in *Ojima 1994* prove that modifying the side chain has the potential to both greatly improve or diminish a compound's potency against normal and/or resistant cells. *Id.* This volatility confirms the teachings of *Kingston 1994* and *Commerçon* regarding the risk of modifying the side chain, *see* pp. 59-60, *supra*, and establishes that when comparing the efficacy of various substitutions to the taxane core, the most relevant comparisons are those made between compounds with the same side chain. Appx13187-13188 (Dr. Heathcock).

Accordingly, the court mistakenly characterized *Ojima 1994* as merely disclosing "a series of taxane compounds with modifications in the C-13 side chain," Appx50. While it is true that one teaching of *Ojima 1994* is that modifications to the side chain "can modulate activity in resistant cell lines," Appx51, this is, as the court properly found, not the reference's only teaching. The POSA would learn from *Ojima 1994* that increased lipophilicity at C-10 was a viable path to improve potency against MDR cells, and the availability of other approaches (*e.g.*, modification of the side-chain) is not dispositive of whether a lipophilic substitution at C-10 would have been obvious. *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014) (obviousness "does not require that the motivation be the best option, only that it be a suitable option from which the prior art did not teach away"). *Ojima*

1994's teachings regarding C-10 substitutions are therefore highly relevant. *Randall*, 733 F.3d at 1363.

Neither is reliance on these references an improper "cherry pick[ing]" of the data—this would condemn Defendants' experts for relying on teachings that the court itself attributed to the references, namely that increased lipophilicity at C-7 and C-10 improved performance against MDR cells. Appx39-40, Appx42-43. Furthermore, these references serve as confirmation for the POSA that modifications to the northern hemisphere to increase lipophilicity improves performance of taxanes in resistant cells. The POSA would have already been focused on making lipophilic changes to the northern hemisphere based on *Hait* and *Lampidis*, and as a result the skilled artisan would have sought out the specific C-7 and C-10 (*i.e.*, northern hemisphere) disclosures of *Golik, EP '910* and *Ojima 1994*, in order to find proof-of-concept for modifications already suggested by other prior art. *See* Appx13155-13156, Appx13159-13160 (Dr. Heathcock).

c) The District Court Erred in Finding No Specific Motivation to Substitute Methoxy at C-7 and C-10.

The District Court further compounded its error by failing to consider the motivation of a skilled artisan to make small, conservative changes and misinterpreted Defendants' use of the *Klein*, *Wong*, and *Kant* references as evidence of hindsight.

When evaluating the *prima facie* obviousness of a chemical compound, the

district court must determine whether the skilled artisan would have identified a "lead compound" from which to begin her work. *BMS*, 752 F.3d at 973. Next, the court must determine whether the skilled artisan would have been motivated to modify the lead compound to arrive at the claimed compound, which motivation need not necessarily be explicit in the art. *Id*. Often, this motivation stems from structurally similar compounds in the prior art with beneficial structural features that a skilled artisan may want to add to the lead compound. *Id.* at 975-76.

Among the motivations considered in *BMS* was a POSA's desire to make "small, conservative changes" to the lead compound's structure. *Id.* at 974. Specifically, this Court found that when faced with the choice of "which bond to modify and how to modify that bond," the POSA would opt for small changes that were easy to make. *Id.* at 975-976. This Court credited the district court's finding of motivation based on the fact that "the modification required to transform [the lead] into the structurally similar [claimed compound] is a minor one: the addition of a single carbon atom to form an exocyclic methylene". *Id.* at 975.

Here, the District Court failed to consider testimony from both sides' experts that POSAs typically develop SAR by making small, incremental changes to the lead compound's chemical structure. Appx13108-13110, Appx13144-13146, Appx13152, Appx13177-13178 (Dr. Heathcock), Appx13579-13582 (Dr. Roush), Appx24262-24263 (Dr. Ojima). The court's only analysis of this topic is a single

sentence in its summary of Dr. Kingston's testimony: "Dr. Kingston further testified that a POSA would be interested in maintaining the entire structure of docetaxel with small modifications at the C-7 and C-10 positions." Appx35, Appx12344 (Dr. Kingston). The court failed to address Dr. Heathcock's testimony on this point altogether. As Dr. Heathcock explained, medicinal chemists are motivated to make small, conservative changes to lead compounds because "if you're going to make a change, you always start [by] making the smallest incremental change because that gives you the best chance of finding out what those changes you're making will do the properties of the molecule." Appx13144-13145. This concept was echoed by both Dr. Roush and Dr. Ojima, who testified that POSAs typically develop SAR by making small, incremental changes to the lead compound's structure. Appx13579-13582 (Dr. Roush), Appx24262-24263 (Dr. Ojima). The court's failure to consider this concept in its analysis not only represented a failure to consider the state of the art, but also the context in which a skilled artisan would interpret the prior art. *Randall*, 733 F.3d at 1363.

The court also ran afoul of this Court's holding in *BMS* that a skilled artisan's motivation to make small, conservative changes to a lead compound establishes *prima facie* obviousness. 752 F.3d at 974. As in *BMS*, the change from hydroxy groups to methoxy groups at C-7 and C-10 is "a minor one"; it involves the smallest possible modification that could be made to a hydroxy group—the addition of a one-

carbon methyl group (-CH_3). 752 F.3d at 975; Appx13144-13145 (Dr. Heathcock). That this change could have been easily accomplished using known conditions in the prior art, Appx13192-13196 (Dr. Heathcock), 25614-25615 (*Greene*) is but further evidence that a POSA would have been motivated to make it. *BMS*, 752 F.3d at 975-76; Appx40.

Had the District Court not engaged in the cascading series of factual and legal errors discussed above, the only reasonable conclusion permitted by the evidence is that the skilled artisan would have been motivated to synthesize cabazitaxel. The skilled artisan would have: (1) been motivated to modify docetaxel to reduce its susceptibility to Pgp-mediated drug resistance; (2) learned from the prior art that this could be accomplished by increasing the lipophilicity of the C-7 and C-10 positions in the northern hemisphere; and (3) determined that installing methoxy groups at these positions would be the smallest, most conservative modification that would achieve this goal. This would necessarily have resulted in cabazitaxel.

d) The District Court Erroneously Characterized Defendants' Experts as "Cherrypicking" Data for Methoxy Substitutions at the C-7 and C-10 Positions.

Having ignored both the prior art teaching how to overcome Pgp resistance and the POSA's motivation to make small conservative changes, the court improperly accused Drs. Kingston and Heathcock of "cherry pick[ing]" data from *Kant*, *Klein*, and *Wong*. Appx52. This represents a fundamental misunderstanding

of how the POSA would have applied these references in light of other prior art. As Dr. Heathcock explained, once a POSA had *already* chosen to install methoxy groups at C-7 and C-10 in order to address MDR, *Kant*, *Klein*, and *Wong* would have simply validated that choice because these references would have provided proof of concept. Appx13179-13180.

Thus, the court's criticism of Defendants' experts for focusing on compounds in *Kant*, *Klein*, and *Wong* that were not the most potent compounds in those references misses the mark. The fact that the compounds substituted with a methoxy group at C-7 and/or C-10 were among the most potent compounds listed would *confirm* the skilled artisan's expectation that this substitution would not destroy potency. Appx25178-25189 (*Klein*), Appx25311-25312 (*Kant*), Appx25318 (*Wong*), Appx13167-13168, Appx13171-13173 (Dr. Heathcock), Appx24270 (Dr. Ojima), Appx12364-12366 (Dr. Kingston). These results, when combined with the Pgp analysis discussed above, make clear that a POSA would perceive the use of methoxy groups as an effective and viable solution to docetaxel's well-known MDR problems. That other potential C-7 and C-10 substitutions may have been more potent in certain circumstances is not dispositive of cabazitaxel's *prima facie* obviousness. *Par Pharm.*, 773 F.3d at 1197–98; *Bayer Pharma*, 874 F.3d at 1328.

4. The District Court's Finding Regarding Unexpected Results Undermines Its Prima Facie Obviousness Determination.

In its analysis of unexpected results, the court afforded "minimal weight" to

Sanofi's arguments that cabazitaxel's superior performance over docetaxel would have been unexpected, finding that the POSA would have expected cabazitaxel to show some improvement over docetaxel, thus rendering its ultimate performance "not entirely unexpected." Appx55. This finding is at odds with the court's ultimate holding of nonobviousness—the POSA's expectation of a compound's improved properties is directly relevant to her motivation to make the compound in the first place. *In re Dillon*, 919 F.2d 688, 697 (Fed. Cir. 1990) (*en banc*).

This court has previously found that "structurally similar compounds often have similar properties." *BMS*, 752 F.3d at 976. Accordingly, a *prima facie* case of obviousness is created if the skilled artisan would have been motivated to arrive at the claimed compound based on a structurally similar compound in the prior art with attractive properties. *Dillon*, 919 F.2d at 692. The patentee can then rebut this case by showing that "the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have." *Id.* at 692-93. These two inquiries are thus inextricably linked; it is the very expectation of superior properties that "affect[s] the motivation of a researcher to make compounds closely related to or suggested by a prior art compound" in the first place. *Id.* at 697.

In *BMS*, this Court held that the antiviral compound entecavir was *prima facie* obvious because the simple modification required to form entecavir from the lead compound had already been disclosed as being beneficial for a structurally-related

prior art compound. *Id.* at 975-976. Although entecavir showed some unexpected properties, they were insufficient to overcome *prima facie* obviousness because the improvements over the lead compound differed only in degree, and not in kind, from what a skilled artisan would have expected. *Id.* at 977-78. The Court linked *prima facie* obviousness with unexpected results, stating that "the prior art, the trial record, and the district court's findings reflect that one of skill in the art would have expected entecavir's hepatitis B's efficacy, safety, and therapeutic window based on one's knowledge of [the lead compound]." *Id.* at 978.

Here, the District Court reached an almost identical conclusion with respect to unexpected results, holding that "[c]abazitaxel's superior performance…cannot be said to be entirely unexpected because it differs not in kind but only in degree, from docetaxel's performance." Appx56. The court explained that the prior art "disclosed that certain taxanes showed improved potency against MDR cell lines." Appx55. Consequently, the district court concluded that the POSA would "expect that cabazitaxel would show improved potency over docetaxel, but would not expect the degree of superiority that cabazitaxel showed." *Id.* This conclusion is at odds with the district court's earlier holding with respect to *prima facie* obviousness. *BMS*, 752 F.3d at 975-76; *Dillon*, 919 F.2d at 697. To the extent Defendants presented sufficient evidence for the district court to conclude that a skilled artisan would have "[expected] that cabazitaxel would show improved potency over

docetaxel," Appx55, that evidence should also have been sufficient to establish motivation for the skilled artisan to have arrived at cabazitaxel. That a POSA could have modified docetaxel at positions other than C-7 and C-10, Appx52, is not dispositive here because the district court did not cite any evidence that specifically taught away from cabazitaxel. *See, e.g.*, *Par Pharm*, 773 F.3d at 1197-98; *Bayer*, 874 F.3d at 1328.

5. The District Court Failed to Address Whether Formulating Cabazitaxel Would Have Been Obvious.

The court's holding regarding *prima facie* obviousness only addressed the cabazitaxel molecule itself, and did not directly consider whether formulating cabazitaxel would have been obvious. Appx45-53.

Defendants presented substantial evidence at trial that formulations of cabazitaxel would have been obvious. The prior art disclosed numerous examples of intravenous formulations of taxanes. Appx24458 (*Verweij*), Appx25318 (*Wong*), Appx25348 (*Pazdur*), Appx25431 (*'470 patent*), Appx25507-25508 (*EP '910*). The skilled artisan would expect that cabazitaxel could be successfully formulated using one or more of the above examples due to the close structural similarity between it and other taxanes (*e.g.*, docetaxel). Appx12376 (Dr. Kingston), Appx11380-11382 (Dr. Heathcock). *See also*, Appx24273 (Dr. Ojima admitting it would be "reasonable" for a skilled artisan to expect success in formulating a new taxane for human administration).

C. Secondary Considerations of Nonobviousness Do Not Overcome the Strong Evidence That Cabazitaxel Was *Prima Facie* Obvious.

Once the clear errors in the District Court's opinion are corrected, there is a strong *prima facie* case of obviousness which cannot be overcome by secondary considerations. Although the court's holding regarding *prima facie* obviousness did not require any analysis of secondary considerations, the court nonetheless addressed three such considerations: unexpected results, failure of others, and commercial success.

The court's conclusions regarding the minimal unexpected results associated with cabazitaxel are summarized above. But the court gave "considerable weight" to Sanofi's failure of others argument given that "only Plaintiffs succeeded in developing a compound that showed superior activity over docetaxel…and obtained FDA approval." Appx56-57. And the court found that although Jevtana did not "command the greatest market share," the product was nonetheless a "commercial success," and thus afforded "considerable weight" to Sanofi's arguments on this point. Appx57-59. These three findings caused the court to conclude that on aggregate, "the secondary considerations weigh in favor of Plaintiffs." Appx45.

The court's secondary considerations analysis is insufficient to rebut Defendants' strong case of *prima facie* obviousness, discussed in detail above. *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1371 (Fed. Cir. 2011). Indeed, as discussed above, the court's holding on unexpected results actually bolsters

defendants' *prima facie* case. Further support for Defendants' position can be found *in BMS*, 752 F.3d at 977-79, where this court determined that very similar facts regarding unexpected results and commercial success could not save the chemical compound claims at issue.

CONCLUSION

If this Court does not agree that Sanofi's previous assertion of claims 1 and 27 of the '592 patent preclude a second suit Sanofi intends to bring against Defendants asserting the '592 patent substitute claims it is seeking, Defendants' respectfully request that the District Court's judgment of invalidity for the disclaimed claims be affirmed. Defendants respectfully request that the District Court's judgment of no invalidity for claims 1 and 2 of the '170 patent be reversed.

Dated: August 20, 2018

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PROOF OF SERVICE

I hereby certify that on this 20th day of August, 2018, I caused a true and correct copy of the foregoing DEFENDANTS – CROSS-APPELLANTS' PRINCIPAL AND RESPONSE BRIEF to be electronically filed with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system, which will serve such filing on all registered CM/ECF users, including counsel for all parties.

I also certify that the foregoing DEFENDANTS – CROSS-APPELLANTS' PRINCIPAL AND RESPONSE BRIEF was served upon all counsel of record via electronic mail on this 20th day of August, 2018.

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