UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ACTAVIS LLC,
Petitioner

v.

ABRAXIS BIOSCIENCE, LLC,
Patent Owner

Case IPR2017-01104
Patent 8,138,229 B2
Issued: March 20, 2012

Title: COMPOSITIONS AND METHODS OF DELIVERY OF PHARMACOLOGICAL AGENTS

PETITION FOR *INTER PARTES* REVIEW

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I. INTRODUCTION

Petitioner Actavis LLC requests *inter partes* review and cancellation of claims 1–48 of U.S. Patent No. 8,138,229 B2 (the "'229 patent"). These claims are directed to nanoparticles combining (1) albumin, a known protein in human blood, with (2) paclitaxel, a known anticancer drug, in which the albumin-paclitaxel ratio is about 9:1. As shown below, the claimed invention was disclosed in a single prior art reference, which anticipates claims 1–19 and 21–48. Independently, all claims would have been obvious to a person of ordinary skill in the art. The allegedly "unexpected" results that were asserted during prosecution lack a nexus to the claims and, in any event, were entirely expected.

***Anticipation*.** First, claims 1–19 and 21–48 are anticipated under 35 U.S.C. §102(b) by an international patent application publication authored by two of the '229 patent's inventors. EX1006 ("Desai"). The very first example in Desai teaches a process of preparing albumin-paclitaxel "nanoparticles," in which 270 mg of albumin and 30 mg of paclitaxel were combined. *Id*. at 62. As confirmed by Petitioner's declarant and nanoparticle formulation expert, Dr. Cory Berkland, the disclosed process necessarily results in the claimed formulation with an albumin-paclitaxel ratio of 9:1. EX1002 ¶107. And just like the '229 patent, Desai teaches methods of administering this formulation by intravenous injection to treat diseases including cancer.

Obviousness. Second, and independently, all claims—even if they were not anticipated—would have been obvious. The prior art "discloses a range encompassing" the claimed range of about 9:1, and thus "is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). That fact alone shifts the burden of production to Patent Owner to show the "criticality" of the claimed ratio (*id*.)—a burden Patent Owner cannot meet.

Moreover, as its preferred embodiment, Desai undisputedly discloses an albumin-paclitaxel nanoparticle formulation trademarked as "Capxol™" that "contains 30 mg of paclitaxel and approximately 400 mg of human serum albumin"—*i.e.*, an albumin-paclitaxel ratio of 13.3:1. EX1006, 38. Reducing Capxol™'s albumin-paclitaxel ratio of 13.3:1 to the claimed ratio of about 9:1 would have been obvious. Indeed, Desai itself expressly encourages "developing formulations of paclitaxel … at higher concentrations" to "reduce the time of administration" for intravenous injection. EX1006, 21. As Desai explains, providing a higher concentration of paclitaxel—*e.g.*, by reducing the albumin-paclitaxel ratio—not only "minimizes patient discomfort at receiving large volumes of fluid," but can "result in a higher response rate" to the drug. *Id*. at 54, 19–20.

In addition, as taught in a prior patent application publication to Kadima et al., "[a]lbumin is an expensive ingredient" and "a cost-limiting component" in drug formulations. EX1004 ("Kadima"), 10, 33. To obtain a "commercially feasible

method for using a serum albumin to administer paclitaxel," Kadima expressly instructs skilled artisans to use "a high … ratio" of paclitaxel to albumin—*i.e.*, a *low* ratio of albumin to paclitaxel. *Id*. at 33. Indeed, the '229 patent inventors selected a ratio of about 9:1 for that very reason, noting that "compositions with lower amounts of albumin are preferred as this can greatly reduce cost…." EX1001, 34:53–55. A skilled artisan would have had the same motivation.

***Secondary considerations*.** During prosecution, the patentee argued that the claimed albumin-paclitaxel ratio of about 9:1 produces "unexpected results." Although Petitioner has no burden at this stage to rebut such objective indicia, Petitioner will show that the unexpected results asserted during prosecution cannot overcome the strong *prima facie* case of obviousness.

According to the patentee, the ratio of about 9:1 unexpectedly provides "enhanced cellular binding of paclitaxel," "is more efficacious," and "has substantially reduced toxicity." EX1023 ¶¶ 7, 23. Yet, the "cellular binding" experiment that the patentee relied on to support these assertions could not have shown any unexpected results of the claimed invention—because the experiment did not test *any* albumin-paclitaxel formulation, let alone one with an albumin-paclitaxel ratio of about 9:1. EX1002 ¶204. Moreover, the patentee's "efficacy" and "toxicity" tests showed only an insignificant difference in degree compared to an albumin-

paclitaxel ratio of 19:1, which is not even the closest prior art. Regardless, all of these results would have been fully expected. *Infra* 58–63.

The Board should institute *inter partes* review and cancel claims 1–48 of the '229 patent as unpatentable under 35 U.S.C. §§ 102(b) and/or 103(a).

II. MANDATORY NOTICES

Pursuant to 37 C.F.R. §42.8(b), Petitioner states as follows:

1. ***Real parties-in-interest.*** Petitioner Actavis LLC is a real party-in-interest. Out of an abundance of caution, and for purposes of this Petition only, Petitioner additionally discloses Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals Europe B.V., Orvet UK, Teva Pharmaceutical Holdings Coöperatieve U.A., IVAX LLC, Teva Pharmaceuticals USA, Inc., Actavis Holdco US, Inc., Watson Laboratories, Inc., and Actavis US Holding LLC as real parties-in-interest.

2. ***Related matters.*** The '229 patent is asserted in two district court litigations filed in the U.S. District Court for the District of New Jersey, captioned *Abraxis BioScience, LLC v. Actavis LLC*, C.A. No. 16-1925-JMV-MF; and *Abraxis BioScience, LLC v. Cipla Ltd*., C.A. No. 16-9074-JMV-MF. Petitioner has also filed petitions for *inter partes* review of U.S. Patent Nos. 8,853,260 (IPR2017-01100), 7,820,788 (IPR2017-01101), and 7,923,536 (IPR2017-01103). Both the '229 patent and the '536 patent are continuations of the '788 patent.

3. ***Lead and back-up counsel.*** Petitioner identifies the following:

- *Lead counsel*: Samuel S. Park (Reg. No. 59,656)
- *Back-up counsel*: George C. Lombardi*
- *Back-up counsel*: Charles B. Klein*
- *Back-up counsel*: Kevin E. Warner*
- *Back-up counsel*: Eimeric Reig-Plessis*

* Back-up counsel to seek *pro hac vice* admission.

4. ***Service information.*** Petitioner identifies the following:

- *Email address*: AbraxaneIPR@winston.com
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  Chicago, IL 60601
- *Telephone number*: 312-558-7931
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Please address all correspondence to lead counsel at the address shown above. Petitioner consents to electronic service at the above listed email address.

III. REQUIREMENTS FOR REVIEW

Pursuant to 37 C.F.R. §42.104, Petitioner states as follows:

a. ***Grounds for standing.*** Petitioner certifies that (1) the '229 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting review of any claim on the grounds identified in this Petition. The Office is authorized to charge authorized to charge all fees due in connection with this matter to Deposit Account No. 50-1814.

b. ***Identification of challenge.*** Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancelation of claims 1–48 of the '229 patent pursuant to the following statement of precise relief requested:

Ground	Claims	Basis	Reference(s)
I	1–19, 21–48	§102(b)	Desai (EX1006)
II.A	1–19, 21–48	§103(a)	Desai (EX1006)
II.B	1–19, 21–48	§103(a)	Desai (EX1006), Kadima (EX1004), and Liversidge (EX1005)
III.A	20	§103(a)	Desai (EX1006) and Taxol® label (EX1008)
III.B	20	§103(a)	Desai (EX1006), Taxol® label (EX1008), Kadima (EX1004), and Liversidge (EX1005)

IV. LEVEL OF ORDINARY SKILL IN THE ART

The '229 patent claims priority to U.S. provisional application no. 60/432,317, which was filed on December 9, 2002. EX1001. Without conceding that this priority claim is valid, Petitioner and declarant Dr. Cory Berkland use December 9, 2002, as the relevant date for analyzing the level of skill and knowledge of a hypothetical person of ordinary skill in the art. EX1002 ¶17.

Such a person would have an advanced degree in chemistry, chemical engineering, pharmaceutics, pharmacy, or a related discipline, and/or having experience formulating compounds for use in pharmaceutical compositions, including nanoparticle suspensions, for several years. *Id*. ¶20. A skilled artisan would know how to evaluate potential drug therapies for *in vitro* and *in vivo* activity, including with biological assays. *Id*.

V. THE PRIOR ART AND THE '229 PATENT

As of December 2002, albumin and paclitaxel were well known in the art, and their combination as albumin-paclitaxel nanoparticles had been claimed in two generations of prior art patents—including with a 9:1 albumin-paclitaxel ratio.

A. Taxol® (paclitaxel) was an FDA-approved "wonder drug," but initially could only be administered with a toxic solvent.

As Desai explains, paclitaxel is a "naturally occurring" drug that was first isolated in the early 1970s, and was known "to have significant antineoplastic [*i.e.*, antitumor] and anticancer effects." EX1006, 6–7. Due to its "excellent antitumor

activity in a wide variety of tumor models," it became known as "the new anti-cancer wonder-drug" and was "approved by the [Food and] Drug Administration" in 1992 under the brand name Taxol®. *Id*. at 7; EX1008.

While paclitaxel's therapeutic effects were impressive, its "poor aqueous solubility" presented "a problem for human administration," because the "delivery of drugs that are inherently insoluble or poorly soluble in an aqueous medium can be seriously impaired if oral delivery is not effective." EX1006, 7. Taxol® was thus formulated with a solvent called "polyethoxylated castor oil"—or Cremophor®—"to solubilize the drug." *Id*.; EX1008, 3.

Cremophor®, however, introduced its own problems. In "clinical trials, [paclitaxel] itself did not show excessive toxic effects," but Cremophor® caused "severe allergic reactions," requiring pre-treatment "with antihistamines and steroids." EX1006, 8. "Although it appear[ed] possible to minimize the side effects of administering Taxol in an emulsion by use of a long infusion duration, the long infusion duration [wa]s inconvenient for patients, and [wa]s expensive due to the need to monitor the patients for the entire 6 to 24-hour infusion," which required a "night in the hospital." *Id*. at 17–18. Thus, Desai recognized that following Taxol®'s approval in 1992, it was "highly desirable to develop a formulation of paclitaxel that obviates the need for premedication," "does not cause hypersensitivity reactions," and "shorten[s] the duration of infusion of Taxol." *Id*. at 20.

B. The inventors repeatedly patented albumin-paclitaxel nanoparticles as a solution to the known problems of Taxol®.

In 1995, two of the '229 patent's inventors obtained U.S. Patent No. 5,439,686 (the "'686 patent"), which disclosed their solution to "the problem of taxol administration"—a formulation that allows "its delivery as an aqueous suspension of micron size particles." EX1003, 10:14–16. "This approach," they explained, "facilitate[s] the delivery of taxol at relatively high concentrations and obviate[s] the use of emulsifiers [*e.g.*, Cremophor®] and their associated toxic side effects." *Id*. at 10:20–22. The particles are "contained within a polymeric shell," preferably consisting of "albumin." *Id.* at 4:9–17, 6:42–43. These albumin-paclitaxel particles "allow[] for the delivery of high doses of the pharmacologically active agent in relatively small volumes." *Id*. at 5:22–25. The "preferred particle radii fall in the range of about 0.1 up to about 5 micron"—*i.e.*, nanoparticles with diameters as small as about 200 nm. *Id*. at 9:15–16.

Despite this earlier patent on albumin-paclitaxel nanoparticles, the inventors later obtained a second round of patents on the very same invention, including U.S. Patent No. 8,853,260 (the "'260 patent," for which Petitioner is seeking review in

IPR2017-01100). In 1999, the inventors published substantially the same disclosure that would later issue as the '260 patent in an international patent publication, Desai. EX1006.[1]

Like the '686 patent, Desai teaches the delivery of paclitaxel "in the form of microparticles or nanoparticles," which "obviates the necessity for administration of substantially water insoluble pharmacologically active agents (*e.g.*, Taxol) in an emulsion containing, for example, ethanol and polyethoxylated castor oil [*i.e.*, Cremophor]," the "disadvantage of such known compositions [being] their propensity to produce allergic side effects." *Id*. at 23. Likewise, in Desai's compositions, "proteins (*e.g.*, human serum albumin) are employed as a stabilizing agent." *Id*.

As Desai explains, "[a] large number of conventional pharmacologically active agents [*e.g.*, paclitaxel] circulate in the blood stream bound to carrier proteins … of which the most common example is serum albumin." *Id*. at 25. Simply put, "albumin … [is] the natural carrier of the drug in the blood stream." *Id*.

Desai "further provides a method for the reproducible formation of … nanoparticles []less than 200 nm diameter." *Id*. at 23. This size corresponds to Desai's "preferred embodiment," in which "the average diameter of the … particles is no greater than about 200 nm." *Id*. at 38.

[1] This disclosure was also issued as U.S. Patent No. 5,916,596 in 1999. EX1026.

C. Desai (EX1006) specifically discloses a nanoparticle formulation with an albumin-paclitaxel ratio of 9:1.

Example 1 of Desai describes a process in which 30 mg of paclitaxel is combined with 27 ml of human serum albumin solution at a concentration of 1% (w/v), which corresponds to 270 mg of albumin—*i.e.*, an albumin-paclitaxel ratio of 270:30, or 9:1. *Id*. at 62; EX1002 ¶71.

Example 1 provides that "the typical diameter of the resulting paclitaxel particles was 160–220[nm]," measured as the "Z-average" using a standard device called a "Malvern Zetasizer." EX1006, 63. Example 1 further provides that the composition was lyophilized (*i.e.*, freeze-dried) and "could be easily reconstituted to the original dispersion by addition of sterile water or saline." *Id*. at 63. "The particle size after reconstitution was the same as before lyophilization." *Id*. at 63.

In sum, as of 1999, Desai taught pharmaceutical compositions for injection comprising albumin-paclitaxel nanoparticles smaller than about 200 nm, including compositions with an albumin-paclitaxel ratio of 9:1.

D. Desai, Kadima (EX1004), and Liversidge (EX1005) taught varying ranges of albumin-paclitaxel ratios, and taught lowering the ratio to increase drug concentration and reduce cost.

In addition to Example 1's albumin-paclitaxel ratio of 9:1, Desai teaches a range of similar albumin-paclitaxel ratios. EX1002 ¶75. For instance, Example 4 combines 30 mg of paclitaxel with 29.4 ml of 1% albumin (*i.e.*, 294 mg), which corresponds to a ratio of 9.8:1. EX1006, 65. Similarly, Example 5 combines 225

mg of paclitaxel and 97.0 ml of 3% albumin (*i.e.*, 291 mg), which corresponds to a ratio of 12.9:1. *Id*. at 66. And Desai's preferred embodiment, Capxol™, "contains 30 mg of paclitaxel and approximately 400 mg of human serum albumin"—*i.e.*, a ratio of 13.3:1. *Id*. at 38.

Aside from teaching a range of ratios, Desai teaches specific reasons for reducing the albumin-paclitaxel ratio of existing formulations such as Capxol™. As Desai explains, "[i]t is desirable to … develop[] formulations of paclitaxel that are stable at higher concentrations so as to reduce the time of administration." *Id*. at 21. By delivering "high doses of [paclitaxel] in relatively small volumes"—*i.e.*, at a high paclitaxel concentration—formulations can "minimize[] patient discomfort at receiving large volumes of fluid and minimize[] hospital stay." *Id*. at 54. Moreover, it is desirable "to obtain a higher loading of drug into the crosslinked protein shell"—*i.e.*, increasing the amount of paclitaxel in the particle relative to albumin, thereby reducing the albumin-paclitaxel ratio. *Id*. at 79.

These teachings are echoed in Kadima, an international patent application published in February 2000. EX1004. Like Desai, Kadima teaches that "the highest concentrations of paclitaxel" are desirable, as "[t]his results in the smallest volumes for … more rapid administration." *Id*. at 13. In particular, Kadima explains that higher concentrations of paclitaxel can be obtained by adjusting the "ratio of paclitaxel:albumin." *Id*.

Kadima also observes that "[a]lbumin is a cost-limiting component for use in drug stabilization." EX1006, 10. Kadima thus emphasizes the importance of a "commercially feasible method for using a serum albumin to administer paclitaxel," as "[a]lbumin is an expensive ingredient." *Id*. at 33. Kadima teaches that the cost can be reduced by selecting "a high … ratio" of paclitaxel to albumin—*i.e.*, a *lower* albumin-paclitaxel ratio. *Id*. at 33–34.

Liversidge, a 1995 patent, also discloses a range of albumin-paclitaxel ratios that includes 9:1. EX1005. The "anticancer agent" of Liversidge is selected from a group including paclitaxel (*id*. at 2:50, 3:20), and "[p]articularly preferred surface modifiers"—*i.e.*, stabilizing carriers—include albumin (*id*. at 4:23, 48). Liversidge teaches that the "[t]he surface modifier can be present in an amount of 0.1–90%." *Id*. at 7:1–4. Consistent with that teaching, claim 1 of Liversidge covers "[p]articles consisting essentially of 99.9–10% by weight of a crystalline medicament useful in treating cancer" and a "surface modifier adsorbed on the surface thereof in an amount of 0.1–90% by weight." *Id*. at 14:7–14, p. 10 (correcting 14:7)—*i.e.*, an albumin-paclitaxel ratio of 0.01:9.99 to 9:1.[2]

[2] In a case that settled before appeal, a jury found that Abraxane®—an alleged embodiment of the '229 patent—infringes Liversidge. EX1011. Patent Owner's expert admitted that Liversidge teaches a "ratio of drug to surface modifier"

Accordingly, as of 2000, the prior art (1) disclosed a range of acceptable albumin-paclitaxel ratios, including a ratio of 9:1 and Capxol™'s ratio of 13.3:1; (2) taught that formulations like Capxol™ could be optimized to deliver more paclitaxel in a shorter period of time by lowering the albumin-paclitaxel ratio; and (3) taught that albumin is an expensive ingredient, and thus lowering the albumin-paclitaxel ratio would save costs.

E. The inventors obtained their *third* round of patents on albumin-paclitaxel by arguing that a 9:1 ratio has "unexpected" benefits.

Two years after publishing Desai, two of the named inventors for both Desai and the earlier '686 patent filed a new patent application that eventually issued as three patents, including the '229 patent, purporting to solve the same problems that the '686 patent and Desai already solved. EX1001. Just like these earlier references, the '229 patent supposedly overcomes the shortcomings of Taxol® with nanoparticle formulations comprising albumin and paclitaxel. *Id*. at 2:55–60.

The '229 patent states that "[t]he amount of albumin included in the pharmaceutical composition of the present invention will vary." *Id*. at 5:60–61. Indeed, a very wide range of albumin-paclitaxel ratios, from "0.01:1 to about 100:1," and "[m]ore preferably … 0.02:1 to about 40:1," are supposedly suitable for the

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(EX1012, 215), and that "nanoparticles, nanoformulations or nanoparticles have been around for a long time" (EX1013, 32–33).

claimed compositions. *Id*. at 11:61–64. Consistent with the prior art, the patent acknowledges that "the ratio of protein to pharmaceutical agent will have to be optimized." *Id*. at 11:64–66. The patent discloses various "preferred" ranges and concludes by stating that "[m]ost preferably, the ratio is about 1:1 to about 9:1." *Id*. at 12:2–3.

Example 46 describes why the inventors reduced the albumin-paclitaxel ratio in certain prior art formulations: "[C]ompositions with lower amounts of albumin are preferred as this can greatly reduce cost...." *Id*. at 34:53–55.

The '229 patent issued with 48 claims. Claim 1 is illustrative:

> 1. A liquid pharmaceutical composition for injection comprising paclitaxel and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises albumin, wherein the albumin and the paclitaxel in the composition are formulated as particles, wherein the particles have a particle size of less than about 200 nm, wherein the weight ratio of albumin to paclitaxel in the composition is about 1:1 to about 9:1, wherein the liquid pharmaceutical composition comprises about 0.5% to about 5% by weight of albumin, and wherein the liquid pharmaceutical composition further comprises saline.

Id. at 37:19–29. Claims 5, 10, 18, 26, 32, 37, and 41 limit the albumin-paclitaxel ratio to about 9:1.

During prosecution, the Examiner rejected the claims of the application for which the '229 patent is a continuation as obvious over an article by Damascelli published in 2001 (EX1017) in view of an article by Ibrahim published in May 2002 (EX1018). As the Examiner explained, Damascelli discloses a composition called "ABI-007, a paclitaxel-human albumin nanoparticle [formulation] having a [particle size] dimension of 150–200 nm." EX1019, 3 (citing EX1017).

While acknowledging that Damascelli does not discuss the albumin-paclitaxel ratio, the Examiner concluded that "[i]t would have been obvious to one of ordinary skill in the art … [to] determin[e] the optimum concentration and/or weight ratio of albumin to paclitaxel." *Id*. at 4. Any difference in the ratio could "not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that [the ratio] is critical." *Id*. (citing cases).

In attempting to distinguish the cited art, the applicants argued that "Damascelli is silent about weight ratio of albumin to pharmaceutical agent, namely, paclitaxel," "[n]or does Damascelli teach or suggest the significance of the albumin/pharmaceutical agent ratio." EX1020, 8.

The Examiner was not persuaded. He again rejected the claims as obvious, and the applicants again attempted to distinguish the cited art. EX1021; EX1022. This time, they submitted a declaration by one of the inventors as evidence that the

albumin-paclitaxel ratio of about 9:1 was inventive. EX1023 (the "Inventor Declaration"). The inventor claimed to have "found, unexpectedly, that the ratio of albumin to paclitaxel in an albumin based paclitaxel nanoparticle composition affects the ability of paclitaxel to bind to endothelial cells," and that "the effect of albumin/paclitaxel ratio on the binding of paclitaxel changes dramatically at an albumin/paclitaxel ratio of about 9:1." *Id*. ¶7.

The inventor declared that "[t]he albumin-based paclitaxel nanoparticle compositions used for the clinical studies reported in the cited references"—*i.e.*, the "ABI-007" formulation discussed in Damascelli and Ibrahim—was "an old formulation developed by [Patent Owner] prior to the filing of the present application" with an "albumin/paclitaxel weight ratio … [of] about 19:1." *Id*. ¶17. The inventor claimed to have "found unexpectedly that Abraxane®, an albumin-based paclitaxel nanoparticle composition having about 9:1 albumin/paclitaxel weight ratio, is more efficacious than the old formulation (about 19:1 albumin/paclitaxel ratio) in treating cancer," and that "Abraxane® has substantially reduced toxicity compared with the old formulation." *Id*. ¶23.

In discussing this "old" formulation with an albumin-paclitaxel ratio of 19:1, the inventor did not mention the 9:1 ratio in Example 1 of Desai, or even the 13.3:1 ratio of Capxol™ that was also disclosed in Desai. Nor did the Examiner evaluate the ratios in Desai's formulations.

Following the Inventor Declaration, the Examiner entered a Notice of Allowance for application no. 11/553,339 (of which the '229 patent is a continuation), finding that the arguments in the declaration were "sufficient to overcome" the rejections for obviousness. EX1024, 7. As discussed in Section VII.B.3, however, the arguments in the Inventor Declaration were incorrect.

VI. PLAIN AND ORDINARY MEANINGS

"A claim in an unexpired patent that will not expire before a final written decision is issued shall be given its broadest reasonable construction in light of the specification of the patent." 37 C.F.R. §42.100(b). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016).

A. "the weight ratio of albumin to paclitaxel in the composition" and "the ratio (w/w) of albumin to the paclitaxel in the pharmaceutical composition"

These terms include the albumin-paclitaxel ratio in the starting ingredients used to make the composition. EX1002 ¶56. That is clear from Examples 47–49, which are the only examples that mention the albumin-paclitaxel ratio. *Id*. ¶¶ 37–39; EX1001, 34:62–36:10.

Example 47 states: "30 mg of paclitaxel was dissolved in 3.0 ml methylene chloride. The solution was added to 27.0 ml of human serum albumin solution

(3% w/v) (*corresponding to a ratio of albumin to paclitaxel of 27*)." *Id*. at 34:62–65 (emphasis added). Example 48 states: "300 mg of paclitaxel was dissolved in 3.0 ml methylene chloride. The solution was added to 27 ml of human serum albumin solution (5% w/v) (*corresponding to a ratio of albumin to paclitaxel of 4.5*)." *Id*. at 35:26–29 (emphasis added). A skilled artisan reading these examples would understand that the "ratio of albumin to paclitaxel" was based on the amounts used to make the composition. EX1002 ¶37.

Similarly, Example 49 states: "135 mg of paclitaxel was dissolved in 3.0 ml methylene chloride. The solution was added to 27 ml of human serum albumin solution (5% w/v)." *Id*. at 35:58–60. In other words, 135 mg of paclitaxel was combined with 1,350 mg of albumin (27 ml of 5% w/v solution), corresponding to a 10:1 ratio. EX1002 ¶39. After reciting several process steps, Example 49 states: "The calculated ratio (w/w) of albumin to paclitaxel in this invention composition is approximately 10." EX1001, 36:9–10.

A skilled artisan reading this example would understand that the ratio was either "calculated" based on starting ingredients, or measured after the process steps were completed, at which point the ratio in the final composition was the same as the initial ratio. EX1002 ¶39. Either way, Example 49 confirms that the albumin-paclitaxel ratio can be calculated based on starting materials. *Id*.

Indeed, there is no suggestion in the '229 patent that the albumin-paclitaxel ratio changes during the manufacturing process. *Id*. ¶40. Nor is there any disclosed assay or discussion of how to measure or predict the albumin-paclitaxel ratio other than by calculating it based on starting ingredients. *Id*.

Interpreting the claims to include the ratio of ingredients used to make the composition comports with the plain meaning of "composition," which covers "the specified ingredients at any time from the moment at which the ingredients are mixed together." *Exxon Chem. Patents, Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1558 (Fed. Cir. 1995). Thus, the Federal Circuit has rejected as "too narrow" the interpretation that a "composition … is limited to the final product made and ready for use." *Id*. Where, as here, claims "contain no temporal limitation to the term 'composition,'" they cover the "composition existing during manufacture that is being used to produce the end product." *Id*.; *Mars, Inc. v. H.J. Heinz Co., L.P.*, 377 F.3d 1369, 1374 (Fed. Cir. 2004) ("the ordinary meaning of 'ingredients' can refer to either starting materials (*e.g.*, as in a recipe)…").

Accordingly, "weight ratio of albumin to paclitaxel in the composition" and "ratio (w/w) of albumin to the paclitaxel in the pharmaceutical composition" include at least the ratio of the starting ingredients used to make the composition.

B. "a particle size of less than about 200 nm"

This term includes sizes of 220 nm or less, measured as the Z-average diameter using a Malvern Zetasizer. EX1002 ¶57. Indeed, every example in the '229 patent that mentions particle size refers to "the typical average diameter" of the particles and discloses a particle size range of "50–220 nm (Z-average, Malvern Zetasizer)." *Id*. ¶41; EX1001, Examples 1, 2, 4–14, 47–49.

Consistent with the 220-nm size limit in the examples, it is generally understood that the plain meaning of "about" in the context of particle sizes includes variations of 10%. EX1002 ¶57; *see Apotex, Inc. v. Cephalon, Inc.*, 2012 WL 1080148, *2 (E.D. Pa. Mar. 28, 2012); *Waddington N. Am., Inc. v. Sabert Corp.*, 2010 WL 4363137, *6 (D.N.J. Oct. 27, 2010); *Wyeth v. Lupin Ltd.*, 579 F. Supp. 2d 711, 720 (D. Md. 2008).

Accordingly, the broadest reasonable interpretation of "a particle size of less than about 200 nm" includes a particle size of 220 nm or less, which is 10% above the stated size of 200 nm. EX1002 ¶57.

C. "about 0.5% to about 5% by weight of albumin" and "about 5% by weight of albumin"

Similarly, the broadest reasonable interpretation of the albumin concentration limitations in claims 1 and 6 includes variations of 10%. Thus, "about 5% by weight of albumin" in claim 6 includes 4.5% by weight of albumin. EX1002 ¶58.

"In determining how far beyond the claimed range the term 'about' extends the claim," the Board should "focus on the criticality of the numerical limitation to the invention." *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1368 (Fed. Cir. 2008) (quotation and alterations omitted). Thus, it is appropriate to "look to the purpose that the 'about [5%]' limitation serves, to determine how much [lower] than [5%] the [concentration] can be and still serve that purpose." *Id*.

Petitioner is not aware of any evidence that the concentration by weight of albumin is critical to the claimed invention. But even assuming that the concentration "is crucial," the '229 patent "shows that [concentrations] below [5%] are effective," and thus "the word 'about' extends the range of the claim downward." *Cent. Admixture Pharmacy Servs., Inc. v. Advanced Cardiac Sols., P.C.*, 482 F.3d 1347, 1356 (Fed. Cir. 2007). Thus, while it is unnecessary for purposes of this Petition to determine the outer limits of the "about 5%" term, it at least includes concentrations that are 10% lower—*i.e.*, 4.5%. EX1002 ¶58.

VII. ANALYSIS OF GROUNDS FOR TRIAL

A. GROUND I: ANTICIPATION UNDER 35 U.S.C. §102(b)

Claims 1–19 and 21–48 are anticipated by Desai (EX1006).

1. Claim 1 is anticipated.

Claim 1 of the '229 patent states the following, with bracketed letters added to delineate its four limitations: "**[a]** A liquid pharmaceutical composition for injection comprising paclitaxel and a pharmaceutically acceptable carrier, wherein

the pharmaceutically acceptable carrier comprises albumin, **[b]** wherein the albumin and the paclitaxel in the composition are formulated as particles, wherein the particles have a particle size of less than about 200 nm, **[c]** wherein the weight ratio of albumin to paclitaxel in the composition is about 1:1 to about 9:1, **[d]** wherein the liquid pharmaceutical composition comprises about 0.5% to about 5% by weight of albumin, and wherein the liquid pharmaceutical composition further comprises saline." Desai anticipates this claim. EX1002 ¶100.

a. Albumin-paclitaxel combination

First, Example 1 of Desai discloses the combination of paclitaxel and albumin as a carrier. EX1006, 62. Desai makes clear that these components are formulated as a liquid pharmaceutical composition for injection. EX1002 ¶101. Example 1 states that "[t]he dispersion was further lyophilized," and "[t]he resulting cake could be easily reconstituted to the original dispersion by addition of sterile water or saline." *Id*. at 63. This lyophilization process "produces a sterile solid formulation useful for intravenous injection," and "a lyophilized powder" is useful "for reconstitution and intravenous administration." *Id*. at 26, 28. Moreover, Desai as a whole is directed to "particulate vehicles for the intravenous administration of pharmacologically active agents," and describes albumin as a "carrier protein[]" and "the natural carrier of the drug in the blood stream." *Id*. at 3, 25. Thus, Desai

discloses claim 1's limitation requiring "[a] pharmaceutical composition for injection comprising paclitaxel and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises albumin." EX1002 ¶101.

b. Particle size of less than about 200 nm

Second, Example 1 of Desai discloses a method of producing albumin-paclitaxel nanoparticles with a typical average diameter of 160–220 nm, measured as the Z-average diameter using a Malvern Zetasizer. EX1006, 63. These average diameters all fall within the "about 200 nm" limitation of claim 1 (which, as discussed in Section VI.B, includes particles of 220 nm or less). Thus, Example 1 necessarily produces a product that satisfies claim 1's "about 200 nm" limitation. EX1002 ¶102. Moreover, Desai's overall "preferred size range of the particles is between about 50 nm – 170 nm," which falls entirely below the "about 200 nm" limit of claim 1. EX1006, 54. *See Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985).

In addition, Desai "enables the reproducible production of unusually small nanoparticles of less than 200 nm diameter." EX1006, 1; *id*. at 23, 52, 54; EX1002 ¶104. Accordingly, Desai discloses claim 1's limitation requiring that "the albumin and the paclitaxel in the composition are formulated as particles, wherein the particles have a particle size of less than about 200 nm." EX1002 ¶105.

c. Albumin-paclitaxel ratio of about 1:1 to 9:1

Third, Example 1 of Desai discloses an albumin-paclitaxel ratio of about 9:1 by providing that "30 mg paclitaxel is dissolved in 3.0 ml methylene chloride," which "was added to 27.0 ml of human serum albumin solution (1% w/v)." EX1006, 62. A skilled artisan would have known that 27 ml of 1% (w/v) albumin contains 270 mg of albumin, which, when combined with 30 mg of paclitaxel, necessarily results in a composition with an albumin-paclitaxel weight ratio of 270:30—*i.e.*, 9:1. EX1002 ¶107. That is an express disclosure of the claimed 9:1 ratio. Even if Patent Owner were to argue that it is not expressly disclosed because the language "9:1" does not appear, the listing of the ingredients and their amounts in the example is still an inherent disclosure of the claimed ratio. *See In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1373 (Fed. Cir. 2007).

Thus, Desai discloses claim 1's limitation requiring that "the weight ratio of albumin to paclitaxel in the composition is about 1:1 to about 9:1." EX1002 ¶107.

d. Weight concentration of albumin

Fourth, Desai discloses a percentage range of about 0.5–5% by weight of albumin, and discloses that the composition comprises saline. *Id*. ¶108. One "object of [Desai's] invention [is] to administer paclitaxel at concentrations greater than about 2 mg/ml," and Example 37 discloses paclitaxel concentrations including 1 mg/ml and 5 mg/ml. EX1006, 35, 116. These disclosures apply to Example 1,

which provides that its composition is "easily reconstituted to the original dispersion by addition of … saline." *Id*. at 63; EX1002 ¶108.

At concentrations of 1, 2, or 5 mg/ml of paclitaxel in saline, Example 1's composition—with an albumin-paclitaxel ratio of 9:1—necessarily contains albumin concentrations of 9, 18, and 45 mg/ml, respectively, corresponding to 0.9%, 1.8%, and 4.5% of albumin. EX1002 ¶109. These weight percentages fall within claim 1's limitation that "the liquid pharmaceutical composition comprises about 0.5% to about 5% by weight of albumin." *Id*.

Independently, Desai discloses a range of paclitaxel concentrations of 0.1–20 mg/ml. EX1006, 28, 32, 39; EX1002 ¶110. Example 37 more narrowly exemplifies a range of paclitaxel concentrations of 1–15 mg/ml. EX1006, 116. As applied to Example 1's 9:1 albumin-paclitaxel ratio, Desai's broader range corresponds to albumin concentrations of 0.09–18%, whereas Example 37's narrower range corresponds to albumin concentrations of 0.9–13.5%. *Id*.

"When a patent claims a range," and "the prior art discloses its own range," that prior art is "anticipatory if it describes the claimed range with sufficient specificity such that a reasonable fact finder could conclude that there is no reasonable difference in how the invention operates over the ranges." *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015). The Federal Circuit has emphasized the "importance of establishing the criticality of a claimed range to the

claimed invention in order to avoid anticipation by a prior art reference disclosing a broader, overlapping range." *Id.* at 870.

Here, nothing suggests that the claimed range of concentrations is "critical to the invention" or that there is any "considerable difference between how the [invention] would operate within the claimed range and within the range disclosed in the prior art." *Id.*; EX1002 ¶110. Accordingly, the range disclosed by Desai anticipates the range of claim 1. *Id.*; *Mylan Pharms. Inc. v. Allergan, Inc.*, IPR2016-01127, Paper 8 at 18–19 (PTAB Dec. 8, 2016) (instituting review for anticipation where "there is insufficient evidence demonstrating the criticality of the claimed amounts or any difference across the range disclosed in the prior art"). Desai thus discloses each limitation of claim 1 and anticipates it. EX1002 ¶110.

2. Claims 3 and 6 are anticipated.

Claim 3 depends from claim 1 and requires that the composition is free of Cremophor—no Cremophor is added to the composition of Example 1 of Desai. EX1006, 62–63. Thus, Desai anticipates claim 3. EX1002 ¶111.

Claim 6 requires "about 5% by weight of albumin." Again, Example 37 of Desai exemplifies a paclitaxel concentration of 5 mg/ml (EX1006, 116), which, applied to a 9:1 albumin-paclitaxel ratio, corresponds to 4.5% of albumin (EX1002 ¶112). As discussed in Section VI.C, a skilled artisan would understand that "about 5%" includes 4.5% albumin. Moreover, Desai discloses a range of

paclitaxel concentrations of 0.1–20 mg/ml, and Example 37 exemplifies a range of 1–15 mg/ml. *Id*. at 28, 32, 39, 116. As applied to a 9:1 albumin-paclitaxel ratio, Desai's broader range corresponds to albumin concentrations of 0.09–18%, whereas Example 37's narrower range corresponds to albumin concentrations of 0.9–13.5%. EX1002 ¶113.

For the same reasons discussed for claim 1, there is no evidence that the claimed range of about 5% is "critical to the invention" or that there is any "considerable difference between how the [invention] would operate within the claimed range and within the range disclosed in the prior art." *Ineos*, 783 F.3d at 870. Accordingly, claim 6 is anticipated. EX1002 ¶113.

3. Claims 15, 19, and 21–23 are anticipated.

Claim 15 claims "[a] sealed container" containing a pharmaceutical composition for injection that meets the first three limitations of claim 1. The only differences between claims 15 and 1 is that the former is directed to "[a] sealed container" instead of "[a] liquid pharmaceutical composition" comprising 0.5–5% albumin and saline. EX1002 ¶114.

As discussed for claim 1, Desai discloses a composition that meets each of claim 15's limitations. *Id*. ¶115. Further, Desai's "Summary of the Presently Preferred Manufacturing Process" instructs skilled artisans to fill lyophilized albumin-paclitaxel into vials, "and seal the vials." EX1006, 76–77. A skilled artisan would

understand this instruction applies to Example 1, which discloses a formulation with a 9:1 albumin-paclitaxel ratio that was "lyophilized" to be later "reconstituted." *Id*. at 63. Thus, Desai anticipates claim 15. EX1002 ¶115.

Claims 19 and 21–23 depend from claim 15 and require "a unit dose container," and that the pharmaceutical composition is "a liquid composition," "a dry composition," and "lyophilized," respectively.

Example 38 of Desai—"Unit Dosage Forms for Capxol™"— teaches that "a desired dosage can be filled in a suitable container and lyophilized to obtain a powder containing essentially albumin and paclitaxel in the desired quantity. Such containers are then reconstituted with sterile normal saline or other aqueous diluent to the appropriate volume at the point of use to obtain a homogeneous suspension of paclitaxel in the diluent." EX1006, 116–17. Alternatively, the compositions "may be prepared as a frozen, ready to use solution in bottles or bags that would be thawed at the time of use and simply administered to the patient," "avoid[ing] the lyophilization step." *Id*. at 117.

These disclosures apply to Example 1, which, can be "lyophilized" to a dry "cake [that] could be easily reconstituted to the original dispersion by addition of sterile water or saline." *Id*. at 63. Thus, Desai discloses sealed unit dose containers that meet claim 15's—and are either a liquid composition, a dry composition, and/or lyophilized—anticipating claims 19 and 21–23. EX1002 ¶118.

4. Claims 29, 34, and 38 are anticipated.

Claim 29 claims a method of treating cancer in humans by injecting an effective amount of claim 1's composition. Claims 34 and 38 depend from claim 29 and require that the cancer is lung and breast cancer, respectively. Desai is directed to treating these diseases. *Id*. ¶119. Indeed, Desai's primary objective is providing paclitaxel formulations that are "significantly less toxic and more efficacious than Taxol®" to "increas[e] the efficacy of treatment of cancers." EX1006, 4. Desai "incorporate[s] by reference" many "patents, scientific articles, and other documents" about using paclitaxel to treat cancers. *Id*. at 12–20.

Desai teaches that "[t]he anticancer agent paclitaxel … has remarkable clinical activity in a number of human cancers including cancers of the … breast[] [and] lung." *Id*. at 27. Desai acknowledges that "the delivery of biologics in the form of a particulate suspension allows targeting to organs such as the … lungs," and "result in higher level concentrations of paclitaxel in the … lung." *Id*. at 29–30; *see id*. at 79, 147, 80–81.

Example 45 of Desai discloses a method of treating mammary tumors, concluding that "the intravenous administration of nanoparticles of paclitaxel can be as efficacious as administering the drug in the soluble form"—*i.e.*, as efficacious as Taxol®. *Id*. at 123; *see id*. at 7, 12. Example 58 discloses treatment of "human mammary tumor fragments." *Id*. at 140. Moreover, Desai discloses the injection

of paclitaxel to treat breast cancer, and Examples 65–66 teach a clinical trial design for metastatic breast cancer in humans. *Id*. at 16, 18–20, 27, 159–61. Desai's claims 7, 15, 22, and 28 claim methods of using albumin-paclitaxel nanoparticles to treat tumors/cancers. *Id*. at 162–65.

Accordingly, Desai discloses methods of injecting the composition of claim 1 of the '229 patent to treat cancer—including lung and breast cancer—and therefore anticipates claims 29, 34, and 38. EX1002 ¶122.

5. Claims 7 and 33 are anticipated.

These claims depend from claims 1 and 29, respectively, and require that "the pH in the composition is about 5.0 to about 8.0." Example 1 of Desai teaches that lyophilized albumin-paclitaxel nanoparticles "could be easily reconstituted to the original dispersion by addition of … saline." EX1006, 63. As a skilled artisan would know, saline (sodium chloride) has a pH of 4.5–7.0. EX1027, 6. The composition of Desai's Example 1 resuspended in saline would have a pH between 5.0–8.0, anticipating claims 7 and 33. EX1002 ¶123.

6. Claims 2, 8, 11–14, 16, 24, 27–28, 30, 35, and 39 are anticipated.

These claims require human serum albumin—the albumin used in Desai's Example 1. EX1006, 62. Desai thus anticipates these claims. EX1002 ¶124.

7. Claims 4–5, 9–10, 17–18, 25–26, 31–32, 36–37, and 40–41 are anticipated.

Claims 4, 9, 17, 25, 31, 36, and 40 require an albumin-paclitaxel ratio of 1:1–9:1, whereas claims 5, 10, 18, 26, 32, 37, and 41 require a ratio of about 9:1. Desai's Example 1 discloses a composition with an albumin-paclitaxel ratio of 9:1 (EX1006, 62–63)—anticipating these claims. EX1002 ¶125.

8. Claims 42–48 are anticipated.

These claims require intravenous injection. Desai as a whole concerns "the intravenous administration of pharmacologically active agents," and in Example 1 "[t]he dispersion was further lyophilized"—"[t]he resulting cake could be easily reconstituted to the original dispersion by addition of sterile water or saline." EX1006, 3, 63. Desai explains this "lyophilized powder" is designed "for reconstitution and intravenous administration." *Id*. at 28. Example 45 discloses a method of treating mammary tumors via injection; Example 52 discloses intravenous delivery of albumin-paclitaxel nanoparticles. *Id.* at 122–23, 131–32. Desai's claims 6, 14, 21, and 27 claim intravenous delivery. *Id*. at 162–64. Thus, Desai anticipates claims 42–48. EX1002 ¶¶ 126–127.

9. The "starting" albumin-paclitaxel ratio does not change.

Despite Desai's unambiguous disclosures, Patent Owner has argued in other proceedings that Example 1 of Desai does not disclose an albumin-paclitaxel ratio of about 9:1, because the "final" ratio after following the steps of Example 1 will

supposedly be higher than the "starting" ratio of the ingredients used to make the composition. To support its assertion, Patent Owner has pointed to Desai's disclosure that "Capxol™ is … produced by the method of Example 1," and "each vial of Capxol™ contains 30 mg of paclitaxel and approximately 400 mg of human serum albumin," corresponding to an albumin-paclitaxel ratio of 13.3:1. EX1006, 38. For several reasons, this argument is incorrect and provides no basis to deny review on Ground I.

First, as discussed in Section VI.A, the plain meaning of the "ratio" limitations in the challenged claims includes at least the ratio of starting ingredients used to make the composition. EX1002 ¶56. Again, every example in the '229 patent that mentions an albumin-paclitaxel ratio bases its calculation on the proportion of starting materials—not some materially distinct "final" ratio. *Id*. ¶37. This makes sense. Ordinary formulators—like chefs—typically measure weight ratios of starting ingredients. *Id*. ¶129. Thus, the fact that Example 1 of Desai discloses quantities of paclitaxel and albumin in a 9:1 ratio is sufficient to establish a reasonable likelihood of anticipation.

Second, even if the claims were limited to a "final" ratio, and even if Patent Owner presented extrinsic evidence that the ratio materially changes, any factual dispute at this stage still would have to "be viewed in the light most favorable to

the petitioner … for purposes of deciding whether to institute an *inter partes* review." 37 C.F.R. §42.108(c). Thus, the Board should institute review and defer resolution of any such dispute for trial. *E.g.*, *nXn P'ners, LLC v. Nissan Chem. Indus., Ltd.*, IPR2016-00694, Paper 7 at 18 (PTAB Aug. 31, 2016).

Third, in any event, there is no evidence that Example 1 results in any loss of paclitaxel during manufacturing that would affect the composition's albumin-paclitaxel ratio. There is no mention in Desai of any paclitaxel loss, and no reason why any of Example 1's steps would result in such loss. EX1002 ¶130.

Although Desai indicates that "Capxol™ is merely a shorthand reference to protein-coated paclitaxel nanoparticles produced by the method of Example 1," (EX1006, 38), Example 1's method is not limited to making Capxol™. EX1002 ¶132. The method can produce multiple different embodiments of Desai's albumin-paclitaxel formulation, including one with an albumin-paclitaxel ratio of 9:1. Indeed, a skilled artisan would have understood that the reference to Capxol™ being made according to Example 1 refers to the method of preparing "nanoparticles … by high pressure homogenization" in *general*. *Id*. ¶131; EX1006, 39.

To conclude otherwise defies the laws of nature. As explained by Dr. Berkland, a skilled artisan would *not* have believed that Capxol™, which contains 30 mg paclitaxel and ***400 mg*** albumin, is made using the specific starting materials of Example 1—*i.e.*, 30 mg paclitaxel and ***270 mg*** albumin. EX1002 ¶133. There is

no step in Example 1 in which any additional albumin beyond the initial 270 mg is added, and thus a skilled artisan would not have believed that following the steps of Example 1 and beginning with its starting materials could possibly produce a composition with 400 mg of albumin—*i.e.*, an end product containing 130 mg *more* albumin than the starting materials. *Id*. Rather, a skilled artisan would have understood that Example 1 provides a method of making an albumin-paclitaxel composition *like* Capxol™—but does not necessarily result in Capxol™ itself, which has an albumin-paclitaxel ratio of 13.3:1.

In reviewing Desai, a skilled artisan would have understood that Example 16 is consistent with Example 1 but more specifically describes the production of Capxol™. *Id*. ¶135. Example 16 combines a total of 431 ml of solution containing human serum albumin at a concentration of 3%, corresponding to 12,930 mg of albumin. EX1006, 75. Example 16 uses 1 g (*i.e.*, 1,000 mg) of paclitaxel, which results initially in an albumin-paclitaxel ratio of 12.93:1. *Id*.; EX1002 ¶73. The resulting suspension is sterile filtered using a 200 nm filter before being filled into vials containing 30 mg of paclitaxel, and then lyophilized. EX1006, 76–66.

That filtration step in Example 16 results in a ratio of 13.3:1. EX1002 ¶74. Elsewhere in the specification, Desai states that approximately "97% of the Taxol was recovered after filtration." EX1006, 65. As applied to Example 16, a skilled artisan would expect to recover approximately 97% of the paclitaxel after sterile

filtration, thereby raising the 12.93:1 ratio of albumin to paclitaxel in the starting materials of Example 16 to ***13.3:1***—the ratio for Capxol™ disclosed in Desai. EX1002 ¶74. Thus, a skilled artisan would have understood that the precise method of obtaining Capxol™'s 13.3:1 ratio was disclosed in Example 16—not Example 1—which instead results in a 9:1 ratio. *Id*. ¶135.

Accordingly, any argument that the ratio "changes" during production is incorrect, and claims 1–19 and 21–48 are unpatentable for anticipation.

B. GROUNDS II–III: OBVIOUSNESS UNDER 35 U.S.C. §103(a)

Claims 1–19 and 21–48 also would have been obvious over Desai—either alone (Ground II.A) or in view of Kadima and Liversidge (Ground II.B). Claim 20 would have been obvious over Desai and the Taxol® label (Ground III.A), and optionally in further view of Kadima and Liversidge (Ground III.B).

1. Claim 1 would have been obvious.

a. GROUND II.A: Desai alone

To a skilled artisan in possession of Desai, it would have been obvious to formulate paclitaxel and albumin as a liquid pharmaceutical composition for injection. EX1002 ¶140. Desai is primarily directed to such compositions, and "[t]he two major components of Capxol™"—a preferred embodiment of Desai—"are unmodified paclitaxel and human serum albumin." EX1006, 28. Moreover, the object of Desai is to provide a "pharmaceutically acceptable formulations" (*id*. at 36), and Capxol™ is designed for "intravenous administration" (*id*. at 28, 38).

Further, it would have been obvious to formulate the paclitaxel and albumin as particles with a size less than about 200 nm. EX1002 ¶141. Desai teaches that "[t]he preferred size range of the particles is between about 50 nm–170 nm." EX1006, 54. And in Desai's "preferred embodiment," "the average diameter of the … particles is no greater than about 200 nm," which is "particularly advantageous." EX1006, 38. As Desai explains, "form[ing] nanoparticles of a size that is filterable by 0.22 micron filters"—*i.e.*, particles that will pass through a 220 nm filter, which is smaller than bacteria—"is of great importance and significance, since formulations which contain a significant amount of any protein (*e.g.*, albumin), cannot be sterilized by conventional methods" of removing bacteria from drugs by heating "due to the heat coagulation of the protein." *Id*. at 24.[3]

In preparing nanoparticles smaller than about 200 nm, a skilled artisan as of December 2002 would have reasonably expected success. EX1002 ¶143. Desai explicitly "enables the reproducible production of unusually small nanoparticles of

[3] *See* EX1012, 37 (inventor testimony—"if the size is greater than 200 nanometers, it is not getting through the filter"); EX1026, 29–30 (FDA: sterilizing "filters usually have a rated porosity of 0.22 micron or smaller."); EX1027, 6 (EMEA: "For sterilisation by filtration," "sizes of 0.22μm or less are acceptable").

less than 200 nm diameter." EX1006, 1; *id*. at 23, 52, 54. And as the Federal Circuit confirmed in a similar case, "a person skilled in the art in 2002 would have believed making nanoparticles … could successfully be implemented with a wide variety of drugs," because by then "the use of nanoparticle technology in formulation chemistry had become fairly reliable," and "one of the key benefits of the nanoparticle technology was its simplicity." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014) (quotation omitted).

Accordingly, claim 1's limitations requiring "[a] pharmaceutical composition for injection comprising paclitaxel and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises albumin, wherein the albumin and the paclitaxel in the composition are formulated as particles, [and] wherein the particles have a particle size of less than about 200 nm," would have been obvious. EX1002 ¶¶ 140–144. The remaining limitations require that "the weight ratio of albumin to paclitaxel in the composition is about 1:1 to about 9:1," "the liquid pharmaceutical composition comprises about 0.5% to about 5% by weight of albumin," and "the liquid pharmaceutical composition further comprises saline." As discussed, these limitation are disclosed by Desai. They also would have been obvious over Desai for the following reasons.

i. The albumin-paclitaxel ratio of about 9:1 falls within a range disclosed by Desai.

First, Desai discloses a range of albumin-paclitaxel ratios, and about 9:1 falls within that range. As discussed, Example 1 discloses a 9:1 ratio, and other examples disclose higher ratios—including 9.8:1, 12.9:1, and 13.3:1. For this reason alone, the ratio of about 9:1 falls within a range in the prior art. EX1002 ¶145.

Even assuming (incorrectly) that Example 1 does not disclose a 9:1 ratio, this ratio falls within a range covered by Desai. *Id*. ¶146. As Desai explains, during preparation of the nanoparticles, albumin "is added at a concentration in the range of about 0.05 to 25% (w/v), more preferably in the range of about 0.5%–5% (w/v)." *Id*. at 50. Thus, albumin concentrations as low as 0.05% are encompassed by Desai, and concentrations as low as 0.5% are "preferred."

This preferred range applies to Desai's various examples, which are "non-limiting." *Id*. at 62. As discussed, Example 1 combined 30 mg of paclitaxel with 27.0 ml of 1% albumin (*i.e.*, 270 mg), resulting in an albumin-paclitaxel ratio of 9:1. *Id*. Using the equally preferred 0.5% concentration of albumin, however, would result in only half as much albumin—*i.e.*, an albumin-paclitaxel ratio of 4.5:1. EX1002 ¶147. A ratio of about 9:1 falls between this lower ratio and the higher ratio of 13.3:1 disclosed for Capxol™, even if the "starting" ratio "changes." *Id*.

Because "there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013).

There is no probative evidence of teaching away, unexpected results, or other secondary considerations, and the claimed ratio of about 9:1 is therefore unpatentable. EX1002 ¶¶ 149–151. Indeed, contrary to any alleged "criticality," the '229 patent purportedly enables albumin-paclitaxel ratios from "0.01:1 to about 100:1," and admits that, from this sprawling range, "the ratio of protein to pharmaceutical agent will have to be optimized." EX1001, 11:64–65. That is dispositive: "[I]t is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997).

ii. Desai would have motivated a skilled artisan to lower Capxol™'s albumin-paclitaxel ratio.

Independent of whether Desai discloses a range that includes an albumin-paclitaxel ratio of about 9:1, it would have been obvious to reduce the albumin-paclitaxel ratio of Capxol™, which Desai discloses as 13.3:1 (EX1006, 38), to a ratio of about 9:1. EX1002 ¶152.

First, as Desai explains, "[i]t is desirable to reduce the[] infusion volume[]" of injectable formulations "by developing formulations of paclitaxel that are stable at *higher concentrations* so as to reduce the time of administration." EX1006, 21 (emphasis added). "[T]he delivery of high doses of the pharmacologically active agent in relatively small volumes"—*i.e.*, by increasing the concentration of paclitaxel relative to other ingredients—"minimizes patient discomfort at receiving large volumes of fluid and minimizes hospital stay." *Id*. at 54.

Second, Desai also teaches that "higher doses of paclitaxel result in a higher response rate." *Id*. at 19. Higher doses can be provided by using higher concentrations of paclitaxel in the same volume. As Desai notes, it has been "shown that higher doses of TAXOL up to 250 mg/m^2 produced greater responses (60%) than the 175 mg/m^2 dose (26%) currently approved for TAXOL." *Id*. at 20.

Thus, it would have been obvious that Capxol™ could be improved to provide higher concentrations of paclitaxel by increasing the paclitaxel, reducing the albumin, or both, thereby reducing the albumin-paclitaxel ratio. EX1002 ¶155. Indeed, Desai expressly teaches that it is desirable "to obtain a higher loading of drug into the crosslinked protein shell." EX1006, 79. In other words, Desai teaches increasing the concentration of paclitaxel by increasing the amount of paclitaxel *per particle* relative to the amount of albumin (rather than, for example, increasing the concentration of the reconstituted composition overall). EX1002 ¶155

As a general principle, moreover, formulators seek to maximize the amount of active drug (here, paclitaxel) and minimize excipients (here, albumin). *Id*. ¶156. Therefore, it would have been obvious to optimize the albumin-paclitaxel ratio of Capxol™ and use lower ratios than 13.3:1—including about 9:1—while retaining Capxol™'s other properties. *Id*.

iii. A skilled artisan would have reasonably expected the claimed albumin-paclitaxel ratio of 9:1 to retain stability.

In preparing a formulation with an albumin-paclitaxel ratio of about 9:1, a skilled artisan also would have reasonably expected success. During prosecution, the applicants argued that a skilled artisan would expect that "reducing the albumin/paclitaxel ratio in the albumin-based paclitaxel nanoparticle composition could destabilize the nanoparticle composition," and thus would not have done so. EX1023 ¶21. This argument is incorrect.

Nothing in Desai suggests that Capxol™'s albumin-paclitaxel ratio of 13.3:1 is critical to maintaining stability. EX1002 ¶158. On the contrary, Example 1 uses a 9:1 ratio, and other examples use similar ratios that are lower than 13.3:1. *Id*. Again, Desai teaches that the albumin concentration in its examples can be varied, and encourages "obtain[ing] a higher loading of drug into the crosslinked protein shell" (EX1006, 79)—all without warning about destabilization. EX1002 ¶158. Although Desai discloses that albumin is a stabilizer, there is no reason why a

skilled artisan would have expected a relatively small reduction from a 13.3:1 ratio to a ratio of about 9:1 to have caused any problematic issue of instability. *Id*. ¶158.

Importantly, "[o]bviousness does not require absolute predictability. Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (citation omitted). Desai provides that reasonable expectation by teaching that the presence of albumin on the surface of the particles—and albumin's inherent stabilizing properties—provide stability to the formulation:

> Since albumin is present on the colloidal drug particles (formed upon removal of the organic solvent), formation of a colloidal dispersion which is stable for prolonged periods is facilitated, due to a combination of electrical repulsion and steric stabilization.

EX1006, 25. Indeed, Desai teaches that its albumin-based formulations have "inherent stability." *Id*. at 34, 158. There is no suggestion in Desai that an albumin-paclitaxel ratio above 9:1 is necessary to achieve this stabilizing effect. EX1002 ¶159. A formulation with a ratio of about 9:1 would also have "albumin … present on the colloidal drug particles," and thus Desai teaches that such a formulation would also be "stable for prolonged periods." *Id*. ¶160; EX1006, 25.

Moreover, Desai makes clear that Capxol™ has unusually exceptional stability, suggesting that less albumin could be used while maintaining a sufficiently

stable formulation. Example 38 shows that Capxol™ was reconstituted at concentrations as high as "15 mg/ ml and stored at room temperature," and the "suspension[] was found to be homogeneous for at least three days" with "no change in [particle] size distribution" and "[n]o precipitation." EX1006, 116. By comparison, the then-existing paclitaxel commercial product, Taxol®, was stable for less than "about 24 hours after reconstitution after reconstitution at the recommended concentrations of 0.6–1.2 mg/ ml." EX1006, 116.

Thus, even if reducing the albumin-paclitaxel ratio from 13.3:1 to about 9:1 could cause some reduction in stability, a minor reduction in stability would not have dissuaded a skilled artisan from making that modification with a reasonable expectation of success. EX1002 ¶161. A skilled artisan would have expected even a substantially less stable formulation than Capxol™ to be stable enough for therapeutic and commercial purposes. *Id*. ¶162. Indeed, to meet claim 1's limitation requiring a "liquid pharmaceutical composition for injection," a skilled artisan would only reasonably need to expect stability for just long enough to infuse a therapeutic dose of the drug. *Id*. ¶163.

In any event, a skilled artisan would have been able to optimize the albumin-paclitaxel ratio and verify the composition's expected stability using the same routine methods shown in Example 38 of Desai. EX1002 ¶164; *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367 (Fed. Cir. 2007) ("one skilled in the art would have had

a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation" using "routine testing").

Accordingly, a skilled artisan would have reasonably expected success in maintaining at least adequate, if not excellent, stability in reducing Capxol™'s albumin-paclitaxel ratio of 13.3:1 to about 9:1. EX1002 ¶165.

iv. The claimed albumin weight percentage when the formulation is reconstituted in saline falls within a range disclosed by Desai.

Desai discloses a 0.1–20 mg/ml range of paclitaxel concentrations, and Example 37 exemplifies a 1–15 mg/ml range of paclitaxel concentrations. EX1006, 28, 32, 39, 116. As applied to the obvious 9:1 albumin-paclitaxel ratio discussed above, Desai's broader range corresponds to albumin concentrations of 0.09–18%, whereas Example 37's range corresponds to albumin concentrations of 0.9–13.5%. EX1002 ¶166. Thus, the range of claim 1—"about 0.5% to about 5% by weight of albumin"—falls within a range disclosed in the prior art. *Id*.

There is no "evidence that (1) the prior art taught away from the claimed [albumin range]; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Galderma*, 737 F.3d at 738; EX1002 ¶167. Thus, the claimed range—which Patent Owner has never alleged is critical—would have been obvious. *Id*.

Moreover, Desai makes clear that its compositions can be "reconstituted in … saline." EX1006, 25–26; *see id.* at 54, 58–60. And the composition of Example 1 with a 9:1 albumin-paclitaxel ratio was "reconstituted to the original dispersion by addition of … saline." *Id*. at 63. Thus, it would have been obvious to reconstitute albumin-paclitaxel nanoparticles in saline at the claimed albumin concentration, and claim 1 as a whole would have been obvious. EX1002 ¶167.

b. GROUND II.B: Desai, Kadima, and Liversidge

Claim 1 is also unpatentable over Desai in view of Kadima and Liversidge—a prior art combination that further confirms the claimed albumin-paclitaxel ratio of about 9:1 would have been obvious.

i. Kadima and Liversidge also disclose ranges of albumin-paclitaxel ratios including 9:1.

Kadima explicitly discloses a range of albumin-paclitaxel ratios that includes a ratio of about 9:1. EX1002 ¶169. As Kadima teaches, "[p]aclitaxel and albumin can be present" in its disclosed formulations "in a ratio of about 1:0.5 to about 1:10 (paclitaxel:albumin)"—*i.e.*, an albumin-paclitaxel ratio of about 0.5:1 to about 10:1, which includes about 9:1. EX1004, 32. Selected ratios within this range from 0.5:1 to 10:1 are recited in Kadima's table of expected costs for various formulations. *Id*. at 34; *id*. at 41, 49–50.

Kadima thus would have informed a skilled artisan that pharmaceutically acceptable albumin-paclitaxel formulations could have low albumin-paclitaxel ratios,

and a skilled artisan would have been interested in exploring, with a reasonable expectation of success, such lower ratios in the context of Desai's nanoparticle-based formulations. EX1002 ¶170.

Indeed, Kadima's albumin-paclitaxel ratios are covered by Liversidge, which is directed to nanoparticle-based formulations that include Desai's and the '229 patent's formulations. *Id*. ¶171; EX1005 (titled "Surface Modified Anticancer Nanoparticles"). In particular, Liversidge discloses and claims "[p]articles consisting essentially of 99.9–10% by weight" of an anticancer agent and "0.1–90% by weight" of a surface modifier, where the anticancer agent may be paclitaxel and the surface modifier may be albumin. EX1005, 14:7–14, p. 10 (correcting 14:7), 14:25 (paclitaxel), 16:8 (albumin). Specifically, the percentages disclosed and claimed in Liversidge correspond to a range of albumin-paclitaxel ratios of 0.01:9.99 to 9:1. EX1002 ¶171.

Again, given the overlapping ranges disclosed in Desai, Kadima, and Liversidge, claim 1's albumin-paclitaxel ratio of "about 1:1 to about 9:1" is *prima facie* obvious:

> [A] *prima facie* case of obviousness arises when the ranges of a claimed composition overlap the ranges disclosed in the prior art. Where the claimed ranges are completely encompassed by the prior art, the conclusion that the claims are *prima facie* obvious is even

> more compelling than in cases of mere overlap. Even without complete overlap of the claimed range and the prior art range, a minor difference shows a *prima facie* case of obviousness.

In re Harris, 409 F.3d 1339, 1341 (Fed. Cir. 2005) (citations and alterations omitted). Here, both Liversidge's range of 0.01:9.99 to 9:1 and Kadima's narrower range of 0.5:1 to 10:1 not only "overlap," but entirely "encompass" claim 1's claimed range of about 1:1 to about 9:1, resulting in a *prima facie* case of obviousness that is "compelling"—and that Patent Owner cannot rebut. *Id*.

Further confirming this showing of obviousness, Liversidge explains that "the particular anticancer agent surface modifier combination can be optimized" by skilled artisans employing routine methods, and describes a "simple screening process" for confirming that "[t]he resulting dispersion is stable." EX1005, 7:5–46, 7:35–36; *PAR Pharm.*, 773 F.3d at 1191.

Thus, in addition to being obvious over Desai alone, the claimed albumin-paclitaxel ratio of about 9:1 also would have been obvious over Desai in view of the ranges disclosed in Kadima and Liversidge. EX1002 ¶172.

ii. Kadima teaches additional reasons to lower Capxol™'s 13.3:1 ratio to about 9:1.

Even apart from the prior art's ranges, Kadima reinforces Desai's specific motivations for reducing the albumin-paclitaxel ratio of Capxol™ to a ratio of about 9:1. *Id*. ¶173. Indeed, Kadima specifically teaches a method of adjusting

"the ratio of paclitaxel or derivative thereof to albumin" as a means of achieving "the smallest volumes for administration or lyophilization/reconstitution, which enables more rapid administration" of the drug. EX1004, 12–13. Because Desai similarly teaches the desirability of reducing the infusion volume to provide more rapid administration, it would have been obvious to apply Kadima's method of reducing the albumin-paclitaxel ratio to Desai's disclosure that Capxol™ has an albumin-paclitaxel ratio of 13.3:1. EX1002 ¶173.

Independently, a skilled artisan also would have been motivated to reduce Capxol™'s albumin-paclitaxel ratio in order to obtain a more cost-effective and commercially viable formulation. *Id*. ¶174. As Kadima explains, "[a]lbumin is a cost-limiting component for use in drug stabilization," because "[a]lbumin is an expensive ingredient." EX1004, 10, 33. Reducing its use "as a bulk stabilizer" thus allows the production of pharmaceutical formulations that are relatively "inexpensive to prepare." *Id*. at 10. Kadima illustrates this point with examples of cost differences for various ratios of albumin to paclitaxel—ranging from to $10.70 for a 0.5:1 ratio to $81:90 for a 10:1 ratio. *Id*. at 38. Based on these significant differences, a skilled artisan would have been motivated to reduce Capxol™'s albumin-paclitaxel ratio in order to reduce the cost of producing the formulation. EX1002 ¶174. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120,

1127–28 (Fed. Cir. 2000) (finding "a motivation to combine" based on the teaching that products containing less of an ingredient will "cost less to produce").

It is no answer to say that Kadima's albumin-paclitaxel formulations differ from the nanoparticle-based formulations of Desai. "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. Thus, [Kadima] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck*, 800 F.2d at 1097 (citation omitted). Here, the motivations that Kadima discloses for lowering the albumin-paclitaxel ratio—*i.e.*, reducing the infusion volume, administration time, and cost of production—apply regardless of the type of formulation that is used, including the nanoparticle-based formulations of Desai, such as Capxol™. EX1002 ¶175.

A skilled artisan would have been motivated to apply the teachings of Kadima to Capxol™ while retaining Capxol™'s nanoparticle-based formulation. *Id*. ¶176. As Desai explains, "nanoparticles" "offer several profound advantages"—including "a preferential targeting effect." EX1006, 3, 34. Thus, a skilled artisan applying Kadima's teachings to optimize the albumin-paclitaxel ratio of Capxol™ would otherwise have retained its nanoparticle-based formulation—rendering claim 1 obvious. EX1002 ¶¶ 177–178.

2. Claims 3 and 6 would have been obvious.

Claim 3 requires that the composition is free of Cremophor. Desai renders this limitation obvious by teaching that Capxol is "a cremophor-free formulation," and by predicting "based on animal studies … that a cremophor-free formulation will be significantly less toxic and will not require premedication of patients," which would otherwise be "necessary to reduce the hypersensitivity and anaphylaxis that occurs as a result of cremophor." EX1006, 27–28. Thus, claim 3 would have been obvious. EX1002 ¶181.

Claim 6 requires about 5% by weight of albumin. Again, Desai discloses a broader range of paclitaxel concentrations of 0.1–20 mg/ml, and Example 37 discloses a range of 1–15 mg/ml. EX1006, 28, 32, 39, 116. As applied to a 9:1 albumin-paclitaxel ratio, Desai's broader range corresponds to albumin concentrations of 0.09–18%; Example 37's range corresponds to 0.9–13.5%. EX1002 ¶182. The claimed range of "about 5%" falls within Desai's ranges, and there is no "evidence that (1) the prior art taught away from the claimed [range]; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Galderma*, 737 F.3d at 738; EX1002 ¶182. Accordingly, claim 6 would have been obvious. *Id*.

3. Claims 15, 19, and 21–23 would have been obvious.

It would have been obvious to provide albumin-paclitaxel nanoparticles in a sealed container, as required by claim 15. EX1002 ¶¶ 183–184. Desai's "Summary of the Presently Preferred Manufacturing Process" instructs skilled artisans to fill lyophilized albumin-paclitaxel nanoparticles into vials, and "seal the vials." EX1006, 76–77. Using a sealed container is desirable because it allows the composition to be "stored indefinitely." *Id*. at 86.

Claim 19 and 21–23 require that the composition is "a unit dose container," "a liquid composition," "a dry composition," and "lyophilized," respectively, each of which would have been obvious. EX1002 ¶185.

Example 38 of Desai—titled "Unit Dosage Forms for Capxol™"—teaches that "a desired dosage can be filled in a suitable container and lyophilized," "then reconstituted with sterile normal saline or other aqueous diluent to the appropriate volume at the point of use to obtain a homogeneous suspension of paclitaxel in the diluent." EX1006, 116–17. Alternatively, compositions "may be prepared as a frozen, ready to use solution in bottles or bags that would be thawed at the time of use and simply administered to the patient," which "avoids the lyophilization step in the manufacturing process." *Id*. at 117.

Thus, Desai teaches albumin-paclitaxel nanoparticles that are in a unit dose container or are either a liquid composition, a dry composition, and/or that are lyophilized. EX1002 ¶187. Claims 19 and 21–23 would have been obvious. *Id*.

4. Claim 20 would have been obvious.

Claim 20 depends from claim 15 and requires that the sealed container "is a multi-dose container." This claim would have been obvious over Desai and the Taxol® label (Ground III.A), optionally in view of Kadima and Liversidge (Ground III.B). EX1002 ¶188. The Taxol® label indicates that Taxol® is supplied in "multidose vials." EX1008, 3, 9. Because the albumin-paclitaxel nanoparticles of Desai are disclosed as an improved, alternative formulation of paclitaxel to Taxol®, it would have been obvious to supply the albumin-paclitaxel nanoparticles of Desai in a similar form as Taxol®. EX1002 ¶188; EX1006, 4.

While Desai's formulations provide therapeutic benefits over Taxol®, nothing in Desai suggests any reason not to provide Capxol™ and other embodiments of the claimed invention using Taxol®'s known multi-dose containers. EX1002 ¶189. Indeed, a skilled artisan at the time would have known that, in general, "[f]ormulations suitable for parenteral administration …. may be presented in unit-dose or multi-dose sealed containers." Ex. 1028, 16:24–31. Thus, claim 20 would have been obvious. EX1002 ¶189.

5. Claims 29, 34, and 38 would have been obvious.

Claim 29 claims a method of treating cancer in humans by injecting an effective amount of claim 1's composition. Claims 34 and 38 require that the cancer being treated is lung and breast cancer, respectively.

Desai acknowledges that paclitaxel was known and approved in the United States to treat cancer in humans. EX1006, 7, 12. Desai teaches that "[t]he anti-cancer agent paclitaxel … has remarkable clinical activity in a number of human cancers including cancers of the … breast[] [and] lung." *Id*. at 27. Desai also acknowledges that "delivery of biologics in the form of a particulate suspension allows targeting to … lungs." *Id*. at 29. And nanoparticles were "demonstrated to result in higher level concentrations of paclitaxel in the … lung … when compared to Taxol." *Id*. at 30; *see id*. at 79, 147, 80–81.

Example 45 discloses a method of treating mammary tumors using albumin-paclitaxel nanoparticles; Example 58 discloses treating "human mammary tumor fragments." *Id*. at 122–23, 140. Desai discloses treating breast cancer, and Examples 65–66 teach a clinical trial design to treat breast cancer. *Id*. at 16, 18–20, 27, 159–61. Claims 7, 15, 22, and 28 of Desai claim methods of treating tumors/cancers. *Id.* at 162–65. Thus, it would have been obvious to inject the composition of claim 1 of the '229 patent to treat cancer—including lung and breast cancer—rendering claims 29, 34, and 38 obvious. EX1002 ¶193.

6. Claims 7 and 33 would have been obvious.

Claims 7 and 33 depend from claims 1 and 29, respectively, and require that "the pH in the composition is about 5.0 to about 8.0." Example 1 of Desai provides that the lyophilized composition "could be easily reconstituted to the original dispersion by addition of … saline." EX1006, 63. As a skilled artisan would have known, saline (sodium chloride) has a pH of 4.5–7.0. EX1027, 6; EX1002 ¶194.

Independently, a skilled artisan would have been motivated, with a reasonable expectation of success, to formulate albumin-paclitaxel nanoparticles with a pH of about 5.0–8.0. EX1002 ¶195. It would have been obvious to prepare any injectable drug at physiological pH (7.4). *Id*. As Liversidge taught: "The pH of the aqueous dispersion media can be adjusted by techniques known in the art," including with "phosphate buffered saline, pH 7.4." EX1005, 2:47–49, 7:44–45.

Thus, claims 7 and 33 would have been obvious. EX1002 ¶195; *see* *Mitsubishi Chem. Corp. v. Barr Labs., Inc.*, 718 F. Supp. 2d 382, 401 (S.D.N.Y. 2010), *aff'd*, 435 F. App'x 927 (Fed. Cir. 2011) ("the pH of the solution to be administered via intravenous injection is extremely important"; "[t]he pH of human blood is approximately 7.4"; "[i]t is important that injectables be as compatible with blood as possible, including with respect to pH").

7. Claims 2, 8, 11–14, 16, 24, 27–28, 30, 35, and 39 would have been obvious.

These claims require human serum albumin, which is the albumin recited and exemplified throughout Desai—including for Capxol. EX1002 ¶196; EX1006, 28. Moreover, it would have been obvious to use human albumin, as opposed to other albumins, in a composition designed for administration to humans. EX1002 ¶196. Thus, these claims would have been obvious. *Id*.

8. Claims 4, 5, 9, 10, 17–18, 25–26, 31–32, 36–37, and 40–41 would have been obvious.

Claims 4, 9, 17, 25, 31, 36, and 40 require an albumin-paclitaxel ratio of 1:1–9:1; claims 5, 10, 18, 26, 32, 37, and 41 require a ratio of about 9:1. As discussed in Section VII.B.1, it would have been obvious to use a 9:1 albumin-paclitaxel ratio in view of Desai—either alone or combined with Kadima and Liversidge. Thus, these claims would have been obvious. EX1002 ¶197.

9. Claims 42–48 would have been obvious.

Claims 42–48 require intravenous injection and would have been obvious over Desai, which is directed to "the intravenous administration of pharmacologically active agents." EX1006, 3. Desai explains: "Intravenous drug delivery permits rapid and direct equilibration with the blood stream which carries the medication to the rest of the body." *Id*. at 4. And Capxol™ is designed for "intravenous administration" (*id*. at 28, 38); Examples 45 and 52 exemplify intravenous delivery

(*id.* at 122–23, 131–32); and claims 6, 14, 21, and 27 of Desai are directed to administration routes including intravenous delivery (*id*. at 162–64). Thus, claims 42–48 of the '229 patent would have been obvious. EX1002 ¶198.

10. There is no probative evidence of secondary considerations.

Petitioner is not aware of any probative evidence of secondary considerations that would undermine the showing of obviousness above. *Id*. ¶199. At this stage, moreover, Petitioner has no burden to rebut secondary considerations. Patent Owner must first present a *prima facie* case for such considerations, which Petitioner may then rebut—panels thus routinely reject arguments against institution based on secondary considerations. *E.g.*, *Petroleum Geo-Services Inc. v. WesternGeco LLC*, IPR2014-01478, Paper 18 at 36 (PTAB Mar. 17, 2015).

Nevertheless, out of an abundance of caution, Petitioner preliminarily addresses the alleged unexpected results that the inventor asserted during prosecution—*i.e.*, that a composition with the claimed albumin-paclitaxel ratio of about 9:1 (i) "unexpectedly shows increased cellular binding" and (ii) "showed higher therapeutic efficacy and substantially reduced toxicity." EX1023, 2, 7. As shown below, these arguments fail to establish probative unexpected results.

a. The allegedly "unexpected" cell-binding results lack a nexus to the '229 patent and were expected.

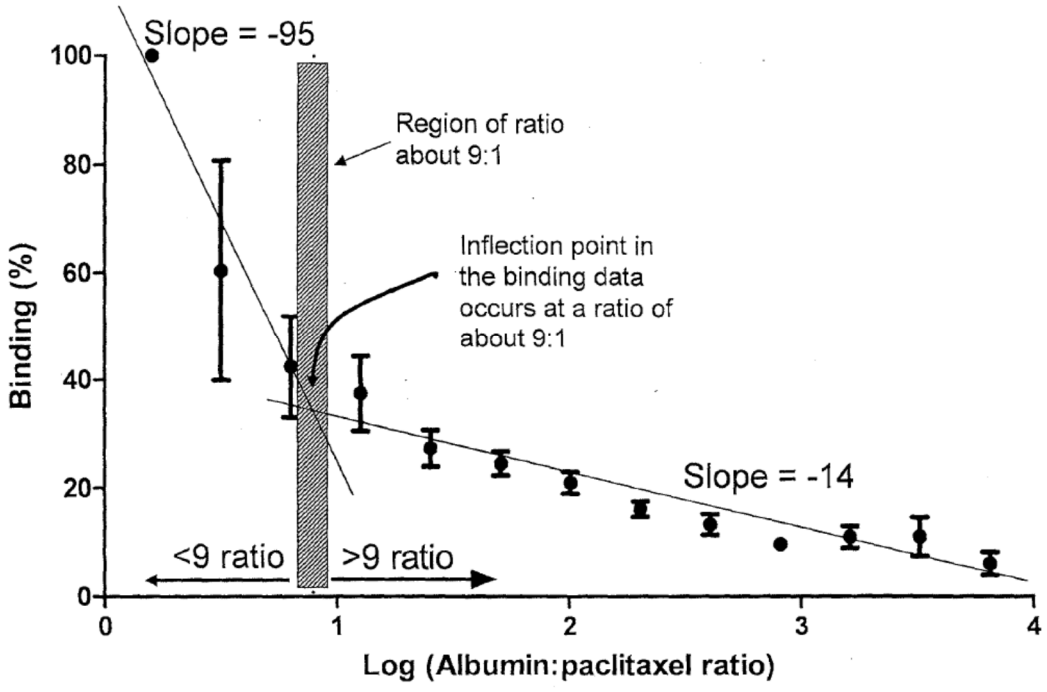
"[F]or objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). Here, for at least two reasons, the "cellular binding" results disclosed in the Inventor Declaration lack the required nexus and relevance to the challenged claims.

First, in performing the "cell-binding" experiment in the Inventor Declaration, the applicants did not test the claimed combination of albumin and paclitaxel. Instead, they tested a *different* combination of albumin and "[*f*]*luorescent* paclitaxel" (EX1023 ¶¶ 9–11)—*i.e.*, a fluorescein-paclitaxel conjugate. EX1002 ¶204. As the '229 patent confirms, the fluorescein-paclitaxel conjugate that the applicants tested, which was commercially available at the time, is sold under the name Flutax®. EX1001, 32:50–34:22 (Examples 40–44, describing use of "Flutax" in albumin-binding experiments).

Importantly, a skilled artisan would have expected Flutax® to have a different molecular weight, different solubility, and different protein-binding properties than paclitaxel. *Id*. ¶205. Indeed, like paclitaxel, fluorescein was also known to bind to human serum albumin. *Id*.; EX1007. As a result, a skilled artisan would not have drawn any conclusions about the cell-binding properties of the combination of paclitaxel and albumin from results obtained with the combination of

Flutax® and albumin, because the results would be equally attributable to the binding of *fluorescein* to albumin as they would be to any relevant properties of paclitaxel. *Id*. The results in the Inventor Declaration lack an adequate nexus to the claimed combination of albumin and paclitaxel for this reason alone. *Id*.

Second, the asserted results also lack a nexus to the challenged claims because the applicants did not test the claimed albumin-paclitaxel ratio of "about 9:1." Rather, as stated in the Inventor Declaration, they tested ratios "*above* about 9:1" and "about 9:1 *or less*." EX1023 ¶14 (emphasis added). This is confirmed by Exhibit 4 to the Inventor Declaration, depicted below, which shows that the tested compositions were *outside* the labeled "[r]egion of ratio about 9:1":



Id. at 19 (Ex. 4). For this reason, too, the results disclosed in the Inventor Declaration lack a nexus to the claimed ratio of "about 9:1." EX1002 ¶206.

Even aside from these nexus problems, a skilled artisan would not have drawn any conclusions from the data depicted above, as the statistical significance of the data was not reported. *Id*. ¶207. Citing the above chart, the Inventor Declaration states that "the effect of the albumin/paclitaxel ratio on the binding of paclitaxel changes dramatically at an albumin/paclitaxel weight ratio of about 9:1." EX1023 ¶14. Yet, given the large, overlapping error bars for the key data points, there is no evidence of *any* "inflection" point, and no basis for extrapolating any trends across the data. EX1002 ¶207.

In any event, a skilled artisan would have expected the results of the experiment. *Id*. ¶208. The Inventor Declaration asserts that it would have been unexpected that "[h]igher albumin/paclitaxel ratios are associated with poor cellular binding of paclitaxel, while lower albumin/paclitaxel ratios are associated with enhanced cellular binding of paclitaxel." EX1023 ¶7. To a skilled artisan, however, that result would have been expected from the experiment's design.

In the experiment, "a hydrophobic surface coated with albumin" was "used to simulate a cellular membrane in a milieu of albumin." *Id*. ¶11. Naturally, as the amount of albumin was increased in the formulation (thereby increasing the albu-

min-paclitaxel ratio), a greater proportion of paclitaxel binded to the albumin in solution, which in turn reduced the paclitaxel that was left available to bind to the hydrophobic surface. EX1002 ¶209. That is exactly what a skilled artisan would have expected. *Id*. The results thus do not suggest any unexpected or even relevant relationship between "cellular binding" and the claimed invention. *Id*.

b. The allegedly "unexpected" clinical data did not compare the closest prior art and were expected.

The clinical results disclosed in the Inventor Declaration are similarly flawed. "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). Here, the allegedly "unexpected" clinical results fail to meet this requirement because they do not compare the ratio of about 9:1 to the closest prior art. EX1002 ¶211.

The clinical data discussed in the Inventor Declaration compared Abraxane®, which allegedly has an albumin-paclitaxel ratio of about 9:1, with "an old formulation developed by [Patent Owner]." EX1023 ¶¶ 23, 17. As the Inventor Declaration states, "[t]he albumin/paclitaxel weight ratio in the old formulation was about 19:1." *Id*. ¶17. However, the "old formulation" with an albumin-paclitaxel ratio of 19:1 is not the closest prior art to the claimed formulation with a ratio of about 9:1. Rather, Example 1 of Desai is the closest prior art because, as discussed, it discloses a composition with an albumin-paclitaxel ratio of 9:1.

EX1002 ¶213. Moreover, other examples in Desai disclose other ratios that are closer to 9:1 than 19:1, including ratios of 9.8:1 and 12.9:1. *Id*.

Even aside from these examples, Capxol™ is closer prior art than the "old formulation" discussed in the Inventor Declaration, because Capxol™ has an albumin-paclitaxel ratio of 13.3:1, which is closer to 9:1 than 19:1. EX1006, 38; EX1002 ¶214. Because the Inventor Declaration does not compare the claimed ratio to the closest prior art, it does not suggest the claimed ratio is nonobvious. *Id*.

For other reasons, moreover, a skilled artisan would not have drawn any conclusions from the clinical data in the Inventor Declaration. The Declaration states that Exhibit 5 shows a lower rate of adverse events in patients taking Abraxane® than in patients taking the 19:1 formulation. EX1023 ¶28; *id*. at 21. As Dr. Berkland confirms, however, there are several problems with these data.

First, the patient group receiving the 19:1 ratio was small (n=22), especially compared to the much larger group receiving Abraxane® (n=104), and no statistical significance was reported. EX1002 ¶217.

Second, the two groups did not receive the same doses: Patients taking Abraxane® received 260 mg/m^2, whereas patients in the 19:1 group received a range of doses up to 350 mg/m^2. Although the mean dose was 250 mg/m^2 (which is lower than the dose given to patients taking Abraxane®), no median is disclosed. Thus, a majority of patients in the 19:1 group could have taken substantially higher

doses, which were known to result in more adverse events—particularly above the 300 mg/m^2 threshold that was administered *only* to the 19:1 group. *Id*. ¶218; EX1018, Ibrahim at 2, 4 (showing dramatic increase in adverse events for albumin-paclitaxel nanoparticles beginning at 300 mg/m^2 dose).

Third, critical details about patient populations and treatment methods that could affect the results are not disclosed—*e.g.*, drug infusion rates and the stage of cancer being treated. EX1002 ¶219.

Fourth, at most, the results suggest that administering Abraxane® instead of the "old formulation" affects the *degree* of adverse effects, but not the *kinds* of effects that paclitaxel formulations were known and expected to produce. *Id*. ¶220. As the Federal Circuit has held, "[u]nexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art." *Galderma*, 737 F.3d at 739 (quotation omitted). Here, while "there are some differences in degree between the properties of [Abraxane® and the 19:1 formulation], the [formulations] expectedly have the same type of biological activity." *In re Merck*, 800 F.2d at 1099. Thus, the Inventor Declaration's clinical "evidence [i]s insufficient to rebut the *prima facie* case" of obviousness. *Id*.

c. Blocking patents prevented others from developing the claimed invention.

Most considerations typically asserted by patentees are not relevant here because, before the '229 patent was filed, Patent Owner held other patents that covered the claimed invention and thus prevented others from developing it.

Patent Owner held the '686 patent (EX1003) and U.S. Patent No. 5,498,421 (EX1014, the "'421 patent"), whose claims cover the '229 patent's subject matter. Both the '686 and '421 patents are listed in the label for Abraxane® (EX1015, 20), the New Drug Application for Abraxane® (EX1016, 20–28), and the Orange Book for Abraxane®, which also lists the '229 patent (EX1025, 31). The '686 patent issued in August 1995, and the '421 patent issued in March 1996. EX1003; EX1014. At least as of those dates, skilled artisans were blocked from developing the claimed invention.[4]

Thus, any "evidence relating to the 'failure of others,' a 'long-felt but unsolved need,' [and] 'commercial success' … is undermined by the fact that those phenomena—to the extent they exist in this case—could have been derived from [Patent Owner's] ownership of [the '686 and '421] patent[s] as much as from the

[4] The Orange Book lists multiple other patents for Abraxane®, including five other expired patents besides the '686 and '421 patents. EX1025, 31.

nonobviousness of [the claimed invention]." *Sanofi-Synthelabo v. Apotex Inc.*, 492 F. Supp. 2d 353, 392 (S.D.N.Y. 2007), *aff'd*, 550 F.3d 1075 (Fed. Cir. 2008).

VIII. CONCLUSION

The Board should institute *inter partes* review and cancel claims 1–48 of the '229 patent as unpatentable.

Dated: April 4, 2017

Respectfully submitted,

/Samuel S. Park/

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

Pursuant to 37 C.F.R. §42.24, I certify that the foregoing PETITION FOR *INTER PARTES* REVIEW contains 13,916 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

Dated: April 4, 2017

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CERTIFICATE OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on April 4, 2017, true and correct copies of the foregoing PETITION FOR *INTER PARTES* REVIEW, and all Exhibits thereto, were served by FedEx overnight delivery on Patent Owner at the correspondence address of record for U.S. Patent No. 8,138,229 B2, and at another address known as likely to effect service, as follows:

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