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Paper 7
Entered: October 10, 2017

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

Before JEFFREY N. FREDMAN, RAMA G. ELLURU, and SUSAN L. C. MITCHELL, *Administrative Patent Judges.*

FREDMAN, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

A. Background

Petitioner Actavis LLC ("Petitioner") filed a Petition (Paper 2, "Pet.") requesting an *inter partes* review of claims 1–48 (the "challenged claims") of U.S. Patent No. 8,138,229 B2 (Exhibit 1001, "the '229 patent"). *See* 35 U.S.C. §§ 311–319. Patent Owner Abraxis Bioscience, Inc. ("Patent Owner") filed a Preliminary Response. Paper 6 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314 and 37 C.F.R. § 42.4(a). To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). For the reasons set forth below, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one of the challenged claims of the '229 patent. Therefore, we institute an *inter partes* review for claims 1–48 of the '229 patent.

B. Related Proceedings

Petitioner indicates that the '229 patent was asserted in *Abraxis BioScience, LLC v. Actavis LLC,* C.A. No. 16-1925-JMV-MF and in *Abraxis BioScience, LLC v. Cipla Ltd.,* C.A. No. 16-9074-JMV-MF. Pet. 4. Petitioner has also filed three additional requests for *inter partes* review of other patents owned by Abraxis, two of which are related to the '229 patent: IPR2017-01100 (involving U.S. Patent No. 8,853,260); IPR2017-01101 (involving U.S. Patent No. 7,820,788); and IPR2017-01103 (involving U.S. Patent No. 7,923,536). *Id*.

C. The '229 Patent (Ex. 1001)

The '229 patent involves methods of formulating pharmaceuticals with carriers to "reduce one or more side effects." Ex. 1001 at 3:57–62. Such methods specifically involve formulating taxol (paclitaxel), an agent active against carcinomas, (*id*. at 4:33–35), with albumin, a protein found in human plasma (*id*. at 5:7–18).

The '229 patent specifically prefers that the composition "have a particle or droplet size less than about 200 nanometers" (*id*. at 9:55) and a "ratio of albumin to pharmaceutical agent in the pharmaceutical composition [that] is about 18:1 or less" (*id*. at 3:28–29). It is also stated in the '229 patent that:

> While the ratio of protein to pharmaceutical agent will have to be optimized for different protein and pharmaceutical agent combinations, generally the ratio of protein, e.g., albumin, to pharmaceutical agent is about 18:1 or less (e.g., about 15:1, about 10:1, about 5:1, or about 3:1). More preferably, the ratio is about 0.2:1 to about 12:1. Most preferably, the ratio is about 1:1 to about 9:1.

Id. at 11:64 to 12:3. The '229 patent also prefers a formulation "essentially free of cremophor" because "cremophor typically is used as a solvent for paclitaxel, and is associated with side effects that can be severe" (*id*. at 12:7–9).

D. Illustrative Claims

Of the challenged claims, claim 1 is the sole independent claim of the '229 patent. The remaining challenged claims 2–48 depend directly or indirectly from claim 1. Claim 1 is illustrative of the challenged claims and recites:

> 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.

Ex. 1001, 37:19–29.

E. The Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable based on the following grounds. Pet. 1–6.

References	Basis	Claims Challenged
Desai[1]	§ 102(b)	1–19 and 21–48
Desai	§ 103(a)	1–19 and 21–48
Desai, Kadima,[2] and Liversidge[3]	§ 103(a)	1–19 and 21–48
Desai and Taxol label[4]	§ 103(a)	20
Desai, Taxol label, Kadima, and Liversidge	§ 103(a)	20

Petitioner relies also on the Declaration of Cory Berkland, Ph.D. Pet. 1–83; *see* Ex. 1002.

[1] WO 99/00113 A1, published Jan. 7, 1999 (Ex. 1006, "Desai").
[2] WO 00/06152 A1, published Feb. 10, 2000 (Ex. 1004, "Kadima").
[3] US 5,399,363, issued Mar. 21, 1995 (Ex. 1005, "Liversidge").
[4] Physicians' Desk Reference® 309, 881–887 (54th ed. 2000) "Taxol® (paclitaxel) Injection" (Ex. 1008, "Taxol® label")

II. ANALYSIS

A. Claim Interpretation

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under the broadest reasonable interpretation approach, claim terms are given their ordinary and customary meaning as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). We determine that the following claim language needs to be discussed.

1. *"the weight ratio of albumin to paclitaxel in the composition"*

Petitioner offers an interpretation of the claim phrase "the weight ratio of albumin to paclitaxel in the composition" as at least "the albumin-paclitaxel ratio in the starting ingredients used to make the composition." Pet. 18 (citing Ex. 1002 ¶¶ 37, 56). Petitioner states a "skilled artisan reading [the '229 patent's] examples would understand that the 'ratio of albumin to paclitaxel' was based on the amounts used to make the composition." Pet. 19 (citing Ex. 1002 ¶ 37).

Patent Owner disagrees, and offers an interpretation that the "claimed ratio term should be construed to mean the weight ratio of albumin-to-paclitaxel in the *finished* pharmaceutical composition for injection." Prelim. Resp. 11 (emphasis added). Patent Owner states

> the claim requires that the ratio be of the albumin to paclitaxel "in the composition," and that "composition" is plainly the claimed "pharmaceutical composition for injection" —*i.e.*, the finished pharmaceutical product. (*Id.*, claims 1 and 15.) . . .

> Thus, based on the plain claim language, the ratio refers to the claimed finished pharmaceutical product, not the albumin and paclitaxel starting materials prior to the formation of the nanoparticles.

Prelim. Resp. 11–12. Patent Owner notes "the prosecution history confirms this construction . . . The Examiner . . . understood that the 9:1 ratio was referring to the finished nanoparticle pharmaceutical composition." Prelim. Resp. 13.

We agree with Patent Owner's proposed construction at this stage of the proceeding on the record before us. The '229 patent claims use the definite article "the" in providing antecedent basis for "the composition" in the claim phrase "the weight ratio of albumin to paclitaxel in the composition." *See* '229 patent, claim 1. The article "the" refers to "a pharmaceutical composition" that is injected into an individual with cancer. *See* '229 patent, claim 1. Therefore, the reasonable intrinsic interpretation requires "the composition" to be the "pharmaceutical composition." *See Warner–Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1356 (Fed. Cir. 2003) ("[I]t is a rule of law well established that the definite article 'the' particularizes the subject which it precedes. It is a word of limitation as opposed to the indefinite or generalizing force of 'a' or 'an.'" (internal quotation omitted)).

Consequently, the reasonable interpretation of the "pharmaceutical composition" is that it refers to the final product because it is injected into the patient. Thus, we agree with Patent Owner on this record that the 9:1 ratio of "the composition" in claim 1 of the '229 patent must be the ratio of albumin to paclitaxel in the final product injected into the patient. We also agree with the Patent Owner that the Specification of the '229 patent and the

prosecution history also tend to support this interpretation, but we need not rely on such evidence here to construe the claim term at this stage of the proceeding as the plain language of the claim supports our interpretation. *See* Prelim. Resp. 11–13.

2. *"a particle size of less than about 200 nm"*

Petitioner offers an interpretation of the claim term "a particle size of less than about 200 nm" to "include[] particle sizes of 220 nm or less, measured as the Z-average diameter using a Malvern Zetasizer." Pet. 21 (citing Ex. 1002 ¶ 57). Petitioner points out that "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).'" Pet. 21 (citing Ex. 1002 ¶ 41; Ex. 1001, Examples 1, 2, 4–14, 47–49).

Patent Owner states that except for the claim term discussed above, "[a]ny other terms do not need construction as they are not determinative of any dispute presented by the Petition." Prelim. Resp. 17.

Because the parties do not disagree about whether the art teaches the claimed particle sizes, *see* Pet. 21; Prelim. Resp. 17, and our decision does not require an express construction to resolve any dispute at this point in the proceeding, we do not need to interpret expressly the claim term "a particle size of less than about 200 nm." *See, e.g., Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999)).

3. *"about 5% by weight of albumin"*

Petitioner offers an interpretation that "about 5% by weight of albumin" in claim 6 includes 4.5% by weight of albumin." Pet. 21.

As already noted, Patent Owner states that "[a]ny other terms do not need construction as they are not determinative of any dispute presented by the Petition." Prelim. Resp. 17.

Because the parties do not appear to disagree about whether the art teaches the claimed particle sizes, *see* Pet. 21; Prelim. Resp. 17, and our decision does not require an express construction to resolve the dispute, we do not need to interpret expressly the claim term "about 5% by weight of albumin" at this point in the proceeding. *Wellman*, 642 F.3d at 1361.

B. Section 325(d) – Discretion to Decline to Institute

Patent Owner urges us to decline to institute the asserted grounds under 35 U.S.C. § 325(d) because the ground "Petitioner's asserted art was already before the Office, and Petitioner's arguments based on that art are the same or substantially the same as what the Office considered (*i.e.*, that the skilled person would have optimized the ratio of albumin to paclitaxel in the composition)." Prelim. Resp. 17–18 (citing Pet. 14). Patent Owner concludes that "[b]ecause Desai provides no relevant disclosures beyond that which the Office considered regarding [another reference], Petitioner's use of Desai adds nothing new . . . . Without any new evidence or other reason to revisit the Examiner's determinations, the Petition merely seeks to have the Board second-guess the Examiner." *Id*. at 19–20.

Under § 325(d), we have discretion to "reject the petition or request because[] the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). Considering

all of the relevant facts and circumstances, Patent Owner's argument is insufficient to persuade us to exercise our discretion to deny the Petition. For example, Petitioner relies on a declaration from Dr. Berkland, which Patent Owner does not allege are duplicative of evidence previously presented to the Office, and Desai was not prior art upon which the Examiner relied for any rejection. *See Tandus Flooring, Inc. v. Interface, Inc*., Case IPR2013-00333, 2013 WL 8595289, at *2 (PTAB Dec. 9, 2013) (Paper 16) (declining to deny petition under § 325(d) where petitioner presented new declaration evidence); *Chimei Innolux Corp. v. Semiconductor Energy Lab. Co*., Case IPR2013-00066, 2013 WL 8595548, at *5 (PTAB Apr. 24, 2013) (Paper 10) (same). Also, the Examiner relied upon testimonial evidence that was not subject to cross-examination in determining patentability of the claims that are contested in this proceeding. *See* Ex. 1023. We, therefore, determine that Petitioner's petition does not present the same or substantially the same prior art or arguments previously presented to the Office.

C. Principles of Law

A claim is unpatentable under 35 U.S.C. § 102 if a single prior art reference expressly or inherently describes each and every limitation as set forth in the claim. *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1375 (Fed. Cir. 2005); *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987). "A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014) (citing *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003)).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In that regard, an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person having ordinary skill:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established

functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We are mindful that the level of ordinary skill in the art also is reflected by the prior art of record.[5] *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc*., 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

D. Anticipation by Desai

Petitioner contends that claims 1–19 and 21–48 are unpatentable under 35 U.S.C. § 102(b) as anticipated by Desai. Pet. 22; *see* Prelim Resp. 21. Petitioner asserts that "Desai as a whole is directed to 'particulate vehicles for the intravenous administration of pharmacologically active agents,'"; that "Example 1 of Desai discloses a method of producing albumin-paclitaxel nanoparticles with a typical average diameter of 160–220 nm"; and that "Example 1 of Desai discloses an albumin-paclitaxel ratio of about 9:1" (Pet. 22–25).

[5] Petitioner states that the level of skill in the art at the time of the invention is a person who has a "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." Pet. 7 (citing Ex. 1002 ¶ 20). Patent Owner "adopts Petitioner's definition of a POSA." *See* Prelim. Resp. 10. We, therefore, apply Petitioner's stated level of ordinary skill in the art, which is supported by Dr. Berkland, because of the sophistication of the technology and the educational level of those who work in this area. *See In re GPAC*, 57 F.3d at 1579.

Petitioner asserts with regard to the albumin-paclitaxel ratio that:

> 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.

(Pet. 25).

Patent Owner asserts that this ground fails, among other reasons, because "Petitioner relies on its incorrect construction of the ratio term as referring to the amounts of the starting ingredients as opposed to the finished nanoparticle composition" and "the measurements in Example 1 concern the *starting amounts* of the albumin and paclitaxel ingredients—*before* the many steps are conducted that are required to form a composition." Prelim. Resp. 22. Patent Owner asserts

> as explained by Patent Owner's declarant and nanoparticle formulation expert, Dr. Nicholas A. Peppas (EX2001), a POSA would understand that the process described in Example 1 would lead to substantial loss of paclitaxel, and thus the finished pharmaceutical product would have a higher ratio of albumin to paclitaxel than the 9:1 starting ratio.

Prelim. Resp. 26. Patent Owner asserts this loss of paclitaxel is based on evidence showing "paclitaxel rapidly and nonspecifically adsorbs (sticks and

accumulates) to most surfaces, including plastic, glass, and metal." Prelim. Resp. 27.

1. Desai (Ex. 1006)

Desai teaches using "anti-cancer drugs, e.g., Taxol, in the form of nanoparticles." Ex. 1006, 26:12–13.

> Capxol™ is a novel, cremophor-free formulation of the anticancer drug paclitaxel . . . . Capxol™ is a lyophilized powder for reconstitution and intravenous administration. When reconstituted with a suitable aqueous medium such as 0.9% sodium chloride injection or 5% dextrose injection, Capxol™ forms a stable colloidal solution of paclitaxel. The size of the colloidal suspension may range from 20nm to 8 microns with a preferred range of about 20-400 nm. The two major components of Capxol™ are unmodified paclitaxel and human serum albumin (HSA).

Ex. 1006, 27:29 to 28:13. Desai teaches "Capxol™ is merely a shorthand means of reference to protein-coated paclitaxel nanoparticles produced by the method of Example 1" and that "[e]ach vial of Capxol™ contains 30 mg of paclitaxel and approximately 400 mg of human serum albumin." Ex. 1006, 38:17–29. Example 1 of Desai teaches

> 30 mg paclitaxel is dissolved in 3.0 ml methylene chloride. The solution was added to 27.0 ml of human serum a[l]bumin solution (1% w/v). The mixture was homogenized for 5 minutes at low RPM (Vitris homogenizer, model: Tempest I.Q.) in order to form a crude emulsion, and then transferred into a 30 high pressure homogenizer (Avestin). The emulsification was performed at 9000-40,000 psi while recycling the emulsion for at least 5 cycles. The resulting system was transferred into a Rotary evaporator, and methylene chloride was rapidly removed at 40°C, at reduced pressure (30 mm Hg), for 20-30 minutes. The resulting dispersion was translucent, and the typical diameter of the resulting paclitaxel particles was 160-220 (Z-average, Malvern Zetasizer).

Ex. 1006, 62:25 to 63:6.

In Example 4, Desai teaches the "dispersion is filtered through a 0.22 micron filter (Millipore), without any significant change in turbidity, or particle size. HPLC analysis of the Taxol content revealed that more than 97% of the Taxol was recovered after filtration." Ex. 1006, 65:24–27. Example 16 of Desai summarizes a preferred manufacturing process with 1 gram of paclitaxel and 431 ml of a 3% albumin solution that is filtered during the manufacturing process. Ex. 1006, 75:17 to 77:24.

2. Analysis

Petitioner asserts "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." Pet. 33. Petitioner asserts "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." Pet. 34 (citing Ex. 1002 ¶ 130). Petitioner supports this assertion by noting

> a skilled artisan would have understood that Example 16 is consistent with Example 1 but more specifically describes the production of Capxol™ . . . 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 ¶64. 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. . . . 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.

Pet. 35–36, citing Ex. 1002 ¶ 74.

In addition, Petitioner's Declarant, Dr. Berkland, states regarding Example 49 of the '229 patent that: "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." Ex. 1002 ¶ 39. Dr. Berkland concludes "therefore, the albumin-paclitaxel ratio of Example 49 was either 'calculated' based on the starting materials, or measured after the process steps were completed, at which point the ratio remained the same as the ratio of starting materials." *Id*. Dr. Berkland also points out that: "There is no suggestion in the '229 patent that the ratio of albumin to paclitaxel materially changes during the manufacturing process. Nor is there any disclosed assay or discussion of how to measure or predict the ratio of albumin to paclitaxel in the final pharmaceutical composition." *Id*. ¶ 40.

Patent Owner asserts that

> Example 1's method is used to produce Capxol™, and "[e]ach vial of Capxol™ contains 30 mg of paclitaxel and approximately 400 mg of human serum albumin," *i.e.*, a 13.3:1 albumin-to-paclitaxel ratio for the finished product. (EX1006, 36:16–19, 28–29.) Thus, the ratio of albumin to paclitaxel does not remain 9:1 for the finished product. Rather, the ratio increases almost 50%.

Prelim. Resp. 23. Patent Owner further asserts "Petitioner attempts to run away from this confirmation by incorrectly arguing that a POSA would understand that Capxol™ was produced not by Desai's Example 1, but rather by its Example 16." *Id*. at 23. Patent Owner asserts "Petitioner's assertion is directly contradicted by the explicit teachings of Desai, which

clearly states that "'Capxol™ . . . is produced by the method of Example 1.'" *Id*. at 23–24.

> Patent Owner also asserts that
>
> as explained by Patent Owner's declarant and nanoparticle formulation expert, Dr. Nicholas A. Peppas (EX2001), a POSA would understand that the process described in Example 1 would lead to substantial loss of paclitaxel, and thus the finished pharmaceutical product would have a higher ratio of albumin to paclitaxel than the 9:1 starting ratio.

Prelim. Resp. 26 (citing Ex. 2001 ¶¶ 28–36). Patent Owner further asserts that: "Due to its notoriously high hydrophobicity and other properties, paclitaxel rapidly and nonspecifically adsorbs (sticks and accumulates) to most surfaces, including plastic, glass, and metal." Prelim. Resp. 27, citing Ex. 2001, 2031–2036.

We are not persuaded that Desai's Example 1 is necessarily used to produce Capxol™. Rather, we agree with Petitioner's interpretation of Desai's statement that Capxol™ is "produced by the method of Example 1" as exemplary, rather than limiting. Because Example 1 of Desai only combines 30 mg of paclitaxel with 270 mg albumin, Petitioner's interpretation is consistent with Desai's further statement, in the same paragraph, that: "Each vial of Capxol™ contains 30 mg of paclitaxel and approximately 400 mg of human serum albumin." Ex. 1006, 36:17–29. If Example 1 were the process used to produce Capxol™, the amounts of albumin should be identical, not different.

We further agree that the current evidence of record, as supported by Dr. Berkland, better supports the position that Example 16 represents the process used to produce Capxol™ itself. Specifically, Example 16 is titled

"[p]resently [p]referred [m]anufacturing [p]rocess" and exemplifies filling vials with 30 mg of paclitaxel. Ex. 1006, 73:16–17, 74:23–24; Ex. 1002 ¶¶ 72–73. Example 1 is therefore reasonably read as one of several alternative embodiments shown by Desai that was not the final process used to produce Capxol™. *See* Ex. 1002 ¶ 75.

Furthermore, Example 4 of Desai could be reasonably understood as teaching a specific working example demonstrating an actual experiment where 97% of the starting amount of Taxol is recovered after filtration. Ex. 1006, 63:9–28.[6]

Thus, as Petitioner points out, the manufacturing process of Example 16 results in a 12.93:1 ratio, and based on Example 4, "one 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, *i.e.*, the ratio of Capxol as disclosed in Desai." Ex 1002 ¶ 74; Pet. 35–36.

Example 1 is therefore reasonably read as one of several alternative embodiments shown by Desai that was not the final process used to produce Capxol™, while Example 16 is a process that matches the ratios used to produce Capxol™. *See* Ex. 1002 ¶¶ 74–75.

Therefore, on this record, the combination of teachings in Example 1 of Desai of a 9:1 starting ratio of albumin to paclitaxel combined with the teaching in Example 4 that 97% of the Taxol was recovered after filtration,

[6] We note that Petitioner (or Patent Owner) may still avail themselves of 37 C.F.R. § 42.65(b) and experimentally reproduce the process of Example 1 of Desai to unequivocally demonstrate whether a starting ratio of 9:1 albumin-paclitaxel does or does not result in a final ratio that is "about 9:1" as required by claim 1 of the '229 patent.

reasonably supports Petitioner's position that Desai teaches a cancer treatment using final pharmaceutical composition with a ratio of albumin to paclitaxel that is "about 9:1" as required by claim 1 of the '229 patent.

This conclusion of a 9:1 ratio in Desai is also supported because the identical processes are performed in Examples 1 and 4 of Desai and Example 49 of the '229 patent. Example 49 of the '229 patent teaches

> 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). Deferoxamine was added as necessary. The mixture was homogenized for 5 minutes at low RPM (Vitris homogenizer, model Tempest I.Q.) in order to form a crude emulsion, and then transferred into a high pressure homogenizer (Avestin). The emulsification was performed at 9000-40,000 psi while recycling the emulsion for at least 5 cycles. The resulting system was transferred into a rotary evaporator, and methylene chloride was rapidly removed at 40° C., at reduced pressure (30 mm Hg) for 20-30 minutes. The resulting dispersion was translucent, and the typical average diameter of the resulting paclitaxel particles was in the range 50-220 nm (Z-average, Malvern Zetasizer). . . . The calculated ratio (w/w) of albumin to paclitaxel in this invention composition is approximately 10.

Ex. 1001, 35:58 to 36:10.

Therefore, Example 49 of the '229 patent used a starting ratio of 10:1 albumin to paclitaxel (Ex. 1002 ¶ 39) and stated, after the process was complete, that the "calculated ratio (w/w) of albumin to paclitaxel in this invention composition is approximately 10." Ex. 1001, 36:10–11. Given the similarities in the processes between Example 49 of the '229 patent and Examples 1 and 4 of Desai, we determine that Desai's examples would likewise yield an amount of Capxol™ that was not significantly different that the starting ratios of materials.

We recognize Patent Owner's assertion that paclitaxel would be lost during Desai's processing as supported by Dr. Peppas.[7] Prelim. Resp. 26 (citing Ex. 2001 ¶¶ 28–36). Patent Owner and Dr. Peppas, however, do not cite specific evidence regarding quantitative amounts of paclitaxel that would have been lost during the processing performed in the Examples of Desai, but rather provide general citations regarding the solubility or adsorption of paclitaxel in other solvent systems (*see, e.g.*, Ex. 2034–2041). Even Fukazawa (Ex. 2036), the closest quantitative comparison to Desai, though not in the same microparticle context as Desai, does not necessarily support Patent Owner's position. In Fukazawa, while paclitaxel was shown to be heavily adsorbed to regular polystyrene microplates, low adsorption microplates showed much lower adsorption levels of paclitaxel, as little as 10% (*see* Ex. 2036, Fig. 6). A 10% change in the 9:1 ratio of Example 1 of Desai could reasonably be interpreted to remain "about 9:1" as required by claim 1 of the '229 patent.

Accordingly, we find that Petitioner has successfully shown that it has a reasonable likelihood that it would prevail on one of claims 1–48 as anticipated by Desai.

B. Obviousness over Desai alone or in combination with Kadima and Liversidge

Petitioner contends that claims 1–19 and 21–48 are unpatentable under 35 U.S.C. § 103 as obvious over Desai alone and over Desai in combination with Kadima and Liversidge. Pet. 36–64.

[7] We note that Patent Owner may wish to provide evidence from actual Capxol™ or Abraxane® production that demonstrates significant loss of paclitaxel during commercial synthesis of the nanoparticles.

Petitioner states "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." Pet. 39 (citing Ex. 1002 ¶ 145). Petitioner further states:

> 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).". . . .
>
> 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.

Pet. 39 (citing Ex. 1006, 52, 1002 ¶ 147). Petitioner asserts that in addition to Desai's teaching overlapping the claimed range, "Desai also teaches that 'higher doses of paclitaxel result in a higher response rate.'" Pet. 41 (citing Ex. 1006, 17:12–13). Petitioner reasons that: "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." Pet. 41 (citing Ex. 1002 ¶ 155).

Petitioner alternatively relies upon Kadima as providing a reason to reduce the "albumin-paclitaxel ratio in order to obtain a more cost-effective and commercially viable formulation" because "'[a]lbumin is an expensive ingredient.'" Pet. 49 (citing Ex. 1004, 10, 33). Petitioner also alternatively cites Liversidge to suggest overlapping ranges where "the percentages

disclosed and claimed in Liversidge correspond to a range of albumin-paclitaxel ratios of 0.01:9.99 to 9:1" Pet. 47, citing Ex. 1002 ¶ 171.

Patent Owner counters that:

> Petitioner identifies no motivation for a POSA to reduce the prescribed 1% albumin solution to 0.5%. The section of Desai on which Petitioner relies is not directed to Example 1, and is not even specifically directed to albumin. Rather, it merely provides a preferred range of about 0.5%–5% (w/v) for the concentration of "[p]rotein" that may be used in the context of the invention.

Prelim. Resp. 33 (citing Ex. 1006, 48:23–25). Patent Owner further notes that "even if a POSA had chosen to use a 0.5% albumin solution, it would not necessarily follow that the ratio of the starting ingredients would be 4.5:1, as Petitioner contends." *Id*. Patent Owner asserts that "Petitioner fails to explain why a POSA would choose to modify the 1% albumin parameter of Example 1 without also modifying other parameters as well that would have impacted the ratio of albumin to paclitaxel." *Id*. Patent Owner contends "with respect to the albumin-bound nanoparticles of the prior art, a POSA would only have been motivated to increase their amount of albumin. A POSA would have expected that the resulting nanoparticles would be more therapeutically effective, since more active ingredient would be delivered to the tumor site." Prelim. Resp. 40, citing Ex. 1006, 28:10–15, 29:4–30:5. Similarly, Patent Owner points out that "crystallization (*i.e.*, precipitation) would similarly have motivated a POSA only to increase or maintain the amount of albumin. It was also well understood that the physical stability of albumin-drug formulations is typically better at higher albumin concentrations." Prelim. Resp. 41.

Patent Owner also contends the ordinary artisan

> would have expected that reducing Capxol™'s albumin-to-paclitaxel ratio would result in a formulation that would be less effective and less stable, *i.e.*, it would (1) result in less endothelial binding and transcytosis, and therefore less efficacy to treat cancer, and (2) destabilize the nanoparticle composition and lead to precipitation, which is the exact problem with Taxol® that Desai sought to alleviate.

Prelim. Resp. 43 (citing Ex. 1006, 1023).

In addition to addressing the teachings of Desai alone, Patent Owner contends the "additional references—Kadima and Liversidge—add nothing in support" of the obviousness analysis. Prelim. Resp. 46. Patent Owner contends "Kadima reports only *molar* ratios, not the relevant *weight* ratio of albumin to paclitaxel . . . Had Kadima calculated the weight ratio of albumin to paclitaxel, the ratios reported would be about *78 times higher* than the molar ratios. (EX2001 ¶ 40.) Thus, Kadima actually *teaches away* from lowering Capxol™'s 13:1 ratio to about 9:1." Prelim. Resp. 47.

Patent Owner contends

> at Capxol™'s ratio of 13.3:1, the cost of paclitaxel ($7) is far greater than the cost of albumin ($1.28)—the albumin is no longer the "cost-limiting component." (Pet. 49.) Moreover, Petitioner has not established that any cost concerns would have outweighed maintaining the perceived benefits of albumin to thus motivate a POSA to lower the amount of albumin used in the prior-art formulations.

Prelim. Resp. 50. Patent Owner contends "Kadima also teaches away from reducing the ratio of Capxol™ for an additional reason: Kadima discloses that the stability of the composition is far better at higher albumin-to-paclitaxel ratios." Prelim. Resp. 51.

Patent Owner contends "POSA would not have found Liversidge informative with regard to the method described in Desai" because "Liversidge does not disclose any albumin and paclitaxel nanoparticles. Nor does Liversidge disclose particles having ratios that encompass ratios claimed in the '229 patent. Furthermore, Liversidge's preparation techniques and final product are completely different than the methods and products disclosed in Desai." Prelim. Resp. 53. Patent owner also contends "Desai teaches that the crystalline form has lower solubility than amorphous paclitaxel, and increasing crystalline paclitaxel can facilitate precipitation. (EX1006, 68:6–15.) Thus, Desai explicitly teaches away from combining Liversidge and Desai." Prelim. Resp. 54.

Patent Owner also relies upon secondary considerations to address the Petitioner's obviousness arguments, contending

> during the development of Abraxane®, the '229 inventors unexpectedly found that: (1) the albumin-to-paclitaxel weight ratio affects the binding of paclitaxel to endothelial cells and simulated cellular membrane; (2) at a lower albumin-to-paclitaxel ratio of about 9:1, there is a dramatic change in the binding of paclitaxel; and (3) the 9:1 formulation showed higher therapeutic efficacy in treating cancer and reduced toxicity compared to the prior art.

Prelim. Resp. 57, citing Ex. 1023 ¶¶ 4–5.

Patent Owner contends a "POSA would have understood that the point of using fluorescent paclitaxel in the patent's Examples 40–44 and Desai's Examples 2–4 was to assess cell-binding properties of the combination of paclitaxel and albumin" and that "applicant ran control experiments to validate the results provided, including but not limited to testing the binding of Flutax alone." Prelim Resp. 58. Patent Owner

contends "it was surprising that the binding of paclitaxel changes dramatically at an albumin/paclitaxel weight ratio of about 9:1" because the "intersection of the two lines (and seven-fold increase in the slope) creates an unexpected inflection point in the binding curve at an albumin/paclitaxel ratio of about 9:1." Prelim Resp. 59–60.

Patent Owner contends "Petitioner erroneously argues that the 19:1 ratio formulation is not the closest prior art, but rather that Example 1 of Desai is" and "Petitioner has made no effort to prove, as it must, what the alleged prior art discloses with respect to finished pharmaceutical compositions." Prelim Resp. 60–61. Patent Owner contends "it was unexpected that reducing the albumin-to-paclitaxel ratio to 9:1 would lead to substantially increased efficacy and reduced adverse events. A reduction in adverse events can be outcome determinative on the success of a therapy." Prelim. Resp. 62. Patent Owner also contends: "It was also unexpected that reducing the amount of albumin compared to paclitaxel in the composition would result in compositions that were as stable as nanoparticle compositions containing higher albumin-to-paclitaxel ratios." Prelim. Resp. 63.

1. *Desai (Ex. 1006)*

In addition to the specific examples disclosed by Desai, discussed above, Desai also provides a more general disclosure regarding nanoparticle formation, teaching:

> The oil phase employed in the preparation of invention compositions typically contains only the pharmacologically active agent dissolved in solvent.
>
> Next, a protein (e.g., human serum albumin) is added (into the aqueous phase) to act as a stabilizing agent . . . 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).

Ex. 1006, 48. Desai teaches to use more concentrated paclitaxel because in the prior art

> Taxol® has to be administered at a final dosing concentration of 0.6 mg/ml, requiring large infusion volumes (typically in the range of about 300-1000 ml.
>
> In contrast, invention formulations do not have these limitations and can be administered at a desired concentration. This enables clinicians to treat patients by a rapid intravenous bolus that can be administered in as little as a few minutes. For example, if the invention formulation is reconstituted to a dosing concentration of 20 mg/ml, the infusion volume for a total dose of 200-500 mg is only 10-25 ml, respectively. This is a great advantage in clinical practice.

Ex. 1006, 133. Desai explains this advantage for "the delivery of high doses of the pharmacologically active agent in relatively small volumes . . . minimizes patient discomfort at receiving large volumes of fluid and minimizes hospital stay." Ex. 1006, 52.

2. *Kadima (Ex. 1004)*

Kadima teaches: "It would be highly advantageous to the therapy of a number of indications, including cancer, to obtain a pharmaceutical formulation comprising an optically clear aqueous solution of paclitaxel." Ex. 1004, 13. Kadima teaches an embodiment where "the composition comprising paclitaxel, a serum albumin and an organic solvent is dried to form a storage-stable composition, stored as a dried composition (e.g., a lyophilized preparation), and then resolubilized with a vehicle prior to administration." Ex. 1004, 14.

Kadima prefers "the amounts of paclitaxel, serum albumin, solvent, and ratios between these ingredients, and pH are such that the composition is optically clear, indicating that none of the components has precipitated or formed crystals." Ex. 1004 14–15. Kadima explains the "serum albumin is present in appropriate amount of solvent so that the final balance between precipitation of paclitaxel from solution and binding of paclitaxel to albumin favor binding of paclitaxel to albumin." Ex. 1004 15.

Kadima teaches "the molar ratios of paclitaxel:albumin, paclitaxel:ethanol and albumin: solvent are such that paclitaxel and albumin remain in solution, such as about 1:4 to about 2:1 (paclitaxel:albumin)." Ex. 1004, 15. Kadima teaches "Albumin is an expensive ingredient. In order to produce a commercially available, pharmaceutically acceptable albumin-bound paclitaxel, the drug must be bound reversibly to the albumin in a high molar ratio." Ex. 1004, 31. Kadima provides a table estimating costs and molar ratios as reproduced below:

Molar ratio	Paclitaxel (mg)	HSA (g)	Paclitaxel Cost	HSA Cost[(1)]	Ingredients Total Cost
1:10	30	23.4	$7	$74.90	$81.90
1:5	30	11.7	$7	$37.40	$44.40
1:2	30	4.7	$7	$15.00	$22.00
1:1	30	2.34	$7	$ 7.49	$14.50
1:0.5	30	1.17	$7	$ 3.74	$10.70

[(1)]The fair 1999 market value of HSA is approximately $3.20 per gram.

The table in Kadima teaches weight ratios of human serum albumin to paclitaxel including a lowest ratio of 1.17 g to 30 mg for a weight ratio of 39:1. *See* Ex. 1004, 32; Ex. 2001 ¶ 41.

3. *Liversidge (Ex. 1005)*

Liversidge demonstrated "anticancer compositions comprising anticancer agents in the form of surface modified nanoparticles exhibit reduced toxicity and/or enhanced efficacy." Ex. 1005, 1:45–48. Liversidge claims:

> Particles consisting essentially of 99.9% by weight of a crystalline medicament useful in treating cancer susceptible to treatment with said medicament, said medicament having a solubility in water of less than 10 mg/ml, and having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 01–90% by weight and sufficient to maintain an average effective particle size of less than 1000 nm, wherein said medicament is selected from the group consisting of . . . taxol and retinoids.

Ex. 1005, claim 1, 14:7–15. Liversidge further includes bovine serum albumin within the list of surface modifier compounds. *See* Ex. 1005, Claim 15, 16:8.

4. *Analysis*

i. *Obviousness*

We agree with Petitioner that based on the evidence of record, the teachings of Desai alone or Desai in combination with Kadima and Liversidge demonstrate a reasonable likelihood that claims 1–19 and 21–48 of the '229 patent would have been obvious over Desai alone or in combination with Kadima and Liversidge.

As already discussed above, we find that Petitioner is likely to prevail in establishing that Desai alone anticipates these claims, and although the reverse is not always true, "it is commonly understood that prior art references that anticipate a claim will usually render that claim obvious . . . ." *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir.

2008); *see also id*. at 1365 (in discussing differing standards for proving anticipation versus obviousness, including application of secondary considerations and inherency, stating "it does not follow that every technically anticipated invention would also have been obvious.") (citation omitted).

Desai provides additional disclosures that support Petitioner's obviousness challenge by suggesting wider ranges of albumin in the range of about 0.5 to 25 % (w/v) and teaching that higher paclitaxel doses allow an "infusion volume for a total dose of 200-500 mg [that] is only 10-25 ml, respectively. This is a great advantage in clinical practice." Ex. 1006, 48, 133.

Thus, we agree with Petitioner that applying Desai's disclosed lower preferred dose of 0.5 % to Example 1 of Desai would result in a starting albumin-paclitaxel ratio of 4.5:1, clearly overlapping the claimed range. Pet. 41, Ex. 1006 48:25.

We recognize, but find unpersuasive Patent Owner's contention that "Petitioner identifies no motivation for a POSA to reduce the prescribed 1% albumin solution to 0.5%." Prelim. Resp. 33. Desai reasonably suggests general ranges of albumin as a stabilizing agent for nanoparticles in ranges as low as 0.05 % and in preferred ranges as low as "about 0.5%." Ex. 1006, 48. Desai's range provides a basis to select values from 0.05 to 0.5% albumin. *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness.")

We agree with Petitioner that Desai teaches the use of higher dose concentrations of paclitaxel are advantageous because "increasing the concentration of paclitaxel relative to other ingredients —'minimizes patient discomfort at receiving large volumes of fluid and minimizes hospital stay.'" Pet. 41 (citing Ex. 1006, 54).

> We recognize, but find unpersuasive, Patent Owner's contention that
>
> even if a POSA had chosen to use a 0.5% albumin solution, it would not necessarily follow that the ratio of the starting ingredients would be 4.5:1, as Petitioner contends. Petitioner fails to explain why a POSA would choose to modify the 1% albumin parameter of Example 1 without also modifying other parameters as well that would have impacted the ratio of albumin to paclitaxel.

Prelim. Resp. 33. As Petitioner points out, Desai suggests using high concentrations of paclitaxel in order to reduce infusion volumes of the pharmaceutical composition because "[t]his is a great advantage in clinical practice." Ex. 1006, 133. This advantage "minimizes patient discomfort at receiving large volumes of fluid and minimizes hospital stay." Ex. 1006, 54. Thus, on this record, we agree with Petitioner that the ordinary artisan, selecting within the preferred overlapping albumin ranges disclosed by Desai, would have reason to retain as high a paclitaxel concentration as feasible in order to improve patient comfort and reduce infusion volumes. Pet. 41–42; *see* Ex. 1006, 54, 135.

We recognize, but find unpersuasive, Patent Owner's contentions that "the only change a POSA would have been motivated to make for the ratio would be to *increase* it—and thereby maximize the benefits conferred by albumin, *e.g.*, therapeutic efficacy, improved solubility, stability, and reduced toxicity." Prelim. Resp. 39.

> [O]bviousness must be determined in light of all the facts, and there is no rule that a single reference that teaches away will mandate a finding of nonobviousness. Likewise, a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine. *See* [*Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349 n. 8 (Fed. Cir. 2000)] ("The fact that the motivating benefit comes at the expense of another benefit, however, should not nullify its use as a basis to modify the disclosure of one reference with the teachings of another. Instead, the benefits, both lost and gained, should be weighed against one another."). Where the prior art contains "apparently conflicting" teachings (i.e., where some references teach the combination and others teach away from it) each reference must be considered "for its power to suggest solutions to an artisan of ordinary skill. . . . consider[ing] the degree to which one reference might accurately discredit another." *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991).

Medichem, S.A. v. Rolabo, S.L.¸437 F.3d 1157, 1165 (Fed. Cir. 2006).

We recognize that Desai provides some reasons to increase the amount of albumin as argued by Patent Owner. Prelim. Resp. 39–42. However, Desai also directly teaches a range for albumin with a lower end that overlaps the claimed ratio and provides reasons to use higher concentrations of paclitaxel in drug delivery compositions. Ex. 1006, 50, 54, 133. Therefore, we find that Desai reasonably provides support for Petitioner's position that the claimed ratio would have been obvious.

We recognize Patent Owner's contention that a "POSA would have expected that reducing Capxol™'s albumin-to-paclitaxel ratio would result in a formulation that would be less effective and less stable" and that "a POSA would expect that reducing the ratio would create manufacturing issues related to the physical stability of the product. Thus, a POSA would

not have expected success in reducing Capxol™'s ratio below 13.3:1." Prelim. Resp. 43.

We do not find this argument persuasive based on the evidence currently of record because Patent Owner presents no evidence in support, only attorney argument that an ordinary artisan would lack a reasonable expectation of success in formulating a composition with a 9:1 ratio. *See, e.g.*, Ex. 2001 ¶ 36. By contrast, the Berkland Declaration states with support from Desai that "a skilled artisan would have had a reasonable expectation of success" and that "a skilled artisan as of December 2002 would have reasonably expected success in maintaining at least adequate, if not excellent, physical stability in reducing Capxol's albumin-paclitaxel ratio of 13.3:1 to about 9:1." Ex. 1002 ¶¶ 143, 165. Thus, the balance of evidence currently of record supports Petitioner's position that "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." Pet. 45.

We also agree that Petitioner has a reasonable likelihood of success in showing that, based on the evidence of record, Desai, Kadima, and Liversidge would have rendered claims 1–19 and 21–48 of the '229 patent obvious.

Kadima teaches that "[a]lbumin is an expensive ingredient" and provides a table showing reduced cost of a paclitaxel dose by reducing the amount of human serum albumin in the pharmaceutical composition. Ex. 1004, 31–32. Liversidge provides a generic disclosure that claims a large number of drugs and surface modifiers, including taxol and serum albumin, and teaches that these may be used in overlapping ranges and

particle sizes. Ex. 1005 14:7–25, 31–32, 16:8. These teachings of Kadima and Liversidge provide additional reasons to select ratios of paclitaxel to albumin as disclosed by Desai with reduced amounts of albumin and provide additional evidence of a reasonable expectation of success in formulating particles with these ratios.

We recognize, but find unpersuasive, Patent Owner's contention that "Kadima reports only *molar* ratios, not the relevant *weight* ratio of albumin to paclitaxel" and that "[h]ad Kadima calculated the weight ratio of albumin to paclitaxel, the ratios reported would be about *78 times higher* than the molar ratios. (EX2001 ¶ 40.)" Prelim. Resp. 47. We agree with Patent Owner that "the lowest weight ratio Kadima discloses is 39:1—more than 4 times the highest ratio claimed in the '229 patent." Prelim. Resp. 49. We also agree with Patent Owner that as the amount of albumin is reduced "the cost of paclitaxel ($7) is far greater than the cost of albumin ($1.28)." Prelim Resp. 50.

However, the issue is an obviousness determination, not anticipation, and Petitioner's position is not that Kadima anticipates claim 1. Rather, Kadima is relied upon to provide reasons to retain the same amount of paclitaxel in a composition but reduce the amount of albumin to reduce costs. Ex. 1004, 31–32. Indeed, Patent Owner's table on page 49 of the Preliminary Response provides specific support for Petitioner's position, because continued reductions in the albumin amounts provide continued savings in pharmaceutical costs. *See* Prelim. Resp. 49. This is consistent with Dr. Berkland's statement that "skilled artisan would have been motivated to reduce the ratio of albumin to paclitaxel in Capxol in order to reduce costs of production." Ex. 1002 ¶ 174.

We recognize, but find unpersuasive, Patent Owner's contention that "Kadima actually *teaches away* from lowering Capxol™'s 13:1 ratio to about 9:1" or that "Kadima also teaches away from reducing the ratio of Capxol™ for an additional reason: Kadima discloses that the stability of the composition is far better at higher albumin-to-paclitaxel ratios." Prelim. Resp. 47, 51. A teaching away requires a reference to actually criticize, discredit, or otherwise discourage the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) ("The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed").

Patent Owner does not identify any teaching in Kadima that criticizes, discredits, or discourages the use of weight ratios of 9:1 as required by the claims of the '229 patent. Nor does Patent Owner identify a teaching in Kadima that discourages the use of lower albumin to paclitaxel ratios because of stability issues. At best, Kadima teaches a preference for higher ratios but preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments. *See In re Susi*, 440 F.2d 442, 446 n.3 (CCPA 1971).

We recognize, but find unpersuasive, Patent Owner's contention that "Desai teaches that the crystalline form has lower solubility than amorphous paclitaxel, and increasing crystalline paclitaxel can facilitate precipitation. (EX1006, 68:6–15.) Thus, Desai explicitly teaches away from combining Liversidge and Desai." Prelim. Resp. 54. Although we agree with Patent Owner that Desai prefers amorphous paclitaxel to the crystalline form, Liversidge is simply relied upon to demonstrate that the prior art recognized

overlapping ratios of pharmaceutical compounds such as taxol and surface modifiers such as albumin. Ex. 1005, 14:7–25, 16:8. So to the extent that Desai discourages the use of crystalline paclitaxel, Desai does not discourage or discredit the ratios of taxol and albumin disclosed by Liversidge.

ii. *Secondary Considerations*

We have considered the evidence of secondary considerations in the Desai Declaration, originally submitted during the prosecution of the '229 patent, but find the secondary evidence currently of record insufficient, when weighed with the Petitioner's likelihood of showing that the claims at issue would have been obvious, to support a conclusion that claims 1–19 and 21–48 of the '229 patent are nonobvious. *See* Ex. 1023.

Patent Owner contends

> the '229 inventors unexpectedly found that: (1) the albumin-to-paclitaxel weight ratio affects the binding of paclitaxel to endothelial cells and simulated cellular membrane; (2) at a lower albumin-to-paclitaxel ratio of about 9:1, there is a dramatic change in the binding of paclitaxel; and (3) the 9:1 formulation showed higher therapeutic efficacy in treating cancer and reduced toxicity compared to the prior art.

Prelim. Resp. 57 (citing Ex. 1023 ¶¶ 4–5).

Petitioner contends "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." Pet. 61 (citing Ex 1002 ¶ 213).

Because we find that the evidence of record currently supports Petitioner's position that Desai anticipates the 9:1 ratio disclosed in claim 1

of the ’229 patent for the reasons already discussed, we also find that Example 1 of Desai is the closest prior art. *See In re Baxter Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir. 1991) (“when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.”).

We recognize Patent Owner’s contention that “Petitioner erroneously argues that the 19:1 ratio formulation is not the closest prior art, but rather that Example 1 of Desai is. Petitioner’s assertion, however, is incorrect. For starters, Example 1 discloses only the amounts of starting ingredients, not the albumin-to-paclitaxel ratio in the finished nanoparticle composition.” Prelim. Resp. 60–61.

We find this argument unpersuasive because, as already noted, Patent Owner has already stated “Example 1’s method is used to produce Capxol™, and ‘[e]ach vial of Capxol™ contains 30 mg of paclitaxel and approximately 400 mg of human serum albumin,’ *i.e.*, a 13.3:1 albumin-to-paclitaxel ratio for the finished product.” Prelim. Resp. 23. Consequently, even as supported by Patent Owner’s own arguments, the 13.3:1 ratio asserted by Patent Owner as disclosed in Example 1 of Desai is closer prior art than the 19:1 ratio tested in the Desai Declaration. Because the comparison in the Desai Declaration is not with Example 1 of Desai, with either a 9:1 or 13.3:1 ratio that is lower than the 19:1 ratio actually compared, the evidence does not reliably demonstrate that the results would have been unexpected when compared to the closest prior art.

We recognize that Exhibits 2–4 of the Desai show the impacts on the amount of albumin in binding in experimental systems. Ex. 1023 ¶¶ 10–14. However, the Desai Declaration data does not directly identify any data

representing the closest prior art of Desai, at either a 9:1 or 13.3:1 ratio. Even the evidence of the inflection point in Exhibit 4 of the Desai Declaration, with a data point that appears to be immediately greater than the 9:1 ratio, neither identifies that point as a 13.3:1 ratio, nor clearly demonstrates that the inflection point is exactly 9:1 and doesn't reasonably encompass values including 13.3:1 as being expected to yield the same results.

We have considered Patent Owner's remaining arguments related to the unexpected results, but find them unpersuasive because they are rooted in logic that the Desai Declaration compared the closest prior art, and we do not agree with that position. *See* Prelim. Resp. 57–63.

We find that Petitioner has shown that it has a reasonable likelihood of prevailing on the obviousness of claims 1–19 and 21–48 of the '229 patent based on the combination of Desai, Kadima, and Liversidge.

C. Obviousness of claim 20 over Desai alone or in combination with Kadima and Liversidge

Petitioner contends that claim 20 is unpatentable under 35 U.S.C. § 103 as obvious over Desai alone and over Desai in combination with Kadima and Liversidge. Pet. 36, 53. Petitioner specifically contends 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®." Pet. 53.

Patent Owner contends

> nothing in the Taxol® label, either alone (Ground III.A), or in combination with Kadima and Liversidge (Ground III.B), cures

> the fundamental deficiencies in the primary reference with respect to the claimed ratio also recited in claim 20. Accordingly, claim 20 would not have been obvious for the same reasons set forth above regarding claims 1–19 and 21–48.

(Prelim Resp. 55–56).

On the current record, we determine that Petitioner has made a sufficient showing for claim 20, for the same reasons as discussed *supra*, for claims 1–19 and 21–48 because Patent Owner does not dispute that the use of multidose vials in itself would represent an unobvious improvement over the Desai, Kadima, and Liversidge.

III. CONCLUSION

After reviewing the information presented in the Petition and the Preliminary Response, as well as the evidence of record, we determine that Petitioner has established a reasonable likelihood that it will prevail in showing that claims 1–48 of the ’229 patent are unpatentable.

IV. ORDER

Accordingly, it is

ORDERED that Pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted on the following grounds;

References	Basis	Claims Challenged
Desai	§ 102(b)	1–19 and 21–48
Desai	§ 103(a)	1–19 and 21–48
Desai, Kadima, and Liversidge	§ 103(a)	1–19 and 21–48
Desai and Taxol label	§ 103(a)	20
Desai, Taxol label, Kadima, and Liversidge	§ 103(a)	20

FURTHER ORDERED that no other ground of unpatentability asserted in the Petition is authorized for this *inter partes* review; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial will commence on the entry date of this Decision.

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