UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ELAN PHARMA INTERNATIONAL LIMITED, Plaintiff, v. ABRAXIS BIOSCIENCE, INC., Defendant.	)	Case No. 06-438-GMS

ABRAXIS'S OPENING CLAIM CONSTRUCTION BRIEF

REDACTED – PUBLIC VERSION

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PRELIMINARY STATEMENT

In litigating this dispute to date, we have focused our advocacy on the "crystalline" limitation in the '363 and '025 patents. We have argued that because Abraxane, our accused product, is amorphous and not crystalline, it cannot possibly infringe those claims. (CMC Statement, pp. 3 & 5 [D.I. 11]; Abraxis's Opening Brief to Rule 11 Motion [D.I. 79].) We have also contended that the "10 mg/min" infusion rate limitation of the '025 patent presents a simple mathematical inquiry: how Elan can possibly show that Abraxis directs the administration of Abraxane at a dosage below the "10 mg/min" level of the '025 patent's claims when the Abraxane administration instructions call for much higher levels. (March 15, 2007 Hearing Tr., p. 49 [D.I. 89].)

Elan has now formally proffered claim constructions that seek to keep its case alive. As to "crystalline," Elan's proposed construction acknowledges that "crystalline" means "not amorphous." But Elan falls back to a proposed construction that rewrites the "consisting essentially of" phrase that is associated with the "crystalline" limitation as if it read "comprising." Apparently, Elan aims to assert infringement by particles in which the drug substance is overwhelmingly amorphous.

As for the infusion rate limitation, to make the arithmetic work, Elan must depart from the plain meaning of the claim and change what the "10 mg/min" refers to. The claims refer to a "drug composition" that is infused at a rate "not exceeding 10 mg/min." The drug composition comprises (a) drug substance particles, (b) a surface modifier (claim 1) or liposome/colloidal polymeric material (claim 13), and (c) a carrier. The composition thus refers to the entire Abraxane suspension as it is administered to patients. But Elan asserts that "drug composition" should be read out of the claim and

that the infusion rate should be based solely on the nanoparticles in the Abraxane suspension — a fraction of the total infused composition.

Basic claim construction principles defeat these proposed constructions. Indeed, these constructions demonstrate how far Elan must stretch in order to attempt to sustain its infringement allegations. And if the Court resolves only these issues, this case would be dismissed. The Court has directed, however, that all claim construction disputes be submitted for resolution now. Six other phrases from the '363 patent claims and six from the '025 patent are in dispute. As to each, Elan has departed from well-settled rules and engaged in what might charitably be labeled as wishful thinking.

The Court will observe that, in certain cases, we are relying on authoritative technical and scientific treatises and dictionaries to answer the basic claim construction question: what a person of ordinary skill in the art would have understood a claim to mean. We acknowledge the Court's skepticism toward "extrinsic" evidence. Unfortunately, for some disputed terms, the intrinsic evidence associated with Elan's patents is inadequate to answer that question. Thus, consistent with Federal Circuit guidelines, we rely on such evidence only where the intrinsic evidence is insufficient to answer the question, and we ensure that any such extrinsic evidence is consistent with the intrinsic evidence.[1] *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1319 (Fed. Cir. 2005) (en banc) *cert. denied*, 126 S. Ct. 1332 (2006).

[1] We have also submitted the Declaration of Dr. Mansoor Amiji, which provides technical background and contextualizes the dictionaries and treatises on which we rely.

CLAIM TERMS REQUIRING CONSTRUCTION

Elan has asserted claims 1-3, 5, 8-12, and 15 of the '363 patent. The parties dispute the construction of the terms appearing in claims 1 and 12 of the '363 patent that are in boldface below. No additional claim construction disputes arise out of the remaining asserted claims. Claim 1 of the '363 patent recites:

> Particles **consisting essentially of** 99.9-10% 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. (Ex. 1, '363 patent, 14:7-28.)[2]

Dependent claim 12 of the '363 patent claims "[t]he particles of claim 1 wherein said surface modifier is a **surfactant**." (*Id.* at 14:67-68.)

Elan has asserted claims 1-3 and 13-15 of the '025 patent. The parties dispute the construction of the terms appearing in claims 1 and 13 of the '025 patent that also are in boldface below. No other claim construction disputes arise out of the remaining asserted claims. Claim 1 of the '025 patent recites:

> A method of administering a nanoparticulate composition to a mammal **without eliciting adverse hemodynamic effects** comprising

[2] All references herein to "Ex. __" are to the May 11, 2007 Declaration of Paul F. Coyne in Support of Abraxis's Opening Claim Construction Brief.

> intravenously administering to said mammal an effective amount of a nanoparticulate drug composition at an **infusion rate not exceeding 10 mg/min**, wherein said drug composition comprises: (a) particles **consisting essentially of** from about 0.1 to about 99.9% by weight of a **crystalline organic drug substance** having a solubility in water of less than 10 mg/ml; (b) a **surface modifier adsorbed on the surface of the drug substance** in an amount of from about 0.1 to about 99.9% by weight and **sufficient to maintain an effective average particle size** of from about 50 nm to about 1000 nm; and (c) a pharmaceutically acceptable carrier therefor. (Ex. 2, '025 patent, 16:56-17:4.)

Claim 13 of the '025 patent recites:

> A method of administering a nanoparticulate composition to a mammal **without eliciting adverse hemodynamic effects** comprising intravenously administering to said mammal an effective amount of a nanoparticulate drug composition at an **infusion rate not exceeding 10 mg/min**, wherein said drug composition comprises: a) particles having an effective average particle size of from about 50 to about 1000 nm and **consisting essentially of** from about 0.1 to about 99.9% by weight of an **organic drug substance** entrapped in from about 99.9 to about 0.1% by weight of liposome or a **colloidal polymeric material**; and b) a pharmaceutically acceptable carrier therefor. (*Id.* at 18:6-19.)

STATEMENT OF FACTS

A. Technological Background of the '363 and '025 Patents.

These patents are about nanoparticles and their use. Nanoparticles are tiny particles that, as claimed here, are less than 1000 nanometers (nm) in size.[3] More specifically, the patents are about nanoparticles of water-insoluble drug substances or diagnostic agents that can be intravenously administered to mammals.[4] The particles are suspended in an aqueous solution (also called a nanoparticulate suspension) before they are administered.

[3] One thousand nanometers equals one thousandth of a millimeter.

[4] The '363 patent concerns a broad range of water-insoluble anticancer drugs, while the '025 patent extends to any water-insoluble, organic therapeutic or diagnostic agent.

Intravenous administration of water-insoluble compounds can be problematic. (*See* Ex. 1, '363 patent, 1:34-42.) These drug substances precipitate as solids in water-based liquids (such as blood) and do not dissolve easily; that makes them difficult to administer intravenously at concentrations that are efficacious and non-toxic. (*See* Ex. 3, '684 patent, 1:20-27.) Water-insoluble medicaments also tend to have poor bioavailability when administered.[5] (Ex. 3, '684 patent, 1:17-23.) Various potential solutions were described in the prior art, including dissolving the drug substance in a solvent such as ethanol or oil before injection (*see* Ex. 26, '363 patent cited reference U.S.P. 5,091,188, 3:15-35), or formulating the drug substance as a nanoparticle. (*See* Ex. 4, '125 App., 10/29/92 Amendment, pp. 3-5.)

According to the patents, drug substances dissolved in solvents or oil had toxicity problems and other practical drawbacks. (*See* Ex. 26, '363 patent cited reference U.S.P. 5,091,188, 3:30-37.) The second approach, nanoparticulate formulations, had its own set of drawbacks, including how to make microscopic particles without introducing unacceptable contaminants. (Ex. 3, '684 patent, 1:58-63, 2:3-14.)

Preventing the individual particles from glomming together to form aggregates (a process known as flocculation or agglomeration) was also a challenge. (*See* Ex. 4, '125 App., 10/29/92 IDS pp. 2-5.) Small particle size was critical for reducing toxicity, increasing bioavailability and/or enhancing efficacy. (*See* Ex. 3, '684 patent 1:28-33.) Prior art researchers thus experimented with adding compounds to their formulations to

[5] Bioavailability means the degree and rate at which a substance (as a drug) is absorbed into a living system or is made available at the site of physiological activity. (*See* Ex. 25, Merriam-Webster's Medical Dictionary, http://www.merriam-webster.com/cgi-bin/mwmedsamp.)

reduce or slow down agglomeration. (*See* Ex. 4, '125 App., 10/29/92 IDS pp. 2-5.) Sometimes these substances were attached to the surface of the nanoparticles. (*See* Ex. 26, '363 patent cited reference U.S.P. 5,091,188, 5:36-38.) Sometimes they were dissolved in the aqueous solution in which the nanoparticles were suspended. (*See* Ex. 27, '363 patent, cited reference U.S.P. 2,671,750, 4:12-15.)

The alleged innovation of the '363 patent was to make nanoparticles out of water-insoluble anti-cancer medicaments that were crystalline and to add a "surface modifier" to reduce agglomeration. (*See, e.g.*, Ex. 1, '363 patent, 7:5-45.) The '363 applicants stressed that their nanoparticles were different from, and superior to, nanoparticles made with medicaments in their amorphous form. (*See, e.g.*, Ex. 5, '105 App., 11/18/1991 Amendment, pp. 6, 9.)

The '025 patent purports to solve the alleged prior art problem that intravenously administering nanoparticles can cause certain unwanted cardiovascular-related side-effects (referred to in the patent as "adverse hemodynamic effects"). (*See, e.g.*, Ex. 2, '025 patent, 1:48-65.) The '025 applicants stated that they solved this problem by administering the nanoparticulate drug substance composition at a very slow infusion rate ("not exceeding 10 mg/min"). (*See, e.g.*, Ex. 6, '754 App., 2/9/1998 Amendment, pp. 4-6.)

B. The Accused Product — Abraxane.[6]

Abraxane is a nanoparticulate composition of amorphous paclitaxel and [redacted] human albumin. (Ex. 7, Abraxane Prescribing Info.; Ex. 8, ABRX 0078827 – ABRX 0078830 (paclitaxel in Abraxane is amorphous); Ex. 9, ABRX 0117313 - ABRX 0117315 and ABRX 0117383 ([redacted]); Ex. 10, ABRX 0168408 - ABRX 0168410 (same).) It has been approved by the FDA for the treatment of breast cancer. [redacted] (Ex. 11, ABRX 0117477 - ABRX 0117478.) Each vial of Abraxane contains 100 mg paclitaxel and approximately 900 mg human albumin. (Ex. 7, Abraxane Prescribing Info. at 1; Ex. 12, Elan's 2nd Amended Resp. to Interrogatory No. 1, Ex. A at 1-2.)

Abraxis instructs doctors to reconstitute each vial of Abraxane with 20 mL of 0.9% saline to form a suspension, and to administer that composition intravenously over 30 minutes. (Ex. 7, Abraxane Prescribing Info. at 18.) For the vast majority of patients, Abraxis recommends a dose of 260 mg of paclitaxel per one square meter of body surface area. (*Id.* at 17.) For patients for whom administration causes peripheral neuropathy or neutropenia (neither of which is a hemodynamic effect), Abraxis recommends lowering the dose to 220 or 180 mg paclitaxel per one square meter of body surface area. (*Id.*)

Taking the lowest dose in the Abraxane prescribing information for a woman of average size yields an infusion rate for the Abraxane suspension of roughly 2,030 mg/min

[6] As the Federal Circuit has recently noted, the significance of the parties' definitional disputes can best be seen when viewed against the accused product. *Wilson Sporting Goods Co. v. Hillerich & Bradsby Co.*, 442 F.3d 1322, 1326-27 (Fed. Cir. 2006).

over 30 minutes, or more than 200 times the infusion rate claimed in the '025 patent.[7] In contrast, administering Abraxane at the claimed 10 mg/min would take just under 101.5 hours.[8]

C. The '363 Patent.

The '363 patent, entitled "Surface Modified Anticancer Nanoparticles" was filed as a continuation-in-part of U.S. Patent Application No. 07/647,105 (the "'105 App."). According to the '105 App., filed January 25, 1991, "poor bioavailability" of water-insoluble drug substances was a "significant problem." (Ex. 3, '684 patent, 1:17-23.) It was already known that bioavailability of drugs in nanoparticle form could be enhanced by decreasing their particle size. (*Id.* at 1:28-30.) The applicants claimed, however, that

[7] Calculating the infusion rate for Abraxane is straightforward, but requires several mathematical steps. The first step is to convert the dosage in the label, *e.g.*, 180 mg paclitaxel per m^2 body surface area, to a total amount of composition to be administered. An average woman receiving Abraxane would be expected to have a body surface area of roughly 1.6 m^2. (*See, e.g.*, Ex. 13, MedicineNet.com, "Definition of Body Surface Area", http://www.medterms.com/script/main/art.asp?articlekey=39851.) Thus, that woman would need a dose of 288 mg paclitaxel (180 x 1.6). As explained above, each vial of Abraxane contains 100 mg paclitaxel. Thus, an average woman would need 2.88 reconstituted vials of Abraxane (288/100). Also as noted above, each vial of Abraxane is reconstituted with 20 mL saline. Because saline has a density of roughly 1.007 g/mL (Ex. 14, J. Dean, Lange's Handbook of Chemistry (13th ed. 1985), 10-77), the weight of the saline can be calculated: 1.007 x 20 = 20.14 g. There are 1000 mg in 1 g, so the saline weighs 20,140 mg. As noted above, each vial of Abraxane contains 1000 mg of material (human albumin and paclitaxel). Adding the Abraxane to the saline yields 21,140 mg total composition weight per vial to be administered. Administering 2.88 vials means an infusion of 60,883.2 mg total material (2.88 x 21,140). The second step is to divide the weight of the total composition to be administered by the number of minutes over which it is given. As noted above, Abraxane is administered over 30 minutes. Thus, the infusion rate is 2029.4 mg/min (60,883.2/30).

[8] Administering 60,883.2 mg at a rate of 10 mg/min would take 6,088.3 minutes, or approximately 101.5 hours. This is similar to the 96-hour infusion time for Taxol (a non-particulate paclitaxel-based composition), that was common as of the '025 patent's filing date. (*See, e.g.*, Ex. 15, G. Hudes, et al., Paclitaxel Plus Estramustine In Metastatic Hormone-Refractory Prostate Cancer, Seminars in Oncology (Oct. 1995).)

the various methods of decreasing particle size had significant drawbacks. Importantly, the applicants said known techniques such as solvent precipitation resulted in the formation of non-crystalline nanoparticles contaminated with solvents, which were toxic and "very difficult, if not impossible, to adequately remove." (*Id.* at 2:3-14.)

The inventors of the '105 App. claimed to solve these problems by making stable nanoparticles of crystalline medicaments that were prepared by milling larger crystalline drug substance particles in the presence of grinding media and in conjunction with a surface modifier. (*Id.* at 2:32-35.) The claimed particles were said to be free of unacceptable contamination, and could safely be administered to mammals intravenously. (*Id.* at 2:61-66.)

On May 17, 1991, the Examiner rejected claims of the '105 App. as obvious over prior art. Specifically, the Examiner found that the Violante reference taught crystalline drug particles, the Motoyama reference taught surface modifiers, and the Oppenheim reference taught nanoparticles. In response, the applicants amended the claims and distinguished the prior art based on how the particles were prepared (milling) and their characteristics (crystallinity of the drug substances and non-crosslinking of the surface modifiers).

Of particular relevance here, the applicants explained that: "[Solvent precipitation] techniques have provided non-crystalline, e.g., amorphous particles smaller than 500 nm. However, solvent precipitation techniques provide amorphous particles which are unstable and contaminated with solvents." (Ex. 5, '105 App., 11/18/1991 Amendment, p. 6.) In explaining how the crystalline phase of the applicants' particles differed from and was superior to non-crystalline and amorphous phases, the applicants

stated that "[t]he crystalline particles of this invention exhibit improved stability compared to particles containing a drug substance in an amorphous phase." (*Id.* at 9.) Distinguishing the Violante reference, the applicants argued that "Violante teaches a solvent precipitation technique for preparing amorphous, noncrystalline particles." (*Id.* at 14.) In distinguishing the Motoyama and Oppenheim references, the applicants relied heavily on the fact that that the surface modifiers taught by these two references were crosslinked, and specifically amended the claims of the '105 App. to clarify that the surface modifier molecules in the applicants' particles were non-crosslinked. (*Id.* at 15-17.) The Examiner accepted these distinctions, and the '105 App. issued as the '684 patent on September 8, 1992.

On July 1, 1992, the applicants filed U.S. Patent Application No. 908,125 (the "'125 App.") as a continuation-in-part of the '105 App. The '125 App. eventually issued as the '363 patent. The '363 patent purports to teach how to prepare a water-insoluble anti-cancer medicament in nanoparticulate form for injection, allegedly resulting in reduced toxicity and enhanced efficacy. (Ex. 1, '363 patent, 1:29-2:7.) As did its parent application, the '363 patent teaches that reduced toxicity and enhanced efficacy are accomplished by using a crystalline medicament and preparing the nanoparticles by wet milling in the presence of grinding media. (*Id.* at 2:27-33, 5:22-30.)

During prosecution of the '125 App., the applicants distinguished myriad references based on method of preparation, crystallinity of the drug substance, and non-crosslinking of the surface modifier. (*See, e.g.*, Ex. 4, '125 App., 10/29/92 IDS, pp. 2-5 (distinguishing prior art reference on crosslinking).) For example, the applicants distinguished U.S.P. 4,826,689 because it was prepared by solvent precipitation, which

"tend[s] to provide solvent contaminated particles" in which the solvent is nigh impossible to remove, and because it resulted in amorphous particles tending to exhibit short shelf lives. (*See, e.g.*, Ex. 4, '125 App., 10/29/92 IDS, p. 3.) The applicants made similar arguments in response to an obviousness rejection over the King and Devissaguet references, and stated that: "On the other hand, applicants' crystalline particles, prepared by wet grinding, a technique entirely different than the technique of Devissaguet et al, are essentially free of solvent contamination." (Ex. 4, '125 App., 9/13/93 Amendment, p. 4.) The Examiner accepted these distinctions and the '125 App. issued as the '363 patent on March 21, 1995.

D. The '025 Patent.

The '025 patent discloses methods of intravenous administration of nanoparticulate drug substance formulations to mammals so as to avoid adverse hemodynamic effects that might otherwise be caused by intravenous administration. The only method asserted against Abraxis is to use a slow rate of infusion so that hemodynamic effects do not occur. Specifically, the applicants purported to discover that "adverse hemodynamic effects associated with intravenous administration of nanoparticulate formulations can be eliminated, or substantially reduced, by maintaining the intravenous infusion rate at less than 10 mg/[min]." (Ex. 6, '754 App., 2/9/1998 Amendment, p. 4.) The applicants argued in the prosecution history of the '025 patent that the use of an infusion rate of less than 10 mg/min "is not merely an optimization of an administration variable, as the use of this specific infusion rate results in dramatic, unexpected results, i.e., the reduction or elimination of hemodynamic side effects." (*Id.* at 6.)

The ’025 patent claims do not tie the infusion rate of “10 mg/min” in any way to the weight of the mammal, the surface area of the mammal, the total dose to be administered, or even the type of mammal. (*See generally* Ex. 2, ’025 patent.) Per the claims, for example, one would administer nanoparticulate drug substance formulations to both a mouse and an elephant at the same rate of “10 mg/min.” The ’025 patent also purportedly covers administration of every “therapeutic or diagnostic agent” as long as it “exists as a discrete crystalline phase.” (*Id.* at 7:27-29.)[9]

LEGAL FRAMEWORK

This Court is well aware of basic claim construction principles. “[I]n interpreting an asserted claim, the court should look first to the intrinsic evidence of record, i.e., the patent itself, including the claims, the specification and, if in evidence, the prosecution history.” *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The Court first examines “the words of the claims themselves, both asserted and nonasserted, to define the scope of the patented invention.” *Id.* at 1582.

“[The] words of a claim ‘are generally given their ordinary and customary meaning,’” that is, as understood by one of ordinary skill in the art at the time of the invention. *Phillips*, 415 F.3d at 1312-13 (*quoting Vitronics*, 90 F.3d at 1582). “[T]he person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire

[9] The ’025 inventors also distinguished their nanoparticles from prior art nanoparticles by arguing that “[t]he crystalline phase differs from a non-crystalline or amorphous phase which results from precipitation techniques, such as described in EPO 275,796.” (Ex. 2, ’025 patent, 7:28-31.) The ’025 patent further refers the reader to the ’684 patent to describe the nanoparticulate drug compositions to be administered, which, as we show above, applies only to compositions with drugs in the crystalline phase. (Ex. 2, ’025 patent, 1:23-24.)

patent, including the specification." *Id.* at 1313. As the Federal Circuit "stated in *Vitronics*, the specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Id.* at 1315 (*quoting Vitronics*, 90 F.3d at 1582).

"[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316. "[T]he specification may [also] reveal an intentional disclaimer, or disavowal, of claim scope by the inventor. In that instance as well, the inventor has dictated the correct claim scope, and the inventor's intention, as expressed in the specification, is regarded as dispositive." *Id.* (*citing Scimed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1343-44 (Fed. Cir. 2001)). "Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question." *See Scimed Life*, 242 F.3d at 1341.

The prosecution history of a patent "is often of critical significance in determining the meaning of the claims." *Vitronics*, 90 F.3d at 1582. The prosecution history reveals any express representations made by the applicant regarding the scope of the claims, limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution, and may provide an explanation of the cited prior art, which supplies clues as to what the claims do and do not cover. *Id.* at 1582-83; *see also Phillips*, 415 F.3d at 1317.

A court may also consider extrinsic evidence to resolve the scope and meaning of a claim term. *Phillips*, 415 F.3d at 1318, 1324. In *Vitronics*, the Federal Circuit stated that technical treatises and dictionaries are extrinsic but worthy of special note; judges may use them "at any time in order to better understand the underlying technology and may also rely on dictionary definitions when construing claim terms, so long as the dictionary definition does not contradict any definition found in or ascertained by a reading of the patent documents." *Vitronics*, 90 F.3d at 1584 n.6; *see also Phillips*, 415 F.3d at 1318.

ARGUMENT

I. THE '363 PATENT.

A. "Consisting Essentially Of."

The legal meaning of "consisting essentially of" could not be more settled. The Federal Circuit has defined it, as did its predecessor court. The phrase "consisting essentially of" has a particular meaning when used in a patent claim; it "is a transition phrase commonly used to signal a partially open claim in a patent." *PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998) ("A 'consisting essentially of' claim occupies a middle ground between closed claims that are written in a 'consisting of' format and fully open claims that are drafted in a 'comprising' format."). "By using the term 'consisting essentially of,' the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention." *Id.; see also In re Herz*, 537 F.2d 549, 551-52 (C.C.P.A. 1976) (holding that the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristics" of the claimed

invention.); The Manual of Patent Examining Procedure defines it the same way. (*See* M.P.E.P. § 2111.03 (same).) So do treatises. *See, e.g.,* 3 *Chisum on Patents* § 8.06[1][b][ii][B], at 8-189 (2005 ed.). Even the AIPLA Model Patent Jury Instructions (http://www.aipla.org/Content/ContentGroups/Publications1/Guide_to_Model_Patent_Jury_Instructions.htm) contains the same definition. (*See* Ex. 24.)

The structure of the claims of the '363 patent relies on "consisting essentially of" to transition between the claimed "particles" and the crystalline medicament and non-crosslinked surface modifier. Applying the well-settled meaning of "consisting essentially of" would lead to a construction in which the claimed particles could consist only of the medicament and surface modifier and unlisted ingredients that do not materially affect the invention.

As for the unlisted ingredients component of the construction, however, the patentees provided further definition. Applying "consisting essentially of" in the particular context of the proposed claims, they stated: "By 'consisting essentially of' it is meant that the claimed particles are essentially free of solvent contamination and other toxic materials…." (Ex. 5, '105 App., 11/18/1991 Amendment, p. 9.) The plain reading of this is that the applicants limited the permissible additional ingredients allowed by "consisting essentially of" only to trace amounts of solvents and other contaminants.[10] Abraxis has thus proposed the following construction: "consisting essentially of" means the claimed particles are composed only of crystalline medicament, surface modifier, and at most trace amounts of solvent or other contaminants.

[10] Our conversion of the negative phrase "essentially free…" to "trace amounts…" is intended only to provide a syntactical, positive construction to the phrase. No substantive change is intended.

Other portions of the '363 prosecution history, and the language of claim 1, further support this construction of "consisting essentially of." During prosecution, the applicants amended the claims, which at that point included only a range of amounts of surface modifier, also to specify that the crystalline medicament be present in a range of amounts:

> Claim 1 has also been amended to recite that the drug substance is present in a specific amount, i.e., 99.9-10% by weight based on the total weight of the particle. Support for this amendment can be found on page 12, lines 7-9 of the instant specification. (Ex. 5, '105 App., 11/18/1991 Amendment, p. 9.)

The cited support for that amendment, however, reveals *nothing* regarding the amount of medicament. Instead, the applicants pointed the Examiner to specification support for the amount of surface modifier in the particles: "The surface modifier can be present in an amount of 0.1-90% … by weight based on the total weight of the dry particle." (Ex. 5, '105 App. as filed, 12:7-9.) But the only way the specification's explication of the percentage range of the *surface modifier* can provide support for the claimed percentage range of the *crystalline medicament* is if the amount of the medicament can be derived by subtracting the amount of surface modifier from 100%.[11] Hence, the sum of the percentages of surface modifier and crystalline medicament must be 100%, leaving room only for trace amounts of solvents or other contaminants.

[11] If the sum of the crystalline medicament and surface modifier were held to be less than 100% of the particle's weight, the claims would be invalid for lack of written description. Based on the specification, a person of ordinary skill in the art would not have understood the inventors to be in possession particles in which the sum of the medicament and surface modifier constitutes less than the entire particle. *See, e.g., LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-45 (Fed. Cir. 2005).

This conclusion is consistent with the claim language. Unlike a composition claim that simply lists ingredients without specifying their amounts, claim 1 requires the sum of the surface modifier and crystalline medicament in the particles to constitute 100% of the particles by weight. Claim 1 requires "particles consisting essentially of 99.9-10% by weight of a crystalline medicament … and having a non-crosslinked surface modifier … in an amount of 0.1-90% by weight…." (Ex. 1, '363 patent, claim 1.) Thus, a particle containing 99.9% by weight of a crystalline medicament must also contain 0.1% by weight of a surface modifier. Conversely, a particle containing 10% by weight of a crystalline medicament must contain 90% by weight of a surface modifier. As we show above, the prosecution history establishes that this same relationship must be true over the entire claimed ranges of crystalline medicament and surface modifier – the sum of both always add up to essentially 100% of the particle weight.

In contrast, Elan's proffered construction contradicts the intrinsic evidence, turning the meaning of "consisting essentially of" on its head. Elan seeks to broaden its claims by rewriting "consisting essentially of" to mean "comprising," urging that "'consisting essentially of' means that the claimed particles, which *include* a 'crystalline medicament useful for treating cancer' and 'a surface modifier,' are essentially free of solvent contamination." (Joint Claim Construction Chart at 1 [D.I. 99] (emphasis added).) The key is Elan's use of the open-ended word "include." Elan's proposed construction is likely intended to permit the claims to cover particles containing crystalline medicament, a surface modifier, trace amounts of solvent contamination, and *anything else*, including amorphous medicament. This construction not only contradicts

the ordinary meaning of "consisting essentially of," it contradicts the limiting statements made by the applicants to secure allowance of Elan's patent.

Elan disclaimed compositions having amorphous medicament and distinguished such compositions over prior art to secure allowance of its claims. Elan should not be permitted to expand its claims to cover amorphous compositions now. *See Phillips*, 415 F.3d at 1316; *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1351 (Fed. Cir. 2001).

B. "Crystalline."

The '363 patent and its file history make clear that the crystalline state is the opposite of the amorphous state:

> 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." (Ex. 1, '363 patent, 2:28-34.)

> "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." (Ex. 5, '105 App., 11/18/1991 Amendment, p. 9.)

The specification states unequivocally that crystalline means "not amorphous." Except for its introduction of the word "phase" into its proposed construction (*see* below), Elan and Abraxis agree on that point.

The principal dispute is whether the Court's claim construction should also include an affirmative definition of "crystalline." Perhaps because the term was so basic to the inventors, the specification does not provide one. From the standpoint of claim construction principles, however, there can be little doubt that a person of ordinary skill would have understood what "crystalline" means, as the term was commonly used in

pharmaceutical science, chemistry, and other fields. (*See, e.g.*, Ex. 16, Webster's Third New Int'l Dictionary (1981) ("Crystalline: having a regular arrangement of the atoms in a space lattice – opposed to amorphous."); Ex. 17, E. Lien and L. Kennon, "Molecular Structure, Properties, and States of Matter," Remington's, Ch. 13, p. 184 ("The structure may be crystalline and lattice-like or noncrystalline, such as in plastic, glass, or gels, which are not lattice-like or only partly so.")[12]

We believe the Court's construction should include an affirmative definition of crystalline as well as a reflection against its opposite. We thus propose that "crystalline" means "having a regular arrangement of atoms [or molecules] in a space lattice, as distinguished from amorphous."[13] This definition is consistent with the intrinsic evidence that distinguishes the claimed particles from those having amorphous medicament. (Ex. 1, '363 patent, 2:28-34; Ex. 3, '684 patent, 3:33-37; Ex. 5, '105 App., 11/18/1991 Amendment, pp. 6, 9, 14; Ex. 4, '125 App., 10/29/92 IDS, p. 3, 9/15/93 Amendment, p. 4 and 9/13/1993 Amendment, Rule 132 Declaration by G. Liversidge, signed 9/8/93, p. 2; Ex. 5, '105 App., 11/18/1991 Amendment, Rule 132 Decl. of Eugene Cooper, signed 11/13/91, p. 2.)

Aside from failing to provide an affirmative definition of "crystalline," Elan creates ambiguity with its construction. Elan posits that "crystalline" means "in a

[12] *See also* Ex. 17, Remington's at 176 ("[The crystalline] form is characterized by a highly ordered arrangement of the molecules, associated with which is a three-dimensional periodicity. The repeating three-dimensional patterns, ideally depicted as lattices, are essential for X-ray structural analysis.").

[13] The phrase "or molecules" was inadvertently omitted from Abraxis's original construction of "crystalline" after "atoms," and is included here for completeness. We do not believe this modification will bear on the issues in this case.

nanoparticulate phase different from an amorphous phase." (Joint Claim Construction Chart at 9 [D.I. 99].) The term "nanoparticulate phase" finds no support in the patent or its file history. Indeed, the term "nanoparticulate phase" does not even appear in the specification. The word "phase" appears only in column 2 of the '363 patent, where it is used to mark the difference between the one or more "crystalline phases" of the drug substance in the particles and an "amorphous phase," that is, the difference between the crystalline and amorphous physical states. (Ex. 1, '363 patent, 2:28-33; *see also* Ex. 3, '684 patent, 3:33-37; Ex. 5, '105 App., 11/18/1991 Amendment, p. 9.) Elan's proposed construction should be rejected.

C. "Medicament Useful In Treating Cancer."

The Court should adopt Abraxis's proposed construction of the phrase "medicament useful in treating cancer" as "a medicine suitable for treating cancer." This definition is supported by the language of the claim and is consistent with the plain meaning of the term as understood by one of ordinary skill in the art. (Ex. 1, '363 patent, claim 1; Ex. 18, Am. Heritage Dictionary of the English Language (1981) ("Medicament" means "[a]n agent that promotes recovery from injury or ailment.").)

Elan's proposed definition as "an anticancer drug as recited in the Markush group of the claim," has two insurmountable defects. First, during prosecution of the '363 patent, the examiner explicitly refused to allow claims to an "anticancer" drug:

> The phrase "anti-cancer" agent is vague and indefinite as said phrase implies/suggests that said "phrase is a cancer cure." The examiner suggests the words "medicament" or "drug" be considered as an alternative for use of "anti-cancer" in said composition claims. A correction is requested.
>
> No claim is allowed.

(Ex. 4, '125 App., 12/19/1993 Office Action, p. 3.) Elan thus proposes to define "medicament" using the very phrase the patent examiner found to be "vague and indefinite."[14] Second, by limiting the definition of "medicament" only to the recited compounds in the Markush group of the claim, Elan renders either "medicament" or the entire Markush group superfluous. That is improper. *See Wright Medical Tech. v. Osteonics Corp.*, 122 F.3d 1440, 1444 (Fed. Cir. 1997) (rejecting a claim construction on the ground that it "would render the contested terms surplusage"). Moreover, Elan's use of the legal term of art "Markush group" will serve only to confuse the jury.

Moreover, while a "medicament" must be something suitable to administer to a patient, Elan would read that limitation right out of the claim, permitting that term to encompass ingredients that would render the claimed compositions toxic.[15] It appears that, despite all evidence to the contrary, Elan is hoping to establish that some intermediate in the production process has crystalline medicament and that, even though it could not be administered to patients, it nevertheless infringes the claims. This Court should thus reject Elan's proposed construction.

D. "Non-Crosslinked."

The Court should adopt Abraxis's proposed construction of "non-crosslinked" as meaning that "the surface modifier molecules are individually adsorbed on the surface of the crystalline medicament and are essentially free of intermolecular crosslinkages

[14] While it is true that the specification uses the term "anticancer agent," the specification was written before the examiner's rejection. Moreover, it is the claims that define the scope of the invention. *Vitronics Corp.*, 90 F.3d at 1582.

[15] Elan's open-ended definition of "consisting essentially of" comes into play here as well.

between surface modifier molecules." The specification of the '363 patent states that "the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages." (Ex. 1, '363 patent, 4:56-59; *see also* Ex. 3, '684 patent, 5:16-19.) Thus, the intrinsic evidence shows that the surface modifier molecules must be essentially free of intermolecular cross-linkages among themselves.

The specification also makes clear that the surface modifier molecules are "individually adsorbed" on the surface of the crystalline medicament (Ex. 1, '363 patent, 4:57-59), like small pins sticking out of a pin cushion. This reinforces the absence of crosslinkages between surface modifier molecules. Like the pins, the surface modifier molecules are not linked to each other.

Elan improperly defines "non-crosslinked" in terms of the relationship not only between the surface modifier molecules but also as to their relationship with the crystalline medicament. The plain language of the claim belies this construction. (Ex. 1, '363 patent, 14:11 ("non-crosslinked surface modifier"). As we explain above, the specification and prosecution history also evidence that the term "non-crosslinked" relates only to the interaction between surface modifier molecules. (Ex. 1, '363 patent, 4: 56-59; Ex. 3, '684 patent, 5:18-19 ("[T]he surface modifier [is] essentially free of intermolecular crosslinkages."); Ex. 4, '125 App., 9/13/1993 Amendment, p. 6 ("[C]laim 1 has been amended to recite . . . that the surface modifier is non-crosslinked.").)

Moreover, Elan proffers overlapping constructions for "non-crosslinked" and "adsorbed," suggesting both mean that the surface modifier and anticancer agent do not chemically react with one another. Elan's construction would render these two claim terms superfluous, which is impermissible. *See Wright Medical Tech.*, 122 F.3d at 1444.

[redacted]

Elan's proffered construction of "non-crosslinked" is an attempt to distract from the claimed requirement of no crosslinkages between surface modifier molecules; Elan misdirects the focus to the interaction between the surface modifier and the medicament.

E. "Surface Modifier."

The Court should construe "surface modifier" as Abraxis proposes, to mean "a substance that physically adheres to the surface of the crystalline medicament but does not chemically bond to it, and which modifies the surface properties of the crystalline medicament." Abraxis's construction comports with the plain meaning of the term "surface modifier" in the context of these claims: a substance that modifies the surface properties of the crystalline medicament. The balance of Abraxis's proposed definition is found in the specification of the '363 patent, (Ex. 1, '363 patent, 3:57-60) ("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."), and is supported by the other intrinsic evidence, (Ex. 3, '684 patent, 4:30-33) ("Useful surface modifiers are believed to include those which physically adhere to the surface of the drug substance but do not chemically bond to the drug.").

Elan's proposed definition of "surface modifier" as a "stabilizing agent capable of hindering aggregation, flocculation and/or agglomeration of the particles" is overly broad. (Joint Claim Construction at 17 [D.I. 99].) This over-breadth stems in part from Elan's proposal to define "surface modifier" by divorcing it from the surface of the claimed particles, which leads to absurd results. As Elan defines it, the "surface

modifier" could be concrete, for example, because concrete is capable of permanently separating the crystalline drug particles (thereby preventing aggregation, flocculation and/or agglomeration). The ocean could also be a "surface modifier," as infinite dilution of the particles would keep the drug particles from agglomerating.

Elan's definition is also overly broad because it defines a "surface modifier" as a "surface stabilizer" that "hinder[s]." That is inconsistent with the specification, which says that "[b]y stable it is meant that the dispersion exhibits *no* flocculation or particle agglomeration…." (Ex. 1, '363 patent, 7:37-39 (emphasis added).)

F. "Adsorbed on the Surface."

The Court should construe the term "adsorbed on the surface" in accordance with the intrinsic evidence to mean "physically adheres to the surface of the crystalline medicament and does not form a chemical bond with the crystalline medicament." The specification of the '363 patent defines adsorption as follows:

> 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. (Ex. 1, '363 patent, 3:55-60; *see also* Ex. 3, '684 patent, 4:28-33.)

Moreover, the patent's definition of "adsorbed on the surface" — physical adhesion without forming chemical bonds — comports with the ordinary meaning of that phrase as understood by persons of ordinary skill in the art. (Ex. 19, C. A. Hampel and G. G. Hawley, Glossary of Chemical Terms (2nd ed. 1982) ("Adsorption: attachment of the molecules … to the surface of another substance [ ]; these molecules form a closely adherent film or layer held in place by electrostatic forces that are considerably weaker than chemical bonds.").)

Elan, in contrast, defines "adsorbed on the surface" to mean "that the surface modifier physically contacts the surface of the 'crystalline medicament useful for treating cancer' and does not chemically react with such medicament." (Joint Claim Construction Chart at 21 [D.I. 99].) Elan's construction deprives the phrase "adsorbed on the surface" of its ordinary meaning, runs counter to the specification, and impermissibly seeks to broaden the scope of the claims.

First, neither the claims nor the specification uses the term "contacts" in the context of adsorption. Instead, the only time the specification speaks of "contact" is when discussing preparing the particles by grinding in conjunction with a surface modifier. (Ex. 1, '363 patent, 5:28-31.) Elan's "support" has nothing to do with adsorption.

Second, Elan's construction seeks to expand the breadth of the claims in the same way Elan's definition of surface modifier did — by divorcing the relationship between the surface modifier and the crystalline medicament. This relationship is set forth clearly by the plain language of claim 1: the particles consist essentially of a crystalline medicament and a surface modifier adsorbed on the surface thereof. (*See* Ex. 1, '363 patent, claim 1.) This language makes the meaning of the term "adsorbed" clear — the medicament and surface modifier stick to each other and form a particle. Defining "adsorbed" to encompass transitory "contact" ignores the fact that the surface modifier and medicament together form a particle. Elan should not be permitted to so broaden its claims.

G. "Sufficient to Maintain an Average Effective Particle Size."

The claimed particles of the '363 patent must "maintain an average effective particle size." The parties agree that "average effective particle size" means that at least

90% of the particles must have the number average particle size specified in the relevant claim. (Joint Claim Construction Chart at 22 [D.I. 99].) The parties also agree that the particles must contain an amount of surface modifier sufficient to maintain the average effective particle size of the particles. (*Id.*) The only substantive difference between the parties' constructions is that Abraxis's construction makes clear that the phrase "average effective particle size" is not limited to a particular time period or condition under which the particles must maintain their size. (*Id.*)

As the '363 patent explains, some combinations of surface modifier and drug substance create particles that exhibit flocculation or agglomeration. (Ex. 1, '363 patent, 7:5-41.) Some combinations may not exhibit flocculation or agglomeration immediately after the particle is formed, but will do so with the passage of time. (*Id.*) The conditions under which the particles are kept can also affect the propensity to flocculate or agglomerate. (*Id.* at 7:42-45.)

Although the specification provides examples that demonstrate the importance of these factors (*id*. at 7:37-45), the claims are not limited to a particular time period or conditions. We think it important that the definition reflect the patentees' choice *not* to limit the time period or conditions under which the particles must maintain their size.

H. "Surfactant."

The '363 patent provides no definition of the term "surfactant," which appears in dependent claim 12. The specifications of both the '363 and '684 patents state only that "[s]uitable surface modifiers" include "surfactants" and "[p]referred surface modifiers include nonionic and anionic surfactants." (Ex. 1, '363 patent, 3:61-66; Ex. 3, '684 patent, 4:34-39.) Thus, the patentees have left us no choice but to consult extrinsic evidence to determine the ordinary meaning of "surfactant" to one skilled in the art.

A "surfactant" is a molecule that consists of two basic parts: a hydrophobic part (a non-polar hydrocarbon chain) and a hydrophilic part (a polar functional group) that reduces interfacial tension between or among immiscible substances.[16] For example, as defined by L. Ulicky & T. J. Kemp, Comprehensive Dictionary of Physical Chemistry (1992):

> [S]urfactant: a substance able to lower the surface tension on an interface. A surfactant molecule consists of two basic parts: a hydrophobic (a non-polar hydrocarbon chain) and a hydrophilic one (a polar functional group. According to the type of polar group, we distinguish between *ionic* and *non-ionic surfactants.* (Ex. 20 (emphasis in original).)

(Ex. 20; s*ee also* Ex. 17, G. Zografi, "Interfacial Phenomena," Remington's, Ch. 19, p. 267 ("It has been shown that both a hydrophobic portion (alkyl chain) and a hydrophilic portion (carboxyl and carboxylate groups) are required for [surfactants'] surface activity."); Ex. 17, H. Schott, "Colloidal Dispersions," Remington's, Ch. 20, p. 293 ("Surfactants are amphiphiles because they contain a hydrocarbon (hydrophobic and lipophilic) portion and one or more ionic or otherwise strongly hydrophilic groups in the same molecule.").) Abraxis's proposed construction is consistent with the ordinary meaning of surfactant.

Elan defines a surfactant as a "stabilizing agent." This construction is unsupported by the intrinsic evidence and impermissibly expands the scope of claim 12. Elan's own evidence does not support its definition either. The phrase "stabilizing agent"

[16] The parties do not dispute that a "surfactant" must reduce interfacial tension between or among immiscible substances. Elan's functional definition is met by Abraxis's proposed construction.

does not even appear in the authorities that Elan cites.[17] Moreover, defining a surfactant as a "stabilizing agent" leads to the same absurd results as Elan's definition of surface modifier. For example, concrete would "stabilize" a drug particle, yet would be inappropriate for use in pharmaceutical compositions.

II. THE '025 PATENT.

A. "Without Eliciting Adverse Hemodynamic Effects."

The Court should construe "without eliciting adverse hemodynamic effects," which appears in both independent claims 1 and 13 of the '025 patent, to mean that "the claimed compositions do not elicit undesired effects on the physical aspects of blood circulation (such as reduction in arterial blood pressure and cardiac function) in substantially all of the mammals to whom the claimed compositions are administered."[18]

The parties dispute three issues in their constructions: First, should the Court read the term "without eliciting" out of the claim? Second, should the Court read the claim as being limited to avoiding adverse hemodynamic effects in a single mammal?

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[17] Indeed, Elan's evidence actually supports Abraxis's construction. For example, Elan's authority states that "surfactants tend to accumulate at interfaces because of their amphiphilic nature." (Joint Claim Construction Chart at 25 [D.I. 99].) Amphiphilic, in turn, means a molecule having a water-soluble polar head (hydrophilic) and a water-insoluble organic tail (hydrophobic). (Ex. 17, Remington's, Chapter 20, H. Schott, Colloidal Dispersions, p. 293 ("Surfactants are amphiphiles because they contain a hydrocarbon (hydrophobic and lipophilic) portion and one or more ionic or otherwise strongly hydrophilic groups in the same molecule.").)

[18] Although part of the preamble, both parties agree that "without eliciting hemodynamic effects" acts as a limitation on the '025 patent's claims, as it is "necessary to give life, meaning and vitality to the claims." *Poly-America, L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309-10 (Fed. Cir. 2004) (internal citations omitted); (Joint Claim Construction Chart, p. 26 [D.I. 99]).

Third, should the Court read a limitation into the claim that it extends only to certain species of mammals?[19]

As to the first dispute, Abraxis's construction is supported by the language of the claim itself — *viz.*, that administration of the claimed compositions does not elicit undesired effects. It also is supported by the specification of the '025 patent. (*See, e.g.*, Ex. 2, '025 patent, 1:48-65 ("intravascular administration of a suspensions <sic> to dogs causes significant cardiovascular dysfunction, such as reduction of arterial blood pressure and cardiac function…. [H]emodynamic effects of suspensions can be eliminated or at least substantially reduced by controlling the rate of infusion….").) In contrast, Elan's construction covers situations where the claimed method of administration reduces or eliminates *preexisting* adverse hemodynamic effects. Such a construction is at odds with the words of the claim itself (which only speaks of not "eliciting"), as well as the patent's abstract and specification. (Ex. 2, '025 patent, abstract ("Disclosed are methods of intravenous administration of nanoparticulate drug formulations to a mammal to avoid adverse hemodynamic effects."); *id*. at 1:48-64; *id*. at 7:17-20; *see also* Ex. 6, '754 App., 2/9/1998 Amendment, p. 4.)

As to the second dispute, Abraxis's construction reflects that the invention described in the patent is avoiding hemodynamic effects in substantially all of the mammals to whom the claimed compositions are administered. The invention of the '025 patent was a method of administering drug substances intravenously so as to avoid

[19] Abraxis's definition of "hemodynamic effects" also more closely comports with the ordinary meaning of that term than does Elan's. (Ex. 21, K.N. Anderson, L. E. Anderson, and W.D. Glanze, Mosby's Medical Dictionary (4th ed. 1994) ("[H]emodynamics [is] . . . the study of the physical aspects of blood circulation, including cardiac function and peripheral vascular physiology.").)

certain side effects – an invention that makes sense only in the general context of intravenous, mammalian drug administration. (*See, e.g.*, Ex. 2, '025 patent, 1:62-65 ("It has now been discovered that hemodynamic effects of suspensions can be eliminated or at least substantially reduced by controlling the rate of infusion and/or the concentration of the active drug in the suspensions."); *id*. at 7:17-20 ("[T]he present invention provides methods which can be utilized to deliver effective amounts of drugs without eliciting adverse hemodynamic effects in dogs.").) Further support is found in the patent's prosecution history. (*See, e.g.*, Ex. 6, '754 App., 2/9/1998 Amendment, p. 4 ("Applicants unexpectedly discovered that such adverse hemodynamic effects associated with intravenous administration of nanoparticulate formulations can be eliminated, or substantially reduced, by maintaining the intravenous infusion rate at less than 10 mg/[min].").) Elan's attempt to rewrite the invention should be rejected.

As to the third dispute, Abraxis's construction reflects the plain language of the claim, which is not limited to any particular species of mammal. If the patentees wanted to claim a method of treating only "sensitive mammals" then they could, and should, have claimed that. Then the Examiner would have had an opportunity to assess whether the specification supports that construction. The patentees did not do so then, and should not be permitted to do so now, particularly by reading a preferred embodiment, (*see* Ex. 2, '025 patent, 2:66-67), into the claims. *See Comark Commc'ns v. Harris Corp.*, 156 F.3d 1182, 1186 (Fed. Cir. 1998). The Court should therefore reject Elan's construction.

B. "Infusion Rate Not Exceeding 10 mg/min."

The primary dispute between the parties regarding the meaning of this claim term, which is recited in independent claims 1 and 13 of the '025 patent, is to what the "mg" in

"10 mg/min" refers. Abraxis relies on the plain language of the claims in proposing that the "mg" refers to the weight of the entire "drug composition." In contrast, Elan proposes that the "mg" be limited to the nanoparticles in the drug composition.

Elan's construction contradicts the plain language of claims 1 and 13, which both require "intravenously administering to said mammal an effective amount of a nanoparticulate drug composition at an infusion rate not exceeding 10 mg/min." It is clear from this language that the entire "nanoparticulate drug composition" and not merely the nanoparticulate particles in the composition, is the antecedent for "mg". "Nanoparticulate" is merely an adjective characterizing the "drug composition."

Claims 1 and 13 also make clear that the "nanoparticulate drug composition" is broader than just the particles. In claim 1, "said drug composition comprises: (a) particles consisting essentially of … a crystalline organic drug substance…; (b) a surface modifier…; and (c) a pharmaceutically acceptable carrier therefor." In claim 13, "said drug composition comprises: (a) particles … consisting essentially of … an organic drug substance entrapped in … liposome or colloidal polymeric material; and (b) a pharmaceutically acceptable carrier therefor."

The specification, moreover, discloses three different approaches to defining "mg" in the infusion rate: the drug composition, the particles, and the drug substance. (*See, e.g.*, Ex. 2, '025 patent, Abstract, 1:16-20, 2:11-20.) The patentees, however, chose to claim but one of those ways — the drug composition.

Abraxis's definition also addresses the meaning of "infusion," left silent by Elan. Here again, the specification does not define the term, compelling resort to extrinsic evidence to determine the ordinary meaning of this term. Authoritative medical

dictionaries show that an "infusion" is intravenously administered by means of gravity flow. (*See*, Ex. 21, Mosby's Medical Dictionary ("[I]nfusion: 1. the introduction of a substance, such as a fluid, electrolyte, nutrient, or drug, directly into a vein or interstitially by means of gravity flow."); Ex. 22, Dorland's Illustrated Medical Dictionary (28th ed. 1994) ("[I]nfusion: 3. the therapeutic introduction of a fluid other than blood, as saline solution, into a vein. Note — an *infusion* flows in by gravity….") (emphasis in original).)

The Court thus should adopt Abraxis's proposed definition of "infusion rate not exceeding 10 mg/min:" "intravenously administering the composition by means of gravity flow, at or below a rate of 10 milligrams per minute of the entire composition, including:

- For claim 1: (a) the drug substance, (b) the surface modifier, and (c) the pharmaceutically acceptable carrier.
- For claim 13: (a) the drug substance, (b) the liposome or colloidal polymeric material, and (c) the pharmaceutically acceptable carrier."

C. "Consisting Essentially of."

Abraxis's proposed construction of "consisting essentially of" for the '025 patent differs slightly from its proposed construction of that term for the '363 patent. For the '025 patent, we propose that it be construed to mean that "the claimed particles are composed only of a "crystalline organic drug substance," a "surface modifier/liposome/colloidal polymeric material,"[20] and at most a trace amount of solvents

[20] "Surface modifier" appears in claim 1, whereas "liposome or a colloidal polymeric material" appears in claim 13.

or other contaminants that would not change the basic and novel characteristics of the particles." Our '363 patent construction did not include the phrase "that would change the basic and novel characteristics of the particles." This difference is due to the differing intrinsic evidence for the two patents.

The '025 patent makes clear that the particles that are to be administered according to the claimed methods are a subset of those set forth in the '684 patent:

> Nanoparticles are well know[n] in the prior art, having been described, for example, in U.S. Pat. No. 5,145,684. These particles *consist of* a crystalline drug substance having a surface modifier adsorbed on the surface of the particles such that the average particle size is less than about 400 nm. (Ex. 2, '025 patent, 1:23-24 (emphasis added).)

As explained above, in Part I.A., during prosecution of the application that issued as the '684 patent, the applicants defined "consisting essentially of" to mean that "the claimed particles are composed only of 'crystalline medicament,' 'surface modifier,' and at most trace amounts of solvent or other contaminants." In addition to incorporating the related '684 patent, the '025 patent independently characterized its particles as "free of trace of any toxic solvents or solubilized heavy metal impurities…." (Ex. 2, '025 patent, 14:25-27.)

In contrast, Elan's proposed definition of "consisting essentially of" as used in claims 1 and 13 of the '025 patent is identical to that proposed by Elan for the '363 patent. And it fails for the same reasons. There is simply no support for Elan's attempt to rewrite "consisting essentially of" to mean "comprising."[21]

[21] Elan goes so far as to make its open-ended rewrite of "consisting essentially of" explicit in its construction of "infusion rate not exceeding 10 mg/[mL]," where Elan says that "the nanoparticles … are *comprised of* the 'organic drug substance'" and the surface modifier, liposome or colloidal polymeric material. (Joint Claim Construction Chart, at 28, 48 (emphasis added) [D.I. 99].)

D. "Crystalline."

The parties agree that the term "crystalline" has the same meaning in the '025 patent as it has in the '363 patent. (*See* Joint Claim Construction Chart at 9, 33 [D.I. 99].) That is because, as noted above, the definition of crystalline in both the '025 patent and the '363 patent stem from the description in the '684 patent — the '363 patent because its parent application issued as the '684 patent, and the '025 patent because it incorporates the crystalline particle compositions from the '684 patent. (Ex. 2, '025 patent, 1:23-24; Ex. 3 '684 patent, 3:33-37 ("The crystalline phase differs from a non-crystalline or amorphous phase which results from precipitation techniques, such as described in EPO 275,796."); *see also* '025 patent, 7:29-32 (same).) Thus, for the reasons set forth in Part I.B., above, the Court should construe "crystalline" as Abraxis proposes: "having a regular arrangement of atoms or molecules[22] in a space lattice, as distinguished from amorphous."

E. "Organic Drug Substance."

The parties agree that an "organic drug substance," as recited in claims 1 and 13 of the '025 patent, is limited to therapeutic and diagnostic agents. The parties further agree that support for this proposition is found in column 7 of the '025 patent: "The particles comprise a therapeutic or diagnostic agent (therapeutic agents are sometimes referred to as drugs or pharmaceuticals. The diagnostic agent referred to is typically a contrast agent such as an x-ray contrast agent but can also be other diagnostic materials)." (Ex. 2, '025 patent, 7:24-28.) However, there are three construction issues that the

[22] As noted above, "or molecules" was inadvertently omitted from Abraxis's original construction of "crystalline."

parties dispute: (1) whether the "organic drug substance" must be crystalline, (2) whether "organic" should be read out of the claims, and (3) whether the "organic drug substance" may be unsuitable for administration to a mammal.

As to the first issue, there is no support anywhere in the patent for a therapeutic or diagnostic agent that is not crystalline. (*See generally*, *id.*) Rather, as explained in the patent, "[t]he therapeutic [] agent exists as a discrete, crystalline phase." (*Id.* at 7:28-32.) Indeed, the patentees explicitly stated that "[t]he present invention will be described particularly in reference to nanoparticulate crystalline drug formulations…." (*Id.* at 1:66-67.) The phrase "organic drug substance" should therefore be limited to crystalline agents. *Honeywell Int'l, Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1319 (Fed. Cir. 2006) ("Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question.").

As to the second issue, Abraxis has proposed that "organic" is a material limitation of the claim. Because the patent nowhere defines "organic," Abraxis has proposed the ordinary meaning of that term – carbon-based. (*See* Ex. 16, Webster's Third New Int'l Dictionary (1981).) Elan's construction, on the other hand, not only fails to define "organic," it reads that term right out of the claim. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005), *cert. denied*, 546 U.S. 972 (2005) ("A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so.").

As to the third issue, Abraxis proposes that the "organic drug substance" must be "suitable for administration to a mammal," because the claim is drawn to methods of administering these substances to mammals. Elan's construction ignores that the claims are drawn to mammalian administration, and would permit administration of substances that would harm the mammal to whom they are administered.

Thus, the Court should construe "organic drug substance" as: "a crystalline carbon-based therapeutic or diagnostic agent suitable for administration to a mammal."

F. "Surface Modifier."

"Surface modifier" has the same meaning in the '025 patent that it does in the '363 patent, and the Court should adopt that definition for the same reasons discussed in Part I.E., above. (*See* Ex. 2, '025 patent, 1:23-24; Ex. 3, '684 patent, 4:30-33.)

Elan's proposed construction for "surface modifier" is "a surface active agent or stabilizing agent capable of hindering the aggregation, flocculation and/or agglomeration of the particles." (Joint Claim Construction Chart at 36 [D.I. 99].) This is the same as Elan's '363 patent construction but for the addition of "surface active agent or." The overlapping portion of Elan's construction fails for the reasons we discuss in Part I.E, above. The new "surface active agent" portion fails because, according to the patent, a surface active agent does not simply "hinder" flocculation as in Elan's construction, it "*prevents*" it. (Ex. 2, '025 patent at 1:37-38.)

G. "Adsorbed on the Surface."

The term "adsorbed on the surface" has the same meaning in claim 1 of the '025 patent that it does in the '363 patent. (*See* Ex. 2, '025 patent, 1:23-24; Ex. 3, '684 patent, 4:28-33.) Elan also proposes the same definition of "adsorbed on the surface" that it

proposed for '363 patent. The Court should thus adopt Abraxis's construction and reject Elan's for the same reasons discussed in Part I.F., above.

H. "Sufficient to Maintain an Effective Average Particle Size."

The parties have two disputes with respect to this term: (1) whether the particle size should be determined with reference to the weight average, and (2) whether the construction should reflect that the claimed particle size is not maintained for a specified time or under specified conditions.[23]

As to the first dispute, we note that although this term looks facially similar to language used in the claims of the '363 patent (*see* part I.G., above), it is different. In particular, the '025 patent defines particle size by "weight average" whereas the '363 patent defines it according to "number average." (*Compare* Ex. 2, '025 patent 15:39-44 *with* Ex. 1, '363 patent 4:65-5:1.) Abraxis's constructions reflect this definitional difference in the specifications. Elan's constructions, however, recite "number average" size for the '363 patent, but neglect to capture the "weight average" definition for the '025 patent. Instead, Elan merely parrots the phrase "effective average particle size" back to the Court in its proposed construction. (Joint Claim Construction Chart at 43 [D.I. 99].)

As to the second dispute, both the '363 patent and the '025 patent (by virtue of its incorporation of the '684 patent), explain that some combinations of surface modifier and

[23] Although the term "sufficient to maintain an effective average particle size" appears in both claims 1 and 13, it is construed in the Joint Claim Construction Chart only with respect to claim 1. Of course, the construction of this term is the same for both claims. *See Inverness Med. Switzerland GmbH v. Princeton Biomeditech Corp.*, 309 F.3d 1365, 1371 (Fed. Cir. 2002) ("A claim term used in multiple claims should be construed consistently.").

drug substance create particles that exhibit flocculation or agglomeration. (Part I.G., above; Ex. 3, '684 patent, 7:21-46.) Some combinations may not exhibit flocculation or agglomeration immediately after the particle is formed, but will begin to do so with the passage of time. (Part I.G., above; Ex. 2, '025 patent, 7:21-46.) Moreover, the '025 patent also recognizes that the conditions under which the particles are kept could affect the particle size. (*See, e.g.*, Ex. 2, '025 patent, 14:38-46.)

Although the specification of the '025 patent provides examples that demonstrate the importance of time and conditions to particle size, the claims are not so limited. As in Part I.G., above, we think it important that the definition reflect the patentees' choice *not* to limit the time period or conditions under which the particles must maintain their size.

I. "Colloidal Polymeric Material."

The term "colloidal polymeric material" appears only in claim 13. The intrinsic evidence offers nothing by which to understand the meaning of this phrase. In the absence of specification support, we turn to dictionaries to determine the meaning of the phrase. "Colloidal" means a stable suspension of microscopic particles, size range one nanometer to one micron, dispersed in a continuous medium.[24] (*See* Ex. 23, J. Walker and M. Cox, The Language of Biotechnology (1988); Ex. 19, C. A. Hampel and G. G. Hawley, Glossary of Chemical Terms (2d ed. 1982).) "Polymeric" means of, relating to, or consisting of a polymer. (*See* Ex. 16, Webster's Third New Int'l Dictionary (1981).) "Material" means "of, relating to, or consisting of matter." (*Id.*)

[24] It is implicit that the particles are composed of a different material than the continuous medium; a colloidal system necessarily is heterogeneous. (Ex. 17, Remington's, Chapter 20, H. Schott, Colloidal Dispersions, p. 271.)

Elan, in contrast, relies on only two passages from the specification, neither of which informs the construction of this term. (Joint Claim Construction Chart at p. 54-55.) One passage defines surface modifiers, a term found in claim 1, but not in claim 13. (*See* Ex. 2, '025 patent, 8:34-37.) The other discusses "colloids when used as *carriers* for an active drug." (*Id.* at 1:45-47 (emphasis added).) But as claim 13 makes clear, the "colloidal polymeric material" and the "pharmaceutically acceptable carrier" are two different portions of the claimed "drug composition." (*Id.* at claim 13.) Thus, Elan's construction should be rejected.

III. CONCLUSION.

For the foregoing reasons, this Court should adopt Abraxis's proffered claim constructions, and reject Elan's constructions.

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CERTIFICATE OF SERVICE

I, Karen E. Keller, Esquire, hereby certify that on May 21, 2007, 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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I further certify that on May 21, 2007**,** I caused a copy of the foregoing document to be served by e-mail on the above-listed counsel of record and on the following non-registered participants in the manner indicated:

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