UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Apotex Inc. and Apotex Corp.,
Petitioners

v.

ABRAXIS BIOSCIENCE, LLC,
Patent Owner

Case IPR2018-00151
Patent 8,138,229 B2

DECLARATION OF CORY J. BERKLAND, Ph.D.
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW

TABLE OF CONTENTS

EXHIBITS CITED

EX	Description
1001	Desai et al., U.S. Patent No. 8,138,229 B2, "Compositions and Methods of Delivery of Pharmacological Agents" (issued Mar. 20, 2012) (the "'229 patent")
1004	Kadima et al., WO 00/06152, "Pharmaceutically Acceptable Composition Comprising an Aqueous Solution of Paclitaxel and Albumin" (published Feb. 10, 2000) ("Kadima")
1005	Liversidge et al., U.S. Patent No. 5,399,363, "Surface Modified Anticancer Nanoparticles" (issued Mar. 21, 1995) ("Liversidge")
1006	Desai et al., WO 1999/000113, "Novel Formulations of Pharmacological Agents, Methods for the Preparation thereof and Methods for the Use thereof" (published Jan. 7, 1999) ("Desai")
1007	Li et al., "Fluorescein Binding to Normal Human Serum Proteins Demonstrated by Equilibrium Dialysis," Arch Ophalmol. vol. 100, 484–87 (March 1982)
1008	Physicians' Desk Reference® 309, 881–887 (54th ed. 2000) "Taxol® (paclitaxel) Injection" ("Taxol label")
1009	FDA Guideline on Sterile Drug Products Produced by Aseptic Processing (June 1987, reprinted June 1991 and Feb. 1997)
1010	EMEA Guidance on Manufacture of the Finished Dosage Form (April 1996)
1011	*Elan Pharma Int'l Ltd. v. Abraxis BioScience, Inc.*, Judgment and Verdict Form, No. 06-438-GMS, Dkt. 614 (D. Del. June 16, 2008)
1017	Damascelli, B et al. "Intraarterial chemotherapy with polyoxyethylated castor oil free paclitaxel, incorporated in albumin nanoparticles (ABI-007)," Cancer 2001 Nov; 92(10):2592–2602 ("Damascelli")
1018	Ibrahim et al., "Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel," Clin Cancer Res. 2002 May; 8:1038–44 ("Ibrahim")

1023	U.S. Application No. 11/553,339, Declaration of Neil P. Desai Pursuant to 37 C.F.R. § 1.132 (dated Apr. 14, 2010)
1027	Remington's Pharmaceutical Sciences (18th ed. 1990), Chapt. 85, "Intravenous Admixtures" ("*Remington's*")
1028	Camden, U.S. Patent No. 6,177,460 B1, "Method of Treatment for Cancer or Viral Infections" (issued Jan. 23, 2001)

I, Cory J. Berkland, Ph.D., hereby declare as follows:

I. INTRODUCTION

1. I am currently appointed as the Solon E. Summerfield Distinguished Professor in the Department of Pharmaceutical Chemistry and the Department of Chemical and Petroleum Engineering at the University of Kansas. I have been retained by Petitioners Apotex Inc. and Apotex Corp. ("Apotex") in connection with its request for *inter partes* review of U.S. Patent No. 8,138,229 ("the '229 patent"). A copy of the '229 patent has been marked EX1001. I have reviewed and am familiar with the '229 patent. Generally, it describes and claims pharmaceutical compositions comprising the anticancer drug paclitaxel bound to the protein albumin and formulated as nanoparticles, and methods of using such compositions to treat diseases including cancer.

2. I have been asked to provide my opinions regarding the patentability of claims 1–48 of the '229 patent (the "challenged claims"). This declaration includes a discussion of my background and qualifications, the legal standards used in my analysis, an overview of the '229 patent from the perspective of a person of ordinary skill in the art at the time that the patent was filed (a "skilled artisan"), and my opinions regarding the patentability of the challenged claims.

3. I am being compensated for my work in this proceeding at my standard hourly consulting rate of $500.00 per hour. My compensation is in no way

contingent on the substance of my opinions or the outcome of this proceeding.

4. As set forth more fully below, it is my opinion that claims 1–19 and 21–48 of the '229 patent are anticipated by a previously published international patent application, WO 99/00113 to Desai et al. ("Desai") (EX1006). Additionally, it is my opinion that claims 1–19 and 21–48 would have been obvious to a skilled artisan in view of Desai, either alone or in combination with another previously published international patent application, WO 00/06152 to Kadima et al. ("Kadima") (EX1004), and a previously issued patent, U.S. Patent No. 5,399,363 to Liversidge et al. (EX1005). It is also my opinion that claim 20 would have been obvious to a skilled artisan in view of Desai and the 2000 FDA-approved labeling for Taxol (the "Taxol label") (EX1008), and optionally in further view of Kadima and Liversidge.

5. The bases for my opinions are set forth in this declaration.

II. BACKGROUND AND QUALIFICATIONS

6. I received a B.S. in Chemical Engineering from Iowa State University in December 1998, and an M.S. in Chemical Engineering from the University of Illinois in May 2001. I received a Ph.D. in Chemical and Biomolecular Engineering from the University of Illinois in May 2003. From 2004 to 2009, I was an Assistant Professor in the Department of Chemical and Petroleum Engineering and the Department of Pharmaceutical Chemistry at The University of Kansas. Since 2009, I have been a Professor in these two departments with tenure.

7. My areas of expertise include drug formulation using particulates and powders, microencapsulation of pharmaceuticals, and controlled-release drug delivery. Through collaborations with industrial and academic partners, and close relationships with other experts in controlled release, I have developed considerable expertise in the formulation and characterization of particles and powders.

8. The primary focus of my research has been the design and analysis of drug delivery approaches for improving the performance of therapeutic agents. I have worked on particles and aspects of pharmaceutical formulation and delivery, including nanoparticle formulations, since 1997. Among other areas, I have conducted research aimed to elucidate important parameters (*e.g.*, particle size, morphology, surface chemistry) for controlling the release or dissolution of drugs.

9. My research group at the University of Kansas currently works on formulation approaches designed to modify drug dissolution kinetics and to control drug release rates. My work has encompassed microencapsulation, nanoparticle formulations, and polymers for delivering small molecules, proteins, and DNA. I have expertise in analyzing the performance of such formulations and in applying mathematical models to elucidate the underlying phenomena controlling the dissolution or release of such drugs. I have also designed and taught classes on drug delivery that focus primarily on drug transport in pharmaceutical formulations and through different biological barriers in the human body.

10. I have been a member of various professional organizations, including the American Institute of Chemical Engineers, the American Chemical Society, the American Association of Pharmaceutical Scientists, and the Controlled Release Society. I am a Fellow of the American Institute of Medical and Biological Engineering, and have received honors and awards from various national and international organizations, including the Leading Light Award from the University of Kansas, the Nagai Foundation Distinguished Lectureship, and the Controlled Release Society Young Investigator Award. Other awards and honors I have received are listed in my CV, which is attached as the Appendix to this declaration.

11. I have sat on editorial and scientific advisory boards of scientific journals including Therapeutic Delivery, the Journal of Pharmaceutical Sciences, and the Journal of Pharmaceutical Innovation.

12. I have published on such topics as drug delivery, nanoparticle formulation, surface modification, controlled release, and biomaterials. I have published approximately 150 articles in peer-reviewed journals, three book chapters, and have been named as a co-inventor on more than 50 U.S. patents or applications.

13. I have served as a consultant in the area of drug formulation and delivery for U.S. and international companies, and have testified as an expert witness in the area of drug formulation and delivery in several trials. My publications, including publications authored within the past ten years, are listed in my CV.

14. I have been involved in the development of numerous pharmaceutical products, both in my capacity at the University of Kansas and as a company founder. For instance, I am a co-founder of four companies: Orbis Biosciences, Inc., Savara Pharmaceuticals, Inc., Orion BioScience, Inc., and Bond Biosciences, Inc. I am the acting Chief Scientific Officer at Orbis Biosciences. Orbis develops controlled-release delivery systems, including parenteral, injectable formulations. I was also a Member of the Scientific Advisory Board and the former Chief Technology Officer for Savara Pharmaceuticals, Inc. in Austin, Texas. Savara specializes in the development of pulmonary drug products. I am also the Chairperson of the Board of Directors of Orion BioScience, Inc., which develops injectable immune-specific therapies for autoimmune diseases.

III. LEGAL STANDARDS USED IN MY ANALYSIS

15. I am not a patent attorney, nor have I independently researched patent law. Counsel for Petitioners have explained certain legal standards to me that I have relied upon in forming my opinions set forth in this Declaration.

A. Prior art

16. I have been informed that the law provides certain categories of information, known as prior art, that may be used to render patent claims anticipated or obvious. The reference materials I discuss in this declaration are prior art at least because they would have been available to members of the public as of December

9, 2002, and are relevant to the subject matter of the '229 patent. The references I discuss herein are from the same field of endeavor as the claimed invention (even if they address a different problem), and/or are reasonably pertinent to the problem faced by the inventor (even if they are not in the same field of endeavor as the claimed invention).

B. Person of ordinary skill in the art

17. I understand that U.S. provisional application no. 60/432,317, to which the '229 patent claims priority, was filed on December 9, 2002, as stated on the front of the patent under the title "Related U.S. Application Data." For purposes of my analysis, and without offering any opinion as to whether the '229 patent's claim to priority is valid or appropriate, I have used the December 9, 2002 date as the relevant date for my analysis of the prior art.

18. I understand that the assessment of the patentability of the claims of the '229 patent must be undertaken from the perspective of a hypothetical person of ordinary skill in the art as of the earliest priority date of the '229 patent, *i.e.*, a skilled artisan. The person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art as of the effective filing date. Factors that may be considered in determining the level of ordinary skill in the art may include, (i) type of problems encountered in the art, (ii) prior art solutions to those problems, (iii) rapidity with which innovations are made, (iv) sophistication of the

technology, and (v) educational level of active workers in the field. I understand that in a given case, every factor may not be present, and one or more factors may predominate.

19. I understand that the hypothetical person having ordinary skill in the art to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art. I further understand that a person of ordinary skill in the art is also a person of ordinary creativity, not an automaton. In many cases a person of ordinary skill will be able to fit the teachings of multiple patents or prior art references together like pieces of a puzzle.

20. Based on these factors, my knowledge and expertise, and the prior art to the '229 patent (*i.e.*, publications before December 9, 2002), it is my opinion that a skilled artisan would include a person with 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. Further, it is my opinion that the skilled artisan would know how to evaluate potential drug therapies for *in vitro* and *in vivo* activity, including with biological assays.

C. Anticipation

21. I have been informed that a claim is not patentable if a single prior art

reference describes every element of the claim, either expressly or inherently, to a skilled artisan. I understand that this principle is called "anticipation." I have also been informed that, to anticipate a patent claim, the prior art reference does not need to use the same words as the claim. However, it must describe the requirements of the claim with sufficient clarity that a skilled artisan would have been able to make and use the claimed invention based on that single prior art reference.

22. In addition, I have been informed and understand that, in order to establish that an element of a claim is "inherent" in the disclosure of a prior art reference, it must be clear to one skilled in the art that the missing element is an inevitable part of what is explicitly described in the prior art reference, and that it would have been recognized as necessarily present by a skilled artisan.

23. I understand that when a patent claims a range, that range is anticipated by a prior art reference if the reference discloses a point within the range. If the prior art discloses its own range, rather than a specific point, then the prior art is anticipatory if it describes the claimed range with sufficient specificity such that a skilled artisan would conclude that there is no difference in how the invention operates over the ranges. Further, I understand that a patentee must establish 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.

D. Obviousness

24. I have been informed that, even if every element of a claim is not found explicitly or implicitly in a single prior art reference, the claim may still be unpatentable if the differences between the claim and the prior art are such that the claim as a whole would have been obvious to a skilled artisan at the time the invention was made. For purposes of obviousness, I understand that a skilled artisan may rely on a single prior art reference, or multiple references in combination.

25. I have been informed that the following four factors are considered when determining whether a patent claim would have been obvious to a skilled artisan: (a) the level of ordinary skill in the art; (b) the scope and content of the prior art; (c) the differences between the prior art and the claim; and (d) any "secondary considerations" tending to prove nonobviousness. These secondary considerations, which I understand are also called "objective indicia" or "objective evidence," may include factors such as: (i) the invention's satisfaction of a long-felt unmet need in the art; (ii) unexpected results of the invention; (iii) skepticism of the invention by experts; (iv) teaching away from the invention in the prior art; (v) commercial success of an embodiment of the invention; and (vi) praise by others for the invention. I have also been informed that there must be an adequate nexus or connection between the evidence that is the basis for an asserted secondary consideration and the scope of the invention claimed in the patent.

26. I understand that when every limitation of a claim is disclosed in the cited prior art references, the question of obviousness turns on whether a hypothetical person of ordinary skill in the art would have been motivated to combine those teachings to derive the claimed subject matter with a reasonable expectation of success. Further, I understand that obviousness does not require absolute predictability. Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness.

27. I have been informed that a claimed invention can be rendered obvious by the combination of teachings in the prior art even if there is no explicit teaching to combine them. Instead, any problem known in the field at the time of the alleged invention can provide a sufficient rationale to combine the elements of the prior art in the manner claimed in the patent.

28. I have been informed that examples of sufficient rationales for establishing obviousness include the following:

- combining prior art elements according to known methods to yield predictable results;
- substituting known elements for other known elements to obtain predictable results;
- using a known technique to improve similar devices, methods, or products in the same way;

- choosing from a finite number of identified, predictable solutions that would be obvious to try; and
- providing some teaching, suggestion, or motivation to modify the prior art reference or to combine teachings in prior art references to arrive at the claimed invention.

29. I understand that where 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. For purposes of this analysis, I understand that a prior art reference does not "teach away" from a claimed invention unless it criticizes, discredits, or otherwise discourages investigation into the invention claimed.

IV. THE '229 PATENT

A. The alleged invention

30. The '229 patent is entitled "Compositions and Methods of Delivery of Pharmacological Agents," and generally relates to pharmaceutical compositions comprising paclitaxel and a pharmaceutically acceptable carrier, such as human serum albumin, and methods of treating diseases, including cancer, by administering such compositions. EX1001, cover, abst.

31. As background, the '229 patent explains that "many drugs for parenteral use, especially those administered intravenously, cause undesirable side effects" that are "administration related." *Id.* at 1:28–32. "Many of these drugs," the patent explains, "are insoluble in water, and are thus formulated with solubilizing agents, surfactants, solvents, and/or emulsifiers that are irritating, allergenic, or toxic when administered to patients." *Id.* at 1:32–35. The patent goes on to state that known "drugs that exhibit administration-associated side effects include, for example, Taxol (paclitaxel)." *Id.* at 1:53–55.

32. Paclitaxel, which as the '229 patent acknowledges is sold under the brand name Taxol, was known to be "active against carcinomas of the ovary, breast, lung, esophagus and head and neck." *Id.* at 4:32–34. "Taxol, however, has been shown to induce toxicities associated with administration." *Id.* at 4:34–35. "Because paclitaxel is poorly soluble in water, cremophor [*i.e.*, polyethoxylated castor oil] typically is used as a solvent, requiring large infusion volumes and special tubing and filters." *Id.* at 4:38–40. "Cremophor is associated with side effects that can be severe, including anaphylaxis and other hypersensitivity reactions that can require pretreatment" with various drugs. *Id.* at 4:40–43.

33. The '229 patent discloses compositions and methods that supposedly reduce or eliminate the cremophor-related side effects that had been associated with the administration of paclitaxel. *Id.* at 2:35–46. Specifically, the patent dis-

closes compositions comprising paclitaxel together with a pharmaceutical carrier, which is preferably human serum albumin. *Id.* at 2:55–59. "Preferably, the formulation is essentially free of cremophor," thus avoiding its "side effects that can be severe." *Id.* at 12:3–9.

34. Human serum albumin is a highly soluble protein, and is the most abundant protein in human blood plasma. *Id.* at 5:15–18. The '229 patent acknowledges that the intravenous use of human serum albumin solution was known in the art. *Id.* at 5:22–23. Human serum albumin has "multiple hydrophobic binding sites," allowing it to bind to hydrophobic, water-insoluble drugs like paclitaxel. *Id.* at 5:30–47. The '229 patent theorizes that "the inclusion of proteins such as albumin in the inventive pharmaceutical compositions results in a reduction in side effects associated with administration of the pharmaceutical composition that is due, at least in part, to the binding of human serum albumin to any free drug that is present in the composition." *Id.* at 5:54–59.

35. The '229 patent states generally that "[t]he amount of albumin included in the pharmaceutical composition of the present invention will vary depending on the pharmaceutical active agent, other excipients, and the route and site of intended administration," so long as "the amount of albumin included in the composition is an amount effective to reduce one or more side effects the active pharmaceutical agent due to the [ ] administration of the inventive pharmaceutical

composition to a human." *Id.* at 5:60–67. In general, "compositions with lower amounts of albumin are preferred as this can greatly reduce cost," among other alleged reasons. *Id.* at 34:53–55.

36. The '229 patent discloses a wide range of albumin-paclitaxel ratios for its compositions: "Exemplary ranges for protein-drug preparations are protein to drug ratios (w/w) of 0.01:1 to about 100:1. More preferably, the ratios are in the range of 0.02:1 to about 40:1." *Id.* at 11:61–64. As the patent explains, "the ratio of protein to pharmaceutical agent will have to be optimized for different protein and pharmaceutical agent combinations." *Id.* at 11:64–66. The patent then discloses certain "preferred" ranges, and concludes by stating: "Most preferably, the ratio is about 1:1 to about 9:1." *Id.* at 12:2–3.

37. The patent includes examples of various pharmaceutical compositions. None of these examples discloses a formulation with an albumin-paclitaxel ratio of about 9:1. The only examples that mention the ratio of albumin to paclitaxel disclose ratios of 27:1, 4.5:1, and 10:1, and each of these examples makes clear that the ratio is calculated based on the ingredients used to make the composition, and/or that the ratio of the final composition remains the same as the ratio of the starting ingredients. See id. at 34:62–65 (Example 47), 35:26–29 (Example 48), 35:58–36:10 (Example 49).

38. For instance, 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. Likewise, 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. In both of these examples, the recited ratio is based on the starting materials used to make the composition.

39. 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. After reciting several process steps, Example 49 states: "The calculated ratio (w/w) of albumin to paclitaxel in this invention composition is approximately 10." *Id*. at 36:9–10. Apparently, 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.

40. 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.

41. The '229 patent provides that the claimed compositions can be prepared as nanoparticles. *Id.* at 9:36–38. Several examples in the patent describe nanoparticle formulations. In each one, the example provides that "the typical average diameter" of the particles ranges from "50–220 nm (Z-average, Malvern Zetasizer)." *See id.* at 14:61–63 (Example 1); 15:23–25 (Example 2); 15:67–16:2 (Example 4); 16:24–26 (Example 5); 16:51–53 (Example 6); 17:12–14 (Example 7); 17:45–47 (Example 8); 18:11–13 (Example 9); 18:42–44 (Example 10); 19:2–4 (Example 11); 19:27–28; (Example 12); 19:47–48 (Example 13); 20:4–6 (Example 14); 35:7–9 (Example 47); 36:39–41 (Example 48); 36:3–5 (Example 49). The "Z-average" is one possible measurement of particle diameter, and a "Malvern Zetasizer" is a particular device that is capable of determining that measurement.

B. Challenged claims

42. Claim 1 of the '229 patent claims a liquid pharmaceutical composition for injection comprising paclitaxel and albumin, formulated as particles having 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."

43. Similarly, claim 15 claims a sealed container containing a pharmaceu-

tical composition for injection comprising paclitaxel and albumin, formulated as particles having 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."

44. Claim 29 claims a method of treating cancer in humans by injecting an effective amount of the liquid pharmaceutical composition of claim 1.

45. Claims 2, 8, 11, 12, 13, 14, 16, 24, 27, 28, 30, 35, and 39 depend from (*i.e.*, incorporate all the limitations of) claims 1, 7, 4, 5, 9, 10, 15, 23, 25, 26, 29, 34, and 38, respectively, and require that the albumin is human serum albumin.

46. Claim 3 depends from claim 1 and requires that the liquid pharmaceutical composition is free of Cremophor.

47. Claims 4, 9, 17, 25, 31, 36, and 40 depend from claims 1, 7, 15, 23, 29, 34, and 38, respectively, and require that "the weight ratio of albumin to the paclitaxel in the pharmaceutical composition is 1:1 to 9:1."

48. Claims 5, 10, 18, 26, 32, 37, and 41 depend from claims 1, 7, 15, 23, 29, 34, and 38, respectively, and require that "the weight ratio of albumin to the paclitaxel in the pharmaceutical composition is about 9:1."

49. Claim 6 depends from claim 1 and requires that "the liquid pharmaceutical composition comprises about 5% by weight of albumin."

50. 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."

51. Claims 19 and 20 depend from claim 15 and require that the sealed container is "a unit dose container" and "a multi-dose container," respectively.

52. Claims 21, 22, and 23 depend from claim 15 and require that the pharmaceutical composition is "a liquid composition," "a dry composition," and "lyophilized," respectively.

53. Claims 34 and 38 depend from claim 29 and require that the cancer being treated is lung cancer and breast cancer, respectively.

54. Claims 42–48 depend from claims 29–34 and 38, respectively, and require that the liquid pharmaceutical composition is injected intravenously.

C. Claim construction

55. Counsel for Petitioners has informed me that in proceedings before the Patent Office, the claims of a patent must be construed to have their broadest reasonable interpretation in light of the specification and prosecution history of the patent. Furthermore, I understand that, in general, the broadest reasonable interpretation of the claims of a patent corresponds to their plain and ordinary meaning from the perspective of a skilled artisan.

56. In my opinion, a skilled artisan would have understood that the broadest reasonable interpretation of the terms "weight ratio of albumin to paclitaxel in the composition" and "ratio (w/w) of albumin to the paclitaxel in the pharmaceutical composition" in the challenged claims includes the ratio of albumin to

paclitaxel in the starting ingredients used to make the composition. A skilled artisan reading the '229 patent would have understood that the desired ratio of albumin to paclitaxel could be determined based on the starting ingredients because, as I discussed above, that is how the ratio was determined in Examples 47, 48, and 49, which are the only examples that mention an albumin-paclitaxel ratio, and no other method of calculating the ratio is provided in the patent.

57. It is also my opinion that a skilled artisan would have understood that the term "less than about 200 nm" in the challenged claims includes particle sizes of 220 nm or less, measured as the Z-average diameter using a Malvern Zetasizer. As I noted above, every example in the '229 patent that mentions particle size refers to the average diameter of the particles, measured as the Z-average using a Malvern Zetasizer, and covers a typical average diameter range up to 220 nm. Moreover, it was understood in the relevant art as December 2002 that the word "about" generally includes sizes above and below 10% of the stated particle size. Thus, a skilled artisan would have understood "about 200 nm" to include 220 nm or less, which is 10% above the stated size of 200 nm.

58. For the same reason, a skilled artisan would have understood that the terms "about 0.5% to about 5% by weight of albumin" in claim 1, and "about 5% by weight of albumin" in claim 6, include percentages above and below 10% of the stated percentage by weight of albumin. Thus, for example, a skilled artisan would

have understood "about 5% by weight of albumin" to include 4.5% by weight of albumin, which is 10% above the stated concentrations of 5%

V. THE PRIOR ART

A. Desai (EX1006)

59. Desai was published on January 7, 1999, and is therefore prior art to the '229 patent. EX1006, 1.

60. Desai "relates to methods for the production of particulate vehicles for the intravenous administration of pharmacologically active agents, as well as novel compositions produced thereby." *Id.* at 3. "In a particular aspect, the invention relates to methods for the *in vivo* delivery of substantially water insoluble pharmacologically active agents (*e.g.*, the anticancer drug Taxol®)," *i.e.*, paclitaxel. *Id.* A "preferred" embodiment of Desai comprises "extremely small particles" that make up a "drug delivery system in either liquid form or in the form of a redispersible powder," providing "pure drug particles coated with a protein." *Id.*

61. Like the '229 patent, Desai describes the "anticancer effects" of paclitaxel, noting that Taxol has been called "the new anticancer wonder-drug." *Id.* at 7. "The poor aqueous solubility of Taxol, however, presents a problem for human administration." *Id.* "Accordingly, currently used Taxol formulations require a cremaphor to solubilize the drug," which "has been linked to severe hypersensitivity reactions … and consequently requires premedication of patients." *Id.*

62. Desai states that "it is an object of this invention to deliver pharmacologically active agents (*e.g.*, Taxol, taxane, Taxotere, and the like) in unmodified form in a composition that does not cause allergic reactions due to the presence of added emulsifiers and solubilizing agents, as are currently employed in drug delivery," and "[i]t is a further object of the present invention to deliver pharmacologically active agents in a composition of microparticles or nanoparticles." *Id.* at 22. "It is yet another object of [Desai] to provide methods for the formation of submicron particles (nanoparticles) of pharmacologically active agents," including "methods [that] use proteins as stabilizing agents." *Id.*

63. According to Desai, its inventors "discovered that substantially water insoluble pharmacologically active agents can be delivered in the form of microparticles or nanoparticles that are suitable for parenteral administration in aqueous suspension. This mode of delivery 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.

64. In Desai's compositions, "proteins (*e.g.*, human serum albumin) are employed as a stabilizing agent." *Id.* Desai teaches "a drug delivery system in which part of the molecules of pharmacologically active agent are bound to the

protein (*e.g.*, human serum albumin)," and "contained within nanoparticles coated by protein." *Id.* at 24. In this system, "advantage is taken of the capability of human serum albumin to bind [to] Taxol," and "[s]ince albumin is present on the colloidal drug particles … , formation of a colloidal dispersion which is stable for prolonged periods is facilitated." *Id.* at 25.

65. Desai "further provides a method for the reproducible formation of unusually small 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.

66. Desai explains that the "submicron particles" of the composition can be provided "in powder form, which can easily be reconstituted in water or saline." *Id.* at 25–26. "The powder is obtained after removal of water by lyophilization," *i.e.*, by freeze-drying, which "produces a sterile solid formulation useful for intravenous injection." *Id.* at 26.

67. An exemplary formulation of Desai is "Capxol," which is described as a "cremophor-free formulation of the anticancer drug paclitaxel." *Id.* at 27. "Capxol™ is a lyophilized powder for reconstitution and intravenous administration," and "[w]hen reconstituted with a suitable aqueous medium … , Capxol™ forms a stable colloidal solution of paclitaxel." *Id.* at 28. The "preferred range" of particle sizes in Capxol is "20–400 nm." *Id.* "The two major components of

Capxol™ are unmodified paclitaxel and human serum albumin (HSA)." *Id.*

68. In certain tissues, "Capxol may be utilized to treat cancers … with a higher efficacy than Taxol," whereas for "other tissues … Capxol is expected to maintain anticancer activity at least equal to that of TAXOL." *Id.* at 30. Capxol's formulation also allows "increased anticancer activity for longer periods with similar doses of paclitaxel." *Id.* at 31. In general, Desai states that it is an "object of the present invention to provide a new formulation of paclitaxel that localizes paclitaxel in certain tissues, thereby providing higher anticancer activity at these sites." *Id.* at 35.

69. According to Desai, "[e]ach vial of Capxol™ contains 30 mg of paclitaxel and approximately 400 mg of human serum albumin," which corresponds to a 13.3:1 ratio of albumin to paclitaxel. *Id.* at 38.

70. Desai also states that Capxol is "produced by the method of Example 1," in the sense that "[t]he nanoparticles are prepared by high pressure homogenization of a solution of USP human serum albumin and a solution of paclitaxel in an organic solvent," which is subsequently "sterile filtered and lyophilized to obtain Capxol™." *Id.* at 38–39.

71. However, while Example 1 generally describes the process of preparing albumin-paclitaxel nanoparticles by high-pressure homogenization, it does not specifically describe a method limited to producing a sterile-filtered composition

with an albumin-paclitaxel ratio of 13.3:1, or any product containing 400 mg of albumin, such as Capxol. Rather, Example 1 specifically describes a method in which 30 mg of paclitaxel is combined with 27.0 ml of human serum albumin solution at a concentration of 1% (w/v), which corresponds to 270 mg of albumin, *i.e.*, a 9:1 ratio of albumin to paclitaxel. *Id.* at 62. Example 1 provides that "the typical diameter of the resulting paclitaxel particles was 160–220 (Z-average, Malvern Zetasizer)." *Id.* at 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.* "The particle size after reconstitution was the same as before lyophilization." *Id.* Example 1 does not recite a sterile filtration step.

72. A skilled artisan would have understood that the process of making Capxol specifically, which is sterile-filtered, has an albumin-paclitaxel ratio of 13.3:1, and is provided in vials of 30 mg paclitaxel and 400 mg of human serum albumin, is more narrowly described in Example 16, which is titled, "Summary of the Presently Preferred Manufacturing Process: Starting with 1 Gram Paclitaxel as the BDS." *Id.* at 75.

73. In the method of Example 16, a 3% solution of human serum albumin is made from 51.7 ml of 25% albumin and 379.3 ml of water, which corresponds to 431 ml of 3% albumin, or 12,930 mg of albumin. *Id.* at 75. Example 16 uses 1 g

(*i.e.*, 1,000 mg) of paclitaxel, which results initially in a 12.93:1 ratio of albumin to paclitaxel. *Id.* at 75. The resulting suspension is then sterile filtered using a 0.2 micron (*i.e.*, 200 nm) filter before being filled into vials containing 30 mg of paclitaxel each, and then lyophilized. *Id.* at 75-77.

74. Notably, Example 4, which describes a similar step of sterile filtration, states that approximately "97% of the Taxol [*i.e.*, paclitaxel] was recovered after filtration." *Id.* at 65. Thus, as applied to Example 16, 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.

75. Aside from disclosing a 9:1 ratio of albumin to paclitaxel in Example 1 and a 13.3:1 ratio in Example 16 and for Capxol, additional examples in Desai confirm that other ratios can also be used. For instance, in Example 4, the composition was prepared from 30 mg of paclitaxel and 29.4 ml of 1% w/v albumin. *Id.* These ingredients correspond to a ratio of albumin to paclitaxel of 294 mg to 30 mg, *i.e.*, 9.8:1. *Id.* Likewise, in Example 5, the composition was prepared from 225 mg paclitaxel and 97.0 ml of 3% w/v human serum albumin. *Id.* at 66. These ingredients correspond to a ratio of albumin to paclitaxel of 2910 mg to 225 mg, *i.e.*, 12.9:1. *Id.*

76. In addition, Desai discloses a preferred range of albumin concentra-

tions for producing albumin-paclitaxel formulations: "Protein 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. Although this range is disclosed as part of the description of a process for forming micron-sized particles (*id.* at 49), the same range applies to the process "for the formation of unusually small submicron particles (nanoparticles), *i.e.*, particles which are less than 200 nanometers in diameter." *Id.* at 52; *see id.* at 53 (explaining that in the process of forming nanoparticles, "human serum albumin … as described above [*i.e.*, as described at page 48] is dissolved in aqueous media").

77. Thus, although Example 1 of Desai exemplifies a process utilizing a 1% (w/v) concentration of albumin, Desai discloses that processes using lower concentrations of albumin, including concentrations as low as 0.5% (w/v), are also preferred. *Compare id. with* 62. As Desai explains, moreover, the examples such as Example 1 are "non-limiting." *Id.* at 62.

78. Desai also discloses reasons for increasing the paclitaxel concentration of existing formulations. As Desai explains, the need to combine Taxol with cremaphor as a solvent meant that the paclitaxel in the formulation was highly diluted, which "results in large volumes of infusion … up to 1 liter and infusion times ranging from 3 hours to 24 hours." *Id.* at 7–8. Taxol's "long infusion duration is inconvenient for patients, and is expensive due to the need to monitor the

patients for the entire 6 to 24-hour infusion duration." *Id.* at 17. Thus, Desai explains that "[i]t is desirable to reduce these infusion volumes, by developing formulations of paclitaxel that are stable at higher concentrations so as to reduce the time of administration." *Id.* at 21. By "allow[ing] for the delivery of high doses of the pharmacologically active agent in relatively small volumes," a formulation can "minimize[] patient discomfort at receiving large volumes of fluid and minimize[] hospital stay." *Id.* at 54.

79. More specifically, Desai discloses that 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 the albumin shell, thereby reducing the albumin-paclitaxel ratio. *Id.* at 79.

80. Further, in addition to reducing infusion volumes and increasing patient tolerability, Desai discloses that "[t]here is evidence in the literature that higher doses of paclitaxel result in a higher response rate." *Id.* at 19.

81. In particular, a specific "object of [Desai's] invention [is] to administer paclitaxel at concentrations greater than about 2 mg/ml." *Id.* at 35. Desai discloses that its albumin-paclitaxel nanoparticle formulations achieve this objective because they "can be reconstituted to any desired concentration of paclitaxel limited only by the solubility limits for HSA" (*i.e.*, human serum albumin), including "concentrations ranging from dilute (0.1 mg/ml paclitaxel) to concentrated (20

mg/ml paclitaxel)." *Id.* at 28; *see also id.* at 39 (same). Similarly, Desai teaches that its disclosed nanoparticle formulations remain "stable when reconstituted in an aqueous medium at several different concentrations ranging from, but not limited to 0.1 – 20 mg/ml." *Id.* at 32; *see also id.* at 33–34 (disclosed formulations "can be administered at much higher concentrations (up to 20 mg/ml) compared with [Taxol]"). Example 37 of Desai confirms that albumin-paclitaxel nanoparticles remained stable for at least three days when "reconstituted with sterile normal saline to concentrations of 1, 5, 10, and 15 mg/ml." *Id.* at 116.

82. The examples of Desai also describe methods of using the disclosed albumin-paclitaxel formulations. For instance, Example 45 is a pilot study showing the effectiveness of albumin-paclitaxel nanoparticles against mammary tumors. *Id.* at 122–23. Example 58 compares the effectiveness of albumin-paclitaxel nanoparticles to Taxol in treating mammary tumors. *Id.* at 140–42. In Example 40, which shows the tissue location of Capxol compared to Taxol, the inventors of Desai conclude that Capxol may be more effective in the treatment of cancers of the prostate, pancreas, kidney, lung, heart, bone, and spleen at equivalent levels of paclitaxel. *Id.* at 146.

B. Kadima (EX1004)

83. Kadima was published on February 10, 2000, and is thus prior art to the '229 patent. EX1004, 1.

84. Kadima generally relates to pharmaceutical compositions comprising paclitaxel and serum albumin, wherein "[a]t least 70% of the paclitaxel is bound to serum albumin, [and] the ratio of paclitaxel to albumin is at least about 1:5," *i.e.*, an albumin-paclitaxel ratio of about 5:1. *Id.*

85. Like Desai, Kadima teaches that "the highest concentrations of paclitaxel" achievable are desirable, as "[t]his results in the smallest volumes for administration or lyophilization/reconstitution, which enables more rapid administration, if desired." *Id.* at 13.

86. Kadima teaches that higher concentrations of paclitaxel can be obtained by adjusting the "ratio of paclitaxel:albumin" and the "concentration of paclitaxel in the albumin solution." *Id.*; *see* 12–13 (discussing the desirability of lower ratios of albumin to paclitaxel).

87. While noting that albumin is an effective stabilizer, Kadima observes that "[a]lbumin is a cost-limiting component for use in drug stabilization." *Id.* at 10. Kadima thus emphasizes the importance of providing a "commercially feasible method for using a serum albumin to administer paclitaxel." *Id.* at 33. Kadima explains that one challenge to achieving this goal is that "[a]lbumin is an expensive ingredient." *Id.*

88. Kadima illustrates the impact of the albumin-paclitaxel ratio on the cost of producing a pharmaceutical composition with the following chart:

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.

Id. at 34.

89. Similar to the nanoparticle-based formulations of Desai, the albumin-paclitaxel formulations of Kadima are "essentially free of toxic ingredients such as Cremophor." *Id.* at 28.

C. Liversidge (EX1005)

90. Liversidge issued on March 21, 1995, and is therefore prior art to the '260 patent. EX1005.

91. I was already familiar with Liversidge prior to my work in this proceeding, as I was a testifying expert for Elan Pharma International, which I understand owns Liversidge, in litigation asserting Liversidge against the Patent Owner in this proceeding. *Elan Pharma Int'l Ltd. v. Abraxis BioScience, Inc.*, C.A. No. 06-438-GMS (D. Del.). In that litigation, a jury determined that Liversidge was a valid patent, and that Patent Owner's product, Abraxane—an alleged embodiment of the '229 patent—infringed Liversidge. EX1011.

92. Liversidge generally discloses particle-based "anticancer compositions" comprising an "anticancer agent having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 1000 nm," and methods of administering such pharmaceutical compositions. EX1005, 1:49–65.

93. The "anticancer agent" of Liversidge may be paclitaxel (*id*. at 2:50, 3:20), and the "[p]articularly preferred surface modifiers" for the particles include albumin (*id*. at 4:23, 48).

94. Liversidge provides that, "[i]n particularly preferred embodiments of the invention, the effective average particle size is less than about 400 nm," and "[i]n some embodiments of the invention, the effective average particle size is less than about 300 nm." *Id*. at 5:1–5.

95. Liversidge teaches that the "[t]he surface modifier can be present in an amount of 0.1–90% … based on the total weight of the dry particle." *Id*. at 7:1–4. Consistent with that teaching, claim 1 of Liversidge is directed to "[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.

96. Liversidge also 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." *Id.* at 7:5–46; *see id.* at 7:35–36.

D. Taxol label (EX1008)

97. The labeling for Taxol in the 54th edition of the Physicians' Desk Reference was published in 2000, and is therefore prior art to the '229 patent. EX1008 ("Taxol label").

98. As relevant here, the Taxol label states that "TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials." *Id.* at 3. Similarly, the label provides that these dosages are each provided in a "multidose vial individually packaged in a carton." *Id.* at 9.

VI. ANTICIPATION

99. In my opinion, claims 1–19 and 21–48 are unpatentable as anticipated by WO 99/00113 to Desai et al. ("Desai") (EX1006), which discloses every limitation of each of these claims. I explain the bases for my opinion below.

A. Claims 1–19 and 21–48 of the '229 patent are anticipated.

1. Claim 1 is anticipated by Desai.

100. Claim 1 of the '229 patent states as follows, with the bracketed letters added to delineate the claim's 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." Each limitation of claim 1 is disclosed in and enabled by Desai, which therefore anticipates this claim.

a. Albumin-paclitaxel combination

101. Example 1 of Desai discloses the combination of paclitaxel and albumin as a carrier. EX1006, 62. As Desai makes clear, these components are formulated as a liquid pharmaceutical composition for injection. 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. Desai explains that this lyophilization process "produces a sterile solid formulation useful for intravenous injection" (*id.* at 26), and that "a lyophilized powder" is useful "for reconstitution and intravenous administration." *Id.* at 28. Desai as a whole is also directed to "methods for the production of particulate vehicles for the intravenous administration of pharmacologically active agents." *Id.* at 3. Thus, Example 1 meets claim 1's requirement of "[a] liquid pharmaceutical composition for injection comprising paclitaxel and a pharmaceutically acceptable carrier,

wherein the pharmaceutically acceptable carrier comprises albumin."

b. Particle size of less than about 200 nm

102. Example 1 of Desai also discloses that the albumin-paclitaxel formulation comprises nanoparticles having a typical average diameter of 160–220 nm, measured as the Z-average using a Malvern Zetasizer. *Id.* at 63. All of the average diameters within this typical range fall within the "about 200 nm" limit of claim 1, which, as I discussed above in paragraph 57, includes particles of 220 nm or less, measured as the Z-average diameter using a Malvern Zetasizer. Example 1 thus necessarily produces a product that satisfies claim 1's "about 200 nm" limitation

103. Moreover, I note that Desai's overall "preferred size range of the particles is between about 50 nm – 170 nm," which falls completely within the "about 200 nm" limit of claim 1. *Id.* at 54.

104. Desai also "enables the reproducible production of unusually small nanoparticles of less than 200 nm diameter." *Id.* at 1; *id.* at 23 ("The invention further provides a method for the reproducible formation of unusually small nanoparticles (less than 200 nm diameter)."), 52 (describing a process "to obtain … particles <200 nm"), 54 (describing the production of "nanoparticles … in the range of about 10 nm – 200 nm diameter"). In my opinion, a skilled artisan would have agreed that the methods recited in Desai allowed for the formation of albumin-paclitaxel particles of less than about 200 nm.

105. Thus, Example 1 of Desai meets 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."

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

106. Example 1 of Desai further discloses a weight ratio of albumin to paclitaxel of about 9:1 by providing that "30 mg paclitaxel is dissolved in 3.0 ml methylene chloride," and further provides that "[t]he solution was added to 27.0 ml of human serum albumin solution (1% w/v)." *Id.* at 62.

107. As a skilled artisan would have understood, 27 ml of 1% (w/v) albumin corresponds to 270 mg of albumin, and, when combined with 30 mg of paclitaxel, necessarily results in a composition with an albumin-paclitaxel weight ratio of 270:30, *i.e.*, exactly 9:1. As I discussed above in paragraphs 37–40 and 56, this method of calculating the ratio of albumin to paclitaxel based on the starting ingredients for making the composition is the same as the method of calculating the ratio in the examples of the '229 patent. Thus, Example 1 of Desai meets claim 1's limitation requiring that "the weight ratio of albumin to paclitaxel in the composition is about 1:1 to about 9:1."

d. Weight percentage of albumin

108. As I discussed above in paragraph 62, an explicit "object of [Desai's] invention [is] to administer paclitaxel at concentrations greater than about 2

mg/ml," and Example 37 of Desai exemplifies concentrations of paclitaxel including 1 mg/ml and 5 mg/ml. *Id.* at 35, 116. These disclosures apply to Example 1 of Desai, which provides that its composition is "easily reconstituted to the original dispersion by addition of sterile water or saline." *Id.* at 63.

109. At concentrations of 1, 2, or 5 mg/ml of paclitaxel reconstituted in saline, the composition of Example 1, with an albumin-paclitaxel ratio of 9:1, will necessarily contain albumin concentrations of 9 mg/ml, 18 mg/ml, and 45 mg/ml, respectively, which correspond to 0.9%, 1.8%, and 4.5% by weight of albumin. All of these weight percentages of albumin fall within claim 1's limitation that "the liquid pharmaceutical composition comprises about 0.5% to about 5% by weight of albumin, and … the liquid pharmaceutical composition further comprises saline."

110. Independently, as I discussed in paragraph 81, Desai expressly discloses a range of paclitaxel concentrations of 0.1–20 mg/ml. *Id.* at 28, 32, 39. More narrowly, Example 37 exemplifies a range of paclitaxel concentrations of 1–15 mg/ml. *Id.* at 116. As applied to the 9:1 albumin-paclitaxel ratio of Example 1, Desai's broader range corresponds to albumin concentrations of 0.09–18% by weight, whereas Example 37's narrower range corresponds to albumin concentrations of 0.9–13.5% by weight. In my opinion, the ranges disclosed by Desai describe claim 1's albumin concentration range of "about 0.5% to about 5% by weight of albumin" with sufficient specificity such that there is no reasonable dif-

ference in how the claimed invention operates over the ranges. In particular, I am not aware of any evidence that concentrations of about 0.5% to about 5%, as compared to other albumin concentrations that fall within Desai's ranges, are critical to the operation of the claimed invention. Accordingly, Desai discloses each limitation of claim 1 and therefore anticipates it.

2. Claims 3 and 6 are anticipated by Desai.

111. Claim 3 depends from claim 1 and further requires that the composition is free of Cremophor, and no Cremophor is added to the composition of Example 1 of Desai. *Id.* at 62–63. Thus, Desai anticipates claim 3.

112. Claim 6 also depends from claim 1 and requires that the composition comprises "about 5% by weight of albumin." Again, Example 37 of Desai exemplifies a paclitaxel concentration of 5 mg/ml, which, as applied to a 9:1 albumin-paclitaxel ratio, corresponds to 4.5% by weight of albumin. *Id.* at 116. As I discussed above in paragraph 58, a skilled artisan would understand that "about 5%" includes 4.5% by weight of albumin, which is 10% below 4.5%.

113. In addition, as I also discussed above, Desai expressly discloses a range of paclitaxel concentrations of 0.1–20 mg/ml. *Id.* at 28, 32, 39. More narrowly, Example 37 exemplifies a range of paclitaxel concentrations of 1–15 mg/ml. *Id.* at 116. As applied to a 9:1 albumin-paclitaxel ratio, Desai's broader range corresponds to albumin concentrations of 0.09–18% by weight, whereas Ex-

ample 37's narrower range corresponds to albumin concentrations of 0.9–13.5% by weight. In my opinion, the ranges disclosed by Desai describe claim 6's albumin concentrations of "about 5% by weight" with sufficient specificity such that there is no reasonable difference in how the claimed invention operates over the ranges. In particular, I am not aware of any evidence that concentrations of about 5%, as compared to other albumin concentrations that fall within Desai's ranges, are critical to the operation of the claimed invention. Thus, claim 6 is anticipated.

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

114. Claim 15 is directed to "[a] sealed container" containing a pharmaceutical composition for injection that otherwise meets the first three limitations of claim 1 discussed above. Thus, the only differences between claim 15 and claim 1 are that claim 15 is directed to "[a] sealed container" instead of "[a] liquid pharmaceutical composition," and claim 15 does not include claim 1's requirements that the composition comprises 0.5% to 5% albumin, and saline.

115. For the same reasons I discussed above in connection with claim 1, Desai discloses a composition that meets each of claim 15's limitations. Furthermore, Desai's "Summary of the Presently Preferred Manufacturing Process" instructs the person of ordinary skill in the art to fill lyophilized albumin-paclitaxel nanoparticles into vials, and to "stopper the vials and seal the vials by crimping them with the 20mm Wheaton aluminum tear-off caps." EX1006, 76–77. A

skilled artisan would understand that this instruction applies to Example 1 of Desai, which discloses a formulation with a 9:1 albumin-paclitaxel ratio that "was further lyophilized" for storage and later use in order to be "easily reconstituted to the original dispersion." *Id.* at 63. Thus, Desai anticipates claim 15.

116. Claim 19 depends from claim 15 and requires that the sealed container is "a unit dose container." Claims 21, 22, and 23 also depend from claim 15 and require that the pharmaceutical composition in the sealed container is "a liquid composition," "a dry composition," and "lyophilized," respectively.

117. Example 38 of Desai, which is titled "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." *Id.* at 116–17. Desai explains: "This reconstituted solution can be directly administered to a patient either by injection or infusion with standard i.v. infusion sets." *Id.* at 117. 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," which "avoids the lyophilization step in the manufacturing process." *Id.*

118. Again, these disclosures apply to the composition of 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 of albumin-paclitaxel nanoparticles that otherwise meet the limitations of claim 15 of the '229 patent, and that are either a liquid composition, a dry composition, and/or lyophilized. Accordingly, Desai anticipates each of claims 19 and 21–23 of the '229 patent.

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

119. Claim 29 claims a method of treating cancer in humans by injecting an effective amount of the liquid pharmaceutical composition of claim 1. Claims 34 and 38 depend from claim 29 and require that the cancer being treated is lung cancer and breast cancer, respectively. Desai's compositions in general are directed to treating these diseases. Indeed, the primary objective of Desai is to provide formulations of paclitaxel that are "significantly less toxic and more efficacious than Taxol®," in order to "increas[e] the efficacy of treatment of cancers." *Id.* at 4. Desai also "incorporate[s] by reference as if reproduced in full" numerous "patents, scientific articles, and other documents" evidencing the use of paclitaxel to treat the claimed diseases. *Id.* at 12–20.

120. In particular, Desai teaches that "[t]he anticancer agent paclitaxel … has remarkable clinical activity in a number of human cancers including cancers of the ovary, breast, lung, esophagus, head and neck region, bladder and lymphomas."

EX1006, 27. Moreover, Desai acknowledges that "[i]t is known that the delivery of biologics in the form of a particulate suspension allows targeting to organs such as the … lungs." *Id.* at 29. Desai specifically teaches that albumin-paclitaxel nanoparticles have "been demonstrated to result in higher level concentrations of paclitaxel in the … lung … when compared to Taxol at equivalent doses." *Id.* at 30; *see also id.* at 79 (same), 147 (same). Furthermore, Example 20 discloses animal testing data that confirms the elevated concentration of administered albumin nanoparticles in the lungs. *Id.* at 80–81.

121. As to breast cancer, Example 45 of Desai discloses a study and method of treating mammary tumors using albumin-paclitaxel nanoparticles, and concludes 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, which was FDA-approved to treat cancer before December 2002. *Id.* at 123; *see also id.* at 7, 12. Example 58 similarly discloses the injection of albumin-paclitaxel nanoparticles to treat "human mammary tumor fragments." *Id.* at 140. Moreover, Desai repeatedly discloses the injection of paclitaxel to treat breast cancer, and Examples 65 and 66 teach a clinical trial design and clinical development program to treat metastatic breast cancer in humans with effective amounts of injectable albumin-paclitaxel nanoparticles. *Id.* at 16, 18–20, 27, 159–61. In addition, claims 7, 15, 22, and 28 of Desai are directed to methods of using albumin-

paclitaxel nanoparticles to treat tumors and/or cancer. *Id.* at 162–65.

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

5. Claims 7 and 33 are anticipated by Desai.

123. 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." As discussed, Example 1 of Desai provides that the lyophilized albumin-paclitaxel nanoparticle composition "could be easily reconstituted to the original dispersion by addition of sterile water or saline." EX1006, 63. As a skilled artisan would have known, saline for injection (*i.e.*, sodium chloride) has a pH of 4.5 to 7.0. EX1027, *Remington's* at 6. Accordingly, the composition of Desai's Example 1 resuspended in saline would have a pH between 5.0 and 8.0, therefore anticipating claims 7 and 33 of the '229 patent.

6. Claims 2, 8, 11, 12, 13, 14, 16, 24, 27, 28, 30, 35, and 39 are anticipated by Desai.

124. Claims 2, 8, 11, 12, 13, 14, 16, 24, 27, 28, 30, 35, and 39 depend from claims 1, 7, 4, 5, 9, 10, 15, 23, 25, 26, 29, 34, and 38, respectively, and require that the albumin is human serum albumin, which is the albumin used in Example 1 of Desai. EX1006, 62. Thus, Desai also anticipates each of these claims.

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

125. Claims 4, 9, 17, 25, 31, 36, and 40 depend from claims 1, 7, 15, 23, 29, 34, and 38, respectively, and require that "the weight ratio of albumin to the paclitaxel in the pharmaceutical composition is 1:1 to 9:1." Similarly, claims 5, 10, 18, 26, 32, 37, and 41 depend from claims 1, 7, 15, 23, 29, 34, and 38, respectively, and require that "the weight ratio of albumin to the paclitaxel in the pharmaceutical composition is about 9:1." As discussed above, Example 1 of Desai discloses a composition with an albumin-paclitaxel ratio of 9:1 (*id.* at 62–63), and thus anticipates claims 4, 5, 9, 10, 17, 18, 25, 26, 31, 32, 36, 37, 40, and 41.

8. Claims 42–48 are anticipated by Desai.

126. Claims 42–48 depend from claims 29–34 and 38, respectively, and require that the liquid pharmaceutical composition is injected intravenously. Desai as a whole concerns "the intravenous administration of pharmacologically active agents," and 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 3, 63. As Desai explains, this "lyophilized powder" is designed "for reconstitution and intravenous administration." *Id.* at 28. Example 45 also discloses a study and method of treating mammary tumors using albumin-paclitaxel nanoparticles as a bolus intravenous injection. *Id.* at 122–23. Similarly, Example 52 discloses the intravenous delivery of albumin-paclitaxel

nanoparticles. *Id.* at 131–32. In addition, claims 6, 14, 21, and 27 of Desai are directed to methods of administering albumin-paclitaxel nanoparticles by routes including intravenous delivery. *Id.* at 162–64. Thus, Desai anticipates claims 42–48.

127. Accordingly, Desai discloses every limitation of each of claims 1–19 and 21–48, and therefore anticipates each of these claims.

B. The "starting" ratio of albumin to paclitaxel does not change.

128. Petitioners' counsel has informed me that Patent Owner may argue that Example 1 of Desai does not disclose an albumin-paclitaxel ratio of about 9:1, because the "final" ratio obtained after following the steps of Example 1 will supposedly be higher than the "starting" ratio of the ingredients used to make the composition, due to the loss of paclitaxel during manufacturing. In support of that argument, I understand that Patent Owner may rely on Desai's disclosure that "Capxol™ is … produced by the method of Example 1," and "[e]ach vial of Capxol™ contains 30 mg of paclitaxel and approximately 400 mg of human serum albumin," which corresponds to an albumin-paclitaxel ratio of 13.3:1. EX1006, 38. I disagree with this argument, and a skilled artisan would disagree as well.

129. As I discussed above in paragraph 56, a skilled artisan would have understood that the "ratio" in the challenged claims includes at least the ratio of the starting ingredients used to make the composition. Indeed, as I explained above in paragraphs 37–40, every example in the '229 patent that mentions an albumin-

paclitaxel ratio calculates this ratio based on the proportion of starting materials—not some materially different "final" ratio. This makes sense because formulators, similar to chefs, typically measure weight ratios of starting ingredients.

130. Moreover, a skilled artisan would not have expected the method of Example 1 of Desai to result in any loss of paclitaxel during manufacturing that would affect the albumin-paclitaxel ratio of the composition. There is no mention in Desai of any such loss of paclitaxel. And there is no reason why any of the steps of Example 1 of Desai would result in such a loss.

131. Although Desai states that Capxol contains albumin and paclitaxel in a 13.3:1 ratio, and states that Capxol is made according to the method of Example 1 (*id*. at 38), a skilled artisan would have understood that the reference to Capxol being made by the method of Example 1 simply refers to the general method of preparing "nanoparticles … by high pressure homogenization of a solution of USP human serum albumin and a solution of paclitaxel in an organic solvent." *Id*. at 39. Indeed, Example 1 is titled "Preparation of Nanoparticles by High Pressure Homogenization," and describes the homogenization of a solution of human serum albumin and a solution of paclitaxel dissolved in methylene chloride. *Id*. at 62.

132. Thus, a skilled artisan would have understood that the method of Example 1 could be used to produce various embodiments of the albumin-paclitaxel nanoparticles disclosed in Desai, and was not limited to making Capxol. In other

words, a skilled artisan would understand that Example 1 provides a method of making an albumin-paclitaxel composition *like* Capxol, but that does not necessarily result in Capxol.

133. Moreover, a skilled artisan would not have believed that Capxol, which contains 30 mg of paclitaxel and *400 mg* of albumin (corresponding to an albumin-paclitaxel ratio of 13.3:1), is made using the disclosed starting materials of Example 1, *i.e.*, 30 mg of paclitaxel and *270 mg* of albumin (corresponding to a ratio of 9:1). Nor would a skilled artisan have believed that the difference between the ratios of Capxol and Example 1 results from the loss of paclitaxel during the steps of Example 1. On the contrary, Capxol contains the same amount of paclitaxel that is used in the starting materials of Example 1. It is the amount of albumin that is different: Capxol contains 400 mg, whereas Example 1 uses only 270 mg. 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 would produce a composition with 400 mg of albumin.

134. A skilled artisan also would have realized that Example 1 was not the precise method of making Capxol, which is sterile filtered and filled into vials containing 30 mg of paclitaxel, because Example 1 does not mention sterile filtration or vials. *Compare id*. at 38–39 *with* 62–63.

135. Instead, from reading Desai as a whole, a skilled artisan would have understood that the more specific process of making Capxol (as opposed to the general process of making nanoparticles by high-pressure homogenization) is disclosed in Example 16, which recites Desai's "Presently Preferred Manufacturing Process." *Id*. at 75. As I discussed above in paragraphs 72–74, Example 16 provides a method of producing a sterile-filtered composition with an albumin-paclitaxel ratio of 13.3:1, which is filled into vials containing 30 mg of paclitaxel.

136. Accordingly, Desai's disclosure that Capxol has a 13.3:1 ratio of albumin to paclitaxel and is made using the method of Example 1 does not change my opinion that Desai anticipates each of the challenged claims

VII. OBVIOUSNESS

137. It is also my opinion that all claims of the '229 patent would have been obvious to a skilled artisan. Specifically, claims 1–19 and 21–48 would have been obvious over Desai, either alone or in combination with Kadima (EX1004) and Liversidge (EX1005). Claim 20 would have been obvious over Desai and the Taxol label (EX1008), and optionally in further view of Kadima and Liversidge.

A. Claim 1 of the '229 patent would have been obvious.

1. Obviousness over Desai alone

138. As I noted above, claim 1 of the '229 patent claims the following, with the bracketed letters added to delineate the claim's four primary 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."

139. In my opinion, to the extent there are any differences between Desai and claim 1 of the '229 patent (and, as discussed above, it is my opinion that there are no differences), any such differences would have been obvious to a skilled artisan as of December 2002 in view of Desai.

140. First, it would have been obvious to a skilled artisan in December 2002 to formulate paclitaxel and albumin as a liquid pharmaceutical composition for injection. Indeed, Desai is primarily directed to such compositions. EX1006, 25. "The two major components of Capxol™"—the main focus of Desai—"are unmodified paclitaxel and human serum albumin (HSA)." *Id*. at 28. Capxol is provided as "a lyophilized powder for reconstitution and intravenous administration. When reconstituted with a suitable aqueous medium such as 0.9% sodium chloride injection [*i.e.*, saline] or 5% dextrose injection, Capxol™ forms a stable colloidal solution of paclitaxel." *Id*. Moreover, the objective of Desai is to provide

a "pharmaceutically acceptable formulation" (*id.* at 36), and Capxol is designed for "intravenous administration" (*id.* at 28, 38).

141. Second, it would have been obvious to a skilled artisan in December 2002 to formulate the paclitaxel and albumin as particles with a particle size of less than 200 nm. Desai states that, "[i]n a preferred embodiment, the average diameter of the above-described particles is no greater than about 200 nm," because "[s]uch particles are particularly advantageous." *Id.* at 38. More specifically, Desai states that "[t]he preferred size range of the particles is between about 50 nm – 170 nm." *Id.* at 54.

142. 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 most microorganisms such as 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. Accordingly, Desai would have motivated a skilled artisan as of December 2002 to formulate paclitaxel and albumin as particles with a size less than 200 nm.[1]

[1] A skilled artisan would have known that regulatory guidelines issued by the FDA and its European counterpart before December 2002 similarly required nanoparticle drug products to have nanoparticles smaller than 220 nm in diameter

143. In so doing, a skilled artisan would have had a reasonable expectation of success. Indeed, Desai expressly "enables the reproducible production of unusually small nanoparticles of less than 200 nm diameter." *Id.* at 1; *see also* 23 ("The invention further provides a method for the reproducible formation of unusually small nanoparticles (less than 200 nm diameter)."); *id.* at 52 (describing a process "to obtain … particles <200nm"); *id.* at 54. Again, a skilled artisan in December 2002 would have agreed that the methods described in Desai enabled the production of albumin-paclitaxel nanoparticles smaller than 200 nm.

144. Third and fourth, in addition to making a pharmaceutical composition for injection made up of albumin-paclitaxel nanoparticles smaller than about 200 nm, it would have been obvious to a skilled artisan as of December 2002 to provide that "the weight ratio of albumin to paclitaxel in the composition is about 1:1 to about 9:1," that "the liquid pharmaceutical composition comprises about 0.5% to about 5% by weight of albumin," and that "the liquid pharmaceutical composition further comprises saline," for the reasons discussed in the subsections below.

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in order to provide for sterile filtration. EX1009, 29–30 (1997 FDA Guideline: "Filtration is a common method of sterilizing drug product solutions…. Such filters usually have a rated porosity of 0.22 micron or smaller."); EX1010, 6 (1996 EMEA Guideline: "For sterilisation by filtration," "sizes of 0.22 μm or less are acceptable").

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

145. With respect to the albumin-paclitaxel ratio, as an initial matter, Desai discloses a range of ratios of albumin to paclitaxel, and a ratio of about 9:1 is among the ratios within that range. As I discussed above in paragraphs 71 and 75, Example 1 of Desai discloses a 9:1 ratio, and other examples in Desai disclose higher ratios, including 9.8:1, 12.9:1, and 13.3:1. Thus, the ratio of about 9:1 falls within a range disclosed in Desai.

146. Even assuming that Example 1 somehow does not expressly disclose a 9:1 ratio because the ratio would increase during manufacturing (an assumption with which I disagree, for the reasons I discussed above), an albumin-paclitaxel ratio of about 9:1 nevertheless falls within a range of ratios covered by Desai. Indeed, Desai specifically states that its examples are "non-limiting," and generally discloses a process for making albumin-paclitaxel nanoparticle formulations in which 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)." EX1006, 50. Thus, concentrations of albumin as low as 0.05% (w/v) are encompassed by Desai, and concentrations as low as 0.5% (w/v) are "preferred."

147. A skilled artisan would have understood that this preferred range could be applied to Desai's various "non-limiting" examples. As applied to the method of Example 1, a 0.5% (w/v) concentration of albumin, as opposed to the

1% (w/v) concentration used by way of example, would result in a composition with half as much albumin, *i.e.*, a ratio of only 4.5:1 albumin to paclitaxel. A ratio of about 9:1 falls between this lower ratio and the higher ratio of 13.3:1 disclosed for Capxol.

148. I understand that where, as here, 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. I am not aware of any evidence that would allow Patent Owner here to meet this burden.

149. First, I understand that a prior art reference does not "teach away" from a claimed invention unless it criticizes, discredits, or otherwise discourages investigation into the invention claimed. Applying this standard, I am not aware of any prior art reference that teaches away from selecting an albumin-paclitaxel ratio of about 9:1 from the broader range disclosed in Desai.

150. Second, as I discuss below in Section VII.J, it is my opinion that the albumin-paclitaxel ratio of about 9:1 has not been demonstrated to produce any new and unexpected results relative to the prior art.

151. Third, I am not aware of any other pertinent secondary considerations that would suggest that a ratio of about 9:1 would be unobvious. Accordingly, it is

my opinion that selecting a ratio of albumin to paclitaxel of about 9:1 would have been obvious to a skilled artisan as of December 2002 for this reason alone.

b. A skilled artisan would have been motivated to lower Capxol's 13.3:1 albumin-paclitaxel ratio.

152. Even assuming that the prior art does not disclose a range that includes an albumin-paclitaxel ratio of about 9:1, or that selecting the ratio of about 9:1 from such a range (both assumptions with which I disagree), it is my opinion that it would have been obvious to a skilled artisan as of December 2002 to modify Capxol by reducing its albumin-paclitaxel ratio from 13.3:1, which is disclosed in Desai, to an albumin-paclitaxel ratio of about 9:1.

153. Desai explains that "[i]t is desirable to reduce the[] infusion volume[]" of parenteral formulations "by developing formulations of paclitaxel that are stable at higher concentrations so as to reduce the time of administration." EX1006, 21. According to Desai, "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." *Id.* at 54. A skilled artisan reading these disclosures as of December 2002 would have understood that delivering higher doses of paclitaxel in smaller volumes, and thereby minimizing patient discomfort and infusion times, could be accomplished simply by increasing the concentration of paclitaxel relative to the only other ingredient in the Capxol formulation, *i.e.*, albumin, resulting in a lower albumin-paclitaxel ratio.

154. Moreover, Desai teaches that "higher doses of paclitaxel result in a higher response rate." *Id.* at 19. Higher doses can be provided more efficiently by using higher concentrations of paclitaxel. 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.

155. Based on these disclosures, a skilled artisan as of December 2002 would have appreciated that Capxol could likewise be improved to provide higher concentrations of paclitaxel by either increasing the amount of paclitaxel, reducing the amount of albumin, or both, which would thereby reduce the composition's ratio of albumin to paclitaxel. In fact, Desai suggests that it is desirable "to obtain a higher loading of drug into the crosslinked protein shell." *Id.* at 79. Desai thus expressly suggests increasing the concentration of paclitaxel in the composition by increasing the amount of paclitaxel per particle relative to the amount of albumin coating the particle, rather than merely increasing the concentration of the reconstituted composition overall without altering the ratio of albumin to paclitaxel.

156. Moreover, as a general principle, formulators always seek to maximize the amount of active drug in a formulation (here, paclitaxel) and to minimize the amount of excipients (here, albumin) that are not needed. Therefore, a skilled artisan would have been motivated to use a ratio of albumin to paclitaxel of about 9:1 instead of Capxol's ratio of 13.3:1, with a reasonable expectation of success in

retaining Capxol's other beneficial properties.

c. A skilled artisan would have reasonably expected an albumin-paclitaxel ratio of 9:1 to retain stability.

157. It is also my opinion that, in preparing a formulation with an albumin-paclitaxel ratio of about 9:1, a skilled artisan as of December 2002 would have reasonably expected success in retaining the stability of the Capxol formulation, notwithstanding albumin's role in the formulation as a known stabilizer.

158. In my opinion, nothing in Desai suggests that the albumin-paclitaxel ratio of 13.3:1 in Capxol is critical to maintaining stability of the formulation. In fact, Example 1, as I discussed above, uses a 9:1 ratio, and other examples in Desai use similar ratios that are also lower than 13.3:1. In addition, Desai teaches that the concentration of albumin used in its "non-limiting" examples can be varied by the skilled artisan, and Desai encourages skilled artisans to "obtain a higher loading of drug into the crosslinked protein shell" (EX1006, 79). Desai never warns about any risks of destabilizing the formulation if the proportion of albumin to paclitaxel used in the formulation is somewhat less than 13.3:1. A skilled artisan in December 2002 would not have been concerned about such risks, either.

159. Although albumin is disclosed as a stabilizer, and a skilled artisan would have expected albumin to stabilize the composition, there is no reason why a skilled artisan would have expected a relatively minor reduction in the albumin-paclitaxel ratio from 13.3:1 to about 9:1 to have caused any problematic issue of

physical instability.

160. Rather, Desai teaches simply that it is the presence of albumin on the surface of the particles, and albumin's inherent stabilizing properties, that 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. There is no suggestion in Desai that an albumin-paclitaxel ratio above about 9:1 is necessary to achieve this stabilizing effect. Nor is there any reason why so much albumin would be needed to form a crosslinked albumin shell around the paclitaxel particles. In fact, because a formulation with an albumin-paclitaxel ratio of about 9:1 would also have "albumin … present on the colloidal drug particles," including on the surface of the particles bound to paclitaxel, Desai expressly suggests that such a formulation would also have been expected to be "stable for prolonged periods." *Id.*

161. Moreover, Desai makes clear that Capxol has unusually exceptional stability, suggesting that less albumin could be used while maintaining a sufficiently stable formulation. Example 37 of Desai discloses 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.

Thus, even if reducing the albumin-paclitaxel ratio from 13.3:1 to about 9:1 could be expected to cause some reduction in stability, a minor reduction in stability would not have dissuaded a skilled artisan from attempting that modification.

162. As Desai explains, Taxol, which was and remains a frequently used and commercially successful formulation, "precipitates in within about 24 hours after reconstitution at the recommended concentrations of 0.6–1.2 mg/ml." *Id.* Thus, a skilled artisan would have expected even a substantially less stable formulation than Capxol to be stable enough for therapeutic and commercial purposes.

163. In fact, a skilled artisan would have only needed the formulation to remain stable for long enough to infuse a therapeutic dose of the drug, and there is no question that such a short amount of time to maintain stability would have been expected. Indeed, articles by Damascelli et al. and Ibrahim et al. each reported that albumin-paclitaxel nanoparticles had been administered to human patients with a 30-minute infusion time, and neither reference reports any problems regarding stability during infusion. EX1017, Damascelli at 4, 10; EX1018, Ibrahim at 1 (each disclosing 30-minute infusions in clinical studies).

164. In any event, a skilled artisan would have been able to optimize the albumin-paclitaxel ratio by balancing the need for stability with the desirability of a higher drug concentration, and verify the typical parameters of stability using the same routine methods shown in Example 37 of Desai. EX1006, 116.

165. Accordingly, for at least these reasons, 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. The modification therefore would have been obvious.

d. The claimed weight percentage of albumin, when the albumin-paclitaxel formulation is reconstituted in saline, falls within a range disclosed by Desai.

166. A skilled artisan adjusting the albumin-paclitaxel ratio of Capxol also would have been mindful of the concentration of albumin by weight in the liquid pharmaceutical composition upon reconstitution, which a skilled artisan would have understood was dependent on both the paclitaxel concentration and the albumin-paclitaxel ratio of the composition. As I discussed above in paragraph 81, Desai expressly discloses a range of paclitaxel concentrations of 0.1–20 mg/ml. *Id*. at 28, 32, 39. More narrowly, Example 37 exemplifies a range of paclitaxel concentrations of 1–15 mg/ml when the composition was "reconstituted with sterile normal saline" (*id*. at 116), which a skilled artisan would have understood to be a standard aqueous medium for injectable drugs (EX1027, *Remington's* at 6). As applied to a 9:1 albumin-paclitaxel ratio, Desai's broader range of paclitaxel concentrations corresponds to albumin concentrations of 0.09–18% by weight, whereas Example 37's narrower range of paclitaxel concentrations corresponds to albumin concentrations of 0.9–13.5% by weight.

167. I understand that where, as here, 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. I am not aware of any evidence that would allow Patent Owner to meet this burden. Thus, in my opinion, it would have been obvious to reconstitute the formulation of claim 1 of the '229 patent in saline at the claimed concentration of albumin, and claim 1 would have been obvious.

2. Obviousness over Desai, Kadima, and Liversidge

168. Even if claim 1 of the '229 patent were not obvious over Desai alone, it would at least have been obvious to a skilled artisan over Desai in combination with Kadima and Liversidge, for the following reasons.

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

169. Kadima discloses ratios of albumin to paclitaxel that include a ratio of about 9:1. Specifically, Kadima teaches that "[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 a ratio of about 9:1. EX1004, 32. Kadima recites selected ratios within this range from 0.5:1 to 10:1 in Kadima's table of expected costs for various

formulations. *Id*. at 34. Other passages in Kadima likewise discuss "a ratio of about 1:0.5 to about 1:10" (paclitaxel-albumin ratio), and disclose data for ratios within that range. *Id*. at 41, 49–50.

170. While Kadima does not focus on nanoparticle-based formulations like Desai's, Kadima nevertheless would have informed a skilled artisan as of December 2002 that pharmaceutically acceptable albumin-paclitaxel formulations could have lower 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.

171. Indeed, Kadima's albumin-paclitaxel ratios are covered by Liversidge, which, as I discussed above, is directed to nanoparticle-based formulations that include Desai's and the '229 patent's formulations. *Id*.; EX1005. Specifically, 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. *Id*. at 14:7–14, p. 10 (correcting 14:7), 14:25 (paclitaxel), 16:8 (albumin). The percentages disclosed and claimed in Liversidge correspond to a range of albumin-paclitaxel ratios of 0.01:9.99 to 9:1.

172. For the same reasons I discussed above in paragraphs 148–151, I am not aware of any evidence that would render the ratio of about 9:1, which falls

within ranges disclosed in both Kadima and Liversidge (as well as Desai), nonobvious. Thus, it is my opinion that making albumin-paclitaxel nanoparticles with a particle size of less than about 200 nm and an albumin-paclitaxel ratio of about 9:1 would have been obvious to a skilled artisan as of December 2002.

b. Kadima teaches additional reasons to lower a 13.3:1 ratio of albumin to paclitaxel to about 9:1.

173. Kadima also corroborates the motivations expressed in Desai for reducing the albumin-paclitaxel ratio of Capxol from 13.3:1 to about 9:1, by explaining a method of adjusting "the ratio of paclitaxel or derivative thereof to albumin" in the composition as a means of achieving "the smallest volumes for administration or lyophilization/reconstitution, which enables more rapid administration, if desired." EX1004 at 12–13. As discussed above, Desai similarly teaches the desirability of reducing the infusion volume to provide more rapid administration, and therefore a skilled artisan would have had a reason to apply Kadima's method of adjusting the albumin-paclitaxel ratio to Desai's disclosure that Capxol has an albumin-paclitaxel ratio of 13.3:1.

174. Furthermore, Kadima shows that a skilled artisan in December 2002 also would have been motivated to reduce Capxol's albumin-paclitaxel ratio from 13.3:1 to about 9:1 in order to obtain a substantially more cost-effective and commercially viable formulation. 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 stabiliz[er]" therefore allows the production of pharmaceutical formulations that are relatively "inexpensive to prepare." *Id*. at 10. As I discussed above, Kadima illustrates this point with examples of cost differences for various ratios of albumin to paclitaxel, confirming that human serum albumin is much more expensive than paclitaxel. *Id*. at 34. Based on these cost differences, a skilled artisan would have been motivated to reduce the ratio of albumin to paclitaxel in Capxol in order to reduce costs of production.

175. Although Kadima does not focus on nanoparticle-based formulations such as Capxol, the motivations it discloses for lowering the albumin-paclitaxel ratio— *i.e.*, reducing infusion volumes, reducing administration times, and reducing costs—apply regardless of the type of formulation that is used, and specifically apply to the nanoparticle-based formulations of Desai, such as Capxol.

176. More specifically, a skilled artisan would have been motivated to apply the teachings of Kadima to Capxol while retaining Capxol's nanoparticle-based formulation. As Desai explains, "nanoparticles can provide a pre-programmed duration of action, ranging from days to weeks to months from a single injection," and were expected to "offer several profound advantages over conventionally administered medicaments, including automatic assured patient compliance with the dose regimen, as well as drug targeting to specific tissues or organs." EX1006, 4.

177. As Desai further explains, it was expected that "the delivery of biologics in the form of a particulate suspension allows targeting to organs such as the liver, lungs, spleen, lymphatic circulation, and the like…." *Id*. at 29. Moreover, as "a nanoparticle formulation," Capxol was expected to "concentrate[] in tissues such as the prostate, pancreas, testes, seminiferous tubules, bone, etc., … at a significantly higher level than a nonparticulate formulation of paclitaxel." *Id*. at 29–30. Desai thus suggests nanoparticle formulations "may be utilized to treat cancers of these tissues with a higher efficacy than" nonparticulate formulations. *Id*. at 30. Desai also notes that "[t]he literature suggests that particles in the low hundred nanometer size range preferentially partition into tumors through leaky blood vessels at the tumor site," and "[t]he colloidal particles of paclitaxel in the Capxol™ formulation may therefore show a preferential targeting effect." *Id.* at 34.

178. In addition, Desai teaches that a "colloidal system of pharmacologically active agent allows for the delivery of high doses of the pharmacologically active agent in relatively small volumes," which "minimizes patient discomfort at receiving large volumes of fluid and minimizes hospital stay." *Id*. at 54. In particular, Desai explains that its albumin-paclitaxel nanoparticle formulations allow the reconstituted solution for injection to be prepared at a paclitaxel concentration of up to "20 mg/ml," which "offers [a] substantial advantage … as it results in smaller infusion volumes." *Id*. at 32.

179. Accordingly, for all of these reasons, a skilled artisan applying Kadima's teachings to modify the albumin-paclitaxel ratio of Capxol would otherwise have retained its nanoparticle-based formulation.

180. For these reasons, claim 1 of the '229 patent would have been obvious to a skilled artisan as of December 2002 over Desai, either alone or, at a minimum, in combination with Kadima and Liversidge.

B. Claims 3 and 6 would have been obvious.

181. Claim 3 depends from claim 1 and further 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." *Id*. at 27–28. Thus, claim 3 would have been obvious.

182. Claim 6 also depends from claim 1 and requires that the composition comprises about 5% by weight of albumin. As I discussed above in paragraph 113, this claimed concentration of albumin falls within the ranges of 0.09–18% and 0.9–13.5% by weight of albumin disclosed in Desai. I am not aware of any evidence (1) that the prior art taught away from a concentration of about 5% by weight of albumin; (2) that there were new and unexpected results relative to the prior art for

such a concentration; or (3) that there are other pertinent secondary considerations. Thus, it would have been obvious to a skilled artisan to reconstitute the formulation of claim 1 of the '229 patent in saline at an albumin concentration of about 5% by weight. Accordingly, claim 6 would have been obvious.

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

183. As I discussed above in paragraph 114, the only differences between claim 15 and claim are are that claim 15 is directed to "[a] sealed container" instead of "[a] liquid pharmaceutical composition," and claim 15 does not include claim 1's requirements that the composition comprises 0.5% to 5% albumin, and that it further comprises saline.

184. It would have been obvious to a skilled artisan to provide an albumin-paclitaxel nanoparticle formulation that meets the limitations of claim 1 in a sealed container, as required by claim 15. In particular, Desai's "Summary of the Presently Preferred Manufacturing Process" instructs the person of ordinary skill in the art to fill lyophilized albumin-paclitaxel nanoparticles into vials, and to "stopper the vials and seal the vials by crimping them with the 20mm Wheaton aluminum tear-off caps." EX1006, 76–77. Using a sealed container is desirable because it allows the composition to be "stored indefinitely." *Id.* at 86.

185. Claim 19 depends from claim 15 and requires that the sealed container is "a unit dose container." Claims 21, 22, and 23 also depend from claim 15 and

require that the pharmaceutical composition in the sealed container is "a liquid composition," "a dry composition," and "lyophilized," respectively. In my opinion, each of these dependent claims also would have been obvious for the following reasons.

186. Example 38 of Desai, which is titled "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." *Id.* at 116–17. Desai explains: "This reconstituted solution can be directly administered to a patient either by injection or infusion with standard i.v. infusion sets." *Id.* at 117. 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," which "avoids the lyophilization step in the manufacturing process." *Id.*

187. Thus, Desai teaches the desirability of providing albumin-paclitaxel nanoparticles that are in a unit dose container and that are either a liquid composition, a dry composition, and/or lyophilized. Accordingly, claims 19 and 21–23 would have been obvious.

D. Claim 20 would have been obvious.

188. Claim 20 depends from claim 15 and requires that the claimed sealed container "is a multi-dose container." As discussed above in paragraph 98, 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 to Taxol.

189. As Desai explains, its preferred embodiment, "Capxol, is significantly less toxic and more efficacious than Taxol®, a commercially available formulation of paclitaxel." EX1006, 4. While Desai discloses that its albumin-paclitaxel formulations provide multiple therapeutic benefits over Taxol, nothing in Desai suggests any reason not to provide Capxol and other embodiments of the claimed invention in the same multi-dose containers as Taxol. In fact, a skilled artisan as of December 2002 would have known that, as a general matter, "[f]ormulations suitable for parenteral administration …. may be presented in unit-dose or multi-dose sealed containers, for example, ampoules or vials." Ex. 1028, 16:24–31. There is no reason why this general knowledge and understanding would not have applied equally to Desai's formulations. Thus, claim 20 would have been obvious to a skilled artisan in view of Desai and the Taxol label, and optionally in further view of Kadima and Liversidge.

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

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

191. As Desai acknowledges, paclitaxel was known and approved in the United States to treat cancer in humans. *Id.* at 7, 12. Specifically, as I discussed above in connection with anticipation, Desai teaches that "[t]he anticancer agent paclitaxel … has remarkable clinical activity in a number of human cancers including cancers of the ovary, breast, lung, esophagus, head and neck region, bladder and lymphomas." *Id.* at 27. Moreover, Desai acknowledges that "[i]t is known that the delivery of biologics in the form of a particulate suspension allows targeting to organs such as the … lungs." *Id.* at 29. In particular, albumin-paclitaxel nanoparticles have "been demonstrated to result in higher level concentrations of paclitaxel in the … lung … when compared to Taxol at equivalent doses." *Id.* at 30; *see also id.* at 79 (same), 147 (same). Furthermore, Example 20 discloses animal testing data that confirms the elevated concentration of administered albumin nanoparticles in the lungs. *Id.* at 80–81.

192. Similarly, Example 45 of Desai discloses a study and method of treating mammary tumors using albumin-paclitaxel nanoparticles, and Example 58 sim-

ilarly discloses the injection of albumin-paclitaxel nanoparticles to treat "human mammary tumor fragments." *Id.* at 122–23, 140. Moreover, Desai repeatedly discloses the injection of paclitaxel to treat breast cancer, and Examples 65 and 66 teach a clinical trial design and clinical development program to treat metastatic breast cancer in humans with effective amounts of injectable albumin-paclitaxel nanoparticles. *Id.* at 16, 18–20, 27, 159–61. Claims 7, 15, 22, and 28 of Desai are also directed to methods of using Desai's disclosed compositions to treat a tumor and/or cancer. *Id.* at 162–65.

193. Accordingly, in view of Desai's disclosures, it would have been obvious to inject the composition of claim 1 of the '229 patent to treat cancer, including lung cancer and breast cancer, rendering claims 29, 34, and 38 obvious.

F. Claims 7 and 33 would have been obvious.

194. 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." As I discussed above, Example 1 of Desai provides that the lyophilized albumin-paclitaxel nanoparticle composition "could be easily reconstituted to the original dispersion by addition of sterile water or saline." EX1006, 63. As a skilled artisan would have known, saline for injection (*i.e.*, sodium chloride) has a pH of 4.5 to 7.0. EX1027, *Remington's* at 6. Accordingly, the composition of Desai's Example 1 resuspended in saline would have a pH between 5.0 and 8.0.

195. Independently, a skilled artisan would have been motivated, with a reasonable expectation of success, to formulate the claimed albumin-paclitaxel nanoparticles with a pH between about 5.0 and about 8.0. Indeed, it would have been obvious to prepare any injectable drug at physiological pH (7.4). As taught by Liversidge, "[t]he 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.

G. Claims 2, 8, 11, 12, 13, 14, 16, 24, 27, 28, 30, 35, and 39 would have been obvious.

196. As I noted above with respect to anticipation, claims 2, 8, 11, 12, 13, 14, 16, 24, 27, 28, 30, 35, and 39 depend from claims 1, 7, 4, 5, 9, 10, 15, 23, 25, 26, 29, 34, and 38, respectively, and require that the albumin is human serum albumin. Desai renders this limitation obvious because human serum albumin is the albumin recited and exemplified repeatedly throughout Desai, including as the type of albumin used for Capxol. *E.g.*, EX1006, 28. Moreover, it would have been obvious to use human albumin, as opposed to other types of albumin, in a pharmaceutical composition designed for administration to humans. Thus, claim 2, 8, 11, 12, 13, 14, 16, 24, 27, 28, 30, 35, and 39 would have been obvious.

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

197. Claims 4, 9, 17, 25, 31, 36, and 40 depend from claims 1, 7, 15, 23,

29, 34, and 38, respectively, and require that "the weight ratio of albumin to the paclitaxel in the pharmaceutical composition is 1:1 to 9:1." Similarly, claims 5, 10, 18, 26, 32, 37, and 41 depend from claims 1, 7, 15, 23, 29, 34, and 38, respectively, and require that "the weight ratio of albumin to the paclitaxel in the pharmaceutical composition is about 9:1." As discussed in the preceding sections, it would have been obvious to make a composition that meets the limitations of claim 1 with a ratio of albumin to paclitaxel of about 9:1 in view of Desai, either alone or in combination with Kadima and Liversidge. Thus, claims 4, 5, 9, 10, 17, 18, 25, 26, 31, 32, 36, 37, 40, and 41 would have been obvious to a skilled artisan.

I. Claims 42–48 would have been obvious.

198. Claims 42–48 depend from claims 29–34 and 38, respectively, and require that the liquid pharmaceutical composition is injected intravenously. It would have been obvious to a skilled artisan to administer the composition of claim 1 intravenously in view of Desai, which is specifically directed to "the intravenous administration of pharmacologically active agents." *Id.* at 3. As Desai explains, "[i]ntravenous drug delivery permits rapid and direct equilibration with the blood stream which carries the medication to the rest of the body." *Id.* at 4. Moreover, Capxol is specifically designed for "intravenous administration" (*id.* at 28, 38); Examples 45 and 52 exemplify intravenous delivery of albumin-paclitaxel nanoparticles (*id.* at 122–23, 131–32); and claims 6, 14, 21, and 27 are directed to

methods of administering Desai's disclosed compositions by routes including intravenous delivery (*id*. at 162–64). Thus, claims 42–48 of the '229 patent would have been obvious to a skilled artisan.

J. There are no relevant secondary considerations indicating that the challenged claims would not have been obvious.

199. I am not aware of any evidence of secondary considerations that would tend to suggest that the challenged claims would have been unobvious.

200. However, I understand that the applicants for the '229 patent argued to the Patent Office that the secondary consideration of "unexpected results" supports the nonobviousness of the claims. Specifically, I have reviewed a declaration by one of the named inventors, Neil P. Desai, which was submitted to the Patent Office as evidence that the albumin-paclitaxel ratio of about 9:1 would not have been obvious. EX1023 (the "Inventor Declaration").

201. The Inventor Declaration alleges the discovery of "unexpected results associated with the claimed albumin/paclitaxel ratio, including striking biological and clinical data relating to the ratio." *Id*. ¶ 6. The Declaration claims that the applicants "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 Declaration further claims that the applicants "found unexpectedly that

Abraxane®, an albumin-based paclitaxel nanoparticle composition having about 9:1 albumin/paclitaxel weight ratio, is more efficacious than [an] old formulation (about 19:1 albumin/paclitaxel ratio) in treating cancer" (called "ABI-007"), and that the applicants "further unexpectedly found that Abraxane® has substantially reduced toxicity compared with the old formulation." *Id.* ¶ 23.

202. After reviewing the Inventor Declaration and its exhibits, my opinion is that they do not demonstrate any relevant unexpected results regarding the claims of the '229 patent. I explain the bases for my opinion below.

1. The allegedly "unexpected" cell-binding results lack a nexus to the '229 patent and would have been expected.

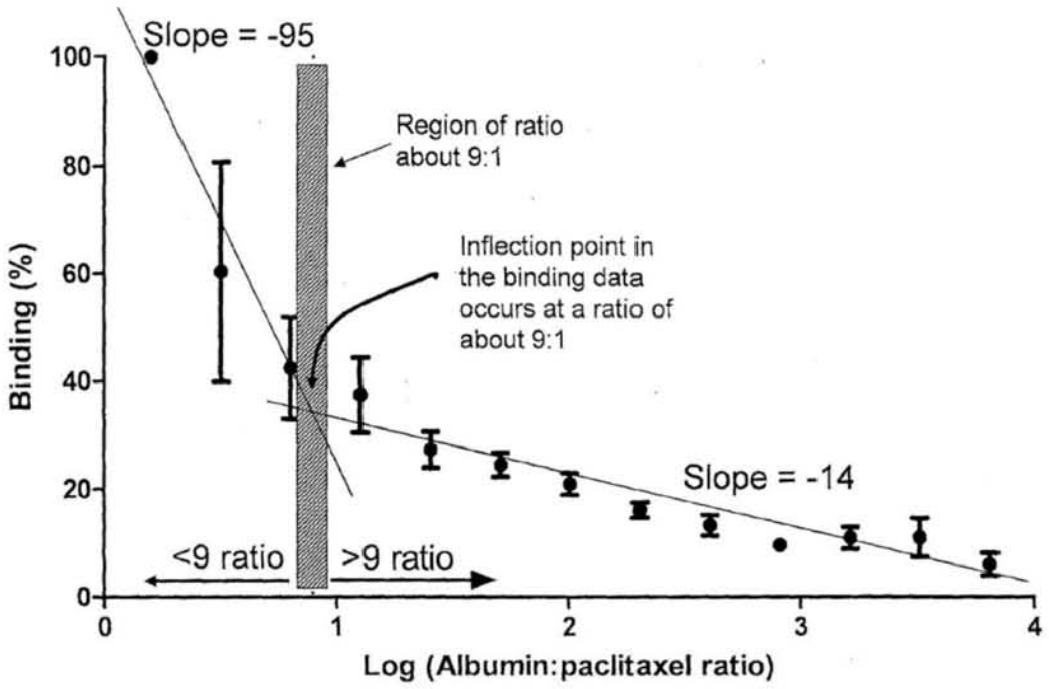
203. I have been informed that a connection or "nexus' must be identified between the alleged unexpected results and the claimed subject matter in order to provide evidence that an alleged invention would not have been obvious. In my opinion, the "cellular binding" results disclosed in the Inventor Declaration lack such a nexus to the challenged claims, for at least two reasons.

204. 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*]*luores-cent* paclitaxel" (EX1023 ¶¶ 9–11)—*i.e.*, a fluorescein-paclitaxel conjugate. As the '229 patent shows, the fluorescein-paclitaxel conjugate that the applicants tested, and which I understand was commercially available at the time, is sold un-

der the name Flutax. *See* EX1001, 32:50–34:22 (Examples 40–44, describing the use of "Flutax" in albumin-binding experiments).

205. Importantly, a skilled artisan would have expected Flutax to have a different molecular weight, different solubility, and different protein-binding properties than paclitaxel alone. In particular, fluorescein was also known to bind to human serum albumin. EX1007. As a result, a skilled artisan would not have drawn 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 could have been driven or largely affected by the binding of the fluorescein moiety of Flutax rather than its paclitaxel moiety. Accordingly, the results in the Inventor Declaration lack an adequate nexus to the combination of albumin and paclitaxel claimed in the '229 patent.

206. Second, the asserted results also lack a nexus to the claims of the '229 patent because the inventors did not test the claimed albumin-paclitaxel ratio of "about 9:1." Rather, as stated in the Declaration, they tested ratios "*above* about 9:1" and "about 9:1 *or less*." EX1023 ¶ 14. This is confirmed by the chart in 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. Thus, the test results disclosed in the Inventor Declaration do not have an adequate nexus to the claimed ratio of "about 9:1."

207. Even putting aside 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. Citing the above chart (Exhibit 4), 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." *Id.* ¶ 14. Yet, given the large, overlapping error bars for the key data points, there is no evidence presented in the Inventor Declaration of any actual "inflection" point, and no disclosed scientific basis for extrapolating trends across the data.

208. In any event, a skilled artisan would have expected the results of the

experiment. 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." *Id.* ¶ 7. To a skilled artisan, however, that result would have been entirely expected from the experiment's design.

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

210. For all of these reasons, the asserted "unexpected" results related to cellular binding in the Inventor Declaration do not change my opinion that the challenged claims of the '229 patent would have been obvious to a skilled artisan.

2. The allegedly "unexpected" clinical data did not compare the closest prior art and would have been expected.

211. I have been informed that when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared to the closest prior art. In my opinion, the clinical results disclosed in the Inventor

Declaration and alleged to be "unexpected" fail to meet this requirement because they do not compare the claimed ratio of about 9:1 to the closest prior art ratio.

212. 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 Abraxis" referred to by the internal code name "ABI-007." EX1023 ¶¶ 23, 17. As the Inventor Declaration states, "[t]he albumin/paclitaxel weight ratio in the old formulation was about 19:1." *Id.* ¶ 17.

213. 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 I discussed above, it discloses a composition with a 9:1 ratio of albumin to paclitaxel. Moreover, as I discussed in paragraph 75, 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.

214. Even aside from these examples, Desai's disclosure of 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 the claimed ratio of about 9:1 than a ratio of 19:1. *See* EX1006, 38–39. Yet, the Inventor Declaration only compares Abraxane to the "old formulation" with a 19:1 ratio. EX1023 ¶¶ 23–30. It does not compare Abraxane to Capxol. Because the Inventor Declaration does not compare the claimed ratio to the closest prior art, it

does not show that the claimed ratio is unobvious.

215. For other reasons, moreover, a skilled artisan would not have drawn any conclusions from the clinical tests referenced in the Inventor Declaration. The declaration refers to "[t]wo clinical studies using Abraxane® ('the 9:1 formulation') and the old formulation ('the 19:1 formulation') [that] were conducted in China with cancer patients having various solid tumors," and compares the tumor shrinkage results observed across these two separate studies. *Id.* ¶¶ 25–27. However, no data, testing protocols, or related publications are included or cited in the Inventor Declaration regarding the tumor shrinkage results. Nor is there any way of knowing whether the separate tests on the two different formulations were conducted under the same or similar conditions.

216. The Declaration also states that adverse events were recorded during these two studies, and a table in Exhibit 5 to the Declaration, depicted below, purports to show a lower rate of adverse events in patients taking Abraxane than in patients taking the 19:1 formulation. *Id.* ¶ 28.

Treatment-related Adverse Events of All Grades by NCI CTCAE Term

NCI CTCAE Term (Reported Adverese Event)	9:1 formulation 260 mg/m² q3 Weeks (n=104)	19:1 formulation 135-350 mg/m² (mean dose about 250 mg/m2) q3 Weeks (n=22)
Neurology: Neuropathy: Sensory	79 (76%)	19 (86%)
Blood/Bone Marrow: Lymphopenia	6 (6%)	8 (36%)
Blood/Bone Marrow: Leukocytopenia	67 (64%)	18 (82%)
Blood/Bone Marrow: Hemoglobinemia	16 (15%)	17 (77%)
Blood/Bone Marrow: Neutropenia	72 (69%)	14 (64%)
Pain: Myalgia	40 (38%)	10 (45%)
Pain: Arthralgia	23 (22%)	6 (27%)
Gastrointestinal: Anorexia	19 (18%)	16 (73%)
Gastrointestinal: Diarrhea	16 (15%)	5 (23%)
Gastrointestinal: Nausea	24 (23%)	8 (36%)
Dermatology/Skin: Rash/Desquamation	27 (26%)	9 (41%)
Dermatology/Skin: Pruritus/Itching	22 (21%)	5 (23%)
Constitutional Symptoms: Fatigue	16 (15%)	8 (36%)

Id. at 21 (EX5).

217. This table reveals several problems. 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.

218. Second, the patients in the two groups did not receive the same doses. The patients taking Abraxane all received 260 mg/m^2, whereas patients in the 19:1 group received a range of doses from 135–350 mg/m^2. Although the mean dose was 250 mg/m^2, there is no median disclosed. Thus, a majority of patients in the

19:1 group could have taken substantially higher doses, which could have had a significant effect on the rate of adverse events. As demonstrated in Tables 1 and 4 of Ibrahim, it was known that adverse events in the old formulation increased dramatically at doses of 300 mg/m^2 and higher:

Table 1 Dose levels

Level	Dose (mg/m^2)	No. patients entered	No. cycles
0	135	4	6
1	200	3	38
2	300	6	35
3	375	6	17

Table 4 Nonhematologic toxicity by dose level[a]

	Level 0 (n = 4)		Level 1 (n = 3)		Level 2 (n = 6)		Level 3 (n = 6)	
Toxicity	Grade 1 or 2	Grade 3	Grade 1 or 2	Grade 3	Grade 1 or 2	Grade 3	Grade 1 or 2	Grade 3
Sensory neuropathy	0	0	0	0	4	1	3	3
Ocular	1	0	0	0	2	0	2	2
Stomatitis	0	0	1	0	4	0	3	2
Nausea	1	0	1	0	3	0	4	1
Vomiting	1	0	1	0	0	0	2	1
Diarrhea	1	0	2	0	3	0	1	1
Arthralgia/myalgia	3	0	3	0	4	0	4	1
Skin	0	0	0	0	5	0	2	0
Fever (non-neutropenic)	0	0	0	0	2	0	3	0

[a] Expressed as the number of patients experiencing the toxic effect during the first two cycles of treatment.

EX1018, 2, 4. In Exhibit 5 of the Inventor Declaration, doses of 300 mg/m^2 were administered only to the 19:1 group, whereas all doses in the 9:1 group were below that threshold. EX1023, 21. Given this difference, in view of Ibrahim, a skilled artisan would have expected more adverse events in the 19:1 group.

219. Third, critical details about the patient populations and treatment methods that could affect the results (both with respect to tumor shrinkage and adverse events) are not disclosed in the Inventor Declaration—e.g., the drug infusion rates and the stage of cancer being treated.

220. Furthermore, I have been informed that to qualify as an "unexpected result," the result must be a difference in kind rather than a mere difference in degree. Here, the alleged unexpected results were not differences in kind, *i.e.*, a differences in the kind of effect that the formulations had on patients. Instead, Abraxane and the older formulation with an albumin-paclitaxel ratio of 19:1 had the same kinds of effects, but simply to a different degree.

221. For all of these reasons, the asserted "unexpected" results related to clinical effects in the Inventor Declaration do not change my opinion that the challenged claims of the '229 patent would have been obvious to a skilled artisan.

VIII. CONCLUSION

222. In sum, for the reasons I have discussed above, it is my opinion that claims 1–19 and 21–48 of the '229 patent are anticipated by Desai (EX1006), and that claims 1–19 and 21–48 would have been obvious over Desai, either alone or in view of Kadima (EX1004) and Liversidge (EX1005). Furthermore, it is my opinion that claim 20 would have been obvious over Desai and the Taxol label (EX1008), and optionally in further view of Kadima and Liversidge.

223. I understand that this declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also understand that I may be subject to cross-examination concerning this declaration, and I will appear for cross-examination, if re-

quired of me, during the time allotted for cross-examination.

224. I hereby declare that all of the statements made herein are true of my own knowledge and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: November 8, 2017

Cory J. Berkland, Ph.D.

APPENDIX

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Education and Professional Training

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Awards

Bellows Scholar, The University of Kansas, Lawrence, KS	2016
Fellow of the American Institute of Medical and Biological Engineering	2015
Bellows Scholar, The University of Kansas, Lawrence, KS	2014
Jim Baxendale Commercialization Award, The University of Kansas, Lawrence, KS	2014
Iowa State University Professional Progress in Engineering Award, Ames, IA	2013
Leading Light Award, The University of Kansas, Lawrence, KS	2013
Miller Scholar, The University of Kansas, Lawrence, KS	2013
Controlled Release Society Young Investigator Award, Quebec City, Canada	2012
Coulter Foundation Fellow, The Coulter Foundation	2012
University Scholarly Achievement Award, The University of Kansas, Lawrence, KS	2012
Nagai Foundation Distinguished Lectureship, Annual DDS Conference, Shizuoka, Japan	2011
Miller Scholar, The University of Kansas, Lawrence, KS	2011
Kemper Fellowship for Teaching Excellence, The University of Kansas, Lawrence, KS	2010
Featured in Science Magazine Online, "The Entrepreneurial Bug"	2009
Bellows Scholar, The University of Kansas, Lawrence, KS	2008
Coulter Translational Research Award, The Coulter Foundation	2008
Teaching Achievement Recognition, Center for Teaching Excellence, Lawrence, KS	2007
Outstanding Reviewer for the Journal of Pharmaceutical Sciences	2007
Miller Scholar, The University of Kansas, Lawrence, KS	2006
Outstanding Reviewer for the Journal of Pharmaceutical Sciences	2005
Genencor Outstanding Paper Award, Controlled Release Society, Honolulu, HI	2004
Best Presentation, Chemical and Biomolecular Engineering Symposium, Urbana, IL	2003
Graduate College Travel Award, Urbana, IL	2003
Highlights of Student Posters Award, Controlled Release Society, Seoul, Korea	2002
Whitaker Award, American Chemical Society, Particles meeting, Orlando, FL	2002
Featured Technology, University of Illinois Technology Showcase, Urbana, IL	2001

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Non-Refereed Publications

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Book Chapters

1. N. El-Gendy, M. Bailey and C. Berkland (2014) "Particle Engineering Technologies for Pulmonary Drug Delivery" Controlled Release Science and Technology: Pulmonary Delivery, Ed. Hugh Smyth and Anthony Hickey, 283-312

2. N.H. Dormer, C.J. Berkland and M. Singh (2014) "Monodispersed Microencapsulation Technology" Microencapsulation in the Food Industry, Ed. N. Vasisht, A.R. Khare and R. Sobel

3. M. Bailey and C. Berkland (2010) "Modified release delivery systems" Biodrug Delivery Systems, Vol. 194, Ed. Mariko Morishita and Kinam Park, 234-247

Invited Presentations

1. C. Berkland "Soluble antigen arrays as antigen-specific autoimmune therapy" Globalization of Pharmaceutics Education Network, Lawrence, Kansas, November 12, 2016

2. C. Berkland "Entrepreneurship: Intellectual Property Strategy" Globalization of Pharmaceutics Education Network, Lawrence, Kansas, November 12, 2016

3. C. Berkland "A few early lessons in entrepreneurship", Chemical and Biomolecular Engineering Department, The University of Illinois, Urbana-Champaign, IL, October 23, 2016

4. C. Berkland "A discussion of venture capital and the role of scientists", The University of Texas, Austin, TX, September 29, 2016

5. C. Berkland "Biomaterials and Controlled Release in Bone Tissue Engineering", The University of Kansas Medical Center, Kansas City, KS, June 15, 2016

6. C. Berkland "Early Lessons in Entrepreneurship: A Venture Capital Perspective", American Thoracic Society, San Francisco, CA, September 15, 2016

7. C. Berkland "Drug delivery systems for improving ocular therapeutics", Allergan, Irvine, CA, June 2, 2016

8. C. Berkland "Barriers to effective gene delivery", Cystic Fibrosis Foundation Pushing the Frontiers workshop, Chantilly, VA, June 3, 2015

9. C. Berkland "Polyelectrolyte complexes for gene delivery to lungs", Cystic Fibrosis Foundation Therapeutics Gene Repair and Delivery workshop, Cystic Fibrosis Foundation, Bethesda, MD, December 3, 2014

10. C. Berkland "A few early lessons in entrepreneurship", Bioengineering Department, The University of California, Berkeley, CA, October 15, 2014

11. C. Berkland "Controlled release delivery of proteins" Genentech, South San Francisco, California, December 21, 2014

12. C. Berkland "A few early lessons in entrepreneurship", Chemistry Department, The University of Kansas, Lawrence, KS, February 19, 2014

13. C. Berkland "Translatable Pharmaceutical Formulations of Aerosolized and Topical Antibiotics", U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD, February 18, 2014

14. C. Berkland "A few early lessons in entrepreneurship", Chemical and Biomolecular Engineering Department 100 year Anniversary Symposium, Iowa State University, Ames, IA, September 27, 2013

15. J. Sestak, S. Thati, L. Northrup, M. Mullins, T.J. Siahaan, and C. Berkland "Single-Step Grafting of Aminooxy-Peptides to Hyaluronan: A Simple Approach to Multifunctional Therapeutics for Experimental Autoimmune Encephalomyelitis", ACS annual meeting, Indianapolis, Indiana, September 9, 2013

16. C. Berkland "Precision Particle Fabrication", ACS annual meeting, Indianapolis, Indiana, September 9, 2013

17. C. Berkland "Designing formulation and delivery with drug properties in mind", Gordon Conference: Preclinical Form and Formulation for Drug Discovery, Waterville Valley, New Hampshire, June 5, 2013

18. C. Berkland "Colloids and polymers for chemical delivery", Iowa State University, Ames, IA, April 19, 2013

19. S.C. Dennis, Q. Wang, S. Kieweg, M.S. Detamore and C.J. Berkland "Colloidal Gels as a New Class of 'Bingham Plastic' Biomaterials for Tissue Regeneration", CMBE annual meeting, Kohala Coast, Hawaii, January 6, 2013

20. C. Berkland "Colloids and polymers for drug and chemical delivery", Kansas State University, Manhattan, Kansas, November 5, 2012

21. C. Berkland "Uniform PLGA Microspheres Sustain NSAID Blood Levels With Zero-Order Kinetics", Controlled Release Society Annual Meeting, Quebec, Canada, July 16, 2012

22. C. Berkland "Personal and Professional Experiences in Controlled Release", Controlled Release Society Annual Meeting Young Investigator Award Presentation, Quebec, Canada, July 16, 2012

23. C. Berkland "Advanced Materials and Drug Delivery", Kimberly-Clark Heritage Lecture Series, Atlanta, Georgia, May 31, 2012

24. C. Berkland "Colloids and polymers for chemical delivery", Program of Excellence in Nanotechnology lecture series at MIT, Cambridge, Massachusetts, April 25, 2012

25. C. Berkland "Precision Particle Fabrication" Reckitt Benckiser, Hull, United Kingdom, April 11, 2012

26. C. Berkland "Precision Particle Fabrication" Kimberly-Clark, Atlanta, Georgia, April 4, 2012

27. C. Berkland "Precision Particle Fabrication" Dow Chemical, Midland, Michigan, December 7, 2011

28. J. Liang and C. Berkland "Polyelectrolyte complexes for oil and gas field applications" Schlumberger, Houston, Texas, November 14, 2011

29. C. Berkland "Engineering particles and colloids for pharmaceutical and biomaterial applications" Nagai Foundation Distinguished Lectureship for the Annual DDS Conference, Shizouka, Japan, September 15, 2011 (Keynote address)

30. C. Berkland "Nanoparticle Aerosol Formulations for Delivery of Current Drugs and Emerging Nucleic Acid Therapeutics" Defense Threat Reduction Agency, Washington D.C., August 1, 2011

31. C. Berkland "Regenerative Nanomaterials" Kinetic Concepts, Inc., San Antonio, Texas, July 11, 2011

32. C. Berkland "NanoCluster Technology and Microcapsule Approaches for Improved Dissolution and Solubilization" IQPC Improving Solubility Conference, Philadelphia, Pennsylvania, March 29, 2011

33. C. Berkland "Precision Particle Fabrication" Bioencapsulation Industrial Symposium, San Antonio, Texas, March 8, 2011

34. C. Berkland "Approaches for Synthesis, Formulation and Targeting of Various Contrast-Enhancing Colloids" General Electric Research Center, Albany, New York, January 6, 2011

35. C. Berkland "Targeted Nanomaterial Therapeutics" University of Pennsylvania, Philadelphia, Pennsylvania, January 7, 2011

36. C. Berkland "NanoClusters as Unique High Performance Aerosols" MAP Pharmaceuticals, South San Francisco, California, December 21, 2010

37. C. Berkland "Precision Particle Fabrication" Genentech, South San Francisco, California, December 21, 2010

38. C. Berkland "Colloids Engineered for Drug Delivery and Biomaterials Applications" University of Geneva, Geneva, Switzerland, October 22, 2010

39. C. Berkland "Engineering Particles: Microencapsulation and Advanced Nanoparticle Colloids" Jannsen Pharmaceuticals, Beerse, Belgium, October 21, 2010

40. C. Berkland "Colloids Engineered for Drug Delivery and Biomaterials Applications" Eidgenössische Technische Hochschule, Zürich, Switzerland, October 19, 2010

41. C. Berkland "NanoClusters as Unique High Performance Aerosols" Nycomed, Konstanz, Germany, October 18, 2010

42. C. Berkland "Precision Particles for Controlled Release" Genentech, South San Francisco, California, September 21, 2010

43. C. Berkland "NanoCluster Formulation Technology" Novartis, South San Francisco, California, July 27, 2010

44. C. Berkland "Nanoparticle Formulation Approaches in Injectable and Pulmonary Medicines" The University of Missouri, Kansas City, Missouri, American Association of Pharmaceutical Scientists Student Chapter Distinguished Lecturer Series, May 26, 2009

45. C. Berkland "Particle Engineering in Aerosol and Injectable Formulations" The University of Wisconsin, Madison, Wisconsin, February 27, 2009

46. C. Berkland "Nanoparticles in Pulmonary Medicine" The University of Kansas Medical Center, Division of Pulmonary and Critical Care Medicine, Kansas City, Kansas, October 21, 2008

47. C. Berkland "Particle Engineering in Inhaled and Injectable Drug Formulations" Genentech, South San Francisco, California, July 30, 2008

48. J. Liang, P. Willhite and C. Berkland "Nanotechnology: From Drugs to Oil Refining" 3M Technical Forum, Minneapolis, Minnesota, June 26, 2008

49. C. Berkland "Translating Therapeutic Nanoparticles" Particles 2008, Orlando, Florida, May 11, 2008

50. C. Berkland "Pharmaceutical Applications of Nanoparticle Technology" Cima Labs, Brooklyn Park, Minnesota, August 27, 2007

51. C. Berkland "Engineering Nanoparticles for Biomedicine" National Institute of Standards and Technology, Gaithersburg, Maryland, May 4, 2007

52. M. Cordova, M. Cheng, P.G. Willhite, J. Liang, and C. Berkland "Polyelectrolyte complexes for oil and gas field applications" Conoco Phillips, Bartlesville, Oklahoma, March 13, 2007

53. C. Berkland "Nanoparticles for Targeted Angiogenesis: Potential Applications in Heart Disease and Spinal Cord Injury" Genentech, South San Francisco, California, November 14, 2006

54. C. Berkland "Engineering Pharmaceutical Nanoparticles" Globalization of Pharmaceutics Education Network, Lawrence, Kansas, October 26, 2006

55. C. Berkland "Nanoparticle Agglomeration for Dry Powder Formulation" Schering Plough's Pharmaceutical Science Seminar Series in Product Development, Kenilworth, New Jersey, September 27, 2006

56. C. Berkland "Nanoparticle Technology in the Pharmaceutical Industry" AAPS Kansas City Discussion Group, Kansas City, Kansas, August 8, 2006

57. C. Berkland "Nanoclusters as a Unique Drug Delivery Platform" ACS Particles Meeting, Orlando, Florida, May 16, 2006

58. C. Berkland "Designing Particulate Vaccine Delivery Systems" Mannkind Corporation, Valencia, California, January 24, 2006

59. C. Berkland "Precision Particle Fabrication Technology" Southwest Research Institute, San Antonio, Texas, January 11, 2006

60. C. Berkland "Engineering Therapeutic Particles" guest lecturer in senior Biochemical Engineering course at Vanderbilt University, Nashville, Tennessee, November 7, 2005

61. C. Berkland "API Particle Engineering" 47th Annual International Industrial Pharmaceutical Research & Development Conference: Emerging Practices for Advancing Drug Development, Merrimac, Wisconsin, June 7, 2005

62. C. Berkland "Engineering micro- and nanoparticles for enhanced drug delivery performance" University of Kansas, Department of Chemistry, Lawrence, Kansas, March 7, 2005

63. C. Berkland "Improvements in Delivery Strategies Using Particulate Technologies to Treat Infectious Diseases" 3rd Annual Great Plains Infectious Disease Meeting, Lawrence, Kansas, September 18, 2004

Thesis Advisor and Postgraduate-Scholar Sponsor

Graduate students
Sam Peterson, Pharmaceutical Chemistry
Melissa Pressnall, Pharmaceutical Chemistry
Jimmy Song, Pharmaceutical Chemistry
Martin Leon, Chemistry
Jonathan Daniel Griffin, Bioengineering
Matthew Christopher, Pharmaceutical Chemistry
Chad Pickens, Pharmaceutical Chemistry
Lorena Antunez, Pharmaceutical Chemistry
Brittany Rover, Bioengineering
Laura Northrup, Pharmaceutical Chemistry
Christopher Kuehl, Pharmaceutical Chemistry
Sharadvi Thati, Pharmaceutical Chemistry
Connor Dennis, Bioengineering
Adel Alghaith, Pharmaceutical Chemistry
Nabil Alhakamy, Pharmaceutical Chemistry
Warangkana Pornputtapitak, Pharmaceutical Chemistry
Auan Rungisee, Chiang Mai University visiting
Abdul Baoum, Pharmaceutical Chemistry
Qun Wang, Chemical Engineering
Milind Singh (co-advisor with Michael Detamore), Chemical Engineering
Mark Bailey, Bioengineering
Carl Plumley, Chemical Engineering
Zahra Mohammdi, Chemical Engineering
Chuda Chittasupho, Pharmaceutical Chemistry
Supang Khondee, Pharmaceutical Chemistry
Joshua Sestak, Pharmaceutical Chemistry
Amir Fakhari, Bioengineering
Matthew Arnold, Chemical Engineering

Postdoc sponsor
Sharadvi Thati, KU, Lawrence
Madhuri Patil, KU, Lawrence
Bradly Sullivan, KU, Lawrence
Ola Alawode, KU. Lawrence
Jun Chen, KU, Lawrence
Jian Qian, KU, Lawrence
Joshua Sestak, KU, Lawrence
Xiang Wang, KU, Lawrence
Qing Shang, KU, Lawrence
Nashwa El Gendy, KU, Lawrence
Sheng-Xue Xie, KU, Lawrence

Tatyana Yakovleva, KU, Lawrence
Huili Guan, KU, Lawrence
Kristin Aillen, KU, Lawrence
Julieta Trejo, KU, Lawrence (co-advised with Paul Willhite and Jenn-Tai Liang)
Stephen Johnson, KU, Lawrence (co-advised with Paul Willhite and Jenn-Tai Liang)
Ying Ying Lin, KU, Lawrence (co-advised with Paul Willhite and Jenn-Tai Liang)
Parthiban Selvam, KU, Lawrence
Yasunori Iwao, University of Shizuoka, Japan
Satish Nune, KU, KU, Lawrence
Navneet Dhillon, KU Medical Center, Kansas City (co-advised with Shilpa Buch)
Lianjun Shi, KU, Lawrence
Min Huang, KU, Lawrence
Laura Peek, KU, Lawrence
Samadhi Vitharana, KU, Lawrence
Na Zhang, Associate Professor, Shandong University, China
Chadarat Duangrat, Assistant Professor, Chiang Mai University, Thailand

Teaching Experience

Pharmaceutical Chemistry PHCH 510 Emerging Trends in Pharmaceutical Chemistry	Fall 2006 Fall 2008 Fall 2010 Fall 2012 Fall 2016
Chemical Engineering/Pharmaceutical Chemistry CPE/PHCH 715 Drug Delivery Coordinated and taught a new graduate-level course in drug delivery principles.	Fall 2005 Fall 2007 Fall 2009 Fall 2011 Fall 2013 Spring 2016 Spring 2017
Pharmaceutical Chemistry PHCH 626 Biopharmaceutics and Drug Delivery	Spring 2016
Chemical Engineering CPE 221 Introduction to Thermodynamics	Spring 2008 Spring 2009 Spring 2010
Chemical Engineering CPE 111 Introduction to Chemical Engineering	Fall 2006
Chemical Engineering CPE 800 Graduate Seminar	Fall 2006
Chemical Engineering CPE 732 Advanced Transport Phenomena II Coordinated and taught the mass transport course to graduate students.	Spring 2005 Spring 2006 Spring 2007

Teaching Recognition

W.T. Kemper Fellowship for Teaching Excellence (2010)

C&PE 656 Introduction to Biomedical Engineering (2006)

Received second most votes for "best teacher" and for "most interesting topic" out of 12 guest lecturers for C&PE 656. Two of these lecturers were Kemper Award winners.

Teaching Achievement Award from CPE graduate students at the CTE Celebration of Teaching (2007)

C&PE 656 Introduction to Biomedical Engineering (2008)

Received most votes for "best teacher" and second most for "most interesting topic" out of 12 guest lecturers for C&PE 656.

Professional Activities

Co-founder, Board Member and acting CSO of Orbis Biosciences, Inc.
Co-founder, Scientific Advisory Board Member and prior CTO of Savara Pharmaceuticals, Inc.
Co-founder, Chairman of the Board of Orion BioScience, Inc.
Co-founder, Board Member and acting CSO, Bond Biosciences, Inc.

Cystic Fibrosis Foundation Workshop panel to determine funding directives (2014)

NIH Study Sections: NHLBI Programs of Excellence in Nanotechnology, NIAID B cell Immunology Program, ETTN special emphasis on pediatric medicine, NANO

Training grants – Advisory Board; NIH NIAID – Multidimensional Vacinogenesis (past)
Advisory Board; NIH NIGMS – Pharmaceutical Aspects of Biotechnology

Journal Advisory Boards – Journal of Pharmaceutical Sciences (2008-present)
Journal of Pharmaceutical Innovation (2008-present)
Therapeutic Delivery (2009-2015)

Academic Advisory Boards – Kansas University Innovation Center, The University of Kansas
D3ET Research Program Steering Committee, The University of Kansas
KU Strategic Initiative Committee "Promoting Well-Being, Finding Cures"

Corporate Advising – Banner Life Sciences (2015-present)
Dauntless Pharmaceuticals (2015-2016)

Lawrence High School, Lawrence, KS – Technology Department Advisory Board (2006-2012). Served to develop/improve curriculum for pre-engineering training of local junior high and high schools.

Education – Director – Pharmaceutical Chemistry Undergraduate Research Program (2006-present)
Director – Education through Outreach with Lawrence High School (NSF sponsored). More than 25 high school students have conducted research at KU through this program. (2008-2013)
Director – Biomolecular Engineering Track, BioEngineering Program at KU (2010-2015)
Drug Delivery; New graduate course offering at KU
Chemical Engineering; Module for College Prep Engineering at Lawrence High School
Short course "Polymers in Drug delivery: Nanocarriers and implantable polymeric drug delivery systems" Globalization of Pharmaceutics Education Network, Lawrence, KS
Short course "Polymers in Drug delivery: Nanocarriers and implantable polymeric drug delivery systems" Globalization of Pharmaceutics Education Network, Lawrence, KS