IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ELAN PHARMA INTERNATIONAL LIMITED, Plaintiff, v. ABRAXIS BIOSCIENCE, INC., Defendant.	)	Civil Action No. 06-438-GMS **REDACTED – PUBLIC VERSION**

ABRAXIS'S RESPONSE TO ELAN'S MOTION IN LIMINE NO. 2
CLAIM CONSTRUCTION, INDEFINITENESS AND EQUITABLE DEFENSES

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INTRODUCTION

Elan's second Motion in Limine is, on examination, three distinct motions: (1) a motion to preclude Abraxis from presenting evidence or argument on the basic and novel properties of the invention, (2) a motion for summary judgment of patent-claim definiteness, and (3) a motion to bifurcate trial. None of Elan's motions has merit.

ARGUMENT

I. ABRAXIS WILL NOT PRESENT EVIDENCE OR ARGUMENT INCONSISTENT WITH THE COURT'S CLAIM CONSTRUCTION.

Notwithstanding the Court's resounding rejection of *Elan's* proposed construction that only a "portion" of the medicament need be crystalline,[1] Elan believes the Court has decided in *its* favor the question whether the claims reach particles with overwhelmingly amorphous medicament, and that contrary evidence or argument from Abraxis should be barred. The Court has done no such thing. Pointing to long-standing case law on the meaning of "consisting essentially of," the Court did conclude that "particles consisting essentially of" means that "the particles, composed of crystalline medicament and surface modifier, *may also include other ingredients that do not affect their basic and novel properties,* and are essentially free of solvent and other contaminants."[2]

But the Court has not yet determined the basic and novel properties of the invention, and that too is a matter of law for the Court. *See General Electric Co. v. Hoechst Celanese Corp.*, 698 F. Supp. 1181, 1187 (D. Del. 1988) (what is basic and novel is issue of law). If the Court disagrees that this is an issue of law, then Abraxis will (without waiving its legal argument) argue it to the jury. In either case, Abraxis will rely on the extensive record in the '363 patent

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[1] D.I. 271 at n.4: "The Court finds no support in the claim language, the specification, or the prosecution history for reading this limitation into the claim, and therefore rejects it."

[2] *Id.* at 1 (emphasis added). The Court rejected Abraxis's specification and file history-focused argument that the '363 applicants had not intended to allow generally for other ingredients, but rather only for trace amounts of solvent and other contaminants.

specification[3] and file history to demonstrate that crystallinity of the medicament and a non-crosslinked surface modifier are basic and novel properties.[4] *See, e.g., Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1574 (Fed. Cir. 1984) ("The '978 claims exclude the presence of nitric acid because the essence of the claimed composition is the elimination of nitric acid and the claim phrase 'consisting essentially of' excludes ingredients that would 'materially affect the basic and novel characteristics' of the claimed composition.").

Abraxis will also show that, assuming *arguendo* that there is *any* crystallinity in Abraxane, the overwhelming amorphousness and substantial cross-linked surface modifiers *do* affect those basic and novel properties, and hence that Abraxane does not infringe. To be precise, Abraxis will respond to Elan's infringement case, as Elan bears the burden of proof on the basic and novel properties leg of infringement analysis. *See Kim v. ConAgra Foods, Inc.*, 465 F.3d 1312, 1319-20 (Fed. Cir. 2006). Because Abraxane is, by even Elan's reckoning, overwhelmingly amorphous and substantially crosslinked, Elan will not be able to carry this burden. *See Talbert Fuel Sys. Patents Co. v. Unocal Corp.*, 275 F.3d 1371, 1375 (Fed. Cir. 2002), *vacated and remanded on other grounds*, 537 U.S. 802 (U.S. 2002), *affirmed on remand*,

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[3] *See, e.g.*, Ex. 1 at col. 2:28-31 ('363 patent) ("The anticancer agent is present in one or more discrete crystalline phases. The crystalline phase differs from an amorphous i.e., non-crystalline phase...").

[4] *See, e.g.*, D.I. 144, Joint Appendix at A0236, '105 App. (from which U.S. Patent No. 5,145,684 issued, which is the parent of the '363 patent) Nov. 18, 1991 Amendment at 9 ("The crystalline phase differs from non-crystalline and amorphous phases. The crystalline particles of this invention exhibit improved stability compared to particles containing a drug substance in an amorphous phase."); *id.* at A0241, Nov. 18, 1991 Amendment at 14 ("The office action indicates that Violante teaches a crystalline drug substance. However, Violante teaches a solvent precipitation technique for preparing amorphous, non-crystalline particles. In fact Violante teaches that the crystalline state is to be avoided . . . . Consequently, Violante teaches away from applicants claimed particles."); D.I. 144, Joint Appendix at A0161, '125 App., (from which the '363 patent issued) Oct. 29, 1992 IDS at 3 ("amorphous materials and formulations tend to exhibit unacceptably poor stability and/or short shelf lives."); D.I. 144, Joint Appendix at A0169, '125 App., Sept. 13, 1993 Amendment at 5 ("Furthermore, there is no suggestion in the cited references or in the art as a whole of the unexpected advantageous properties associated with the claimed crystalline anticancer particles."); D.I. 144, Joint Appendix at A0236, A0242-244, '105 App., Nov. 18, 1991 Amendment at 9, 15-17 ("to further distinguish applicants' claims from the teachings of Oppenheim, claim 1 has been amended to recite that the particles include a non-crosslinked surface modifier.").

347 F.3d 1355 (Fed. Cir. 2003) ("the signal 'consisting essentially of' allows for the presence of *small amounts* of components outside of the [claimed elements] ....") (emphasis added).

Elan's claim that Dr. Amiji's rebuttal report opinion is inconsistent with the Court's construction (Elan's Motion in Limine No. 2 ("Motion")) is incorrect. Dr. Amiji pointed out that Dr. Brittain improperly read the "particles consisting essentially of 99.9-10% by weight of a crystalline medicament" language to allow for 0.1%-90% by weight of amorphous medicament, and thereby ignored the surface modifier element of the claim. (Ex. 2 ¶¶ 66-68.)

Finally, Elan's contention that Abraxis is arguing that the asserted claims include a suspension limitation is incorrect. (Motion at 4.) Instead, for purposes of our non-enablement defense, Abraxis is arguing that one skilled in the art would understand that particle size is to be maintained in a suspension – as described by the '363 patent at column 7, lines 5-45.

II. ELAN'S MOTION TO BAR ABRAXIS FROM ARGUING INDEFINITENESS SHOULD BE DENIED.

Mixing claim construction issues with indefiniteness questions, Elan argues that the mere fact that this Court construed the claims of the '363 patent means that the Court considered indefiniteness and, essentially, granted summary judgment on that issue in Elan's favor. (Motion at 2-4 (terms amenable to construction "[are] by law, definite.") Elan has not been listening. As this Court has repeatedly made clear, the Court does not consider issues of indefiniteness coincident with claim construction. *See, e.g.,* Ex. 3, *Telcordia Techs. v. Lucent Techs., Inc.*, CA Nos. 04-874 GMS, 04-875 GMS, 04-876GMS (D. Del. Apr. 21, 2006) ("the court does not permit summary judgment arguments, including indefiniteness arguments, during the claim construction phase of the litigation...."); Ex. 4, *R2 Tech., Inc. v. Intelligent Sys. Software, Inc.*, C.A. No. 02-472-GMS, Tr. at 57:14-18 (D. Del. Apr. 29, 2003) (declining to address indefiniteness during claim construction hearing); Ex. 5, *Keurig Inc. v. Kraft Foods Global, Inc.*, C.A. No. 07-017-GMS, Tr. at 60:20-25 (D. Del. Dec. 2, 2007) (same).

Here, the Court's construction of "in an amount of 0.1-90% by weight and sufficient to maintain an average effective particle size of less than 1000nm" does not preclude Abraxis's

argument that the term is indefinite. Based on the explicit definition in the specification, the Court found the only possible construction to be that "90% of the particles have a number average particle size of less than 1000 nanometers." (D.I. 271 at 3.) Our indefiniteness argument is that it is impossible to take an average of 90% of something; to apply this claim term, one must ignore either the word "average" or the 90% requirement.[5] Tellingly, Elan's own expert Dr. Byrn could not consistently apply the claim as construed, at one point stating that the claim meant that 50% of the particles had to be smaller than 1000 nm, and at another point stating that 90% needed to be smaller. (*Compare* Ex. 6 at 196:14-21, 197:17-198:4 with 225:22-226:11. (Byrn Dep.).)

Similarly, the Court was not asked to and did not determine the time or conditions under which the particle size must be maintained, instead using the claim term "maintains" in the construction itself. (D.I. 271 at 3.) As may emerge at trial, however, Elan's experts have been all over the map on what "maintain" means.

On the basis of these insoluble ambiguities, we will ask the Court to decide, as a matter of law, that the asserted claims are indefinite. *IPXL Holdings, L.L.C. v. Amazon.com, Inc.*, 430 F.3d 1377, 1380 (Fed. Cir. 2005) ("indefiniteness is a question of law."). No ruling of the Court so far undermines such a request.

III. ELAN'S MOTION TO BIFURCATE ABRAXIS'S EQUITABLE DEFENSES SHOULD BE DENIED.

Abraxis's equitable defenses of inequitable conduct and unclean hands should be presented to the jury.[6] As this Court has recognized, the evidence of materiality and intent underlying inequitable conduct are appropriately considered by the jury, even though the Court

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[5] [redacted]

[6] Abraxis is not presenting its defense of patent misuse at trial.

will ultimately decide the issue. *ISCO Int'l, Inc. v. Conductus, Inc.*, 279 F. Supp. 2d 489, 499-500 (D. Del. 2003) (Sleet, J.). Elan mis-cites *AGFA Corp. v. Creo Prods., Inc.* as holding to the contrary. 451 F.3d 1366, 1375 (Fed. Cir. 2006) ("this court today does not decide that the factual issues underlying a charge of inequitable conduct must be adjudicated by a judge.") Similarly, as this Court as already found, the jury may also appropriately render an advisory verdict on the facts underlying Abraxis's equitable defense of unclean hands. (*See* Ex. 7 (Final Jury Instructions from *Telcordia Techs., Inc. v. Cisco Sys., Inc.*, No. 04-876 (GMS) at 34-35.)

In this case, presenting inequitable conduct and unclean hands to the jury is particularly appropriate. First, the trial will be more efficient, as evidence underlying Abraxis's inequitable conduct and unclean hands defenses also underlies Abraxis's enablement defenses. For example, [redacted] are also the material information that the applicants withheld from the PTO during prosecution. *See* Ex. 8 ¶¶ 464, 470; *see also id.* ¶¶ 178-85, 191-95, 208-24, 322-43, 462-72. Second, in response to Abraxis's non-enablement and written description arguments, Elan will argue that the PTO considered these issues during prosecution and that the presumption of validity is dispositive. Abraxis should be allowed to respond that information material to invalidity under 35 U.S.C. § 112 was withheld from the PTO and that the PTO was not afforded a full opportunity to consider the issue during prosecution. *See KSR Int'l, Inc. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1745 (2007) (noting that rationale underlying presumption of validity, "that the PTO, in its expertise, has approved the claim," is diminished when relevant prior art was not before PTO during prosecution). Elan's request to bifurcate Abraxis's equitable defenses should be denied.

CONCLUSION

For all of the above reasons, Elan's Motion should be denied.

Dated: April 4, 2008

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CERTIFICATE OF SERVICE

I, Karen E. Keller, Esquire, hereby certify that on April 15, 2008, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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EXHIBIT 1

US005399363A

United States Patent [19]

Liversidge et al.

[11] Patent Number: 5,399,363

[45] Date of Patent: Mar. 21, 1995

[54] **SURFACE MODIFIED ANTICANCER NANOPARTICLES**

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[73] Assignee: **Eastman Kodak Company,** Rochester, N.Y.

[21] Appl. No.: **908,125**

[22] Filed: **Jul. 1, 1992**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 647,105, Jan. 25, 1991, Pat. No. 5,145,684.

[51] **Int. Cl.**[6] **A61K 9/14**
[52] **U.S. Cl.** **424/490;** 424/489
[58] **Field of Search** 424/490, 487; 514/352

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[57] **ABSTRACT**

Dispersible particles consisting essentially of a crystalline anticancer agent having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 1000 nm. Anticancer compositions comprising the particles exhibit reduced toxicity and/or enhanced efficacy, and can be administered by IV bolus injection.

17 Claims, No Drawings

SURFACE MODIFIED ANTICANCER NANOPARTICLES

CROSS REFERENCED TO RELATED APPLICATION

This application is a continuation-in-part of U.S. patent application Ser. No. 647,105, filed Jan. 25, 1991, now U.S. Pat. No. 5,145,684, the disclosure of which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

1. Field of Invention

This invention relates to anticancer agents in the form of particles, to anticancer compositions comprising the particles, and to methods employing the particles.

2. Description of the Prior Art

The therapeutic index is a measure of how selective a drug is at producing its desired effects and can be defined as the ratio of the median lethal dose to the median effective dose, i.e., (LD_{50}/ED_{50}) (see Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, Eight Edition, p. 68–69). Virtually all anticancer agents have a low therapeutic index, e.g., less than about 1.0. Increasing the therapeutic index, e.g., by reducing toxicity or enhancing efficacy would provide more latitude to physicians in their duty of administering anticancer drugs to patients in need thereof. Consequently, methods to reduce toxicity and/or enhance efficacy of anticancer drugs and thus increase the therapeutic indices of such drugs would be of great value in the treatment of cancers.

In addition, poorly water-soluble drugs, such as poorly water-soluble anticancer agents, are not readily injectable via an intravenous (IV) bolus injection. The creation of injectable forms of poorly soluble drugs represents a formidable problem. It would be highly desirable to be able to provide poorly soluble drugs, such as poorly soluble anticancer agents, in an IV bolus injectable form.

SUMMARY OF THE INVENTION

We have discovered that anticancer compositions comprising anticancer agents in the form of surface modified nanoparticles exhibit reduced toxicity and/or enhanced efficacy.

More particularly, in accordance with this invention, there are provided particles consisting essentially of a crystalline anticancer agent having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 1000 nm.

This invention further provides an anticancer composition comprising the above-described particles.

In another embodiment of the invention, there is provided a method of treating a mammal comprising administering to the mammal the above-described anticancer composition.

In yet another embodiment of the invention, there is provided a method of enhancing the efficacy and/or reducing the toxicity of an anticancer agent which includes the step of administering the agent in the form of the above-described particles.

It is an advantageous feature of this invention that anticancer compositions are provided exhibiting reduced toxicity.

It is another advantageous feature of this invention that anticancer compositions are provided exhibiting improved efficacy.

Yet another advantageous feature of this invention is that compositions are provided featuring poorly soluble anticancer agents that can be administered by IV bolus injection.

Still another advantageous feature of this invention is that compositions are provided containing poorly soluble anticancer agents exhibiting prolonged circulation in the blood pool after IV bolus injection.

Other advantageous features will become readily apparent upon reference to the following descriptions of preferred embodiments.

DESCRIPTION OF PREFERRED EMBODIMENTS

This invention is based partly on the discovery that surface modified anticancer nanoparticles exhibit reduced toxicity and/or enhanced efficacy. While the invention is described herein primarily in connection with its preferred class of drugs, i.e., anticancer agents including immunosuppressive agents, it is also useful in conjunction with poorly water soluble drugs, particularly those with low therapeutic indices, from other classes of drug substances.

The particles of this invention comprise an anticancer agent. The anticancer agent is present in one or more discrete crystalline phases. The crystalline phase differs from an amorphous, i.e., non-crystalline phase which results from conventional solvent precipitation techniques for the preparation of particles in the submicron size range, such as described in U.S. Pat. No. 4,826,689.

The invention can be practiced with a wide variety of anticancer agents. However, the anticancer agent must be poorly soluble and dispersible in at least one liquid medium. By "poorly soluble", it is meant that the drug substance has a solubility in the liquid dispersion medium, e.g., water, of less than about 10 mg/ml, and preferably, of less than 1 mg/ml at processing temperature, e.g., room temperature. The preferred liquid dispersion medium is water. However, the invention can be practiced with other liquid media in which the anticancer agent is dispersible including, for example, aqueous salt solutions, safflower oil, and solvents such as ethanol, t-butanol, hexane, and glycol. The pH of the aqueous dispersion media can be adjusted by techniques known in the art.

The anticancer agent preferably is selected from alkylating agents, antimetabolites, natural products, hormones and antagonists, and miscellaneous agents, such as radiosensitizers.

Examples of alkylating agents include alkylating agents having the bis-(2-chloroethyl)-amine group such as, for example, chlormethine, chlorambucile, melphalan, uramustine, mannomustine, extramustinephoshate, mechlore-thaminoxide, cyclophosphamide, ifosfamide, and trifosfamide;

alkylating agents having a substituted aziridine group such as, for example, tretamine, thiotepa, triaziquone and mitomycine;

alkylating agents of the alkyl sulfonate type, such as, for example, busulfan, piposulfan, and piposulfam;

alkylating N-alkyl-N-nitrosourea derivatives, such as, for example, carmustine, lomustine, semustine, or streptozotocine; and alkylating agents of the mitobronitole, dacarbazine and procarbazine type.

Examples of antimetabolites include folic acid analogs, such as, for example, methotrexate;

pyrimidine analogs such as, for example, fluorouracil, floxuridine, tegafur, cytarabine, idoxuridine, and flucytosine; and

purine derivatives such as, for example, mercaptopurine, thioguanine, azathioprine, tiamiprine, vidarabine, pentostatin, and puromycine.

Examples of natural products include vinca alkaloids, such as, for example, vinblastine and vincristine;

epipodophylotoxins, such as, for example, etoposide and teniposide;

antibiotics, such as, for example, adriamycine, daunomycine, doctinomycin, daunorubicin, doxorubicin, mithramycin, bleomycin, and mitomycin;

enzymes, such as, for example, L-asparaginase;

biological response modifiers, such as, for example, α-interferon;

camptothecin;

taxol; and

retinoids, such as retinoic acid.

Examples of hormones and antagonists include adrenocorticosteroids, such as, for example, prednisone;

progestins, such as, for example, hydroxyprogesterone caproate, medroxyprogesterone acetate and megestrol acetate;

estrogens, such as, for example, diethylstilbestrol and ethinyl estradiol;

antiestrogens, such as, for example, tamoxifen;

androgens, such as, for example, testosterone propionate and fluoxymesterone;

antiandrogens, such as, for example, flutamide;

and gonadotropin-releasing hormone analogs, such as, for example leuprolide.

Examples of miscellaneous agents include radiosensitizers, such as, for example, 1,2,4-benzotriazin-3-amine 1,4-dioxide (SR 4889) and 1,2,4-benzotriazine-7-amine 1,4-dioxide (WIN 59075);

platinum coordination complexes such as cisplatin and carboplatin;

anthracenediones, such as, for example, mitoxantrone;

substituted ureas, such as, for example, hydroxyurea;

and adrenocortical suppressants, such as, for example, mitotane and aminoglutethimide.

In addition, the anticancer agent can be an immunosuppressive drug, such as, for example, cyclosporine, azathioprine, sulfasalazine, methoxsalen and thalidomide.

The anticancer agents useful in the practice of this invention are known compounds and/or can be prepared by techniques known in the art.

The anticancer agent can be used alone or in combination with one or more anticancer agents.

The particles of this invention contain an anticancer agent as described above having a surface modifier adsorbed on the surface thereof. Useful surface modifiers are believed to include those which physically adhere to the surface of the anticancer agent but do not chemically bond to the anticancer agent.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens™, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the *Handbook of Pharmaceutical Excipients,* published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

Particularly preferred surface modifiers include polyvinylpyrrolidone, tyloxapol, polaxomers, such as Pluronic™ F68, F108 and F127, which are block copolymers of ethylene oxide and propylene oxide available from BASF, and poloxamines, such as Tetronic™ 908 (T908), which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine available from BASF, dextran, lecithin, Aerosol OT™ (AOT), which is a dioctyl ester of sodium sulfosuccinic acid, available from American Cyanamid, Duponol™ P, which is a sodium lauryl sulfate, available from DuPont, Triton™ X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas, Tween 20, 40, 60 and 80, which are polyoxyethylene sorbitan fatty acid esters, available from ICI Speciality Chemicals, Span 20, 40, 60 and 80, which are sorbitan esters of fatty acids, Arlacel 20, 40, 60 and 80, which are sorbitan esters of fatty acids, available from Hercules, Inc., Carbowax™ 3550 and 934, which are polyethylene glycols available from Union Carbide, Crodesta™ F-110, which is a mixture of sucrose stearate and sucrose distearate, available from Croda Inc., Crodesta SL-40, which is available from Croda, Inc., hexyldecyl trimethyl ammonium chloride (CTAC), bovine serum albumin and SA90HCO, which is $C_{18}H_{37}$ CH_2 (CON (CH_3) CH_2 $(CHOH)_4CH_2OH)_2$. Surface modifiers which have been found to be particularly useful include polyvinylpyrrolidone, Pluronic F-108, polyvinyl alcohol and gum acacia.

The surface modifier is adsorbed on the surface of the anticancer agent in an amount sufficient to maintain an effective average particle size of less than about 1000 nm. The surface modifier does not chemically react with the anticancer agent or itself. Furthermore, the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages.

As used herein, particle size refers to a number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. By "an effective average particle size of less than about 1000 nm" it is meant that at least 90% of the particles have a number average particle size of less than about 1000 nm when measured by the above-noted tech-

niques. In particularly preferred embodiments of the invention, the effective average particle size is less than about 400 nm. In some embodiments of the invention, the effective average particle size is less than about 300 nm. With reference to the effective average particle size, it is preferred that at least 95% and, more preferably, at least 99% of the particles have a particle size of less than the effective average, e.g., 1000 nm. In particularly preferred embodiments, essentially all of the particles have a size less than 1000 nm.

Motoyama et al, U.S. Pat. No. 4,540,602 disclose that a solid drug can be pulverized in an aqueous solution of a water-soluble high molecular substance, and that as a result of such wet grinding, the drug is formed into finely divided particles ranging from 0.5 μm or less to 5 μm in diameter. However, there is no suggestion that particles having an average particle size of less than about 1 μm can be obtained. Attempts to reproduce the wet grinding procedures described by Motoyama et al resulted in particles having an average particle size of much greater than 1 μm.

The particles of this invention can be prepared by a method comprising the steps of dispersing an anticancer agent in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the anticancer agent to an effective average particle size of less than about 1000 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

A general procedure for preparing the particles of this invention is set forth below. The anticancer agent selected is obtained commercially and/or prepared by techniques known in the art in a conventional coarse form. It is preferred, but not essential, that the particle size of the coarse anticancer agent selected be less than about 100 μm as determined by sieve analysis. If the coarse particle size of the anticancer agent is greater than about 100 μm, then it is preferred that the particles of the anticancer agent be reduced in size to less than 100 μm using a conventional milling method such as airjet or fragmentation milling.

The coarse anticancer agent selected can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of the anticancer agent in the liquid medium can vary from about 0.1–60% and preferably is from 5–30% (w/w). It is preferred, but not essential, that the surface modifier be present in the premix. The concentration of the surface modifier can vary from about 0.1 to about 90% and preferably is 1–75%, more preferably 20–60%, by weight based on the total combined weight of the drug substance and surface modifier. The apparent viscosity of the premix suspension is preferably less than about 1000 centipoise.

The premix can be used directly by subjecting it to mechanical means to reduce the average particle size in the dispersion to less than 1000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the anticancer agent and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation, e.g., a roller mill or a Cowles type mixer, until a homogeneous dispersion is observed in which there are no large agglomerates visible to the naked eye. It is preferred that the premix be subjected to such a premilling dispersion step when a recirculating media mill is used for attrition.

The mechanical means applied to reduce the particle size of the anticancer agent conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, a planetary mill, media mills such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the intended result, i.e., the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is from about 100 to about 1000 centipoise. For ball milling, the apparent viscosity of the premix preferably is from about 1 up to about 100 centipoise. Such ranges tend to afford an optimal balance between efficient particle fragmentation and media erosion.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of material for the grinding media is not believed to be critical. However, zirconium oxide, such as 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are believed to be acceptable for the preparation of pharmaceutical compositions. Further, other media, such as stainless steel, titania, alumina, and 95% ZrO stabilized with yttrium, are expected to be useful. Preferred media have a density greater than about 2.5 g/cm^3.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills, processing times of up to five days or longer may be required. On the other hand, processing times of less than 1 day (residence times of one minute up to several hours) have provided the desired results using a high shear media mill.

The particles must be reduced in size at a temperature which does not significantly degrade the anticancer agent. Processing temperatures of less than about 30°–40° C. are ordinarily preferred. If desired, the processing equipment can be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process. For example, ambient processing pressures are typical of ball mills, attritor mills and vibratory mills. Processing pressures up to about 20 psi (1.4 kg/cm^2) are typical of media milling.

The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed, e.g., by shaking vigorously. Optionally, the dispersion can be subjected to a sonication step, e.g., using an ultrasonic power supply. For example, the dispersion can be subjected to ultrasonic energy having a frequency of 20–80 kHz for a time of about 1 to 120 seconds.

The relative amount of the anticancer agent and surface modifier can vary widely and the optimal amount of the surface modifier can depend, for example, upon the particular anticancer agent and surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of the anticancer agent, etc. The surface modifier preferably is present in an amount of about 0.1–10 mg per square

meter surface area of the anticancer agent. The surface modifier can be present in an amount of 0.1–90%, preferably 0.5–80% and more preferably 1–60% by weight based on the total weight of the dry particle.

A simple screening process has been developed whereby compatible surface modifiers and anticancer agents can be selected which provide stable dispersions of the desired particles. First, coarse particles of an anticancer agent are dispersed in a liquid in which the anticancer agent is essentially insoluble, e.g., water at 2% (w/v) and milled for 120 hours in a roller mill under the following milling conditions:

Grinding vessel: 8 oz. (250 ml) glass jar
Available volume of grinding vessel: 250 ml
Media volume: 120 ml
Media type: 1.0 mm pre-cleaned zirconium oxide beads (distributed by Zircoa, Inc.)
Milling time: 120 hours
Slurry volume: 60 ml
RPM: 92
Room Temperature

The slurry is separated from the milling media by conventional means, e.g., by pouring the slurry out of the vessel, or by using a pipette. The separated slurry is then divided into aliquots and surface modifiers are added at a concentration of between 2 and 50% by weight based on the total combined weight of the anticancer agent and surface modifier. The dispersions are then sonicated (1 minute, 20 kHz) or vortexed using a multitubed vortexer for one minute, to disperse agglomerates and subjected to particle size analysis, e.g., by photon correlation spectroscopy (PCS) and/or by examination under an optical microscope (1000× magnification). If a stable dispersion is observed, then the process for preparing the particular anticancer agent surface modifier combination can be optimized in accordance with the teachings above. By stable it is meant that the dispersion exhibits no flocculation or particle agglomeration visible to the naked eye and, preferably, when viewed under the optical microscope at 1000×, at least 15 minutes, and preferably, at least two days or longer after preparation. In addition, preferred particles exhibit no flocculation or agglomeration when dispersed in 0.1N HCl and/or phosphate buffered saline, pH 7.4 (PBS) or rat plasma.

The resulting dispersion is stable and consists of the liquid dispersion medium and the above-described particles. The dispersion of surface modified anticancer agent nanoparticles can be spray coated onto sugar spheres or onto a pharmaceutical excipient in a fluid-bed spray coater by techniques well known in the art.

Anticancer pharmaceutical compositions according to this invention include the particles described above and a pharmaceutically acceptable carrier therefor. Suitable pharmaceutically acceptable carriers are well known to those skilled in the art. These include non-toxic physiologically acceptable carriers, adjuvants or vehicles for parenteral injection, for oral administration in solid or liquid form, for rectal administration, nasal administration, intramuscular administration, subcutaneous administration, and the like.

A method of treating a mammal in accordance with this invention comprises the step of administering to the mammal in need of treatment an effective amount of the above-described anticancer composition. The selected dosage level of the anticancer agent for treatment is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage can be readily determined by one skilled in the art and depends upon the particular anticancer agent, the desired therapeutic effect, the route of administration, the desired duration of treatment and other factors.

It is a particularly advantageous feature that the anticancer compositions of this invention exhibit reduced toxicity and/or enhanced efficacy as illustrated in the examples that follow. Further, the particles of this invention exhibit prolonged circulation in the blood pool.

Moreover, anticancer agents which heretofore could not be administered by injection, when prepared as nanoparticles and formulated in anticancer compositions according to this invention, can be effectively administered by injection, e.g., by an intravenous bolus injection.

The following examples further illustrate the invention.

EXAMPLES 1–4 Nanoparticulate Piposulfan

EXAMPLE 1

Piposulfan (purchased from Eastman Kodak) was milled in a mixture of 0.33% polyoxyethylene sorbitan monooleate, Tween 80, (ICI Americas, Inc., Wilmington, Del.) and 0.67% sorbitan monooleate, Span 80, (ICI) using 1 mm zirconium oxide beads for about 96 hours to produce particles approximately 240 nm in diameter. The final piposulfan concentration in the suspension was 10 mg/mL. The particles were stable to flocculation/aggregation in rat plasma.

Milling Conditions: A coarse suspension of piposulfan was prepared by adding 300 mg of the drug to a 4 oz. (120 mL) amber bottle which was previously filled with 60 mL of 1 mm precleaned zirconium oxide beads (Zircoa Inc., Solon, Ohio) and 30 mL of 1% Tween 80/Span 80 (1 to 2 ratio) solution. The surfactant solution was prepared by accurately weighing 333 mg of Tween 80 and 667 mg of Span 80 in a volumetric flask followed by addition of sterile water for injection to dissolve/disperse the surfactants. Sufficient quantity of water was added to make the final volume 100 mL. Zirconium oxide beads were cleaned by first rinsing in 1N sulfuric acid followed by several rinses with deionized water. The media was dried in a vacuum oven at about 100° C. overnight.

The sealed primary container was loaded into a secondary padded aluminium containment can to ensure a tight fit. It was milled on a roller mill (US Stoneware, Mawah, N.J.) at 144 RPM for about 96 hours. At the end of the milling time the slurry was separated from the media and particle size was measured using a PCS device. Stability of these particles to rat plasma was assessed by optical microscopy at 1000× magnification. The final pH of the formulation was 6.

Control A (unmilled), a coarse suspension containing 40 mg of bulk piposulfan was dispersed in water in the presence of 3% ethanol and 1% Tween 80. This suspension could not be injected IV.

Example 1 was evaluated for efficacy studies in female mice (avg. wt. 22 g) which were implanted with early stage Mammary Adenocarcinoma #16/C on day 0. The formulation was injected starting from day 1 for several days. The antitumor activity was assessed by monitoring tumor weight and comparing it to the control animals. The results were as follows:

Treatment	Route of Adm.*	Total Dose (mg/kg)	% Wt. Loss	T/C %	Log10 Cell Kill
Control	—	—	+5.5	—	—
Example 1	IV	356	−5.5	0	2.75
(243 nm)	IV	220	−5.5	2	2.75
	IV	137	−1.8	2	2.25
	IV	85	0	18	1.0
Control A	SC	800	−10.8	0	2.1

*Administration - IV Intravenous; SC Subcutaneous

Example 1 could be injected directly as 10 mg/ml suspension. There was no acute toxicity after injection of 78 mg/kg single dose.

T/C=Tumor weight in treated animals divided by the tumor weight of the control animals, reported as percent value. Lower value indicates better efficacy, 0% suggests cures. <10% is considered highly active, 10 to 42% is moderately active formulation. >42% is considered inactive.

Log Kill=(T−C)/3.32 (Td), where T is the time in days for the median tumor to reach 1000 mg mass in treated animals, C is the time in days for the median tumor to reach 1000 mg in control animals and Td is the tumor volume doubling time in days. Cures (tumor free animals) are excluded from (T−C) calculations.

Example 1 demonstrates that a composition of this invention exhibited reduced toxicity and enhanced efficacy compared to a prior art composition and could be administered by IV bolus injection.

EXAMPLES 2–4

The milling procedure described in Example 1 was repeated except that the ratio of Tween 80 to Span 80 was 2:1. The resulting average particle size was 297 nm.

The milling procedure described in Example 1 was repeated except that the ratio of Tween 80 to Span 80 was 1:1. The resulting average particle size was 380 nm.

The milling procedure described in Example 1 was repeated except that the surface modifier was a 1:1 ratio of Tween 60 and Span 60. The resulting average particle size was 301 nm.

Stable pipsulfan nanoparticles were also prepared using bovine serum albumin as the surface modifier.

EXAMPLES 5–7 Nanoparticulate Camptothecin

EXAMPLE 5

Approximately 60 mL of precleaned zirconium oxide beads (1 mm) were placed in a 120 mL wide mouth round amber bottle. To it was added 0.35 g of Tetronic 908 (BASF) followed by 0.35 g of Camptothecin (Sigma Chemicals, 95% pure). To the above mixture, 35 mL of water for injection (Abbott) was added. The bottle was sealed and mounted on a roller mill. Milling was effected by rotating the bottle at 100 RPM for 7 days.

At the end of milling, an aliquot (100 μL) was checked for particle size using a Malvern Zetasizer. The particles were determined to have an average particle size of 240 nm.

EXAMPLE 6

Example 5 was repeated except that the Tetronic 908 was replaced by polyvinyl alcohol (MW 30 to 70K). The final particle size was 256 nm.

EXAMPLE 7

Example 5 was repeated except that Tetronic 908 was replaced by gum acacia. The final particle size was 298 nm.

Nanocamptothecin formulations were evaluated for efficacy in two murine tumor models, i.e., Mammary Adenocarcinoma #16/C and Pancreatic Ductal Adenocarcinoma #03. The antitumor activity was assessed by monitoring tumor weight from experimental and control animals.

1. Efficacy Studies in Pancreatic Ductal Adenocarcinoma #03:

Example	Route	Dose mg/kg	Wt % Loss	Drug Deaths	T/C %
Control B	SC	60	−24.1	6/6	—
	SC	40.2	−21.8	5/5	—
	SC	26.7	−18.2	5/5	—
	SC	18	−10.9	1/5	62
6	IV	83.1	−16.7	1/4	14
	IV	78.2	−14.6	1/4	55
	IV	48.6	−8.3	0/4	0
	IV	24.3	−4.2	0/4	18
PVA Control	IV	—	+6.3	0/4	100
7	IV	93.5	−16.7	1/4	7
	IV	46.8	−14.6	0/4	17
	IV	23.4	−8.3	0/4	11
Cum Acacia Control	IV	—	0.0	0/4	60

The Control B formulation consisted of 1% coarse camptothecin in 3% ethanol, and 1% Tween 20. Control B could only be administered subcutaneously and even at the lowest SC dose (18 mg/kg) was inactive. Control B was toxic to 1/5 animals tested. In contrast, doses of the nanocamptothecin formulations of this invention ranging from 24–93 mg/kg were administered intravenously (IV) and were shown to be safe and efficacious.

2. Efficacy Studies in Mammary Adenocarcinoma #16/C Murine Tumor Model

Example	Route	Dose mg/kg	% Wt Loss	Drug Deaths	T/C %
Control B	SC	60	−23.5	5/5	—
	SC	30	−20.9	5/5	—
	SC	15	−18.3	3/5	14**
5	IV	65	−17.4	0/5	23
	IV	33	−18.7	1/5	33
	IV	16	−2.2	0/5	63
T908 Control	IV	—	+4.3	0/2	100
6	IV	65	−21.7	5/5	—
	IV	33	−15.7	0/5	100
PVA Control	IV	—	+4.3	0/2	100

**% T/C for the control animals was determined from the surviving animals, N = 2.

The T908 and PVA controls consisted of 1% aqueous solutions of the respective surface modifiers. The Control B was injected subcutaneously, and it was toxic at all doses tested. Efficacious doses of the nanocamptothecin formulations of this invention were administered intravenously.

3. Blood and Tumor Clearance

To determine if the increased efficacy was related to alterations in pharmacokinetic properties, blood clear-

ance and tumor distribution were studied in the Mammary adenocarcinoma #16/C murine tumor model.

Tumor bearing mice were injected via the tail vein with 10 mg/ml of camptothecin formulated as described in Examples 5 and 6 and a control which was 5 mg/ml camptothecin solubilized by the addition of 0.1N NaOH. At various times after injection, i.e., 5 min., 30 min., 60 min., 2 hrs., 4 hrs., 8 hrs., 16 hrs., 24 hrs. and 48 hrs., animals were euthanized and a blood sample was collected and the tumor excised. Concentrations of drug samples were quantified using HPLC. Results show that the compositions of this invention affect the clearance of the drug from the circulating pool of blood and the tumor.

	$T_{\frac{1}{2}}$ Blood and Tumor	
Formulation	Blood	Tumor
Example 6	18 hrs.	>48 hrs.
Example 5	13 hrs.	>48 hrs.
Control	1.6 hrs.	13.5 hrs.

When formulated in accordance with this invention, the elimination half-life and the residence time of camptothecin in the tumor were prolonged significantly. It was concluded that pharmacokinetic parameters of the nanoparticulate formulation of camptothecin are directly related to the improved performance of the drug.

EXAMPLES 8–10 Nanoparticulate Etoposide

EXAMPLE 8

Example 5 was repeated except that 1.7 g of etoposide was combined with 1.7 g of PVA and the milling time was 14 days. The final particle size was 310 nm. The particles were stable in acid and plasma.

EXAMPLE 9

Example 8 was repeated except that the PVA was replaced by Pluronic F-108 (BASF). The final particle size was 312 nm. The particles were stable in acid and plasma.

EXAMPLE 10

Etoposide (2%) was milled in sterile water for 7 days. A 1:1 mixture of the milled slurry was prepared with 2% Pluronic F127 solution. The mixture was vortexed before measuring particle size. The final size was 277 nm. The slurry was stable in simulated gastric fluid, PBS (pH 7.4) and rat plasma.

EFFICACY STUDIES

Nanoetoposide formulations were evaluated in two separate efficacy studies in pancreatic ductal adenocarcinoma #03 (PANC #03). Control C was a 2% non-aqueous etoposide solution prepared using the formula described on pages 741–743 of the 46th Edition of the Physicians' Desk Reference. As described above, antitumor activity was assessed by monitoring tumor weight from experimental and control animals. These studies demonstrate that the etoposide compositions of this invention provide a means to deliver high doses of the drug without evidence of severe toxic reaction.

1. Efficacy Studies for Nanoetoposide in PANC #03 Murine Tumor Model

Example	Route	Dose mg/kg	% Wt Loss	Drug Deaths	T/C %
Control C	IV	120	−24.0	0/5	4.0
	IV	75	−4.0	0/5	20.0
7	IV	160	−12.0	0/5	18.0
	IV	100	0.0	0/5	32.0
	IV	62	2.0	0/5	42.0
8	IV	160	−12.0	0/5	26.0
	IV	100	+2.0	0/5	35.0
	IV	62	+4.0	0/5	35.0
9	IV	170	−18.5	1/5	16
	IV	85	−2.0	0/5	35
	IV	43	+2.5	0/5	41

EXAMPLES 11–16 Nanoparticulate Taxol

EXAMPLE 11

Approximately 18 mL of precleaned zirconium oxide media (1 mm) was added to a 30 mL amber jar. To it was added 240 mg of taxol (Sigma Chemicals) and 180 mg of Tween 20. Finally, 12 mL of water for injection was added to the jar, it was sealed and mounted on a roller mill for 11 days. The final particle size was 327 nm. The formulation was stable when exposed to PBS (pH 7.4) and rat plasma.

EXAMPLE 12

Example 11 was repeated except that the Tween 20 was replaced with PVA (MW 30 to 70 k). The final particle size was 365 nm.

The above samples were evaluated in efficacy studies in mice bearing early stage mammary adenocarcinoma #16/C. The antitumor activity was assessed by comparing tumor weights of taxol treated animals with the tumor weights of untreated animals. The toxicity was assessed by dose ranging studies with death and weight loss as end points. All samples were injected IV.

Example	Dose mg/kg	% Wt Loss	Deaths	Median Tumor on Day 11	T/C %
Control D	—	+6.1	—	1539 mg	—
Example 11	108.5	−1.5	0/5	1528	13
Example 12	108.5	−3.0	0/5	201	99

A control sample of taxol (NCI) was not available. However, a single dose of taxol formulated in Cremophore EL causes immediate deaths at 25 mg/kg total dose. However, taxol formulated in compositions of this invention could be injected at a dose of 88 mg/kg with no apparent adverse effects.

A taxol suspension prepared in a manner similar to Example 11 was treated separately with several surface modifiers. After addition of the new surface modifier the mixture was vortexed and evaluated for particle size and fluid stability. All the suspensions contained 1% taxol and 0.75% Tween 20. The results are as follows.

Example/ Surface Modifier	Concentration %	Size (nm)	Fluid Stability PBS	Fluid Stability Rat Plasma
13 CTAC	0.25	364	OK	Flocculation
14 AOT	0.25	322	SA*	SA
15 F68	0.5	297	SA/OK	SA/OK

-continued

Example/ Surface Modifier	Concentration %	Size (nm)	Fluid Stability PBS	Fluid Stability Rat Plasma
16 T908	0.5	313	SA/OK	SA/OK

*SA = Slight Aggregation

EXAMPLES 17–18 Nanoparticulate WIN 59075

Approximately 60 mL of precleaned zirconium oxide (1 mm) media was transferred into a 4 oz amber jar. It was followed by addition of 1.5 g of WIN 59075 and 28.5 mL of water for injection. The jars were sealed, loaded onto a roller mill and cascaded at 95 RPM for 48 hrs. PCS analysis determined the particle size to be 322 nm, however, the presence of larger particles was suggested. Milling was continued for 5 additional days.

Studies were conducted by mixing 0.5 mL of the WIN 59075 slurry prepared above with 0.5 mL of 6% surface modifier solutions. The final concentration of the drug was 2.5% and that of the surface modifiers was 3%. The surface modifier stabilized nanosuspensions of WIN 59075 were then treated with either PBS (pH 7.0) or 0.1N HCl (pH 1). Optical microscopic observations were made to determine fluid stability. The results are as follows;

Example	Surface Modifier	Stability pH 1	Stability pH 7	Human Plasma
17	PVP (12K) (BASF)	Fine	Fine	Fine
18	Gum Acacia (Aldrich)	—	SA/OK	SA/OK

It was concluded that stable nanoparticles of WIN 59075 could be prepared.

EXAMPLES 19–22 Nanoparticulate SR 4889

7.5 mL of precleaned zirconium oxide media (1 mm) was transferred into a 15 mL amber jar along with 18.75 mg of SR 4889 and 3.75 mL of water. After 11 days of milling the nanosuspension was separated from the media. To each of the 100 μL aliquots of the suspension, 100 μL of a surfactant solution (2%) was added giving a final concentration of 0.25% drug and 1% surfactant. The mixture was vortexed and analyzed for particle size. Fluid stability was assessed microscopically by mixing 10 μL of the suspension with 90 μL of rat plasma. The results are as follows:

Example	Surface Modifier	Particle Size (nm)	Fluid Stabilty Rat Plasma
19	PVP (12K)	134	Fine
20	Gum Acacia	344	SA/OK
21	Tween 80	128	Fine
22	T908	130	Aggregates

EXAMPLE 23 Nanoparticulate Retinoic Acid

30 mL of precleaned zirconium oxide media was transferred to a 60 mL amber jar. To it was added 1 g of transretinoic acid (Sigma), 470 mg of tyloxapol and 15 mL of water. The mixture was milled on a roller mill for 15 days. The final particle size was 140 nm. The nanosuspension was stable when exposed to either rat plasma or simulated gastric fluid.

The invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

What is claimed:

1. Particles consisting essentially of 99.9% by weight of a crystalline medicament useful in treating cancer susceptible to treatment with said medicament, said medicament having a solubility in water of less than 10 mg/ml, and having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 0.1–90% by weight and sufficient to maintain an average effective particle size of less than 1000 nm, wherein said medicament is selected from the group consisting of alkylating agents selected from the group consisting of alkylating agents having a bis-(2-chloroethyl)-amine group, alkylating agents having a substituted aziridine group, alkyl sulfonates, and N-alkyl-N-nitrosoureas; antimetabolites; natural products selected from the group consisting of vinca alkaloids, epipophylotoxins, adriamycine, daunomycine, doctinomycine, daunorubicin, doxorubicin, mithramycin, bleomycin, mitomycin, enzymes, biological response modifiers, camptothecin, taxol and retinoids; hormones and antagonists: radiosensitizers; platinum coordination complexes; anthracenediones; and adrenocortical suppressants.

2. The particles of claim **1** having an average effective particles size of less than 400 nm.

3. The particles of claim **1** having an average effective particle size of less than 300 nm.

4. The particles of claim **1** wherein said surface modifier is present in an amount of 1 to 75% by weight.

5. The particles of claim **1** wherein said anticancer agent is selected from the group consisting of piposulfan, piposulfam, camptothecin, etoposide, taxol, 1,2,4-benzotriazin-3-amine 1,4-dioxide, 1,2,4-benzotriazin-7-amine 1,4-dioxide and retinoic acid.

6. The particles of claim **1** wherein said surface modifier is selected from the group consisting of polyvinyl alcohol, a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine, gum acacia, a block copolymer of ethylene oxide and propylene oxide, a polyoxyethylene sorbitan fatty acid ester, and a sorbitan ester of a fatty acid.

7. The particles of claim **1** wherein said anticancer agent is taxol and said surface modifier comprises a polyoxyethylene sorbitan fatty acid ester.

8. An anticancer composition comprising the particles of claim **1**.

9. A method of treating a mammal comprising administering to the mammal an effective amount of the anticancer composition of claim **8**.

10. In a method of treating a mammal comprising administering to the mammal an effective amount of an anticancer agent, the improvement wherein the efficacy of said anticancer agent is increased by administering said anticancer agent in the form of the particles of claim **1**.

11. In a method of treating a mammal comprising administering to the mammal an effective amount of an anticancer agent, the improvement wherein the toxicity of said anticancer agent is reduced by administering said anticancer agent in the form of the particles of claim **1**.

12. The particles of claim **1** wherein said surface modifier is a surfactant.

13. The particles of claim 1 wherein said surface modifier is a nonionic surfactant.

14. The particles of claim 1 wherein said surface modifier is an anionic surfactant.

15. The particles of claim 1 wherein said surface modifier is selected from the group consisting of gelatin, casein, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinyipyrrolidone, poloxomers, tyloxapol, poloxamines, dextran, a dioctyl ester of sodium sulfosuccinic acid, sodium lauryl sulfate, an alkyl aryl polyether sulfonate, a mixture of sucrose stearate and sucrose distearate, hexyldecyl trimethyl ammonium chloride, bovine serum albumin and $C_{18}H_{37}CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$.

16. The particles of claim 1 wherein said surface modifier is present in an amount of 10 to 60% by weight based on the total weight of the dry particle.

17. The particles of claim 1 wherein said surface modifier is present in an amount of 10 to 30% by weight based on the total weight of the dry particle.

* * * * *

EXHIBIT 2

REDACTED IN ITS ENTIRETY

EXHIBIT 3

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TELCORDIA TECHNOLOGIES, INC., Plaintiff, v. ALCATEL USA, INC., Defendants.	)	Civil Action No. 04-874 GMS
TELCORDIA TECHNOLOGIES, INC., Plaintiff, v. LUCENT TECHNOLOGIES, INC., Defendants.	)	Civil Action No. 04-875 GMS
TELCORDIA TECHNOLOGIES, INC., Plaintiff, v. CISCO SYSTEMS, INC., Defendants.	)	Civil Action No. 04-876 GMS

ORDER

WHEREAS, on July 16, 2004, the plaintiff, Telcordia Technologies, Inc. ("Telcordia"), filed the above-captioned patent infringement actions against Alcatel USA, Inc. ("Alcatel"), Lucent Technologies, Inc. ("Lucent"), and Cisco Systems, Inc. ("Cisco") (collectively, the "defendants");

WHEREAS, on February 17, 2006, the parties submitted a Final Joint Claim Chart (the "Chart") (D.I. 98);

WHEREAS, upon inspection of the Chart, the court has discovered that many of the defendants' proposed constructions for U.S. Patent Nos. Re. 36,633 and 4,835,763[1] are not constructions but, rather, arguments that the claim limitations at issue are indefinite for failure to satisfy the requirements of 35 U.S.C. § 112(2); and

WHEREAS, the court does not permit summary judgment arguments, including indefiniteness arguments, during the claim construction phase of the litigation;

IT IS HEREBY ORDERED that:

1. The court will not entertain indefiniteness arguments during the *Markman* Claim Construction hearing.

2. The defendants shall prepare their arguments consistent with this Order.

Dated: April 21, 2006

/s/ Gregory M. Sleet
UNITED STATES DISTRICT JUDGE

[1] Telcordia's action against Alcatel does not include U.S. Patent No. 4,835,763.

EXHIBIT 4

IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

- - -

R2 TECHNOLOGY, INC. and SHIH-PING WANG,	:	CIVIL ACTION
Plaintiffs	:	
vs.	:	
INTELLIGENT SYSTEMS SOFTWARE, INC., ISSI ACQUISITION CORPORATION and iCAD INC.,	:	
Defendants	:	NO. 02-472 (GMS)

- - -

Wilmington, Delaware
Tuesday, April 29, 2003
10:07 o'clock, a.m.

- - -

BEFORE: HONORABLE GREGORY M. SLEET, U.S.D.C.J.

- - -

APPEARANCES:

MORRIS, NICHOLS, ARSHT & TUNNELL
BY: MARYELLEN NOREIKA, ESQ.

-and-

LATHAM & WATKINS
BY: MATTHEW B. LEHR, ESQ.
(Menlo Park, California)

Counsel for Plaintiffs

Valerie J. Gunning
Official Court Reporter

ORIGINAL

to discuss the '838 patent.

Now, today, we're only going to discuss six of the terms. We believe that the rest of the terms have been adequately briefed and can be decided that way.

THE COURT: All right.

MS. LANE-WHITE: I'll be discussing the term independent from the '838 patent. Mr. Greenbaum will discuss status information upon completion of scanning of a first film-based medical image and graphically displaying in the '929 patent, and then Mr. Greenbaum will discuss selectively showing from the '620 patent and then the indefiniteness.

Now, I just want to address that just very briefly. The reason we decided to address indefiniteness at this point was based on the Amgen case, which we cited in our brief.

THE COURT: But I'm not going to hear you on indefiniteness today, Amgen notwithstanding.

MS. LANE-WHITE: Very good. All right.

R2 makes much of the fact that iCAD, in its estimation, relies on preferred embodiments. Mr. Lehr said I've been in the shoes of the defendant before. I've done the same thing, your Honor.

Well, iCAD's counsel has been in the shoes of the patentee before and so we understand also that it's

MS. MATTERER: They have been filed and R2 has responded.

MR. LEHR: Letter submissions, your Honor.

THE COURT: Okay. I have not reviewed them. I apologize. I did not realize we had set this and I should have recalled it. I think what we're going to have to do, since I have not read them yet, is to go ahead and schedule a teleconference.

MR. LEHR: Yes, sir, and that's fine.

THE COURT: We'll do that ASAP.

MS. MATTERER: Thank you.

THE COURT: Thank you for calling it to my attention.

MR. LEHR: Thank you.

THE COURT: I'm advised by my able staff, because they know I've seen it, that we actually do have a teleconference already set for that very purpose. Okay?

MR. LEHR: Thank you, your Honor.

MR. GREENBAUM: Thank you, your Honor.

(Court recessed at 12:50 p.m.)

- - -

I hereby certify that the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

Valerie J. Gunning

Official Court Reporter
U. S. District Court

EXHIBIT 5

IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

- - -

KEURIG, INCORPORATED,	:	CIVIL ACTION
Plaintiff,	:	
v	:	
KRAFT FOODS GLOBAL, INC., TASSIMO CORPORATION, and KRAFT FOODS, INC.,	:	
Defendants.	:	NO. 07-017 (GMS)

- - -

Wilmington, Delaware
Monday, December 2, 2007 at 9:29 a.m.
CLAIM CONSTRUCTION HEARING

- - -

BEFORE: HONORABLE GREGORY M. SLEET, Chief Judge

- - -

APPEARANCES:

YOUNG CONAWAY STARGATT & TAYLOR, LLP
BY: JOHN W. SHAW, ESQ.,
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and

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Counsel for Plaintiff

Brian P. Gaffigan
Registered Merit Reporter

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There was a rejection over the '189 patent. And in overcoming that rejection, the applicant stated, and I quote: In U.S. Patent No. 5,841,089, Sylvan, et al, the cover 16 overlies the inner chamber but not the outer chamber 36.

So it directly overlies this chamber but it indirectly overlies this chamber. But when they said or they use the word overlies, they clearly are meaning directly overlies. They were disclaiming or disavowing indirect. Keurig should not be allowed to recapture what it disavowed or disclaims through claim construction. That is simply the point here.

Now, Mr. Albert talks about this filter and so filter intervenes between the lid and the second chamber. That is not what we're asking Your Honor. As you see, there are a lot of arguments that Mr. Albert argued against we haven't made.

Let's go the claim construction.

"A second section overlying said second chamber."

"A portion of the lid laying directly over the enclosed space from which the beverage exits the container (i.e., the second chamber) such that there is no chamber -- we're not talking about intervening chamber -- such that there is no chamber in between said portion of the lid and

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said second chamber." That's all. We're saying don't allow them to recapture what they disclaimed during the prosecution. That's it. That's it, plain and simple.

THE COURT: Are there statements made by Keurig that support your position that there was a clear disavowal or do you argue that the disavowal manifests in some circumstantial way?

MR. SCHLITZ: Your Honor, with all due respect, when they say in U.S. No. '189, the cover overlies, 16 overlies the inner chamber but not the outer chamber, I don't think that is circumstantial or indirect. I think that is a very clear statement of disavowal of a cartridge in which the lid indirectly overlies the second chamber. I mean, to me, it's quite clear. And they made that statement for reasons of patentability. They made that statement in order to overcome the rejection.

If there is no more questions on this claim term, I'll go to the last claim term.

THE COURT: Go ahead.

MR. SCHLITZ: Okay. Your Honor, the last claim term is "a filter element received in and configured and arranged to subdivide the interior of said container into first and second chambers."

Keurig's counsel asked you to construe first and second chambers in isolation but in fact those words have

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meaning in the context of the whole claim element. The filter element creates the first and second chamber and you have to understand, I believe, the whole.

Now, it is explained in the specification that the filter element is formed from sheet material shaped to conform. Here, it's formed and shaped to create a first and second chamber.

It says, "when thus positioned -- so it's formed and shaped -- and "when thus positioned, the filter element defines a first chamber A separate from a second chamber B, the latter being in communication with open channels separating the support ribs."

Clearly, with the specification, what is depicted is a filter element that starts out as a planar piece of material that is shaped and configured and placed in the container such that it creates a first chamber and a second chamber.

And if you go to the next slide.

You will see that when it is placed into the container, it creates and defines a first chamber and a second chamber.

Now, both the specification and the claims made clear that the first chamber has a particular purpose. It is for storing the beverage medium. And the second chamber has a particular purpose. It is the enclosed space from

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which the beverage exits the cartridge.

As earlier seen in Claim 1, a soluble beverage medium is stored in the first chamber. The lid has a section that overlies the first chamber so it can be pierced and the liquid goes directly into the first chamber to infuse with the coffee. And that the coffee -- and this is in the claim -- the coffee exits the second chamber.

So these chambers A and B, the first chamber and the second chamber have very particular important purposes. It is a fundamental part of the invention that the first chamber is for the storing of the coffee grounds or the beverage and the second chamber is from you exit.

This concept of using a filter to create a first chamber to store beverage and the second chamber to exit the beverage -- go to the next slide -- was well known in the prior art. You see here in the prior art -- and this is the '765 patent. Again, part of the intrinsic evidence. This was cited in column 1 of the '762 patent.

THE COURT: But your opponent says not incorporated by reference?

MR. SCHLITZ: Well, whether it's incorporated by reference, the Federal Circuit said if you cite it in the patent, it's part of the intrinsic evidence.

You have a container. You have a filter element. And the container, before you place the filter

EXHIBIT 6

REDACTED IN ITS ENTIRETY

EXHIBIT 7

READ IN OPEN COURT
5/9/07

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TELCORDIA TECHNOLOGIES, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 04-876-GMS
	)	
CISCO SYSTEMS, INC.,	)	
	)	
Defendant.	)	
	)	

FINAL JURY INSTRUCTIONS

Plaintiff Telcordia Technologies, Inc. and Defendant Cisco Systems, Inc. submit the following jury instructions.

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Cisco Systems, Inc. in C.A.

excusable delay does not give rise to an estoppel. Second, Cisco must prove that it reasonably relied on that conduct. Cisco must prove this reliance by specific evidence. Third, Cisco must prove that, as a result of its reliance, it will be materially prejudiced if Telcordia is allowed to proceed with its claim. As with laches, prejudice may be economic or evidentiary. The same principles apply. Damages attributable to a finding of liability do not constitute economic prejudice supporting an estoppel theory. Evidentiary prejudice may arise from loss of records, death or disappearance of witnesses, or the unreliability of memories of long past events. Economic prejudice may result where the accused infringer will suffer the loss of monetary investments or incur damages that likely would have been prevented by an earlier suit. However, it is not prejudice simply that the alleged infringer will have to pay damages if it loses the lawsuit. The proper question is whether there has been a change in the economic position of the alleged infringer during the period of delay. That change must have been caused by and be a result of the delay, not merely a business decision to capitalize on a market opportunity. Conclusory statements are not sufficient to show prejudice.

5.3 UNCLEAN HANDS

Cisco alleges that Telcordia's patent infringement claims are barred by the doctrine of unclean hands. To show that Telcordia has unclean hands, Cisco must show by clear and convincing evidence that Telcordia engaged in fraud, perjury, or other unconscionable conduct when obtaining its '306, '763, or '633 patents or enforcing the '306, '763, or '633 patents against Cisco. Unclean hands requires an "unconscionable act" that has an "immediate and necessary relationship" to the claims of patent infringement asserted against Cisco.

While unclean hands can reach other egregious forms of conduct, a patentee does not have unclean hands merely by asserting that someone has infringed its patent or by suing a competitor it believes is infringing its patent. Even if the patentee is mistaken in its belief of infringement, the patentee does not have unclean hands by seeking to enforce what it thinks are its patent rights in court.

Finally, Cisco cannot rely on unclean hands as a defense, or any other equitable defense, if Cisco itself has unclean hands, including any unconscionable conduct related toward the patents in suit. One example of such unclean hands by Cisco would be willful infringement.

5.4 INTERVENING RIGHTS

For the '633 patent only, Cisco alleges that Telcordia's patent infringement claims are barred by the doctrine of intervening rights. Because the '633 patent is a reissue patent that includes claims that are broader in scope than its parent '978 patent (including the asserted claims in this case), Telcordia cannot recover patent infringement damages for any physical product that was manufactured prior to the issuance of the '633 patent. Telcordia does not seek damages for '633 patent infringement prior to the issue date of the '633 patent, so this form of intervening rights is not at issue.

Intervening rights may also apply to products that were made or sold by Cisco after the '633 patent issued, but only if Cisco establishes by a preponderance of the evidence that (1) before the issuance of the '633 patent, Cisco made substantial preparations to make, purchase, offer for sale, or use the products, including, for example, substantial investment in the development of the products, and (2) Cisco has not recouped its investment.

5.5 INEQUITABLE CONDUCT – GENERALLY

EXHIBIT 8

REDACTED IN ITS ENTIRETY