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

# In the United States Court of Appeals for the Federal Circuit

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

*Plaintiffs-Appellants,*

v.

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

*Defendants-Appellees,*

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

*Defendants – Cross-Appellants.*

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

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

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

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

Dated: November 28, 2018

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

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

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   Fresenius Kabi AG

   Fresenius SE & Co. KGaA

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

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

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

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

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

Dated: November 28, 2018

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

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

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

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

Dated: November 28, 2018

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

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

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   Mylan Laboratories Limited

   Mylan Pharmaceuticals Inc.

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

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

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

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

Dated: November 28, 2018

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# TABLE OF ABBREVIATIONS

| **Abbreviation** | **Meaning** |
|---|---|
| ’170 Patent | United States Patent No. 5,847,170 (JTX-1) |
| Appx_ | Page number citation for Joint Appendix |
| *Commerçon* | Commerçon *et al.*, Practical Semisynthesis and Antimitotic Activity of Docetaxel and Side-Chain Analogues, Chapter 17 in TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS, (Georg et al., Eds.) ACS Symposium Series American Chemical Society, Washington, DC, 583:233-246 (1994) (JTX-109) |
| Defendants | Defendants – Cross-Appellants |
| Defendants – Appellees | Defendants – Appellees Dr. Reddy’s Laboratories, Inc., Dr. Reddy’s Laboratories, Ltd., Sandoz Inc. |
| Defendants – Cross-Appellants | Defendants – Cross-Appellants Fresenius Kabi USA, LLC, Accord Healthcare, Inc., Apotex Corp. and Apotex Inc., Mylan Laboratories Ltd., Actavis LLC. |
| *EP ’910* | European Patent No. EP 0 604 910 A1 (JTX-125) |
| *Golik (EP ’577)* | European Patent No. 0 639 577 A1 (JTX-111) |
| *Greenberger* | Greenberger, *et al*., Photoaffinity Probes for the $\alpha_1$-Adrenergic Receptor and the Calcium Channel Bind to a Common Domain in P-glycoprotein, JOURNAL OF BIOLOGICAL CHEMISTRY, 265(8): 4394-4401 (1990) (DTX-2203) |
| *Hait* | Hait & Aftab, Rational Design and Pre-Clinical Pharmacology of Drugs for Reversing Multidrug Resistance, BIOCHEMICAL PHARMACOLOGY, 43(1):103-107 (1992) (JTX-102) |
| IPR | *Inter partes* review pursuant to 35 U.S.C. §§ 311-319 |

| | |
|---|---|
| *Kant* | Kant *et al.*, A Chemoselective Approach to Functionalize the C-10 Position of 10-Deacetylbaccatin III. Synthesis and Biological Properties of Novel C-10 Taxol Analogues, TETRAHEDRON LETTERS, 35(31):5543-5546 (1994) (JTX-114) |
| *Kingston 1994* | Kingston, Recent Advances in the Chemistry and Structure-Activity Relationships of Paclitaxel, Chapter 15 in TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS, (Georg et al., Eds.) ACS Symposium Series American Chemical Society, Washington, DC, 15:203-216 (1994) (JTX-107) |
| *Klein* | Klein *et al.*, Chemistry and Antitumor Activity of 9(R)-Dihydrotaxanes, Chapter 20 in TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS, (Georg et al., Eds.) ACS Symposium Series American Chemical Society, Washington, DC, 583:276-287 (1994) (JTX-110) |
| *Lampidis* | Lampidis, Relevance of the Chemical Charge of Rhodamine Dyes to Multiple Drug Resistance, BIOCHEMICAL PHARMACOLOGY, 38:4267-4271 (1989) (DTX-2241) |
| MDR | Multi Drug Resistance |
| MTM | Methylthiomethoxy (Methylthiomethyl ether) |
| *Ojima 1994* | Ojima *et al.*, Synthesis and Structure-Activity Relationships of New Taxoids, Chapter 19 in TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS, (Georg et al., Eds.) ACS Symposium Series American Chemical Society, Washington, DC, 583:262-275 (1994) (JTX-104) |
| Pgp | P-Glycoprotein |
| Plaintiffs - Appellants | Plaintiffs – Appellants Sanofi-Aventis U.S. LLC, Aventis Pharma S.A., and Sanofi, and including |

| | |
|---|---|
| | predecessor company Rhone-Poulenc Rorer ("RPR"). |
| POSA | Person of ordinary skill in the art |
| RedBr_ | Page number citation to Defendants – Cross-Appellants' Principal and Responsive Brief (Filed August 20, 2018) |
| *Riou* | Riou *et al.*, Effects of Taxotere On Murine And Human Tumor Cell Lines, BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 187(1):164-170 (1992) (JTX-98) |
| *Safa* | Safa *et al*., The α-adrenergic photoaffinity probe [$^{125}$I]arylazidoprazosin binds to a specific peptide of P-glycoprotein in multidrug-resistant cells, BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 166(1): 259-266 (1990) (DTX-2320) |
| Sanofi | *See* Plaintiffs - Appellants. |
| SAR | Structure-activity relationship(s) |
| *Verweij* | Verweij, Paclitaxel (Taxol) and docetaxel (Taxotere): not simply two of a kind, ANNALS OF ONCOLOGY, 5(6):495-505 (1994) (JTX-29) |
| *Wong ('140 patent)* | United States Patent No. 6,201,140 (JTX-115) |
| YellowBr_ | Page number citation to Response and Reply Brief for Plaintiffs – Appellants (D.I. 80, Filed October 24, 2018) |

## INTRODUCTION

The district court's obviousness holding for the '170 patent rests on legal and factual error and should be reversed. "A finding is 'clearly erroneous' when although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *U.S. v. U.S. Gypsum Co.* 333 U.S. 364, 395 (1948). While Plaintiffs note that "absent contradictory extrinsic evidence," the district court's factual findings "can virtually never be clear error," YellowBr46, contradictory evidence is exactly what the record reflects.

The district court made several factual findings in Defendants' favor that should have compelled the conclusion that the claims are obvious. In holding the claims non-obvious, the district court erred in rejecting the relevance of the prior art *Hait* and *Lampidis* references to taxanes. Appx50. Plaintiffs rehash the district court's findings and try to characterize *Hait* as relating to "interactions with phenothiazines, which are antipsychotic compounds completely unrelated to taxanes," YellowBr8, but this ignores the express intention of *Hait* as a general review of drugs as "modulators of MDR, including the implications of these studies for the definition of the drug binding site on the molecule." Appx25093. Likewise, *Lampidis* compared uptake of compounds to evaluate intracellular drug

accumulation. Appx16953-16954. Such information was directly related to taxanes, drugs that require entrance to a cell in order to effect treatment.

Based on this fundamental error, the district court then erroneously concluded that there was no motivation to simultaneously modify C-7 and C-10, despite acknowledging motivation in the prior art to modify those positions. Appx53; *cf. U.S. Gypsum Co.*, 333 U.S. at 396 ("Where such testimony is in conflict with contemporaneous documents we can give it little weight."). Finally, the district court's finding that "[a] POSA would…expect that cabazitaxel would show improved potency over docetaxel" directly undermines the Court's conclusion that the modifications at C-7 and C-10 were not *prima facie* obvious. Appx55.

## ARGUMENT

### I. This Case Is Substantively and Procedurally Distinct from the Mylan IPR

Contrary to Plaintiffs' claim, Defendants' obviousness position is not a "rehash" of Mylan's IPR. YellowBr13. At trial, Defendants identified docetaxel as the lead compound and focused on drug resistance caused by Pgp, citing *Hait* and *Lampidis* as motivation to arrive at cabazitaxel. RedBr15-18. In contrast, Mylan's IPR did *not* rely on drug resistance as a motivating factor and did not cite *Hait* or *Lampidis*. *Mylan Labs. Ltd. v. Aventis Pharma S.A.*, IPR2016-00627, Paper 3 at 14-15 (P.T.A.B. February 17, 2016) ("Mylan Petition"). Additionally,

at trial, *Kant* and *Klein* provided only support and proof of concept that changes at C-7 and C-10 to methoxy substituents retain activity. Appx13179-13180 (Dr. Heathcock). In contrast, Mylan's IPR relied on *Kant* and *Klein* as primary references and focused on *Kant* Compound 20 as the lead compound. Mylan Petition at 29-38. Plaintiffs attempted to rely on the IPR proceedings at trial, *see, e.g.*, Appx11219-11220, but the district court, properly recognizing the distinct nature of the two proceedings, did not once reference the IPR in its opinion.

## II. The District Court Made Numerous Factual Findings Supporting *Prima Facie* Obviousness

Although the district court ultimately erroneously held cabazitaxel to be non-obvious, it did credit much of Defendants' evidence. The district court correctly identified docetaxel as a lead compound and properly found that a POSA would have been motivated to modify it to address MDR, including at the C-7 and C-10 positions. Appx45-46, Appx53.

### A. The District Court Correctly Found Docetaxel to Be a Lead Compound

Docetaxel was the most promising taxane available in 1994 and had superior biological properties to paclitaxel. Appx12319-12324 (Dr. Kingston); Appx13100-13107 (Dr. Heathcock). The district court found the testimony of Drs. Kingston and Heathcock "credible" on this subject. Appx45. Plaintiffs' argument that selecting docetaxel as a lead and then modifying C-7 and C-10

somehow "reject[s]" its key structural features is inconsistent with the evidence presented at trial. YellowBr54. Plaintiffs incorrectly credit docetaxel's decreased lipophilicity with docetaxel's improved properties over its predecessor paclitaxel. *Id*.[1] Based on this mischaracterization, Plaintiffs further assert that a POSA would *not* have changed the hydrophilic northern hemisphere. YellowBr44-45. This ignores docetaxel's *boc* sidechain, which differs from paclitaxel's, and which the prior art taught resulted in increased potency. Appx13114-13115 (Dr. Heathcock). Defendants do not argue that a POSA would have been motivated to modify docetaxel's side chain. RedBr20-21. Nor do they propose re-installing paclitaxel's acetoxy group at C-10. Instead, defendants contend that a POSA would utilize a methoxy group—the smallest, most conservative modification to make docetaxel's C-10 hydroxy group more lipophilic. RedBr21. Thus, Defendants' obviousness position does *not* reject the key structural features of docetaxel.

### B. The District Court Correctly Found That a POSA Would Have Modified Docetaxel to Address Pgp-Mediated MDR

The district court correctly found that a POSA would recognize Pgp as a cause of taxane MDR and would modify docetaxel to address it. Appx52-53 ("Pgp overexpression presented an area of interest for research during the relevant time period."). Plaintiffs concede that a POSA would have modified docetaxel to

[1] None of the testimony cited by Sanofi attributes the increased activity of docetaxel to the decrease in lipophilicity.

address MDR, but dispute that a POSA would have focused on Pgp instead of other possible mechanisms of resistance. YellowBr6-8. Plaintiffs presented this same theory at trial, Appx11214-11215, but the district court properly found that Pgp-mediated resistance was an interest for the POSA to research. Appx53. Additionally, the evidence was clear from Plaintiffs' own documents and expert (Dr. Ojima) that Pgp was by far the most well-known MDR mechanism for taxanes. Appx24259; RedBr15-16.

### C. The District Court Correctly Found That a POSA Would Have Been Motivated to Modify C-7 and C-10

Although the district court declined to find a specific motivation to simultaneously modify the C-7 and C-10 positions, it did find that the prior art (*Ojima 1994*, *EP'910*, and *Golik*) taught that lipophilic modifications at these positions would improve performance against MDR cells. Appx39-40, Appx42-43. Plaintiffs point to the court's findings that changes at C-7 and C-10 would not have been obvious because modifications were being made at many positions around the taxane skeleton. YellowBr5. But this is irrelevant because the results of that work had already been published before the priority date. Appx25161 (*Commerçon*); Appx13113-13117, Appx13174-13175, Appx30520 (Dr. Heathcock). The pertinent question here is the POSA's motivation as of the *priority date*. As of that date, the prior art reported that the only modifications known to modulate MDR were at the C-7, C-10, and C-3'positions. *See, e.g.*,

Appx25206 (*Golik*); Appx25114-25115 (*Ojima 1994*). The prior art also established that docetaxel's *boc* substituent at the C-3' nitrogen was known to have better potency against both normal and MDR cell lines than paclitaxel's phenylcarbonyl ("PhCO") substituent. Appx12358-12359 (Dr. Kingston); Appx13114-13115, Appx13154-13155, Appx13157-13159 (Dr. Heathcock); Appx25114-25115 (*Ojima 1994*); Appx25161, Appx25169 (*Commerçon*). Plaintiffs' citation of prior modifications made at other positions therefore does not undermine the obviousness of modifying C-7 and C-10 as of the priority date. While Plaintiffs note that Dr. Ojima modified taxanes at other positions, YellowBr55, they ignore the fact that Dr. Ojima also modified taxanes at C-7 and C-10. *See* Appx25114-25115 (*Ojima 1994*). The availability of other alternatives is not dispositive of obviousness. *Galderma Labs. L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738-39 (Fed. Cir. 2013) (holding that the presence of alternatives in the prior art did not teach away from alleged invention); *Par Pharm. Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197-98 (Fed. Cir. 2014) ("Our precedent, however, does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art did not teach away." (emphasis in original) (internal citations omitted)).

### D. The District Court Correctly Found No Teaching Away From Increasing the Lipophilicity of Docetaxel

Plaintiffs repeatedly argue that a POSA would not take steps to increase the lipophilicity of docetaxel due to concerns about solubility. YellowBr52-55. But Plaintiffs presented this same argument at trial, Appx11217-11218, and the district court did not make any finding to this effect. This is fully consistent with the record evidence, which indicated that although solubility was once a significant concern in the taxane field, it was no longer a concern as of the priority date—MDR was by far the more pressing issue. Appx12306-12309 (Dr. Kingston); Appx13118-13119, Appx13188-13190 (Dr. Heathcock).[2] *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014) (when analyzing teaching away, it is error to examine "the state of the art *before* the time of the invention" rather than at the time of the invention (emphasis in original)).

Indeed, *Verweij* reports that a key concern raised by Plaintiffs—toxicity caused by "harsh excipients" used to solubilize taxanes—was "no longer considered a major clinical problem" as of 1994. YellowBr54; Appx24465 (*Verweij*); Appx13188-13190 (Dr. Heathcock). Furthermore, the most recent prior art in the taxane field was replete with examples of researchers making potent taxanes that were more lipophilic than their respective lead compounds. *See, e.g.*,

[2] Plaintiffs' claim that "both sides' experts agreed that a POSA would focus on improving water solubility", YellowBr55, is therefore plainly false.

Appx25311 (*Kant*); Appx25178 (*Klein*); Appx25206 (*Golik*); Appx25114-25115 (*Ojima 1994*); Appx25318 (*Wong*). The district court even cited *Ojima 1994*, *EP '910*, and *Golik* as teaching that increasing lipophilicity at C-7 and/or C-10 could improve performance against MDR cells. Appx39-40; Appx42-43. Plaintiffs thus misconstrue the timing of how solubility was perceived in the art, and the district court was correct not to find any teaching away.

### E. The District Court Correctly Found That Cabazitaxel's Beneficial Properties Were Not Entirely Unexpected

The district court found that "cabazitaxel's superior activity over docetaxel [was]…not entirely unexpected." Appx55-56. This directly supports Defendants' *prima facie* case with respect to both motivation to modify and reasonable expectation of success. *See* 26-30, *infra*.

## III. The District Court Clearly Erred in Concluding That Defendants Failed to Establish a *Prima Facie* Obviousness Case

The most significant error in the district court's opinion was its ruling that *Lampidis* and *Hait* were inapplicable to taxanes. Appx50. These references supply a substantial motivation for a POSA to modify the C-7 and C-10 positions of docetaxel. Plaintiffs' attempts to justify the district court's rejection of these references fall flat.

### A. The District Court Erroneously Found *Lampidis* Inapplicable to Taxanes

The district court's holding that *Lampidis* does not apply to taxanes is clearly erroneous because it is directly contradicted by both the record evidence and other findings made by the court. Plaintiffs seek to justify the district court's rejection of *Lampidis* by citing the court's finding regarding the differences between the dye compounds discussed therein and taxanes. YellowBr47-50. But these differences do not justify rejecting the reference's broader applicability. Nowhere does *Lampidis* state that its teachings should be limited to rhodamine dyes, something the district court recognized in its initial summary of the reference, where it described *Lampidis* as teaching a strategy for overcoming Pgp-mediated resistance by "increas[ing] the lipophilicity and, therefore, cell permeability of ***a drug***" generally. Appx42 (emphasis added).

Plaintiffs' own expert Dr. Ludueña similarly made no attempt to limit the teachings of *Lampidis* to rhodamine dyes. Appx24243-24245. Plaintiffs' attempts to minimize these admissions, characterizing Dr. Ludueña as recognizing this teaching only as a "hypothesis," YellowBr51, are inconsistent with the district court's finding that Dr. Ludueña "acknowledged" *Lampidis*' core principle. Appx42 (citing Appx24244-24245). Thus, when the court dismissed *Lampidis* as being inapplicable to taxanes, Appx50, this was clear error that contradicted its

own prior analysis, Plaintiffs' own expert's testimony, and the conclusion of the article itself.

The district court's finding is further undermined by other evidence at trial demonstrating that the teachings of *Lampidis* are, in fact, applicable to and reflected in the taxane art. Dr. Heathcock explained that *Ojima 1994*—a taxane-specific reference—shows that as taxane compounds become more lipophilic, they perform better in MDR cells, as predicted by the teachings of *Lampidis.* RedBr53-54; Appx13225-13227 (Dr. Heathcock); Appx30417 (Cross Examination Demonstrative). Plaintiffs note that the district court "criticized" Dr. Heathcock's analysis of *Ojima 1994* for allegedly ignoring the data for one of the compounds in the reference (SB-T-1212), YellowBr50, but this argument is misleading.

Dr. Heathcock identified *all* taxane compounds in *Ojima 1994* that were tested in both the non-resistant and resistant versions of the same cell line (P388), *see* Appx25113-25115, and then compared the lipophilicity of these compounds with their measured susceptibility to MDR. Appx13225-13227 (Dr. Heathcock). Dr. Heathcock did not "ignore" SB-T-1212; rather, the compound could not be included because *Ojima 1994* does not report potency data for it in the P388 cell line. Appx25115.

The results demonstrated a clear trend—as the taxane compounds become more lipophilic (greater CLogP), they show reduced susceptibility to MDR (lower

Resistance Index). Appx30417; Appx13227 (Dr. Heathcock). This is exactly what *Lampidis* teaches, thus contradicting the district court's determination that a POSA would not have applied *Lampidis*' teachings to taxanes. Accordingly, the district court's finding that *Lampidis* is inapplicable to taxanes should be reversed.

### B. The District Court Erroneously Found *Hait* Inapplicable to Taxanes

The district court made similar factual and legal errors in holding that *Hait* is irrelevant to taxanes. Appx50. Plaintiffs point to the district court's finding that *Hait* cannot adequately represent the binding of taxanes to Pgp because it studies a different class of compounds and describes only a "hypothetical" binding model based on a different protein. *Id.*; YellowBr47-48. But this is a fundamental misunderstanding of the evidence presented at trial. First, *Hait*'s model is derived from actual SAR experiments conducted with phenothiazines and cancer cells that overexpress Pgp, and is thus anything but "hypothetical." Appx25093 (*Hait*); Appx13149-13150 (Dr. Heathcock). Neither Plaintiffs nor their experts dispute either the source or the legitimacy of *Hait*'s underlying ***data***. Plaintiffs' criticism was instead aimed at *Hait*'s ***visual model***, described as a "hypothetical drug binding site on P-gp based on analogies with the binding of antipsychotic drugs to calmodulin." Appx25094. Any criticism of *Hait*'s ***visual model*** as being too hypothetical is irrelevant, as the importance of the *Hait* reference does not come from its visual representation, but rather from the underlying data it reports. Thus,

even if the visual model is "hypothetical," that does not justify disregarding the very real underlying data and the teachings that flow from them. *See Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 1581-82 (Fed. Cir. 1983) ("The proper test is whether the references, taken as a whole, would suggest the invention to one of ordinary skill in the art.").

The district court's holding here is also directly at odds with the testimony of Plaintiffs' own expert, Dr. Ojima, who acknowledged that *Hait* could be understood to address taxanes. Appx24266-24267. In fact, Dr. Ojima, a leader in the taxane field, admitted that he himself took *Hait*'s Pgp binding model into account when designing new taxanes as of the priority date. *See* Appx24286. Plaintiffs' attempt to sidestep this admission by claiming that Dr. Ojima was in fact referring to a different, older reference from the same author, *Ford and Hait*, should be rejected. YellowBr49-50. While both references were discussed at Dr. Ojima's deposition, only one—*Hait*—discloses a Pgp binding model, and the testimony is clear that Dr. Ojima was referring to *Hait*, and not the earlier reference:

> **Q:** Okay. So you did rely in part on ***Hait's proposed binding model.*** Is that correct?
> **A:** I think we took – take into account – took into account his result.

Appx24286 (emphasis added). Furthermore, Plaintiffs' contention that Dr. Ojima relied on other references in his taxane research, YellowBr50, is irrelevant because

it does not change the fact that Dr. Ojima considered *Hait* when designing new taxane compounds as of the priority date, which directly contradicts the district court's finding that *Hait* is inapplicable to taxanes.

Other evidence at trial also supported the applicability of *Hait* to taxanes. Specifically, the *Greenberger* and *Safa* references taught that both taxanes and reversal agents like phenothiazines (the compounds in *Hait*) attach to Pgp through a common site on the protein, thereby drawing a direct connection between *Hait*'s Pgp binding model and taxanes. Appx16801-16802 (*Greenberger*); Appx17014-17015 (*Safa*); Appx13259-13260 (Dr. Heathcock). The district court disregarded these prior art references in its analysis of *Hait*, making no mention of either. This Court has repeatedly emphasized the importance of considering the prior art as whole when evaluating obviousness, and has reversed decisions that fail to do so. *See, e.g.*, *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013); *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1325-26 (Fed. Cir. 2017). It was thus clear error for the district court to ignore *Greenberger* or *Safa.*

Plaintiffs try to justify the court's failure to consider *Greenberger* and *Safa* by citing this Court's opinion in *Medtronic, Inc. v. Daig Corp.*, 789 F.2d 903, 906 (Fed. Cir. 1986) for the proposition that a factfinder is presumed to have considered all the evidence absent an explicit statement to the contrary. YellowBr48-49. But this Court's more recent precedent makes clear that

obviousness findings may be overturned for failure to consider prior art even absent such an explicit statement. *Randall*, 733 F.3d. at 1363; *Bayer*, 874 F.3d at 1325-26.

Plaintiffs also attempt to characterize Dr. Ludueña's testimony as somehow disputing that taxanes and phenothiazines bind to the same site on Pgp. YellowBr49. This is plainly wrong. Dr. Ludueña did not dispute that the two types of compounds bind to Pgp at the same place; he simply speculated that any structural differences between the compounds might cause them not to attach to that place in "the same way." Appx24249. Dr. Ludueña's speculation finds no explicit support in any of the prior art references presented at trial and is in any event a distinction without a difference. The district court's finding that *Hait* was inapplicable to taxanes is clearly erroneous and should be reversed.

### C. The District Court Did Not Account for the Implicit Teachings of *Lampidis* and *Hait*

The district court committed legal error by failing to account for the implicit teachings of *Hait* and *Lampidis*. This Court held in *Alza Corp. v. Mylan Labs., Inc.* that a motivation to combine "may be found *implicitly* in the prior art" and that "an actual teaching to combine" is not required. 464 F.3d 1286, 1291 (Fed. Cir. 2006) (emphasis in original). Plaintiffs attempt to distinguish *Alza* from the instant case by arguing that the teachings of *Hait* and *Lampidis* are somehow "inconsistent" with the taxane art. YellowBr51-52. But the evidence at trial showed that *Hait*

and *Lampidis* are, in fact, consistent with the taxane literature. Specifically, *EP '910*, *Golik* and *Ojima 1994* confirm that increasing lipophilicity at C-7 and/or C-10 improves performance against MDR cells. *See* 20-22, *infra*; RedBr60-64. In *Alza*, like here, the prior art recited general rules applicable to a variety of compounds. 464 F.3d at 1294-95. It is the "general predictive utility" of these teachings that is most important to the analysis, *id.* at 1295, and the evidence in the instant case demonstrates that *Hait* and *Lampidis* have substantial utility in predicting the efficacy of taxanes against MDR cells. The implicit teachings of *Hait* and *Lampidis* therefore establish their applicability to taxanes, which is confirmed by the taxane art. Finally, this court should reject Plaintiffs' citation of the IPR decision as evidence that *Alza* should not apply here, YellowBr51-52, because neither *Lampidis* nor *Hait* was ever raised in the IPR.

### D. The Court's Error with Respect to *Hait* and *Lampidis* Impacted Its Reading of Other Prior Art

The district court's error with respect to *Hait* and *Lampidis* is particularly significant because it infected the court's subsequent analysis of the taxane art. Having erroneously found the references inapplicable to taxanes, the court then failed to address Defendants' substantive arguments regarding the specific motivation these references supplied a POSA to modify docetaxel at C-7 and C-10. Plaintiffs' assertion that the court rejected *Hait* and *Lampidis* as providing a "requisite motivation" for a POSA to make docetaxel more lipophilic,

YellowBr64-65, is thus incorrect—the district court failed to substantively address what motivation the references provided after dismissing them as irrelevant to taxanes generally. *See* Appx50. Plaintiffs do not directly address the substantive teachings of the references either, and instead argue only that a POSA would not have been motivated by *Hait* and *Lampidis* to focus on Pgp. YellowBr48; YellowBr64-65. But this is inconsistent with the facts and the district court's findings. *See* 9-15, *supra*.

*Lampidis* and *Hait* presented the POSA with two complementary strategies to reduce docetaxel's susceptibility to Pgp. First, *Lampidis* taught the POSA that increasing a compound's overall lipophilicity could improve cellular permeability and thus overwhelm the Pgp pump. Appx16954 (*Lampidis*); Appx13141-13142 (Dr. Heathcock); Appx24243-24244 (Dr. Ludueña). Second, *Hait* taught that a compound's binding affinity for Pgp could be reduced if the compound was modified such that it did not have discrete lipophilic and hydrophilic regions. Appx25093-25094 (*Hait*); Appx13151-13152 (Dr. Heathcock). Furthermore, both sides' experts agreed that docetaxel's structure was characterized by a lipophilic southern hemisphere and side chain and a hydrophilic northern hemisphere. Appx13143-13144, Appx13151 (Dr. Heathcock), Appx24266 (Dr. Ojima). Consequently, the only modification that would satisfy the teachings of both *Hait* and *Lampidis* would be making the northern hemisphere of docetaxel more

lipophilic by modifying its hydrophilic hydroxy groups at C-7 and C-10. Appx13143-13145, Appx13151-13152 (Dr. Heathcock).

As explained below, the district court's clear error in rejecting *Hait* and *Lampidis* as irrelevant had a significant effect on its broader obviousness analysis. This error caused the court to disregard an important motivation to modify the C-7 and C-10 positions of docetaxel and also obscured the crucial role played by taxane references such as *Ojima 1994*, *Kant*, and *Golik*. While Plaintiffs and the district court label Defendants' reliance on these references as "cherry-picking" data to supply motivation, they fail to recognize that these taxane-specific references provide proof-of-concept for the modifications already suggested by *Hait* and *Lampidis*.

#### 1. The District Court's Failure to Apply the Teachings of *Commerçon* and *Kingston 1994* Regarding the "Flexibility" of C-7 and C-10 Was Error

The district court's erroneous finding that *Hait* and *Lampidis* were irrelevant to taxanes prevented the court from acknowledging that *Commerçon* and *Kingston 1994* established a "finite number of identified, predictable solutions" to explore in implementing the strategy suggested by *Hait* and *Lampidis*: namely, modifications to C-7 and C-10. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007). *Commerçon* and *Kingston 1994* teach that C-7 and C-10 of the docetaxel compound are "flexible" and can be modified without a loss in potency, and thus

would motivate a POSA to modify docetaxel at these two locations to address MDR. RedBr56-60. Once *Hait* and *Lampidis* directed the POSA to increase the lipophilicity of docetaxel, *Commerçon* and *Kingston 1994* would have directed the POSA to focus on C-7 and C-10.

Plaintiffs argue that the district court correctly found that *Commerçon* and *Kingston 1994* "[do] not support focusing on C7 and C10," YellowBr56-57. But this finding is contradicted by Plaintiffs' own expert Dr. Ojima, who confirmed that *Commerçon* teaches that C-7 and C-10 substituents could be removed or replaced without significant detriment. Appx24263-24264.

Plaintiffs' other attempts to minimize *Commerçon* and *Kingston 1994* similarly fail. First, Plaintiffs allege that Figure 2 of *Commerçon* does not support focusing on C-7 or C-10, because Plaintiffs' predecessor chose to withhold certain patent-pending compounds (*i.e.*, cabazitaxel) from the *Commerçon* publication. YellowBr57. But this does not diminish the relevance of *Commerçon*, which was published prior art and would have nonetheless focused the POSA on C-7 and C-10. Likewise, Plaintiffs' claim that Defendants "ignored" *Commerçon*'s teachings regarding modifications at C-9 and C-3' is incorrect. YellowBr56-57. Defendants explicitly presented evidence that a POSA would not have focused on these positions because the C-9 position was substantially more difficult to modify than C-7 or C-10, RedBr58 n.9, and *Commerçon* itself confirmed the benefit of

docetaxel's *boc* group at the C-3' nitrogen over paclitaxel's phenylcarbonyl group at that position. Appx25161, Appx25169. Similarly, Plaintiffs' claim that *Kingston 1994* was not raised at trial is incorrect. YellowBr57. Dr. Roush testified about this reference, and the district court discussed the reference in its opinion. Appx42, Appx13772. Plaintiffs also argue that *Commerçon* and *Kingston 1994* cannot support modifications to improve activity in resistant cancer cells because they do not include data on resistant cells. YellowBr56-57. However, it is axiomatic that a POSA is not required to examine prior art references in a vacuum. *KSR*, 550 U.S. at 418. Plaintiffs ignore all of the additional prior art references that *do* present data for resistant cancer, including *Ojima 1994* and *Golik*, both of which confirm the modifications suggested by *Commerçon* and *Kingston 1994*.

Finally, Plaintiffs are wrong that Defendants did "[not] point to any reference with simultaneous modifications at C-7 and C-10." YellowBr56. Defendants cited numerous references that provide data for compounds in which both C-7 and C-10 are substituted. *See, e.g.*, Appx25178-25179 (*Klein*), Appx25311-25312 (*Kant*), Appx25318 (*Wong*). In any event, Plaintiffs' argument that not one prior art reference discloses each and every element of the cabazitaxel compound simultaneously, YellowBr55-56, improperly conflates obviousness with anticipation.

### 2. The District Court Failed to Recognize the Confirmatory Role of Taxane Art for Modification of C-7 and C-10

By dismissing the applicability of *Hait* and *Lampidis* to taxanes, the district court failed to appreciate that the teachings of the taxane specific prior art confirmed the motivation supplied by *Hait* and *Lampidis* to modify C-7 and C-10. As discussed above, the court erroneously dismissed the teachings of *Commerçon* and *Kingston 1994* that would have reinforced the POSA's motivation from *Hait* and *Lampidis* to work on C-7 and C-10. The court also ignored the confirmatory role of the prior art *Golik*, *EP '910*, and *Ojima 1994* references. These references confirm that the use of small lipophilic groups at C-7 and C-10 improved performance against MDR cells.

Plaintiffs argue that the district court correctly focused "on significant differences" between the compounds disclosed in these references and cabazitaxel to find that *Golik*, *EP '910*, and *Ojima 1994* would not have suggested the modifications to make cabazitaxel. YellowBr58. But this argument ignores other explicit findings made by the district court that suggest the opposite—that these references provide direct confirmation for the modifications suggested by *Hait* and *Lampidis*. *See* 14-15, *supra*. In its summaries of *Golik*, *EP '910*, and *Ojima 1994*, the district court correctly found that these references teach that making the C-7 and/or C-10 hydroxy groups more lipophilic improves MDR performance.

Appx39-40, Appx42-43. Unsurprisingly, Plaintiffs disregard these findings, and only point to the district court's later discussion where it failed to incorporate its own earlier factual findings.

With respect to *Golik*, Plaintiffs do not dispute that the addition of a small lipophilic MTM group at C-7 caused dramatic improvement against MDR cells. Plaintiffs argue only that the reference does not teach methylation at C-7 (as in cabazitaxel), but instead teaches a different "MTM group." YellowBr58-59. Defendants' experts explained, however, that a POSA would modify the MTM group to a methoxy group in order eliminate the sulfur atom present in the MTM group which was known to cause toxicity and metabolism issues *in vivo*, and could easily confirm efficacy of the methoxy group from additional references such as *Wong*. Appx12361-12362 (Dr. Kingston), Appx13160 (Dr. Heathcock). Plaintiffs characterize Defendants' view as "contrived" by citing to data from *Golik* itself that they claim contradicts the notion that a POSA would prefer methoxy over MTM. YellowBr58-59. *Golik*, however, discloses only *in vitro* (not *in vivo*) **potency** studies of the MTM compound (Example 1a). Appx25205-25206.

With respect to *Ojima 1994*, Plaintiffs misleadingly allege that the reference teaches only that side chain modifications can help with MDR. YellowBr9-10. However, the reference reports data for compounds SB-T-1101 and SB-T-1102, which differ only with respect to C-10 and clearly demonstrate that adding a small

lipophilic group at this position improves potency against MDR cells. Appx43; Appx25114-25115 (*Ojima 1994*); Appx13154-13155 (Dr. Heathcock). The presence of other data showing that side chain modifications could also be beneficial does not diminish this teaching. *Par*, 773 F.3d at 1197-98. *Ojima 1994* thus would have confirmed a POSA's motivation to modify C-10.

Finally, Plaintiffs' fail to rebut Dr. Kingston's testimony that a POSA would understand the "additive principle" in drug design, *i.e.*, that if two independent modifications to a compound each improve its properties then the simultaneous modifications would be expected to improve its properties even more. YellowBr61. The testimony Plaintiffs cite to "undermine" this principle in fact further supports it. Dr. Kingston testified that the prior art reference at issue showed that when two modifications at C-7 and C-10 each independently worsened cellular potency, the simultaneous modifications made the compound even worse than either one alone. Appx12423-12425.

### 3. *BMS* Requires an Obviousness Finding in the Instant Matter

Plaintiffs' attempts to distinguish this case from *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967 (Fed. Cir. 2014) ("*BMS*") fail. In *BMS,* this Court affirmed a lower court ruling that a POSA's desire to make "small, conservative changes" to select locations on a lead compound can establish a motivation to modify in an obviousness analysis. *Id.* at 974-75. Plaintiffs appear

to agree that a small conservative change rendered the claimed compound in *BMS* obvious, but attempt to distinguish this case by arguing that addition of one carbon to the C-7 and C-10 hydroxy groups of docetaxel to form methoxy groups was not the smallest, most conservative change available. YellowBr61-62. But *BMS* also involved the addition of a single carbon atom. *BMS*, 752 F.3d at 975-76. This was considered to be the simplest, and thus an obvious, change in *BMS*. *Id.*

Plaintiffs' argument that there was no evidence that small, conservative changes were the norm in the taxane prior art is belied by Plaintiff's own expert Dr. Ojima, who admitted that his own work in *Ojima 1994* teaches precisely these types of small, conservative changes. Appx24262-24263. Indeed, both sides' experts agreed that medicinal chemists design new compounds based on SAR data, which is generated by making incremental changes to a lead compound's structure. RedBr65-66.

Plaintiffs also incorrectly allege that Dr. Heathcock focused "without support" on methoxy as the smallest, most conservative change, to the exclusion of other changes, such as acetoxy. YellowBr62. But a methoxy substitution is the smallest possible chemical change that could be made to docetaxel's C-7 and C-10 hydroxy groups, leading a POSA to focus on it.[3] *See, e.g.*, RedBr66-68. Acetoxy

[3] Dr. Heathcock's testimony is not "inconsistent" with what he said in *BMS*, where he also proposed the addition of a single carbon atom to the position to be modified. *Compare* Appx13144-13145 *with BMS*, 752 F.3d at 975-76.

is twice the molecular weight when compared to methoxy, and thus would be less attractive to a POSA in this respect. *See, e.g.*, Appx13156 (Dr. Heathcock).

Plaintiffs' allegation that Defendants offered no evidence from the prior art that converting docetaxel's C-7 and C-10 hydroxy groups to methoxy would be easy is also wrong. YellowBr62-63. There was, in fact, ample evidence of successful methylation at both C-7 and C-10 in the prior art, demonstrating the ease with which it could be done. *See, e.g.*, Appx25311-25312 (*Kant*), Appx25318 (*Wong*). Plaintiffs cite only to irrelevant non-prior art lab notebooks in alleging that this modification would have been difficult. YellowBr63.

**4. Defendants Have Not Engaged in "Cherry-Picking"**

Both the district court and Plaintiffs incorrectly accuse defendants of "cherry-picking" from the *Kant*, *Klein*, and *Wong* references. Appx52; YellowBr63-64. This accusation misconstrues the confirmatory nature of these references. *See* 17, *supra*. Once the POSA had already decided to utilize methoxy groups at C-7 and C-10, she would consult these references to confirm that methoxy groups could be used without sacrificing potency. RedBr67-68.

Moreover, Defendants did not selectively focus on a subset of data from these references. For example, Plaintiffs claim that by focusing on Compound 20 in *Kant*, Defendants "overlooked the most potent compound in cells, Compound 18," YellowBr64. But this claim is undercut by testimony from Plaintiffs' own

expert, Dr. Roush, that a POSA would view the *Kant* compounds (including both Compounds 18 and 20) as having "essentially the same activities" in cells. Appx13672-13673. Plaintiffs also fault Defendants for ignoring Example 8 of *Wong*, which Plaintiffs (and the district court) identify as the most potent, YellowBr59, but this ignores the evidence that a POSA would avoid this compound because it was a prodrug. Appx12365-12366 (Dr. Kingston); *cf.* Appx24280-24282 (Dr. Ojima). Plaintiffs also argue that Defendants ignore a teaching in *Klein* that would have motivated a POSA to modify C-9 to hydroxy. YellowBr52-53. But beyond the potential synthetic challenges involved in making the C-9 hydroxy, a POSA would avoid this modification because it would make the northern hemisphere less lipophilic, counteracting the very strategy suggested by *Hait* and *Lampidis* to overcome MDR.

#### 5. Plaintiffs' Reliance on Comparative B to Inform a POSA's Reasonable Expectation Is Misplaced

Plaintiffs devote significant effort to arguing that a compound discussed during prosecution of the '170 patent, "Comparative B," would have undermined the POSA's expectation that simultaneous small C-7 and C-10 changes would yield improved properties. YellowBr59-60. However, Plaintiffs' expert Dr. Roush admitted that Comparative B is irrelevant to a POSA's expectation of success, because it is not prior art. Appx13750; *cf. Cordis Corp. v. Boston Sci. Corp.*, 561 F.3d 1319, 1333 (Fed. Cir. 2009), *cert. denied*, 558 U.S. 1049 (2009); *N. Telecom,*

*Inc. v. Datapoint Corp.*, 908 F.2d 931, 936 (Fed. Cir. 1990), *cert. denied*, 498 U.S. 920 (1990). Plaintiffs attempted to make this same argument at trial, Appx11228, and the district court found it unpersuasive—the district court's opinion makes no mention of Comparative B. Contrary to Plaintiffs' assertion, Defendants did address Comparative B at trial and elicited the admission from Dr. Roush that the compound is irrelevant as non-prior art. Appx11148-11149. The district court thus properly disregarded Comparative B, and this Court should as well.

### E. The District Court's Finding Regarding Unexpected Results Supports Defendants' *Prima Facie* Case

Despite ultimately finding that cabazitaxel was not obvious, the district court correctly found that the POSA would have expected cabazitaxel to show some improvement over docetaxel, thus rendering its ultimate performance "not entirely unexpected." Appx55-56. The district court found that cabazitaxel's superior performance differed "not in kind but only in degree, from docetaxel's performance," noting the presence of other taxanes in the prior art that showed improved potency in MDR cells. Appx56. Because the expectation of improved properties supplies a motivation necessary to make a compound, this finding is at odds with the district court's conclusion that the POSA would not have been motivated to arrive at cabazitaxel. RedBr70-71; *In re Dillon*, 919 F.2d 688, 697 (Fed. Cir. 1990) (en banc).

The finding that cabazitaxel's properties were "not entirely unexpected" comports with the facts at trial. This Court has held that "structurally similar compounds often have similar properties," such that a POSA would expect the efficacy, safety, and therapeutic window of a compound based on the properties of a structurally similar lead compound. *BMS*, 752 F.3d at 976-78. Here, the similarities between cabazitaxel and docetaxel would have led the POSA to expect that cabazitaxel would show potency against the same type of MDR targets that docetaxel did, but with improved potency, due to the modifications of the molecule. *See* RedBr70-71.

### 1. Plaintiffs Mischaracterize the District Court's Unexpected Results Finding

Plaintiffs incorrectly argue that "[b]ased upon the evidence, the district court found that cabazitaxel's properties were unexpected…". YellowBr66. In fact, the court declined to adopt Plaintiffs' reasoning, and gave "minimal weight" to Plaintiffs' unexpected results argument. Appx56. The district court specifically found that the POSA would expect that cabazitaxel would show improved properties over docetaxel, and that cabazitaxel's properties differed only in degree, but not in kind. Appx55-56; *accord BMS*, 752 F.3d at 977. The district court correctly relied on the evidence and this Court's precedent to find that the improvements made to docetaxel to get cabazitaxel would be expected to increase its potency against MDR cells. Appx54-55.

Plaintiffs attempt to dismiss the district court's finding by citing to this Court's recent precedent in *Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1274 (Fed. Cir. 2018). There, an increase of 66% in bioavailability due to a claimed formulation was found to be a difference in kind, and not in degree. *Id.* But nowhere in *Orexo* did this Court conclude that there exists a certain numerical threshold for unexpected results. In fact, the *Orexo* court noted that "*in the context of this invention*, [a 66% increase in bioavailability] is more than a trivial 'degree.'" *Id*. (emphasis added). Nothing about *Orexo* changes the law regarding unexpected results being a fact-based inquiry that considers the specifics of each case. For example, this Court has found that a 300% difference in a result was not sufficient to constitute an unexpected result probative of nonobviousness. *Galderma*, 737 F.3d at 739.

For the same reason, Plaintiffs' citation to *Daiichi Sankyo Co. v. Mylan Pharms. Inc.*, 670 F. Supp. 2d 359, 382-84 (D.N.J. 2009) is unavailing. The district court explicitly declined to follow *Daiichi* because the compound at issue in that case exhibited "an activity totally lacking in the [comparator] compound". Appx56. Here, cabazitaxel does not exhibit any new properties compared with docetaxel—the only difference is in the ***degree*** of potency against MDR cells.

Plaintiffs next attempt to rely on the alleged unexpectedness of ***docetaxel's*** properties compared to paclitaxel to support the argument that the results for

cabazitaxel were unexpected. YellowBr67. As an initial matter, the degree to which docetaxel represented an improvement over paclitaxel is irrelevant to whether cabazitaxel's properties were unexpected compared to docetaxel's. Moreover, while Dr. Heathcock testified that docetaxel's four-fold improvement in MDR potency over paclitaxel was a "significant difference," Appx13206-13209, he did not characterize this result as *unexpected*. As the district court's finding here indicates, a statistically significant difference need not be unexpected. Appx54-56. Likewise, the fact that the title of a prior art reference referred to docetaxel and paclitaxel as "[n]ot simply two of a kind," YellowBr67, says nothing about the extent to which the properties of cabazitaxel would not have been expected.

Finally, Plaintiffs' argument that cabazitaxel's activity in docetaxel-resistant *in vivo* models is evidence of unexpected results falls flat. YellowBr68. The prior art disclosed numerous data-driven examples of C-7 and/or C-10 substituted taxanes with improved performance against both normal and resistant cancers. *See* 20-22, 24-25, *supra*. Given the significant structural similarity between these potent prior art compounds and cabazitaxel, a POSA would have had a reasonable expectation that cabazitaxel would have similar properties. Appx12368-12369 (Dr. Kingston); Appx13179-13180 (Dr. Heathcock); *see also BMS*, 752 F.3d at 976. Cabazitaxel's efficacy in *in vivo* models was therefore not unexpected.

### 2. The District Court's Unexpected Results Finding Requires a Finding of Obviousness

Under this Court's precedent, there is a clear link between unexpected results and the *prima facie* obviousness of a claimed compound. RedBr69. Because medicinal chemists design compounds based on their expected properties, an expectation that a compound would have improved properties provides the motivation to make that compound. *Dillon*, 919 F.2d at 697 ("Properties, therefore, *are* relevant to the creation of a *prima facie* case in the sense of affecting the motivation of a researcher to make compounds closely related to or suggested by a prior art compound…") (emphasis in original); *see also BMS*, 752 F.3d at 976 (citing *Dillon*). A compound's biological activity is based on its structure, and the only structural differences between docetaxel and cabazitaxel are the methoxy groups at C-7 and C-10. Where, as here, the district court found that a POSA would have expected these changes to result in improved properties, this is sufficient motivation for the POSA to make cabazitaxel in the first place and thus leads to the conclusion that the compound would have been obvious.

## F. The District Court Did Not Conclude That Claim 2 Was Nonobvious for Independent Reasons

Defendants presented substantial evidence at trial that claim 2 was obvious because a POSA would reasonably expect that existing taxane formulations in the literature could be successfully applied to cabazitaxel. RedBr71. Plaintiffs do not

rebut this evidence and instead argue that the court's *prima facie* finding regarding the cabazitaxel molecule (claim 1) vitiated the need to address cabazitaxel formulations (claim 2). YellowBr68. But this incorrectly assumes that the district court's underlying *prima facie* decision was valid. As described in detail above, the district court's ultimate decision regarding cabazitaxel was both factually and legally erroneous and should be reversed. Thus, to the extent this Court finds claim 1 obvious, it must also find claim 2 obvious based on Defendants' unrebutted evidence presented at trial regarding claim 2.

## IV. Defendants' Strong *Prima Facie* Case Cannot Be Overcome by Secondary Considerations

While the district court found cabazitaxel's superior properties were "not entirely unexpected," it also erroneously found evidence of two other secondary considerations—failure of others and commercial success.

While Plaintiffs note that the district court found that cabazitaxel demonstrated commercial success, YellowBr65, the district court also acknowledged its failure to command any significant market share. Appx58. The district court also failed to apportion any commercial success of Jevtana® to anything other than claims 1 and 2 of the '170 patent, despite acknowledging that "there are multiple patents that cover Jevtana in the FDA's Orange Book." Appx58-59.

Plaintiffs also point to the district court's giving "considerable weight" to Plaintiffs' failure of others argument, YellowBr65. The district court did so despite the fact that others had *not* failed to develop alternative compounds, but merely to obtain FDA approval. Appx56-57. These factors are not sufficient to overcome defendants' strong *prima facie* obviousness case. *Ohio Willow Wood Co. v. Alps South, LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013).

## CONCLUSION

This Court should reverse the district court's judgement that claims 1 and 2 of the '170 patent are valid and infringed.

Dated: November 28, 2018

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**PROOF OF SERVICE**

I hereby certify that on this 28th day of November, 2018, I caused a true and correct copy of the foregoing DEFENDANTS – CROSS-APPELLANTS' REPLY BRIEF to be electronically filed with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system, which will serve such filing on all registered CM/ECF users, including counsel for all parties.

I also certify that that the foregoing DEFENDANTS – CROSS-APPELLANTS' REPLY BRIEF was served upon all counsel of record via electronic mail on this 28th day of November, 2018.

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