IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ELAN PHARMA INTERNATIONAL LIMITED,	)	**REDACTED: PUBLIC VERSION**
Plaintiff,	)	
v.	)	C.A. No. 06-438-GMS
ABRAXIS BIOSCIENCE, INC.,	)	
Defendant.	)	

PLAINTIFF ELAN PHARMA INTERNATIONAL LIMITED'S ANSWERING CLAIM CONSTRUCTION BRIEF

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I. Preliminary Statement

This case is about stable, therapeutically effective drug nanoparticles for treating cancer, and safer methods of administering such drug nanoparticles. While the parties skirmish about the meaning of multiple claim terms, the issues come down to this: what is a "crystalline medicament useful for treating cancer;" what is a "non-crosslinked surface modifier;" and what does "an infusion rate not exceeding 10 mg/min" mean?

[redacted]

Abraxis protests that it could not infringe either asserted patent by contending that the term "crystalline" is dispositive. Abraxis has sought to establish a non-infringement position by representing that Abraxane® is amorphous. Moreover, Abraxis contends that

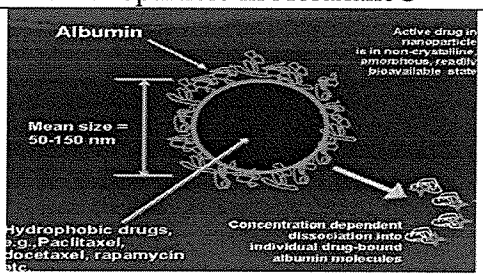
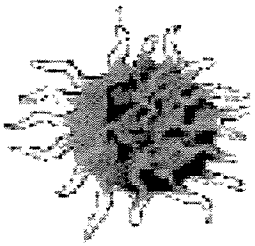
infringement by an intermediate product created during the manufacturing of Abraxane® could not possibly be a viable theory.

> We have provided Elan now with voluminous information, both of a public and a very confidential nature, that demonstrate that Abraxane®, the product they accused of infringement, has only amorphous particles and not crystalline particles. Our contention is that that is all that matters in this context, the final product. It doesn't matter how we got there. D.I. 47, Feb. 16, 2007 Discovery Telecon. Tr. 3:17-24; *see also id.* at 7:20-23.

Abraxis has engaged in a public relations campaign to attach the word "amorphous" to Abraxane® at every opportunity. D.I. 21 Nov. 6, 2006 Rule 16 Telecon. Tr. at 7:15-16 (stating that Abraxane® is "amorphous, not crystalline"); *see also* D.I. 11, Oct. 30, 2006 Joint Status Report at 3 (stating that "the paclitaxel in Abraxane® is in its amorphous form"). The problem here is two-fold. First, we do not yet have a claim construction. Second, by asserting that "Abraxane®" is amorphous, Abraxis confuses apple pie with apples: the infringement allegation in this case is about constituent nanoparticles in Abraxane®, not Abraxane®, but all of Abraxis's "voluminous information" related to the product, not the nanoparticles. Thus, Abraxis's Opening Brief, which reads more as a premature attempt at a motion for summary judgment than an effort to properly define claim terms, falls short on both accounts.

Abraxis contends that the parties' definitional disputes can best be evaluated when viewed in light of the *accused product*. Abraxis Br. at 7 (citing *Wilson Sporting Goods Co. v. Hillerich & Bradsby Co.*, 442 F.3d 1322, 1326-27 (Fed. Cir. 2006)).

Elan submits that the dispute can best be seen when viewed against the *particles* contained in the accused product.

Abraxis's Nanoparticle in Abraxane®[1]	Elan's Nanoparticle of Patents-In-Suit[2]
	

While Elan is content to follow the Court's scheduling order, it also wants to set the record straight. The claimed invention of the '363 Patent is directed to particles of less than 1000 nm, *i.e.,* nanoparticles, which are made up of a non-crosslinked surface modifier adsorbed to a crystalline medicament useful in treating cancer. Abraxane® is made up of nanoparticles of human albumin adsorbed to a core of paclitaxel. *See, e.g*, Ex. 19 at A0257 (Prescribing Information for Abraxane®, p. 1). The ratio of the human albumin to the paclitaxel is roughly 9:1 by weight. *See id.* Human albumin is amorphous. Ex. 20 at A0284 [redacted]. Therefore it is no surprise, and of no significance that the Abraxane® product as a whole – which contains amorphous surface modifier and a significant excess of

[1] Ex. 41 at A0792 (Nanoparticle Albumin Bound (nab) Technology: A nanotechnology platform for biologically interactive drug delivery and targeting, Desai, N., Abraxis Bioscience, p. 2). (Elan notes that all references to "Ex." refer to the exhibits submitted in the Joint Appendix.

[2] Ex. 42 at A0804 (Nanocrystals: The Product of Nanonization, ELANP0031797).

amorphous human albumin – appears amorphous. The issue here is whether the *particles* in Abraxane® meet the limitations of the claims of the '363 Patent; an issue that necessarily depends on the Court's construction of the claims and its consideration of relevant evidence.

Abraxis, through its counsel, initially conceded the possibility that it may not have understood these issues:

> If we are wrong, Your Honor, about this being straightforward, then the facts are going to be quite complicated. D.I. 21, Nov. 6, 2006 Rule 16 Telecon. Tr. at 5:13-16.

The progress of this case demonstrates, however, that Abraxis departed from this nuanced view in favor of an inflexible position of certainty, albeit without the benefit of a claim construction or the right facts. More recently, Abraxis indicated a new and refreshing evolution in its understanding of the issues. Abraxis now characterizes Abraxane® as being "*overwhelmingly* amorphous," Abraxis Br.[3] at 1, suggesting that the issues in this case are not so "straightforward" as it once assumed. Indeed, when the claims are properly construed based primarily on the intrinsic evidence, the basis for Elan's assertion that Abraxane® directly or indirectly infringes these patents, either literally or under the doctrine of equivalents, become self-evident.

[3] Citations to "Abraxis Br." refer to D.I. 105, May 11, 2007 Abraxis's Opening Claim Construction Brief. Similarly, citations to "Elan Br." refer to D.I. 104, May 11, 2007 Elan's Opening Claim Construction Brief.

II. Summary of Argument

While Abraxis quietly shifts its position, it loudly accuses Elan of stretching its claim construction propositions to sustain its infringement position in this case. *See* Abraxis Br. at 2 ("Indeed, [Elan's] constructions demonstrate how far Elan must stretch in order to attempt to sustain its infringement allegations"). Elan bases its constructions almost exclusively on the intrinsic evidence, which is no "stretch." Elan utilizes extrinsic evidence to support the intrinsic evidence, except in the case of a disputed term that was well known in the art at the time of the invention. By contrast, Abraxis selectively looks to extrinsic evidence to support its constructions and its story of non-infringement. Indeed, Abraxis goes too far by submitting an expert's declaration, disregarding the Court's clear instruction not to submit expert testimony.[4]

> THE COURT: Let me step aside for a moment. A notice, a proposal for deposition for any claim construction declaration. That strikes me as the possible presentation of extrinsic evidence, which I don't take in a patent case. Is that what was decided to do?
>
> COUNSEL FOR ELAN: Yes.
>
> THE COURT: You can eliminate that.
>
> D.I. Nov. 6, 2006 Rule 16 Telecon. Tr. at 11:18-24.

As advised by the Federal Circuit, the Court should consider Abraxis's claim construction based primarily on extrinsic evidence, including the unsolicited expert

[4] Neither party has sought leave of the Court to submit expert declarations in this claim construction. Abraxis fails even to ask the Court's indulgence to consider the proffered Declaration of Dr. Mansoor Amiji. Plaintiff therefore requests that the Court, in accordance with its instructions to the parties, strike the Amiji Declaration unless and until it invites or permits expert declarations or testimony from both parties to assist the Court in construing the claims.

declaration, with a keen eye towards skepticism. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1319 (Fed. Cir. 2005) (en banc), *cert. denied*, 126 S.Ct. 1332 (2006).

In sum, Abraxis's proposed claim construction provides strained definitions of the claim terms based primarily on extrinsic evidence to support its strident non-infringement position.

III. Argument[5]

A. U.S. Patent No. 5,399,363 ("the '363 Patent")

1. "Consisting Essentially of" Means That the Nanoparticles Are Essentially Free of Solvent Contaminants and Does Not Preclude Additional Ingredients That Would Not Materially Affect the Novel and Basic Characteristics of the Claimed Invention

The proper construction for the term "consisting essentially of" is that the particles contain: (a) a crystalline medicament useful in treating cancer; and (b) a surface modifier, but not contaminating amounts of solvent. This interpretation is consistent with the case law. *PPG Industries v. Guardian Industries Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998) ("'consisting essentially of' means that the claimed [] invention includes the ingredients specifically identified in the claim and that other ingredients may also be present in the claimed invention, although not specifically identified in the claim, so long as those other unlisted ingredients do not have a material effect on the basic and novel characteristics of the [invention]"). To exclude ingredients that have a material effect on

[5] For ease of reference, Elan's response to Abraxis's claim construction brief is set forth in the order presented in Abraxis's Opening Claim Construction Brief.

the basic and novel characteristics of the invention, as the case law instructs, we consider those characteristics in the context of the '363 Patent.

The proper source for the basic and novel characteristics of the claimed invention is the specification. *See, e.g., AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1239 (Fed. Cir. 2003) ("To determine [the basic and novel] properties we need to look no further than the present specification."). The '363 Patent specification noted that "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." Ex. 1 at A0002; '363 Patent 1:29-33. The specification then teaches that enhanced efficacy and reduced toxicity are the novel and basics characteristic of the claimed invention:

> We have discovered that anticancer compositions comprising anticancer agents in the form of surface modified nanoparticles exhibit **reduced toxicity** and/or enhanced efficacy. Ex. 1 at A0002 ('363 Patent 1:44-48) (emphasis added).
>
> [T]here is provided a method of enhancin g 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. *Id.* ('363 Patent at 1:61-65) (emphasis added).
>
> It is an advantageous feature of this invention that anticancer compositions are provided exhibiting **reduced toxicity**. *Id.* ('363 Patent 1:66-68) (emphasis added).
>
> It is another advantageous feature of this invention that anticancer compositions are provide exhibiting **improved efficacy**. *Id.* ('363 Patent 2:1-3) (emphasis added).

The specification goes on to point out that these basic and novel properties are the result of the particle size (nanoparticle) and surface modifier present in the nanoparticles. *Id.* at A0002 ('363 1:61-65; 2:19-21).

The prosecution history further supports and elaborates on these properties.

> The particles of this invention have been formulated into anticancer compositions which demonstrate enhanced efficacy and/or **reduced toxicity** and which can be administered by IV bolus injection. Ex. 7 at A0068 ('363 Patent Prosecution History, Paper No. 6/a, Sept. 9, 1993 Amendment, p. 5) (emphasis added).
>
> The crystalline particles described in U.S. Patent Application Serial No. 908,125 are **essentially free of solvent contamination**. emphasis added. *Id.* at A0072 (Paper No. 7, Liversidge Decl., p. 2) (emphasis added).
>
> By "consisting essentially of" is meant that the claimed particles are **essentially free of solvent contamination and other toxic materials . . . .**" Ex. 6 at A0046 ('684 Patent Prosecution History, Paper No. 10a, Nov. 18, 1991 Amendment, p. 9) (emphasis added).

Elan agrees with the legal meaning of "consisting essentially of" set forth by Abraxis. Abraxis Br. at 14-15. Elan agrees that "consisting essentially of" precludes the addition of any unidentified claim elements, except at most trace amounts of solvent and other contaminants.[6] Abraxis Br. at 15. Abraxis errs, however, in asserting that "the particles are composed *only of* the 'crystalline medicament,' 'surface modifier,' and at most trace amounts of solvent or other contamination." D.I. 99, April 20, 2007 Joint Construction Chart p. 1. Despite citing the correct law, Abraxis instead offers a

[6] Elan does not dispute that "consisting essentially of" excludes contaminants that have a material effect on the basic and novel characteristics of the invention.

construction that would be appropriate for the limitative transitional phrase "consisting of," but not for "consisting essentially of."

In *Conoco, Inc. v. Energy & Environ. Int'l. L.C.*, 460 F.3d 1349 (Fed. Cir. 2006), the Federal Circuit upheld literal infringement of a claim even though the claim recited "consisting of" language and the accused product included elements not recited in the claim. The Court noted that "although 'consisting of' is a term of restriction, that restriction is not absolute." *Id.* at 1360. Thus, "consisting of" signals that the scope of the claim is closed to unclaimed ingredients, with the exception of impurities. *Id.* Abraxis's contention that the nanoparticles contain only the crystalline medicament useful for treating cancer and the surface modifier, and at most trace contaminants, is just such a "consisting of" construction. The intrinsic evidence coupled with the longstanding legal interpretation of the term "consisting essentially of" supports a conclusion which would allow for particles that are "essentially free of solvent contamination" as proposed by Elan.

Abraxis asserts that the sum of: (a) a "crystalline medicament useful in treating cancer;" and (b) a "surface modifier" must equal 100%. *See* Abraxis Br. at 16-17. Abraxis's argument relies on an amendment made to the "drug substance" of the particles claimed in the '684 Patent. This amendment added the range of 99.9 - 10% by weight to the claim. Abraxis Br. at 16. However, Abraxis is improperly reading limitations into the claims. Neither the '684 Patent claims nor the '363 Patent claims *require* the sum to equal 100%. The range limitations are consistent with the sum not *exceeding* 100%. Neither the claim amendment nor the part of the specification supporting that amendment

require the sum of the "crystalline medicament useful in treating cancer" and the "surface modifier" claimed in the '363 Patent to always equal 100%.

Abraxis's argument is also flawed because it fails to consider that the invention claimed in the '684 Patent is different from that claimed in the '363 Patent. Specifically, the claim amendment affected a claim term (drug substance) not recited in any claim of the '363 Patent. *See, e.g., Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1027 (Fed. Cir. 1997) (finding that statements made in the parent application must be confined to their proper context and properly acknowledge the distinctions between claims directed to different embodiments.).

Abraxis's contention also contradicts its own proposed definition of "consisting essentially of." If the particle includes trace amounts of solvents and other contaminants, as proposed by Abraxis, then the sum of the "medicament useful in treating cancer" and the "surface modifier" of the '363 Patent could not equal 100%.

Abraxis also contends that the claims of the '363 Patent would be invalid if they are not construed to require the sum to equal 100%. Abraxis Br. at 16 n.11 (citing *LizardTech, Inc. v. Earth Resource Mapping, Inc.* 424 F.3d 1336, 1344-45 (Fed. Cir. 2005)). Suffice it to say that this convoluted assertion is needlessly confusing and the case it cites is irrelevant.

Lastly, Abraxis argues that Elan disclaimed compositions having any amount of amorphous medicament during prosecution. *See* Abraxis Br. at 18 ("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.") Abraxis must provide evidence that amounts to a clear and unmistakable intentional disavowal of claim scope to support its argument. *Omega Eng'g v. Raytek Corp.*, 334 F.3d 1314, 1326 (Fed. Cir. 2003) (disclaimers based on "disavowing actions or statements during prosecution [must] be both clear and unmistakable"). It provides no evidence at all. Abraxis Br. at 18.

For the foregoing reasons, Abraxis's proposed claim construction that employs the closed term "only" should be rejected.

2. "Crystalline" When Construed in Context Qualifies the "Medicament Useful in Treating Cancer" as Having a Nanoparticulate Phase Different Than an Amorphous Phase

Elan has sought to construe "crystalline medicament useful in treating cancer" as a single term. Elan bases its position on the language of the claims, *See* Elan Br. at 18, and the description in the specification. *See* Ex. 1 at A0002 ('363 Patent at 1:45-46) ("anticancer agents in the form of surface modified nanoparticles"); *id.* at 2:19 ("surface modified anticancer nanoparticle"). The prosecution history also supports Elan's construction. *See* Elan Br. at 17. All of these sources establish that these words should be considered as a single term.

Considering the term "crystalline" in isolation nonetheless requires consideration of the context of the nanoparticle technology and the claimed invention. *See, e.g.*, *Network Commerce, Inc. v. Microsoft Corp.*, 422 F.3d 1353, 1359 (Fed. Cir. 2005) (citing *Phillips*, 415 F.3d at 1314 (finding it proper to rely on a term's "particular meaning in a field of art," when construing claims)); *see also Datamize, LLC v. Plumtreee Software, Inc.*, 417 F.3d 1342, 1349 (Fed. Cir. 2005) (holding that a disputed claim phrase should

be considered in the context of the claim). Accordingly, Elan submits that the term "crystalline" is properly construed in context with "medicament useful in treating cancer." It means that the medicament useful in treating cancer has a nanoparticulate phase that is different from an amorphous phase.

It should go without saying that "crystalline" refers to a material in the solid state.

> The most significant physical property of the solid state is the high degree of order in which substances such as metals and minerals exist. 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. Ex. 29 at A0363 (Remingtons's Pharmaceutical Sciences (17th ed. 1985), p. 184).

The other pharmaceutically important states of matter are liquid and gas. *Id.* at A0357. There are significant differences in the behavior of molecules in the solid state compared to liquid or gaseous states. *Id.* Accordingly, to the extent "crystalline medicament useful in treating cancer" is construed as a single phrase, or crystalline is construed separately, they both necessarily require that the anticancer drug be evaluated in the solid state. In other words, a nanoparticulate phase is a solid phase. This is in contrast to a solution or emulsion, *i.e.*, liquid phase, characteristic of the prior art preparations of poorly water soluble drugs. Ex. 38 at A0476 (U.S. Patent No. 5,091,188 at 3:1-59); *see also Novartis Pharm. Corp. v. Abbott Laboratories*, 375 F.3d 1328, 1330 (Fed. Cir. 2004) (discussing solubilization of cyclosporin in a microemulsion). The nanoparticulate phase is also different from the solvent-contaminated prior art discussed above.

In contrast to Elan, Abraxis extracts "crystalline" from the claim and it proffers a dictionary definition of the term:

> [C]rystalline: having a regular arrangement of the atoms in a space lattice." *See* Abraxis Br. at 19 (quoting Ex. 28 at A 0334, Webster's Third New Int'l Dictionary (1981)).

Abraxis further contends that "crystalline" means "the opposite of the amorphous state," Abraxis Br. at 18, as if the issue were simply a binary one. Abraxis provides no real support for its position from either the patent or the field of art. These sources establish that absolute crystallinity is an ideal, not a reality. Thus, the presence of some amorphousness in the nanoparticle would not offend the proper construction of "crystalline."

Both parties consider the term "crystalline," however, by relation to "amorphous." *Compare* Abraxis Br. at 18 ("[t]he specification states unequivocally that crystalline means 'not amorphous'") *with* Elan Br. at 16 ("an anticancer agent as recited in the Markush group of the claim in a nanoparticulate phase, different from an amorphous phase"). Both parties cite to the same quotation from the specification of the '363 Patent.

> The anticancer agent is present in one or more discrete crystalline phases and further that the crystalline phase differs from an amorphous, i.e., non-crystalline phase. Ex. 1 at A0002 ('363 Patent 2:28-34).

Thus, a proper appreciation of the term "crystalline" requires consideration of the meaning of the word "amorphous." The plain and ordinary meaning of the term "amorphous" is:

> [A]morphous: without definite form or shape: formless; without real or apparent crystalline form; without crystal

> structure. Ex. 42 at A 0781 (Webster's Third New Int'l Dictionary (1986)).

Consistent with the plain and ordinary meanings of these terms, a "nanoparticulate phase different than an amorphous phase" means that the medicament useful in treating cancer has at least one phase that includes a regular arrangement of atoms in a space lattice or apparent crystalline form. This phase is different than an amorphous phase devoid of *any* structure, *i.e.,* without real or apparent crystalline form. Indeed, the specification of the '363 Patent supports this construction. *See* Ex. 1 at A0002 ('363 Patent 2:29-30) (reciting that the anticancer agent is present in one or more discrete crystalline phases). Accordingly, Elan's construction is supported by *all* of the evidence, including Abraxis's.

3. A "Medicament Useful in Treating Cancer" Is an Anticancer Agent Recited in the Claim

Claim 1 of the '363 Patent clearly states that the "medicament useful in treating cancer" is a specified anticancer agent. The language of the claim requires it. Claim 1 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 at A0008 and A00010 ('363 Patent, 14:7-28).

Instead of construing the term in accordance with the express words of the claim, Abraxis resorts to extrinsic evidence:

> "Medicament" means "[a]n agent that promotes recovery from injury or ailment." Abraxis Br. at 20 (quoting Ex. 30 at 0440, Am. Heritage Dictionary of the English Language (1981)).

Abraxis proposes that the "medicament useful in treating cancer" is "a medicine suitable for treating cancer." Abraxis Br. at 20. Abraxis argues that "a 'medicament' must be something suitable to administer to a patient." Abraxis Br. at 21.

The "crystalline medicament useful in treating cancer" means an anticancer active pharmaceutical ingredient ("API") listed in the claim. Because it is part of the claim, this API is present as a nanoparticulate solid. The nanoparticulate nature of the medicament provides the bioavailability necessary to improve the drug's therapeutic index. *See* Ex. 1, A0002 ('363 Patent, 2:18-26). As noted above, the claim language permits no other conclusion.

Together with a surface modifier, the nanoparticulate medicament useful for treating cancer forms the nanoparticulate medicine with sufficient stability for use in therapy, as recited in claims 8 and 9 of the '363 Patent. Claim 8 is directed to an

anticancer composition comprising the particles, and claim 9 is directed to a method of treatment using the *composition* of claim 8. Ex. 1 at A0008 ('363 Patent 14: 51-55). These differences between claim 1 and claims 8 and 9 refute Abraxis's argument. *See, e.g., Phillips*, 415 F.3d at 1314 (relying on *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1538 (Fed. Cir. 1991) (differences among claims can be a useful guide to understanding the meaning of particular claim terms)).

Abraxis's extrinsic evidence also supports Elan's position because it establishes that a "medicament useful in treating cancer" is a chemical compound that promotes recovery from cancer. It is an anticancer agent selected from the compounds listed in the claim itself.

Abraxis spins the intrinsic evidence, including, for instance, the prosecution history of the '363 Patent, to try to support its position. However, the specification consistently describes the compounds recited in the claim as anticancer agents. During prosecution, the Examiner suggested replacing "anticancer agent" with "medicament." Ex. 7 at A0076 ('363 Patent Prosecution History, Paper No. 9, Dec. 2, 1993 Office Action, p. 3). Instead of merely substituting "medicament" for "anticancer agent" in the claim, however, the inventors stated their intent clearly:

> Responsive to the Examiner's suggestion, the claims have been amended to recite that **the anticancer agent is a specific medicament useful in treating cancer susceptible to treatment with such medicament.** *Id.* at A0079 (Paper No. 12B, June 22, 1994 Amendment, p. 2) (emphasis added).

Abraxis finally contends that a Markush group renders the term "medicament useful in treating cancer" superfluous with the listed anticancer agents in the claim. *See* Abraxis Br. at 21. Abraxis's position is legally incorrect.

> A Markush group is a sort of homemade generic expression covering a group of two or more different materials (elements, radicals, compounds, etc.), mechanical elements, or process step that will work in the combination claimed. Ex. 43 at A0783 (Landis on Mechanics of Patent Claim Drafting, (3rd ed. 1990), § 50, p. 149).
>
> A typical example, [is]:...a **halogen** selected from the group **consisting of chlorine and bromine**." *See Id.* (emphasis added).

The Markush group is a well-established patent drafting technique. Abraxis's contention, if correct, would render antecedent terms in all claims drafted in this style superfluous. In the above example, the term halogen would be superfluous with the recited halogens: chlorine and bromine.

Furthermore, Abraxis's reliance on *Wright Medical Tech. v. Osteonics Corp.*, 122 F.3d 1440, 1444 (Fed. Cir. 1997) in support of its contention is confusing at best. The holding in *Wright Medical* had nothing to do with a Markush group; none of the claims at issue in that case were drafted in the form of a Markush group.

Lastly, the case law is well-settled that a Markush group by its very nature is closed. *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1372 (Fed. Cir. 2005). Accordingly, the only proper way to interpret the phrase "medicament useful in treating cancer" is to construe it to mean an anticancer agent as recited in the claim.

4. "Non-Crosslinked" Means the Surface Modifier Does Not Chemically React With Itself to Form a Crosslinked Shell or Matrix Encapsulating the Medicament Useful in Treating Cancer or Crosslinking of Surface Modifier and Medicament

The proper construction of the term "noncrosslinked" is evident from the prosecution history of the '684 Patent. *See Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp.*, 93 F.3d 1572, 1580-1581 (Fed. Cir. 1996) (construing term in accordance with what the prosecution history as a whole would convey to one of ordinary skill about what the inventor intended).

During prosecution, the Examiner alleged that prior art, Oppenheim (4,107,288) and Motoyama (4,540,602) would render certain pending claims obvious. Ex. 17 at A0215-A0216 ('684 Prosecution History, Paper No. 4, Office Action, p. 6-7). In response, the inventors amended claim 1 "to specify that the 'surface modifier' is ***non-crosslinked*** and present in a specific amount, i.e., 0.1-90% by weight based on the total weight of the particle." Ex. 7. at A0039 ('684 Prosecution History, Amendment dated 11/18/1991, p.2) (emphasis added). The inventors also remarked that the Motoyama prior art reference involved crosslinking reactions, and that the Oppenheim prior art reference incorporated its pharmaceutically active agent in a crosslinked matrix.

> Motoyama is primarily directed to processes (radically different then applicants' method) which involve emulsification steps and/or heating and gelling, i.e., crosslinking reactions. *Id.* at A0052 ('684 Prosecution History, Amendment dated 11/18/1991, p. 15).
>
> * * *
>
> Oppenheim teaches particles in the size range from about 10 to about 1000 nm which comprise a crosslinked matrix of macromolecules. A pharmaceutically active material

> can be supported on or incorporated into the matrix. Such particles require the presence of a crosslinker or hardening agent and differ substantially form applicants' claimed particles. Oppenheim's crosslinkers, such as formaldehyde or glutaraldehyde, like polymerization initiations, can be toxic and must be removed from solution (col. 4, lines 28-42). *Id.* at A0053-A0054 ('684 Prosecution History, Amendment dated 11/18/1991 16-17).

The inventors clarified that "***to further distinguish applicants' claims from the teaching of Oppenheim***, claim 1 has been amended to recite that the particles include a non-crosslinked surface modifier." *Id.* at A0054 ('684 Prosecution History, Amendment dated 11/18/1991, p. 17) (emphasis added).

The inventors' statements made during prosecution of the '684 Patent clearly indicate that the term "non-crosslinked" was introduced into the claim to differentiate the inventive particles having a surface modifier adsorbed to the surface of the medicament useful in treating cancer from the prior art, which disclosed crosslinking reactions or adding a crosslinker agent to form an encapsulating shell or a matrix.

Abraxis's proposed definition that "noncrosslinked" means the "surface modifier molecules are individually adsorbed on the surface of the crystalline medicament and are essentially free of intermolecular crosslinkages between surface modifier molecules" is ambiguous at best. Abraxis Br. at 21-22. Information about Abraxane® cited in Abraxis's opening brief provides some clarity. *See* Abraxis Br. at 7. [redacted] Consequently, Abraxis seeks a construction in which such albumin [redacted] to be the same as a shell or matrix surrounding the drug core. Furthermore, to the extent that Abraxis's construction allows

for some [redacted] ("*essentially free* of crosslinkages"), it offers no indication of the extent of permissible [redacted] (or crosslinking). In contrast, Elan's definition would exclude crosslinking to the extent of forming a shell or matrix. Accordingly, the Court should adopt Elan's construction, which is consistent with *all* of the evidence.

5. A "Surface Modifier" Is a Stabilizing Agent Capable of Hindering Aggregation, Flocculation and/or Agglomeration of the Particles

Elan's proposal that a surface modifier is a stabilizing agent capable of hindering aggregation, flocculation, and/or agglomeration of the particles is indisputably supported by the language of the claims themselves: "surface modifier adsorbed on the surface thereof in an amount … sufficient to maintain an average effective particle size…" Ex. 1 at A0002 ('363 Patent, 14:11-14). The specification teaches the same:

> This application is a continuation-in-part of U.S. patent application Ser. No. 647,105, filed Jan. 25 1991, now U.S. Patent No. 5,145,684, **the disclosure of which is hereby incorporated by reference in its entirety**. Ex. 1 at 0002 ('363 Patent, 1:7-11) (emphasis added).
>
> ...the surface modifier **hinders the flocculation and/or agglomeration of the particles** by functioning as a mechanical or steric barrier between the particles, minimizing the close, interparticle approach necessary for agglomeration and flocculation. Alternatively, if the surface modifier has ionic groups, stabilization by electrostatic repulsion may result." Ex. 5 at A0032 ('684 Patent 8:22-30)(emphasis added).
>
> The amount and type of surface modifier was sufficient to provide colloidal **stability to agglomeration**...." *Id.* at A0033 ('684 Patent 9:53-55).

> The dispersion was prepared in the absence of a surface modifier and a **post addition of Lecithin**[7] **and a sonication step were required to stabilize the dispersed phase of Steroid A**[8] **and prevent agglomeration** and rapid sedimentation. *Id.* at A0034 ('684 Patent 11:43-47) (emphasis added).
>
> A drop of the above dilute slurry was ....compared to the slurry similarly diluted with water only (**no surface modifier). The unmodified dispersion exhibited extensive particle agglomeration.** *Id.* ('684 Patent 12:8-14) (emphasis added).

Abraxis's asserts that Elan's definition would include "cement" and the "ocean" as potential surface modifiers. Abraxis Br. at 24. However, one of skill in the art would certainly understand that the surface modifier could be neither "cement" nor the "ocean," as these surface modifiers would render the particle unsuitable for its intended purpose, treating cancer.

They would also not be the "adsorbed on the surface" as required by the claim (discussed below). Abraxis's construction offers almost the same definition for "surface modifier" and "adsorbed on the surface." Thus, Abraxis's construction should be rejected in favor of Elan's.

6. "Adsorbed on the Surface" Means That the Surface Modifier Physically Contacts the Surface of the Medicament Useful in Treating Cancer

The proper construction for the phrase "adsorbed on the surface" is that the surface modifier physically contacts the surface of the medicament useful in treating cancer, but does not bond to it.

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[7] Lecithin is disclosed to be a suitable surface modifier. Ex. 5 at A0030 ('684 Patent 4:40).

[8] Steroid A is disclosed to be a suitable drug substance. Ex. 5 at A0030 ('684 Patent 4:20).

> The particles of the 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 at A0003 ('363 Patent 3:55-60); *see also* Ex. 5 at A0030 ('684 Patent 4:28-33) (emphasis added).

The plain language of the intrinsic evidence suggests that "physical adhe[sion]" is just one way in which the surface modifier can be adsorbed to the surface of the anticancer agent. Indeed, even Abraxis agrees that the word "include" is an open non-limiting term. Abraxis Br. at 17 ("The key is Elan's use of the open-ended word 'include'"). Thus, Abraxis concedes that suitable surface modifiers *include* those that physically adhere to the surface of the "medicament useful in treating cancer," but are not limited to physical adhesion.

Abraxis asserts that the "medicament and the surface modifier stick to each other and form a particle," Abraxis Br. at 25, which is true to a point. The particles stick, but as Abraxis agrees, they do not chemically bond, so individual surface modifiers are free to dissociate from and associate with the medicament. *See, e.g.,* Ex. 1, A0004 ('363 Patent, 5:30-31).

The extrinsic evidence offered by Abraxis further supports Elan's construction. Abraxis states:

> Moreover, the patents definition of "adsorbed on the surface"...comports with the ordinary meaning of that phrase as understood by persons of ordinary skill in the art. ([] 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."). Abraxis Br. at 24 (quoting Ex. 31 at A 0442).

Thus, Abraxis's own evidence confirms that the surface modifier physically contacts the "crystalline medicament useful in treating cancer" through forces that are considerably weaker than chemical bonds.

7. "Sufficient to Maintain an Average Effective Particle Size" Means an Amount of Surface Modifier That Maintains the Size of the Particles Such That at Least 90 Percent of the Particles Have a Number Average Particle Size of Less Than 1000 Nm[9]

The patentee acted as its own lexicographer and expressly defined the term "average effective particle size" to mean that 90% of the particles must have the number average particle size specified in the relevant claim. Abraxis Br. at 26.

There is no principled reason to construe the term to reflect what the claim does not recite. That would be an infinite exercise. Thus, Abraxis's gratuitous proposal to introduce negative limitations for the time period and the conditions under which the particle maintains its size is improper.

Abraxis attempts to support its contention by citing to a portion of the specification that discloses a screening process for guiding a person skilled in the art to select compatible anticancer agents and surface modifiers in order to achieve the invention. *See* Ex. 1 at A0005 ('363 Patent 7:5-8) ("A simple screening process has been developed whereby compatible surface modifiers and anticancer agents can be selected to

[9] This construction of this claim term in context of dependent claims 2 and 3 should be construed in accordance with the size limitation recited in those claims, i.e., 400 nm and 300 nm, respectively. *See* Ex. 1 at A 0008 ('363 Patent 14:29-32). This term relates both to the size of the claimed nanoparticles and to their stability, a property imparted by the surface modifier.

provide stable dispersions of the desired particles"). The specification teaches the parameters for testing stability of nanoparticles, as Abraxis concedes here. The specification points out that this will depend on the particular combination. Any further recitation in the claims is superfluous.

8. A "Surfactant" Is an Amphiphilic Substance That Reduces the Surface Tension at the Interface Among Substances

Elan agrees that the term "surfactant" should be defined in accordance with the ordinary meaning. Elan further agrees that in accordance with that meaning a surfactant is substance that lowers the surface tension on an interface and further that a surfactant molecule has a hydrophobic part and a hydrophilic part. Furthermore, in the context of this patent, it cannot be denied that the "surfactant" stabilizes the "medicament" by hindering agglomeration or combination of the nanoparticles.

Abraxis's proposed construction is unnecessarily complex and narrow. It should be rejected.

B. U.S. Patent No. 5,832,025 ("the '025 Patent")

1. Without Eliciting Adverse Hemodynamic Effects" Means Reducing, Eliminating, or Not Eliciting Cardiovascular Dysfunction in Mammals Susceptible to Hemodynamic Effects (Associated with Administration of Nanoparticles)

The parties do not significantly dispute the meaning of "adverse hemodynamic effects." Both parties agree that the adverse hemodynamic effects occur in mammals to whom nanoparticulate drug compositions are administered.[10] Indeed, the dispute largely

[10] Abraxis takes the position that Elan has proffered some other meaning, but the invention clearly relates to not eliciting hemodynamic effects that result from administration of nanoparticles. This is clear from the language of the claims: "A method of administering a nanoparticulate composition to a continued ...

turns on the nature of the "mammal" administered with the particulate composition, and it would perhaps be more accurate to recast the disputed term as "*to a mammal* without eliciting adverse hemodynamic effects." In any event, Elan has proffered the reasonable construction that the term mammal in the claims refers a mammal, such as a dog, that is sensitive to the adverse hemodynamic effects, for the reasons pointed out below.

Abraxis complained that Elan's initial construction would: (a) read "without eliciting" out of the claim and thus treatment of hemodynamic conditions other than those associated with administration of a nanoparticulate composition; (b) is limited to avoiding adverse hemodynamic effects in a single mammal; and (c) should not be limited to any particular species of mammal. Each of these contentions lacks merit.

In an effort to reduce issues raised by Abraxis, Elan proposes to construe "to a mammal without eliciting adverse hemodynamic effects" to mean "the claimed method of intravenous administration of a nanoparticulate drug composition that reduces, eliminates, or does not elicit cardiovascular dysfunction, such as reduction in arterial blood pressure and cardiac function, including heart rate, cardiac output, and ventricular contractility in mammals that are sensitive to hemodynamic effects associated with the administration of the nanoparticulate drug composition." With this in mind, we consider Abraxis's arguments.

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mammal without eliciting adverse hemodynamic effects…" Ex. 2 at A0019; ('025 Patent, 16:56-58); *see also id.* at A 0012; ('025 Patent, 1:49-53 ("We have observed that intravascular administration of a [sic] [nanoparticulate] suspensions to dogs causes significant cardiovascular dysfunction, such as reduction in arterial blood pressure and cardiac function, including heart rate[,] cardiac output and ventricular contractility.")).

(a) "Without Eliciting"

In the context of the '025 Patent, "without eliciting" properly means reduces, eliminates, or does not draw forth. Abraxis's citation to the specification of the '025 Patent actually supports Elan's contention. "It [Abraxis's construction] also is supported by the specification of the '025 Patent. *See, e.g.*, Ex. 2 at A0012 ('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...')" Abraxis Br. at 29 (emphasis added). *See also* Ex. 2 at A0011 ('025 Patent Abstract, stating: "the delivery of which to a mammal, **reduces/eliminates** adverse physiological effects" (emphasis added); *id.* at A0014 ('025 Patent 6: 49-51) (stating "[t]o avoid overt deleterious hemodynamic effects the following parameters should be controlled"); *id.* at A0015 ('025 Patent 7:5-7) (noting "at 5 ml/min delivery of <sic> the hemodynamic effect was about half of that of the 10 ml/min infusion."). Even Abraxis uses the term "avoid" as a synonym for "without eliciting." *See, e.g.*, Abraxis Br. at 29 (stating "... Abraxis's construction reflects that the invention described in the patent is **avoiding hemodynamic effects** ....") (emphasis added).

Abraxis's argument is flawed because it ignores the specification and the prosecution history. Both sources describe the invention as *at least substantially reducing* hemodynamic effects by controlling the rate of infusion.

> 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. Ex. 2 at A0012 ('025 Patent 1:62-65) (emphasis added).
>
> 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/ml <sic>, or by pretreating the patient with an antihistamine. Ex. 14 at A0148 ('025 Prosecution History, Paper No. 9B, Amendment dated 02/04/1998) (emphasis added).

(b) "A Single Mammal(?)"

The basis of Abraxis's purported second criticism is difficult to ascertain. Suffice it to say that nothing in Elan's proffered construction invites the Court to read the claim as being limited to avoiding adverse hemodynamic effects in a single mammal, as Abraxis alleges. *See* Abraxis Br. at 28. Abraxis does not even explain which "single mammal" the claim is alleged to cover.

(c) "A Particular Species of Mammal"

Relying on the specification as well as the language of the claims, Elan proposes to construe the claim with respect to mammals that are sensitive to hemodynamic effects associated with the administration of the nanoparticulate drug composition.

Abraxis bases its third challenge to Elan's construction by disputing that the claim is not directed to every mammal, but only to sensitive mammals. In doing so, Abraxis ignores the express words of the specification. The specification defines the term "mammal" narrower than its zoological meaning: "[t]his invention provides a method of administering a nanoparticulate composition to a mammal **such as a dog or other sensitive species**" Ex. 2 at A0012 ('025 Patent, 2: 8-9) (emphasis added).

The specification provides an express definition as well: "as used herein, mammal preferably means a dog and other sensitive species including human species." Elan's construction acknowledges the clear language of the specification: "a mammal such as a dog *or other sensitive species* [*e.g.*, in addition to human]. Abraxis disregards of the "best source" of understanding a claim term, the specification, when reading the term more broadly. *Phillips*, 415 F.3d at 1315 (reaffirming that the "specification is the 'single best guide to the meaning of a disputed term'") (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

Accordingly, the Court should construe the phrase to mean "the claimed method of intravenous administration of a nanoparticulate drug composition that reduces, eliminates, or does not elicit cardiovascular dysfunction, such as reduction in arterial blood pressure and cardiac function, including heart rate, cardiac output, and ventricular contractility in mammals that are sensitive to hemodynamic effects associated with the administration of the nanoparticulate drug composition," as proposed by Elan.

2. "Infusion Rate Not Exceeding 10 mg/min" Means 10 mg of Nanoparticles Per Min

The parties agree that claims 1 and 13 are directed to administration of a *composition*. Claim 1 is directed to a composition made up of (nano)particles of a crystalline organic drug substance with a surface modifier adsorbed on the surface and a pharmaceutically acceptable carrier. Claim 13 is directed to a composition made up of an organic drug substance entrapped in liposomes or a colloidal polymeric material, and a pharmaceutically acceptable carrier. *See* Abraxis Br. at 31.

Abraxis proposes in its construction that the "mg" recited in the claims refers to the weight of the entire drug composition, including the pharmaceutically acceptable carrier. In doing so, it departs from the ordinary and customary meaning of the claim terms in favor of a construction that might be best described as "forced," though unrealistic may be a more accurate characterization. Its construction would require a person of skill in the art to undertake the unusual step of interpreting "mg" (milligrams) as "ml" (milliliters). Its interpretation also introduces as much as a 1000-fold or greater error in the meaning of the claim when compared to the examples. Thus, Abraxis's construction leads to an absurd result neither required by the claim nor consistent with the cannons of construction.

The plain language of the claim refutes Abraxis's position. The skilled person, who would be a physician and thus familiar with basic chemistry, would measure amounts of solids in terms of mass or weight, *e.g.,* mg. *See* Ex. 45 at A0785. In contrast, mass units are used rarely if ever in measuring the amount of a liquid, which is typically measured in units of volume, *i.e.*, capacity, *e.g.,* ml. *See id.* at A0786. Abraxis's construction correctly includes the pharmaceutically acceptable liquid carrier as part of the composition. , the drug composition would only be in liquid form. An infusion rate tied to the liquid would be in a volume, *i.e.,* milliliter per minute ("ml/min"). Reference to "mg/min" therefore concerns the nanoparticle solids suspended in the carrier.

The Examples clearly disclose infusion rate of a liquid composition based on the volume of the liquid suspension in terms of volume (ml), ***not mass (mg)***, per minute. *See, e.g.*, Ex. 2 at A0014 ('025 Patent 5: 10-11) ("infused at a rate of 5 ml/min"); *see*

also id. ('025 Patent, Table 3, first column; Table 4, first column; Table 7, second column).

The '025 specification states "[i]t 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." Ex. 2 at A0012 ('025 Patent, 1:62-65). The specification teaches that the active drug is present in a nanoparticle. *Id.* (1:67 to 2:4).

Table 7 summarizes the experimental results of effects of infusing nanoparticles. This Table ties the examples together, providing the basis for relating the infusion rate of nanoparticles to avoiding hemodynamic effects. *Id.* Table 7 discloses percent solids of various test solutions in units of mg/ml to obtain a particle infusion rate in units of mg/ml/min, *i.e.*, mg/min. Thus, the specification supports the construction that the unit "mg" is used only to refer to the mass of a solid, *i.e.,* the nanoparticle. Accordingly, Abraxis's construction is inconsistent with the specification. The correct construction would require the infusion rate to relate to the *nanoparticles*, which are present in the liquid suspension[11].

Abraxis's acknowledges that "[t]he specification, moreover, discloses three different approaches to defining 'mg' in the infusion rate: the drug composition, the particles, and the drug substance." *See* Abraxis Br. at 31 (citing Ex. 2 at A0011) ('025 Patent, Abstract, 1:16-20, 2:11-20). Each of these sections of the application relate to

[11] The pharmaceutically acceptable carrier would be the liquid in the suspension. Abraxis contends that the infusion rate relates to the entire liquid suspension including the nanoparticles within it.

infusion of a composition of nanoparticulate drug products, further supporting Elan's construction of the term "infusion rate" as the infusion rate of nanoparticles (mg) per unit of time (min).

Abraxis's opening claim construction brief illustrates the degree to which its proposed claim construction yields absurd results. Abraxis provides a calculation of the infusion rate based on the mass of the volume of liquid as well as the solid nanoparticles and excess human albumin in Abraxane®. *See* Abraxis Br. at 8, n. 7. Using this analysis, Abraxis calculates an infusion rate of Abraxane® of nearly 2030 mg/min for the average woman of 1.6 m^2. This is more than 200 times the maximum infusion rate recited in the asserted claims. Abraxis further proposes that its unlikely claim construction provides that "administering Abraxane® at the claimed 10 mg/min would take just under 101.5 hours." Abraxis Br. at 8. Either calculation represents an extreme departure from the meaning "infusion rate" in light of the specification.[12]

Abraxis also proposes that "infusion" be restricted to "gravity infusion," a gratuitous suggestion that is not supported--much less required--by the intrinsic evidence or necessary to understand and practice the invention. The person of ordinary skill in the

[12] Abraxis's cherry picking of a clinical study as evidence that 96 hour infusions of chemotherapeutic drugs is of no moment. For one thing, it is not an infusion rate of a nanoparticulate drug, but instead that of Cremaphor solubilized paclitaxel. Ex. 27. For another, it represents an extreme protocol for a clinical trial in combination with another anti-cancer agent, not the standard of the time for approved infusion of Taxol®. *Id.* Analysis of abstracts were obtained from PubMed for publications in just 1995 related to infusion of Taxol®. *See generally* Ex. 46. A review of these abstracts revealed the following infusion times: about 57% report infusion times of 3 hours; about 20% of 24 hours; about 3% of 1 hour. An additional about 14% did not report the infusion time and 2% reported other times. Thus, only 4% of the abstracts reported infusion times on the order of 96 hours. *See generally* Ex. 46. Thus, Abraxis relies on a tiny minority of cases to imply that its claim construction is somehow reasonable.

art would regard a specific "infusion rate" as requiring appropriate control of the flow of the composition into the patient, which might be achieved by gravity but might as easily involve mechanical apparatus, *e.g.,* an infusion pump. *See, e.g.,* Ex. 47 at A863 (Stedman's Medical Dictionary, 25th ed. 1990, p. 783 "infusion"); *See also,* Ex. 33 at A0451 (Mosby's Medical Dictionary, 4th ed., p. 812 "infusion pump").

Accordingly, an "infusion rate not exceeding 10 mg/min" should be construed as "intravenously administering the *nanoparticles* at a rate not exceeding 10 milligrams per minute based on the weight of the nanoparticles."

3. "Consisting Essentially of" Means the Nanoparticles Are Essentially Free of Solvent Contamination

Elan submits that the settled law defining "consisting essentially of" and the prosecution history of the '684 Patent has not changed since drafting the first part of this brief. Accordingly, Elan's construction for this claim term in the '025 Patent is consistent with that proposed in the '363 Patent in Part III.A.1. Thus, the term "consisting essentially of" in claim 1 means that the particles, which include a "crystalline organic drug substance" and a "surface modifier" are essentially free of solvent contamination. In claim 13, the term means that the particles, which include an organic drug substance and a liposome or colloidal polymeric material, are essentially free of solvent contamination. Indeed, the term "consisting essentially of" as used in the

'025 Patent signals that the scope of claims 1 and 13 may include additional ingredients that do not affect the basic and novel characteristics of the invention.[13]

4. "Crystalline" Means in a Nanoparticulate Phase Different From an Amorphous Phase

Elan only submits that a proper construction of the word "crystalline" in the context of the asserted patents, which each relate to nanoparticles, needs to be consistent with construction of "crystalline medicament useful in treating cancer" in claim 1 of the '363 Patent. Indeed, the "organic drug substance" recited in the '025 Patent is not limited to anticancer agents.

The term "crystalline" in "crystalline organic substance" should be construed in the context of nanoparticles. As such the phrase means that the term should be construed as a therapeutic or diagnostic agent in a nanoparticulate phase different from an amorphous phase. Since the nanoparticles of the '363 Patent and the '025 Patent both relate to the nanoparticles of the '684 Patent, either by priority (Ex. 1 at A0001 ('363 Patent, bibliographic page)) or by reference (Ex. 2 at A0012 ('025 Patent 1:23-28)) the phrase "crystalline organic drug substance" recited in claim 1 of the '025 Patent should be construed so as to appreciate that in the context of nanoparticles, the term crystalline drug substance, whether it be a "medicament useful in treating cancer" or an "organic drug substance" not limited to treating cancer --means that the drug substance has any degree of crystal structure as opposed to amorphous, which means having no crystalline structure, as discussed in Section III.A.2 in connection with the '363 Patent.

[13] Elan does not dispute that this transitional phrase also excludes other contaminants that would change the basic and novel characteristics of the nanoparticles.

5. "Organic Drug Substance" Means a Therapeutic or Diagnostic Agent

There is no credible dispute over this term: the '025 specification expressly states that the drug substance is a therapeutic or diagnostic agent. The inventors have provided a clear signal when they intend the "organic drug substance" to be crystalline: they use the term "crystalline organic drug substance," as in claim 1. Moreover, a construction of the term "organic drug substance," which imports "crystalline" into the definition is superfluous when considered in the context of claim 1, which plainly recites a "crystalline organic drug substance." A claim construction that renders a claim term superfluous cannot be correct. *See Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) ("A claim construction that gives meaning to all terms of the claim is preferred over one that does not do so."); *see also Pause Tech. LLC v. Tivo Inc.*, 419 F.3d 1326 (Fed. Cir. 2005).

Notwithstanding these certain cannons of claim construction, Abraxis misconstrues the term "organic drug substance" to require a "crystalline" limitation and further requires the "organic drug substance" to be "suitable for administration to a mammal." *See* Abraxis Br. at 28. Neither of these limitations correspond to features of the claim or with any teaching of the specification.

The term "organic drug substance" in the context of claim 13 simply means a therapeutic or diagnostic agent. In fact, that is the only construction supported by the specification. As such, that is the definition proposed by Elan.

6. "Surface Modifier" Means a Surface Active Agent or Stabilizing Agent Capable of Hindering Aggregation, Flocculation and/or Agglomeration

The term "surface modifier" has essentially the same meaning in the '025 Patent as it does in the '363 Patent for essentially the same reasons. On this issue, the parties agree. *See* Abraxis Br. at 36.

7. "Adsorbed on the Surface" Means the Surface Modifier Physically Contacts the Surface of the Drug Substance and Does Not Chemically React With Such Drug Substance

The term "adsorbed on the surface" has essentially the same meaning in the '025 Patent as it does in the '363 Patent. On this point as well, the parties agree. *See* Abraxis Br. at 36-37.

8. "Sufficient to Maintain an Effective Average Particle Size" Means That the Size of the Particles as Claimed Is Maintained Such That at Least 90 Percent of the Particles Have a Weight Average Particle Size From About 50 Nm To About 1000 Nm

The phrase "sufficient to maintain an effective average particle size" in the context of the '025 Patent is similar to the same phrase recited in the '363 Patent. However, in the '025 Patent, the effective average particle size is based on a weight average as indicated in the specification. The Court should construe these phrases in similar vein, noting that the '025 Patent refers to the effective average particle size as meaning that the size of the particles as claimed is maintained such that at least 90 percent of the particles have a weight average particle size from about 50 nm to about 1000 nm.

9. A "Colloidal Polymeric Material" Is a Carrier or Vehicle for the Organic Drug Substance

Abraxis asserts that the specification is devoid of support for the term "colloidal polymeric material" in order to design an excuse to offer separate and distinct definitions for each term recited in the phrase. Indeed, the specification supports Elan's construction that a "colloidal polymeric material" is a polymeric carrier.

> In order to provide nanometer-size particles, the drug substance is comminuted in the presence of a surface active agent or, alternatively, the surface active agent is allowed to be adsorbed to the nanoparticulate drug substance after the process of comminution. The surface active agent prevents flocculation or congregation of the nanoparticles. The achievements of nanoparticulate technology in the pharmaceutical industry affords the opportunity to prepare parenteral formulations of water-insoluble or poorly water-soluble drugs. These formulations by their nature are suspensions rather than solutions since the particles are dispersed/suspended in a pharmaceutically acceptable vehicle. Liposomes, emulsions and colloids when used as carriers for an active drug are also suspensions rather than solutions. Ex. 2 at A0012 ('025 Patent 1:34-45).

Thus, Abraxis's argument misses the mark. In the context of the specification, which is usually dispositive to the meaning of a claim term, a colloidal polymeric material, like a liposome, entraps and carries the active drug.

The pharmaceutically acceptable carrier recited in the context of claim 13 is not superfluous with Elan's construction, as implied by Abraxis. Rather it provides the continuous liquid medium to create the suspension that includes the nanoparticles of drug and colloidal polymeric carrier.

IV. Conclusion

For the foregoing reasons, Elan respectfully requests that its construction of the claims be adopted by the Court and that Abraxis's proposed interpretation be rejected.

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