UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 11-12226-RGS

CEPHALON, INC. and ACUSPHERE, INC.

v.

CELGENE CORP. and ABRAXIS BIOSCIENCE, LLC

MEMORANDUM AND ORDER ON CLAIM CONSTRUCTION

December 3, 2013

STEARNS, D.J.

Acusphere, Inc., and its exclusive licensee Cephalon, Inc. (collectively, Acusphere), brought this lawsuit against Celgene Corp. and Abraxis BioScience, LLC (collectively, Celgene),[1] alleging that Celgene's antitumor drug Abraxane infringes U.S. Patent RE40, 493, "Porous Paclitaxel Matrices and Methods of Manufacture Thereof" (the '493 patent). To resolve the dispute over the reach of the '493 patent, the parties ask the court to construe the meaning of eleven of the patent's asserted claims. A hearing on the joint request was held on August 28, 2013.

BACKGROUND

[1] Acusphere's Complaint also named Abraxis BioScience, Inc. as a defendant in the suit. The parties subsequently stipulated to the dismissal of Abraxis based on Celgene's representation that Abraxis is merely a holding company that does not manufacture, market, sell, distribute, or profit from Abraxane.

The '493 patent teaches a pharmaceutical composition of paclitaxel that dissolves more than a thousand times faster than non-formulated paclitaxel. Paclitaxel is a taxane compound extracted from the bark of the Pacific yew tree. Taxanes are chemotherapeutic agents that slow the spread of tumor cells in the body by inhibiting cell division. Taxanes, however, are nearly indissoluble in water, making dosages difficult to administer without causing extreme discomfort. The prior formulation of paclitaxel required several hours to infuse and contained Cremophor – a solubizing agent that can cause severe allergic reactions. The '493 patent teaches a remedy for insolubility by integrating paclitaxel (or another taxane) into a dry, porous matrix containing pharmaceutical excipients. Immersed in water, the matrix releases nanoparticles and microparticles of paclitaxel. These particles, in turn, exhibit increased aqueous solubility and dissolve rapidly when diluted in a parenteral fluid medium prior to intravenous injection.

CLAIM CONSTRUCTION

Legal Standards

Claim construction is a question of law for the court's determination. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 970-971 (Fed. Cir. 1995) (en banc). In performing the required analysis, the court first looks to the language of the claims themselves. "It is a bedrock principle of patent law

that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotation marks and citation omitted). A claim term is to be construed in accordance with its "ordinary and customary meaning," which is the "meaning that the term would have to a person of ordinary skill in the art [PHOSITA] in question at the time of the invention, i.e. as of the effective filing date of the patent application." *Id.* at 1312. The ordinary and customary meaning of a claim term is determined "in the context of the entire patent, including the specification." *Id.* at 1313.

Because the purpose of the specification is to teach one skilled in the art the process for replicating the invention, the specification will, in most cases, be "'dispositive; it is the single best guide to the meaning of a disputed term.'" *Id.* at 1315, quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "[T]he specification may reveal a special definition given to a claim term by a patentee that differs from the meaning it would otherwise possess." *Id.* at 1316. However, "the written description in such a case must clearly redefine a claim term so as to put a reasonable competitor or one reasonably skilled in the art on notice that the patentee intended to so redefine that claim term." *Elekta Instrument S.A. v. O.U.R. Scientific Int'l, Inc.*, 214 F.3d 1302, 1307 (Fed. Cir. 2000) (internal quotations and citation omitted).

"Absent an express intent to impart a novel meaning, claim terms take on their ordinary meaning." *Id*.

The final element of intrinsic evidence to which a court may turn for guidance is the prosecution history of the patent. While it may not be as reliable as the specification, the 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, making the claim scope narrower than it would otherwise be." *Phillips*, 415 F.3d at 1317. "Where an applicant argues that a claim possesses a feature that the prior art does not possess in order to overcome a prior art rejection, the argument may serve to narrow the scope of otherwise broad claim language." *Seachange Int'l, Inc. v. C-COR Inc.*, 413 F.3d 1361, 1372-1373 (Fed. Cir. 2005).

Disputed Terms

The disputed terms are part of all asserted claims. Independent Claim 1 of the '493 patent is representative.

> A pharmaceutical composition comprising a porous matrix formed of a hydrophilic excipient, a wetting agent and nanoparticles and microparticles of a taxane, wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5μm and a total surface area greater than about 0.5m^2/mL, wherein the porous matrix is in a dry powder form, and wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane

> nanoparticles and microparticles, wherein the dissolution rate of the taxane nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed taxane.

A. "Nanoparticles" and "Microparticles"

All of the asserted claims require a matrix formed of, *inter alia*, "nanoparticles and microparticles of taxane . . . hav[ing] a mean diameter between about 0.01 and 5μm . . . ." Acusphere argues that because there are no universally accepted size ranges distinguishing nanoparticles from microparticles, it acted as its own lexicographer for purposes of the '493 patent in assigning the particles an undifferentiated diameteric range. Celgene responds that for a PHOSITA, the terms refer to two distinct types of particles, differentiated from one another by size, with nanoparticles being the smaller of the two. Celgene argues that in ordinary usage, nanoparticles are understood to have a diameter between 1 and 1,000 nanometers (nm),while microparticles have a diameter between 1 to 1,000 microns (μm). Morever, according to Celgene, Acusphere's lexicographic argument conflates the diameters of particles in a composition with the *mean* diameter of the population, which renders any distinction between nanoparticles and microparticles in the claims meaningless. As Celgene sees it, "a mean diameter value does not inform a PHOSITA about the size of any particle in a composition, and therefore cannot define whether a composition contains

nanoparticles, microparticles, or both." Def.'s Reply Br. at 1-2. Stated another way, if "nanoparticles *and* microparticles" are defined indistinguishably by their mean diameter, the population could theoretically be comprised entirely of nanoparticles *or* microparticles, contrary to the conjunctive language of the claim.

Finally, Celgene argues that the prosecution history contradicts Acusphere's proposed construction. Claim 1 of what is now the '493 patent originally described the porous matrix as formed of "microparticles of a taxane," with no mention of nanoparticles. The Examiner rejected the claim as obvious based principally on the Desai and Hanes prior art. The Examiner wrote that "a composition and methods for making such, containing paclitaxel and a surfactant, *in micron size* and with a reduced surface area would have been known to one with ordinary skill in the art." Office Action, Nov. 28, 2001, at 4 (emphasis added). In response to this rejection, Acusphere substituted "nanoparticles and microparticles" in place of "microparticles" in the claims, without altering the size range of the particles (0.01 to 5μm), arguing that the Hanes patent disclosed compositions containing microparticles, but not nanoparticles. PTO Corr., Feb. 22, 2002, at 6.

The Examiner again rejected the claims, writing that although Acusphere "asserts that Hanes does not teach the use of nanoparticles in his formulation

. . . it is the examiner's understanding that nanoparticles is merely the size of a particle, and whereas Hanes does not explicitly state the use of nanoparticles, Hanes does teach using particles the same size as the instant invention (5μm)." Office Action, June 3, 2002, at 3. Again responding, Acusphere argued that Desai teaches compositions of nanoparticles and Hanes compositions of particles greater than 5μm. PTO Corr., Aug. 7, 2002, at 5. In distinguishing the '493 patent from the prior art, Acusphere wrote that

> [t]he combination of Desai and Hanes would not lead one skilled in the art to form a porous matrix which dissolves immediately upon exposure to an aqueous medium to release nanoparticles and microparticles of a taxane that have a high surface area and dissolve rapidly. Rather, the combination would lead one to design a formulation where the matrix dissolved rapidly to yield a colloidal solution of taxane. None of the art teaches making a taxane with a faster dissolution rate. None of the art teaches that the available surface area of the taxane should be increased so that the dissolution rate of the taxane rather than the matrix should be increased.

Id. at 5 (emphasis deleted).

While there is no universally agreed definition of the size of a nanoparticle (some sources place the upper range as low as 100nm), the better evidence is that Acusphere's '493 patent in fact relies on the widely accepted definition propounded by Celgene. Telling in this regard is a 1996 textbook co-authored by Howard Bernstein, one of the named inventors on the '493 patent, which states that "[t]he size range covered by microparticles is, according to

definition, between 1 and 1000μm," while nanoparticles range from "1 to 1000nm." *Microparticulate Systems for the Delivery of Proteins and Vaccines* (Smadar Cohen and Howard Bernstein eds., 1996) at 62. Even more telling is the fact that other Acusphere patents in the same field, many credited to the inventors of the '493 patent, incorporate the definition taught by Cohen & Bernstein.

It is true, as Acusphere reminds us, that an inventor is entitled to deference when it acts as its own lexicographer. *See CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366-1367 (Fed. Cir. 2002) (the heavy presumption in favor of ordinary meaning can be overcome when the patentee-lexicographer clearly sets forth a definition of the disputed claim term in either the specification or the file history). Here, however, there is very little evidence in the disputed patent or its history to suggest that Acusphere left a Websterian imprint on the '493 patent. While the '493 patent defines other terms in a definitional format (consistent with Acusphere's practice in other of its patents), it does not formally define nanoparticles or microparticles. While the definition of a patent claim term may be drawn by implication from the specification, to rely successfully on this canon, the patentee must use the disputed term "throughout the entire patent specification, in a manner consistent with only a single meaning . . . ." *Bell Atl. Network Servs., Inc. v.*

Covad Commc'ns Grp., Inc., 267 F.3d 1258, 1271 (Fed Cir. 2001) (citation omitted). But, the only sentence that Acusphere can point to in the specification as supporting a definition by inference, does not even mention nanoparticles. *See* '493 patent col.1 ll.66-67, col.2 ll.1-5 ("Paclitaxel is provided in a porous matrix form which forms nanoparticles and microparticles of paclitaxel when the matrix is contacted with an aqueous medium. The porous matrix with paclitaxel yields upon contact with an aqueous medium *microparticles having a mean diameter between about 0.01 and 5μm . . . .*") (emphasis added).[2]

Acusphere's proposed construction is difficult to square with the claims language of the patent. Claim 1 requires that the matrix be "formed of . . . nanoparticles and microparticles of a taxane, wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5μm and a total surface area greater than about 0.5m²/mL . . . ." If Acusphere intended to define "nanoparticles and microparticles" by the mean diameter of the

[2] Acusphere also argues that Claim 6, which refers to "the mean diameter of the taxane microparticles" as being "between about 0.50 and 5μm," defeats Celgene's proposed construction because it is impossible to have a population of microparticles that are each larger than 1μm in diameter and yet collectively exhibit a mean diameter as low as .50μm. Any inconsistency, however, is a product of Acusphere's at times seemingly random omission of the term "nanoparticles" in the patent.

particles, the separate limitation "wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5μm" would be superfluous. Moreover, if the court were to adopt Acusphere's construction, a natural reading of the claim would transform the surface area requirement ("greater than about 0.5m^2/mL") from a separate limitation into a component of the definition of the particles. Acusphere offers no explanation as to why its construction of nanoparticles and microparticles does not also include the specified surface area, nor does it offer any evidence that surface area has ever been used to define the terms.

Finally, the prosecution history provides convincing evidence that Acusphere limited the scope of the '493 patent by distinguishing nanoparticles and microparticles by their size. After an initial rejection by the Examiner based in part on the "micron size" of the particles disclosed in the patent, Acusphere added nanoparticles to the claims and distinguished the claimed invention from the prior art by asserting that Hanes' compositions did not include nanoparticles. Although the Examiner appears to have rejected Acusphere's traversal because of the upper range (5μm) of the particles disclosed in the '493 composition, it is clear from the prosecution history that Acusphere's position before the PTO was that the formulations of the '493 patent included two separate types of particles, characterized by their size. *See*

Andersen Corp. v. Fiber Composites, LLC, 474 F.3d 1361, 1374 (Fed. Cir. 2007) ("We have made clear that an applicant's argument that a prior art reference is distinguishable on a particular ground can serve as a disclaimer of claim scope even if the applicant distinguishes the reference on other grounds as well.") (alterations deleted).

For the above reasons, Celgene's construction will be adopted. *See Texas Digital Sys., Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 1202 (Fed. Cir. 2002) ("[U]nless compelled otherwise, a court will give a claim term the *full range of its ordinary meaning* as understood by persons skilled in the relevant art.") (emphasis added).

B. "Nanoparticles and Microparticles *of a taxane*"

The parties next dispute whether the claim term "of a taxane" requires that the particles be composed *only* of a taxane drug. Claim 1 reads in relevant part: "A pharmaceutical composition comprising a porous matrix formed of a hydrophilic excipient, a wetting agent and nanoparticles and microparticles of a taxane . . . ." Acusphere argues that because the claim uses the term "comprising," the composition includes, but is not limited to, taxane particles. *See, e.g., Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l, Inc.*, 246 F.3d 1336, 1348 (Fed. Cir. 2001). The term "comprising" as used in patent law is an open-ended transitional term, and as utilized in the '493 patent,

appears intended to accommodate additional unspecified components of the claimed "pharmaceutical composition." *See Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1271 (Fed. Cir. 1986) (the term "comprising" means "all of the preceding and more"). The term by its positioning in the claim, however, does not operate to unzip the phrase "nanoparticles and microparticles of a taxane" because the claim does not specify "nanoparticles and microparticles *comprising a* taxane." *See Tivo, Inc. v. Echostar Commc'ns Corp.*, 516 F.3d 1290, 1304 (Fed. Cir. 2009) ("[A]lthough the open ended term 'comprising' is used to refer generally to the limitations of the hardware claims, the 'assembles' limitation itself does not contain that term.").

As a fallback, Acusphere points to the structure of the matrix in which the taxane particles are suspended. In addition to the particles, the matrix is composed of hydrophilic excipients and wetting agents, some of which, according to the specification, are not water soluble. The specification also provides that "[u]pon contact with an aqueous medium, water penetrates through the highly porous matrix to dissolve *the water soluble excipients* in the matrix." '493 patent col.3 ll.54-57 (emphasis added). From this, Acusphere argues that "one skilled in the art would know that the microparticles and nanoparticles of a taxane that remain when the matrix dissolves would not only be comprised of the drug, but would include other components, like excipients,

associated with them as well." Pl.'s Br. at 17. Acusphere also points out that neither the claims nor the specification require a "purification step or purity measurement after dissolution of the matrix." Pl.'s Reply Br. at 9. Moreover, "the method and equipment used in the file history to measure particle size cannot distinguish between particles of pure taxane and particles associated with other components of the paclitaxel matrix"; thus, Acusphere contends "it is illogical to conclude that the patent would require that the claimed particles be pure taxane." *Id*.

Celgene responds that it is beside the point that the matrix may be formed of components in addition to the taxane particles, because as Celgene reads the patent, "the specification always and consistently describes the active ingredient, i.e., the nanoparticles and microparticles of a taxane (such as paclitaxel), as being separate and distinct from excipients that form the matrix, and describes the nanoparticles and microparticles of a taxane as being left or remaining after the excipients (including the hydrophilic excipient and wetting agent) that form the matrix dissolve upon exposure to an aqueous medium . . . ." Def.'s Br. at 20; *see, e.g.*, '493 patent col.3 ll.54-58 ("Upon contact with an aqueous medium, water penetrates through the highly porous matrix to dissolve the water soluble excipients in the matrix. A suspension of paclitaxel particles in the aqueous medium remains."); '493 patent col.1 ll.66-67, col.2 l.1

("Paclitaxel is provided in a porous matrix form which forms nanoparticles and microparticles of paclitaxel when the matrix is contacted with an aqueous medium.").

Celgene also cites the prosecution history in support of its proposed construction. After an initial rejection based on the prior art, Acusphere amended claims 1 and 17 to add, among other elements, the limitation that "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles." PTO Corr., Feb. 22, 2002 at 2, 4. In the course of amending the claims, Acusphere distinguished the prior art as follows.

> Hanes discloses a formulation that has two embodiments, one formed of a biodegradable hydrophic, non-water soluble polymer encapsulating drug, which can include a surfactant . . . and the other just of drug and surfactant . . . Desai discloses controlled release, polymer encapsulated formulations. Desai teaches away from anything that would dissolve almost immediately upon administration, to release drug in particulate form.

Id. at 6.

In describing the claimed composition to the PTO, Acusphere wrote, "[t]he matrix is rapidly dissolved upon contact with an aqueous solution, yielding nanoparticles and microparticles of the taxane, *no longer associated with the matrix*. The nanoparticles and microparticles of the taxane lead to an increase[d] rate of dissolution of the taxane." *Id.* at 6 (emphasis added).

Celgene argues that the plain meaning of this description is that Acusphere "relinquished any construction that would permit the nanoparticles and microparticles of a taxane to be formed of the other components that form the matrix, i.e., the hydrophilic excipient or the wetting agent, in addition to the taxane drug." Def.'s Br. at 23. "In particular, the applicants made explicit that the claimed nanoparticles and microparticles of a taxane did not encompass controlled release, polymer encapsulated particles containing paclitaxel and albumin, such as was taught in the prior art." *Id*.

After a second rejection, Acusphere responded that "[t]he combination of Desai and Hanes would not lead one skilled in the art to form a porous matrix which dissolves immediately upon exposure to an aqueous medium to release *nanoparticles and microparticles of a taxane that have a high surface area and dissolve rapidly*." PTO Corr., Aug. 7, 2002, at 5 (emphasis added). According to Celgene, a PHOSITA would understand this statement to mean that taxane is on the surface of the claimed "nanoparticles and microparticles of a taxane," and that the particles' surfaces are free of any additional material or ingredient – such as a polymer of albumin – that would otherwise encapsulate the drug.

Acusphere attempts to distance itself from the prosecution history by arguing that its characterizations of the prior art were mere descriptions, and

should not be viewed as attempts to draw distinctions with Desai and Hanes profound enough to serve as limitations on the claims. As Acusphere phrases it: "[W]hen the Applicants sought to distinguish Desai and Hanes, it was on the basis of the nanoparticles and microparticles themselves dissolving and not whether or not other excipients were associated with those particles." Pl.'s Reply Br. at 10; *see* PTO Corr., Aug. 7, 2002. Acusphere also objects to Celgene's reading of its statement to the Examiner that upon dissolution of the matrix, the taxane particles are "no longer associated with the matrix." According to Acusphere, the inventors were simply describing the "system of the matrix changing state," and did not mean to imply that every non-taxane component of the matrix had to dissolve to leave pure taxane. Pl.'s Reply Br. at 9.

When the plain language of the claim is read in the context of the prosecution history and particularly the effort to escape the teachings of Desai and Hanes, Acusphere's after-the-fact assertion that what was said to dissuade the Examiner from yet another rejection was nothing more than inconsequential rhetoric, is unconvincing at the least.[3] "All limitations in a

[3] "It is well established that statements made during prosecution are used to interpret the scope and meaning of ambiguous claim terminology." *Schumer v. Lab. Computer Sys., Inc.*, 308 F.3d 1304, 1312-1313 (Fed. Cir. 2002).

claim must be considered meaningful." *Lantech, Inc. v. Kelp Machine Co.*, 32 F.3d 542, 546 (Fed. Cir. 1994). Consequently, the court construes the term "of a taxane" to mean "particles formed of only a taxane drug."

C. "Hydrophilic excipient"

Celegene would construe the term "hydrophilic excipient" to mean "an inert component of a pharmaceutical product that will *dissolve upon contact with an aqueous medium*." In support of this construction, Celgene points to the claim language requiring the matrix to dissolve upon exposure to an aqueous medium so as to leave the nanoparticles and microparticles of taxane. Because the matrix is formed, in part, of a hydrophilic excipient, Celgene argues that it follows logically that the hydrophilic excipient, too, dissolves upon exposure to the aqueous medium.

Acusphere responds that it is the *system* of the matrix that must dissolve, and not the components comprising the matrix. Because the matrix is made up of "at least 1 to 95% of the taxane," and the claims depend on the matrix leaving behind nanoparticles and microparticles of taxane upon dissolution, Acusphere argues that nothing in the claim requires every component of the matrix to dissolve. Acusphere further points out that the specification implies that not every excipient, but only water soluble excipients, will dissolve. *See* '493 patent col.3 ll.54-57 ("Upon contact with an aqueous medium, water

penetrates through the highly porous matrix to dissolve the *water soluble excipients* in the matrix.") (emphasis added).

There is nothing in the intrinsic evidence that alters the ordinary and customary meaning of "hydrophilic."[4] The term is not limited to substances that dissolve in water. Both standard and technical dictionaries support Acusphere's construction.[5] *See* Merriam-Webster's Collegiate Dictionary (10th Edition) (1999) ("of, relating to, or having a strong affinity for water"); Stedman's Medical Dictionary (1995) ("Having an affinity for water; readily absorbing or dissolving in water"); International Union of Pure and Applied Chemistry, "Glossary of Terms Used in Physical Organic Chemistry," Pure & Appl. Chem., Vol. 66, pp. 1077-1184, at 1123 (1994) ("water loving"). Thus, the court construes the term "hydrophilic" to mean "an inert substance in a drug vehicle having an affinity for water."

D. "[A porous matrix] formed of a hydrophilic excipient, a wetting agent and nanoparticles and microparticles of a taxane"

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[4] The parties do not substantively dispute the meaning of the term "excipient."

[5] "[D]ictionaries, encyclopedias and treatises, publicly available at the time the patent is issued, are objective resources that serve as reliable sources of information on the established meanings that would have been attributed to the terms of the claim by those of skill in the art." *Texas Digital Sys., Inc.*, 308 F.3d 1193, 1202 (Fed. Cir. 2002).

Based on the prosecution history, Celgene contends that the matrix must be formed of four separate and distinct components: (1) a hydrophilic excipient, (2) a wetting agent, (3) nanoparticles of a taxane, and (4) microparticles of a taxane. Acusphere initially claimed a porous matrix formed of only a wetting agent and microparticles of a taxane, but added a hydrophilic excipient and nanoparticles of a taxane after an obviousness rejection by the Examiner. It wrote that the Hanes prior art disclosed a surfactant and drug, but "there are no nanoparticles, nor is there a matrix formed of a hydrophilic excipient that dissolves upon contact with water . . . ." PTO Corr., Feb. 22, 2002, at 6. Celgene argues that because a surfactant disclosed in the Hanes patent is also a wetting agent, Acusphere's addition of "hydrophilic excipient" to the claims must mean a substance other than the wetting agent.

No amount of argument, however, can overcome the plain language of the claims and the specification. Dependent claims 45-47 explicitly states that "the hydrophilic excipient is the wetting agent."[6] '493 patent cls.45-47. Moreover, the specification states that "hydrophilic excipients, such as water soluble polymers or sugars . . . can serve . . . as wetting agents . . . ." *Id*. at col.3

[6] Celgene argues that because these claims were added during the reissue process, they impermissibly seek to recapture subject matter surrendered during prosecution and are thus invalid. As discussed above, the prosecution history does not support this argument.

ll.51-54. Although Acusphere wrote that the prior art contained a wetting agent but not a hydrophilic excipient, there is no indication that it intended to include a limitation that the substances be distinct. "[A porous matrix] formed of a hydrophilic excipient, a wetting agent and nanoparticles and microparticles of a taxane," is therefore construed to mean that the porous matrix is formed of at least three components including (1) a hydrophilic excipient, (2) a wetting agent, and (3) nanoparticles and microparticles of a taxane, wherein the hydrophilic excipient and the wetting agent need not be distinct from one another.

E. "Mean diameter" and "wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5µm and a total surface area greater than about 0.5m²/mL, wherein the porous matrix is in a dry powder form"

Celgene first contends that the claim term "mean diameter" is indefinite because nothing in the intrinsic evidence specifies the mean diameter to be calculated or the calculation methodology to be used. *See Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1341 (Fed. Cir. 2003) (finding claims invalid because, depending on the preparation method chosen, "the testing results will necessarily fall within or outside the claim scope"). The prosecution history makes clear, however, that the '493 patent refers to a

volume mean diameter measurement. As discussed earlier in Section A, Acusphere attempted to distinguish the Hanes patent, in part, based on the size of the taxane particles. In his exchanges with Acusphere, the Examiner compared the size of the Hanes particles with those claimed in the '493 patent. The Hanes patent measured particle size by "mass mean diameter," which is a synonym for "volume mean diameter." '913 patent col.7 l.54. Thus, in order to make the particle size comparison with Hanes, the Examiner and Acusphere recognized that the volume mean diameter defined the particle size for the '493 patent as well.

The Hanes patent also disclosed that "the mass mean diameter of the particles can be measured using a Coulter Multisizer II." *Id*. at col. 7 l.55. Acusphere's provisional application (from which the '493 patent derives) states that "[t]otal surface area values can be provided using standard Coulter Counter equipment and techniques." U.S. Provisional Application No. 60/158,659. Acusphere argues persuasively that the prosecution history runs counter to Celgene's claim that the patent does not specify a technique to be used to measure mean diameter. Acusphere also points to the instruction in the '493 patent's specification that the "[t]otal surface area values of the microparticles can be determined using standard particle sizing equipment and techniques." '493 patent col.3 ll.21-23. And, finally, Acusphere maintains that

a PHOSITA would have no difficulty measuring particle size with a reasonable degree of accuracy using any one of a number of standardized techniques.

Celgene next argues that if the claim is not indefinite, it should be construed to mean that the diameter and surface area measurements refer only to nanoparticles and microparticles of taxane, and further, that the measurements are to be made when the matrix is in a dry powder form. Why Celgene is right in the first instance is discussed in Section B. However, the specification makes clear that the measurements are to be made after the matrix comes into contact with an aqueous medium. There it is said that "[t]he porous matrix with paclitaxel *yields upon contact* with an aqueous medium microparticles having a mean diameter between about 0.01 and 5 um and a total surface area greater than about 0.5 m^2/mL." '493 patent col.2 ll.1-5 (emphasis added); *see also id.* at col.3 ll.15-21 ("The matrix *must yield* microparticles of paclitaxel, *upon contact* with an aqueous medium which preferably have a diameter between about 10nm and 5µm, more preferably between about 50nm and 5µm.") (emphasis added). This construction is reinforced by the "m^2/mL" unit of measurement used to describe the surface area of the nanoparticles and microparticles in the claims. If the taxane particles were intended to be measured in powder form, the unit of measurement would be "m^2/g" – the units used in the specification to describe

the results of surface area analysis of the dry porous matrix.[7]

The court will construe the disputed claim term "mean diameter" as a proxy for the term "volume mean diameter." The court sees no need to construe the phrase "wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5μm and a total surface area greater than about 0.5m²/mL, wherein the porous matrix is in a dry powder form." It has a plain and ordinary meaning when read in context with the court's ruling in Section B.

F. "Matrix dissolves" and "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles"

Celgene argues that this claim limitation is indefinite on two grounds. First, it asserts that the claim is "nonsensical" because the patent claims as a whole require that the matrix be formed of nanoparticles and microparticles of a taxane, while also requiring that the matrix dissolve to leave the taxane particles. The court does not see the inconsistency. While the claim language

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[7] Celgene also contends that the specification states that the claim phrase "total surface area" means the "sum of internal and external surface area." But the specification refers to the surface area of the dry porous matrix as measured by BET analysis, not the surface area of the nanoparticles and microparticles remaining in suspension after the matrix is dissolved.

and specification repeatedly state that the matrix must dissolve to leave behind taxane particles, nowhere is it said that the dissolving of the matrix is defined "by reference to whether all of the taxane nanoparticles and microparticles dissolve." Def.'s Br. at 38. The specification states that "[u]pon contact with an aqueous medium, water penetrates through the highly porous matrix to dissolve the water soluble excipients in the matrix. *A suspension of paclitaxel particles in the aqueous medium remains.*" '493 patent col.3 ll.54-58 (emphasis added). The patent thus contemplates two distinct steps: "(1) dissolution of the porous matrix to leave nanoparticles and microparticles of paclitaxel suspended in the aqueous reconstitution medium; and (2) the subsequent dissolution of the nanoparticles and microparticles of paclitaxel that occurs in a larger volume of aqueous medium or once administered to the patient." Pl.'s Reply Br. at 20. This construction is confirmed by the prosecution history. In distinguishing the '493 patent from Hanes, Acusphere wrote that "[n]one of the art teaches that the available surface area of the taxanes should be increased so that the dissolution rate of the taxane *rather than the matrix* should be increased." PTO Corr., Aug. 7, 2002, at 5 (emphasis in original); *see also id.* at 6 ("Applicants' claimed process *yields taxane that dissolves* at a rate that may be 1000 times shorter than for bulk taxane.") (emphasis added).

Celgene's second argument for indefiniteness is that the claim phrase states only a "functional" limitation and that the patent "fails to provide the qualitative parameters necessary for a PHOSITA to determine whether, for any given composition, the matrix dissolves to leave the taxane nanoparticles and microparticles." Def.'s Reply Br. at 23. "In particular, the claims do not specify the conditions, such as the specific volume or type of aqueous medium, that must be added to satisfy the limitation that the matrix will dissolve but the taxane nanoparticles and microparticles will not . . . ." Def.'s Br. at 39. Acusphere responds that the patent provides that the formulations do not require a particular aqueous medium, but clearly contemplates various embodiments. Pl.'s Reply Br. at 22 (citing the specification statement "an aqueous medium, such as physiological saline" and the T80/PBS solution disclosed in Example 3). Thus, Acusphere contends, "the patent only requires assessing infringement in the given aqueous medium and volume used as the reconstitution medium. If taxane nanoparticles and microparticles are left in the reconstitution medium, the claim limitation is met." *Id*. Because the court agrees with Acusphere on this point, it will construe "matrix dissolves" as conforming to its plain and ordinary meaning.

However, for the reasons discussed in Section B, the court will largely adopt Celegene's proposed interpretation that the hydrophilic excipients and

wetting agents may not attach to the taxane drug. The second part of the disputed claim is therefore construed to mean that the porous matrix must dissolve to leave only taxane drug in the form of nanoparticles and microparticles that are no longer associated with either the hydrophilic excipient or the wetting agent.

G. "Solution" and "wherein the dissolution rate of the taxane nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed taxane"

Celgene also contends that this claim phrase is indefinite because, as discussed above in Section F, "dissolution rate is concentration dependent, and the claims do not specify the particular concentrations at which this claim limitation must be met." Def's Br. at 44. Acusphere responds that Example 3 of the patent clearly defines the method of determining the dissolution rate of the taxane particles relative to unprocessed taxane and notes that in explaining the new claim limitation, it specifically referred the Examiner to Example 3 and the results associated with the testing in Figure 1. PTO Corr., Aug. 7, 2002, at 3, 6. The court will therefore adopt Acusphere's construction of the phrase "wherein the dissolution rate of the taxane nanoparticles and microparticles in an aqueous solution is increased relative to unprocessed

taxane" to include "as measured according to Example 3 of the '493 patent."[8] Finally,"solution" is a word of ordinary meaning that is given no special definition in the '493 patent. Consequently, the court will adopt Celgene's construction: "a homogenous mixture of two or more substances."

ORDER

The disputed claim terms will be construed for all further purposes in this litigation as the court has indicated in the body of this opinion.

SO ORDERED.

/s/ Richard G. Stearns

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UNITED STATES DISTRICT JUDGE

[8] Celgene argues that, if Acusphere's construction is adopted, it should be further construed to exclude formulations in which after exposure to an aqueous medium, particles of paclitaxel and albumin can remain stable in a suspension for at least 3 days at a concentration between 1.2 to 3mg/ml. This interpretation is based on Acusphere's statement to the Examiner that "Desai teaches that the dry particles reconstituted in aqueous solutions (col. 6, lines 10-17) are stable for at least three days (*see* col. 12, lines 33-40). Not only do Desai's taxane particles not dissolve upon contact with water, but it is critical to have them remain as a suspension in order to achieve the desired tissue distribution and concentration (col. 6, lines 46-56)." PTO Corr., Aug. 7, 2002, at 6. It is unclear how this description of the dissolution of the matrix and the stability of the remaining taxane particles relates to the dissolution rate of the taxane particles themselves.