2018-1804, -1808, -1809

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.

On Appeal from the United States District Court for the District of New Jersey in 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 and 3:16-cv-05678-MAS-LHG, Honorable Michael A. Shipp

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OCTOBER 24, 2018

CERTIFICATE OF INTEREST

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Sanofi-Aventis U.S. LLC *et al.*, *Appellants* *v.* Fresenius Kabi USA, LLC *et al.* *Appellees*

Case Nos. 2018-1804, 2018-1808, 2018-1809

Counsel for Appellant Aventis Pharma S.A. certifies the following:

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

Sanofi-Aventis U.S. LLC

Aventis Pharma S.A.

Sanofi

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:

Sanofi-Aventis U.S. LLC

Aventis Pharma S.A.

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:

Sanofi U.S. Services Inc.

Aventis, Inc.

Sanofi

sanofi-aventis Amérique du Nord

4. The names of all 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:

Fitzpatrick, Cella, Harper & Scinto: Joshua I. Rothman, Melinda R. Roberts, Una C. Fan (no longer with the firm), Jayita Guhaniyogi (no longer with the firm), Cali R. Roth (no longer with the firm)
Walsh Pizzi O'Reilly Falanga LLP: Liza M. Walsh, Katelyn O'Reilly, Tricia O'Reilly
Saul Ewing Arnstein & Lehr LLP: Charles M. Lizza, William C. Baton, David L. Moses

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

/s/ William E. Solander
Date: October 24, 2018 Signature of counsel

William E. Solander
Cc: Opposing Counsel of Record Printed name of counsel

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Parties:

Defendants	Cross-Appellants (Fresenius Kabi USA, LLC, Accord Healthcare, Inc., Apotex Corp., Apotex Inc., Actavis LLC, Actavis Elizabeth LLC, Mylan Laboratories Limited) and Appellees (Dr. Reddy's Laboratories, Inc., Dr. Reddy's Laboratories, Ltd., Sandoz, Inc.)
Sanofi	Sanofi Aventis U.S., LLC, Aventis Pharma S.A., and Sanofi

Citations:

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FWD Appeal Brief	*Aventis Pharma S.A. v. Mylan Labs. Ltd.*, No. 2018-1203, D.E.19 Brief for Appellant (Fed. Cir. Mar. 15, 2018)
RedBr_____	Defendants'–Cross-Appellants' Principal and Response Brief

Terms:

ANDA	Abbreviated New Drug Application
EDTA	Disodium edetate
FDA	Food and Drug Administration
FWD	Final Written Decision
FWD Appeal	*Aventis Pharma S.A. v. Mylan Labs. Ltd.*, No. 2018-1203
IPR	*inter partes* review
ITC	International Trade Commission
MDR	Multi-drug resistance
MTM	Methylthiomethyl group
Pgp	P-glycoprotein
POSA	Person of ordinary skill in the art
PTAB	Patent Trial and Appeal Board

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'170 Patent	U.S. Patent No. 5,847,170 B2 (Appx321-347)
'592 Patent	U.S. Patent No. 8,927,592 B2 (Appx348-369)
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Klein	L. L. Klein *et al.*, *Chemistry and Antitumor Activity of 9(R)-Dihydrotaxanes*, Ch. 20 in TAXANE ANTICANCER AGENTS: BASIC SCI. & CURRENT STATUS, (Georg et al., Eds.) ACS Symposium Series American Chemical Society, Washington, DC, 583:276-287 (1994) (Appx25173-25184)

Lampidis	Theodore J. Lampidis, *Relevance of the Chemical Charge of Rhodamine Dyes to Multiple Drug Resistance*, 38(23) BIOCHEMICAL PHARMACOLOGY 4267-4271 (1989) (Appx16950-16954)
Ojima 1994	Iwao Ojima *et al.*, *Synthesis and Structure-Activity Relationships of New Taxoids*, Ch. 19 in TAXANE ANTICANCER AGENTS: BASIC SCI. & CURRENT STATUS, (Georg et al., Eds.) ACS Symposium Series American Chemical Society, Washington, DC, 583:262-275 (1994) (Appx25104-25117)
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Safa	Ahmad 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(1) BIOCHEMICAL & BIOPHYSICAL RESEARCH COMMUNICATIONS 259-266 (1990) (Appx17010-17017)
Wong	U.S. Patent No. 6,201,140 (Appx25313-25330)

STATEMENT OF THE ISSUES: CROSS-APPEAL OF THE '170 PATENT

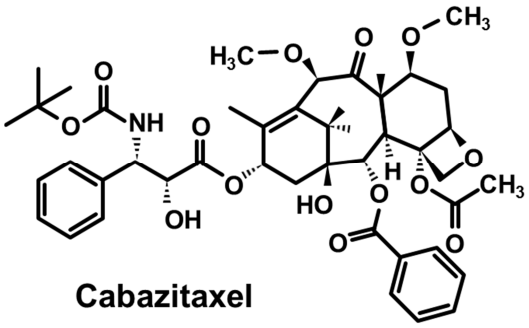
1. Whether the district court erred in its finding that Claims 1 and 2 of U.S. Patent No. 5,847,170 were not obvious having fully considered the references offered as prior art and expert testimony.

STATEMENT OF THE CASE: CROSS-APPEAL OF THE '170 PATENT

This action arises under the Hatch-Waxman statute and is based on Defendants' attempts to market a generic version of Sanofi's JEVTANA®, which is approved for treating certain resistant prostate cancers. Defendants stipulated to infringement of claims 1 and 2 the '170 patent and, during an eight-day bench trial, raised obviousness as their sole invalidity defense. Appx32, Appx45. The district court found the claims were not invalid. Appx45.

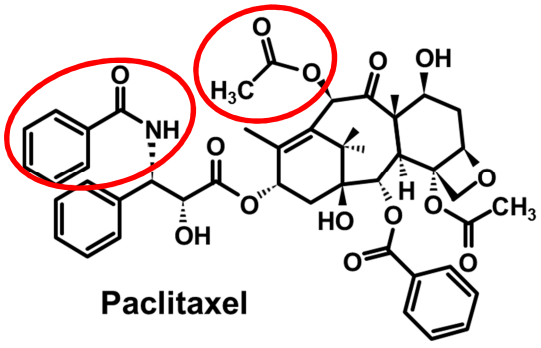
STATEMENT OF FACTS: CROSS-APPEAL OF THE '170 PATENT

Claims 1 and 2 of the '170 patent are directed to a single taxane chemotherapy compound, cabazitaxel, and pharmaceutical compositions containing cabazitaxel. Appx321-347, Appx13567-13566, Appx13570-13572.



Cabazitaxel

Cabazitaxel, the active ingredient in JEVTANA®, is only one of three taxanes that have received FDA approval. Appx56-57. In 1992, FDA approved the first taxane, paclitaxel, which is the active ingredient in TAXOL®. Paclitaxel has the following structure:

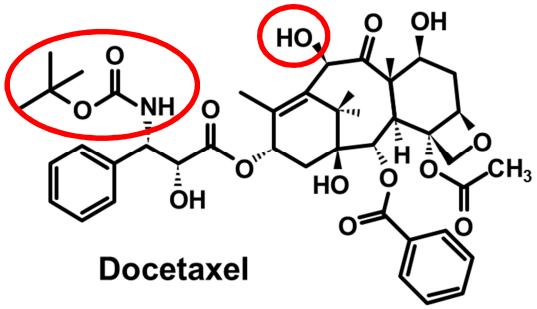


Paclitaxel

While useful in treating cancer patients, paclitaxel has several limitations. It is less active in certain cancer cells that have become resistant to chemotherapy, a problem known as multi-drug resistance ("MDR"). Appx13662-13664,

Appx24470-24471, Appx25034; *see also* Appx30639-30640, Appx30643. Paclitaxel also exhibits extremely poor water solubility, making it difficult to formulate for intravenous administration without the use of harsh additives. Appx13662-13664.

Docetaxel, the active ingredient in TAXOTERE®, was the second taxane approved by FDA in 1996. Docetaxel has the following structure:



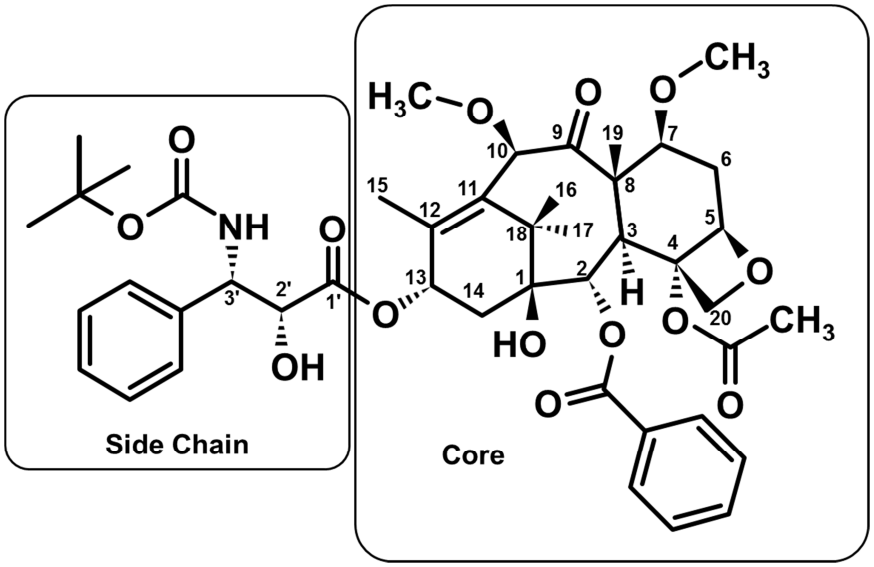
Docetaxel

As shown in the figures above, paclitaxel and docetaxel differ in the C-10 position (circled on right) and the side chain (circled on left). While these two changes resulted in significant improvements in docetaxel as compared to paclitaxel (Appx12386-12388, Appx12415, Appx13205-13207, Appx13209), docetaxel still had its limitations, including low water solubility and low activity in MDR cancer cells. Appx13664.

Due to the anticancer properties of paclitaxel and docetaxel, the district court found that a person of ordinary skill in the art ("POSA") would use either paclitaxel or docetaxel as a lead compound, and that a POSA would have been motivated to modify them in an attempt to address MDR. Appx45; RedBr15.

I. Prior Art Taxanes Were Modified at Almost Every Possible Position, Not Just at C-7 and C-10

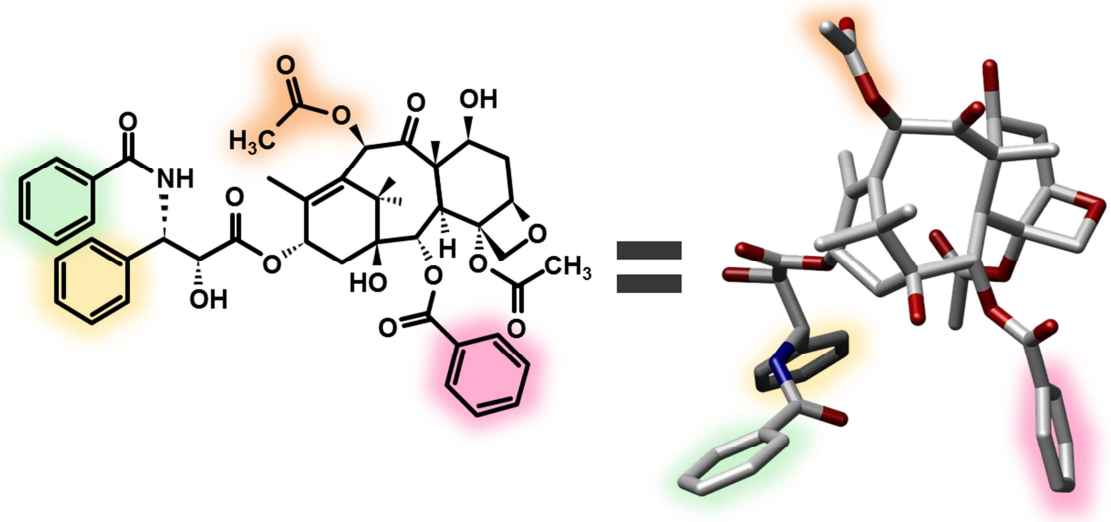
Modifications to the chemical structure of taxanes, including paclitaxel and docetaxel, are not an easy task. Taxanes are large, complex molecules that are comprised of a "core" portion, with twenty carbon positions (e.g., C-1, C-2, . . . C-20), and a "side chain" that includes three more carbon positions (C-1', C-2', C-3'). Appx13604-13605.



As of the March 27, 1995 priority date, multiple research groups around the world (including Sanofi, Bristol-Myers Squibb, and several universities) were searching for new taxanes. Appx20, Appx12381-12383, Appx13611-13612, Appx30634. The district court found that modifications were made to paclitaxel and docetaxel at the C-2, C-4, C-5, C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-2', and C-3' positions. Appx53.

Research groups were also trying many types of substituents at these

positions. Appx13615-13618. This is because taxanes have a complex three-dimensional structure such that any modification, no matter how large or small, could drastically impact biological activity. Appx13596-13600, Appx30628.



In particular, while taxane binding can be affected by structural modifications, how a particular modification affects a taxane's spatial orientation, and thereby its binding, is unpredictable. Appx13587-13588. Moreover, due to the unpredictable nature of taxane chemistry, including the chemical sensitivity of the "core" to synthetic conditions, some taxanes were exceptionally difficult to synthesize. Appx13320-13321.

II. The Cause of Taxane Resistance Was Not Known

Taxanes possess anticancer properties because they bind to microtubules within cancer cells, disrupting their proliferation. Appx13403. Over time, tumors that initially responded to a chemotherapy compound may develop resistance to

treatment with that compound and other chemotherapies. Appx13121-13122, Appx25038-25040. As a result, chemotherapy becomes less effective in treating these cancers. Appx13121-13122, Appx25038-25040.

As the district court correctly found, a POSA would have been motivated to address the problem of MDR. Appx52-53, Appx45; *see also* RedBr15. Although a POSA would have known of several unproven theories behind MDR, its actual cause was unknown. Appx13641. One theory involved mutations to the drug target tubulin potentially affecting drug binding. Appx13643-13644, Appx24470-24471; *see also* Appx12390. Another potential mechanism involves P-glycoprotein ("Pgp"), a protein located in all cell membranes that is responsible for pumping a wide variety of foreign substances out of cells, including many drugs. Appx13437, Appx13639-13640.

While Defendants erroneously focus on Pgp as the only possible cause of resistance, its structure and how it binds to taxanes prior to removing them from the cell, was not known in the art. In fact, the *Hait* reference cited by Defendants discusses Pgp, but as shown in the figure below from *Hait*, it only does so with reference to a "hypothetical" model of Pgp based upon calmodulin, an unrelated protein:

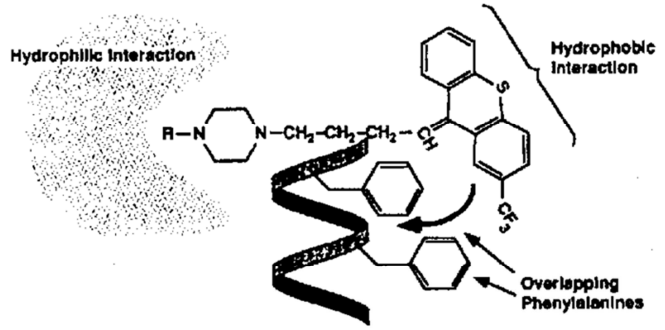


Fig. 2. Hypothetical drug binding site on P-gp based on analogies with the binding of antipsychotic drugs to calmodulin. The phenylalanine side chains are depicted extending outward from the α-helical backbone. The two aromatic rings of the phenylalanines are oriented in such a way by the α-helix to "sandwich" the tricyclic ring of the thioxanthene through π orbital electron interactions. The hydrophobic region is separated from a hydrophilic region of the protein which interacts with the basic side chain of the drug. Adapted from *J Theor Biol* **105**: 63–67, 1983 [12] with permission.

Appx25094[1], Appx13657-13661, Appx30646-30648; *see also* Appx13655-13656. Moreover, *Hait's* hypothetical model is based upon interactions with phenothiazines, which are antipsychotic compounds completely unrelated to taxanes.

To complicate matters, the possible binding site(s) on Pgp is unknown for phenothiazines and taxane compounds. Appx13652-13653. While Pgp had been correlated with possible resistant tumors in certain patients (Appx17051), whether it actually caused that resistance was (and still is) unknown. Appx13648-13649.

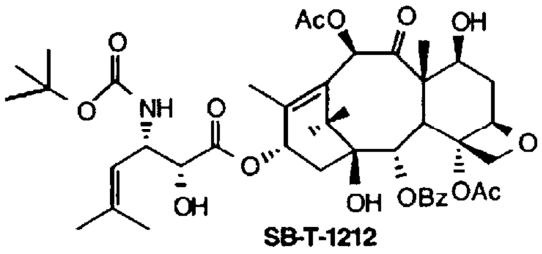
[1] Highlighting and all emphasis added unless otherwise noted.

III. There Was Little Prior Art Data on Resistant Cancer Cells to Guide a POSA

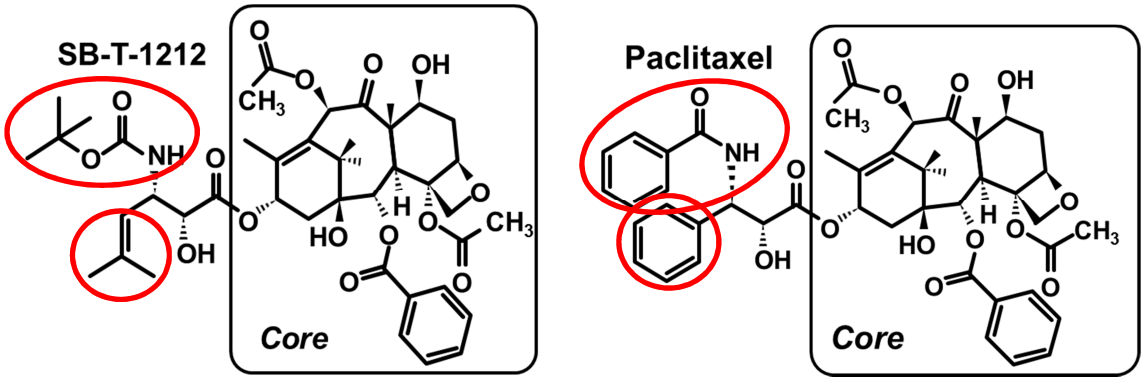
Data in resistant cell assays is critical for guiding a POSA in proposing modifications to taxanes to potentially address MDR. Appx13635-13636. However, the vast majority of prior art references, including *Commerçon*, *Klein*, *Kant*, and *Kingston 1994*, have no resistant cell data. Data from tubulin binding and sensitive cell lines is not predictive of efficacy in resistant cell lines; data in resistant cell lines is required. Appx13408, Appx13415-13416, Appx13635-13636, Appx13671-13672.

The prior art provided limited resistant cell data for a small number of taxane compounds. For example, docetaxel was found to be more active than paclitaxel in a cell line that was made resistant to doxorubicin, another chemotherapy compound (denoted P388/DOX). Appx13636-13637, Appx25034. Additionally, *Golik* contained data in resistant cell lines, but that data was limited to a few compounds with unique substituents unrelated to cabazitaxel. *See* Appx13686-13688.

The *Ojima 1994* reference, which included data from another resistant cell line (MCF7-R), ultimately concluded that improvement in activity against resistant cells was due to side chain modifications, highlighted by data from the following compound, SB-T-1212:



Appx25114-25115. SB-T-1212 has the exact same "core" as paclitaxel, with a 25-fold improvement in MCF7-R due to side chain modifications. Appx13222-13223, Appx30416.



However, none of these references include animal data in resistant tumor models. Appx13674, Appx13684, Appx13688-13689, Appx13694. Thus, there was little guidance in the prior art regarding chemical modifications to increase potency in resistant cancer cell lines, let alone in animals or humans.

IV. Water Solubility of Taxanes Was a Major Problem

Poor water solubility, i.e., high lipophilicity, was another major problem for taxanes, which presented formulation problems for intravenous administration. Appx13662, Appx12418-12419. Additives, such as Cremophor, were used to

overcome insolubility, but were problematic because they can cause life-threatening hypersensitivity reactions in patients, warranting the administration of additional drugs to suppress them. Appx13664-13665. While a significant benefit of docetaxel over paclitaxel is its increased water solubility, taxanes in general were still considered insoluble. Appx13663, Appx12306, Appx13118.

None of the prior art references relied upon in this appeal expressly discuss or suggest increasing lipophilicity of taxanes, including *Ojima 1994* and *Golik*, Defendants' two primary references. RedBr19-20.

V. Cabazitaxel Was Discovered After Years of Work on Hundreds of Compounds

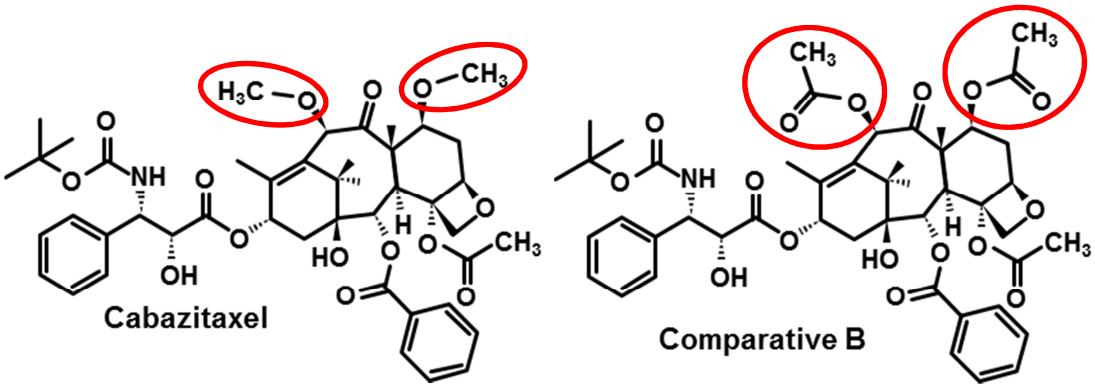
Cabazitaxel was discovered through a laborious research program at Sanofi which lasted from 1989 until 1996 to search for taxanes with improved properties over docetaxel. Appx13310-13314. Sanofi researchers synthesized and tested 450+ taxane derivatives that were modified at "almost every part" of the taxane molecule. Appx13313-13314, Appx13320, Appx25627-25740, Appx30547.

In November 1994, Sanofi synthesized cabazitaxel for the first time. Appx13351. Its synthesis was particularly time-consuming and difficult due to the aggressive and unusual reaction conditions required to simultaneously methylate the C-7 and C-10 positions on the "core." Appx13350-13351, Appx28417, Appx28437, Appx13347-13351, Appx13699-13703, Appx13716-13718,

Appx13727-13728, Appx13777.

Once synthesized, cabazitaxel showed surprisingly high levels of activity across multiple cell lines and *in vivo* tumor models, including docetaxel-resistant cell lines and tumors. Appx13440-13445. Of the over 450+ compounds in the program, only two made it to clinical studies, and only cabazitaxel had positive Phase III clinical trial results. Appx13353, Appx13445-13346.

During prosecution of the '170 patent, the Patent Examiner requested data on certain taxanes. Appx13625-13626. Applicants provided a declaration which included a compound labeled "Comparative B." Appx24289-24296, Appx13626-13627. Comparative B differs from cabazitaxel only in the C-7 and C-10 positions, wherein Comparative B replaces the methoxy substituents with acetoxy substituents:



Appx13627. Comparative B lacked the same activity in resistant KB cancer cells exhibited by cabazitaxel, whereas cabazitaxel was twelve times better than docetaxel in that cell line. Appx24289-24296, Appx13630.

VI. Defendants' Cross-Appeal Is a Rehash of Mylan's Failed IPR Petition

In August 2016, claims 1 and 2 were unsuccessfully challenged in an IPR petition filed by Defendant Mylan. *Mylan Labs. Ltd. v. Aventis Pharma S.A.*, IPR2016-00627, Paper 10 at 12, 16-17 (P.T.A.B. Aug. 23, 2016). Mylan relied on virtually the same prior art references (e.g., *Kant* and *Klein*) and the lipophilicity arguments (e.g., *Lampidis* and *Hait*) advocated before the district court and in this appeal. *Id.* at 3, 13-14, 19. The PTAB denied institution principally because Mylan's invalidity theories were based upon impermissible hindsight. *Id.* at 14; *see also Mylan Labs. Ltd. v. Aventis Pharma S.A.*, IPR2016-00627, Paper 12 at 5-6 (P.T.A.B. Jan. 26, 2017) ("Petitioner 'errs by starting with a hindsight-biased structural comparison of docetaxel, Kant Compound 20, and cabazitaxel in side-by-side fashion.'").

SUMMARY OF THE ARGUMENT

I. Appeal of the '592 Patent

Once disclaimed, claims 7, 11, 14-16, and 26 of the '592 patent were canceled, and any dispute regarding them was moot. Defendants nonetheless improperly ask this Court for an advisory opinion regarding their hypothetical claim or issue preclusion defense to a possible lawsuit on unissued amended claims that Sanofi seeks in the '592 patent IPR.

Defendants' efforts to manufacture a continuing case or controversy over the disclaimed claims fail. The fact that the amended claims ***may*** only issue if Sanofi is successful on appeal demonstrates that the alleged dispute is not ripe. The potential impact of a judgment on the disclaimed claims on a potential lawsuit asserting unissued patent claims is too conjectural to meet the immediacy and reality requirements of justiciability.

Recognizing the weakness of their claim preclusion arguments in the district court, Defendants improperly interject a wholly new preclusion theory based on claims 1 and 27, which were not part of the district court's judgment. Regardless, claim preclusion does not bar Sanofi's potential future assertion of the amended claims under *Senju* and *Aspex Eyewear*. The amended claims create a new cause of action that did not exist when this litigation began because those claims are materially different from their original counterparts. Because a material difference

inquiry requires factual findings based on a complete record that does not exist here, this Court should decline to take up Defendants' hypothetical controversy now.

Lastly, Defendants cannot equate the instant case with the circumstances of *Senju* based on Sanofi's purported "malfeasance" in removing the disclaimed claims from litigation and seeking amended claims. The inevitable cancellation of the disclaimed claims and Sanofi's motion to amend were the natural consequence of Mylan's delayed IPR and Defendants' opposition to a litigation stay.

II. Cross-Appeal of the '170 Patent

The district court correctly found claims 1 and 2 of the '170 patent nonobvious because Defendants' arguments were hindsight-driven, and their expert witnesses "cherry-picked" through the prior art. The district court also found that the evidence of objective indicia of nonobviousness weighed significantly in favor of Sanofi. On cross-appeal—to which only seven of ten original Defendants have joined—Defendants rehash their previously made obviousness arguments without pointing to any clear error by the district court. This Court should affirm the district court's judgment that the claims are not invalid.

STANDARD OF REVIEW: CROSS-APPEAL OF THE '170 PATENT

A district court's findings of fact supporting its obviousness conclusions are reviewed for clear error. *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1123 (Fed. Cir. 2018). "The burden of overcoming the district court's factual findings is, as it should be, a heavy one." *Id.* (quoting *Polaroid Corp. v. Eastman Kodak Co.*, 789 F.2d 1556, 1559 (Fed. Cir. 1986)). Absent contradictory extrinsic evidence, it is not legal error for the district court to agree with one expert even though both experts may have provided plausible opinions. *Anderson v. Bessemer City*, 470 U.S. 564, 575 (1985) ("[W]hen a trial judge's finding is based on his decision to credit the testimony of one of two or more witnesses, each of whom has told a coherent and facially plausible story that is not contradicted by extrinsic evidence, that finding, if not internally inconsistent, can virtually never be clear error."); *Honeywell Int'l, Inc. v. Hamilton Sundstrand Corp.*, 523 F.3d 1304, 1314 (Fed. Cir. 2008); *see also Bayer Pharma Ag. v. Watson Labs.*, 874 F.3d 1316, 1324 (Fed. Cir. 2017) (rejecting reliance on credibility ruling only in light of a "wealth of evidence" not considered by the district court).

In a compound case, proof of obviousness requires clear and convincing evidence that a POSA: (a) would have selected a particular lead compound as a starting point; (b) would have been motivated to make specific chemical modifications that would have led to the claimed invention; and (c) would have

been able to predict that those chemical modifications would have resulted in the claimed compound and the unique combination of all of its properties. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012); *Daiichi Sankyo v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010). Whether the prior art would motivate a POSA to make the claimed invention is a question of fact. *Insite Vision, Inc. v. Sandoz, Inc.*, 783 F.3d 853, 860 (Fed. Cir. 2015).

ARGUMENT

I. Appeal of the '592 Patent

A. There Was No Justiciable Case or Controversy Over the Disclaimed Claims When the District Court Issued Its Decision

Defendants do not dispute the "general" rule that "when a claim is cancelled, the patentee loses any cause of action based on that claim, and any pending litigation in which the claims are asserted becomes moot." *Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 721 F.3d 1330, 1340 (Fed. Cir. 2013); *cf. In re Baird*, 52 C.C.P.A. 1747, 1760 (1965) ("[W]e will not knowingly deal with imaginary issues such as the patentability of canceled claims."). Nor do they dispute that, prior to the district court's merits decision, claims 7, 11, 14-16, and 26 of the '592 patent had already been canceled by the disclaimer, and even if not disclaimed, would inevitably have been canceled because Sanofi did not appeal the PTAB's decision invalidating those claims. Accordingly, under *Fresenius v. Baxter*, any dispute regarding the disclaimed claims was moot, and therefore not justiciable when the merits decision issued below. *See* BlueBr25-28.

Defendants nonetheless argue that there is a continuing case or controversy over the nonexistent disclaimed claims because Defendants may raise the affirmative defenses of claim preclusion or collateral estoppel (i.e., issue preclusion) should Sanofi successfully overturn the PTAB's Final Written Decision, obtain amended claims, and sue Defendants for infringement. RedBr26,

RedBr46-47; *Mylan Labs. Ltd. v. Aventis Pharma S.A.*, IPR2016-00712, Paper 99 (P.T.A.B. Sept. 21, 2017) ("FWD"). But Defendants cite no authority even suggesting that courts maintain subject matter jurisdiction to invalidate canceled patent claims solely to create affirmative defenses to a possible future lawsuit that could not then and may never be brought. Also, because the amended claims had not been allowed when the district court issued its decision, any dispute regarding those claims is too speculative and unripe to meet the *MedImmune* immediacy and reality requirements for justiciability. *See MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 127 (2007).

1. There Are No "Collateral Consequences" That Avoid Mootness Here

Defendants misplace reliance on *Minnesota Mining & Manufacturing (3M) Co. v. Barr Laboratories, Inc.* and *Microsoft Corp. v. ITC* to argue that their potential issue preclusion defense to assertion of the amended claims is a "collateral consequence" that avoids mootness here. RedBr45-46. Neither case supports Defendants' argument.

Indeed, the rationale of *3M* is inapplicable here for the same reasons that *Apotex v. Daiichi Sankyo* is inapposite. *See* BlueBr29-30. The issue in *3M* was whether, under the Hatch-Waxman Act market forfeiture provision, a dismissal with or without prejudice would trigger a first ANDA filer's 180-day marketing exclusivity allowing the second ANDA filer to launch its product sooner. 289 F.3d

775, 780 (Fed. Cir. 2002). Thus, like in *Apotex v. Daiichi Sankyo*, the parties had concrete adverse interests in sales that they stood to gain or lose.[2] No such adverse interests are present here because the market forfeiture provisions that formed the basis for a justiciable case or controversy in *3M* and *Apotex v. Daiichi Sankyo* are not involved. No Defendant asserts that a judgment on the disclaimed claims will cause forfeiture of another Defendant's marketing exclusivity and allow earlier launch.

Microsoft Corp. v. ITC is also inapplicable. Motorola belatedly argued that the parties' dispute was mooted by expiration of the patent-in-suit only after this Court denied its request for rehearing of an unfavorable decision on appeal from the ITC. No. 2012-1445, 2014 U.S. App. LEXIS 215, at *5-6 (Fed. Cir. Jan. 3, 2014). A parallel damages litigation between the parties on the same patent had been stayed pending resolution of the ITC appeal, and "money [wa]s at stake" in the parallel litigation based on the outcome of the ITC appeal. *Id.* at *2-3. Here, in contrast, the parties' dispute regarding the disclaimed claims was moot before the district court reached its merits decision. Nor is there any parallel infringement

[2] *Caraco Pharmaceutical Laboratories, Ltd. v. Forest Laboratories, Ltd.* is similarly inapposite. In *Caraco*, a covenant not to sue did not moot the parties' dispute because a judgment would trigger the first ANDA filer's 180-day marketing exclusivity and allow the accused infringer to launch sooner. 527 F.3d 1278, 1296-97 (Fed. Cir. 2008).

litigation on either the disclaimed or unissued amended claims where money damages or any other adverse interests remain at stake.

Notably, for Defendants' potential issue preclusion defense to apply, a court must find that (1) "the identical issue" was (2) "actually litigated" and (3) "necessary to the [prior] decision." *Source Search Techs., LLC v. Lending Tree, LLC*, 588 F.3d 1063, 1074 (Fed. Cir. 2009) (quotations and citations omitted). Defendants argue that the district court's judgment as to disclaimed claim 11 precludes litigation of the validity of claim limitations directed to doses of cabazitaxel beyond 20 mg/m^2. RedBr47-48. But because the district court did not decide whether any dose of cabazitaxel was obvious in methods where "increasing survival" is a claim limitation (as Sanofi asserts it is in the amended claims, *see infra* Argument Sections I.A.2, I.C.3), an "identical issue" was not "actually litigated" in the district court, as required for issue preclusion to apply.[3] Nor have Defendants shown that any district court discussion of doses beyond 20 mg/m^2 was "necessary" to its judgment on claim 11.

Defendants also argue that a judgment on the disclaimed claims may have some collateral estoppel effect on continuation applications from Sanofi's '592 patent. RedBr46 n.7. But because prosecution of continuation applications is still

[3] Obviousness requires consideration of the patent claims "as a whole," not of individual elements. 35 U.S.C. § 103 (pre-AIA); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406, 418-19 (2007).

ongoing, and the substance of future claims could change, any dispute over whether Sanofi's potential suit on continuation claims would be claim or issue barred is even more speculative and unripe for resolution than a dispute regarding the amended claims, and thus cannot create a justiciable case or controversy over the disclaimed claims. *See infra* Argument Section I.A.2.

2. A Potential Dispute over Whether Claim or Issue Preclusion Bars Assertion of the Amended Claims Is Not Immediate and Real

Defendants acknowledge that the "collateral consequences" of a judgment may support a continuing case or controversy only if those consequences are not "unduly speculative." RedBr46; *see also Prasco, LLC v. Medicis Pharm. Corp.*, 537 F.3d 1329, 1338 (Fed. Cir. 2008) (the "injury-in-fact" must not be "conjectural or hypothetical" (quotations omitted)). Here, issuance of the amended claims and their construction represent contingent future events "that may not occur as anticipated, or indeed may not occur at all." *Texas v. United States*, 523 U.S. 296, 300 (1998) (quotations and citations omitted); *First Data Corp. v. Inselberg*, 870 F.3d 1367, 1374-75 (Fed. Cir. 2017) (quoting *Texas*, 523 U.S. at 300). As such, the dispute Defendants anticipate here is not ripe for review. *Id.*; *Sandoz Inc. v. Amgen Inc.*, 773 F.3d 1274, 1278 (Fed. Cir. 2014) ("[R]ipeness principles in particular reinforce the importance of contingency in the analysis.").

Defendants also assert that the amended claims "exist, and are specific, [and] defined." RedBr41. However, the question of whether "increasing survival" limits the claims is a claim construction issue that is currently contested in the FWD appeal. *Aventis Pharma S.A. v. Mylan Labs. Ltd.*, No. 2018-1203, D.E. 19 Brief for Appellant at 24-25 (Fed. Cir. Mar. 15, 2018) ("FWD Appeal Brief"). Thus, the outcome of that appeal may significantly alter a court's future consideration of Defendants' claim or issue preclusion defenses should the amended claims issue and be asserted. For this reason alone, a dispute about these affirmative defenses is not ripe for resolution now and is unduly speculative. *See Nat'l Park Hospitality Ass'n v. DOI*, 538 U.S. 803, 807-08, 812 (2003) (dispute regarding a legal issue was unripe because "further factual development would significantly advance our ability to deal with the legal issues presented"); *Sandoz*, 773 F.3d at 1280-81 (no immediacy and reality where "further factual development would significantly advance a court's ability to identify and define issues for resolution" (quotations and citations omitted)).

Defendants also rely in error on Sanofi's appeal of the FWD to support a case or controversy. RedBr39. The question here is whether there was a case or controversy ***when the district court's judgment*** was entered, not when the FWD appeal was fully briefed. *Janssen Pharmaceutica, N.V. v. Apotex, Inc.*, 540 F.3d 1353, 1362-63 & n.9 (Fed. Cir. 2008). When the district court issued its decision,

a dispute regarding the yet-to-issue amended claims was particularly speculative because the FWD appeal was still in its early stages, with the appeal briefing not yet filed, such that there was no way to predict whether the amended claims would issue. *See AIDS Healthcare Found., Inc. v. Gilead Scis., Inc.,* 890 F.3d 986, 992 (Fed. Cir. May 11, 2018), *petition for cert. filed*, (U.S. Aug. 7, 2018) (No. 18-182) ("The uncertainty of whether future infringement might occur at all weighs against the immediacy and reality requirement of declaratory action.").

While Defendants dismiss Sanofi's *Amana Refrigeration* and *Spectronics* cases (BlueBr43) because they were decided before Defendants' *Teva v. Novartis* case (discussed *infra* Argument Section I.A.3), Defendants cite no authority refuting that potential disputes over unissued claims are not immediate and real. RedBr42.[4] In fact, *Teva v. Novartis* cites *Spectronics*, undermining Defendants' contention that this case is not good law. *Teva Pharms. USA, Inc. v. Novartis Pharms. Corp*., 482 F.3d 1330, 1338 n.3 (Fed. Cir. 2007) (citing *Spectronics Corp. v. H.B. Fuller Co*., 940 F.2d 631, 634 (Fed. Cir. 1991)).

[4] *Liquid Dynamics Corp. v. Vaughn Co*. merely notes that invalidity counterclaims are not moot simply because no infringement is found. 355 F.3d 1361, 1370-71 (Fed. Cir. 2004). *Vestcom International, Inc. v. Information Planning and Management Services, Inc*. affirmatively cites *Amana Refrigeration*, but notes that a reasonable apprehension of suit is no longer required for justiciability. No. 4-08-CV00276, 2008 U.S. Dist. LEXIS 129096, *7-8, *18-19 & n.1 (E.D. Ark. Aug. 12, 2008).

Importantly, Defendants do not address *GAF Building Materials Corp. v. Elk Corp.*, where this Court found no justiciable case or controversy over allowed but unissued claims even though the declaratory judgment plaintiff who received a cease and desist letter had a reasonable apprehension of suit. 90 F.3d 479, 480-82 (Fed. Cir. 1996). The dispute was "purely hypothetical" because there was only "a possible future patent not then in existence." *Id.* The dispute here is even more hypothetical because at the time the district court issued its decision the amended claims had not and could not be allowed without court intervention. Although *GAF Building Materials* is a pre-*Medimmune* decision, it was not limited to the now-defunct "reasonable apprehension of suit" test, and has been cited by this Court post-*Medimmune* for the principle that claims cannot be asserted until they issue. *Id.* at 481-82; *Radio Sys. Corp. v. Lalor*, 709 F.3d 1124, 1131 (Fed. Cir. 2013); *see also John Bean Techs. Corp. v. Morris & Assocs.*, 887 F.3d 1322, 1328 (Fed. Cir. 2018), *petition for cert. filed*, (U.S. Oct. 17, 2018) (No. 18-495) ("[F]or claims that have not issued, there is no case or controversy.").

3. Principles of "Patent Certainty" Do Not Support a Case or Controversy Here

Defendants rely on *Teva v. Novartis* to argue that there is a continuing case or controversy over the disclaimed claims for purposes of obtaining "patent certainty" on the amended claims. RedBr38-40. But Defendants misstate the significance of that decision. Novartis sued Teva on one of five Orange Book-

listed patents for which Teva had made paragraph IV certifications, and declined to give Teva a covenant not to sue on the four unasserted patents. 482 F.3d at 1334-35. Thus, absent a declaratory judgment of invalidity of the unasserted patents, Teva was at risk of being sued on those patents at any time. *Id.* at 1341. The Court reasoned that if Teva's ANDA filing created an immediate case or controversy allowing Novartis to sue Teva, it "logically" followed that "the same action should create a justiciable declaratory judgment controversy for the opposing party." *Id.* at 1342.

Unlike in *Teva v. Novartis*, Sanofi could not sue Defendants on any disputed claims of the '592 patent when the district court issued its decision. As explained in the Blue Brief, because Sanofi appealed the FWD only as to claims 21 and 30 before the deadline for the notice of appeal passed on November 24, 2017, all other challenged claims would inevitably be canceled. BlueBr26. The disclaimed claims had been canceled when the court's decision issued, and there were (and still are) no issued amended claims. Thus, unlike in *Teva v. Novartis*, after those events, there were no patent claims on which Sanofi could sue Defendants.

This case is more akin to *Pfizer Inc. v. Ranbaxy Laboratories, Ltd.* where Pfizer gave Ranbaxy a covenant not to sue on the original claims of a patent that was in reissue proceedings. 525 F. Supp. 2d 680, 684-85 (D. Del. 2007). Like Defendants here, Ranbaxy contended that there was a continuing controversy over

its declaratory judgment claim for patent unenforceability based on the risk it would be sued on the reissue claims. *Id.* at 685. The court rejected this argument under the *MedImmune* standard, reasoning that the "existence of issued and presently enforceable patent claims . . . is a necessary prerequisite to continued litigation of a declaratory judgment action." *Id.* at 686. The court further reasoned that there was no continuing controversy because one patent claim had already been invalidated in prior litigation, there was a covenant not to sue on the original claims, and the reissue claims had not and might never issue. *Id.* at 686-87.

Similarly here, because Sanofi could not assert the disclaimed or amended claims against Defendants at the time the district court issued its decision, there was no justiciable controversy over the former claims solely for the purpose of preventing suit on the latter claims. As this Court explained in *GAF Building Materials*, rights are created only upon the formal issuance of a patent, and therefore disputes regarding unissued patent claims are "necessarily hypothetical" and would call for "an impermissible advisory opinion." 90 F.3d at 482-83; *Brown v. Toscano*, 254 F.R.D. 690, 696-97 (S.D. Fla. 2008); *Pfizer Inc.*, 525 F. Supp. 2d at 687 ("[E]xercise of jurisdiction in these circumstances would result in nothing more than an advisory opinion regarding the enforceability of a yet to be reissued patent, a result wholly inconsistent with the most basic precepts of jurisdictional jurisprudence.").

B. Defendants' New Issue 1 Is Not Appropriately Before This Court

Defendants raise a new issue for resolution by this Court: whether Sanofi will be barred on claim preclusion grounds from asserting its yet-to-issue amended claims against Defendants based on Sanofi's initial (and later withdrawn) assertion in the district court of '592 patent claims 1 and 27. RedBr3 (Defendants' "Issue 1"). Issue 1 should not be decided by this Court.

The sole issue in this appeal regarding the '592 patent is whether the district court had subject matter jurisdiction to invalidate the disclaimed claims. The district court did not invalidate claims 1 or 27, which were not disclaimed. Appx4-14. Defendants' Issue 1 is therefore unrelated to the sole issue on appeal or the underlying judgment, and should therefore not be raised in this Court. Indeed, Defendants concede that they seek a ruling on Issue 1 solely for purposes of deciding whether to oppose Sanofi's appeal. RedBr3, RedBr25-26.

Moreover, as a "general rule . . . a federal appellate court does not consider an issue not passed upon below." *Singleton v. Wulff*, 428 U.S. 106, 120 (1976); *SimpleAir, Inc. v. Google LLC*, 884 F.3d 1160, 1170-71 (Fed. Cir. 2018) (declining to consider new appeal issue where the raising party did not provide sufficient justification). Defendants cannot justify raising the issue of claim preclusion based on claims 1 and 27 for the first time on appeal. Indeed, resolution of Defendants' new Issue 1 is particularly inappropriate in this Court because, as explained below,

it requires factual findings that should be made by the district court in the first instance on a complete record that does not exist here. *Infra* Argument Section I.C.2.

Finally, this Court should decline to rule in the first instance on Defendants' Issue 1 because such a ruling would be an impermissible advisory opinion on "what the law would be upon a hypothetical state of facts," namely, that the amended claims ultimately issue and are asserted against Defendants. *MedImmune*, 549 U.S. at 127 (quoting *Aetna Life Ins. Co. v. Haworth*, 300 U.S. 227, 240-41 (1937)); *GAF Bldg. Materials Corp.*, 90 F.3d at 482-83 (finding it would be an advisory opinion to rule on a dispute relating to unissued patent claims); *see also* BlueBr42 (discussing Supreme Court precedent finding that rulings on the merits of affirmative defenses to suits that cannot and have not been brought are impermissible advisory opinions).

C. ***Aspex Eyewear* and *Senju* Do Not Bar Sanofi on Claim Preclusion Grounds From Asserting the Amended Claims Against Defendants**

Even if this Court were to consider Defendants' new Issue 1 concerning claims 1 and 27, Sanofi should not be barred from asserting the amended claims against Defendants based on either: (1) Sanofi's initial assertion of claims 1 and 27 or (2) the district court's judgment on the disclaimed claims. Under *Senju* and *Aspex Eyewear*, a claim preclusion analysis considers whether new amended

claims are materially different from the original claims such that the amended claims support a new cause of action. Importantly, the district court should determine in the first instance whether these material differences exist based on a complete factual record. No such determination was made here, where the relevant record below was far from complete. And, in any event, even a cursory review of the amended claims reveals that they include new limitations that make them materially different from their original counterparts. Accordingly, Sanofi should not be barred by claim preclusion from asserting a new cause of action on the amended claims, which did not exist during the original litigation.

1. The Test for Claim Preclusion Looks to Material Differences Between the Claims

In the district court, Defendants advocated for claim preclusion on grounds that the yet-to-issue amended claims are narrower than disclaimed claims 7, 11, 14-16, and 26. Appx14172, Appx14182, Appx14185-14186. But now, having recognized that this is largely incorrect, Defendants focus instead on independent claims 1 and 27 as a basis for claim preclusion. RedBr25-26; BlueBr37-38. At the same time, Defendants acknowledge that the test for whether the amended claims create a new cause of action that avoids claim preclusion is not whether the amended claims are narrower than the original claims, but whether the amended claims are "insubstantially different." RedBr30-31, RedBr37, RedBr40. Indeed,

this test is reflected in this Court's *Aspex Eyewear* and *Senju* decisions on which Defendants rely.

In *Aspex Eyewear,* amended claim 23 (issued in reexamination) matched the original claim except for added limiting words that were "already implicit" in the original claim. *Aspex Eyewear, Inc. v. Marchon Eyewear, Inc*., 672 F.3d 1335, 1341 (Fed. Cir. 2012) (also recognizing that new reexamined claim 35, dependent on amended claim 23, merely required "said magnetic members" to be "magnets"). In finding that claim preclusion barred a second suit on the reexamined claims, this Court found that the differences from the original claims were "insignificant" and that the patentee could have, but chose not to include original claim 23 in the first suit. *Id.*

In *Senju*, the original claims were directed to ophthalmic formulations of gatifloxacin with EDTA, which was included to improve passage of the gatifloxacin into the eye. *Senju Pharm. Co. v. Apotex*, 746 F.3d 1344, 1346-47 (Fed. Cir. 2014). During reexamination, the claims were amended to specify the amount of gatifloxacin, the amount of EDTA, and the pH of the formulation. *Id.* at 1347. Under these circumstances, the district court noted that the amended claims were "essentially the original claims with limiting words added." *Id.* at 1353. Notably, although this Court found on that particular record that claim preclusion applied, the Court left open the possibility that reexamination could "result in the

issuance of new patent claims that were so materially different from the original patent claims as to create a new cause of action, but at the same time were sufficiently narrow so as not to violate the rule against reexamined claims being broader than the original claims." *Id.* This Court found that in the "absence of a clear showing that ***such a material difference in fact exists***," "it can be assumed" that no new cause of action will be created by a patentable claim that issued in reexamination. *Id.* Thus, to find that claim preclusion does not apply here, a court need only find that the amended claims are materially different from the original claims, even if narrower in scope. Significantly, this Court need not overrule *Senju* (or *Aspex Eyewear*) to reject claim preclusion here, as Defendants erroneously contend.

2. This Court Should Not Resolve the Fact-Intensive "Material Difference" Inquiry in the First Instance

A determination whether amended claims are materially different so as to support a new cause of action requires analysis of the "transactional facts" and involves potential matters such as claim construction and consideration of expert testimony. *See SimpleAir*, 884 F.3d at 1165; *Senju*, 746 F.3d at 1349; *see also Purdue Pharma L.P. v. Mylan Pharms. Inc.*, C.A. No. 15-1155, 2017 U.S. Dist. LEXIS 28460, at *25-26 (D. Del. Mar. 1, 2017) (Because "the question of whether the difference in claim language materially alters the patentability of claim 16 is

fact-intensive, the court cannot rule at this [motion to dismiss] stage of the proceedings that collateral estoppel should apply to invalidate claim 16").

Here, the district court should decide in the first instance whether Sanofi can make the "clear showing" of material difference that *Senju* requires (746 F.3d at 1353), and should do so only when and if Sanofi obtains the amended claims and sues Defendants for infringement. The issue should not be decided in the first instance by this Court on an incomplete record and before the amended claims have even been allowed. *See SimpleAir,* 884 F.3d at 1168-69 ("[W]e leave to the district court's discretion on remand whether formal claim construction is necessary."); *Foster v. Hallco Mfg. Co.*, 947 F.2d 469, 480 (Fed. Cir. 1991) (finding it "inappropriate" to rule on whether there were "material differences" between products in the first instance and "leav[ing] it to the trial court to determine whether this suit is based on a different claim"); *Wi-LAN Inc. v. Apple Inc.*, C.A. No. 6:12-cv-920, 2014 U.S. Dist. LEXIS 194048, at *4-5 (E.D. Tex. 2014) ("This Court is not in a position to compare the original claims 1, 2, and 5 with reexamined claims that have yet to issue. That determination lies with the court handling any subsequent litigation between Wi-LAN and Apple.").

3. The Amended Claims Are Materially Different from the Original Claims

Because they were never part of the litigation in this case, there is little record evidence regarding the substance of the amended claims. However, should

this Court consider the issue in the first instance, on their face, the amended claims have significant and material differences from the original claims.

First, the amended claims were drafted to make "increasing survival" a claim element (an issue currently before this Court in Sanofi's appeal from the FWD). RedBr7-8, RedBr35; FWD Appeal Brief at 24-25. The district court and PTAB found this "increasing survival" limitation not to be part of any original claim. Appx364-369, Appx4603-4604, Appx10735-10737. Sanofi repeatedly argued during prosecution, before the district court, and before the PTAB that the increase in overall survival demonstrated in the TROPIC clinical study described in the '592 patent was surprising, unexpected, and thus a major point of patentability over the prior art. *See, e.g.*, Appx1312, Appx1323-1325, Appx1497-1500, Appx1536, Appx1538-1542, Appx10766, Appx10795-10799, Appx11249-11251. If "increasing survival" is found to be a limitation of the amended claims, as Sanofi urges, that alone would make the amended claims materially different from their original counterparts.

Second, the amended claims require administering three drugs before cabazitaxel is administered. Appx10793-10794; BlueBr10. None of the original claims required any such premedication. Appx368-369. And, unlike in *Senju* and *Aspex Eyewear*, this three-component premedication requirement does not represent the mere addition of words that narrow existing aspects of the claims or

make implicit limitations explicit. Rather, the three-component premedication is a distinct part of the disclosure of the '592 patent that was not previously claimed. Appx362 (6:41-45: "One aspect of the invention comprises a method of reducing the risk of a severe hypersensitivity reaction . . . comprising administering to the patient a medication to prevent hypersensitivity prior to the administration of cabazitaxel.").[5] Thus, regardless of whether "increasing survival" is ultimately construed to be part of the amended claims, the validity analysis for these claims will necessarily be different from that analysis for the original claims. *John Bean Techs*., 887 F.3d at 1327-28.

Research reveals that no court has yet to apply *Senju*'s "materially different" test to determine whether claim preclusion applies to bar suit on IPR amended patent claims based on previously asserted original claims. However, patent claim analyses performed in other contexts, such as equitable estoppel, support the conclusion that there is a new cause of action here where new limitations not appearing in any original claims were added to the amended claims.

[5] Defendants' attempt to equate original claim 1 with original claim 11, and then to equate claim 11 with the amended claims is both unsupported and circular. RedBr40. If dependent claim 11 is "insubstantially different" from claim 1 only because claims 1 and 11 were found obvious, then the amended claims will be "substantially different" from the original claims because they must be found nonobvious in order to issue. Further, claim 11 is not broader than the amended claims. BlueBr37.

For example, in *John Bean Technologies*, amendments during reexamination added, among other things, "new limitations" such as chilling water at a certain level that did not appear in the original claims. 887 F.3d at 1325-26, 1328. Because these amendments were found sufficiently "substantial and substantive," equitable estoppel did not bar a suit filed years after the defendant had been notified of but not sued for infringement of the original patent.[6] *Id.* at 1328-29. Similarly, at issue in *Gruskin* was whether final rejection of parent patent claims, whose rejection by the examiner had been affirmed by the Board of Appeals and then on appeal to a district court, barred issuance of continuation claims on "res judicata" grounds. *In re Gruskin*, 234 F.2d 493, 495-97 (C.C.P.A. 1956). The *Gruskin* court held that res judicata did not apply because of new claim limitations—the continuation required an inorganic acid neutralizing salt that acted as an abrasive, while the previously finally rejected parent claims required only an abrasive. *Id.* at 496-97.

Thus, under the rationale of *Senju* and *Aspex Eyewear*, as well as analogous precedent discussed above, because the amended claims here have new limitations incorporating previously unclaimed aspects of the invention disclosed in the '592 patent, those claims are materially different from the original claims. As such,

[6] Equitable estoppel bars an infringement action if the accused infringer relies on representations by the patentee to reasonably infer that no suit will be brought, and the accused infringer would be materially prejudiced by an infringement action. *Id*. at 1327.

claim preclusion will not bar assertion of those claims against Defendants, should they ultimately issue.

Lastly, Defendants' attempts to distinguish *Target Training* fail. Defendants assert that this Court's rejection of claim preclusion in *Target Training* is distinguishable because that rejection was premised on the absence of a district court merits judgment. RedBr36-37. But Defendants ignore a second, separate rational for the *Target Training* result, namely, that claim preclusion "does not apply to bar the assertion of ***new claims*** acquired during the pendency of a litigation that could have been but were not, litigated or adjudicated in the action." *Target Training Int'l, Ltd. v. Extended Disc N. Amer.*, 645 Fed. App'x 1018, 1025-26 (Fed Cir. Apr. 22, 2016). Defendants' contentions notwithstanding, it matters not whether this Court's rationale contemplated later-acquired litigation claims (i.e., causes of action) as opposed to patent claims. While context suggests that the Court was referring to the reexamined patent claims at issue in *Target Training* (*id.* at 1025-26), the present case involves both new patent claims and a new cause of action (as explained directly above) that did not exist when Sanofi sued Defendants in the court below (and still do not exist today). Thus, the reasoning of *Target Training* applies, and Sanofi is not barred from asserting an after-acquired cause of action on the amended claims here. 645 Fed. App'x at 1025-26.

D. Sanofi Has Not Engaged in "Gamesmanship," Let Alone "Malfeasance," and Has Litigated in Good Faith

Attempting to dismiss the differences between this case and *Senju* that Sanofi has identified (BlueBr33), Defendants argue that claim preclusion bars future assertion of the amended claims because of Sanofi's "gamesmanship" and "malfeasance." RedBr33-36. Citing no legal support for this result, Defendants rely on Sanofi's (1) purported delay in bringing its stay motion, (2) decision to drop claims during the course of litigation and purported failure to "timely withdraw" claims 7, 11, 14-16, and 26, and (3) efforts to amend the claims during the IPR. *Id.* Defendants' accusations are demonstrably false.

1. The Timing of Sanofi's Stay Motion Was Appropriate

Sanofi's motion to stay the district court litigation was timely. Sanofi notified Defendants that it intended to seek a stay of the '592 patent litigation on November 16, 2016, less than two months after the IPR was instituted.[7] Appx5043, Appx15054. Because many courts have declined to issue a litigation stay before an IPR is formally instituted, it was appropriate, if not necessary, for Sanofi to wait for institution before moving to stay. *Loyalty Conversion Sys. Corp. v. Am. Airlines, Inc.*, No. 2:13-CV-655, 2014 U.S. Dist. LEXIS 102978, at *5-7 (E.D. Tex. July 29, 2014) ("[T]he majority of courts that have addressed the issue

[7] The motion to stay was not filed until December 16, 2016 because the parties were required to meet and confer on the issue. Appx4982.

have postponed ruling on stay requests or have denied stay requests when the PTAB has not yet acted on the petition for review."); *see also VirtualAgility Inc. v. Salesforce.com, Inc.*, 759 F.3d 1307, 1315-16 (Fed. Cir. 2014) ("[T]he case for a stay is stronger after post-grant review has been instituted."); *SSL Servs., LLC v. Cisco Sys.*, No. 2:15-cv-433-JRG-RSP, 2016 U.S. Dist. LEXIS 83370, at *6 (E.D. Tex. June 27, 2016) (finding it "reasonable for [the defendant] to wait for the PTAB to institute IPR before filing its Motion to Stay").

Furthermore, the PTAB's decision denying institution of Mylan's first IPR petition challenging the '170 patent, to which the 30-month stay was associated, issued on August 23, 2016. Appx11334-11335. As explained in the Blue Brief, that institution denial was the first indication that stay of the '592 patent litigation could be appropriate because resolution of any '592 patent issues could occur while the '170 patent effectively kept Defendants' cabazitaxel products off the market. BlueBr5-9.

2. Sanofi Limited the Issues in Dispute in Good Faith to Claims 21 and 30

Defendants' accusations demonstrate that Sanofi narrowed the disputed issues during litigation by ceasing to assert certain claims. RedBr33-35. Rather than malfeasance, these actions reflect the normal course of litigation where parties focus their arguments and limit the issues to conserve the resources of the parties and courts. *See Union Pac. Resources Co. v. Chesapeake Energy Corp.*, 236 F.3d

684, 694 (Fed. Cir. 2001) (noting that "[c]laims and defendants frequently are dropped and amended during the course of a lawsuit" and that "sound judicial policy encourages a narrowing of issues"); *Medtronic Navigation, Inc. v. BrainLAB Medizinische Computersysteme GmbH*, 603 F.3d 943, 959 (Fed. Cir. 2010) ("A decision by a party to narrow its case for presentation to a jury does not generally suggest manipulation of the litigation process."); *NXP B.V. v. Blackberry, Ltd.*, 58 F. Supp. 3d 1313, 1318-19, 1321 (M.D. Fla. 2014) (no exceptional case because it was reasonable for the plaintiff to withdraw some asserted patents after an unfavorable claim construction and it was a permissible "strategic choice" to withdraw patent claims at trial).

Defendants focus on Sanofi's decision to assert only claims 21 and 30 after the FWD issued in the middle of trial. RedBr33-34. In fact, because Defendants had opposed the litigation stay, Sanofi was compelled to decide in only a few days how to proceed on the '592 patent claims after the PTAB found them invalid, while continuing to try the case on the '170 patent. BlueBr9, BlueBr11. Ultimately, Sanofi proceeded only on what Sanofi believed reflected its strongest position at the time: claims 21 and 30 of the '592 patent. BlueBr11. As soon as it made this decision, Sanofi notified Defendants and the district court that it was limiting the asserted claims. *Id.* The timing and substance of this decision were reasonable and appropriate.

Defendants also incorrectly assert that Sanofi failed to timely withdraw its assertion of claims other than 21 and 30 "even during post-trial briefing." RedBr34. There can be little dispute that the district court knew which claims Sanofi was asserting (and therefore which had been dropped) more than a month before the merits decision was reached. Sanofi so informed the court on the last day of trial, in its post-trial briefing, and at closing argument in which only claims 21 and 30 were addressed. BlueBr11, BlueBr23-24. Indeed, contrary to Defendants' Statement of Jurisdiction (RedBr3), the district court found only claims 21 and 30 infringed because the court recognized that these were the only asserted claims. Appx63, Appx80 n.24.

Sanofi could not "formally" dismiss individual patent claims from the litigation (as Defendants contend it should have done) because Sanofi's complaints asserted counts of infringement of "at least one claim" of the '592 patent, and Sanofi continued to assert infringement of claims 21 and 30.[8] BlueBr6. Nor was Sanofi required to formally dismiss particular patent claims in order to remove them from dispute. *See Alcon Res. Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1983 (Fed. Cir. 2014) (no "formal motion or stipulation" required); *Teva Pharm. Indus. v. Dr. Reddy's Labs., Ltd.*, No. 07-2894, 2008 U.S. Dist. LEXIS 16958, at *11-14

[8] The deadline for amended pleadings had long passed, and a request to amend infringement contentions would have delayed resolution and not have accomplished more than what Sanofi had already achieved: notice to Defendants and the court that there were now only two asserted patent claims. Appx522-524.

(D.N.J. Mar. 4, 2008) (brief stating that patent claim was not asserted was sufficient to remove subject matter jurisdiction as to that claim where the complaint did not identify particular claims, and no Fed. R. Civ. P. 41 dismissal had taken place).

Defendants also challenge the timing of Sanofi's decision to forego appeal of the FWD with respect to claims other than claims 21 and 30. RedBr34. However, Sanofi filed its Notice of Appeal from the FWD on November 17, 2017 (one week before the deadline) and notified the district court that same day that the unappealed claims (all challenged claims except 21 and 30) would inevitably be canceled. BlueBr3. Again, this timing was reasonable considering the importance of the decision regarding which claims to appeal and Sanofi's concurrent efforts to prepare post-trial briefing due October 31, 2017 and closing arguments scheduled for November 8, 2017. Appx10879, Appx12181.

Defendants further accuse Sanofi of "manipulat[ing]" jurisdiction by filing the statutory disclaimer. RedBr48. To the contrary, as explained in the Blue Brief, Sanofi had already made clear that it was not asserting the disclaimed claims before filing the disclaimer, and litigation regarding those claims had already become moot at least by virtue of their inevitable cancellation at the hands of Mylan's IPR. BlueBr24, BlueBr26-27. While unnecessary, the disclaimer was filed not to manipulate the court's jurisdiction, but rather because Defendants had

baselessly argued that subject matter jurisdiction remained merely because the '592 patent claims had not yet been officially canceled by the PTAB. Appx14131, Appx14135.

Finally, Defendants' citation of *City of Erie v. Pap's A.M.* fails to support their argument that Sanofi manipulated jurisdiction. In *City of Erie*, the trial and appeals court decisions had already issued when the dispute was belatedly alleged to be moot, and the City of Erie faced the ongoing injury of being unable to enforce its ordinance that had been found unconstitutional. 529 U.S. 277, 286-88 (2000). In contrast, here, Sanofi promptly notified the district court that the parties' dispute regarding the disclaimed claims was moot well before the court reached its merits decision. *See* BlueBr24, BlueBr26-27.

3. Sanofi's Motion to Amend Was Appropriate and Made in Good Faith

Defendants suggest that Sanofi's motion to amend was gamesmanship, arguing that (1) Sanofi should have filed the application that led to the '592 patent earlier before publication of the "Phase III Disclosures," or (2) should have requested reexamination "shortly after the ['592] patent issued." RedBr36. But the "Phase III Disclosures" were not published by Sanofi, nor has it been shown that Sanofi had control over their publication or even knew of their existence before this litigation started. Appx17002, Appx17113 (both listings of uro-oncology trials in Canada), Appx16810 (Annual Report from Gujarat Cancer &

Research Institute). Furthermore, Sanofi had no reason to amend the claims prior to the PTAB's institution of the IPR (or prior to the district court's claim construction decision that issued the same day) because Sanofi previously believed the claim preambles, directed to increasing survival and treating patients, to be limitations of the original '592 patent claims. Appx3506-3512, Appx5111, Appx5117-5120; *see also* Appx4603-4605. Once the claims were not so construed, Sanofi carefully considered the disclosure of the '592 patent and drafted patentable proposed amended claims, as expressly permitted by the IPR statute. *See* 35 U.S.C. § 316(d).

At bottom, Defendants seek to prevent Sanofi from asserting valid amended claims that it rightfully sought in the IPR. As explained in the Blue Brief, claim amendments are an important aspect of IPR proceedings, and Sanofi should not be effectively foreclosed from pursuing that opportunity. BlueBr33-34. Defendants' contentions notwithstanding, this conclusion is not undermined by the fact that *Senju* was also a Hatch-Waxman case, or that IPR proceedings replaced reexamination. RedBr30 n.6, RedBr35-36. Unlike reexamination proceedings which, as in *Senju*, can be initiated by the patentee after litigation has failed, IPR proceedings cannot be filed by the patent owner. 37 C.F.R. § 42.101. Defendant Mylan forced Sanofi into the IPR proceeding knowing that it would provide Sanofi an opportunity to amend the challenged claims. Applying claim preclusion to

prevent Hatch-Waxman patentees from asserting valid amended claims against ANDA filers who, like Mylan here, strategically delay in filing an IPR and then oppose a litigation stay, would create a windfall for ANDA filers that was contemplated by neither the Hatch-Waxman Act nor the America Invents Act provisions establishing IPRs. *See* BlueBr33-35.

II. Cross-Appeal of the '170 Patent

A. The District Court Correctly Ruled That the '170 Patent Claims Are Nonobvious

This Court reviews for clear error the district court's factual finding that a POSA would not have been motivated to make simultaneous modifications at the C-7 and C-10 positions of docetaxel with a methoxy group to arrive at cabazitaxel. *Vanda Pharms.*, 887 F.3d at 1123; *Insite Vision*, 783 F.3d at 860. There was no clear error here. Defendants insist that the district court erred "factually and legally" because it found, among other things, that (i) *Hait* and *Lampidis* were ***not relevant*** to taxanes, (ii) there was ***no motivation*** to simultaneously modify the C-7 and C-10 positions of the taxane core with methoxy groups, and (iii) that Defendants' theories were based on impermissible hindsight. *See* Appx50-52. But these findings were based on expert witness testimony,[9] language in *Hait* and

[9] The district court explicitly undertook an "individualized credibility assessment of each witness and assigned the appropriate weight to the testimony based on the Court's conclusions with respect to credibility." Appx18 n.3.

Lampidis themselves, and other evidence thoroughly considered by the district court. Appx50-52. Defendants do not argue that the district court failed to consider *Hait* and *Lampidis*; rather, they essentially complain that the district court did not weigh the facts in their favor. But when a trial court carefully considers and bases its decision on the evidence, as the district court did here, that finding "can virtually never be clear error" absent contradictory extrinsic evidence. *Anderson*, 470 U.S. at 575. Given that the district court expressly found that the opinions of both of Defendants' experts, Drs. Kingston and Heathcock, were not credible, the district court did not commit clear error.[10] Appx51-52.

B. The District Court Did Not Err in Reaching Its Ultimate Decision on Validity of the '170 Patent Claims

Defendants argue that the district court erred in its fact finding but fail to provide the evidence necessary to show clear error. Throughout their brief, Defendants offer only selective quotes and portions of evidence to support their arguments. However, the "[obviousness] issue cannot fairly be decided on only one party's part of the evidence," and the prior art must be considered "as a whole, including portions that would lead away from the invention in suit." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1570 (Fed. Cir. 1987). As discussed below, rather than consider all of the evidence, Defendants continue to "cherry

[10] This is not the first time that Dr. Heathcock's credibility has been criticized as using impermissible hindsight. Appx13247-13248.

pick" evidence that supports their erroneous obviousness arguments, ignoring the evidence that undercuts their position—the exact criticism levied against Drs. Heathcock and Kingston. Appx51-52.

C. The District Court Correctly Found That the *Hait* and *Lampidis* References Did Not Apply to Taxanes

The district court "did not find credible the lines of reasoning" used by Dr. Heathcock, including his theory that a POSA would have applied *Hait* and *Lampidis* to taxanes. Appx51-52. In fact, Defendants admit that both *Hait* and *Lampidis* do not expressly discuss taxanes. Appx50, RedBr18, RedBr51. The district court also made detailed factual findings regarding the stark differences between taxanes and compounds discussed in *Hait* and *Lampidis*. As the district court correctly found, it would take "leaps" to arrive at cabazitaxel from *Hait* and *Lampidis*.

1. The Evidence Fails to Support Applying *Hait* to Taxanes

The district court found that *Hait* discussed compounds that "differ from taxanes in size and chemical structure," and "was not cited in any prior art taxane references, including the references discussed by Defendants' experts." Appx50; *see also* RedBr18. Moreover, the district court correctly found that *Hait* only describes a ***hypothetical*** binding model based on proteins unrelated to Pgp and binding with molecules unrelated to taxanes. Appx50, Appx25094, Appx13237-13238, Appx13657-13661, Appx30646-30648; *see also* Appx13655-13656.

To make *Hait* appear relevant to taxanes, Defendants misrepresent other evidence. For example, Defendants state that "[a]s of 1995, the prior art taught that Pgp overexpression ***caused*** taxane resistance," citing the district court's opinion. RedBr16. But the district court found only that Pgp was one area of "interest"—not the ***cause*** of taxane resistance. Appx52-53. The district court relied on testimony from Dr. Ludueña that there were "several known mechanisms" of taxane resistance, not just Pgp overexpression. Appx52-53. Additionally, Dr. Roush testified that in 1995 multiple mechanisms of taxane resistance had been proposed, but the cause of taxane resistance was not known. Appx13641. Thus, it was not known that Pgp "caused taxane resistance" as Defendants erroneously argue.

Moreover, the district court correctly found that "nothing from Hait suggests that the binding interactions between phenothiazine and Pgp reflect or would be similar to the binding interactions between a taxane and Pgp." Appx41. Because this undermines Defendants' argument concerning *Hait*, they resort to *Safa* and *Greenberger*, references they allege the district court failed to consider. RedBr54-55.

As an initial matter, simply because the district court did not discuss a specific reference in its opinion does not mean that reference was not considered. *Medtronic, Inc. v. Daig Corp.*, 789 F.2d 903, 906 (Fed. Cir. 1986) ("We presume

that a fact finder reviews all the evidence presented unless he explicitly expresses otherwise."). Here, the district court expressly "considered the evidence presented at trial" which includes *Safa* and *Greenberger.* Appx18.

Defendants erroneously state that *Safa* and *Greenberger* "taught that both Pgp inhibitors (like those in *Hait*) and Pgp substrates (like taxanes) bind to the ***same*** site on Pgp." RedBr19. This statement is contradicted by Dr. Ludueña's testimony (1) that *Safa* only raises the "possibility" that phenothiazines and taxanes bind to an "overlapping" binding site, that "[t]here could be more than one binding site [on Pgp]," and that *Safa* "did not identify the actual region where [Pgp] binds," and (2) that *Greenberger* "suggests a common domain for binding a specific region" for various drugs, but does not suggest that region is "going to bind all of these [compounds] the same way." Appx24246-24247, Appx24249; *see also* Appx13651-13653. Thus, Dr. Ludueña's testimony is clear that the prior art fails to show that phenothiazines and taxanes bind to the ***same*** binding site on Pgp as erroneously argued by Defendants.

Defendants next misrepresent Dr. Ojima's testimony. RedBr19, RedBr54. First, Defendants cite to Dr. Ojima's testimony discussing a different article by Dr. Hait (*Ford and Hait*) which does not discuss the same hypothetical Pgp binding model discussed in the *Hait* reference. RedBr19 (citing to Appx24284 (clip 83, lines 23-01)); *see also* Appx24283 (noting JTX-100 [*Ford and Hait* at

Appx25048]; not JTX-102 [*Hait*]). Second, contrary to Defendants' argument, Dr. Ojima unambiguously testified that his taxane work was not inspired by *Hait*, but rather by a reference by Kobayashi, which Defendants do not argue discusses or relates to Pgp or taxane resistance. Appx24284, Appx24286. As a result, Dr. Ojima's testimony does not bridge the noticeable gap between *Hait* and taxanes.

2. The Evidence Fails to Support Applying *Lampidis* to Taxanes

Arguments concerning *Lampidis* fare no better. The district court correctly found—and Defendants do not dispute—that *Lampidis* "does not discuss taxane compounds," and was not applicable because "taxane compounds do not have a positive charge like the [rhodamine dye] Lampidis compounds." Appx50, Appx16953-16954, Appx13218-13219; *see also* Appx13661. In fact, the rhodamine dyes discussed in *Lampidis* are very structurally different compounds from taxanes. *See* Appx13218-13219.

To overcome the express teachings of *Lampidis*, Defendants imply that Dr. Heathcock's analysis of *Ojima 1994* somehow "confirm[s] that Lampidis applies to taxanes."[11] RedBr53-54. But the district court criticized Defendants' analysis of *Ojima 1994* for ignoring another equally "noteworthy" molecule (SB-T-1212) that did not fit into Defendants' hindsight-based argument. Appx51, Appx25115.

[11] Defendants also cite to *Golik*, but as discussed *infra* in Argument Section II.D, it also does not support this argument.

Moreover, while Defendants erroneously argue that Dr. Ludueña agreed that "cellular permeability is generally correlated with increased lipophilicity," he only testified that the authors in *Lampidis* state that as a "hypothesis" within the reference. Appx24243-24245. More importantly, Defendants fail to cite any evidence that taxanes needed increased lipophilicity. *See* Appx13664-13667, Appx13669-13670.

3. *Alza* Does Not Support Defendants' Arguments Seeking to "Implicitly" Apply *Hait* and *Lampidis* to Taxanes

Because *Hait* and *Lampidis* do not apply expressly to taxanes, Defendants argue that they "implicitly" apply, citing this Court's decision in *Alza*. RedBr18-19, RedBr52-56. But Defendants significantly misconstrue that case.

In *Alza*, the Federal Circuit affirmed a district court's finding of obviousness based on the district court's crediting of expert testimony that a POSA would have been motivated to combine references that "[were] in fact ***not*** inconsistent." *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1294 (Fed. Cir. 2006). Here, the district court found ample evidence that *Hait* and *Lampidis* are not applicable to taxanes due to, among other things, the stark differences between the compounds discussed in these references and taxanes. Appx50-52. The district court found Dr. Heathcock's testimony on these references not credible due to impermissible hindsight. Appx51-52. Notably, the PTAB has also considered and rejected the same "implicit" theories advanced by Defendants here. *Mylan Labs.*, IPR2016-

00627, Paper 10 at 14 ("[W]e are not persuaded by Petitioner's argument that a POSA would have been motivated to optimize lipophilicity in a paclitaxel or docetaxel analogue via simultaneous substitution of the C-7 and C-10 positions.") Thus, *Alza* does not support "implicitly" applying the teachings of *Hait* and *Lampidis* to taxanes, and this Court should decline to do so.

* * *

Having fully considered the evidence, the district court correctly found that a POSA would not have been motivated to apply *Hait* and *Lampidis*'s teachings to taxanes. Appx50-52.

D. ***Hait* and *Lampidis* Are Inconsistent with the Taxane Art, Which Teaches Increasing Water Solubility, Not Lipophilicity**

By advocating that *Hait* and *Lampidis* "implicitly" teach a POSA to increase the lipophilicity of taxanes, Defendants ignore the explicit teachings of the taxane art. RedBr19. Both sides' experts agreed that making a taxane more lipophilic will ***decrease*** water solubility, which is the opposite of the express goal in the art to increase water solubility. Appx12418, Appx12306-12308, Appx13117-13118, Appx13664.

The district court correctly found that several prior art references advocated for the need to increase water solubility of taxanes. For example, in *Golik*, the

researchers focused on more water-soluble taxanes.[12] Appx39, Appx25186, Appx25491. *Klein* also described water solubility as the motivation; the district court correctly found that *Klein*'s C-9 modified taxanes "have greater solubility and stability and show excellent *in vivo* activity in several solid tumor models." Appx49, Appx25173, *see also* Appx13680-13682. While Defendants acknowledge the C-9 position was a "flexible" core position (RedBr20, RedBr57-58), they paradoxically argue that it was harder to modify, citing only unsupported expert testimony, while completely ignoring *Klein*'s express teachings of increasing water solubility using these C-9 modifications. Appx49, RedBr58.

Georg 1994, considered by Dr. Heathcock to be the taxane "Bible," also named water solubility as a major concern for taxanes. *E.g.*, Appx25173-25184, Appx13170. *Ojima 1994* also names water solubility as an improved property of some of its C-14 taxane analogs. Appx25104-25105. More importantly, contrary to Defendants' argument about increasing lipophilicity, its own taxane expert Dr. Kingston was developing more water-soluble taxanes by modifying the side chain. Appx12380-12381. A district court is free to discount an expert's conflicting testimony in light of his or her own work in the area at the relevant time. *See Insite Vision, Inc.*, 783 F.3d at 861.

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[12] *Golik* and European Patent Application 0604910 (also by Golik) include almost the same disclosures, with some differences including the disclosure of Example 14-B in *Golik*. Appx25490-25585, Appx25185-25308.

Furthermore, when arguing that docetaxel is a better lead compound than paclitaxel, Defendants praised docetaxel's superior properties, which are due to the structural differences between the two compounds, making docetaxel less lipophilic (more water soluble). Appx12313-12314, Appx12387-12388, Appx13107-13108, Appx13205-13209, Appx13608; *see also* Appx30170, Appx30443. But Defendants would remove the substituents that gave these properties, and make docetaxel more lipophilic. It is legally improper to argue that a POSA would select docetaxel over paclitaxel due to its superior properties "only to reject that very feature to obtain [the claimed compound]." *Daiichi Sankyo*, 619 F.3d at 1356.

The taxane art also discussed the problem of the harsh excipients needed to solubilize taxanes for infusion into patients. Defendants' experts admitted that the poor water solubility of taxanes, such as paclitaxel, required formulation with the harsh solvent Cremophor that caused allergic reactions in patients.[13] Appx12306-12307, Appx12377-12378. Dr. Heathcock admitted that if a POSA could have increased the water solubility of a taxane such as paclitaxel or docetaxel, they could avoid use of Cremophor and the need for premedication. Appx13216-13217.

[13] On appeal, Defendants do not address the need for harsh excipients to formulate taxanes. At trial, Defendants argued that these problems were purportedly solved by reducing the infusion time to patients. Appx12370, Appx16740. However, Dr. Kingston admitted this change did not solve the problem. Appx12379-12380.

Thus, the prior art makes plain, and both sides' experts agreed, that a POSA would focus on improving water solubility of taxanes, not lipophilicity. The district court correctly rejected the "implicit" and contradictory teachings advocated by Defendants.

E. The District Court Correctly Found No Motivation to Simultaneously Modify the C-7 and C-10 Positions of Docetaxel with Methoxy Groups

1. The Prior Art Was Not Solely Focused on Modifications at the C-7 and C-10 Positions

After fully considering Defendants' theories, the district court was not persuaded that a POSA would have been motivated to make simultaneous modifications of docetaxel at the C-7 and C-10 positions, finding Defendants' conclusion that "all paths led to cabazitaxel" to be impermissible hindsight. Appx50-53. The district court correctly found that "C-7 ***or*** C-10 position" were just two of the "multiple locations" being modified by taxane researchers in the prior art. Appx53.

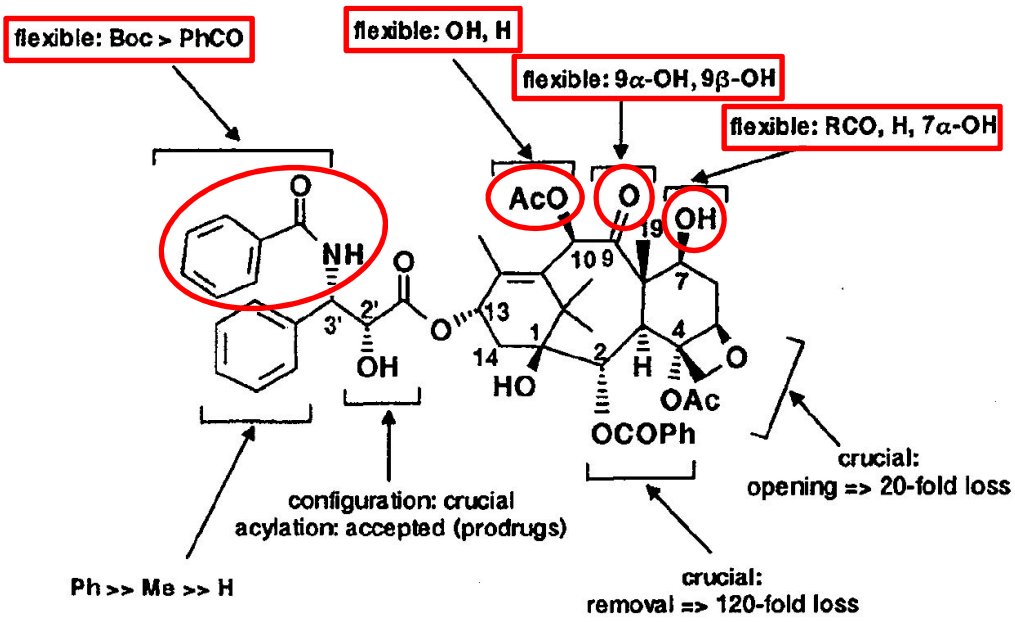
As Dr. Heathcock admitted, taxane researchers such as Dr. Ojima were modifying taxanes without changing the C-7 and C-10 positions. Appx13229-13230. Dr. Kingston conceded that he did not make the supposedly obvious changes at C-7 and C-10 despite working on taxanes for 30 years. Appx12290, Appx12416; *see also Insite Vision, Inc.*, 783 F.3d at 861. Each prior art reference

Defendants' experts relied on was also missing either a C-7 or C-10 modification. Nor did Defendants point to any reference with simultaneous modifications at C-7 or C-10, let alone to a reference showing methoxy groups there. Appx46-53.

2. *Commerçon* and *Kingston 1994* Do Not Focus on the C-7 and C-10 Positions

In an effort to focus on the C-7 and C-10 positions alone, Defendants cite to a figure in *Commerçon* that labels the C-7 and C-10 positions of paclitaxel as "flexible" based upon the prior art. RedBr20-21. But Figure 2 also labels the side chain (C-3') and C-9 positions as "flexible" too, which Defendants ignore. Appx25161.

Figure 2. Modifications influencing the cytotoxicity of paclitaxel.



With respect to what "flexible" means, *Commerçon* only addresses potency in sensitive cell lines and ***does not*** address whether those changes impact potency in

resistant cell lines, which is the POSA's motivation in this analysis. Appx25168-25169. Indeed, most of the references in the prior art lack data in resistant cancer cells, a point Defendants' experts conceded. Appx12409, Appx12413-12414, Appx13230-13232.

Defendants incorrectly allege that Dr. Bouchard, one of the inventors of cabazitaxel, agreed that Figure 2 of *Commerçon* represented all of Sanofi's knowledge until March 1994 because Dr. Bouchard specifically testified that Figure 2 excluded information that was in pending patent applications, including modifications to the side chain. Appx13390-13391. Dr. Bouchard also testified that Sanofi's taxane research program (creating 450+ compounds) included modifications all over the taxane structure. Appx30-31. Thus, Figure 2 of *Commerçon* does not support focusing on C-7 or C-10, particularly for modifications useful to improve activity in resistant cancer cells, which is necessary for Defendants' obviousness argument. Appx25161.

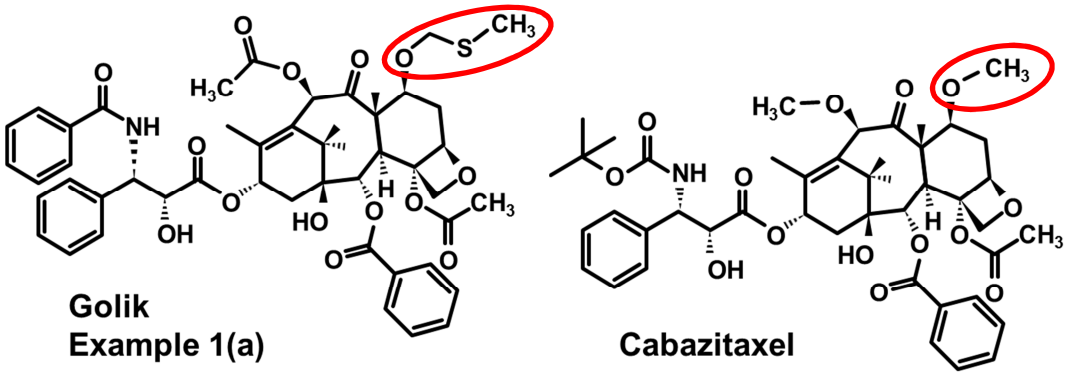
Defendants also rely on *Kingston 1994* to focus on the C-7 and C-10 positions. RedBr23. As an initial matter, Defendants' arguments about *Kingston 1994* were not raised at trial. "[T]hose issues not raised below at the district court cannot be heard for the first time on appeal." *SimpleAir*, 884 F.3d at 1170. Also, *Kingston 1994* cannot provide a motivation to focus on the C-7 and C-10 positions of docetaxel to improve activity in resistant cancers because its teachings discuss

modifying locations all over the taxane core, including significant discussion and presentation of data regarding various modifications of the C-2 position, and *Kingston 1994* does not discuss activity in resistant cancers. Appx25150-25154.

3. No Prior Art Discloses a Methoxy Modification at Both the C-7 and C-10 Positions

The district court analyzed the specific modifications at the C-7 and C-10 positions in the prior art and found significant differences as compared to cabazitaxel. Appx46-53. Defendants do not refute these differences.

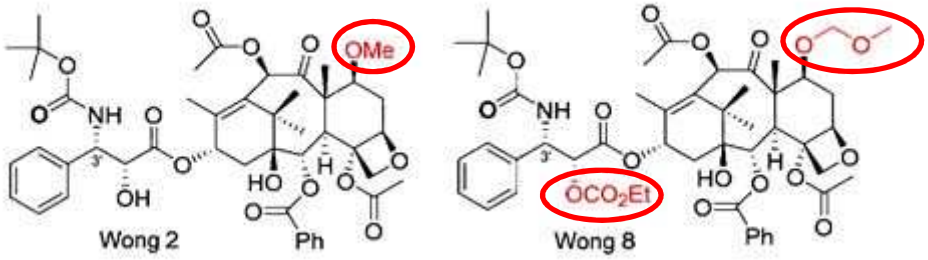
For example, for *Golik* the district court differentiated the compound that Defendants relied on, Example 1(a), because it had a "unique" methylthiomethyl ("MTM") group (circled), and because there was no evidence that the methoxy group of cabazitaxel confers a similar benefit to the MTM group of Example 1(a). Appx46-47 (citing Appx13233-13234, Appx13686-13687, Appx13691).



Defendants also offer a contrived argument that a POSA would avoid the sulfur atom in the MTM group and use the simpler methoxy group. RedBr61. But this argument is clearly contradicted by the data in *Golik*, which reports that the

MTM compound is "much more potent against the resistant cell line." Appx13687, Appx25205-25206, Appx30668-30669.

Also, the district court differentiated *Wong* Example 2 which Defendants relied on, by noting that it was not the most potent. Appx47. Rather, *Wong* Example 8 was the most potent, but had a modification on the side chain, not the C-7 or C-10 positions. Appx47.

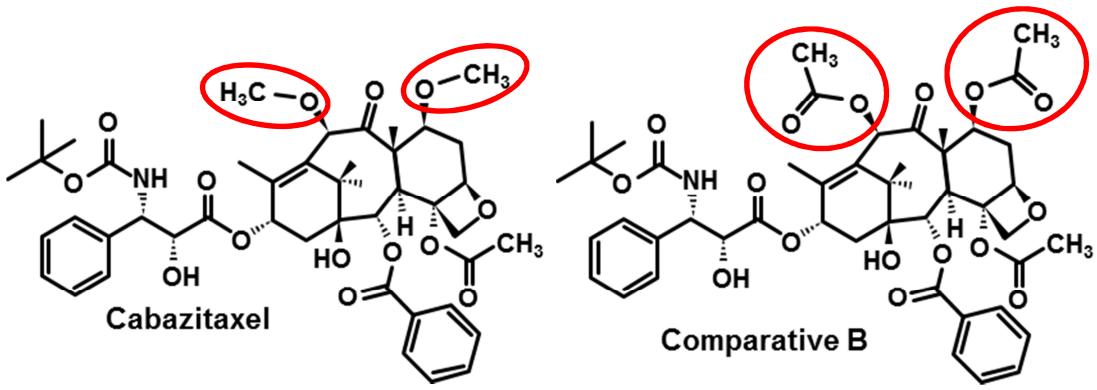


Wong also discloses no compound that has the C-10 methoxy of cabazitaxel. Appx47 (citing to Appx25318, Appx12413).

4. Even If One Looks at Only the C-7 and C-10 Positions, There Would Have Been No Reasonable Expectation of Success

The district court found that a POSA would not have been motivated to make simultaneous modifications at the C-7 and C-10 positions. Appx53. That is correct because there was virtually no data in the art to support simultaneous modification at the C-7 and C-10 positions, and there was significant unpredictability of making changes to taxanes. *See supra* Argument Sections II.E.1-II.E.3. Other than cabazitaxel, the only compound in the record with

simultaneous substitution at C-7 and C-10 was a compound called "Comparative B":



Data from testing of this compound was submitted during prosecution of the '170 patent and demonstrates that "small," simultaneous substitutions at the C-7 and C-10 positions of docetaxel do not impart improved activity in resistant cancer cells. Appx24289-24296. Rather, such improved activity depends on which specific modifications are made. Tellingly, Defendants did not address this evidence at trial or in their appeal brief because it demonstrates the unpredictable nature of the taxane art.

Instead, Defendants relied upon references by *Kant* and *Klein* to selectively focus on methoxy groups at the C-7 or C-10 positions. RedBr68. Not only do these references lack any data in resistant cancer cells (Appx13674, Appx13684), Defendants ignore data that demonstrates no reasonable expectation of success for making cabazitaxel. For example, while Defendants argue for making "small" modifications, they fail to explain why, given that Comparative B showed no

improvement over docetaxel against resistant cancers, a POSA would reasonably expect cabazitaxel to have those properties.

This is fully consistent with the taxane art, which is unpredictable and where minor changes may yield substantially different results. *Kao Corp. v. Unilever U.S., Inc.*, 334 F. Supp. 2d 527, 558 (D. Del. 2004), *aff'd*, 441 F.3d 963 (Fed. Cir. 2006). In fact, the trial evidence showed that several taxanes similar to cabazitaxel were less active or inactive in resistant cell lines. *E.g.*, Appx25627-25740, Appx24289-24296, Appx25309-25312, Appx25173-25184, Appx25313-25330, Appx25185-25308, Appx25490-25585, Appx13327-13329, Appx13625-13632.

To cure these deficiencies, Dr. Kingston argued—without support—that a POSA would have been motivated by the "additive principle" that the district court quoted, but explicitly did not credit. Appx49, Appx51-52. This "principle" was undermined upon cross-examination with published data showing that simultaneous removal of the C-7 and C-10 substituents from paclitaxel resulted in an unpredictable loss of activity, not simply a predictable "additive" amount. Appx12423-12425.

5. ***BMS* Is Taken Out of Context and Does Not Support a Reasonable Expectation of Success**

Unable to rely on the prior art to make their obviousness argument, Defendants instead rely on language from the *BMS* case saying that a POSA's desire is to make "small, conservative changes" that are "easy." RedBr65. In

BMS, this Court found that a particular nucleoside analog was obvious where experts on both sides agreed that a POSA would have been motivated to make "small, conservative changes" to those compounds. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 975 (Fed. Cir. 2014). The particular compounds at issue "[were] modified slightly from their natural counterparts to interfere with the replication of viral DNA." *Id.* at 969. Here, no prior art was presented to show that "small, conservative changes" were the norm or that "slight modifications" were the goal in the context of taxane research. To the contrary, the district court credited Dr. Roush's testimony that diverse changes were being made at many different positions on taxanes. Appx53. And, unlike in *BMS*, the experts here fundamentally disagree that a POSA would use the smallest conservative change. Appx13623-13624. And even if "small, conservative changes" were relevant in this case—they are not—Defendants' expert Dr. Heathcock was focused (without support) on the methoxy group, at the exclusion of all other possible "small" changes, such as acetoxy groups, which do not work. Appx13156; *see also supra* Facts Section V, Argument Section II.E.4.

In addition, Defendants have not offered any evidence that methoxy groups qualify as "small, conservative changes" that a POSA would consider "easy."[14] Rather, Dr. Roush testified that the side chain offered the easiest modifications, not

[14] In *BMS*, Dr. Heathcock inconsistently opined that a methylene, not methoxy, would be the more conservative choice. *Bristol-Myers Squibb*, 752 F.3d at 975.

the C-7 or C-10 positions. Appx13623-13624. Furthermore, the record shows that methoxy groups were extremely difficult to put on the C-7 and C-10 positions. Appx28417, Appx28437, Appx13347-13348, Appx13698-13703, Appx13716-13718, Appx13727-13728, Appx13777.

Thus, the statements in *BMS* that a POSA would consider "small, conservative changes" that were "easy" do not apply to the facts of this case.

F. The District Court Properly Found Defendants Were "Cherry-Picking" Their Way to Cabazitaxel

Defendants complain that the district court erroneously found that they "cherry-picked" data from *Kant*, *Klein*, and *Wong* (RedBr24), yet fail to show that the district court made any clear error in its determination. After considering the evidence and expert testimony, the district court "did not find credible the lines of reasoning employed by Dr. Kingston and Dr. Heathcock," and "it was clear to the Court from their testimony that 'all paths led to cabazitaxel'" due to impermissible hindsight. Appx51-52.

It was also clear to the district court that Defendants ignored contrary evidence. With respect to *Ojima 1994*, the district court found that Dr. Heathcock focused on two of the many disclosed compounds, and ignored the "noteworthy" compound that was most active in resistant cancer cells. Appx51. With respect to *Kant,* the district court found that Defendants selectively chose Compound 20, but

overlooked the most potent compound in cells, Compound 18.[15] Appx25311, Appx13167-13168, Appx13674-13675.

G. The District Court Did Not Find That Defendants Made a *Prima Facie* Case of Obviousness

The district court explicitly found that Defendants ***failed*** to show that there was a motivation to combine references to arrive at cabazitaxel. Appx45. The district court also found that lipophilicity or cell permeability concerns would not have motivated a POSA to make simultaneous C-7 and C-10 modifications, calling Defendants' conclusions "leaps . . . to their ultimate obviousness conclusions." Appx52.

Instead, the district court afforded weight to Sanofi's experts' interpretation of the prior art, including that the prior art included modifications at multiple positions. Appx52-53. This finding is supported by Dr. Heathcock's admission that researchers "were trying lots of different approaches," and Dr. Ojima's efforts to modify the side chain and not the C-7 and C-10 positions. Appx13225, Appx13229.

The district court also correctly rejected *Hait* and *Lampidis* as providing a POSA's requisite motivation to modify a taxane to be more lipophilic. Appx52, Appx13655. At most, the district court noted that the issue of Pgp overexpression

[15] A POSA would consider cell assays to be more informative than tubulin assays because cell assays mimic living organisms, while the tubulin assay is only the purified drug target. Appx13672, Appx12394-12395.

might have been "***an*** area of interest," but, based on Drs. Ludueña and Roush's testimony, there are "several [known] mechanisms [of resistance]" and a POSA could have been studying any one or more of these mechanisms. Appx52-53. Plainly there was no clear path to combine references as Defendants argue.

H. The District Court Correctly Found That Objective Indicia Weigh in Favor of Nonobviousness of the '170 Patent

Defendants' argument that objective indicia "did not require analysis" misstates the law. RedBr72. Objective indicia are "not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness." *Leo Pharm. Prods. Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Also, they "are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements." *Id.* Objective indicia are "taken in sum," and analyzed as a whole. *Id.* at 1359. However, the lack of objective evidence does ***not*** weigh in favor of obviousness. *Miles Labs., Inc. v. Shandon Inc.*, 997 F.2d 870, 878 (Fed. Cir. 1993).

1. The District Court Properly Found Objective Indicia Favored Nonobviousness

The district court credited Sanofi's commercial success and failure of others arguments based upon independent evidence in the record. Appx45, Appx56-59. Defendants do not dispute the district court's findings on these two factors. RedBr72-73.

Defendants instead seize on the district court's statement that cabazitaxel's properties were "not entirely unexpected." RedBr69. But the district court also found "that it was unexpected that adding methoxy groups at C-7 and C-10 positions of docetaxel could have resulted in a compound with significant improvements in its properties as compared to docetaxel." Appx55. In doing so, the district court still afforded some weight to this factor. Appx56. Thus, the district court found at least three objective indicia weighing in favor of nonobviousness.

2. The District Court's Finding of Unexpected Properties Is Well-Supported by the Evidence

Based upon the evidence, the district court found that cabazitaxel's properties were unexpected because it is "a compound with significant improvements in its properties as compared to docetaxel," and "researchers modified thousands of taxane analogs at almost all locations around the taxane core and side chain." Appx55-59. While the district court found that "activity that is five to ten times better[] is not entirely unexpected," it did not have the benefit of this Court's recent guidance. *See Orexo AB v. Actavis Elizabeth LLC*, No. 2017-1333, 2018 U.S. App. LEXIS 25531 at *20-21 (Fed. Cir. Sept. 10, 2018) ("The district court erred in discounting the enhanced bioavailability [of 66%] in the '330 Patent's formulation as a 'difference in degree,' not a difference in 'kind.'" (quotations omitted)).

The evidence showed that cabazitaxel was five to twelve times more potent than docetaxel in resistant cancer cells, including in cell lines that have no overexpression of Pgp. Appx24617, Appx24619, Appx16688, Appx13351-13352, Appx13440-13445, Appx13471, Appx13705, Appx24289-24296, Appx13630; *see also* Appx13212. A five- to twelve-fold improvement or more in the properties of a compound is a difference in kind, not degree. *See, e.g.*, *Daiichi Sankyo Co. v. Mylan Pharms. Inc.*, 670 F. Supp. 2d 359, 382-84 (D.N.J. 2009) (finding that a two- to four-fold increase in potency and a difference in biological interactions were unexpected properties), *aff'd sub nom*, 619 F.3d 1346 (Fed. Cir. 2010).

Cabazitaxel also had a five- to ten-fold improvement in its resistance factor in the P388/DOX cell assay as compared to docetaxel. Appx13210-13212. This is a significant difference in the taxane art and is therefore unexpected. Dr. Heathcock testified that a four-fold improvement in its resistance factor in the same P388/DOX cell assay for docetaxel as compared to paclitaxel was a "significant difference." Appx13133, Appx13206-13209. The prior art also characterized the difference between the properties of docetaxel and paclitaxel as "[n]ot simply two of a kind." Appx24458. Thus, a five-fold improvement of cabazitaxel over docetaxel in this assay is a difference in "kind" and therefore unexpected.

Additionally, cabazitaxel had significant improvements in activity *in vivo* in mice that had docetaxel-resistant tumors (B16/TXT). Appx24613-24631, Appx25714 (RPR 116258). Such an improvement is a difference in kind because this model was engineered to be resistant to docetaxel, but was not resistant to cabazitaxel. Appx13481-13482.

I. The District Court Need Not Have Addressed Whether Formulating Cabazitaxel Would Have Been Obvious

Defendants argue the district court did not formally address its obviousness argument for Claim 2. RedBr71. Given the overwhelming evidence that cabazitaxel is not obvious, a claim requiring cabazitaxel in a formulation is also not obvious. *See Synqor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1375 (Fed. Cir. 2013) (declining to consider arguments that dependent claim limitations would have been obvious when the independent claim had not been proven invalid).

CONCLUSION AND RELIEF SOUGHT

For the foregoing reasons, this Court should reverse the district court's determination that it had subject matter jurisdiction over claims 7, 11, 14-16, and 26 of the '592 patent and vacate the invalidity judgment for those claims. This Court should also decline to consider Defendants' Issue 1, but if reached, this Court should find that Sanofi will not be claim barred from asserting the amended claims, if they issue, against Defendants.

For the foregoing reasons, this Court should affirm the district court's judgment that claims 1 and 2 of the '170 patent are nonobvious and therefore valid.

Respectfully submitted,

Date: October 24, 2018

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PROOF OF SERVICE

The undersigned counsel for Appellants certifies that, on October 24, 2018, the **RESPONSE AND REPLY BRIEF FOR PLAINTIFFS-APPELLANTS** was caused to be filed via CM/ECF with:

Clerk of the Court
United States Court of Appeals for the Federal Circuit
717 Madison Place, NW
Washington, DC 20439

The undersigned also certifies that, on October 24, 2018, a true and correct copy of the **RESPONSE AND REPLY BRIEF FOR PLAINTIFFS-APPELLANTS** was caused to be served on counsel of record via CM/ECF and electronic mail.

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME, TYPE-FACE, AND TYPE-STYLE REQUIREMENTS

The undersigned counsel for Plaintiffs-Appellants hereby certifies that this brief by Plaintiffs-Appellants complies with the type-volume limitation of Fed. Cir. Rule 28.1(b). This brief contains 13,811 words, excluding portions exempted by Fed. R. App. P. 32(f) and Fed. Cir. Rule 32(b). The undersigned counsel also certifies that this brief complies with the type-face requirements of Fed. R. App. P. 32(a)(5) and the type-style requirements of Fed. R. App. P. 32(a)(6). The brief was prepared in Microsoft Word 2010 using a proportional 14-point Times New Roman type-face.

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