IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

PLAINTIFF ELAN PHARMA INTERNATIONAL LIMITED'S
OPENING CLAIM CONSTRUCTION BRIEF

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Plaintiff Elan Pharma International Limited ("Elan") respectfully submits its Opening Claim Construction Brief in support of its proposed claim constructions of the disputed terms in the patents-in-suit, U.S. Patent No. 5,399,363 ("the '363 Patent") and U.S. Patent No. 5,834,025 ("the '025 Patent").

I. NATURE AND STAGE OF THE PROCEEDINGS

Elan filed its Complaint on July 19, 2006 alleging that Defendant Abraxis BioScience, Inc. ("Abraxis") infringes the '363 Patent and the '025 Patent under 35 U.S.C. § 271 by making, using, selling, and/or offering to sell Abraxane®, contributing to the use of Abraxane® by others, and/or inducing others to use Abraxane®. (D.I. 1). Abraxis filed an Answer and Counterclaims to Elan's Complaint requesting a declaration of invalidity and non-infringement of the '363 and '025 Patents. (*See* D.I. 7, D.I. 84). This matter is set for trial on June 2, 2008.

In order to evaluate the merits of the Parties' claims, the Court is tasked with construing the disputed claim terms at issue. Elan and Abraxis submitted a Joint Claim Chart on April 20, 2007 (D.I. 99), as required by the Court's Scheduling Order. (D.I. 20). Elan submits this brief in support of its proposed claim constructions.

II. SUMMARY OF ARGUMENT

Elan's proposed claim constructions are well-grounded in the principles recently re-affirmed by the United States Court of Appeals for the Federal Circuit ("Federal Circuit") in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*). In accordance with those principles, Elan's proposed claim construction primarily relies on the intrinsic evidence, *i.e.,* the claims, the specifications, and the file histories of the patents-in-suit and of the parent patent to the '363 Patent.

To the extent that Elan's proposed claim constructions refer to extrinsic evidence, such evidence wholly supports the intrinsic evidence. Accordingly, Elan employs the correct canons of claim construction articulated by the Federal Circuit.

Abraxis's proposed claim constructions, on the other hand, often include definitions that differ from the ordinary and customary meaning given a term interpreted by one skilled in the pertinent art. At other times, Abraxis proposes constructions that are neither based on the intrinsic evidence nor on relevant extrinsic evidence. Accordingly, Abraxis's proposed claim constructions are inconsistent with the Federal Circuit precedent and must be denied.

III. INTRODUCTION

The patents-in-suit relate to nanoparticle technology.[1] The inventors' discoveries permit (1) formulation of poorly water soluble chemotherapeutic drugs so they are stable during storage, more effective, and less toxic; and (2) a safer way to administer nanoparticles[2] intravenously. These pioneering discoveries, which resulted in grant of the '363 and '025 patents, respectively, lay the foundation for cancer patients to receive more effective, safer treatment for their cancer.

Abraxis's product, Abraxane® employs Elan's important advances in formulating and delivering poorly soluble chemotherapeutic drugs. The Abraxane® product is nanoparticle paclitaxel, a potent chemotherapeutic agent, coated with human

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[1] *See generally* Ex. 1 ('363 Patent); Ex. 2 ('025 Patent).

[2] *See* Ex. 3 at A0024 (*Webster's Ninth New Collegiate Dictionary*, pg. 786 (1991) (Nanoparticles in the context of these patents are particles that are less than 1000 nanometers ("nm") (and preferably less than 400 and 300 nm) in size. For perspective, a "nanometer" is defined as "one-billionth of a meter.").

serum albumin, as claimed in the '363 patent. Abraxis instructs others to administer these nanoparticles at a rate that avoids or reduces adverse hemodynamic effects, as claimed in the '025 patent.

A. *The '363 Patent*

1. The Problem

The delivery of drugs that do not dissolve well in water, otherwise known as poorly water soluble drugs, has always been problematic. Poor solubility hampers drug dissolution in the body, which is necessary for drug bioavailability. "Bioavailability" refers to the extent to which a drug reaches its site of action.[3] When a drug does not reach its site of action, it cannot be effective. Most anticancer drugs are poorly water soluble and consequently have correspondingly lower therapeutic value because of their reduced bioavailability.

One approach to enhancing the bioavailability, and therefore the effectiveness of anticancer agents, is to use organic solvents. The organic solvents increase the solubility/bioavailability of the anticancer agent, but are often toxic to the patient. Thus, although organic solvents can help the solubility of drugs, they also may be harmful to patients.

2. The Solution

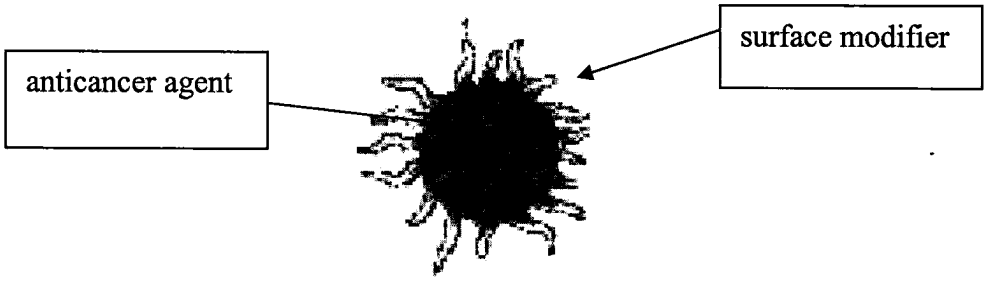
The inventors of the '363 Patent developed a nanoparticle technology useful for the delivery of poorly water soluble anticancer drugs, and they used this technology to

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[3] Ex. 4 at A0027 (*The Pharmacological Basis of Therapeutics*, pg. 5 (7th ed. 1985)).

successfully create an anticancer drug particle with improved bioavailability that avoids solvent-related toxicity.[4]

The novel nanoparticles, depicted below, have two main components (1) a drug substance; and (2) a surface modifier, which is coated onto the surface of the drug substance.[5]



Typically, nanometer-sized drug particles combine with each other to form larger drug particles. This process is known as aggregation or flocculation. Importantly, the inventors discovered that the nanometer-sized drug particles could be stabilized or maintained by the surface modifier coating on the drug surface, such that aggregation or flocculation is hindered.

The discovery described in the '363 Patent has significant advantages over then-existing technology. The maintenance of the very small sized particles enhanced the effectiveness of the poorly water soluble anticancer agent by increasing its bioavailability. To illustrate, consider how sugar dissolves in a cup of tea. Given a sugar cube and an equal amount of granular sugar, the granular sugar dissolves more

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[4] Ex. 1 at A0002 ('363 Patent 1:44-47; 2:18-27).

[5] *Id.* ('363 Patent 1:48-54).

easily. When granular, the sugar is more soluble because it has a much larger surface area.

Equally important to the discovery was that the inventors' approach avoided solvent-related toxicity. Advantageously, the nanoparticles described by the '363 Patent are essentially free of solvent contamination and therefore do not magnify the toxicity of the anticancer drug.

B. *The '025 Patent*

1. The Problem

For some unknown reason, intravascular administration of nanoparticles was observed to cause significant cardiovascular dysfunction in a sensitive mammal receiving the nanoparticles.[6] The significant cardiovascular dysfunction, known as hemodynamic effects, encompasses reduction in arterial blood pressure and cardiac function, including heart rate cardiac output and ventricular contractility.[7]

2. The Solution

The invention of the '025 Patent is based on the discovery that the significant cardiovascular dysfunction observed with intravenous administration of nanoparticles is associated with the surface modifier-particle combination.[8] Armed with this knowledge, the inventors developed a method for administering nanoparticles such that the adverse hemodynamic effects are eliminated or reduced. The inventive method of administration is based on the discovery that adverse hemodynamic effects could be

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[6] Ex. 2 at A0012 ('025 Patent 1:49-52).

[7] *Id.*

[8] *Id.* at A0014 ('025 Patent 6:61-62).

eliminated or reduced by controlling the intravenous infusion rate of the nanoparticles at less than 10 milligrams per minute.[9]

IV. LEGAL STANDARDS

The basic principles of claim construction were recently restated by the Federal Circuit in *Phillips,* 415 F.3d 1303. There, the court reaffirmed the principles of claim construction outlined in three prior decisions, namely, (1) *Markman v. Westview Instruments, Inc.,* 52 F.3d 967 (Fed. Cir. 1995) (*en banc*), *aff'd* 517 U.S. 370 (1996); (2) *Vitronics Corp. v. Conceptronic, Inc.,* 90 F.3d 1576 (Fed. Cir. 1996); and (3) *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.,* 381 F.3d 1111 (Fed. Cir. 2004).[10]

Claim construction begins with the intrinsic evidence of the subject patent, *i.e.*, the claims, specification, and prosecution history.[11] "Because claim terms are normally used consistently throughout the patent, the usage of a term in one claim can often illuminate the meaning of the same term in other claims."[12] Further, differences among claim terms can be a useful guide in understanding the meaning of a particular claim

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[9] Ex. 2 at A0012 ('025 Patent 1:62-65).

[10] *Phillips,* 415 F.3d at 1312 ("What we said in those cases bears restating, for the basic principles of claim construction outlined there are still applicable, and we reaffirm them today.").

[11] *Vitronics Corp.*, 90 F.3d at 1582.

[12] *Phillips,* 415 F.3d at 1314 (citing *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1342 (Fed.Cir. 2001); *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F3d 1146, 1159 (Fed. Cir. 1997).

term.[13] Therefore, the starting point for proper claim construction is a review of all of the claims of the subject patent.[14]

Although the words of a claim are given their ordinary and customary meaning to a person of ordinary skill in the pertinent art in question at the time of the invention, it would be legal error to construe a claim by considering it in isolation.[15] Rather, a claim must be read in view of the specification of which it is a part.[16] In this regard, the Federal Circuit in *Phillips* noted that:

> Importantly, the 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 patent, including the specification.[17]

Additionally, the person of ordinary skill in the art is deemed to have knowledge of any special meaning to the claim terms.[18]

"[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution . . .".[19] During prosecution, a patent

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[13] *Id.*

[14] *See id.*

[15] *Bell Commc'ns Research, Inc. v. Vitalink Commc'ns Corp.*, 55 F.3d 615, 620 (Fed. Cir. 1995).

[16] *Id.*

[17] *Phillips,* 415 F.3d at 1313.

[18] *Id.*

[19] *Nystrom v. Trex Co.*, 424 F.3d 1136, 1142 (Fed. Cir. 2005) (quoting *Phillips*, 415 F.3d at 1317).

applicant may consistently and clearly use a term in a manner either more or less expansive than it is used in the relevant art, thereby expanding or narrowing the scope of the term in the context of the patent claims.[20] Notably, "in order to disavow claim scope, a patent applicant must clearly and unambiguously express surrender of subject matter during prosecution." [21]

In addition to the intrinsic evidence, a court may look to extrinsic evidence to discern the meaning of a claim term.[22] Such evidence includes dictionaries, learned treatises and expert testimony.[23] The use of extrinsic evidence is especially helpful when the ordinary meaning of an art-specific term is not immediately apparent to judges and others outside the pertinent field.[24] Since extrinsic evidence is potentially less reliable in interpreting claim terms than intrinsic evidence, the Federal Circuit has endorsed the use of extrinsic evidence when it serves as an aid to "help educate the court regarding the field of the invention." and to "determine what a person of ordinary skill in the art would understand claim terms to mean."[25] In this manner, the Federal

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[20] *Sorenson v. Int'l Trade Comm'n*, 427 F.3d 1375, 1378 (Fed. Cir. 2005).

[21] *Id.*

[22] *Phillips*, 415 F.3d at 1317.

[23] *Id.*

[24] *Id.* at 1214 (citing *Innova/Pure Water, Inc. v. Safari Water Filtration Systems, Inc.* 381 F.3d 111, 116 (Fed. Cir. 2004)).

[25] *Id.* at 1319.

Circuit has enunciated that the extrinsic evidence should be viewed in the context of the intrinsic evidence.[26]

V. CLAIM CONSTRUCTION

A. *Disputed Claim Terms Common to Both Patents-in-Suit*

1. "consisting essentially of"

The disputed phrase "consisting essentially of" is found in claim 1 of the '363 Patent and in claims 1 and 13 of the '025 Patent. The contentions of the parties regarding the proper construction is shown below.

Claim 1 of the '363 Patent	
Elan's Construction	*Abraxis's Construction*
The particles, which include a "crystalline medicament useful for treating cancer" and "surface modifier," are essentially free of solvent contamination.	The particles are composed only of "crystalline medicament," "surface modifier," and at most trace amounts of solvent or other contamination.
Claim 1 of the '025 Patent	
Elan's Construction	*Abraxis's Construction*
The particles, which include a "crystalline organic drug substance" and a "surface modifier," are essentially free of solvent contamination.	The particles are composed only of a "crystalline organic drug substance," a "surface modifier," and at most a trace amount of solvents or other contaminants that would not change the basic and novel characteristics of the particles.
Claim 13 of the '025 Patent	
Elan's Construction	*Abraxis's Construction*
The particles, which include an "organic drug substance" and "liposome or colloidal polymeric material," are essentially free of solvent contamination.	The particles are composed only of a "crystalline organic drug substance," a "surface modifier," and at most a trace amount of solvents or other contaminants that would not change the basic and novel characteristics of the particles.

[26] *Id.*

"Consisting essentially of" is a standard transitional phrase in patent law. Specifically, this transition allows for elements (such as materials) not listed in a patent claim "provided that they do not materially affect the basic and novel properties of the invention."[27]

During prosecution of the parent patent application to the '363 Patent, U.S. Patent Appln. No. 07/647,105, which issued as U.S. Patent No. 5,145,684 ("the '684 Patent"),[28] the patentee indicated what "basic and novel properties" were relevant.

> The particles are free of unacceptable solvent contamination and consist essentially of the crystalline drug substance and the surface modifier adsorbed on the surface thereof.[29]

The resulting particles "consist essentially of" drug and modifier because they are free of contaminating solvents. Such contaminants are the *only* materials that an ordinary artisan would conclude are excluded, based on the file history.

The Summary of the Invention emphasizes reduced toxicity.[30] The first sentence describing the preferred embodiments identifies reduced toxicity as a basis for

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[27] *AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1239 (Fed. Cir. 2003) (quoting *PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998)).

[28] Ex. 1 at A0001 ('363 Patent, Related U.S. Application Data, Continuation-in-part of Ser. No. 647,105, Jan. 25, 1991, Pat. No. 5,145,684).

[29] Ex. 6 at A0044 ('684 Patent Prosecution History, Amendment, pg. 7); Ex. 6 at A0046 ('684 Patent Prosecution History, Amendment, pg. 9 ("By 'consisting essentially of' it is meant that the claimed particles are essentially free of solvent contamination and other toxic materials, e.g., monomer or initiator, resulting from solvent precipitation and polymerization methods of particle preparation.")).

[30] Ex. 1 at A0012 ('363 Patent 1:24-27); *Id.* ('363 Patent 1:44-47); *Id.* ('363 Patent 1:60-65).

the invention.[31] Additionally, the prosecution history of the '363 Patent specifies that prior art particles made from conventional solvent precipitation techniques are contaminated with toxic solvents.[32] The specification and file history indicate which materials should be excluded from the compositions of the invention—solvent contamination.

The specification of the '025 Patent refers to the disclosure of the '684 Patent for a description of nanoparticles.[33] Thus, the particles of the '684 Patent are relevant to the nanoparticles claimed in the '025 Patent. Those nanoparticles are essentially free of solvent contamination. The term "consisting essentially of" should be construed to have the same meaning in both patents, as both parties have proposed.

Abraxis's construction would allow solvent contaminants as the *only* permissible ingredient beyond those listed in the claims. As emphasized in the specification and file history, this construction is *opposite* the purpose of the invention, which is to avoid contaminating solvents. It would also exclude the preferred embodiment of the '363 Patent, which includes material other than the recited drug and modifier—namely, a dispersion medium.[34]

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[31] *Id.* ('363 Patent 2:18-21).

[32] Ex. 7 at A0059 ('363 Patent Prosecution History, Information Disclosure Statement, pg. 2); Ex. 7 at A0064-A0070 ('363 Patent Prosecution History, Amendment); Ex. 7 at A0071-A0073 ('363 Patent Prosecution History, Liversidge Decl. ("The crystalline particles described in [this application] are essentially free of solvent contamination")).

[33] Ex. 2 at A0012 ('025 Patent 1:23-27).

[34] *Vitronics Corp.*, 90 F.3d at 1583 (claim construction excluding preferred embodiment is "rarely, if ever, correct and would require highly persuasive evidentiary support").

Abraxis's construction is more consistent with another transitional phrase the patentee chose not to employ: "consisting of." That phrase, in contrast to "consisting essentially of," signifies that the scope of the claim is closed, *i.e.,* precludes additional components with the exception of impurities.[35] In effect, Abraxis is reading "essentially" out of the claims.

2. "surface modifier"

The term "surface modifier" is used in claim 1 of the '363 Patent and in claim 1 of the '025 Patent. The contentions of the Parties are shown below.

Claim 1 of the '363 Patent	
Elan's Construction	*Abraxis's Construction*
a stabilizing agent capable of hindering the aggregation, flocculation and/or agglomeration of the particles.	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.
Claim 1 of the '025 Patent	
Elan's Construction	*Abraxis's Construction*
a surface active agent or stabilizing agent capable of hindering the aggregation, flocculation and/or agglomeration of the particles.	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 drug substance.

The term "surface modifier" defines a property for these materials. To determine what that property is, we look to the claims themselves and the specifications. The claims of each patent explicitly state that the surface modifier maintains the effective average particle size.[36] Moreover, the specifications explain that the "surface modifier" stabilizes the particle by hindering or preventing flocculation,

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[35] *Conoco, Inc. v. Energy & Environ. Int'l L.C.*, 460 F.3d 1349, 1360-61 (Fed. Cir. 2006).

[36] Ex. 1 at A0008 ('363 Patent, claim 1); Ex. 2 at A0019-A0020; ('025 Patent, claim 1).

agglomeration, and/or congregation of the particles.[37] Notably, small particles were typically known to combine or agglomerate to form larger particles.

The specification of the '684 patent explains that the surface modifier minimizes or hinders the close contact between the particles necessary for agglomeration or flocculation to occur. This is achieved by the surface modifier functioning as a barrier between drug particles thereby minimizing close contact or alternatively by preventing the close contact between the particles by repulsion.[38] Elan's construction gives effect to these defined properties of the "surface modifier."

On the contrary, Abraxis's construction does not address the basis properties of a "surface modifier." Rather, Abraxis merely exemplifies how a surface modifier might interact with a drug substance, whether it is the "crystalline medicament" of the '363 Patent or the "crystalline organic drug substance" of the '025 Patent. This construction of improperly collapses two distinct claim terms, *i.e.,* "surface modifier" and "adsorbed on the surface."

3. "adsorbed on the surface"

The term "adsorbed on the surface" is used in claim 1 of the '363 Patent and in claim 1 of the '025 Patent. The contentions of the Parties are shown below.

Claim 1 of the '363 Patent	
Elan's Construction	*Abraxis's Construction*
means that the surface modifier physically contacts the surface of the "crystalline medicament useful for treating cancer" and does not chemically	means that the surface modifier physically adheres to the surface of the crystalline medicament and does not form a chemical bond with the crystalline medicament.

[37] Ex. 1 at A0003 (The '363 Patent 4:53-56); Ex. 1 at A0005 ('363 Patent 8:31-32); Ex. 1 at A0006 ('363 Patent 9:44-45); Ex. 2 at A0012 ('025 Patent 1:37-38).

[38] Ex. 5 at A0032 ('684 Patent 8:22-29).

react with such medicament.	
Claim 1 of the '025 Patent	
Elan's Construction	*Abraxis's Construction*
means that the surface modifier physically contacts the surface of the drug substance and does not chemically react with such drug substance.	means that the surface modifier physically adheres to the surface of the crystalline drug substance and does not form a chemical bond with the crystalline drug substance.

The sole dispute is whether this term is limited to "adherence" to a surface, or is broad enough to encompass any contact. The specification of the '363 Patent teaches that "[u]seful 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."[39] Thus, "adsorbed on the surface" must cover more than adherence. And the specification teaches there are other ways in which the surface modifier interacts with the medicament or anticancer agent. For example, "particles can be contacted with a surface modifier after attrition."[40] Accordingly, the proper construction of the term "adsorbed on the surface" in the '363 Patent is not limited to adhesion.

Regarding the '025 Patent, neither the claims nor specification explicitly define "adsorbed on the surface." The specification does, however, indicate that surface modified nanoparticles are "described in U.S. Patent No. 5,145,684."[41] Like the '363 Patent, the specification of the '684 Patent states "useful surface modifiers include those which physically adhere to the surface of the drug substance"[42] and that the "particles

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[39] Ex. 1 at A0003 ('363 Patent 3:57-60).

[40] *Id.* at A0004 ('363 Patent 5:28-31).

[41] Ex. 2 at A0012 ('025 Patent 1:23-25).

[42] Ex. 5 at A0030 ('684 Patent 4:28-33).

can be contacted with a surface modifier after attrition."[43] Finally, extrinsic evidence of this term suggests "collection of one substance on the surface of another."[44]

Rather than applying sound claim construction procedures, Abraxis limits the term to one embodiment even though the specification was drafted expressly to include others.

4. "sufficient to maintain an average effective particle size"

The term is used in claim 1 of both patents-in-suit. The Parties' positions are summarized below.

Claim 1 of the '363 Patent	
Elan's Construction	*Abraxis's Construction*
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 nanometers.	means that the particles contain an amount of surface modifier sufficient to maintain the effective average particle size of the particles for an unspecified period of time and under unspecified conditions, wherein the effective average particle size means that at least 90% of the particles have the number average particle size specified in the claim.
Claim 1 of the '025 Patent	
Elan's Construction	*Abraxis's Construction*
means sufficient surface modifier to maintain the size of the particles at an effective average particle size from about 50 to about 1000 nanometers.	means that the particles contain an amount of surface modifier sufficient to maintain the effective average particle size of the particles for an unspecified period of time and under unspecified conditions, wherein the effective average particle size means that at least 90% of the particles have the weight average particle size specified in the claim.

The claims and the specification of the '363 Patent require the surface modifier be "adsorbed on the surface" of the anticancer agent in an amount "sufficient to

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[43] *Id.* at A0031 ('684 Patent 5:16-19).

[44] Ex. 8 at A0082 (Steven S. Zumdahl, *Chemistry*, pg. A25 (1986)).

maintain an effective average particle size of less than 1000 nm."[45] The specification expressly defines "effective average particle size less than 1000 nm." as "at least 90% of the particles have a number average particle size of less than about 1000 nm."[46]

This is a clear instance of the patentee acting as his own lexicographer. Elan's construction is based on this definition in the specification. Abraxis's definition includes a number of extraneous limitations not found in the patentees own, express definition of this term.

B. *Disputed Terms of the '363 Patent*

Elan has asserted claims 1-3, 5 and 8-12 of the '363 Patent against Abraxis. In addition to the terms discussed above, the parties dispute the construction of three terms and phrases.

1. "crystalline medicament useful in treating cancer"

Elan's Construction	*Abraxis's Construction*
an anticancer drug as recited in the Markush group of the claim in a nanoparticulate phase different from an amorphous phase.	"crystalline" means having a regular arrangement of atoms in a space lattice, distinguished from amorphous. "medicament useful in treating cancer" means a medicine suitable for treating cancer.

Rather than construing the phrase "crystalline medicament useful in treating cancer," Abraxis breaks it into two separate terms: "crystalline" and "medicament useful in treating cancer." The intrinsic evidence supports Elan's construction, that is,

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[45] Ex. 1 at A0002 ('363 Patent 1:50-54); *Id.* at A0008 ('363 Patent claim 1).

[46] *Id.* at A0003-A0004 ('363 Patent 4:60 - 5:10).

"an anticancer agent as recited in the Markush group of the claim in a nanoparticulate phase, different from an amorphous phase."[47]

The claim itself defines the term "medicament" as specific, listed anticancer agents.[48] This is consistent with the use of "anticancer agent" throughout the specification of the patent.

The prosecution history is also consistent with Elan's construction. The claims were amended from "crystalline anticancer agent" to "crystalline medicament useful in treating cancer" because the Examiner thought the former term suggested a cure for cancer and requested that the term "medicament" or "drug" be substituted for it.[49] In response, the claim was amended to include a Markush group of anticancer agents and further to recite a "medicament useful in treating a cancer susceptible to treatment with such medicament."[50] Additionally, the inventors noted that the "invention can be practiced with poorly soluble crystalline anticancer agents known in the art to be useful in treating susceptible cancer."[51] The express words of the claim require a construction of "medicament" as limited to the anticancer agents recited in the claim's Markush group.

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[47] "A Markush group lists specified alternatives in a patent claim, typically in the form: a member selected from the group consisting of A, B, and C." *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1372 (Fed. Cir. 2005) (citing *Manual of Patent Examining Procedure* § 803.02 (2004)).

[48] Ex. 1 at A0008 ('363 Patent claim 1).

[49] Ex. 7 at A0076 ('363 Patent Prosecution History, Office Action, pg. 3).

[50] *Id.* at A0078 ('363 Patent Prosecution History, Amendment, pg. 2).

[51] *Id.* at A0079 ('363 Patent Prosecution History, Amendment, pg. 3).

Abraxis's proposed construction of "a medicine suitable for treating cancer" is not consistent with the claim's recitation of specific anticancer agents. These agents are not "medicines suitable for treating cancer," because they could not be administered to a patient without some form of carrier or excipient. The claim language requires that the "medicament useful in treating cancer" is a single component, selected from a group of specific possible compounds, of a multi-component particle. An ordinary reading of the claim language compels the conclusion that the "medicament useful in treating cancer" is only one component of a multi-component particle.

Differences between claims 1, 8 and 9 support a construction that "crystalline medicament useful in treating cancer" is one component of a multi-component article. Claim 8 recites an anticancer composition comprising the particles of claim 1, *i.e.,* a composition comprising the medicine;[52] claim 9 recites a method of treating a mammal comprising administering the anticancer composition (of claim 8).[53] It is well established that different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope.[54] Taken in context, differences among claims 1, 8, and 9 indicate that the term "anticancer composition" is a "medicine suitable for treating cancer" because it is administered to a mammal, and this medicine, which contains the nanoparticles, includes the "crystalline medicament

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[52] Ex. 1 at A0008 ('363 Patent claim 8).

[53] *Id.* ('363 Patent claim 9).

[54] *Karlin Tech. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 971-72 (Fed. Cir. 1999) ("The doctrine of claim differentiation . . . which is ultimately based on the common sense notion that different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope . . .").

useful in treating cancer," *i.e.,* an anticancer agent, as one component of the nanoparticle.

Abraxis's construction of the term "crystalline" is based on an isolated dictionary definition and unsupported by the intrinsic evidence. Throughout the '363 Patent, nanoparticles are identified as for the delivery of poorly water soluble anticancer agents. The specification describes "crystalline"[55] in contradistinction to amorphous materials that "result[ ] from conventional solvent precipitation techniques."[56] Elan's construction is based upon this distinction drawn in the specification. It is also consistent with statements in lines 28-29 of column 2, that "the anticancer agent is present in one or more discrete crystalline phases."[57]

"Crystalline" has a special meaning in the nanoparticulate art and in this patent. In the 1980's, persons of ordinary skill in this art recognized that the "crystallinity was a variable property that ranged from 100% (a perfect crystal) to 0% (amorphous) depending on the state of order/disorder in the lattice.[58] It was also recognized that milling or grinding processes reduced a material's crystallinity.[59] The '363 Patent

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[55] Ex. 1 at A0002 ('363 Patent 1:48-50).

[56] *Id.* ('363 Patent 2:30-31).

[57] Ex. 1 at A0002 ('363 Patent 2:28-29).

[58] Ex. 9 at A0083-A0084 (R. Suryanarayanan and A.G. Mitchell, *Evaluation of Two Concepts of Crystallinity Using Calcium Glucepate as a Model Compound,* 24 Int'l J. of Pharmaceutics, pgs. 1-2 (1985)); *see also* Ex. 10 at A0100 (R. Cahn, *Strategies to Defeat Brittleness,* 332 Nature, pg. 112); *see also*; Ex. 11 at A0102 (A. Saleki-Gerhardt *et al., Assesment of Disorder in Crystalline Solids,* 101 Int'l J. of Pharmaceutics, pg. 237 (1994)).

[59] *See Id.*

teaches these processes as the way to reduce the anticancer agent to nanoparticulate sizes.

The phrase "crystalline medicament useful in treating cancer" properly interpreted, in the context of the intrinsic evidence,[60] means "an anticancer agent as recited in the Markush group of the claim in a nanoparticulate phase, which is different from an amorphous phase."

2. "non-crosslinked"

This term is used in claim 1 of the '363 Patent. The Parties' contentions are found below.

Elan's Construction	*Abraxis's Construction*
means that the surface modifier does not chemically react with the anticancer agent or itself.	means that 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.

The specification of the '363 Patent notes that the "surface modifier does not chemically react with the anticancer agent or itself."[61] As no significant chemical reaction occurs between the anticancer agent and the surface modifier or with the surface modifier itself, both the "medicament" and the "surface modifier" are essentially chemically unaltered by the physical adsorption of the surface modifier to the medicament. This is consistent with the specification, which states that the

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[60] *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1317 (Fed. Cir. 2005).

[61] Ex. 1 at A0003 ('363 Patent 4:56-57).

"individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages."[62]

Abraxis contends that the term "noncrosslinked" means that the surface modifier is essentially free of cross linkages between surface modifier molecules. This definition is circular; it attempts to define a term by using the words of that term itself. In other words, Abraxis defines the term "noncrosslinked" by suggesting that it means "free of cross linkages" without further defining crosslinkage. Accordingly, the term "non-crosslinked" remains undefined by Abraxis and is inconsistent with the express definitions in the specification of the '363 Patent.

3. "surfactant"

The Parties' contentions regarding the proper construction of the term "surfactant" as found in claim 12 of the '363 patent is found below.

Elan's Construction	*Abraxis's Construction*
a stabilizing agent that reduces interfacial tension between or among immiscible substances.	a molecule that consists of two basic parts: a hydrophobic part (a non-polar hydrocarbon chain) and a hydrophilic part (a polar functional group).

"Surfactant" is defined in a general-purpose dictionary as a "surface-active substance,"[63] which in turn is defined as "altering the properties and esp. lowering the tension at the surface of contact between phases."[64] Regarding "surfactants," the

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[62] *Id.* ('363 Patent 4:58-59).

[63] Ex. 3 at A0025 (*Webster's Ninth New Collegiate Dictionary*, pg. 1187 (1991)); *See also* Ex. 12 at A0128 (H. Schott, *Colloidal Dispersions,* Remington's Pharmaceutical Sciences, pg. 286 (17th ed.) (cited on the face of the '363 Patent)); *See also* Ex. 13 at A0144 (*Grant & Hackh's Chemical Dictionary*, pg. 564 (5th ed. 1987)).

[64] Ex. 3 at A0025. (*Webster's Ninth New Collegiate Dictionary*, pg. 1187 (1991)).

specification states only that "preferred surface modifiers include nonionic and anionic surfactants."[65] Nothing in the specification or file history limits these "surfactants" to the ones identified by Abraxis—*i.e.*, molecules having hydrocarbon chains and polar functional groups.

C. *Disputed Terms of the '025 patent*

Elan has asserted claims 1-3 and 13-15 against Abraxis. In addition to the terms discussed above, the parties dispute the construction of the following terms and phrases:

1. "without eliciting adverse hemodynamic effects"

Elan's Construction	*Abraxis's Construction*
means the claimed method of intravenous administration, 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 species of mammals that are sensitive to hemodynamic effects..	means 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.

The claims of the '025 Patent are directed to a method of administering a nanoparticulate composition and not to the composition *per se*.[66] Abraxis's is, in effect, construing these as composition claims, by requiring that the composition achieve specific results in all instances. As a method, the claim is satisfied in each case where the result (avoiding hemodynamic effects) is achieved.

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[65] Ex. 1 at A0003 ('363 Patent 3:65-66); *Id.* at A0008 ('363 Patent claim 12 (further, claim 12 of the '363 Patent illuminates that a "surfactant" is a "surface modifier")).

[66] *See, e.g.*, Ex. 2 at A0011 ('025 Patent Abstract ("Disclosed are methods of intravenous administration of nanoparticulate drug formulations . . .")).

From the plain ordinary meaning of the word "elicit," the claimed method of administration does not "draw forth" adverse hemodynamic effects.[67] These "hemodynamic effects" are defined in the specification: "cardiovascular dysfunctions, such as reduction in arterial blood pressure and cardiac function, including heart rate cardiac output and ventricular contractility."[68] Tables 1-7 report the "hemodynamic and hematological response" of dogs to the claimed methods. Those tables show variations in the mean arterial blood pressure of the test subjects.

Elan's construction is consistent with the prosecution history, in which United States Patent and Trademark Office was told that:

> [a]pplicants unexpectedly discovered that [] 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, or by pretreating the patient with an antihistamine.[69]

Abraxis's construction—requiring results "in substantially all of the mammals to whom the claimed compositions are administered"—is not. The patentees indicates they had made the invention based solely on tests in dogs. Based on this discovery, the inventors recognized that reducing the rate of administration of nanoparticle

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[67] Ex. 3 at A0023 (*Webster's Ninth New Collegiate Dictionary*, pg. 404 (1991) (The word "elicit" means "to draw forth or bring out (something latent or potential).")).

[68] Ex. 2 at A0012 ('025 Patent 1:49-52 ("We have observed that intravascular administration of [] 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.")).

[69] Ex. 14 at A0148 ('025 Patent Prosecution History, Amendment, pg. 4).

compositions below the stated threshold would benefit other sensitive species, such as humans.

2. "infusion rate not exceeding 10 mg/min"

The Parties' contentions for this term as found in the '025 Patent are found below.

Claim 1 of the '025 Patent	
Elan's Construction	*Abraxis's Construction*
means intravenously administering the nanoparticles, which are comprised of the "organic drug substance" and the "surface modifier," at a rate not exceeding 10 milligrams per minute.	means intravenously administering the composition by means of gravity flow, at or below a rate of 10 milligrams per minute of the entire composition, including: (a) the drug, (b) the surface modifier, and (c) the pharmaceutically acceptable carrier.
Claim 13 of the '025 Patent	
Elan's Construction	*Abraxis's Construction*
means intravenously administering the nanoparticles, which are comprised of the "organic drug substance" and the "liposome or colloidal polymeric material," at a rate not exceeding 10 milligrams per minute.	means intravenously administering the composition by means of gravity flow, at or below a rate of 10 milligrams per minute of the entire composition, including: (a) the drug, (b) the liposome or colloidal polymeric material, and (c) the pharmaceutically acceptable carrier.

The focal point of the dispute seems to be what the term infusion rate refers to, *i.e.*, the subject matter being infused at a rate not exceeding 10 milligrams per minute ("mg/min"), although Elan is also uncertain as to what is meant by "means of gravity flow" and where Abraxis finds support for such construction. Abraxis contends that the nanoparticulate composition, *i.e.*, the nanoparticles plus the pharmaceutically acceptable carrier, is infused at a rate not exceeding 10 mg/min. This construction, however, is inconsistent with the plain meaning of the claim terms, specification, including the examples, and the prosecution history.

The claims recite a method of infusing a composition. This composition comprises drug particles or a drug, a surface modifying agent or a liposome or colloidal polymeric material, and a pharmaceutically acceptable carrier, at a particular infusion rate: at or less than 10 mg/min. The teaching of the specification and subject matter of the claims concerns the rate at which the *nanoparticles*, *i.e.*, the organic drug substance coated by a surface modifying agent or the organic drug substance in a liposome or colloidal polymeric material, are infused. While the nanoparticles are infused in suspension in a pharmaceutical carrier, the rate of infusion is not tied to the mass of the carrier. The specification notes that "[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*."[70] The specification further points out that the "[h]emodynamic effect is associated with the surfactant-particle combination."[71] Thus, it is the infusion rate of administration of the nanoparticles, which includes the drug, that is determinative.

To suggest otherwise would essentially eliminate the contribution of the nanoparticles to the recited administration rate, since the suspension liquid forms a much greater part of the whole composition by weight. This requires ignoring that the claims are directed to reducing hemodynamic affects caused by infusion of the nanoparticles above the threshold rate.

The examples disclosed by the inventors convey that one cannot measure the rate of infusion based on the total amount of the composition including the carrier

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[70] '*See* Ex. 2 at A0012 ('025 Patent 1:62-65 (emphasis added)).

[71] Ex. 2 at A0014 ('025 Patent 6:61-62).

because the results experiments are analyzed in terms of the dry weight of the nanoparticles, *i.e.*, milligrams per minute.[72] The values in Table 7 are determined by taking the concentration of nanoparticles in suspension, provided as percent solids, converting that to a weight to volume value, e.g., mg/ml, and multiplying that by the infusion rate of the suspension, provided in milliliters per minute.[73] Thus, the term is explicitly defined as the rate of administration of the nanoparticle.

Furthermore, any contrary definition, *e.g.*, the definition proposed by Abraxis, would exclude the examples from within the claim scope, since the examples describe the rate of administration of the entire suspension in ml/min. Since water is known to weigh about 1000 mg per ml, and infusion rate of suspension of 1 ml/min corresponds to 1000 mg/min; 0.5 ml/min corresponds to 500 mg/min. It is abundantly clear that the infusion rate provided in mg/min refers to the solids infusion rate, and not the suspension infusion rate. The cannons of claim construction disfavor a construction that excludes the specific embodiments.[74]

The prosecution history confirms this construction.

> After identifying the problem to be solved (i.e., adverse hemodynamic reactions associated with intravenous administration of nanoparticulate compositions), Applicants developed experiments designed to distinguish and separate effects arising from components of nanoparticulate formulations and effects of intravenous injections. The experiments comprised using inert polystyrene nanoparticles,

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[72] *Id.* ('025 Patent Table 7).

[73] *Id.*

[74] *See Vitronics Corp.*, 90 F.3d at 1583 (claim construction excluding preferred embodiment is "rarely, if ever, correct and would require highly persuasive evidentiary support").

> surfactant-coated polystyrene nanoparticles, and surfactant alone in *in vivo* tests...Applicants discovered that hemodynamic effect is associated with the surfactant-particle combination.[75]

One skilled in the art would also recognize that the infusion rate not exceeding 10 mg/min refers to the nanoparticles. As noted by John D. Slack *et al.*, intravenous administration of particulate matter, *i.e.*, microspheres, may be associated with significant hemodynamic deterioration effects.[76] Accordingly, the evidence is clear; the term "infusion rate not exceeding 10 mg/min." should be interpreted as the rate of administration based on the infused mass of nanoparticles, whether they are composed of "crystalline organic drug substance" and "surface modifier" or "organic drug substance" and "liposome or colloidal polymeric material," as recited in claims 1 and 13, respectively.

3. "crystalline organic drug substance"

The Parties' contentions of this term as found in claim 1 of the '025 patent are found below.

Elan's Construction	*Abraxis's Construction*
a therapeutic or diagnostic agent in a nanoparticulate phase different from an amorphous phase.	"crystalline" means having a regular arrangement of atoms in a space lattice, as distinguished from amorphous. "organic drug substance" means a crystalline carbon-based therapeutic or diagnostic agent suitable for administration to a mammal.

[75] Ex. 14 at A0149 ('025 Patent Prosecution History, Amendment, pg. 5).

[76] Ex. 15 (John. D. Slack *et al.*, *Acute Hemodynamic Effects and Blood Pool Kinetics of Polystyrene Microspheres following Intravenous Administration*, 70 J. of Pharmaceutical Sciences 6 (1981) (cited in the Specification of the '025 Patent 1:54-55)).

The first and most obvious flaw in Abraxis's construction is that it is superfluous; the term "crystalline" is defined, and the term "organic drug substance" is defined in part as "crystalline." Further, Elan is unaware of any intrinsic evidence that supports this construction of "crystalline." Indeed, as discussed above with reference to the term "crystalline medicament useful in treating cancer," nanoparticles have a nanoparticulate phase, which is recognized by one skilled in the art.

The specification of the '025 Patent references the '684 Patent's description of nanoparticles.[77] Like the '363 Patent discussed above, the '684 Patent informs one skilled in the art that the nanoparticles comprise a drug substance which exists as a discrete, crystalline phase that differs from a noncrystalline or amorphous phase.[78]

The parties agree in part that the term "organic drug substance" means a therapeutic or diagnostic agent. Because Abraxis's construction is unsupported by the intrinsic evidence and further any extrinsic evidence that it may eventually rely upon would be unsupported in the context of this patent, the term "crystalline organic drug substance" should be construed as a therapeutic or diagnostic agent in a nanoparticulate phase different from an amorphous phase.

4. "organic drug substance"

The Parties' contentions regarding the term "organic drug substance" as that term is used in claim 13 of the '025 Patent are found below.

Elan's Construction	*Abraxis's Construction*
a therapeutic or diagnostic agent	a crystalline, carbon-based therapeutic or diagnostic agent suitable for administration to a mammal.

[77] Ex. 2 at A0012 ('025 Patent 1:24-27).

[78] Ex. 5 at A0030 ('684 Patent 3:32-36); *Id.* ('684 Patent 4:28-31).

In accordance with the plain language of claim 13, the claim is directed to a method of administering a nanoparticulate composition to a mammal without eliciting adverse hemodynamic effects. The nanoparticulate drug composition includes particles, which have two main components; the first one being an "organic drug substance"; and the second on being a "liposome or a colloidal polymeric material."[79]

The specification states that the particles "comprise a therapeutic or diagnostic agent" and that such agents "are sometimes referred to as drugs or pharmaceuticals."[80] Nothing in the specification requires that these materials be crystalline. When the patentees intend a crystalline substance, they use the word "crystalline." For example, claim 1 refers to a "crystalline organic drug substance." If "organic substances," per Abraxis's construction are "crystalline," then the use of that word in this phrase would be redundant. Claims are not construed so that terms like crystalline are redundant or surplusage.[81] Abraxis improperly imports a limitation from the specification into the claim by suggesting that the "organic drug substance" must be "crystalline."[82]

Abraxis assertion that the therapeutic or diagnostic agent must be "suitable for administration to a mammal" cannot be square with the structure of the claims. In addition to the "organic drug substance" the claim recites a drug composition that

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[79] Ex. 2 at A0020 ('025 Patent claim 13).

[80] *Id.* at A0015 ('025 Patent 7:24-27).

[81] *See K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1363 (Fed. Cir. 1999); *Elekta Instrument S.A. v. O.U.R. Scientific Int'l, Inc.*, 214 F.3d 1302, 1307 (Fed. Cir. 2000); *Gen. Am. Transp. Corp. v. Cryo-Trans, Inc.* 93 F.3d 766, 770 (Fed. Cir. 1996).

[82] *See Tate Access Floors, Inc. v. Interface Architectural Resources, Inc.*, 279 F.3d 1357, 1371 (Fed. Cir. 2002).

includes particles and a pharmaceutically acceptable carrier thereof. It is this drug composition—not the component "organic drug substance"—that is "suitable for administration to a mammal."

5. "colloidal polymeric material"

The Parties' contentions regarding this disputed term from claim 13 of the '025 patent is represented below.

Claim 13 of the '025 Patent	
Elan's Construction	*Abraxis's Construction*
polymeric carrier or vehicle for the organic drug substance capable of forming a suspension or dispersion.	"colloid" means a stable suspension of microscopic particles, size range one nanometer to one micron, dispersed in a continuous medium. "polymeric" means of, relating to, or consisting of a polymer. "material" means of, relating to, or consisting of matter.

For some unknown reason, Abraxis ignores the teaching of the specification and fragments the claim term into separate, unconnected words. The claim term properly construed is "colloidal polymeric material." The specification notes that in a liposome or colloidal drug delivery system, the bioactive drug is entrapped in the liposome or colloidal particles.[83] Thus, the "colloidal polymeric material" is a carrier or vehicle for the organic drug substance capable of forming a suspension or dispersion. Indeed, the specification notes that colloids are used as carriers for an active drug and form suspensions.[84] Even Abraxis concedes that the colloidal drug delivery system forms a suspension or a dispersion (in a continuous medium).

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[83] Ex. 2 at A0012 ('025 Patent 2:56-60).

[84] *Id.* ('025 Patent 1:45-47).

The claim language further supports Elan's construction. The claim requires a "pharmaceutically acceptable carrier," which would constitute the "continuous medium" for the colloidal drug delivery system to form a dispersion or a suspension. The specification further supports this conclusion, *i.e.*, the organic drug substance is entrapped in the liposome or colloidal polymeric material, for the formation of a suspension or dispersion.

VI. CONCLUSION

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

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