IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AVENTIS PHARMA S.A., and SANOFI-AVENTIS U.S., LLC, Plaintiffs, v. HOSPIRA, INC., Defendant.	)	C.A. No. 07-721-GMS
AVENTIS PHARMA S.A., and SANOFI-AVENTIS U.S., LLC, Plaintiffs, v. APOTEX, INC., and APOTEX CORP., Defendants.	)	C.A. No. 08-496-GMS

MEMORANDUM

I. INTRODUCTION

In this consolidated patent infringement action, plaintiffs Aventis Pharma S.A. and Sanofi-Aventis U.S., LLC (collectively, "Sanofi" or "the plaintiffs") allege that pharmaceutical products proposed by defendants Hospira, Inc. ("Hospira") and Apotex, Inc. ("Apotex") (collectively, "the defendants") infringe the asserted claims of the patents-in-suit. (D.I. 1.) The court held a seven-day bench trial in this matter on October 26 through November 3, 2009. (D.I. 369-375.) Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity and enforceability of the patents-in-suit and whether

the defendants' proposed products infringe the patents-in-suit. (D.I. 378 & 383.)

Pursuant to Fed. R. Civ. P. 52(a), and after having considered the entire record in this case and the applicable law, the court concludes that: (A) claims 2 and 10 of the '561 Patent are invalid due to indefiniteness; (B) all asserted claims of the patents-in-suit are invalid due to obviousness; (C) the asserted claims are unenforceable due to inequitable conduct; (D) the asserted claims are not invalid due to double patenting; (E) the defendants' proposed products infringe asserted claims 2, 5, and 10 of the '561 Patent and claim 33 of the '512 Patent; and (F) each of the parties Rule 52(c) motions are granted in part and denied in part. These findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT[1]

A. The Parties

1. Plaintiff Aventis Pharma S.A. is a French corporation with its principal place of business in Paris, France.

2. Plaintiff sanofi-aventis U.S., LLC is a Delaware corporation with its principal place of business in Bridgewater, New Jersey.

3. Aventis Pharma S.A. and sanofi-aventis U.S., LLC will be collectively referred to as "Sanofi" or "Plaintiffs."

4. Rhone-Poulenc Rorer, SA is a predecessor in interest to Aventis Pharma SA.

5. Defendant Hospira, Inc. is a Delaware corporation with its principal place of business in Lake Forest, Illinois. Hospira and Maybe Pharma, will be collectively referred to as "Hospira".

6. Defendant Apotex, Inc. is a Canadian company with a principal place of business in Toronto, Ontario, Canada.

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[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 315, Ex. A.) The court takes most of its findings of fact from the parties' uncontested facts. Where necessary, the court has overruled objections to the inclusion of these facts. The court has also reordered and renumbered some paragraphs, corrected some spelling and formatting errors, and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the pretrial order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional.

The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in the Discussion section of this opinion, preceded by the phrase "the court finds."

7. Defendant Apotex Corp. is a Delaware corporation with a principal place of business in Florida.

8. Apotex, Inc. and Apotex Corp. will be collectively referred to as "Apotex".

9. The Court has subject matter jurisdiction, as well as personal jurisdiction over all parties.

B. Background

10. Taxanes are a group of chemotherapeutic agents which include the compounds paclitaxel and docetaxel.

11. Derived from a yew tree, i.e., *taxus brevifolia*, paclitaxel (also known by its commercial name "Taxol") and docetaxel (which is also derived from a yew tree), are both hydrophobic antineoplastic agents demonstrating significant antitumor activity.

12. Docetaxel and paclitaxel work by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular function. Thus they are referred to as "anti-mitotic" drugs.

13. Taxanes interfere with cell division and thus preferentially disrupt the growth of cells, such as tumor cells, undergoing rapid cell division.

C. The Patents-in-Suit

14. U.S. Application Number 07/930,392, from which U.S. Patent No. 5,714,512 B1 (the "'512 patent") issued, was filed on August 23, 1993. The '512 patent issued on February 3, 1998 to Jean-Pierre Bastart, Thierry Depechez, and Jean-Louis Fabre.

15. U.S. Application Number 07/930,393, from which U.S. Patent No. 5,750,561 B1 (the "'561 patent") issued, was filed on August 4, 1993. The '561 patent issued on May 12, 1998 to Jean-Pierre Bastart, Thierry Depechez, and Jean-Louis Fabre.

16. Both the '512 patent and '561 patent refer to French patent application FR 91 08527, which was filed on July 8, 1991.

17. Sanofi-aventis U.S. LLC is the current holder of approved New Drug Application ("NDA") No. 020-449 for a docetaxel injection product, which has the proprietary name Taxotere®.

18. The FDA's Orange Book lists the following patents associated with NDA 20-449: the '512 patent, the '561 patent, U.S. Patent No. 4,814,470 ("'470 patent"), U.S. Patent No. 5,438,072, and U.S. Patent No. 5,698,582.

19. Sanofi sells a commercial version of a docetaxel formulation called Taxotere®. Taxotere® was first commercially available in the U.S. on or about May 14, 1996.

20. The first commercial version of Taxotere® used Formulation 2. That formulation was submitted in Sanofi's NDA 30-449. The label for this formulation stated that perfusions should be administered as soon as possible.

21. NDA 20-449 (for Taxotere®) was approved on May 14, 1996.

22. In 1997, Sanofi submitted a supplemental NDA or "sNDA" to the FDA with the same reference number, 20-449. This submission referred to what Sanofi called "Formulation 3" for Taxotere®. Formulation 3 was the same as Formulation 2 except that citric acid was added to the formulation.

23. Formulation 3 for Taxotere® was approved by the FDA in 1999. Taxotere® is currently commercially sold using Formulation 3.

24. Taxotere® is sold as a two-vial product. One vial is called a concentrate and the other is called a diluents. The concentrate vial has docetaxel, along with polysorbate 80, and residual amounts of ethanol. The diluent has water and ethanol.

25. The Taxotere® concentrate includes 40 mg/ml of docetaxel dissolved in polysorbate 80. The Taxotere® diluent includes 13% ethanol and the rest is water.

26. The concentrate vial and the diluents vial are then combined to form a "premix." The premix is a solution that can be added to an IV bag to make a perfusion. According to the Taxotere® label, the premix is stable for up to 8 hours.

27. The premix can be diluted with 0.9% sodium chloride or 5% glucose solutions to prepare a perfusion for administration to patients. The recommended docetaxel concentrations in the perfusions are between 0.3 and 0.74 mg/ml. According to the Taxotere® label, the perfusion is stable for up to 4 hours.

28. Other than Taxotere®, there is not now and has never been another clinically tested or commercially available formulation of docetaxel in the U.S.

29. There is not now and has never been a clinically tested or commercially available formulation of paclitaxel in a formulation including polysorbate 80.

30. On July 3, 1992, applicants filed two applications under the Patent Cooperation Treaty ("PCT"). The first PCT application, PCT/FR/00624 ("PCT624"), entered the national phase in the United States in the priority chain leading to issuance of the '512 patent. The second PCT application, PCT/FR/00625 ("PCT625"), entered the national phase in the United States in the priority chain leading to issuance of the '561 patent. The specifications for PCT524 and PCT 625 are not identical.

31. The application for the '512 Patent was filed on December 1995 and was assigned serial number 08/568, 760 ("the '760 Application"). The '760 Application was filed as a continuation-in-part application claiming priority through U.S. Patent Application Serial No. 08/398, 011

("'011 Application") back to French national application serial number 91 08527 ("FR527"). The application was originally filed with 35 claims and was assigned to a different examiner than the person that had examined and allowed the '011 Application.

32. On May 23, 1997, the PTO issued a Notice of Allowability of all pending claims on the '512 patent.

1. '512 Patent Specification

33. According to the '512 patent, the prior art formulation of paclitaxel caused "manifestations of alcohol poisoning during treatment." According to the '512 patent, "the present invention provides compositions that make it possible either to reduce the ethanol concentrations greatly, or to eliminate Cremophor and ethanol completely from the perfusions."

34. The specification of the '512 patent beings with the following introductory paragraph:

> The present invention relates to compositions and especially pharmaceutical dosage forms containing therapeutic agents having antitumor and antileukemic activity. It relates more especially to compositions suitable for injection containing taxane derivatives, such as, in particular, taxol or one of its analogues or derivatives of the formula (I) [ILLUSTRATION SHOWN] in which R1 and R2 each represent a hydrogen atom or one of R1 and R2 represents a hydrogen atom and the other represents a hydroxyl, acyloxy, or acylcarbonylocy radical, or R2 represents a hydrogen atom and R1 forms a single bond together with the methyl carbon atom situated in the alpha position, so they can form together a cyclopropane ring, one of R3 and R4 represents a hydrogen atom and the other represents a hydroxyl radical, or R3 and R4 taken together form a oxo radical, R5 and R6 taken together form a oxo radical, R7 represents an alkoxy, alkenyloxy, cycloakyloxy or phenyl radical and Ar represents an aryl radical or preferably a phenyl radical optionally substituted by one or several atoms or radicals identical or different and selected from halogen, alkyl, alkoxy, dialkylamoni, acylamino, alkylcarbonylamino or trifluoromethyl, or a 5 membered heterocyclic radical with one or more identical or different heteroatoms chosen from nitrogen, oxygen or sulfur, it being understood that alkyl radical are straight chain or branched chain and contain 1 to 8 carbon atoms and the alkenyl radicals contain 2 to 8 carbon atoms and provided that when R2 is a hydrogen atom and R1 is a hydroxyl radical, R3 and R4 cannot be simultaneously an oxo radical when R6 is a hydrogen atom, R5 is a dydroxy, aceyloxyradical, R7 is a t.butoxy or a phenyl radical and Anticipatory repudiation is a phenyl radical.

['512 Patent, Col. 1, lines 7 – 52]. The specification further discloses that known taxane derivates encompassed by the general forums (I) [above] include two compounds which are known by the name of Taxol and the name Taxotere.

35. The specification describes one of the problems to be solved by the alleged subject

invention in the following terms: "Unfortunately, these products possess such low solubility in water that it has been necessary to prepare formulations for injection containing surfactant and ethanol." ['512 Patent, Col. 2, lines 8 – 10].

36. The specification compares the alleged subject invention to a prior art composition of Rowinsky that solubolized Taxol in a mixture of ethanol and Cremophor EL. The specification describes Cremophor EL as follows:

> ...polyethoxylated castor oil, also known as glycerol polyethyleneglycol ricinoleate, as marketed, e.g., under the name Cremophor, preferably CREMOPHOR® EL... CREMOPHOR® EL is a non-ionic solubulizer and emulsifier that can be obtained by reacting ethylene oxide with castor oil in a molar ration of 35-40 mol ethylene oxide to 1 mol glyceride and is commercially available from BASF and has been assigned CAS Registry Number 61791-12-6. The main component of CREMOPHOR® EL is glycerolpolyethyleneglycol ricinoleate, which together with fatty acid esters of polyethylene glycol, represents the hydrophobic part of the product. The smaller, hydrophilic part consists of polyethylene glycols and ethoxylated glycerol. ['512 Patent, Col 2, line 58 – Col 3, line 4].

37. The specification describes a preferred method of making a "stock solution" in the following terms:

> The stock solution may be prepared by dissolving the active principle in ethanol, which is the best biocompatible solvent for the taxane derivatives, and then gradually adding the surfactant. Solutions containing 10 to 100 mg/ml of active principle in a mixture containing approximately 50% of surfactant can be prepared in this manner. The ethanol is then completely, or almost completely, eliminated.
>
> To prepare, according to the present invention, the solution having a low ethanol content, the taxane derivative is dissolved in ethanol, and the surfactant, which enables micelles to be formed in [sic] containing the taxane derivative encapsulated in the surfactant after dilution in an aqueous medium, is then added. The ethanol contained in this solution is then removed at least partially by evaporation under vacuum or by any other suitable means. ['512 Patent, Col 3, lines 5-19].

38. The specification describes an alternative means for making a stock solution composition with a low ethanol content:

> According to a second method of preparing the stock solution, the taxane derivative is dissolved directly in the surfactant. According to a preferred method, a solution of surfactant containing, in particular, 1 to 2% of ethanol is prepared, and the taxane derivative is added continuously to this solution with stirring, e.g. using a helical grinder or a centrifugal disintegrator. The presence of

a small amount of ethanol provides several advantages: the medium possesses a lower viscosity, and the wetting of the powder and the final filtration of the solution are improved. ['512 Patent, Col 3, lines 20 – 29].

39. The specification includes a "Comparative Example According To The Prior Art" which states, at column 4, as follows:

> Taxol (0.180 g) is dissolved in ethanol (15 ml). The mixture is made to volume with Cremophor to obtain a solution (30 ml) which contains taxol (6 mg/ml). This solution is diluted in a 5% glucose perfusion solution in a proportion of 1 mg/ml; the perfusion solution in a proportion of 1 mg/ml; the perfusion solution contains 87.7 ml/, of Cremophor and 87.7 ml/l of ethanol. The perfusion solution is stable for more than 21 hours. ['512 Patent, Col 4, lines 21-28].

2. '561 Patent Specification

40. Neither the '512 patent or the '561 patent discloses PEG 300 or citric acid.

41. As with the specification for the '512 patent, the '561 specification begins by stating that it relates to taxane derivatives, including taxol and taxotere. [Col 1, lines 6 – 30].

42. The specification states that it is desirable to be able to inject sufficient doses of active principle: "to this end, clinicians would like to inject concentrations of active principle of between approximately 0.3 and 1 mg/ml in the perfusion fluid." ['561 Patent, Col 1, lines 56 – 59].

43. The specification identifies two problems in the prior art that needed to be overcome:

> Now, it is desirable to be able to inject sufficient doses of active principle; to this end, clinicians would like to inject concentrations of active principle of between approximately 0.3 and 1 mg/ml in the perfusion fluid; above these doses, anaphylactic shock phenomena which are difficult to control, due in the main to the Cremophor, are seen (see the publication by Rowinsky, page 1250, second column, last paragraph).
>
> This publication also discloses that, to obtain such concentrations (between 0.3 and 1 mg/ml), it is necessary to inject solutions containing, as well as the active principle, concentrations of each of the following compounds, ethanol and most especially Cremophor, of approximately 8 g per 100 mil of solution. Since the treatment often requires the administration of high doses of active principle, and since the concentration of the active principle in the solution is relatively low, the injection of a large volume has the effect of causing, in addition to anaphylactic manifestations, manifestations of alcohol intoxication during the treatment.
>
> It has been discovered that, by the use of the pharmaceutical dosage forms of the present invention, it is possible to avoid the use of Cremophor and greatly to

reduce the ethanol concentrations used.

['561 Patent, Col 1, line 56 – Col 2, line 11].

44. The specification teaches that use of the pharmaceutical dosage of the invention made it possible to avoid the use of Cremophor and "greatly reduce" the ethanol concentrations used. ['561 Patent, Col 2, lines 8 – 11]. The specification teaches the preparation of a "stock solution" in the following manner:

> For this purpose, a stock solution is prepared, containing the active principle of formula I in a solvent mixture composed of ethanol, which is the best biocompatible solvent for active principles of this class, and a polysorbate surfactant, e.g. as marketed, in particular, under the name "Tween".
>
> The stock solution is prepared by dissolving the active principle in ethanol and then gradually adding the surfactant. Solutions containing 10 to 100 mg/ml of active principle in a mixture containing approximately 50% of surfactant can be prepared in this manner. ['561 Patent, Col 2, lines 12-22].

45. Polysorbate (or "Tween") is the only surfactant that is identified for use in the alleged invention claimed in the '561 Patent.

46. The specification includes the following "comparative example according to the prior art":

> Taxol (0.180 g) is dissolved in ethanol (15 ml). The mixture is made to volume with Cremophor to obtain a solution (30 ml) which contains taxol (6 mg/ml).
>
> This solution is diluted in the same perfusion solution as above to five [sic] a final concentration of 1 mg/ml; the perfusion solution contains 87.7 ml/l of Cremophor and 87.7 ml/l of ethanol.

['561 Patent, 3, lines 7-15].

3. The Asserted Claims

47. Plaintiffs are asserting claims 7 and 33 of the '512 patent against both Hospira and Apotex in this case.

48. Plaintiffs are asserting claims 2, 5, and 10 of the '561 patent against both Hospira and Apotex in this case.

4. '512 patent, Claim 7

49. Claim 1 of the '512 patent, upon which asserted Claim 7 depends, reads (including alterations made by a Certificate of Correction indicated by brackets): "A composition comprising a compound of: (I) [ILLUSTRATION SHOWN] in which A_r is unsubstituted phenyl,

R_7 is phenyl or [tert-butoxy], R_6 is hydrogen, R_5 is aceyloxy or hydroxyl, R_3 and R_4 taken together form an oxo radical, R_1 is hydroxyl and R_2 is hydrogen, said composition being dissolved in a surfactant selected from polysorbate, polyoxyethylated vegetable oil, and polyoxyethylated castor oil, said composition being essentially free or free of ethanol.

50. Claim 6, upon which asserted Claim 7 depends, reads (including alterations made by a Certificate of Correction indicated by brackets): The composition of claim 1 wherein R_5 is hydroxyl and R_7 is [tert-butoxy].

51. Claim 7 reads: The composition of claim 6, wherein said surfactant is polysorbate.

52. The '470 patent's "Composition Example" discloses a docetaxel formulation with a concentration of 2 mg/mL docetaxel, 5% by volume ethanol and 5% by volume Emulphor (a surfactant). ['470 Patent, Col 10, lines 5-11].

53. Apotex's infusion prepared from Apotex's proposed product in accordance with the proposed prescribing information set forth in Apotex's NDA, at a docetaxel concentration of 0.3 mg/mL, would contain approximately 1.8 ml/L of ethanol, or 0.18% v/v of ethanol.

54. Apotex's infusion prepared from Apotex's proposed product in accordance with the proposed prescribing information set forth in Apotex's NDA, at a docetaxel concentration of 0.74 mg/mL, would contain approximately 4.5 ml/L of ethanol, or 0.45% v/v of ethanol.

5. '512 patent, Claim 33

55. Claim 24 of the '512 patent, upon which asserted Claim 33 depends, reads (including alterations made by a Certificate of Correction indicated by brackets): A stock solution comprising a compound of the formula (I) [ILLUSTRATION] in which A_r is unsubstituted phenyl, R_7 is phenyl or [tert-butoxy], R_6 is hydrogen, R_5 is aceyloxy or hydroxyl, R_3 and R_4 taken together form an oxo radical, R_1 is hydroxyl and R_2 is hydrogen, said compound being dissolved in a surfactant selected from polysorbate, polyoxyethylated vegetable oil, and polyoxyethylated castor oil, wherein said stock solution contains from 10 to 200 mg/mL of said compound of formula (I).

56. Claim 32, upon which asserted Claim 33 depends, reads (including alterations made by a Certificate of Correction indicated by brackets): the stock solution of claim 24, wherein R_5 is hydroxyl and R_7 is [tert-butoxy].

57. Claim 33 reads: The stock solution of claim 32, wherein said surfactant is polysorbate.

58. Apotex's premix contains docetaxel.

59. Apotex's premix contains polysorbate.

60. Apotex's premix, when prepared according to Apotex's prescribing information it submitted to the FDA, contains 10 mg/mL of docetaxel.

6. '561 patent, Claim 2

61. Claim 1 of the '561 patent, upon which asserted Claim 2 depends, reads (including alterations made by a Certificate of Correction indicated by brackets): A composition consisting essentially of a compound of formula (I) [ILLUSTRATION] in which R represents a hydrogen atom or an acetyl radical and R_1 represents a tert-bytoxycarbonylamino or benzoylamino radical, dissolved in a mixture of ethanol and a polysorbate whereby said composition is used to form an injectable solution which contains up to about 1 mg/ml of the compound of formula I, said injectable solution being capable of being injected without anaphylactic or alcohol intoxication manifestations being associated therewith.

62. Claim 2 reads: A composition according to claim 1, wherein, in the compound of formula (I), R represents a hydrogen atom and R_1 represents a tert-bytoxycarbonylamino radical.

63. Plaintiffs assert that Hospira's proposed product would infringe Claim 2.

64. Plaintiffs assert that Apotex's premix, when prepared according to Apotex's proposed prescribing information, would infringe Claim 2.

7. '561 patent, Claim 5

65. Claim 5 of the '561 patent reads as follows: "A perfusion, which contains approximately 1 mg/ml or less of compound of formula as defined in claim 1 and which contains less than 35 ml/l of ethanol and less than 35 ml/l of polysorbate, wherein said perfusion is capable of being injected without anaphylactic or alcohol intoxication manifestations being associated therewith."

66. Plaintiffs assert that Apotex's infusion prepared from Apotex's proposed product according to Apotex's proposed prescribing information would infringe Claim 5.

8. '561 patent, Claim 10

67. Claim 8 of the '561 patent, upon which asserted Claim 10 depends, reads: "A therapeutic composition consisting essentially of a taxane derivative dissolved in a mixture of ethanol and a polysorbate, whereby said therapeutic composition forms or is used to form an injectable solution which contains up to about 1 mg/ml of the compound of formula as defined in claim 1, said injectable solution being capable of being injected without anaphylactic or alcohol intoxication manifestations being associated herewith."

68. Claim 10 reads: "The composition of claim 8 wherein said taxane derivative is Taxotere or an analogue or derivative thereof."

69. Plaintiffs assert that Apotex's premix made according to Apotex's proposed prescribing information, would infringe Claim 10.

D. Clinical Testing

70. Sanofi-aventis began enrolling patients for Phase I clinical testing on June 21, 1990. This study was called the "TAX 001" study. The TAX 001 study continued until May 13, 1992. The results from the TAX 001 study were reported in a study reported dated May 24, 1994. Testing under TAX 001 used what Sanofi referred to as "Formulation 1."

71. Formulation 1 had a formulation of docetaxel in 50% polysorbate 80 and 50% ethanol.

72. Sanofi-aventis then began Phase II clinical testing. During Phase II testing, Sanofi-aventis used what it referred to as "Formulation 2."

73. Formulation 2 had a formulation of docetaxel that was almost all polysorbate 80, because ethanol used during the manufacturing process has been evaporated away.

E. The Accused Products

1. NDA 22-234 (Hospira's NDA)

74. Hospira filed New Drug Application No. 22-234 with the FDA to obtain FDA approval for the commercial manufacture, use, and sale of a docetaxel injection product in the following dosage forms: 20 mg/2ml, 80 mg/8ml, and 160 mg/16 ml. Hospira filed its NDA No. 22-234 to obtain approval to market a generic docetaxel formulation before the expiration of certain Sanofi patents, including the '512 and '561 patents.

2. Hospira's NDA Product

75. Hospira's docetaxel product is a one-vial product. Hospira's one-vial product is a stock solution that can be used to make a perfusion, without the need to make a premix.

76. Hospira's one-vial product is suitable for "multi-dose" applications, which means that amounts can be used as needed from the vial, and then the vial can be reused.

77. The concentrations of each of the ingredients of Hospira's proposed product found in Hospira's infusion when the docetaxel concentration is 0.3 mg/mL are as follows: PEG 300, 18.0 mg/mL; polysorbate 80, 7.81 mg/mL; ethanol, 5.47 mg/mL; citric acid, 0.12 mg/mL.

78. The concentrations of each of the ingredients of Hospira's proposed product found in Hospira's infusion when the docetaxel concentration is 0.74 mg/mL are as follows: PEG 300, 44.0 mg/mL; polysorbate 80, 19.3 mg/mL; ethanol, 13.5 mg/mL; citric acid, 0.30 mg/mL.

3. NDA 22-312 (Apotex's NDA)

79. Apotex filed New Drug Application 22-312 with the FDA to obtain FDA approval for the commercial manufacture, use, and sale of a docetaxel injection product in the following dosage forms: 40 mg/ml, 20 mg/0.5 ml and 80 mg/2ml. Apotex filed its NDA No. 22-312 to obtain approval to market a generic form of Taxotere®, before the expiration of certain Sanofi patents, including the '512 and '561 patents. Apotex currently does not make, sell, offer for sale, or use in

the United States, or import into the United States, any product described in NDA 22-312.

80. Apotex sent a letter dated Jun 27, 2008 to Sanofi-aventis to provide notice, pursuant to 21 U.S.C. § 355(b)(2)(B), that Apotex had filed NSA 22-312. The letter further provided notice that Apotex had filed with the FDA, pursuant to 21 U.S.C. § 355(b0(2)(A)(iv), a certification ("Paragraph IV certification") alleging that four of the five Sanofi-aventis patents for Taxotere®, including the '512 and '561 patents, are invalid, not infringed, and/or unenforceable.

4. Apotex's NDA Product

81. Apotex's docetaxel injection product (hereinafter "Apotex's proposed product") consists of two vials – an injection concentrate and a diluent. The injection concentrate is diluted twice before being administered to a patient. The first dilution is referred to herein as a "premix."

82. The injection concentrate vial contains 40 mg/mL of docetaxel in approximately 1088 mg/mL (q.s. to 1 mL) of PEG 300.

83. The diluents vial contains the following ingredients in the following concentrations: ethanol (90 mg/mL), polysorbate 80 (346.8 mg/mL), and water (q.s. to 1 mL).

84. The concentration of the components of Apotex's premix, derived from a review of the concentrations of Apotex's two vials set forth in the Apotex NDA, is as follows: docetaxel, 10 mg/mL; PEG 300, 272 mg/mL; polysorbate 80, 260.1 mg/mL; ethanol, 52.5 mg/mL; water for injection, q.s. to 1 mL.

85. The concentrations of each of the ingredients of Apotex's proposed product found in Apotex's infusion when the docetaxel concentration is 0.74 mg/mL are as follows: PEG 300, 20.13 mg/mL; polysorbate 80, 19.24 mg/mL; ethanol, 3.6 mg/mL (3.89 mg/mL when 95% alcohol is used).

F. Alleged Invalidity

86. Taxanes are poorly soluble in water. Docetaxel and paclitaxel are both poorly soluble in water.

87. Taxol is still commercially available today as a cancer treatment pharmaceutical product.

88. Cremophor is a surfactant. A surfactant is a surface active agent that helps to dissolve an otherwise poorly soluble compound.

89. Tween 80 is a trade name of polysorbate 80. Polysorbate 80 is a surfactant.

90. The Taxol formulation was described and known in the prior art. One prior art publication describing the Taxol formulation was by Eric K. Rowinsky et al., Taxol: A Novel Investigational Antimicrotubule Agent)"Rowinsky") was published in August 1990.

91. Rowinsky reported that the Taxol stock solution has a paclitaxel active ingredient concentration of 6 mg/ml. Rowinsky reports that paclitaxel is available in 5 ml ampoules with equal parts of Cremophor (2.5 ml) and ethanol (2.5 ml).

92. Rowinsky reported that the Taxol perfusion has a paclitaxel active ingredient concentration of between 0.03 and 0.6 mg/ml. Rowinsky reports that Taxol perfusions are stable for up to 24 hours.

93. The prior art '470 patent was issued to Rhone-Poulence Sante and subsequently assigned to Sanofi and published in March 1989. The '470 patent expired on May 14, 2010.

94. The '470 patent is titled "Taxol Derivatives, Their Preparation, and Pharmaceutical Compositions Containing Them." The '470 patent lists Colin, Guenard, Gueritte-Voegelein, and Potier as named inventors.

95. The '470 patent disclosed copunts that are paclitaxel derivatives, including docetaxel. The '470 patent disclosed formulation for such compounds.

96. The '470 patent reported that docetaxel was tested in an in vitro test and was "found to be approximately twice as active as taxol [paclitaxel]." The '470 patent also reported that docetaxel was tested in an in vivo test and "showed an antitumour efficacy greater than that of taxol [paclitaxel] (i.e. an increased survival time, with the animals surviving long-term)."

97. The '470 patent reported that "the parenteral route, and especially the intravenous route, is the preferential route for administration."

98. The '470 patent provided a "composition example" of a formulation made using docetaxel. In that example, a formulation of 20 mg/ml docetaxel was dissolved in a formulation containing 50% Emulphor (Cremophor) and 50% ethanol. Also in that example, this formulation is diluted 10-fold with saline. Applying this initial dilution resulted in the example stock solution having 2 mg/ml docetaxel, 5% Emulphor, and 5% ethanol.

99. The '470 patent reported that docetaxel formulations can be administered "by the intravenous (perfusion) route for an adult."

100. Docetaxel was disclosed in the '470 patent.

101. The '470 patent is owned by the same assignee as the patents-in-suit.

102. The '470 patent discloses the use of docetaxel as an anti-cancer remedy.

103. The following disclosure appears in Columns 9 and 10 of the '470 patent:

> The present invention also provides pharmaceutical compositions containing a compound of formula (I) in combination with one or more pharmaceutically acceptable, inert of physiologically active, diluents or adjuvants.

These compositions may be presented in any form appropriate for the administration route envisaged. The parenteral route, and especially the intravenous route, is the preferential route for administration.

The compositions according to the invention for parenteral administration may be aqueous or nonaqueous sterile solutions, suspensions or emulsions. Propylene glycol, vegetable oils, especially love oil, and injectable organic esters, e.g. ethyl oleate, may be used as the solvent or the vehicle. These compositions may also contain adjuvants, especially wetting agents, emulsifiers or dispersants. The sterilization may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilizing agents into the composition, by irradiation or by heating. They may also be in the form of sterile solid compositions which may be dissolved or dispersed in sterile water or any other injectable sterile medium.

The products of general formula (I) are more particularly used in the treatment of acute leukaemias and solid tumours, at daily doses which are generally between 1 nd 2 mg/kg by the intravenous (perfusion) route for an adult.

The following Example illustrates a composition according to the invention.

COMPOSITION EXAMPLE

The product of formula I obtained in Example 1 (40 mg) is dissolved in Emulphor EL 620 (1 cc) and ethanol (1 cc) and the solution is then diluted by adding physiological saline (19 cc).

This composition may be administered by introduction into an intravenous perfusion of physiological saline given over a period of 1 hour.

['470 Patent, Co. 9 – 10].

104. Claim 6 of the '470 patent states as follows: "6. A pharmaceutical composition which contains a taxol derivative as claimed in claim 1 combined with one or more pharmaceutically acceptable, inert of physiologically active diluents or adjuvants."

105. The prior art publication F. Lavelle, Experimental Properties of RP 56976, a taxol derivative, was published in 1989 by Sanofi-aventis.

106. RP 56976 was the number Rhone-Poulenc assigned to docetaxel.

107. Before the filing in July 1991 or FR537, at least two articles were published by Tarr et al.: Tarr, B.D. & Yalkowsky, S.H., A New Parenteral Vehicle for the Administration of Some Poorly Water Soluble Anti-Cancer Drugs, JOURNAL OF PARENTERAL SCIENCES & TECHNOLOGY, Vol. 41, No. 1, Jan-Feb 1987, pp. 31-33 ("Tarr") and Tarr, B.D., Sambandan T.G., and Yalkowsky, S.H., A New Parenteral Emulsion for the Administration of Taxol, PHARMACEUTICAL RESEARCH, Vo. 4, No. 2, 1987, pp. 162-165. ("PR87").

108. The prior art publication Tarr, B.D. & Yalkowsky, S.H., A New Parenteral Vehicle for the Administration of Some Poorly Water Soluble Anti-Cancer Drugs, JOURNAL OF

PARENTERAL SCIENCES & TECHNOLOGY, Vol. 41, No. 1, Jan-Feb 1987, pp. 31-33 ("Tarr") was published in February 1987.

109. The prior art patent U.S. Patent No. 4,206,221 ("'221 patent") was issued and published in June 1980.

110. The '221 patent discloses the use of cephalomannine for treating leukemic tumors.

111. NCI Investigational Drugs, Pharmaceutical Data, U.S. Department of Health and Human Services, NIH Publication No. 81-2141, March 1981 ("NCI81") discloses an anti-cancer therapy supplied by Bristol Laboratories of Syracuse, New York for clinical trials sponsored by the Division of Cancer Treatment, National Cancer Institute.

112. The active ingredient of the anti-cancer therapy discussed in NCI81 is known as Etoposide and its molecular structure is graphically depicted at page 117 of NCI81.

113. The following information appears on page 118 of NCI81:

> How Supplied:
> Injection, 100 mg, ampule, with citric acid, anhydrous 10 mgl benzyl alcohol, 150 mgl polysorbate 80, purified, 400 mgl polyethylene glycol 300, 3.25 Gm; absolute alcohol qs 5.12 Gm; The product is prepared as a solution in 5 ml ampoules. There are ten ampoules in a box.
> Solution Preparation:
> Ampule/100 mg: Etoposide, as supplied, is a non-aqueous solution. The solution in the ampule must be diluted with 20-50 volumes of 0.9% Sodium Chloride Injection, USP, before administration by slow intravenous infusion. Discard solutions that show evidence of a precipitate.

[NCI81 at 118].

114. NCI81 discloses the following at page 118: "How supplied, Injection 100 mg, ampule, with citric acid, anhyfrous 10mg; benzyl alcohol 150 mg; polysorbate 80, purified 400 mgl polyethylene glycol 300, 3.25 Gm; absolute alcohol qs 5.12 Gm The product is prepared in 5 ml ampoules." [NCI81, p. 118].

115. The publication Bissery et al., Experimental Antitumor Activity of Taxotere® (RP 56976, NSC 628503, a Taxol Analogue, Cancer Research 51, 4845-4852 ("Bissery") was published in September 1991.

116. The Bissery paper was received by the publisher on March 21, 1991. The Bissery paper was officially accepted by the publisher on July 2, 1991.

117. Bissery reported results of testing the anti-tumor activity of docetaxel and paclitaxel for various types of cancer models.

118. Footnote 1 to Bissery states: "Presented in part at the 81st Annual Meeting of the American Association for Cancer Research, May 1990, Washington, DC." This presentation is referred to as "AACR90."

119. Column 2 of page 4845 of Bissery contains the following statement:

> Taxotere® (RP 56976, NSC 628503) was first dissolved in ethanol, then polysorbate 80 was added and the final dilution of Taxotere® was obtained with 5% glucose in water (5/5/90; v/v/v). The pH of the final solution was 5. It was injected i.v., 0.4 ml/mouse. Taxol (NSC 125973) was obtained from the National Cancer Institute (Bethesda, MD). It was prepared as described above for Taxotere®, and injected in the same volume.
>
> Reference compounds were obtained from various suppliers: cyclophosphamide (Laboratoire Lucien, Colombes, France); 5-fluorouracil (Laboratoire Roche, Neuilly sur Seine, France); doxorubicin (Laboratoire Roger Bellon, Neuilly sur Seine, France, and Mead Johnson, Evansvill, IN): cis-platinum (Laboratoire Roger Bellon). All reference compounds were prepared in 5% glucose in water, except for cix-platinum, which was prepared in 0.9% sodium chloride solution, pH 4.5. The volume of injection of all reference compounds was 0.2 ml/mouse.

[p. 4845, col. 2].

120. The prior art publication Gueritte-Voegelein, et al., Relationships between the Structure of Taxol Analogues and Their Antimitotic Activity, JOUNRLA OF MEDICINAL CHEMISTRY 34, 992-998, March 1991 (the "GV reference") was published in March 1991.

121. JMC91/GV discloses relationships between the structure of taxol analogues and their anti-mitotic activity.

122. JMC91/GV reported that: "Moreover, Taxotere (13a) showed a better solubility in excipient system (polysorbate 80/ethanol, 1:1) than the two other most active compounds taxol and [a taxol derivative]." 1:1 formulation means having 50% of each stated excipient.

123. The '470 patent discloses an "intravenous perfusion." Col. 10, line 10.

124. The '221 patent discloses as its active ingredient cephalomannine.

125. The example given in footnote 2 of Table V of the '221 patent includes polysorbate 80 (Tween 80) and ethanol.

126. Cremophor EL can cause an anaphylactic reaction. (*See* PR87; Tarr).

127. The *Dictionnaire Vidal: 65th Edition* ("*Vidal*") was published in 1989. The *Vidal* lists various commercially available drugs, including anti-cancer drugs for parenteral administration.

128. The *Vidal* disclosed prior art formulations for etoposide and teniposide.

129. The *Vidal* reported that teniposide was available under the brand name Vehem. The *Vidal* reported that the Vehem formulation includes Cremophor. The *Vidal* reported a warning for Vehem that Cremophor is likely to lead to anaphylactogenic reactions and that it is important to have oxygen readily available in the case of such a severe reaction.

130. Etoposide and teniposide are anti-cancer drugs.

131. Thierry Dupechez was named on correspondence also describing the prior art etoposide and teniposide prior art formulations. SA00879661-62.

132. The *Vidal* reference discloses the teniposide prior art drug formulation, which used Cremophor, and discloses that the Cremophor ingredient used in teniposide caused anaphylaxis.

133. The *Vidal* reference discloses the etoposide prior art drug formulation for an anti-cancer drug and that polysorbate 80 was used as a surfactant.

134. The prior art publication R.T. Dorr et al., Development of a Parenteral Formulation for the Anti-Tumor Agent Acronycine, (1988) ("Dorr") was published in 1988.

135. Dorr reported testing using the Vepesid formulation, which it referred to as the "VP-16" formulation. Dorr reported using the Vepesid formulation with the drug acroncyine. Acronycine is a poorly water-soluble anti-cancer compound.

136. Dorr disclosed Emulphor as a surfactant that had been used in parenteral formulations with acronycine.

137. Dorr reported that: "Since the co-solvent system used in the present study is identical with that used in the commercial formulation of etoposide (VP-16 of Vepesid), substantial toxicology information on the vehicle is already reported."

138. Dorr reported that: "In clinical etoposide studies however, this solvent has not produced excessive local venous toxicities nor general hypersensitivity reactions [18]."

139. Dorr reported that: "This benign toxicity profile is not found with polyoxyethylated castor oil-based solvents such as those used in the parenteral formulations of the anticancer drug teniposide and the immunosuppressant cyclsporin. Both Cremophor and Emulphor contain this castor oil-derived product and both diluents increase lipid deposition in organs, cause skin flushing and edema, and can alter circulating platelet levels."

140. The specification of the '561 Patent states that: "The anaphylactic shock phenomena which were observed with the solutions of the prior art are not observed with these solutions." ('561 Patent, column 2, lines 48-51).

141. Finnegan, Henderson, Farabow, Farrett & Dunner, LLP ("Finnegan") began prosecuting

the application which resulted in the '512 Patent on behalf of the applicants on December 7, 1995.

142. Finnegan began prosecuting the application which resulted in the '561 Patent on behalf of the applicants on April 12, 1995.

143. Polysorbate 80 had been used in at least one intravenous pharmaceutical formulation before 1991.

G. Secondary Considerations

144. Taxotere®, Plaintiffs' commercial product, is sold in two vials, as Taxotere® (docetaxel) Injection Concentrate in strengths of 80 mg/ 2 mL of docetaxel and 20 mg/0.5 mL of docetaxel in solution with polysorbate 80. The Injection Concentrate accompanied by a diluent. The diluent vial contains 14% ethanol in water.

145. A medical professional dilutes the Taxotere® (docetaxel) Injection Concentrate twice prior to administration according to the prescribing information directions. First, the Taxotere® (docetaxel) Injection Concentrate is diluted with the diluent to prepare a "premix." This premix is then diluted with either a 0.9% sodium chloride solution of 5% glucose solution, resulting in a perfusion for administration to patients.

146. Apotex states in its NDA that polysorbate 80 keeps the docetaxel in solution without any precipitation both in the intial diluted solution of its proposed docetaxel injection product and the final dilution solution of its proposed docetaxel infusion produce.

147. The Taxotere® formulations used by Sanofi-aventis in its Phase 1 clinical trials were one-vial formulations.

148. Hospira has stated in its NDA that "Hospira's Docetaxel Injection was developed by Hospira as a generic equivalent of Taxotere®."

149. Hospira has stated in its NDA that: "The concentration of Polysorbate 80 is the same for both Hospira's Docetaxel Injection and Taxotere® when diluted into infusion solutions. However, it is theoretically possible that the additional excipients in Hospira's Docetaxel Injection may lead to altered biological properties relative to Taxotere®. Comparative studies of the two formulations, which are listed in Table 2, have been sponsored by Hospira to examine the comparability of the extent of release of docetaxel from micelles, the extent of binding to plasma proteins, and pharmacokinetic properties in a Beagle dog study. The results of these studies demonstrated that Hospira's Docetaxel Injection is comparable to Taxotere® with respect to the extent of release of docetaxel from micelles, the extent of binding to plasma proteins, and pharmacokinetics in dogs."

150. Hospira has stated in its NDA that: "Although the proposed formulation is different from Taxotere® with respect to additional PEG 300 and citric acid, and higher levels of dehydrated alcohol, the PS 80 which is critical to micelle formation and stability (le Garrac et al., 2004), is

present at the same concentration in both the proposed Docetaxel Injection and the Taxotere® premix (and therefore in the infusion solutions) . . . the additional excipients present in docetaxel injection do not appear to affect the physicochemical properties of micellar structure relative to Taxotere®."

151. The proposed labeling for Hospira's Docetaxel Injection Product indicates that Hospira's infusion is chemically and physically stable for up to four hours – the same time that is indicated on Taxotere®'s package insert.

H. Inequitable Conduct Allegations

152. During prosecution of the '512 patent, patentees did not amend pending claims 24-35 to add the "essentially free of free of ethanol" limitation.

153. Patentees represented to the Patent Office that it used "Tarr's three-solvent system." Patentees reported tests using only the combination of 60% pluronic L64, 30% ethanol, and 10% polysorbate 80.

154. The named inventor Fabre knew of the TAX 001 study. The named inventor Fabre knew the results of the TAX 001 study.

155. The *Vidal* reference, the etoposide prior art product formulation, and the teniposide prior art formulation were not disclosed to the Patent Office during prosecution of either the '512 or '561 patents.

156. The named inventors Fabre and Dupechez were aware of the *Vidal* reference before and during prosecution of the '512 and '561 patents. The named inventors Fabre and Dupechez were aware of the etoposide and teniposide prior art formulations before and during prosecution of the '512 and '561 patents.

157. The GV reference was not disclosed to the Patent Office during the prosecution of the applications that led to the patents-in-suit.

III. DISCUSSION AND CONCLUSIONS OF LAW

The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338, and 2201. Venue is proper in this court under 28 U.S.C. §§ 1391 and 1400(b). After having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that: (A) claims 2 and 10 of the '561 Patent are invalid due to indefiniteness; (B) all asserted claims of the patents-in-suit are invalid due to obviousness; (C) the asserted claims are unenforceable due to inequitable

conduct; (D) the asserted claims are not invalid due to double patenting; (E) the defendants' proposed products infringe asserted claims 2, 5, and 10 of the '561 Patent and claim 33 of the '512 Patent; and (F) each of the parties Rule 52(c) motions are granted in part and denied in part. The court's reasoning follows.

A. Indefiniteness

The defendants assert that several claims of the patents-in-suit are invalid due to indefiniteness. A patent claim satisfies the definiteness requirement of 35 U.S.C. § 112 if a person of ordinary skill in the art would understand the bounds of the claim when read in light of the specification. Section 112, paragraph 2, requires that the claims of a patent, "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention." 35 U.S.C. § 112 (2000). "A claim is considered indefinite if it does not reasonably apprise those skilled in the art of its scope." *Microprocessor Enhancement Corp. v. Texas Instruments Inc.*, 520 F.3d 1367, 1374 (Fed. Cir. 2008) (quoting *IPXL Holdings, L.L.C. v. Amazon.com, Inc.*, 430 F.3d 1377, 1383-84 (Fed. Cir. 2005)).

1. Claims 2 and 10 of the '561 Patent – "formed or is used to form"

The defendants first assert that claims 2 and 10 of the '561 Patent are indefinite because they impermissibly mix two categories of patentable subject matter. Specifically, the defendants assert that claims 2 and 10, both of which are composition claims, impermissibly include a process limitation: "whereby said composition *is used to form*" for claim 2, and "whereby said therapeutic composition *forms or is used to form*" for claim 10. *Compare* '561 Patent at 3:55-56 *with* id. at 4:20-21 (emphasis added). The court agrees, and concludes that claims 2 and 10 are invalid due to indefiniteness.

The Federal Circuit has addressed the issue of mixing different types of patentable subject matter in two fairly recent cases. In 2004, the Federal Circuit held in *IPXL Holdings, L.L.C. v. Amazon.com, Inc.* that when a claim impermissibly mixes two or more classes of patentable subject matter, the claim is indefinite. 430 F.3d 1377, 1383-84 (Fed. Cir. 2005). The *IPXL Holdings* court struck down a claim reciting "a *system* of claim 2 [including an "input means"] wherein . . . *the user uses* the input means to either change the predicted transaction information or accept the displayed transaction type and transaction parameters." *Id.* at 1384 (emphasis added). The court held that the claim was indefinite because the claim recited both an apparatus (the "system") and a method for using that system ("the user *uses* the input means . . ."). The court concluded:

> [I]t is unclear whether infringement of claim 25 occurs when one creates a system that allows the user to change the predicted transaction information or accept the displayed transaction, or whether infringement occurs when the user actually uses the input means to change transaction information or uses the input means to accept a displayed transaction. Because claim 25 recites both a system and the method for using that system, it does not apprise a person of ordinary skill in the art of its scope, and it is invalid under section 112, paragraph 2.

Id. at 1384.

In 2008, however, the Federal Circuit clarified the scope of the *IPXL Holdings* opinion in *Microprocessor Enhancement Corp. v. Texas Instruments Inc.*, and held that the inclusion of functional language in apparatus claims does necessarily render such claims indefinite:

> [T]he use of functional language in a claim may "fail 'to provide a clear-cut indication of the scope of subject matter embraced by the claim' and thus can be indefinite." Claim 7 of the '593 patent, however, is clearly limited to a pipelined processor possessing the recited structure and *capable* of performing the recited functions, and is thus not indefinite under *IPXL Holdings*.

520 F.3d 1367, 1375 (Fed. Cir. 2008) (emphasis in original). Thus, after the *Microprocessor Enhancement Corp.* decision, an apparatus claim may state that the apparatus is capable of performing particular functions. It cannot, however, include functional limitations that create ambiguity as to when the mixed subject matter claim has been infringed, as was the case in *IPXL Holdings*.

Claims 2 and 10 of the '561 Patent are composition claims, since the claims specify that they cover "a composition" (claim 2) and "a therapeutic composition" (claim 8). The dispute is over whether the words "is used to form" or "forms or is used to form" constitute an impermissible process limitation or step. The plaintiffs assert that the disputed phrases simply define the claimed compositions and state the intended use of those compositions:

> Claims 2 and 10 merely define the two types of compositions discussed throughout the patent and claimed as the inventions covered by the '561 patent – stock solutions and perfusions. A composition that is *used to form* an injectable solution is a stock solution – a term the Court construed to mean a concentrated solution. A composition that forms an injectable solution is a *perfusion*.

(D.I. 383 at 47 (emphasis in original).)

Based on the evidence presented at trial, the court rejects the plaintiffs' argument and concludes that the asserted claims are indefinite. The disputed claims suffer from precisely the lack of clarity that drove the Federal Circuit's decision in *IPXL Holdings – i.e.*, it is not clear when the mixed subject matter claim would be infringed. Unlike the claims that were upheld in *Microprocessor Enhancement Corp.*, the disputed claim language in this case does not merely provide the context in which the claimed composition is intended to be used. On the contrary, by its own terms, the claimed stock solution actually *forms* an injectable solution or actually *is used*

to form an injectable solution.[2] Had the patentees wished to state that the composition was merely "capable of" being formed into a perfusion, they could easily have said so explicitly. Indeed, the disputed claims describe the inherent properties and intended subsequent use of the resulting "injectable solution" in precisely these terms, stating that the injectable solution must be "*capable of* being injected without anaphylactic or alcohol intoxication manifestations . . . ."[3] ('561 Patent 3:57-59.) The court concludes that the inventors did not intend for "forms or is used to form" to have the same meaning as "capable of" appearing in the same claim. Consequently, the court concludes that the disputed phrase, which appears in claims that purport to cover only a "composition," serves as a process limitation in each of the claims in which it appears.

These claims fall squarely within the category of indefinite claims discussed in *IPXL Holdings*, even as that holding was limited by *Microprocessor Enhancement Corp.* As the court in *IPXL Holdings* stated, when "two separate statutory classes of invention" are impermissibly mixed, "a manufacturer or seller of the claimed apparatus would not know from the claim whether it might also be liable for contributory infringement because a buyer or user of the apparatus later performs the claimed method of using the apparatus." *IPXL Holdings*, 430 F.3d at 1384 (citing *Lyell*, 17 US-PQ2d at 1550). That is precisely the case with claims 2 and 10. Dr. Myrdal's testimony aptly illustrates the ambiguity as to whether additional steps beyond the

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[2] The plaintiffs' post-trial brief on this issue cites only a single ten-line portion of the trial transcript, in which Dr. Kaler, a witness for the plaintiffs, testified that he "read [the disputed words] in a harmonious way by interpreting ['is] used to form[' as] meaning creating a stock solution that *subsequently* is made into an infusion." (*See* D.I. 383 at 47, citing Tr. 522:7-17 (emphasis added).) But neither the plaintiffs nor Dr. Kaler cite any evidence – intrinsic or extrinsic – supporting their assertion that the present-tense terms "forms" or "is used to form" somehow refer to a *subsequent* or *future* process.

Furthermore, the plaintiffs themselves assert that "[a] composition that is *used to form* an injectable solution is a stock solution" while "a composition that *forms* an injectable solution is a perfusion." (D.I. 383 at 47.) Consequently, both the plaintiffs' construction and the plain language of the claims require two separate compositions (a stock solution and a perfusion) that are necessarily connected by a process step ("is used to form"), rather than a single composition that can be or is intended to be formed into another composition.

[3] Similarly, while the '512 Patent abstract states that the claimed stock solutions "*can be used* to prepare perfusion solutions," the '561 Patent abstract states the claimed stock solutions "*are used* to prepare perfusions."

creation of a suitable stock solution are necessary in order to infringe the disputed claims, and whether particular acts constitute infringement. A manufacturer who creates only a stock solution (seemingly covered by claims 2 and 10) could not know when he would be liable for infringement if the stock solution is only used to form an injectable solution (also seemingly covered by claims 2 and 10) at a later time and in a different place. Certainly, the performance of additional affirmative process steps is necessary in order for the injectable solution to be formed. In the case of both defendants' products, the prescribing information indicates that the perfusion is only stable for four hours and thus must be administered to a patient within that time, meaning that this step is not performed until well after the defendant-manufacturers sell the stock solution. (*See* JTX 37 at Hospira0049062; ATX 552 at API-DOC-0000042.)

Moreover, it is quite possible that the stock solution will be discarded before it is ever "used to form an injectable solution." In such a case, it is not clear whether infringement ever occurred. (*See* Tr. 894:1-895:18.) The court is persuaded that other competitors and persons of ordinary skill in the art reading the disputed claims would likewise be unable to make "an accurate determination of the 'metes and bounds' of protection" provided. *See Ex parte Lyell*, 17 US-PQ2d 1548, 1550-51 (1990).

The defendants' proposed products aptly illustrate this ambiguity. Apotex's product is sold in two separate vials, one containing docetaxel dissolved in PEG 300 (the "docetaxel vial"), and the other containing polysorbate 80, ethanol, and water (the "diluent vial"). According to the prescribing information, the docetaxel vial is to be diluted twice before it is administered to a patient: first by mixing it with the diluent vial (forming a "premix"), and then again by mixing the premix with a perfusion fluid (e.g., saline or dextrose solution) before it is infused into a

patient. (*See* PTX 701 at 11.) It is only after the premix is formed that a "composition" exists containing docetaxel, polysorbate 80, and ethanol, as required by claims 2 and 10. Then, it is only when that "premix" is mixed with perfusion fluid that "an injectable solution which contains up to about 1 mg/ml" of docetaxel is formed. Hospira's product, on the other hand, is sold in a single vial that can be used to make a perfusion without the need to make a premix. Like Apotex's premix, however, Hospira's product must be diluted with perfusion fluid – presumably at a later time and in a different place, given the prescribing information – before there is an injectable solution meeting the requirements of the claims.

A person of ordinary skill in the art reading the patents-in-suit could not be sure at what point during these processes the infringement is complete. The natural reading of the claim language is that the infringement is only complete when the product actually "forms or is used to form" the perfusion. On the other hand, if one takes the view that the claims are analogous to those upheld in *Microprocessor Enhancement Corp.*, then the infringement is complete when the Hospira stock solution is prepared (prior to sale) or when Apotex's vials are combined to form the premix (presumably after sale), since those are stock solutions capable of being used to form an "injectable solution" as recited in the claims. As mentioned above, each of those steps is likely to be performed by different individuals at different times in different places. Neither the claims nor the specification provide guidance as to when direct infringement is complete.[4]

[4] Moreover, it is not clear whether the plaintiffs are asserting direct infringement, as discussed in the preceding paragraph, or indirect infringement. As to indirect infringement, the plaintiffs focus one section of their post-trial brief (*See* id. at 13) and their Rule 52(c) motion on the defendants' prescribing information, which they say "encourages acts which constitute direct infringement." (*See* D.I. 364 at 3-4.) On that basis, infringement would be complete when the product was actually sold with the included prescribing information, and the resulting infringement would be inducement to infringe under § 271(b) – or perhaps, as the plaintiffs also suggest, the sales of the products would constitute contributory infringement under § 271(c) – rather than direct infringement under § 271(a). Of course, the ambiguity over when direct infringement is complete blurs the issue of what acts constitute indirect infringement.

For these reasons, the court concludes that the defendants have established by clear and convincing evidence that claims 2 and 10 of the '561 Patent are indefinite. Those claims are therefore invalid under § 112 ¶ 2.

2. Claims 2, 5, and 10 of the '561 Patent – "anaphylactic manifestations"

The court is not persuaded by the defendants' remaining indefiniteness arguments. The defendants assert that the term "anaphylactic manifestations" is indefinite. The court disagrees, and finds that this term can be construed to have a definite meaning that would be readily understood by a person of ordinary skill in the art. Specifically, the court agrees with the plaintiffs that a person of ordinary skill in the art would readily interpret "anaphylactic manifestations" in the context of the patents-in-suit as a reference to the Grade 4 hypersensitivity reaction known as anaphylaxis and the symptoms associated therewith – particularly shock. (*See* Tr. 117:22-119:14 (discussing the various grades of hypersensitivity reactions under the NCI's Common Toxicity Criteria, under which grade 4 is anaphylactic shock).) The term does not extend to all symptoms (e.g., hives and bronchospasms) that are (or can be) *associated with* anaphylaxis, regardless of whether the patient is actually suffering from anaphylaxis itself. Rather, the term refers to those symptoms when – and only when – the patient is actually suffering from anaphylaxis. In other words, the '561 Patent requires that the formulation be capable of being injected without causing anaphylaxis and, *by extension*, the symptoms associated with anaphylaxis. With this reasonable construction, the term "anaphylactic

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The question of infringement becomes murkier still if the docetaxel vial is discarded prior to dilution, or if the premix either is discarded prior to being formed into an injectable solution or fails to form a solution when mixed with the perfusion fluid. The prescribing information makes clear that these are more than academic possibilities. The premix is only to be stored "for a maximum of 8 hours." (PTX 701 at 11.) Moreover, "[i]f the [premix] or final dilution [*i.e.*, injectable solution/perfusion] is not clear or appears to have precipitation, these should be discarded." (Id.)

manifestations" is not indefinite.

B. Anticipation

"[I]nvalidity by anticipation requires that the four corners of a single[] prior art document describe every element of the claimed invention, either expressly or inherently." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). The standards for inherent disclosure were recently discussed by the Federal Circuit in *Verizon Services Corp. v. Cox Fibernet Virginia, Inc.*, 602 F.3d 1325 (Fed. Cir. 2010):

> "[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." However, a patent claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." "The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102, however, differs from the enablement standard under section 112." It is well-settled that utility or efficacy need not be demonstrated for a reference to serve as anticipatory prior art under section 102.

Id. at 1337 (internal citations omitted). Whether a prior art reference anticipates a patent claim is a question of fact. *Advanced Display Sys.*, 212 F.3d at 1281.

1. Safety, Efficacy, Stability, and the Construction of "Perfusion"

The court was not asked to construe "perfusion" at the claim construction phase, since the parties indicated in their joint claim chart that they had agreed to a construction of this term. The parties' proposed construction of perfusion was "a solution suitable for infusion into patients including at least active pharmaceutical ingredient and an aqueous infusion fluid such as physiological saline or glucose." (D.I. 44 at 3.) The parties later realized, however, that there had not been a meeting of the minds on the meaning of the phrase "suitable for infusion into patients" in their agreed construction. The defendants filed a motion in limine seeking to

preclude the plaintiffs' experts from testifying at trial as to the construction of "perfusion." (*See* D.I. 272.)

At the pretrial conference, the court heard argument on this motion and indicated that it would hear testimony at trial as to the meaning of term "perfusion." The court now recognizes that its decision was based on a misapprehension as to the source of the phrase "suitable for infusion into patients." The parties' lengthy discussion at the pretrial conference regarding the meaning of that phrase caused the court to believe that the phrase appeared either in the claim itself or in a construction that had been adopted as part of the court's *Markman* order. In reality, however, "suitable for infusion into patients" appears nowhere in the patent or in the court's order. In effect, the parties are not asking the court to construe "perfusion" or clarify a construction that appears in the court's *Markman* order; rather, they are asking the court to construe a phrase that appears in *the parties'* claim construction chart.

Specifically, the plaintiffs' argue that the court should impose limitations for safety, efficacy, and stability on claim 5 of the '561 Patent (the only asserted claim including the word "perfusion") because of the appearance of "suitable for infusion into patients" in the parties' chart.[5] Of course, the parties' proposed constructions do not bind the court. Consequently, the court need not consider arguments that stem solely from the parties' proposed constructions, even if the parties themselves thought they had agreed on a construction. The parties did not propose alternative constructions of the term "perfusion" at trial, nor are proposed constructions included in either of the parties' post-trial briefs. Instead, the parties' arguments before and during the trial focused on whether the term "perfusion" includes the plaintiffs' proposed

[5] *See, e.g.*, D.I. 289 at 2 ("Hospira's proposal is clearly at odds with any rational understanding of the phrase 'suitable for infusion into patients.'"); D.I. 383 at 8 ("At the Pretrial Conference, it became apparent that the parties did not have a common understanding as to what it meant to be "suitable for infusion into patients . . . .").

limitations relating to safety, efficacy, and stability.[6]

Based on the evidence presented at trial, the court concludes that a person of ordinary skill in the art reading the term "perfusion" in the context of the claim would not understand that term to include the plaintiffs' proposed limitations. At the formulation stage, researchers simply cannot know whether a perfusion will be sufficiently safe and effective to be useful in clinical settings. Indeed, this is why clinical trials are necessary before patented pharmaceutical compositions can be marketed to the general public.[7] Under the plaintiffs' proposed construction, a formulator could not know whether his solution was a "perfusion" – and therefore whether it infringed claim 5 – until after clinical trials demonstrated that the solution was sufficiently safe and effective. The court concludes that this is neither true of the term "perfusion" as it is generally used nor of the term as it was used in claim 5.[8]

The court agrees with Dr. Myrdal, who explained that a "perfusion," as that term is used in pharmaceutical composition claims, is simply an injectable solution containing the active pharmaceutical ingredient and an aqueous infusion fluid.[9] The word "perfusion" applies to any

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[6] Neither the claims nor the specification of the '561 Patent mention the terms "safe," "effective," or any derivatives thereof. The specification does indicate that the claimed perfusion was physically stable for at least 8 hours, but nothing in the specification or otherwise suggests that a solution with less than 8 hours of stability cannot be a "perfusion." The court will not import this statement from the specification to the claims so that it imposes a general limitation on what solutions qualify as "perfusions." *See, e.g.*, *Advanced Cardiovascular Systems, Inc. v. Scimed Life Systems, Inc.*, 261 F.3d 1329, 1338 (Fed. Cir. 2001) ("While it is true that claims are to be interpreted in light of the specification and with a view to ascertaining the invention, it does not follow that limitations from the specification may be read into the claims . . . .") (internal quotation omitted).

[7] *See, e.g.*, Tr. 926:25-927:3 (Dr. Myrdal describing how a prior art formulation "worked from a solubility perspective . . . That's what I'm worried about [with] my formulation. It's the chemistry that we're doing. What happens to it afterwards, that's a regulatory affairs issue").

[8] Despite the fact that the word "perfusion" only appears in claim 5, Dr. Park seemed to blur this issue at trial by arguing that all five asserted claims of the patents-in-suit require safety, efficacy, and stability. (*See* Tr. 1492:3-11.) Dr. Park's attempt to impose these limitations on *all* asserted claims is emblematic of the plaintiffs' failure to start with the actual language of the claims in many of its arguments concerning the scope of the asserted claims.

[9] In the asserted claims, a perfusion is formed by diluting a "stock solution" as defined in the court's claim construction order with the aqueous infusion fluid. (*See, e.g.*, Tr. 929:9-16; 1212:16-1213:1; 1214:14-18.) A perfusion is distinguished from other injectable pharmaceutical solutions in that it is administered intravenously

such solution, regardless of whether later testing and use reveals the composition to be stable for less than eight hours (which is the plaintiffs' proposed cutoff point for stability), unacceptably toxic to patients, or insufficiently effective in treating the condition it was designed to treat. (*See* Tr. 929:9-21.) Dr. A. Hilary Calvert agreed, noting that this definition is consistent with the NCI definition of the related term "infusion" ("a method of putting fluids including drugs into the bloodstream"). (Tr. 1031:24-1032:22; HTX 357, at 17 (NCI Glossary).)

The plaintiffs' witnesses also seemed to recognize that the word "perfusion" is not generally understood to include the limitations the plaintiffs assert. The '470 patent used the term "perfusion" to describe a docetaxel formulation even before Sanofi "determined whether docetaxel would be safe and effective," yet plaintiffs' witness Dr. Kinam Park did not dispute that this "was a proper use of the word perfusion." (Tr. 1493:21-1494:12.) Similarly, Dr. Howard Burris acknowledged that Taxol is a "perfusion" even though it has "caused death" and "sometimes . . . does not make a difference" in treating a patient's cancer. (Tr. 236:2-18.)

Consequently, the court concludes that the claims do not include limitations relating to safety, efficacy, and stability other than the two explicit limitations that actually appear in the claims: 1) the asserted claims of the '561 Patent require that the injectable solution must be "capable of being injected without anaphylactic or alcohol intoxication manifestations being associated therewith;" and 2) all asserted claims require that the docetaxel be "dissolved" in polysorbate 80 and (in the case of the '561 Patent) ethanol.[10] The court will not shoehorn the

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rather than through, *e.g.*, an intramuscular or subcutaneous injection. This does not mean, however, that for the purposes of determining invalidity, a person of ordinary skill in the art – which, in this case, is a formulator rather than a clinician (*See* section III.C.2, *infra*) – would ignore prior art injectable cancer drug formulations that were administered by a route other than intravenous infusion.

[10] The "dissolved" limitation does not require that the resulting composition be stable for any period of time after the initial dissolution is complete, and certainly not for eight hours, as the plaintiffs argue. The plaintiffs note that the specifications of the patents-in-suit state that "the new perfusions are stable from a physical standpoint, that

plaintiffs' proposed limitations into the claims based on the *parties'* construction of a single term in a single claim. Consequently, the court rejects the plaintiffs' construction of "perfusion" and their proposed limitations for safety, efficacy, and stability.

2. Claim 33 of the '512 Patent and Claims 2 and 10 of the '561 Patent

The defendants assert that claim 33 of the '512 patent and claims 2 and 10 of the '561 patent are anticipated by the GV reference. The following table summarizes the limitations of these claims:

'512 Patent, claim 33	**'561 Patent, claims 2 and 10**[11]
1) A stock solution comprising . . .	1) A composition consisting essentially of . . .
2) docetaxel	2) docetaxel
3) dissolved in polysorbate 80	3) dissolved in ethanol and polysorbate 80
4) stock solution contains 10 to 200 mg/ml of docetaxel	4) composition is used to form an injectable solution
	5) injectable solution contains up to about 1 mg/ml of docetaxel
	6) solution is capable of being injected without anaphylactic or alcohol intoxication manifestations

The GV reference describes, in relevant part, an experiment in which "taxotere [docetaxel] showed a better solubility in excipient system (polysorbate 80 / ethanol, 1:1)" than did two other taxane compounds. (JTX-93 at 996.)

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is to say no precipitation phenomenon is seen to appear within approximately 8 hours." '561 Patent 2:43-45. See also '512 Patent 3:42-46. It is axiomatic, however, that courts should not import limitations into the claims from the specification. *See, e.g., Abbott Laboratories v. Sandoz, Inc.*, 566 F.3d 1282, 1288 (Fed. Cir. 2009); *Kara Technology Inc. v. Stamps.com Inc.*, 582 F.3d 1341, 1347-48 (Fed. Cir. 2009). But the plaintiffs cite no basis for importing this description as a limitation on the claims beyond the mere presence of the word "perfusion," which only appears in one of the five asserted claims. Even for that claim, the patent gives no indication that the word "perfusion" should be limited by that description. Consequently, the court will not import a stability limitation into the claims.

[11] Claims 2 and 10 differ in ways not material to the court's determination of whether the GV reference anticipates them.

As discussed in Section III.A, *supra*, the defendants also assert that these claims are invalid for indefiniteness. For the moment, the court addresses each limitation of the claims as if it the claims are valid and definite for the purposes of the anticipation analysis. The court's obviousness analysis applies regardless of which party's construction of "forms or is used to form" is adopted.

It is not disputed that the GV reference discloses a stock solution containing docetaxel dissolved in both ethanol and polysorbate. Thus, the GV reference discloses elements 1, 2, and 3 of the disputed claims. As to the fourth and final element of claim 33 – that the solution contains 10 to 200 mg/ml of docetaxel – the defendants contend that this concentration is an inherent property of the GV formulation. (*See* D.I. 378 at Ex. B.) At trial, Dr. Myrdal and Dr. Robert Michael Williams testified that concentration levels are measured in a "routine experiment" called a solubility study. (Tr. 888:16-819:10; *accord* Tr. 1193:5-1194:14.) Furthermore, Dr. Williams testified that Sanofi's own data showed that docetaxel inherently has a concentration in polysorbate of approximately 160 mg/ml, within the claimed 10 to 200 mg/ml range. (Tr. 1194:17-1195:11.)

The plaintiffs, on the other hand, cite Table III in the GV reference as evidence that the concentration of docetaxel in the GV reference was 0.13 μg/mL (*See* JTX-93, at 996 Table III), well below the 10 mg/mL lower limit recited in claim 33. The plaintiffs' witness testified that this concentration was merely "the concentration that inhibit[s] 50 percent of the cell, tumor cell growth or differentiation." (Tr. 1460:1-3.) The witness did not testify, and the GV reference does not state, that this was the highest concentration used in the described experiments. Thus, it is possible that the experiments discussed in the GV reference produced compositions with concentrations within the recited range. Nonetheless, the GV reference does not, on its face, disclose any concentration within that range. While Dr. Williams testified that one "could easily get into that concentration range doing the most routine experiment the formulators would do" (Tr. 1194:14-17), the defendants cite no evidence that such tests were actually done – much less disclosed in the GV reference. The evidence presented at trial was not sufficient to establish by

clear and convincing evidence that the claimed concentration is an inherent property of the docetaxel / polysorbate 80 composition described in the GV reference.

Similarly, while the court recognizes that the composition described in the relevant portion of the GV reference *could* be used to form an injectable solution, claims 2 and 10 of the '561 Patent require that the composition *actually* be used to form an injectable solution.[12] The court does not dispute that, as Dr. Williams suggested, the "only thing [the composition described in GV] can be used for or useful for would be to form a perfusion in an aqueous solution." (Tr. 1200:3-7.) The law governing anticipation, however, narrowly confines the court's analysis to "the four corners" of the specific prior art reference in question. Inferences as to how the described composition was used might appropriately be considered in an obviousness analysis, but not on the issue of anticipation. In this case, the GV reference does not indicate that the disclosed composition was actually used to create an injectable solution. Consequently, the court concludes that the GV reference does not anticipate the asserted claims.

C. Obviousness[13]

1. Legal Standard

35 U.S.C. § 103(a) provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." Obviousness is a question of law that is predicated upon several factual inquiries. *Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, the trier of fact must consider four

[12] As noted above, under an alternative construction of "formed or is used to form," the phrase would refer to how the composition could be used subsequently. See Section III.A.1, *supra*. Were the court to adopt that construction of the claims, the stock solution described in GV would meet this element of the asserted claims.

[13] The court's findings and conclusions on obviousness would be the same even if the court accepted the plaintiffs' argument that "is used to form" means "capable of being formed into." (*See* section III.A.1, *supra*.)

issues: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long felt but unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

A party seeking to challenge the validity of a patent based on obviousness must demonstrate by "clear and convincing evidence" that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made.[14] *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359-60 (Fed. Cir. 2007). However, in determining what would have been obvious to one of ordinary skill in the art at the time of invention, the use of hindsight is not permitted. *See KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 421, 127 S. Ct. 1727, 1742, 167 L. Ed. 2d 705, 724 (2007) (cautioning against "the distortion caused by *hindsight bias*" and "arguments reliant upon *ex post reasoning*" in determining obviousness) (emphasis added). In *KSR*, the Supreme Court rejected a rigid application of the principle that there should be an explicit "teaching, suggestion, or motivation" in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art, in order to find obviousness. *See KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. at 415. The *KSR* Court acknowledged, however, the importance of identifying "'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus. v. Alphapharm Pty.,*

[14] "Clear and convincing evidence is evidence that places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Alza Corp. v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 631 (D. Del. 2009) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

Ltd., 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (quoting *KSR*, 550 U.S. at 418).

2. Level of Ordinary Skill in the Art

A person of ordinary skill in the art with respect to the patents-in-suit holds a bachelor's of science degree with two to four years of experience in pharmaceutics and drug development, or a Ph.D. with commensurate experience to obtain the training and background necessary to understand the development of pharmaceutical formulations. (Tr. 833:1-18; 1437:10-15.) Thus, a person ordinary skill in the art with respect to the patents-in-suit is a formulator, not a clinician.

3. Scope and Content of Prior Art and Differences Between Claimed Subject Matter and Prior Art

As a threshold matter, it is important to understand what the asserted claims of the patents-in-suit invention are not. First, the claims do not cover a new drug. Instead, the claims cover a formulation containing an *old* cancer drug, docetaxel. Sanofi's U.S. Patent No. 4,814,470 – prior art issued in 1989 – already claimed docetaxel itself and, in fact, also claimed docetaxel in a pharmaceutical formulation. (*See* JTX 9, at 10:42-45 ("A pharmaceutical composition which contains [docetaxel] combined with one or more pharmaceutically acceptable, inert or physiologically active diluents or adjuvants.").) In the example disclosed in the '470 patent, docetaxel was formulated in ethanol and Cremophor (also called "Emulphor"). (JTX 9, at 10:5-11.)

Second, the asserted claims are not method or process claims. They are composition claims. Indeed, the asserted claims of the '512 Patent do not even state the compositions are "pharmaceutical" or "therapeutic" in nature or include limitations indicating that it is intended for use in humans. The asserted claims of the '561 Patent, by comparison, include limitations stating that it is "capable of being injected without anaphylactic or alcohol intoxication

manifestations" and claim 8, upon which asserted claim 10 depends, specifies that the ingredient is a "therapeutic composition." These terms signal that the "perfusions"/"injectable solutions" that are the end result of the claimed compositions are intended for use in humans. Even these claims, however, cover only a composition with certain properties and limitations described in the remainder of the claims. None of the asserted claims in either patent cover methods of treatment and, excepting the '561 Patent's limitations for anaphylaxis and alcohol intoxication, they do not contain limitations regarding efficacy, toxicity, or other *in vivo* properties of the drug. Indeed, as the court stated in its anticipation analysis, those properties of a formulation cannot be known until clinical trials are conducted, an event that occurs well after the initial formulation of the drug.

Both at trial and in their post-trial briefing, the plaintiffs focused their nonobviousness arguments on one aspect of the claimed invention – the substitution of polysorbate 80 in place of Cremophor in the docetaxel formulation. (*See, e.g.*, D.I. 383 at 26 (asserting that in order to establish obviousness, the "[d]efendants must prove that it would have been obvious to formulate taxanes using polysorbate 80 for intravenous administration despite the established use of Cremophor at the time . . .").) That issue dominated the parties' invalidity arguments at trial. Consequently, while the court concludes that the prior art renders every element of the asserted claims obvious, it will focus its discussion on the switch from Cremophor to polysorbate 80.[15]

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[15] Even though the plaintiffs do not seem to seriously dispute the obviousness of the other limitations, Dr. Williams' testimony included a thorough limitation-by-limitation analysis on how each limitation of the asserted claims was either anticipated or rendered obvious by one or more of these prior art references. *See* Tr. 1173-1225. The court found his testimony highly persuasive. By contrast, the plaintiffs' witnesses who testified on invalidity, particularly Dr. Park, focused inordinately on the safety, efficacy, and stability (or lack thereof) of the prior art formulations rather than on the limitations that actually appear in the asserted claims.

The only limitation for which the court did not find Dr. Williams' testimony persuasive was the "essentially free of ethanol" limitation in claim 7. Dr. Williams' analysis of this element appears to have been based at least in part on accepting *arguendo* the plaintiffs' interpretation of the "essentially free" limitation – an interpretation that

Both polysorbate 80 and Cremophor are surfactants. Since taxanes are poorly soluble in water, surfactants are included in taxane formulations to help dissolve the taxane in water and keep it in solution. (*E.g.*, Findings of Fact ¶ 88, *supra*; Tr. 848:19-25.) Early formulations of the first taxane to be developed, paclitaxel, included a 50:50 mixture of ethanol and Cremophor. (*E.g.*, Findings of Fact ¶ 91, *supra.*) The preferred embodiment of the stock solution in the first patent claiming docetaxel, which is prior art to the patents-in-suit, also contained a 50:50 mixture of ethanol and Cremophor. (*See, e.g.*, Tr. 836:8-17; JTX 9 at 10:5-8.)

During the years preceding the filing of these applications, a number of prior art references appeared disclosing formulations of taxanes (including docetaxel) and other poorly water-soluble cancer drugs with either Cremophor or polysorbate 80. A number of these references anticipated the switch from Cremophor to polysorbate 80 that the plaintiffs assert was the "innovation" of the asserted claims. The court discusses these prior art reference below.

a. Prior Art Taxane Formulations

The set of prior art references that plaintiffs identify as the departure point for the claimed invention consists of Cremophor-based taxane formulations. Researchers' experience with Cremophor-based paclitaxel formulations is summarized in the Rowinsky reference (JTX 15), a 1990 research review article that both patents-in-suit cite as prior art illustrating the problem the patents-in-suit were designed to address. ('512 Patent 2:12-47; '561 Patent 1:40-2:7.) While most of Rowinsky is devoted to discussing the promising anti-tumor activity of a

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the court rejects for the reasons stated in section III.F.5, *infra.* Nonetheless, the court agrees with the defendants that the prior art renders this limitation obvious. In particular, the specification and claims of the prior art '470 Patent – the first to claim docetaxel – disclose and contemplate both ethanol-containing and essentially ethanol-free stock solutions and perfusions. *E.g.*, '470 Patent at 9:17-40; id. at 10:41-44 (claim 6). Consequently, the court concludes that that the '470 Patent renders this limitation obvious. Moreover, even if the court were to find that the prior art did not render this limitation obvious, the court concludes that the defendants' products are not "essentially free of ethanol" and thus do not infringe. *See* section III.F.5, *infra.*

paclitaxel formulation (JTX 15 at 1247), the reference also describes how researchers encountered a high incidence of anaphylaxis during the Phase I clinical trials for the paclitaxel-Cremophor formulation. According to Rowinsky, these incidents "threatened the prospects of taxol's further development." (JTX 15 at 1251; Tr. 111:19-112:19.) Rowinsky notes that "other drugs formulated in cremophor . . . have been associated with similar hypersensitivity reactions." (JTX 15 at 1253.) The reference also states, however, that "it is . . . unclear whether taxol itself or its cremophor vehicle is principally responsible for hypersensitivity reactions." (Id.)

The patent first claiming docetaxel was U.S. Patent No. 4,814,470, issued in 1989 with a 1986 original foreign filing date. (*See* JTX 9 (hereinafter "the '470 Patent").) As noted above, the only preferred embodiment of a stock solution disclosed in the '470 Patent contained a 50:50 mixture of ethanol and Cremophor. The patent's specification made clear, however, that a wide variety of other formulations may be possible:

> The present invention also provides pharmaceutical compositions containing [docetaxel] in combination with one or more pharmaceutically acceptable, inert or physiologically active, diluents or adjuvants.
>
> These compositions may be presented *in any form appropriate for the administration route envisaged.* The parenteral route, and especially the intravenous route, is the preferential route for administration.
>
> The compositions according to the invention for parenteral administration may be aqueous or nonaqueous sterile solutions, suspensions or emulsions. Propylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be used as the solvent or the vehicle. These compositions may also contain adjuvants, especially wetting agents, emulsifiers or dispersants. The sterilization may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilizing agents into the composition, by irradiation or by heating. They may also be in the form of sterile solid compositions which may be dissolved or dispersed in sterile water or any other injectable sterile medium.

('470 Patent 9:17-40.)

The plaintiffs argue that the "innovation" of the formulation claimed in the patents-in-suit was that using polysorbate 80 instead of Cremophor "allows . . . docetaxel to be administered to patients without the life-threatening anaphylaxis associated with the prior Cremophor-based formulation." (D.I. 383 at 1. *See also, e.g.*, Tr. 21:11-22.) This statement obscures the multi-pronged approach, of which the claimed formulations were only a part, that researchers took to address the anaphylaxis that occurred in Cremophor-based taxane formulations.

Researchers considered at least three alternative solutions to the anaphylaxis issue: pretreatment regimens, alternative schedules, or a reformulated preparation. (*See* PTX 553 at 607.) Clinicians tried premedication first, which solved the immediate problem by significantly reducing the incidence and severity of hypersensitivity reactions.[16] (Tr. 215:2-20; JTX 15 at 1251, 1253-54.) To this day, in fact, a paclitaxel-Cremophor formulation (brand name Taxol) is marketed and administered to patients after premedication. (Tr. 1189:5-13.) While the Taxol clinical trials continued with premedication, research continued into new taxane formulations.

The foreign priority application that led to the patents-in-suit was filed on July 8, 1991. By that time, at least two prior art references disclosed compositions containing a taxane and polysorbate 80. The lead author of the first reference, the GV reference, was also one of the co-inventors of the prior '470 Patent. (*See* JTX 9 & JTX 93.) As discussed in the court's anticipation analysis, the GV reference discloses a composition containing docetaxel dissolved in

[16] The premedication approach had the virtue of avoiding the delays that would ensue from halting the clinical trials altogether while researchers searched for a new, better-tolerated formulation. The court is persuaded by the testimony of Dr. Calvert, who testified that reformulation would have set back work on a promising cancer medicine for "several years." (994:25-995:14.) Dr. Calvert, who was actually involved in paclitaxel clinical trials at the time, explained that nobody "wanted to stop the momentum and back off in using this drug for the several years it would have taken to undertake a reformulation exercise." (Id.) Such delays would have been inevitable, as Dr. Williams explained, since reformulation "would require that all of the preclinical and clinical testing would have to be done over again." (Tr. 1188:7-1189:4.)

ethanol and polysorbate 80.[17] The GV reference described both the docetaxel compound and the polysorbate-based solution in a favorable manner, stating that the compound "showed a better solubility" in the polysorbate-containing stock solution "than the two others most active compounds . . . ."[18] (JTX 309 at 996.) The GV reference thus disclosed a docetaxel formulation containing polysorbate 80 instead of Cremophor, the switch that forms the very core of the alleged invention. As Dr. Williams stated, a formulator reading the GV reference would find this description in the conclusion of the polysorbate-ethanol excipient system to be "the most important piece of information" in the paper. (Tr. 1247:15-21.)

Another prior art reference, U.S. Patent No. 4,206,221 (the "Miller patent"), includes a table reporting significant anti-cancer activity in live animals using a polysorbate 80 based (and Cremophor-free) formulation for two taxanes: cephalomannine and paclitaxel. Consequently, compositions containing both polysorbate 80 and a taxane – indeed, containing both polysorbate 80 and docetaxel specifically – were in the prior art at the time the applications for the patents-in-suit were filed.

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[17] In fact, the GV reference disclosed the very same "1:1" formulation that Sanofi first brought to clinical trials in June 1990 – a 50:50 formulation of ethanol and polysorbate 80. (Tr. 471:15-24.) The plaintiffs argue that the GV reference is not invalidating because it describes only *in vitro* testing. The court rejects this argument for two reasons. First, the court is persuaded by the testimony of Dr. Myrdal and Dr. Williams that GV in fact discloses a pharmaceutical formulation rather than an *in vitro* solution. Dr. Myrdal noted that GV used the phrase "excipient system," which is clearly "a pharmaceutical system" given the context in which the phrase appears. (Tr. 841:9-21.) Dr. Williams explained that 50% ethanol "is toxic to cells in *in vitro* testing" and 50% polysorbate "is a cell membrane disrupting molecule, and that's also toxic." (Tr. 1191:14-1192:11.) Furthermore, even if the reference did refer only to *in vitro* testing, the claims in question contain no limitations restricting themselves to *in vivo* solutions. The person of ordinary skill in the art with respect to the asserted claims is a formulator, and a formulator searching the prior art surely would not overlook a reference to docetaxel formulations in the *Journal of Medicinal Chemistry*.

[18] This reference does not "compar[e] the solubility of docetaxel in polysorbate 80/ethanol to the solubility of docetaxel in any other solvent," but rather provides the "relative solubility of docetaxel . . . in polysorbate 80/ethanol, compared to the solubility of two other [taxane] compounds . . . in that same polysorbate 80/ethanol mixture." (Tr. 958:1-12.) Nonetheless, the court concludes from the evidence presented at trial that persons of ordinary skill in the art reading this description would have noted the favorable reference to the solubility of docetaxel, particularly in light of the Miller, Vidal, O'Dwyer, and Dorr references disclosing successful solutions of other water-insoluble cancer drugs in polysorbate 80.

b. Other Prior Art Cancer Drug Formulations: Cremophor, Polysorbate 80, and Anaphylaxis

The 1989 *Dictionnaire Vidal* (the French equivalent of the *Physicians' Desk Reference*) describes the experience of Sandoz Laboratories with two anti-cancer compounds – teniposide (with Cremophor) and the related, later-developed etoposide (with polysorbate). (JTX 101, at 1-4; Tr. 864:8-19.) For teniposide, a warning in the *Vidal* states that the medication "contains . . . Cremophor EL as an excipient, which is likely to lead to anaphylactogenic reactions" – a danger that required requires "a source of oxygen . . . available near the patient's bed." (JTX 101 at 0155161; Tr. 863:12-19.) In contrast, the *Vidal* describes the later-developed etoposide without any side effects specifically attributable to polysorbate 80. (*See* JTX 101 at 055162-63; Tr. 863:20-864:7.) It also reports milder overall side effects, with only rare hypersensitivity (2% of cases) even without special premedication.[19] (Id.) The etoposide formulation is intravenously administered, and the court finds that it is both a "perfusion" and an "injectable solution" as those terms are used in the asserted claims of the patents-in-suit. (*See, e.g.*, JTX 101 at 155749 (describing a presentation of etoposide as an "[i]njectable solution for IV perfusion").)

The O'Dwyer reference (JTX 102), published in 1984, similarly indicates that the reduced number of hypersensitivity reactions in etoposide as compared to teniposide was due to

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[19] A Sanofi internal memorandum that was written during the early stages of docetaxel formulation research indicated that Sanofi's formulators were aware of Sandoz's experience with teniposide and etoposide and recognized its potential significance in formulating docetaxel:

> Cremophor is accepted less and less often by clinicians and registration authorities alike. Research is underway to find replacement products such as [polysorbate 80]. This is why Sandoz, having developed the anti-neoplastic drug teniposide with Cremophor, then developed an analog product from it called etoposide in [polysorbate 80].

(JTX 162 at 00879661; Tr. 407-09, 462-63.) While this memorandum predates the publication of the *Vidal* reference, it is probative of the understanding a skilled artisan would have regarding the teachings of the Sandoz experience of switching from Cremophor to polysorbate 80.

the switch from Cremophor to polysorbate 80. The reference notes that "one explanation" for the "greater frequency of allergic reactions" with teniposide "may lie in the formulation of these agents." (JTX 102, at 960.) O'Dwyer then specifically cites teniposide's use of Cremophor as a potential culprit, noting that two other drugs formulated with Cremophor, phytonadione and miconazole, "may cause similar hypersensitivity reactions." (Id. at 960-61.)

Another prior art reference, a 1988 article by Professor Robert T. Dorr, describes the formulation of yet another poorly water-soluble cancer drug called acronycine. (*See* JTX 215). Acronycine had been previously formulated with Cremophor (Tr. 854:19-855:9), but Dorr concluded that a "[Cremophor] based solution should be avoided" due to its potential for hypersensitivity reactions. (JTX 215 at 32; Tr. 855:19-856:1.) He addressed the problem by swapping surfactants based on Sandoz's clinical experience, noting that while Cremophor in teniposide had been associated with hypersensitivity, "clinical etoposide studies" with polysorbate 80 had "not produced excessive local venous toxicities nor general hypersensitivity reactions." (JTX 215 at 38; *accord* Tr. 859:23-860:10.) Like the *Vidal* and O'Dwyer references, the Dorr reference teaches that a cancer drug formulator wishing to avoid the hypersensitivity reactions known to occur with Cremophor-based formulations should switch to polysorbate 80. (*See*, e.g., Tr. 860:11-24; Tr. 1501:14-17.)

The plaintiffs argue that Dorr and the etoposide references should be disregarded because formulators only consider references about structurally related compounds. Based on the evidence presented at trial, the court rejects this argument. The court is persuaded on this point by the testimony of Dr. Myrdal and Dr. Williams. As Dr. Myrdal explained, formulators assessing the solubility of different drugs routinely consider formulations for drugs "that are not

related at all with respect to their chemical structure." (Tr. 856:21-858:1.) Formulators assessing the potential of a particular solvent system for different drugs will focus primarily on the solubility characteristics of the drugs rather than the drugs' chemical structures. (Id.; *accord* Tr. 1204:21-1205:3 (Dr. Williams testifying that "formulators really don't care about the structure. They care about the . . . solubility characteristics of the drug").). This approach is confirmed by the references cited during this case. For instance, Professor Dorr followed Sandoz's etoposide work for acronycine, another insoluble anti-cancer drug, even though they are structurally different. (Tr. 856:21- 858:14.). The Tarr reference likewise used the same formulation for three cancer drugs that were quite different structurally. (*See* Tr. 1180:23-1181:5.) The court thus finds based on the evidence presented at trial that a skilled artisan would find the prior art etoposide and acronycide references highly relevant to potential formulations for taxanes, including docetaxel.

The plaintiffs also argue that these prior art references should be disregarded because the references did not teach the ratios of polysorbate 80 and ethanol that ultimately were chosen by Sanofi. The court is persuaded by the testimony of Dr. Williams, however, that a person of ordinary skill in the art would not test merely the "exact ratio" of ingredients "that was already described" in the prior art, "take the active [ingredient] and plop it in the formulation without making any changes to ingredients or ingredient levels," and then give up if that exact prior art formulation did not work for their tested drug. (Tr. 1205:4-12.) Rather, as Dr. Williams testified, "[i]t's completely in the routine, mundane part of being a formulator [to] vary the volumes and the ratios of [ingredients in a formulation] . . . it's called optimization of your formulation." (Tr. 1205:4-21. *See also* Tr. 926:4-16 (Dr. Myrdal).) Consequently, the fact that

the precise mixture that was used for etoposide did not work for docetaxel does not detract from the compelling teaching of the etoposide prior art – that a skilled artisan seeking to formulate a water-insoluble cancer drug that avoids the anaphylaxis seen with a Cremophor-based formulation should make a formulation using polysorbate 80 in place of Cremophor.

c. Reasonable Expectation of Success

The plaintiffs further argue that the defendants failed to demonstrate that a skilled artisan who decided to create a polysorbate 80-based formulation for docetaxel would have done so with a reasonable expectation of success. In support of this proposition, the plaintiffs assert that "the literature raised concerns about the toxicity of polysorbate in a perfusion." (D.I. 383 at 33.) The plaintiffs further contend that "[n]othing in the prior art provided a reasonable expectation of success in using polysorbate to formulate taxanes, either with regard to achieving the necessary physical stability or with regard to the safety and effectiveness of the formulation." (Id. at 34.)

Based on the evidence presented at trial, the court rejects these arguments. Stability, safety, and efficacy are not requirements of the asserted claims of the patents-in-suit, for the reasons discussed above. *See* section III.B.1, *supra*. Consequently, "success" in the context of the asserted claims would require that a person of skill have a reasonable expectation that he be able to "dissolve[]" docetaxel in the polysorbate 80-based system. With respect to the '561 Patent, a practitioner of the art would also need a reasonable expectation that he would be able to form an injectable solution/perfusion that could be injected without causing the symptoms of alcohol intoxication or anaphylaxis. Based on the references discussed above, the court concludes that a skilled artisan would have had a reasonable expectation of success in both these regards. Beyond that, there need not be a "reasonable expectation of success" with respect to

safety, efficacy, or stability.[20]

The plaintiffs' assertions regarding the possible toxicity of polysorbate 80 are similarly unavailing. The asserted claims of the '512 Patent contain no limitations regarding toxicity, making the '561 Patent's limitations regarding alcohol intoxication and anaphylaxis the only toxicity-related limitations in the asserted claims. The plaintiffs cite no evidence that would lead a person of ordinary skill in the art to believe that a polysorbate 80/docetaxel solution would cause such symptoms. If anything, the court finds that the *Vidal*, O'Dwyer, and Dorr references would lead a person of ordinary skill to believe that a polysorbate 80-based formulation would avoid the symptoms of anaphylaxis seen in Cremophor-based formulations.

Even if other toxicity concerns were relevant to the asserted claims, the court finds that a person of ordinary skill would not have the concerns about toxicity urged by the plaintiffs. The plaintiffs' evidence of the toxicity of polysorbate 80 is largely dependent on their assertion that polysorbate 80 in E-Ferol may have caused deaths in infants who had "pre-existing respiratory distress." (*See* Tr. 1330:21-1331:19; 1362:1-11.) But Dr. Rodricks, the plaintiffs' witness on this point testified on direct that it remains unclear how or why the deaths happened and "what contributed to" those deaths. (Tr. 1331:10-19.) The deaths easily could have resulted from "very high levels of Vitamin E itself" in E-Ferol. (Tr. 999:25-1000-14.) Indeed, Dr. Calvert noted that "[t]he later articles that we reviewed actually don't mention the polysorbate 80 and imply that the problem was due to the Vitamin E itself." (Tr. 1000:5-7.) Alternatively, the deaths could have been the result of "contaminated polysorbate," which Dr. Rodricks admitted

[20] Moreover, even if some level of stability beyond the initial dissolution of the docetaxel in a polysorbate 80 system were a requirement of the asserted claims, the court concludes that a skilled artisan reading all these references would have a reasonable expectation that the solution would be sufficiently stable to serve its intended purpose.

nobody could determine "one way or the other." (Tr. 1363:5-14.) The court finds that the E-Ferol incident thus raised no concerns about polysorbate 80's safety, particularly for adults.[21] In any case, the plaintiffs' arguments on this point once again overlook the fact that the claims in question are composition claims, containing no limitations as to the safety or toxicity of the drugs beyond their potential for producing analphylaxis and alcohol intoxication. Given the nature of the asserted claims and the limitations that actually appear in them, the court finds that a skilled artisan at the time of the filing of the patents-in-suit would have had a reasonable expectation of success.[22]

For the reasons stated above, the court concludes from the evidence presented at trial that at the time of the filing date, a person of ordinary skill in the art examining these prior art references would have been motivated to formulate docetaxel with polysorbate 80. The *Vidal*, O'Dwyer, and Dorr references would teach a person of ordinary skill in the art who wished to reformulate a poorly water-soluble drug like docetaxel in order to avoid the anaphylaxis

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[21] The plaintiffs cite only one other prior art reference for their assertion that there were concerns about the toxicity of polysorbate 80 in humans. In that study, a formulation of a drug called amiodarone containing polysorbate 80 "adversely affected the blood pressure of patients taking the drug." (D.I. 383 at 32 (citing Tr. 1325:25-1328:10; PTX 356).) Like with E-Ferol, however, the plaintiffs' witness admitted that it "wasn't certain at all" whether the polysorbate 80 or other ingredients in the cited formulation were responsible for the adverse reactions. (Tr. 1326:20-22.) The court finds that these two seemingly isolated incidents – which plaintiffs did not argue were connected – would not have led skilled artisans to have concerns about the toxicity of polysorbate 80.

The plaintiffs also cite the pending patent application on Hospira's docetaxel formulation as further evidence that the patents-in-suit are nonobvious. (*See* D.I. 383 at 33-34.) The court rejects this argument. The validity of Hospira's pending application is not at issue in this case, and the evidence presented at trial did not concern that application. The court is not in a position to assess or comment on the validity of still-pending patent applications, and fails to see how such applications – which could end up being withdrawn or rejected by the patent office – are relevant with respect to the validity of the patents-in-suit.

[22] In addition, the court notes that it is not convinced that the claimed formulations have been as effective in preventing anaphylaxis as the plaintiffs claim. The asserted reduction in the incidence of anaphylaxis is based on a comparison to prior art *paclitaxel*/Cremophor formulations (i.e., Taxol) rather than *docetaxel*/Cremophor formulations. The court also is not aware of the incidence of anaphylaxis with Taxol administered with premedication. Consequently, the proffered improvements were not based on an apples-to-apples comparison with alternative approaches available at the critical date. Furthermore, it appears clinicians remain sufficiently concerned about the possibility of anaphylaxis with Taxotere that they administer premedication (*see* JTX 70 at §§ 2.6 & 5.3) and keep a "shock cart" on hand during administration of Taxotere. (*See* Tr. 984:10-985:2.)

associated with Cremophor-based formulations that he should attempt to create a formulation based on polysorbate 80. By the time of the filing date, the prior art actually included formulations containing docetaxel dissolved in polysorbate 80 systems, as explicitly disclosed in the GV reference and suggested by the Miller Patent's paclitaxel/polysorbate 80 formulation. The routine testing and optimization that skilled artisans then would undertake would have quickly led them to the ingredient amounts and ratios disclosed in the asserted claims. (*See, e.g.*, Tr. 887:17-889:10; 926:4-16; 1193:5-1194:14; 1205:4-21.) Consequently, the prior art available at the time of filing renders obvious every limitation of each of the asserted claims.

4. Secondary Considerations

The evidence in the record on several relevant secondary considerations weighs neither for nor against a finding of obviousness, and thus does not inform, one way or the other, the court's finding that the patents-in-suit are obvious in light of the prior art. Once a *prima facie* case of obviousness has been established, the burden shifts to the applicant to come forward with evidence of secondary considerations of non-obviousness to overcome the *prima facie* case. *E.g.*, *In re Huang,* 100 F.3d 135, 139 (Fed. Cir. 1996). Secondary considerations can include evidence of commercial success, long felt but unsolved needs, and failure of others, *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), as well as unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans before the invention. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). "Evidence of commercial success, or other secondary considerations, is only significant if there is a nexus between the claimed invention and the commercial success." *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1311-12 (Fed.

Cir. 2006).

a. Long Felt Need and Failure of Others

The plaintiffs assert that there was an "urgent need for a Cremophor-free taxane formulation" due to "the fatal results of the 1984 Phase I trials of paclitaxel." Based on the evidence presented at trial, the court rejects this argument. First, the use of premedication and alternative administration schedules had significantly reduced the incidence of anaphylaxis with Taxol, a drug that remains in use today. *See* section III.C.3.a, *supra*. Consequently, the court finds that there was no specific need – much less an urgent need – for a Cremophor-free taxane formulation. Second, the claims in question were composition claims, and at least two prior art references disclose Cremophor-free taxane formulations – the GV reference and the Miller '221 Patent.[23] Thus, even if the plaintiffs' proposed "need" existed, "the need was not for advancements on the existing prior art, but rather for a drug manufacturer to recognize the commercial potential of what already existed in the prior art." *See Santarus v. Par Pharmaceutical*, C.A. 07-551, 2010 WL 1506017, at *23 (D. Del. Apr. 14, 2010).[24]

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[23] In support of their position that there was a long felt but unmet need, the plaintiffs cite an article stating that, "[f]or the past eight years, a number of investigators have attempted to develop more pharmaceutically acceptable formulations for this compound that eliminate Cremophor and do not precipitate upon dilution." (*See* D.I. 383 at 34 (citing PTX 413 at 170).) The plaintiffs neglect to mention, however, that this statement was made in an article discussing *paclitaxel* that was published in 1998, *seven years after the filing of the patents-in-suit*. This reference thus is not prior art, and in any case the quoted statement does not appear to suggest that efforts to create Cremophor-free taxane formulations had begun in earnest prior to 1990 (*i.e.*, eight years before the reference was published, and only one year before the filing of the patents-in-suit). The earliest reference to an effort to create a Cremophor-free taxane formulation cited in Yalkowsky was the Tarr reference (co-authored by Yalkowsky), which the court discusses in section 3.b, *infra*.

[24] Moreover, since Sanofi held the original, prior art patent on docetaxel at the time the applications for the patents-in-suit were filed, formulators from other companies did not have a particularly powerful incentive to search for alternative formulations of docetaxel. *See Sanofi-Synthelabo v. Apotex Inc.*, 488 F. Supp. 2d 317, 337 (S.D.N.Y. 2006) (discounting alleged failure of others, long felt but unresolved need, and commercial success because the same company that brought suit held a prior patent and "no other entity could have brought a similar drug to market throughout the duration of that patent"). It would undermine the goals of the patent act if inventors could effectively extend the life of drug patents by first obtaining a patent on the active ingredient of a drug, and later obtaining new patents with later expiration dates on subtly-different formulations of the same drug, including ones that were in their possession before or during the prosecution of the active ingredient patent.

b. Teaching Away

The plaintiffs cite a 1987 article by Bryan D. Tarr and Samuel H. Yalkowsky as teaching away from a polysorbate 80 formulation. The Tarr reference describes a "new parenteral vehicle [that] was developed for three poorly water soluble cancer drugs." (JTX 16 at 31.) One of the three drugs tested was paclitaxel. (Id.) The Tarr system contained three solvents: Pluronic L64 (60%), ethanol (30%), and polysorbate 80 (10%). (Id.)

The plaintiffs assert that this reference reports a failure, since the formulation that included paclitaxel did not remain stable long enough to be suitable for IV administration. (Id. at 32.) The defendants, on the other hand, argue that the Tarr reference reports a success, since the paclitaxel formulation remained stable for three days in the study after the formulation was diluted with water (as would happen with a perfusion). The article certainly concludes optimistically, stating that "[t]he pluronic L64 cosolvent system may prove to be a useful cosolvent for solubilizing poorly water-soluble drugs. The three drugs tested are chemically as well as physically stable within this vehicle." (Id.)

Based on the evidence presented at trial, the court concludes that the Tarr reference teaches neither toward nor away from using polysorbate 80 as the primary vehicle in taxane formulations. First, the reference makes clear that the results reported in the Tarr reference were performed primarily to assess the feasibility of using pluronic L64 as a solvent, not polysorbate 80.[25] Second, Tarr was not part of an effort to create a new formulation for taxanes (much less

[25] The reference repeatedly refers to the tested vehicle as "the pluronic L64 system," "the pluronic L64 cosolvent system," or a "pluronic cosolvent system." Besides providing the polysorbate 80 content of the formulation (10%), the only reference to polysorbate 80 in the reference is a sentence stating that "[p]olysorbate 80 (10%) was added to slow the crystallization of the drugs once added to water." (JTX 16 at 32.)

Similarly, another article by the same authors describes research done using "an emulsion as a possible alternative to the use of cosolvents in taxol administration." (JTX 92 at 162.) As with the Tarr paper on pluronic L64, this paper teaches nothing about the potential use of polysorbate 80 as the dominant solvent, and it is pointless

docetaxel), but rather was an effort to assess a new vehicle for administration for poorly water soluble cancer drugs generally. (*See* Tr. 942:4-943:3.) The Tarr experiment therefore was not an effort to solve the problem – finding a docetaxel formulation that avoids anaphylaxis – that the plaintiffs contend the patents-in-suit were designed to address. Lastly, since the Tarr system contained far more pluronic L64 and ethanol than polysorbate 80, it is not clear how the reference teaches anything about creating a formulation containing mostly polysorbate 80 and no pluronic L64 – a point that the patentees themselves seemed to acknowledge during prosecution. (*See* JTX 59 at 4 ("Certainly there is no teaching or suggestion in Tarr that Tarr's composition would work when missing a component which makes up over half of its solvent base.").) These facts, combined with the mixed results of the stability tests, render the Tarr reference at worst neutral with regard to its teachings on the elimination of Cremophor or the use of polysorbate 80.

The plaintiffs also argue that the prior art taught away from polysorbate 80 because some prior art references, including O'Dwyer and the Miller Patent, were available at the time the first, Cremophor-based docetaxel formulations were introduced. Similarly, the plaintiffs argue that the Tarr reference should be taken as evidence of nonobviousness because it is "inherently implausible" to argue "that Dr. Yalkowsky tried and failed a combination of pluronic L64 and polysorbate 80 when it was obvious . . . to use polysorbate 80 alone." These arguments, while superficially tempting, miss the mark. The application leading to the '470 Patent was filed in 1986, and the Tarr reference appeared in January 1987. The patents-in-suit were not filed until several years later, in July 1991. The issue in this case is not whether the asserted claims would have been obvious at the date that docetaxel was first formulated or when the Tarr reference was published, but rather whether it was obvious as of the critical dates for the *patents-in-suit*.

to speculate as to the authors' motivations in choosing to try formulations using other ingredients.

Indeed, the '470 Patent and the Tarr reference are themselves prior art with respect to the patents-in-suit.

The plaintiffs themselves framed the issue when they asserted that the "innovation" of the asserted claims is that they reduced the risk of anaphylaxis *as compared to the prior art Cremophor-based formulations*. (*See* D.I. 383 at 1 (stating that the "innovation" of introducing "a polysorbate-based formulation" allows "docetaxel to be administered to patients without the life-threatening anaphylaxis associated with the prior Cremophor-based formulation.").) A person of ordinary skill in the art in 1991 trying to resolve problems that arose with those Cremophor-based formulations would not ignore prior art simply because it had been available earlier.[26]

Finally, the plaintiffs argue more generally that the prior art available at the time of the invention taught that Cremophor was essential to the anti-tumor activity of docetaxel. This argument fails for several reasons. First, the plaintiffs once again overlook the fact that the claims in question are composition claims, not method of treatment claims, and that the claims do not require efficacy. Moreover, the plaintiffs failed to offer a single prior art reference drawing any connection between Cremophor and the anti-tumor activity of docetaxel. The only article from before 1992 that Sanofi relied on was the Weiss paper, which discusses paclitaxel (not docetaxel) and does not even state Cremophor is essential to biological activity of *that* drug. Instead, it merely states that "[a]t present, there is no suitable substitute for Cremophor EL in taxol formulation." (JTX 145, at 1267.) While true – the only available formulation of paclitaxel at the time (there were not yet any available formulations of docetaxel) did use

[26] This is particularly true in a case, such as this, where one company holds a prior patent covering the active ingredient of the drug in question. *See* footnote 24. Indeed, it was in the '470 Patent that the early Cremophor-based docetaxel formulation was disclosed.

Cremophor – the statement says nothing at all about whether Cremophor itself is essential to paclitaxel's (much less docetaxel's) biological activity. (Tr. 219:1-8; 996:11-21.) Furthermore, Weiss is a clinical paper rather than a formulation paper, it does not mention polysorbate 80 or docetaxel, and it fails to cite the Miller '221 patent. (Tr. 217:17-23; JTX 145, at 1263, 1268.)

Beyond that, the plaintiffs strangely relied on what was merely an obvious mistake by the authors of the 2001 van Zuylen reference – published a full ten years after the critical date. (PTX 209, at 125.) The van Zuylen paper suggests that Cremophor could be important to the biological activity of *paclitaxel* (not docetaxel). (PTX 209, at 135.) In support of this assertion, however, van Zuylen cited only the Rose paper – published in 1992, and therefore also not prior art – which says the exact opposite of Sanofi's contention. (JTX 94, at 317; Tr. 866:15-869:1.) In plain English, Rose teaches there is no difference in performance between polysorbate 80 and Cremophor: "taxol achieved similar maximum effects using either vehicle."[27] (JTX 94, at 317.)

This is in accord with the prior art that actually was available at the critical date. The Miller '221 Patent, for example, reports significant anti-cancer activity in live animals using a Cremophor-free formulation with polysorbate 80 for the taxanes cephalomannine and paclitaxel.[28] Certainly, the plaintiffs cite no prior art reference available at the time of the

[27] The plaintiffs argue that "Rose could say in 1992 that polysorbate worked with a taxane only because the inventors proved, for the first time, that it worked." (D.I. 383 at 37.) This statement recognizing that Rose said "polysorbate worked with a taxane" appears to concede that van Zuylen misread Rose's teaching with regard to the essentiality of ethanol. Moreover, even if true, the plaintiffs' contention that Rose could only say this because of the inventors' own work is beside the point. The issue with regard to teaching away is whether the prior art available at the critical date taught away from the alleged the invention. Rose was not prior art, and it did not teach away, regardless of whose work is (partially) responsible for the fact that it did not teach away. That is all that is relevant for the purposes of this secondary consideration.

[28] The plaintiffs cite the Douros article (PTX 334, at 170) to undermine the Miller teaching that a polysorbate 80 formulation was effective with paclitaxel. But the data from Douros is based on a different set of experiments from testing with different mice by different researchers at different times using different doses on different schedules. (Tr. 1511:13-1512:11; Tr. 1283:7-1285:1.) Given all these differences – including a dosing difference of "almost ten times" – Dr. Williams explained, "it's not good science to directly compare the specific data" between Douros and Miller. (Tr. 1283:7-1284:19.)

invention that teaches that Cremophor is essential for the anti-cancer activity of docetaxel, or that teaches away from the use of polysorbate 80. For these reasons, the court concludes that the prior art available at the time of the invention did not teach away from the elimination of Cremophor or the use of polysorbate 80.

c. Commercial Success

The plaintiffs assert that the commercial success of Taxotere, Sanofi's branded drug product containing docetaxel dissolved in polysorbate 80, is evidence of the nonobviousness of the patents-in-suit. Commercial success, however, is "only significant if there is a nexus between the claimed invention" and the secondary consideration at issue. *E.g.*, *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-1312 (Fed. Cir. 2006). Here, there is no nexus for at least two reasons. First, it is not clear that Taxotere itself is covered by the asserted claims. For example, the Taxotere premix has 12% ethanol and thus is not "essentially free of ethanol" as required by asserted claim 7 of the '512 Patent. (*See* Tr. 695:21-696:7.)

Second, and most important, "the asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art." *J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). In this case, the only formulation of docetaxel that has been approved is Taxotere, the polysorbate 80-based formulation sold by Sanofi. None of the evidence presented at trial has persuaded the court that the commercial success of Taxotere was due to the polysorbate 80-based *formulation* rather than the use of the *active ingredient* docetaxel – which, as the court has already noted, was first introduced in a prior art patent. On the contrary, as the plaintiffs' expert Dr. Bokhart acknowledged, it appears that docetaxel's "efficacy of curing cancer is the primary driver of

Sanofi's sales of Taxotere." (Tr. 358:9-19, 367:6-16. *See also* Tr. 1080:15-18.) Dr. Bokhart further stated that he had "no independent opinion whether Taxotere would have been successful if the formulation used Cremophor instead of polysorbate 80." (Tr. 364:8-12.) Sanofi's director of marketing further stated: "If you're asking specifically that I'm aware if anybody speaks about polysorbate 80, I've never seen that per se." (1083:23-1084:8.) Since there is no evidence that the commercial success of Taxotere is due to anything besides its (prior art) active ingredient, the court concludes that there is no nexus between the commercial success of Taxotere and the asserted claims of the patents-in-suit.

d. Unexpected Benefits

The plaintiffs argue that there were unexpected benefits derived from the use of polysorbate 80 rather than Cremophor. To show unexpected benefits, the patent owner must first show "what properties were expected." *Pfizer v. Apotex*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). In *Pfizer*, for instance, the claimed unexpected benefits failed because "the record [was] devoid of any evidence of what the skilled artisan would have expected." *Id.* The same is true here. Dr. Burris acknowledged that "before polysorbate 80 was actually tested, there wasn't any expectation one way or the other about what would happen with it." (Tr. 201:9-203:8.) He explained that each property "just had to be tested." (Tr. 201:3-203:8.) Similarly, asserted benefits such as alleged reduced neuropathy side effects, which Dr. Handy also addressed, are also unavailing because no evidence shows they were unexpected. (Tr. 1405:8-1407:4.)

Furthermore, the plaintiffs fail to cite evidence tying the allegedly unexpected benefits of polysorbate 80 to the asserted claims of the patents-in-suit. The plaintiffs assert that "polysorbate 80 is rapidly metabolized and hence removed from the patients' blood stream,

reducing the likelihood of side-effects and drug-drug interactions." (*See* D.I. 383 at 38.) But just as the patents-in-suit were not the first to claim docetaxel (*See* section c, *supra*), they also were not the first to claim polysorbate 80. On the contrary, polysorbate 80 had been available for decades prior to the filing of the patents-in-suit, and its use as a surfactant had long been known among skilled artisans. (*See*, e.g., Tr. 1228:12-1229:1; 1515:17-1516:16.) The court concludes that the evidence presented at trial failed to demonstrate any connection between the allegedly unexpected benefits of taxotere and the asserted claims of the patents-in-suit.

e. Copying

The plaintiffs assert that the defendants in this case copied the formulation claimed by the patents-in-suit. First, the court does not agree that either of the defendants "copied" Sanofi's product. The defendants' products differ from Taxotere in several respects. While both defendants' products contain polysorbate 80 and docetaxel, Hospira uses a one-vial system with two extra ingredients (PEG 300 and citric acid). Apotex's product is a two-vial system where the docetaxel is first dissolved in PEG 300 rather than ethanol or polysorbate 80; only later is polysorbate 80 added to Apotex's formulation. (*See, e.g.*, Tr. 1151:6-11.) While these differences are not necessarily sufficient to establish non-infringement, they are relevant as to whether the defendants simply "copied" the formulation described in the patents-in-suit. This is particularly true in this case, since the prior art on the filing date included polysorbate 80/taxane formulations. (*See* section III.C.3.a, *supra*.)

Moreover, even if the court were to find that the defendants engaged in some level of copying, evidence of copying is less persuasive as objective evidence of nonobviousness in lawsuits brought by brand name drug companies against generic drug companies. *Cf. Aventis*

Pharma Deutschland GmbH v. Lupin Ltd., No. 2:05CV421, 2006 WL 2008962, at *45 (E.D. Va. July 17, 2006), *rev'd on other grounds by* 499 F.3d 1293 (Fed. Cir. 2007). While this reasoning is more persuasive in ANDA cases, the court finds that it applies with some force in this case as well. To the extent that the defendants engaged in copying, such conduct is not strong objective evidence of non-obviousness under the facts of this case.

5. Conclusion on Obviousness

In their post-trial brief, the plaintiffs do not assert any bases for finding the asserted claims to be non-obvious besides the claims' inclusion of polysorbate 80 instead of Cremophor. The plaintiffs assert that this switch was made in order to create a taxane formulation that reduced the incidence of anaphylaxis associated with Cremophor-based formulations. For the reasons stated above, however, this switch was obvious in light of the prior art, and the prior art rendered every limitation of the asserted claims obvious. The court therefore concludes the record at trial established by clear and convincing evidence that the asserted claims of the patents-in-suit are invalid due to obviousness.

D. Double Patenting

The defendants assert that both asserted claims of the '512 patent are invalid for obviousness-type double patenting over Claims 1 and 44 of U.S. Patent No. 5,698,582, another *Orange Book* patent scheduled to expire on the same day as the '512 patent, July 3, 2012. This argument is obviated by a terminal disclaimer, transmitted to the PTO on November 8, 2007. (*See* JTX 286 at FIN01-000394-398; *see also* 1348 Official Gazette 420 (Nov. 24, 2009), *available at* http://www.uspto.gov/web/offices/com/sol/og/2009/week47/TOC.htm#ref16).) Despite the fact that this terminal disclaimer was not transmitted until after this action commenced, the court

concludes that this is sufficient to overcome the defendants' double patenting challenge.

E. Inequitable Conduct

The defendants assert that the patents-in-suit are unenforceable due to inequitable conduct on the part of the applicants. A party alleging inequitable conduct must establish by clear and convincing evidence that the applicant: (1) made an affirmative misrepresentation of material fact, failed to disclose material information, or submitted false material information to the PTO; and (2) intended to deceive the PTO. *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1365 (Fed. Cir. 2008). These two elements are often shortened to "materiality" and "intent to deceive." *See, e.g., id.* ("[A]t least a threshold level of each element – i.e., both materiality and intent to deceive – must be proven by clear and convincing evidence."). "Once the threshold levels of materiality and intent have been established, the trial court must weigh materiality and intent to determine whether the equities warrant a conclusion that inequitable conduct occurred. The more material the information misrepresented or withheld by the applicant, the less evidence of intent will be required in order to find inequitable conduct." *Honeywell Intern. Inc. v. Universal Avionics Systems Corp.*, 488 F.3d 982 (Fed. Cir. 2007) (internal citations omitted).

"Information is material when a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent." *Symantec Corp. v. Computer Associates Intern., Inc.*, 522 F.3d 1279, 1297 (Fed. Cir. 2008) (internal citation omitted). Information is also material if it is not cumulative and it (1) establishes, by itself or in combination, a prima facie case of unpatentability; or (2) refutes or is inconsistent with a position the applicant takes in arguing for patentability. *See* 37 C.F.R. § 1.56(b).

Intent "need not, and rarely can, be proven by direct evidence." Indeed, "it is rarely proven by such evidence." *eSpeed, Inc. v. BrokerTec USA, L.L.C.*, 480 F.3d 1129, 1138 (Fed. Cir. 2007). Rather, intent to deceive is generally inferred from the facts and circumstances surrounding the applicant's overall conduct." *Impax Labs., Inc. v. Aventis Pharm. Inc.*, 468 F.3d 1366, 1375 (Fed. Cir. 2006) (quoting *Merck & Co., Inc. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1422 (Fed. Cir. 1989)). In order to establish the requisite intent, "the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." *Kingsdown Medical Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876 (Fed. Cir. 1988). For omissions, absent a credible explanation, "intent to deceive is generally inferred from the facts and circumstances surrounding a knowing failure to disclose material information." *Ferring B.C. v. Barr Labs*, 437 F.3d 1181, 1191 (Fed. Cir. 2006).

One of the named inventors, Jean-Louis Fabre, testified at trial. Mr. Fabre's deep involvement in the docetaxel formulation work and his role as project leader were discussed at length during his testimony. Mr. Fabre stated during his direct examination that in his capacity as project leader, representatives from "the Biology Department, the Chemistry Department, the Department of Chemical Processes, the Toxicology Department, the Biodynamics Department, the Gallenic Department, the Marketing Department" and maybe "others" all reported to him on the Taxotere project. (*See* Tr. 383:8-22.) His responsibilities included reviewing both internal and external documents concerning the formulation and later clinical testing of Taxotere. For instance, Mr. Fabre stated that he had approved the GV reference prior to its publication (Tr. 469:8-10) and acknowledged that because he was project leader, he was the first recipient of a

clinical investigator's brochure relating to docetaxel in 1992. (Tr. 472:12-22. *See also* JTX 161 and 162 (internal memoranda received by Mr. Fabre).) In September 1992, Mr. Fabre and his co-applicants signed a sworn declaration confirming that they had "a duty to disclose to the Office information they are aware of which is material." (JTX 4, at 12927.) Mr. Fabre admitted at trial that he knew he had this duty of disclosure. (*See* Tr. 474:22-475:10.)

The court concludes that Mr. Fabre engaged in inequitable conduct by failing to disclose two prior art references: 1) The prior art, specifically the *Vidal* reference, disclosing Sandoz's experience with the teniposide and etoposide formulations; and 2) the GV reference. These references are not cumulative of other evidence, and are highly material for three independent reasons. First, they are inconsistent with the position that the plaintiffs took in asserting the patentability of the asserted claims. *See* 37 C.F.R. § 1.56(b)(2). Second, for the reasons stated in the court's obviousness analysis, the court finds that these references were sufficient to render the asserted claims of the patents-in-suit obvious. (*See* id. § 1.56(b)(1).) Lastly, there certainly is a substantial likelihood that a reasonable examiner would have considered the references important in deciding whether to allow the asserted claims. Indeed, the court concludes that a reasonable examiner would find these references to be key references in determining the patentability and proper scope of the asserted claims. The references therefore easily meet the threshold materiality requirement. The court's discussion of the issue of deceptive intent with respect to each of the references follows.

1. Vidal and the Teniposide/Etoposide Formulations

When developing a docetaxel formulation, the Sanofi inventors recognized there was a problem with Cremophor because of its suspected hypersensitivity reactions, and Mr. Fabre was

copied on a December 1988 memo with this understanding: "Cremophor is accepted less and less often by clinicians and registration authorities alike." (JTX 162, at 1.) Sanofi's inventors disclosed that known problem from the December 1988 memo to the Patent Office, citing Rowinsky for the hypersensitivity associated with Taxol: "anaphylactic manifestations are seen (*See* the publication by Rowinsky, page 1250, second column, last paragraph)." (JTX 3, '561 patent, at 1:60-64; Tr. 478:10-16.) To solve this problem, Mr. Fabre and his co-inventors at Sanofi adopted the same approach that Sandoz had used for etoposide – swapping Cremophor for polysorbate 80 in the formulation. In the same paragraph of the same December 1988 internal memo, Sanofi indicated that it would follow Sandoz's approach: "This is why SANDOZ, having developed the antineoplastic drug TENIPOSIDE with CREMOPHOR, then developed an analogue product from it called ETOPOSIDE, in [polysorbate 80]." (JTX 162, at 1.)

Unlike the Rowinsky prior art relating to the *problem*, however, Mr. Fabre and his co-inventors did not inform the Patent Office about this key source for the *solution* they adopted. (*See* Tr. 478:17-23.) Mr. Fabre acknowledged at trial that he "learned from [his] review of the prior art Sandoz compounds that you could substitute polysorbate 80 for Cremophor." (*See* Tr. 467:19-22.) He also learned that etoposide formulated with polysorbate 80 – unlike teniposide formulated with Cremophor – "doesn't have any warnings," has "no reference to requiring strict medical supervision," and cites no "side effects that are specifically attributable to polysorbate 80." (Tr. 467:6-18.)

Despite this, there is no reference in the patent record to Sandoz's etoposide formulation even though, like the claimed formulation, it was a formulation for an insoluble cancer drug that used polysorbate 80 instead of Cremophor as the surfactant. (JTX 1, '512 patent; JTX 3, '561

patent; JTX 4, prosecution history; Tr. 463:17-24.) It is clear that Mr. Fabre and his colleagues at Sanofi recognized the importance of Sandoz's prior art formulations, since Mr. Fabre admitted it was one of the two main references for selecting polysorbate 80. (*See* Findings of Fact, ¶ 155, *supra*.) The court therefore finds that Mr. Fabre was aware of the materiality of these references, and nonetheless chose not to disclose them to the patent office.

In an effort to excuse concealing the Sandoz prior art, Mr. Fabre argued that his earlier reliance on "the Sandoz experience was invalidated by the tests that" he and his colleagues later conducted with "etoposide-type" formulations. (Tr. 475:16-23; JTX 60-T, at Appx. 12.) For a number of reasons, however, Sanofi's etoposide-type experiments cannot possibly excuse Mr. Fabre's concealment of the Sandoz prior art. First, Sanofi's etoposide experiments were internal, unpublished, and confidential experiments. Such activities cannot excuse the concealment of published prior art.[29]

Second, Mr. Fabre's excuse rests on his assertion that the "etoposide-type" perfusions were "failures" due to insufficient physical stability. (Tr. 446:4-12.) As the court has explained, however, stability is not a requirement of the patents-in-suit. So long as the docetaxel can be dissolved in the claimed composition, the requirements of the asserted claims are met.[30]

Furthermore, even if stability *were* a requirement of the claims, some of the tested formulations that Sanofi's contemporaneous documents referred to as "etoposide-type" were

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[29] In effect, allowing such a defense to inequitable conduct would be permitting the inventor rather than the patent examiner to determine whether a prior art reference is potentially invalidating. Inventors could conceal highly material prior art and later justify this concealment by citing only a subset of their previously unpublished experiments, which is precisely what Mr. Fabre did in this case when he cited only 14 of the 22 "etoposide-type" formulations. Accepting such confidential tests as a justification for concealing prior art would eviscerate the rule requiring disclosure of prior art to the patent office. That is precisely why the law requires the applicant to disclose prior art references, and places the responsibility on the examiner – not the applicant – to determine whether the prior art is sufficient to invalidate the claims.

[30] Moreover, even if the tested *perfusions* were considered a "failure," all but one of the claims (claim 5 of the '561 patent) cover stock solutions or perfusions.

actually successes, not failures. (Tr. 447:17-448:7.) On direct, Mr. Fabre assumed eight hours of physical stability as the cutoff point for when the formulations in question were a "success." (*See* Tr. 420:12-423:5.) The product insert for Taxotere – the product that Sanofi ultimately developed based on Mr. Fabre's work – states that the Taxotere perfusion remains stable for only four hours, and that it takes only one hour to administer Taxotere to a patient. (*See* Tr. 447:8-16.) During direct examination, Fabre mentioned only fourteen of the twenty-two "etoposide-type" formulations they made. (Tr. 440:6-14, 443:5-24.) Even among the fourteen formulations that Mr. Fabre mentioned on direct, thirteen of those were stable for at least one hour and five were stable for at least four hours. (Tr. 447:22-448:7.) The eight that Mr. Fabre did *not* disclose remained stable even longer, ranging from 5 hours and forty minutes to 32 hours. (Tr. 450:10-17, 443:5-24.)

In an effort to discount the results of these tests, Mr. Fabre denied that they were "etoposide-type formulations." (Tr. 445:13-446:6.) Sanofi's contemporaneous documents, however, specifically called them "etoposide-type" formulations. (JTX 60-T, at Appxs. 7-9.) The court does not find credible Mr. Fabre's witness-stand assertion, twenty years after the documents were prepared, that the contemporaneous description of these formulations as "etoposide-type" did not reflect how Sanofi's researchers actually viewed the formulations.[31]

As the Sanofi internal memorandum indicated (*See* JTX 162) and Mr. Fabre himself stated (*See* Tr. 476:20-478:5), the Sandoz experience was one of the two "main factors that shaped [his] thinking" in choosing polysorbate 80 for Sanofi's docetaxel formulation. There

[31] Moreover, Mr. Fabre's credibility was further undermined by his decision on direct to disclose only those tested formulations that supported his assertions regarding the "irrelevance" of the etoposide prior art. Then, as now, it seems to the court that Mr. Fabre chose to disclose some of the material information in his possession, but not to disclose other information that could have jeopardized the validity or enforceability of his patents.

simply is no justification for telling the Patent Office about the prior art disclosing the problem he examined while concealing key prior art disclosing the solution he chose. Consequently, for the reasons stated above, the court finds based on the evidence presented at trial that Mr. Fabre knew that the *Vidal* reference and the other etoposide prior art were relevant to the patentability of his alleged invention, but nonetheless chose not to disclose it to the patent office. Based on this finding, the court concludes that Mr. Fabre acted with intent to deceive with respect to his decision not to disclose the *Vidal* reference.

2. The GV Reference

The court also finds that Mr. Fabre knew the GV reference was material but knowingly withheld it from the patent office. As project leader of Sanofi's Taxotere development, Mr. Fabre reviewed the GV reference "with some care to make sure it was a proper article for the company to be publishing." (Tr. 469:11-20.) To justify his decision not to disclose the GV reference, Mr. Fabre testified on redirect that he read only a March 1990 draft of the GV article; that draft did not include the concluding sentence disclosing the polysorbate 80/docetaxel formulation. (Tr. 502:4-7; 503:6-503:15.) Mr. Fabre claimed that during the two and half year period between the time the March 1990 draft was prepared and the day he signed his patent declaration in September 1992, he never read a final draft of the March 1991 published GV article disclosing the clinical formulation. (Tr. 504:8-13.)

Mr. Fabre's assertion that he had only reviewed the March 1990 draft was not offered prior to redirect, and the court does not find his testimony on this point credible. First, Mr. Fabre took steps in March 1992 to disclose the final version of GV to clinical investigators, since he was not satisfied that the clinical brochure omitted the GV reference and thus insisted in a memo

that it be cited. (*See* Tr. 473:8-22; 478:24:479:3.) The GV reference had been published a year earlier by that time, and Mr. Fabre signed his patent declaration six months later.

Second, Mr. Fabre had to approve the GV article prior to its publication, as he himself conceded:

> Q: Before [the GV reference] was published, you had to give approval. Correct?
> A: Yes.
>
> Q. So you reviewed the article with some care to make sure that it was a proper article for the company to be publishing?
> A. Yes.

(Tr. 469:8-14.) In fact, one of Mr. Fabre's colleagues, Dr. Francois Lavelle, was a co-author of the GV reference (Tr. 469:1-3), and the lead author of the GV reference was one of the co-inventors of Sanofi's '470 Patent, which first claimed docetaxel. (*See* JTX 9 & JTX 93.) Even standing alone, Mr. Fabre's role as project leader and his role in approving the article for publication make it highly unlikely that he never read the final version of a prominent Taxotere publication co-authored by his colleagues. Since he reviewed the article "with some care," approved it, and – a year *after* its publication – insisted on its disclosure to clinical investigators, the court rejects Mr. Fabre's claim on redirect that he never read the final version of the GV reference prior to signing the patent declaration. Based on the evidence presented at trial, therefore, the court finds that Mr. Fabre had not only reviewed, but "reviewed . . . with some care" the final version of the GV reference prior to signing the patent declaration, was aware of the reference's materiality to the prosecution of his patents, and purposefully decided not to disclose it despite this knowledge. Based on this finding, the court concludes that Mr. Fabre

acted with deceptive intent with respect to the non-disclosure of the GV reference.[32]

3. Conclusion

With respect to both the Sandoz prior art described in *Vidal* and the GV reference, the withheld information was highly material and the evidence of deceptive intent is clear and compelling. Indeed, each of these non-disclosures would be sufficient on its own to constitute inequitable conduct. Certainly, the combination of both non-disclosures reveals a course of conduct whereby Mr. Fabre intentionally withheld highly material prior art from the patent office during the prosecution of the patents-in-suit. The fact that Mr. Fabre engaged in this conduct with respect to two separate, highly material prior art references reinforces the court's conclusion that he acted with deceptive intent. *See, e.g.*, *Semiconductor Energy Lab. Co. v. Samsung Elecs. Co.*, 204 F.3d 1368, 1375 (Fed. Cir. 2000) ("Proof of high materiality and that the applicant knew or should have known of that materiality makes it difficult to show good faith to overcome an inference of intent to mislead."); *Pharmacia Corp. v. Par Pharma., Inc.*, 417 F.3d 1369, 1373 (Fed. Cir. 2005) (finding inequitable conduct due to "highly material nature" of pattern of misconduct including the failure to submit key prior art). The balance of equities clearly weighs in favor of a finding of inequitable conduct. The court therefore concludes that the defendants have established by clear and convincing evidence that the patents-in-suit are unenforceable due

[32] The court finds that Mr. Fabre did not, however, act with deceptive intent with regard to the incidence of anaphylaxis with the claimed formulation. The specification of the '561 Patent states that "[i]n effect, when an injectable solution containing ethanol and a polysorbate 80 surfactant in place of Cremophor was used in the clinical situation, it became apparent that the anaphylactic reactions were greatly reduced compared with the use of the same solution prepared with Cremophor." '561 Patent at 2:25-30. The court finds that this sentence, though somewhat inartfully worded, is comparing the incidence of anaphylactic reactions with the claimed polysorbate 80/docetaxel solution to the prior art Cremophor/*paclitaxel* solution. While some tests performed after the filing of the applications for the patents-in-suit but prior to the signing of the patent declaration resulted in hypersensitivity reactions, those incidents did not appear to rise to the level of anaphylaxis, which is how the court interprets the term "anaphylactic manifestations" (*See* section III.A.2, *supra*). Thus, the inventors had a good faith basis for asserting that the incidence of anaphylactic reactions had been greatly reduced in tests using the claimed formulation.

to inequitable conduct.

F. Infringement[33]

The defendants' infringement defenses fall into four categories. First, they assert that their proposed products are not "capable of being injected without anaphylactic . . . manifestations," as required by all three asserted claims of the '561 patent. Second, the defendants assert that their proposed products do not meet the "consisting essentially of" requirement for claims 2 and 10 of the '561 patent because their products contain PEG 300. Third, Apotex asserts that its proposed product is not "dissolved in" polysorbate 80 or ethanol. Lastly, both defendants assert that their proposed products are not "essentially free of ethanol," as required by asserted claim 7 of the '512 patent. For the reasons that follow, the court rejects the first three of these arguments and concludes that the defendants' products would infringe all of the asserted claims of the '561 Patent as well as claim 33 of the '512 Patent. Apotex further asserts that the plaintiffs have failed to meet their burden of showing infringement under § 271(b). The court rejects this argument as well. The court concludes that the defendants' products are not, however, "essentially free of ethanol" as required by asserted claim 7 of the '512 Patent.

1. Inducement to Infringe and Contributory Infringement

The court interprets the "forms" and "is used to form" language in the '561 Patent in the manner discussed in section III.A.1, *supra – i.e.*, that it refers to actually using the claimed stock solutions to form perfusions, and not merely to stock solutions that are capable of being used to form perfusions. Consequently, for the asserted claims of the '561 Patent, the defendants'

[33] For the purposes of the infringement analysis, the court assumes *arguendo* that the patents-in-suit are valid and enforceable.

infringement liability is premised on inducement to infringe under § 271(b) and contributory infringement under § 271(c), since their proposed stock solutions would not actually be used to form perfusions until after they are sold. Apotex asserts that the plaintiffs have failed to demonstrate inducement to infringe under § 271(b), since the plaintiffs failed to show a specific intent to induce infringement. The court disagrees.

Where the act of infringement is the filing of a B2 application, the infringement analysis is hypothetical, comparing the asserted claims against the product that is likely to be sold should the FDA approve the application. *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1248-49 (Fed. Cir. 2000). In Hatch-Waxman cases, "[s]tatements in a package insert that encourage infringing use of a drug product are alone sufficient to establish intent to encourage direct infringement" within the meaning of 35 U.S.C. § 271(b). *AbraxisBioscience, Inc. v. Navinta, LLC*, 640 F. Supp. 2d 553, 570-71 (D.N.J. 2009). *See also 3M Co. v. Chemque, Inc.*, 303 F.3d 1294, 1305 (Fed. Cir. 2002) (defendant who is aware of a patent and supplies a product to a customer with instructions for use, which when followed lead to infringement, has encouraged acts constituting direct infringement). In order to establish liability for "contributory infringement" under 35 U.S.C. § 271(c), "in addition to proving an act of direct infringement, the plaintiff must show that defendant knew that the combination for which its components were especially made was both patented and infringing, and that the defendant's components have no substantial non-infringing uses." *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1320 (Fed. Cir. 2009) (internal quotation and citation omitted).

In this case, both defendants have filed B2 applications with the FDA seeking approval to market generic docetaxel intravenous infusion products. (*See* Findings of Fact ¶¶ 53, 58.) Both

defendants' products are labeled for "intravenous use only," (PTX 503 at Hospira0152578; ATX 552 at API-DOC-0000042), and both will be sold accompanied by prescribing information instructing physicians and pharmacists to prepare perfusions from the defendants' products in accordance with the prescribing information. (JTX 37 at Hospira0049062; ATX 552 at API-DOC-0000025; ATX 552 at API-DOC-0000042.) The sole lawful and intended use for the defendants' products is the preparation of such perfusions for the treatment of cancer; there is no other substantial non-infringing use. (*See* JTX 37 at Hospira0049158; ATX 552 at API-DOC-0000013-14. *See also* Tr. 1201:1-4 (discussing how a person of ordinary skill in the art "would know what the stock solution" described in the GV reference "is going to be used for").) Accordingly, if the perfusions made from the defendants' products in accordance with the accompanying prescribing information would infringe the asserted claims, then the defendants' B2 applications indirectly infringe under both inducement and contributory infringement theories. For the reasons discussed below, the court finds that they would directly infringe claims 2, 5, and 10 of the '561 Patent and claim 33 of the '512 Patent, but that they would not infringe claim 7 of the '512 Patent.

2. Anaphylactic Manifestations ('561 patent, all asserted claims)

The defendants argue that their product is not "capable of being injected without anaphylactic . . . manifestations" as required by the asserted claims of the '561 Patent. In support of this assertion, the defendants note that clinical data indicates that 14% of patients administered their products will, as with Taxotere, experience some of the symptoms associated with anaphylaxis. (*See* D.I. 378 at 46.) As the court explained in its indefiniteness analysis, however, the term "anaphylactic manifestations" does not extend to all symptoms that are

associated with anaphylaxis. Rather, the term refers to those symptoms in the narrower context of patients who are actually suffering from anaphylaxis, a Grade 4 hypersensitivity reaction. (*See* section III.A.2, *supra*. *See also* Tr. 116:20-119:14.) Thus, the court rejects the defendants argument that some of the patients in question exhibit "anaphylactic manifestations" simply because they experience some of the "multiple symptoms" associated with anaphylaxis.

The defendants also argue that their drugs do not meet this limitation because "[g]iven the tens of thousands of Taxotere patients, there is certainty that Defendants' products will cause severe hypersensitivity, specifically including anaphylaxis" in at least *some* patients – however few in number. (D.I. 378 at 46.) In support of this argument, the defendants note that the "[d]efendants' products will still cause anaphylaxis in at least 0.6% of patients," which "works out to about 1 in 170 patients." (Id.) This argument misapprehends the court's claim construction order. The court construed the term "capable of being injected without anaphylactic or alcohol intoxication manifestations" to mean "having a *reasonable expectation* of being injected without causing anaphylactic or alcohol intoxication manifestations." (D.I. 347 at 3 (emphasis added).) Under the defendants' argument, a drug does not have a "reasonable expectation" of avoiding anaphylactic manifestations unless that drug *never* causes those manifestations. If the court were to accept this argument, the term "reasonable expectation" in its construction would be rendered virtually meaningless.

The court's construction refers not to whether the formulation will ever cause anaphylaxis, but rather whether it can be injected into an individual patient with a reasonable expectation that it will not cause anaphylaxis. The defendants do not appear to dispute the plaintiffs' assertion that anaphylaxis will occur in the defendants' products, as with Taxotere,

only rarely. (*See* D.I. 378 at 40-42, 46-47.) Indeed, the defendants appear to concede that with premedication, the incidence of anaphylaxis with their products will be less than 1% (*See* id. at 41, 46), which is consistent with the evidence presented at trial. The court concludes that this is sufficient to constitute a reasonable expectation that the defendants' products can be injected without anaphylactic manifestations.

3. PEG 300 and "Consisting Essentially Of" ('561 Patent, Claims 2 & 10)

The defendants argue that their products do not meet the "consisting essentially of" limitation for claims 2 and 10 of the '561 Patent because the inclusion of PEG 300 alters the basic and novel properties of the invention in two ways: 1) by increasing the solutions' stability; and 2) by adding a third solvent. When a claim includes the transition phrase "consisting essentially of," adding ingredients that "materially affect the basic and novel properties of the invention" avoids infringement. *E.g., AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1239 (Fed. Cir. 2003). Both the plaintiffs and the defendants attempt to thread a needle with respect to their arguments on the degree to which stability is a basic and novel property of the asserted claims. The defendants argue that both physical and chemical stability are basic and novel properties of the claims even though, as they themselves assert in their argument on the construction of "perfusion," stability is mentioned nowhere in the claims. The plaintiffs assert that *physical* stability is a basic and novel property of the claims, but that *chemical* stability is not. The plaintiffs also assert that a physical stability of at least eight hours is all that is required; once that threshold level of stability is met, the plaintiffs assert, it is irrelevant whether physical stability is improved further.

The court is not persuaded by either party's arguments, and concludes that neither

physical nor chemical stability is a basic and novel property of the claims. As discussed above (*See* section III.B.1), the court rejects the plaintiffs' attempt to shoehorn a stability limitation into the claims. Certainly, such a limitation cannot be read into claims 2 and 10, since those claims do not include the term "perfusion," which the plaintiffs cite as the basis for a stability limitation. The claims require only that the docetaxel be "dissolved" in polysorbate 80 and (in the case of the '561 Patent) ethanol. Once this dissolution occurs, the claims require nothing in terms of the composition's stability.[34] Thus, stability is not required in the claims, and certainly is not discussed in the patents as a novel characteristic of the alleged invention.[35] The court concludes from the evidence presented at trial that neither physical nor chemical stability is a basic or novel property of the claims. Consequently, the enhanced stability of the defendants' products is irrelevant to the infringement analysis.

The defendants also argue that their proposed products' use of a three-solvent system alters the basic and novel properties of the invention. During the prosecution of the '561 Patent, the applicants distinguished the Tarr reference in a Request for Consideration by stating:

> Present claim 1, as written, "consists essentially of" a two-solvent system. For Tarr to render the present claims obvious, the addition of the solvent pluronic L64 would have to <u>not</u> "materially affect the basic and novel characteristics of the

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[34] Indeed, the plaintiffs' expert testified that "chemical stability is not claimed as a basic and novel property of the '561 Patent," which he knew from "[r]eading the patent. The inventors don't claim that." (Tr. 528:18-22.) Of course, the same logic applies to physical stability, which the inventors do not claim in any of the asserted claims. Moreover, even if court were to construe the asserted claims as being limited to stable pharmaceutical formulations, the plaintiffs' effort to isolate and trumpet the reference to physical stability would still be unavailing, since the specification also mentions chemical stability. For example, the specification states that the "physico-chemical stability of the solution is adequate" in describing a preferred embodiment, and the court agrees this is a reference to both physical and chemical stability. (*See* '561 Patent 2:61-62; Tr. 900:1-8. *See also* Tr. 897:16-25.)

[35] One could argue that it is a basic property of the claimed stock solution that they remain stable long enough to be formed into a perfusion, and that the resulting perfusion remain stable long enough to be administered to a patient. However, since the court did not hear sufficient evidence at trial to determine what these stability thresholds might be for the various formulations at issue, it would have to engage in arbitrary line-drawing to define what types and levels of stability are sufficient to serve those purposes. The court is not willing to engage in such an exercise, particularly for a property that is discussed only in passing in the specifications of the patents-in-suit and is mentioned nowhere in the asserted claims.

> claimed composition." However, pluronic L64 constitutes 60% of the solvent system, a considerable percentage.

(JTX 59 at JA1426.) The plaintiffs argue, however, that the defendants' reliance on this statement is misplaced, stating that the "[a]pplicants distinguished the invention from Tarr because it, like both accused products, uses polysorbate as the sole surfactant." (D.I. 383 at 46.) The plaintiffs cite the examiner's statement in allowing the claims that "*carriers* having similar characteristics as pluronic L64 are excluded from the claims." (*See* JTX 4 at SA13141 (emphasis added).)

The court agrees with the plaintiffs that the prosecution history does not support excluding all three-solvent systems from the claims, but only those systems where the third solvent (i.e., besides polysorbate 80 and ethanol) is a surfactant. In other words, the court concludes that the use of polysorbate 80 as the sole surfactant is a basic and novel property of the invention, but that the presence of only two solvents is not. Since the defendants do not contend that PEG 300 acts as a surfactant in their products – only that it acts as an additional solvent – the court concludes that its presence does not alter the basic or novel properties of the invention.[36]

4. "Dissolved in" ('512 Patent, claims 7 & 33; '561 Patent, claims 2 & 10)

Apotex contends that because its product used PEG 300 to "liquefy" docetaxel before polysorbate 80, it cannot meet the limitation requiring the docetaxel to be "dissolved in" either polysorbate 80 (in both asserted claims of the '512 Patent) or a mixture of polysorbate 80 and ethanol (in claims 2 and 10 of the '561 Patent). The examples and embodiments set forth in the '512 patent, however, teach that a composition according to the invention can be created by first

[36] Mr. Fabre testified that he believed that "including PEG in a formulation makes it different from" his claimed invention. (*See* Tr. 448:23-449:13; 450:18-22.) He did not elaborate, however, on how or why PEG made such formulations different. Moreover, Mr. Fabre made this comment while testifying on the issue of validity, not infringement.

"dissolving" the docetaxel in ethanol, and only then adding the surfactant to the mixture. *E.g.*, '512 Patent at 4:33-34 (Examples 1-7: "Taxotere (32 g) is dissolved in absolute ethanol (340 ml) and Polysorbate 80 (830 g) is then added"). The specification of the '561 Patent similarly states that the docetaxel is dissolved in ethanol prior to the incorporation of polysorbate 80. *E.g.*, '561 Patent at 2:18-19. Thus, Apotex's reading of "dissolved" would run contrary to the specifications of the patents-in-suit and would exclude nearly all of the preferred embodiments. *See, e.g., Anchor Wall Sys., Inc. v. Rockwood Retaining Walls, Inc.*, 340 F.3d 1298, 1308 (Fed. Cir. 2003) ("it is axiomatic that a claim construction that excludes a preferred embodiment . . . 'is rarely, if ever correct and would require highly persuasive evidentiary support.'"). Consequently, the fact that Apotex uses PEG 300 to initially dissolve the docetaxel does not take their product outside the scope of the asserted claims.

5. "Essentially Free of Ethanol" ('512 Patent, claim 7)

The final issue with respect to infringement is whether the defendants' products are "essentially free of ethanol," a limitation that appears in only one of the five asserted claims. In its claim construction order, the court explicitly rejected the plaintiffs' proposed claim construction and adopted a version of Hospira's construction. For a stock solution, the court construed "essentially free of ethanol" to mean "no more than 5% ethanol by volume." (D.I. 347 at 2.) For a perfusion, Hospira initially proposed that the court construe the term to mean "made from a stock solution having no more than 5% ethanol by volume." At the *Markman* hearing, Hospira's counsel clarified that this proposed construction was not meant to introduce a method step, as one could imply from the words "made from," but rather to reflect that "the perfusion has the same amount of ethanol as the corresponding stock solution." (*See* D.I. 140 at 49-50.)

The court's ultimate construction of the term, "the same amount of ethanol as a stock solution with no more than 5% ethanol by volume," reflects this understanding of the term.

There is no dispute that a perfusion, as that term relates to both of the patents-in-suit, is formed by diluting a stock solution with an aqueous perfusion fluid. The language of the '561 Patent makes this clear in the claims themselves by stating that the stock solution "forms" or "is used to form" an injectable solution – *i.e.*, a perfusion. The plaintiffs do not contend that the '512 Patent contemplates a different definition of perfusions, nor could they since both the abstract[37] and the specification[38] of the '512 Patent itself demonstrate that the perfusions described therein are formed from stock solutions containing the recited ingredients. Since the relevant perfusion fluids are ethanol free, each perfusion covered by claim 7 has, at most, the same amount of ethanol as the stock solution from which it was prepared. To define what qualifies as "too much" ethanol for this purpose, the '512 patent specifies a *percentage* of ethanol in the stock solution. (*See* Tr. 885:12-887:4; JTX 1, '512 patent, at 3:28-30.) Once the stock solution is prepared, what *amount* of ethanol is "too much" does not change when that stock solution is diluted in the perfusion fluid. In short, the '512 Patent defines the maximum allowable amount of ethanol by the percentage of ethanol in the stock solution (5%, as the court adopted in its claim construction order); if there is too much ethanol in the stock solution, the same amount must be too much in the corresponding perfusion. (Tr. 875:1-876:24.)

Hospira's stock solution has 23% ethanol, which means it is not "essentially free of ethanol." Hospira's perfusion would have, by definition, the same *amount* of ethanol as the

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[37] *See* '512 Patent Abstract: "This invention relates to compositions containing taxane derivatives, consisting of a solution of such derivatives in a surfactant. These compositions can be used to prepare perfusion solutions."

[38] *See, e.g.*, '512 Patent at 3:60-4:2.

stock solution from which it was prepared. Consequently, the perfusion is not essentially free of ethanol and does not infringe claim 7. Similarly, Apotex's premix has 6.3% ethanol. Assuming that Apotex's premix is a stock solution as Sanofi contends, this stock solution contains greater than 5% ethanol and thus is not "essentially free of ethanol." Consequently, a perfusion made from the premix and thus containing the same amount of ethanol also is not "essentially free of ethanol." As Dr. Myrdal explained, this reading of the claims is consistent with the stated purpose of the ethanol limitation, which is to avoid alcohol intoxication manifestations. (Tr. 888:16- 889:21; JTX 1, '512 patent, at 3:9-30.)

The plaintiffs urge the court to adopt a formula where the cutoff for "essentially free" with respect to an accused product would be based on a comparison with a stock solution that appears nowhere in the '512 Patent, but rather is derived from an example in the prior art '470 Patent. Specifically, the plaintiffs seized upon an example stock solution from the '470 Patent that the defendants' experts used in their invalidity analysis, trumpeted that stock solution as one that the parties "agreed" was essentially free of ethanol, and used that stock solution to "define the maximum level at which a stock solution (and therefore, a perfusion with the same amount of ethanol) could be essentially free of ethanol." (*See* D.I. 383 at 48-49.) This argument is unavailing. As with their arguments concerning the proposed construction of "perfusion," the plaintiffs overlook the fact that purported "agreements" between the parties are not binding on the court.[39] In this case, the court certainly would not use an *example* of a stock solution in a *prior art* patent to define the maximum allowable concentration of ethanol in a perfusion under the *'512 Patent*. After all, if the '470 patent example happened to recite a different concentration

[39] Moreover, the court does not have sufficient information to determine whether the parties actually reached any "agreement" that the example stock solution in question was "essentially free of ethanol."

– or if the defendants' experts had chosen a different example to use in their invalidity analysis – the plaintiffs' definition of "essentially free" would change. The definition of a claim term cannot be subject to the changing winds of which prior art examples the parties' experts choose to use.

The plaintiffs note that under the court's interpretation of "essentially free," one perfusion with a particular amount of ethanol might be "essentially free" while a different perfusion with the same amount of ethanol is not "essentially free." (Tr. 883:24-885:3; Tr. 712:15-24.) That is true, depending on whether the corresponding stock solution is "essentially free." (Tr. 884:16-886:5.) However anomalous that result, it is dictated by the fact that the '512 Patent, and thus the court's claim construction, defines "essentially free" by the percentage of ethanol in the stock solution.[40] (*See, e.g.*, Tr. 886:21-887:4.) If that percentage is below 5%, the maximum concentration supported by the specification and file history of the patents-in-suit, then the stock solution is essentially free of ethanol. By extension, any perfusion formed from such a stock solution would be essentially free of ethanol, since the perfusion would contain no more ethanol than was in the stock solution. Since both of the defendants' proposed stock solutions are essentially free of ethanol, their perfusions are as well. Consequently, the defendants' proposed products do not infringe claim 7 of the '512 Patent.

G. Rule 52(c) Motions

The plaintiffs filed a motion for judgment on partial findings pursuant to Rule 52(c) of the Federal Rules of Civil Procedure. In it, they contend that they proved infringement of claim 5 of the '561 Patent and claim 33 of the '512 Patent, and that the defendants failed to prove

[40] The plaintiffs' proposal also suffers from contradictions of its own. Most obviously, since their proposal is based on examples chosen by the parties' experts, the definition of "essentially free" presumably would shift from lawsuit to lawsuit if the defendants' experts in other cases chose different examples.

inequitable conduct. For the reasons stated in section III.F, the court agrees with the plaintiffs that they met their burden on proving infringement for claim 5 of the '561 Patent and claim 33 of the '512 Patent. For the reasons stated in III.E, however, the court concludes that the defendants easily met their burden of proving inequitable conduct. The court will therefore grant in part and deny in part the plaintiffs' Rule 52(c) motion.

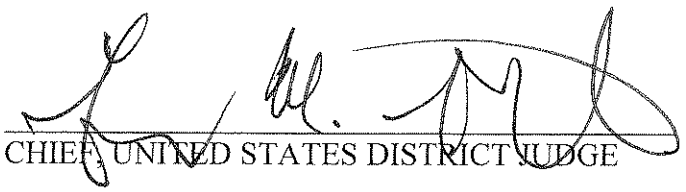
Each of the defendants also filed a Rule 52(c) motion. Hospira's motion urges the court to conclude that their proposed product does not infringe because it does not meet the "consisting essentially of" (claims 2 and 10), "without anaphylactic manifestations" (claims 2, 5, and 10), and "essentially free of ethanol" (claim 7) limitations in the asserted claims. Apotex urges non-infringement on the same three grounds, and also asserts that their product does not meet the "dissolved" limitation (all claims except claim 5) and that the plaintiffs have not shown inducement to infringe. For the reasons stated in section III.F, the court rejects the defendants' arguments with respect to inducement to infringe and the "consisting essentially of," "without anaphylactic manifestations," and "dissolved" limitations. The court agrees, however, that their products are not "essentially free of ethanol." Consequently, the court will grant in part and deny in part each of their Rule 52(c) motions.

IV. CONCLUSION

For the reasons stated above, the court concludes that: (A) claims 2 and 10 of the '561 Patent are invalid due to indefiniteness; (B) all asserted claims of the patents-in-suit are invalid due to obviousness; (C) the asserted claims are unenforceable due to inequitable conduct; (D) the asserted claims are not invalid due to double patenting; (E) the defendants' proposed products infringe asserted claims 2, 5, and 10 of the '561 Patent and claim 33 of the '512 Patent; and (F)

each of the parties Rule 52(c) motions are granted in part and denied in part. An appropriate order will follow.

Dated: September 22, 2010



CHIEF, UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AVENTIS PHARMA S.A., and SANOFI-AVENTIS U.S., LLC, Plaintiffs, v. HOSPIRA, INC., Defendant.	)	C.A. No. 07-721-GMS
AVENTIS PHARMA S.A., and SANOFI-AVENTIS U.S., LLC, Plaintiffs, v. APOTEX, INC., and APOTEX CORP., Defendants.	)	C.A. No. 08-496-GMS

ORDER

At Wilmington, this 17th day of September, 2010, IT IS HEREBY ORDERED THAT:

1. The asserted claims of the patents-in-suit are invalid due to obviousness.

2. Asserted claims 2 and 10 of the '561 Patent are invalid due to indefiniteness.

3. The asserted claims of the patents-in-suit are unenforceable due to inequitable conduct.

4. Hospira's Rule 52(c) motion (D.I. 362) is GRANTED IN PART AND DENIED IN PART.

5. Apotex's Rule 52(c) motion (D.I. 363) is GRANTED IN PART AND DENIED IN PART.

6. The plaintiffs' Rule 52(c) motion (D.I. 364) is GRANTED IN PART AND DENIED IN PART.

7. The defendants' motion for leave to file a reply and objections to new exhibits (D.I. 385) are DENIED AS MOOT.[1]

8. The Clerk of Court is directed to enter judgment in favor of the defendants and against the plaintiffs.

CHIEF UNITED STATES DISTRICT JUDGE

[1] None of the disputed exhibits would alter the court's conclusions with respect to any of the issues discussed in this opinion. The court notes for the benefit of future parties, however, that the court's pre-trial order that all objections to exhibits are overruled without prejudice – thus allowing each party to object in real-time – was not intended to have the effect that the plaintiffs assert. The parties' post-trial briefs should be based only on evidence actually presented at trial, and not any evidence that could have been presented at trial.