Nos. 2014-1411, -1442

United States Court of Appeals for the Federal Circuit

CEPHALON, INC. AND ACUSPHERE, INC.,

Plaintiffs-Appellants,

v.

ABRAXIS BIOSCIENCE, LLC. AND CELGENE CORP.,

Defendants-Cross-Appellants,

and

ABRAXIS BIOSCIENCE INC.,

Defendant.

Appeal from the United States District Court for the District of Massachusetts, No. 11-CV-12225, Hon. Richard G. Stearns.

BRIEF FOR DEFENDANTS-CROSS-APPELLANTS

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CERTIFICATE OF INTEREST

Counsel for Defendants-Cross-Appellants Abraxis Bioscience, LLC and Celgene Corporation hereby certifies the following:

1. *The full name of every party represented by me is*:

Abraxis Bioscience, LLC and Celgene Corporation.

2. *The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is*:

Not applicable.

3. *All parent corporations and any publicly held companies that own 10 percent of more of the stock of the party or amicus curiae represented by me are*:

Abraxis Bioscience, LLC is owned by Abraxis Bioscience, Inc., which in turn is directly owned by Celgene Corporation. No other publicly held company owns 10 percent or more of the stock of Abraxis Bioscience, LLC or Celgene Corporation.

4. *The name of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are*:

Jones Day (J. Patrick Elsevier, Ph.D.; Christopher M. Morrison; Anthony M. Insogna; Gregory A. Castanias; Philip T. Sheng; Julie M. Baher (no longer with firm) and Danielle Olivotto (no longer with firm)).

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Parties

Acusphere	Plaintiffs-Appellants Cephalon, Inc. and Acusphere, Inc.
Celgene	Defendants-Cross-Appellants Celgene Corporation and Abraxis Bioscience, LLC

Patent-in-Suit

the ’493 patent	U.S. Patent No. RE40,493

Defined Terms

A__	Joint Appendix page(s)
District Court	United States District Court for the District of Massachusetts
Court	United States Court of Appeals for the Federal Circuit
Desai	U.S. Patent No. 6,096,331
Hanes	U.S. Patent No. 5,855,913
the ’317 Patent	U.S. Patent No. 6,610,317
AcuBr.	Brief of Plaintiffs-Appellants Cephalon, Inc. and Acusphere, Inc.

STATEMENT OF RELATED CASES

No other appeal in or from the same civil action was previously before this or any other appellate court. Counsel for Defendants-Cross-Appellants are not aware of any other cases pending in this or any other court that will directly affect or be directly affected by this Court's decision in this appeal.

STATEMENT OF JURISDICTION

The District Court had jurisdiction over this patent-infringement action under 28 U.S.C. §§ 1331 and 1338(a). This Court has jurisdiction over this appeal under 28 U.S.C. § 1295(a). The parties' notices of appeal from the March 18, 2014 Final Judgment were timely filed. *See* Fed. R. App. P. 4(a)(1)(A), 4(a)(3).

On May 23, 2014, Acusphere moved to dismiss Celgene's cross-appeal of the District Court's ruling that the claims in suit are not indefinite as a matter of law. Dkt. No. 17. On June 30, 2014, the Court denied Acusphere's motion, concluding: "Because [Celgene's] appeal in furtherance of its invalidity defense does not appear to be seeking affirmance on an alternative ground but to alter the judgment to include invalidity, it appears that the cross-appeal is proper." Dkt. No. 22 (citing *Bailey v. Dart Container Corp. of Mich*., 292 F.3d 1360, 1362 (Fed. Cir. 2002)).

STATEMENT OF THE ISSUES

A. Acusphere's Appeal:

Following the District Court's claim-construction order, Acusphere stipulated to a judgment of non-infringement because it could not prove infringement under any one of four constructions now on appeal—"nanoparticles," "microparticles," "nanoparticles and microparticles of a taxane," and "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane

nanoparticles and microparticles." A28–31. Because Acusphere stipulated that it cannot prove infringement under the District Court's construction of any of these four terms, affirmance is appropriate if even one of those challenged constructions is correct.

Celgene's counter-statement of the issues is:

1. Did the District Court correctly construe the claim terms "nanoparticles" and "microparticles" to refer to those terms' ordinary and customary meanings in the field of pharmaceutical science (i.e., "particles that have a diameter of between about 1 to 1000 nanometers and less than that of microparticles," and "particles that have a diameter of between about 1 to 1000 microns and greater than that of nanoparticles," respectively)?

2. Did the District Court correctly construe the claim terms "nanoparticles and microparticles of a taxane," and "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles," to mean "particles formed of only a taxane drug," and that when the matrix is exposed to an aqueous medium, "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," respectively?

B. Celgene's Cross-Appeal:

1. Did the District Court err in holding that the claim phrase "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles" is not indefinite: where the claims require that the matrix be formed of, *inter alia*, nanoparticles and microparticles of taxane, while at the same time requiring that the matrix dissolves *to leave* the nanoparticles and microparticles of taxane; where there is no known assay for determining when this limitation is met; and where uncontroverted expert testimony confirms that such is scientifically impossible?

2. Did the District Court err in holding that the claim term "mean diameter" is not indefinite: where there are numerous different types of "mean diameters" used in the art (e.g., number mean diameter, intensity weighted mean diameter, aerodynamic mean diameter, Stokes mean diameter); where there are different techniques for measuring the characteristics of particles necessary to calculate each type of mean diameter; where there is no industry standard type of mean diameter or measurement technique; where, depending on which type and measurement technique is selected, the resulting values will vary either within or outside the scope of the claims; and where no part of the intrinsic patent record informs a person of ordinary skill of the type of mean diameter or measurement technique to use.

Celgene's cross-appeal is conditional—if the Court affirms the judgment of noninfringement, the cross-appeal may be dismissed.

STATEMENT OF THE CASE

A. Preliminary Statement

Celgene developed the accused product, Abraxane®—a novel, innovative cancer drug—long before the effective filing date of the '493 patent. Indeed, in order to obtain the '493 patent, Acusphere had to distinguish its claims from Celgene's own U.S. Patent No. 6,096,331 ("Desai"), A3266–82, which is directed to Abraxane®, as well as from U.S. Patent No. 5,855,913 ("Hanes"), A3283–97.[1] To overcome this prior art, and a series of rejections based on it, Acusphere amended its claims to add further, specific limitations that, according to the inventors' own statements during prosecution, "traversed" patentability rejections over Desai and Hanes. A1016–21.

In an effort to read the claims of the '493 patent to cover Abraxane®, however, Acusphere urged the District Court to ignore both the specific limitations it added by amendment and the clear positions it took based thereon during prosecution. The District Court correctly refused to do so and repeatedly explained in its claim-construction order how the prosecution history directly contradicts

[1] Celgene solved the side-effect problems of paclitaxel years before the '493 patent was even filed. *Compare* AcuBr. 4–5 (listing the side effects of paclitaxel) *with* A3269, 5:38–6:3 (same).

Acusphere's outcome-driven claim-construction arguments. The District Court also recognized that Acusphere's proposed constructions would violate fundamental principles of claim-construction law and even contradict definitions for those terms expressly set forth in publications and other patent applications—attributable to the named inventors of the '493 patent and Acusphere's own expert—outside the context of litigation. This is a straightforward case of applying well-settled law. This Court should affirm.

B. Procedural History

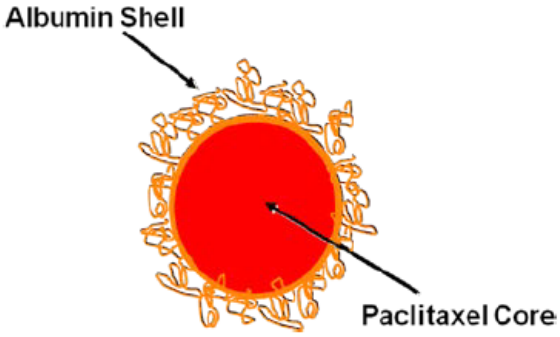
On December 14, 2011, Acusphere sued Celgene in the United States District Court for the District of Massachusetts for allegedly infringing the '493 patent. A1. The District Court conducted a *Markman* hearing, and issued a claim-construction order on December 3, 2013. A1–27. In addition to construing the disputed claim terms, that order also rejected Celgene's indefiniteness arguments as a matter of law. A20–22; A23–25. As a result of that claim-construction order, Acusphere conceded that it could not prove infringement of any one of four construed terms: "nanoparticles"; "microparticles"; "nanoparticles and microparticles of a taxane"; and "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles." A28–31. The parties thus stipulated to a final judgment dated March 18, 2014, wherein each party "reserve[d] its right to appeal." *Id*. On appeal, Acusphere challenges

the District Court's constructions of these four claim terms. Celgene cross-appeals the District Court's rulings that the "wherein upon exposure" and "mean diameter" claim terms are not indefinite.

STATEMENT OF FACTS

A. The Accused Abraxane® Product

Abraxane® is a novel pharmaceutical composition consisting of nanoparticles in which paclitaxel drug is encased in a polymeric shell formed of a protein called human serum albumin ("albumin"):[2]



A2087; A2011. This formulation results in delivery of greater concentrations of paclitaxel to cancerous tumors in the organs of patients. A3269, 6:46–53; A3279, 25:47–52.

[2] Even though the '493 patent's claims require the presence of "a hydrophilic excipient, a wetting agent, and nanoparticles and microparticles of a taxane," Acusphere contends that Abraxane® infringes even though it consists of only two components, paclitaxel and albumin, in the form of nanoparticles. Acusphere's mistaken position is that albumin can satisfy both the "a hydrophilic excipient" and "a wetting agent" limitations, A2055, and that nanoparticles are the same as microparticles, A3258.

Celgene invented compositions having nanoparticles of albumin-bound paclitaxel years before the alleged date of invention of the ’493 patent. Celgene’s inventions are described in and protected by numerous patents, including Desai, that are prior art to the ’493 patent. A2012–13. As reflected in the ’493 patent’s prosecution, the Examiner recognized the similarity between the invention claimed in the application that became the ’493 patent and those described in the prior art, and repeatedly rejected Acusphere’s claims to the extent they could have included nanoparticles of albumin-bound paclitaxel as taught in Desai. A1008–40.

B. The Asserted ’493 Patent Claims

The ’493 patent is a reissue of the ’317 Patent. The ’493 patent contains 47 claims: claims 1–32 were present in the original ’317 patent (although certain claims were amended as part of the reissue prosecution process); claims 33–47 were added during the reissue process. The claim terms disputed in Acusphere’s appeal—and in Celgene’s cross-appeal—appear in all asserted claims. Accordingly, as the parties agreed in the District Court, independent claim 1 is representative:

> 1. 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 5 μm and a total surface area greater than about 0.5 m^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.

A43, cl. 1.

C. The Level of Ordinary Skill in the Art

Acusphere's expert testified that the level of ordinary skill in the field of the '493 patent is relatively low: someone with only a "bachelors degree in chemistry . . . or a related discipline" and "several years of [industry] experience." A1545. For purposes of this appeal, Celgene concurs.

D. The District Court's Claim-Construction Order

1. "nanoparticles" and "microparticles"

The central dispute in this case is the meaning of the terms "nanoparticles" and "microparticles." Consistent with well-established law, Celgene argued, and the District Court agreed, that these terms should be given their ordinary and customary meanings in the field of pharmaceutical science. That is, "nanoparticles" are "particles that have a diameter of between about 1 to 1000 nanometers and less than that of microparticles," and "microparticles" are "particles that have a diameter of between about 1 to 1000 microns and greater than that of nanoparticles." A5–11; A28–29. These ordinary meanings are consistent with the understandings of the parties' experts and are also confirmed by an overwhelming mass of contemporaneous references, including Acusphere's

own related patent applications and a textbook co-edited by one of the named inventors of the ’493 patent and co-authored by Acusphere’s expert. A2161–69.

Acusphere, on the other hand, argued that the terms “nanoparticles” and “microparticles”—despite being called out separately in the claims—mean the same thing. A3258. Although the terms were added serially, at separate stages during prosecution, and appear as separate limitations in the claims, Acusphere contended (and urges here) that both terms synonymously mean: “[p]articles of a taxane having a mean diameter between about 0.01 and 5 μm.” *Id*.

The District Court agreed with Celgene. It found that the terms’ ordinary meanings as proposed by Celgene were the “widely accepted” definitions of the terms. A7, A5, A11. The District Court found it “[t]elling” that “a 1996 textbook co-authored [*sic*; co-edited] by Howard Bernstein, one of the named inventors of the ’493 patent, . . . states that ‘[t]he size range covered by microparticles is, *according to definition*, between 1 and 1000μm,’ while nanoparticles range from ‘1 to 1000nm.’” A7–8 (emphasis added). The District Court further found it “[e]ven more telling” that “other Acusphere patents in the same field, many credited to the inventors of the ’493 patent, incorporate the definition taught by Cohen & Bernstein.” A8.

The District Court rejected Acusphere’s contention that it acted as its own lexicographer and—contrary to the ordinary meanings embraced “according to

definition" by its inventor—redefined "nanoparticles" and "microparticles" away from these ordinary and customary meanings. A8–9. Specifically, the District Court detected "very little evidence in the disputed patent or its history to suggest that Acusphere left a Websterian imprint on the '493 patent." A8. The District Court also found that Acusphere did not clearly redefine those terms by implication, noting that "the only sentence that Acusphere can point to in the specification as supporting a definition by inference, does not even mention nanoparticles." A9.

Finding no support in the patent for Acusphere's view, the District Court then looked to the prosecution history and found that it, too, supported Celgene's proposed constructions by "provid[ing] convincing evidence that Acusphere limited the scope of the '493 patent by distinguishing nanoparticles and microparticles by their size." A10. For example, the District Court described how the examiner rejected the claims (which at the time specified that only "microparticles" must be included), in view of the "micron size" particles disclosed in Hanes. A10. The District Court explained that in response to this prior-art rejection, "Acusphere added nanoparticles to the claims and distinguished the claimed invention from the prior art by asserting that Hanes' compositions did not include nanoparticles." A10. After a thorough review of this exchange in the prosecution history, among others, the District Court concluded: "[I]t 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." A10–11.

The District Court offered two additional reasons for rejecting Acusphere's proposed constructions of the terms "nanoparticles" and "microparticles": (1) they could not be squared with the claim language, and (2) they would render separate claim limitations superfluous. A9–10. For example, in addition to specifying that the matrix be "formed of . . . nanoparticles and microparticles of a taxane," the claims further recite the additional limitations "wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5μm and a total surface area greater than about 0.5 m2/mL." *Id*. The District Court recognized that because Acusphere's position is that nanoparticles and microparticles are by definition "particles of a taxane having a mean diameter between about 0.01 and 5 μm," Acusphere's proposed construction made the separate limitation "wherein the nanoparticles and microparticles have a mean diameter between about 0.01 and 5μm" entirely redundant and meaningless. *Id*. The District Court further noted that "if the court were to adopt Acusphere's construction, a natural reading of the claim would transform the surface area requirement ("greater than about 0.5m²/mL") from a separate limitation into a component of the definition of the particles." A10.

2. "nanoparticles and microparticles of a taxane"

The parties also disputed the meaning of the term "nanoparticles and microparticles of a taxane." Celgene argued that the plain language of the claims, the specification, and the prosecution history plainly show that the nanoparticles and microparticles of taxane are formed of taxane drug only and are separate from the hydrophilic excipient and wetting agent, which are the other components used to form the matrix. A13–15. Acusphere, on the other hand, urged that the nanoparticles and microparticles of taxane can encompass the hydrophilic excipient and wetting agent (neither of which is a taxane). A11–13.

The District Court agreed with Celgene and construed the term "nanoparticles and microparticles of a taxane" to mean "nanoparticles and microparticles formed of only a taxane drug." A17. The District Court rejected Acusphere's argument that a person of ordinary skill reading the specification would somehow know that the nanoparticles and microparticles of taxane could also include the hydrophilic excipient or wetting agent. A12. The District Court cited Celgene's reasoning that "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." A13. The District Court also pointed to the '493 patent (A39, 3:54–58), which teaches: "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." A13.

The District Court also concluded that the prosecution history contravenes Acusphere's arguments. During prosecution, Acusphere distinguished the claimed invention over the prior art by emphasizing that "[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*." A14 (emphasis in original). After a second rejection, as the District Court noted, Acusphere argued 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*." A15 (emphasis in original).

The District Court rebuked "Acusphere[']s attempts to distance itself from the prosecution history," A15–16, and concluded:

> 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.

A16.

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

For much the same reasons, the District Court properly construed the claim limitation "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles" to mean that, when the matrix is exposed to an aqueous medium, "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." A25–26. While Celgene agrees that this is the proper construction of this limitation to the extent it can be construed, Celgene also argued before the District Court, and contends in its cross-appeal, that this limitation in the context of the claimed invention renders the claims nonsensical and indefinite. The District Court held—prior to the Supreme Court's decision in *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120 (2014)—that this limitation is not indefinite.

4. "mean diameter"

The claims of the '493 patent each require that "the nanoparticles and microparticles have a *mean diameter* between about 0.01 and 5 μm."[3] A43, cl. 1

[3] The claims specify that the nanoparticles and microparticles of a taxane must be within the claimed mean diameter range and within a total surface area range, "wherein the porous matrix is in a dry powder form." A43, cl. 1. Notwithstanding this clear claim language, the District Court inexplicably found that "the measurements are to be made after the matrix comes into contact with an aqueous medium." A22. Although not an issue for this Court at this time, such

(emphasis added). While it is undisputed that numerous types of "mean diameters" and measuring techniques were used in the art, the claims and the specification fail to explain what type of mean diameter and what measurement techniques should be used. *See*, *e.g.*, A39, 3:15–23. The prosecution history is equally silent on the subjects. *See* A1007–61. Because the mean diameter for the same set of particles can vary either within the scope of the claims or outside the scope of the claims depending on the type of mean diameter to be calculated, and on the measurement technique selected, Celgene argued before the District Court that the term "mean diameter" was indefinite. A20. However, relying solely on a disclosure in a prior-art reference, the District Court concluded that "the Examiner and Acusphere recognized that the volume mean diameter defined the particle size for the '493 patent," and was not indefinite. A21.

(continued…)

measurements cannot be made—and the patent fails to provide an example showing how such measurements could be made—after the matrix comes into contact with an aqueous medium. This is because the nanoparticles and microparticles of a taxane will dissolve immediately upon exposure to the aqueous medium. A3233:8–12; A3231:11–A3232:5.

SUMMARY OF THE ARGUMENT

As to Acusphere's Appeal:

Although upholding even one of the four challenged claim constructions compels affirmance of the noninfringement judgment, each one of the District Court's constructions is correct.

I. The District Court properly construed "nanoparticles" and "microparticles" as having distinct meanings, consistent with those terms' ordinary and customary meanings in the field of pharmaceutical science. That is, "nanoparticles" are particles that have a diameter of between about 1 to 1000 nanometers, and "microparticles" are particles that have a diameter of between about 1 to 1000 microns. And, in accord with ordinary scientific conventions, a "nano-" particle is different from and smaller than a "micro-" particle. These ordinary meanings are consistent with the understandings of the parties' experts and are also confirmed by an overwhelming mass of contemporaneous references, including Acusphere's own related patent applications as well as a textbook co-edited by one of the named inventors of the '493 patent and co-authored by Acusphere's own expert.

A patentee is certainly free to act as her own lexicographer by clearly and unmistakably redefining a claim term away from its ordinary meaning, but Acusphere did not do so here. There is no intrinsic evidence even hinting that

Acusphere intended to impart any special definition to the terms "nanoparticles" and "microparticles." In fact, Acusphere concedes that it did not expressly redefine those terms, but instead, argues on appeal that it defined those terms "by implication" to both mean the same thing: "[p]articles of a taxane having a mean diameter between about 0.01 and 5 μm." Acusphere's only intrinsic support for this assertion is a single, obscure statement in the specification—a statement that does not even mention the word "nanoparticles," let alone provide any evidence that Acusphere intended to redefine "nanoparticles" and "microparticles" by reference to their combined mean diameters.

The prosecution history is also fatal to Acusphere's position that it redefined "nanoparticles" and "microparticles" to mean the same size particle. During prosecution, Acusphere unequivocally took the position that the '493 patent's claims required two separate types of particles, differentiated by their size; indeed, to obtain allowance over the prior-art Hanes and Desai references, Acusphere *amended* its claims to require "nanoparticles" in addition to "microparticles." In that light, it is inconceivable that Acusphere now urges that its addition of "nanoparticles" was mere surplusage that made no substantive change to the scope and meaning of the claim.

Lastly, Acusphere's proposed construction violates the most basic canons of claim construction—that (i) all limitations of a claim must be considered

meaningful, (ii) different terms in a claim are presumed to have different meanings, and (iii) constructions that render other claim terms redundant or superfluous should be avoided. Acusphere's proposed construction not only ignores the fact that "nanoparticles" and "microparticles" appear as separate limitations in the claims, but would render other express limitations in the claims entirely superfluous.

II. The District Court properly construed "nanoparticles and microparticles of a taxane" to mean "nanoparticles and microparticles formed of only a taxane drug." That is, the "nanoparticles and microparticles of a taxane" contain only taxane drug and not the other components that form the matrix—the hydrophilic excipient and wetting agent. Not only is this construction compelled by the plain language of the claims, but also, the specification always and consistently describes the nanoparticles and microparticles of a taxane as being separate and distinct from the hydrophilic excipient and wetting agent, and as always being left or remaining after the matrix is exposed to an aqueous medium. The prosecution history is to the same effect, making clear that the "nanoparticles and microparticles of taxane" are not associated with the hydrophilic excipient and wetting agent. In fact, Acusphere expressly disclaimed from the scope of the claims "polymer encapsulated formulations" as taught by Desai and as used in the accused product, Abraxane®.

III. Based on its proper construction of "nanoparticles and microparticles of a taxane," the District Court properly construed the limitation "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles" to mean that when the matrix is exposed to an aqueous medium, "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." Again, this construction is supported by the specification and prosecution history, which repeatedly make clear that the nanoparticles and microparticles of taxane are left or remaining upon exposure to an aqueous medium and no longer associated with the hydrophilic excipient or wetting agent.

As to Celgene's Cross-Appeal:

I. Although Celgene agrees that the District Court's construction of the limitation "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles" is proper insofar as this limitation can be construed, Celgene maintains that this limitation, in the context of the claimed invention, renders the claims indefinite. Each of the claims specify that the "matrix [is] formed of . . . nanoparticles and microparticles of a taxane," and yet also requires that "the *matrix dissolves to leave* the taxane nanoparticles and microparticles." Not only does this claim language render the claims

nonsensical, but the uncontroverted expert testimony established that it is in fact scientifically impossible. That is, when the matrix is placed in an aqueous medium, the entire matrix will dissolve at once, including the nanoparticles and microparticles of taxane. There is no biphasic dissolution.

Furthermore, there is no known test for even measuring when just the hydrophilic excipient and wetting agent dissolve, but the nanoparticles and microparticles of taxane do not. Both experts agreed that the assay specified in the patent for measuring the dissolution of the matrix actually measures only the dissolution of the taxane nanoparticles and microparticles. Accordingly, competitors trying to practice the invention or to design around it are unable to discern the bounds of the invention. For these reasons, the claims are indefinite.

II. The claims also require that "the nanoparticles and microparticles have a *mean diameter* between about 0.01 and 5 μm." It is undisputed that, at the time of invention, numerous types of "mean diameters" were used in the art, such as the number mean diameter, intensity weighted mean diameter, aerodynamic mean diameter, and the Stokes mean diameter. Furthermore, numerous different techniques for measuring the size-related characteristics of particles were also used in the art, such as electron microscopy, electrozone sensing, and laser diffraction. The parties agree that there is no industry standard type of mean diameter or technique for measuring the size-related characteristics of particles, and depending

on the type of mean diameter calculated and measurement technique used, the resulting value varies, such that one can arrive at a value that is either within the scope of the claims or outside the scope of the claims.

Here, the specification and prosecution history fail to explain what type of mean diameter or what measurement technique should be used. Thus, the claims are indefinite. The District Court erred in reaching the opposite conclusion by surmising only what Acusphere and the Examiner might have subjectively understood solely in view of the specification of a prior-art reference, as opposed to considering whether, in view of the specification and prosecution history of the '493 patent, a person of skill would be objectively informed with reasonable certainty about the scope of the invention.

STANDARD OF REVIEW

Claim construction is reviewed *de novo*, *Lighting Ballast Control LLC v. Philips Elecs. North Am. Corp.*, 744 F.3d 1272, 1276–77 (Fed. Cir. 2014) (en banc), although this Court has recognized that as a practical matter it gives "informal deference" to the District Court's claim constructions. *Id.* at 1294 (Lourie, J., concurring). Indefiniteness is reviewed *de novo*. *Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1319 (Fed. Cir. 2008).

Federal Rule of Civil Procedure 52(a) requires that "[f]indings of fact, whether based on oral or other evidence, must not be set aside unless clearly

erroneous." Fed. R. Civ. Proc. 52(a)(6). On March 31, 2014, the United States Supreme Court granted certiorari in *Teva Pharms. USA Inc. v. Sandoz, Inc.*, 723 F.3d 1363 (Fed. Cir. 2013), *cert. granted*, 2014 U.S. LEXIS 2312, 1 (U.S. Mar. 31, 2014). The question presented there is: "Whether a district court's factual finding in support of its construction of a patent claim term may be reviewed *de novo*, as the Federal Circuit requires (and as the panel explicitly did in this case), or only for clear error, as Rule 52(a) requires." *Id.* *Teva* will be argued on October 15, 2014.

ARGUMENT

I. THE DISTRICT COURT'S JUDGMENT OF NONINFRINGEMENT SHOULD BE AFFIRMED.

A. The District Court Properly Construed the Terms "nanoparticles" and "microparticles."

1. The terms "nanoparticles" and "microparticles" have ordinary and customary meanings that are widely accepted in the art.

Each asserted claim requires a matrix formed of, *inter alia*, both "nanoparticles" and "microparticles" of a taxane. A43, cl. 1. There is no facial ambiguity or obscurity in these terms, nor did the inventors set out a special definition for them anywhere in the intrinsic record. "Nanoparticles" and "microparticles" have ordinary and customary meanings in the art that are "widely

accepted."[4] A7. "Nanoparticles" are particles that have a diameter of between about 1 to 1000 nanometers, and "microparticles" are larger particles, having a diameter of between about 1 to 1000 microns. A5; A3100:2–20; A2161–70; A2552–54. And, of course, because "nano-" conventionally describes something that is smaller than a "micro-" something, a nanoparticle has a diameter that is necessarily smaller than that of a microparticle.

These ordinary meanings accord with the understanding of Acusphere's own expert, Dr. Robert Langer, who stated that "the *ordinary meanings* of 'nanoparticles' and 'microparticles' are directed to particle size, with 'nanoparticles' referring to particles with a diameter in the nanometer (nm) range and 'microparticles' referring to particles with a diameter in the micrometer (μm) range." A1550 (emphasis added). These meanings are also confirmed by contemporaneous references, including a publication co-edited by one of the named inventors of the '493 patent and co-authored by Dr. Langer—outside the context of litigation. A2161–69.

[4] As Acusphere concedes in its opening brief: "Everyone agrees that the only difference between a 'nanoparticle' and a 'microparticle' is size: both are small, but the nanoparticle is smaller." AcuBr. 20. Acusphere, however, contends that the terms lack ordinary meanings merely because there are no "universally" accepted definitions. *Id*. at 20–21. That misstates the standard. This Court's precedent teaches that an ordinary meaning need only be "widely accepted," not universally accepted. *Phillips v. AWH Corp*., 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc); *Wilson Sporting Goods Co. v. Hillerich & Bradsby Co*., 442 F.3d 1322, 1328 (Fed. Cir. 2006).

Indeed, in a book published before the filing date of the '493 patent, and co-edited by Dr. Howard Bernstein, a named inventor on the '493 patent, the terms "nanoparticles" and "microparticles" are defined in the exact same manner as did the District Court:

> The size range covered by microparticles is, *according to definition*, between 1 and 1000 μm. In contrast, smaller particles, designated as nanoparticles, with sizes ranging from 1 to 1000 nm.

A2621 (emphasis added); A2615; *see ArcelorMittal France v. AK Steel Corp*., 700 F.3d 1314, 1322 (Fed. Cir. 2012) ("[W]hen an inventor's understanding of a claim term is expressed in the prior art, it can be evidence of how those skilled in the art would have understood that term at the time of the invention."). And in the same textbook, Dr. Langer wrote: "*Nanoparticles* (also called nanospheres) are defined as solid colloidal particles, less than 1 μm in size." A2624 (emphasis in original); A2623.

Numerous other contemporaneous references define "nanoparticles" and "microparticles" in an identical or nearly identical manner as the District Court. *E.g.*, A2192 ("Nanoparticles are solid colloidal particles ranging in size from 1 to 1000 nm (1 μm)."); A2205 ("Nanoparticles are solid particles ranging in size from 10nm to 1000nm (1 μm). . . . Microparticles are similar particles in the size range of 1 μm to 1000 μm (1 mm)."); A2218 ("Moreover, there are known, by the name of nanoparticles, colloidal particles which are much smaller in size than

microparticles since their size is generally of the order of 10 to 1000 nm."); A2224 (same); A2234 ("[N]anoparticles hav[e] a diameter in the range from 1.0 to 1000 nanometers . . . microparticles hav[e] a diameter in the range from about 1 to about 1000 microns.").

Even Acusphere's other patent applications that share common inventors with the '493 patent, and which are directed to the same technology as the invention claimed in the '493 patent, all define "nanoparticles" and "microparticles" in the same manner as the District Court. *E.g.*, A2367 ("As used herein, the term 'microparticle' . . . denotes particles having a size of 1 to 1000 microns. As used herein, "nanoparticles" have a size of 1 to 1000 nm."); A2392 (same); A2431 (same); A2461–62 (same); A2489 ("As used herein, the term microparticle refers to a solid particle typically ranging in size between approximately 1 and 1000 microns."); *see Laryngeal Mask Co. Ltd. v. Ambu A/S*, 618 F.3d 1367, 1373 (Fed. Cir. 2010) (where non-asserted patent was related to the same technology and named the same inventor as the asserted patent, "prior art use of the [disputed] term would further inform one of skill in the art as to the common meaning of the [disputed] term").

In sum: The District Court correctly construed the terms "nanoparticles" and "microparticles" consistent with the terms' ordinary meanings.

2. Acusphere did not act as its own lexicographer or disavow the ordinary and customary meanings of the terms "nanoparticles" and "microparticles."

Ordinary meanings prevail unless the patentee: (i) acts as her own lexicographer by clearly setting forth her own definition of the disputed claim term, or (ii) makes a clear and unmistakable disavowal of the full scope of the claim term. *Thorner v. Sony Co. Ent. Am., LLC*, 669 F.3d 1362, 1365–67 (Fed. Cir. 2012). Any departure from a term's ordinary meaning must be made "explicit" and "clear and unmistakable." *Id* at 1362. This Court "indulge[s] a 'heavy presumption' that claim terms carry their full ordinary and customary meaning, unless the patentee unequivocally imparted a novel meaning to those terms or expressly relinquished claim scope during prosecution." *Omega Eng'g, Inc. v. Raytek Corp*., 334 F.3d 1314, 1323 (Fed. Cir. 2003) (citations omitted); *see also Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1381 (Fed. Cir. 2008) (explaining that inventors must "clearly express an intent" to redefine a term).

Here, the District Court looked to the intrinsic patent record and found no "unequivoca[l]" or "clearly express[ed]" evidence even suggesting that Acusphere intended to impart a special definition for the terms "nanoparticles" and "microparticles." A8–9. Indeed, Acusphere concedes that it did not expressly set forth any definitions, but instead argues that it defined those terms by implication.

AcuBr. 21. It did not. To define a term by implication, "the 'implied' redefinition must be so clear that it equate[s] to an explicit one." *Thorner*, 669 F.3d at 1368. The disputed term must be used "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*., 262 F.3d 1258, 1271 (Fed. Cir. 2001). "[A] person of ordinary skill in the art would have to read the specification and conclude that the applicant has clearly . . . acted as its own lexicographer. Simply referring to two terms as alternatives or disclosing embodiments that all use the term the same way is not sufficient to redefine a claim term." *Thorner*, 669 F.3d at 1368.

Here, the *only* statement from the specification Acusphere cites to in support of its "implied redefinition" argument is column 1, line 65–column 2, line 4:

> 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 5 μm and a total surface area greater than about 0.5 m^2/mL.

A38, 1:65–2:4; AcuBr. 22–23. Needless to say, this is far from a clear re-definition of "nanoparticles" and "microparticles." The first sentence merely states that both nanoparticles and microparticles of taxane are formed when the matrix is contacted with an aqueous medium. The second sentence does not even mention "nanoparticles" and merely describes a further characteristic of the *population* of "microparticles" that are yielded in some circumstances; i.e., the microparticles

yielded upon exposure to an aqueous medium should have "a *mean* diameter between about 0.01 and 5 μm." *Id.* (emphasis added).

Describing a *population* of microparticles as having a certain *mean* diameter upon contact with an aqueous medium says nothing about the definition of a microparticle, much less the definition of a nanoparticle. For one thing, a person of ordinarily skill in the art would understand that there is a marked difference between the "*diameter*" of an individual particle in a population (which defines the type of particle it is) versus a "*mean* diameter" (which is a characteristic of the population of particles as a whole). A3103:21–A3104:4. The latter may provide a useful generalization about the average size of the particles in the population, but it does not inform a person of ordinary skill as to which types of particles are in the population. *Id*: A3104:12–15; A2558.

By analogy, suppose a claim limitation required the presence of teenagers (i.e., persons aged 13–19) and adults (i.e., persons aged 20 and over). If one was informed only that the mean age of the persons in a cohort was 18 years, there would be no way to discern if both teenagers and adults were in the group. There could be a mixture of adults and teens (and perhaps other age groups) whose average age was 18, or all of the persons could be 18 (in which case the mean age would be 18, but the cohort would be only teenagers). One must know the actual ages or ranges of ages of the individuals present. It would be absurd to define

"teenagers" and "adults" as referring to the combination of their mean ages, i.e., both terms mean "persons having a mean age of 18 years old." But that is exactly what Acusphere would have this Court believe it did for "nanoparticles" and "microparticles."

And, Acusphere can cite only this single statement in the specification to support this contention. AcuBr. 22–23. This Court requires far more clarity for an implicit redefinition. At minimum, the disputed term must be used "throughout the entire patent specification, in a manner consistent with only a single meaning." *Bell Atlantic*, 262 F.3d 1258 at 1271. The single statement Acusphere cites merely describes a preferred characteristic of a population of *microparticles*—not a definition. This is confirmed elsewhere in the specification, where the population of microparticles is described as having a mean diameter in a range other than "between about 0.01 and 5 μm." That is, the mean diameter is "*more preferably* between about 50 nm and 5 μm." A39, 3:15–18 (emphasis added).

The simple truth is that Acusphere never imparted any special definition to the terms "nanoparticles" and "microparticles." Tellingly, Acusphere knew how to set forth a definition for a claim term: Where Acusphere intended to act as its own lexicographer, it did so by placing the term in quotations and stating, "[a]s used herein, '[the term]' means," followed by the definition. A41, 8:5–10, 8:62–63; A3156:13–24. That Acusphere did not set "nanoparticles" and "microparticles"

off in quotes or state "[a]s used herein, 'nanoparticles' mean . . ." or "[a]s used herein, 'microparticles' mean . . ." provides further confirmation that Acusphere did not intend to impart special definitions to those terms. *See Abbott Labs v. Andrix Pharm., Inc*., 473 F.3d 1196, 1210 (Fed. Cir. 2007) (where specification "unambiguously provides definitions of other claim terms" . . . by using "as used herein, means . . .", a description from the specification merely stating that a "pharmaceutically acceptable polymer is . . . ," was not a definition).

In sum, the specification is devoid of any of the hallmarks of lexicography or definition by implication necessary to overcome the heavy presumption that the terms "nanoparticles" and "microparticles" should be ascribed the full range of their ordinary meanings. "[A] clear ordinary meaning is not properly overcome (and a relevant reader would not reasonably think it overcome) by a few passing references that do not amount to a redefinition or disclaimer." *Ancora Techs. v. Apple, Inc*., 744 F.3d 732, 738 (Fed. Cir. 2014).

3. The prosecution history confirms that the District Court's constructions for the terms "nanoparticles" and "microparticles" are correct.

If any doubt remained respecting the District Court's construction, it is conclusively resolved by the prosecution history. "Arguments and amendments made during prosecution of a patent application must be examined to determine the meaning of terms in the claims." *Rheox, Inc. v. Entact, Inc*., 276 F.3d 1319, 1325

(Fed. Cir. 2002). Claim scope must be limited "[w]here an applicant argues that a claim possesses a feature that the prior art does not possess in order to overcome a prior art rejection." *Seachange Int'l., Inc. v. C-COR Inc*., 413 F.3d 1361, 1372–73 (Fed. Cir. 2005).

The prosecution history for the '493 patent contravenes Acusphere's contention that "nanoparticles" and "microparticles" both encompass the same particles. As the District Court found, "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." A10–11. On December 3, 2001, the examiner rejected the claims, which at the time specified that only microparticles must be present, on the grounds that "at the time the invention was made, a composition, and methods for making such, containing paclitaxel and a surfactant, in micron size [i.e., microparticle size] and with a reduced surface area would have been known to one with ordinary skill in the art." A1012. In response, Acusphere amended the claims to recite "nanoparticles and microparticles" and stated:

> Claims 1, 11 and 17 have been amended to clarify that the claimed composition is a porous matrix formed of a wetting agent and hydrophilic excipient having within the matrix *nano- and microparticles of taxane*, such that the matrix dissolves upon contact with an aqueous solution to yield taxane *nano- and microparticles of taxane*.

A1020 (emphases added).

Acusphere further contended:

> As the claims now clearly define, the claimed composition is a taxane formulation comprising *taxane nanoparticles and microparticles* in a matrix formed of a hydrophilic excipient and wetting agent. The 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 rate of dissolution of the taxane.

A1020–21 (emphases added).

Acusphere then distinguished its claimed invention over the cited prior art. In regard to Hanes, Acusphere argued: "*There are no nanoparticles* [in Hanes], nor is there a matrix formed of a hydrophilic excipient that dissolves upon contact with water, to release *nanoparticles and microparticles* of a taxane."[5] A1021 (emphases added). Acusphere concluded:

> Accordingly, Hanes and Desai in combination . . . would lead one to controlled, sustained release formulation for pulmonary administration, where the drug formulation had a total particle size of *less than five microns*, not a formulation having dispersed therein *nanoparticles and microparticles* of drug, released immediately upon dissolution of the surrounding matrix.

A1021 (emphases added).

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[5] Acusphere's position that Hanes does not teach nanoparticles is fatal to its argument that it implicitly defined "nanoparticles" to mean particles "having a mean diameter between about 0.01 and 5 μm." Hanes clearly teaches particles "having a mean diameter between about 0.01 and 5 μm." *See* A3296, Table 4 (disclosing various compositions of particles with mass mean diameters of 4.4 μm, 2.0 μm, 3.0 μm, and 4.3 μm). Accordingly, Hanes would necessarily teach compositions comprising both nanoparticles and microparticles under Acusphere's litigation-inspired constructions.

On June 3, 2002, the examiner again rejected the claims on the grounds that although Hanes does not expressly teach the use of nanoparticles, "Hanes does teach using particles the same size as the instant invention (5μm)." A1038. In response, Acusphere asserted: "Hanes . . . forms *microparticles* by spray drying." A1046 (emphasis added). Acusphere also again distinguished Desai on the ground that "[t]he compositions contain paclitaxel and albumin (Capxol^{TM}) (col. 6, lines 8-10) in the form of *nanoparticles* (col. 6, lines 46-47)." A1045 (emphases added).

Ultimately, the claims of the '493 patent were allowed only because they required the presence of both nanoparticles (which Acusphere told the examiner Hanes does not teach) and microparticles (which Acusphere told the examiner Desai does not teach). Acusphere certainly understood the difference—it amended its claims to recite both "nanoparticles" and "microparticles," and distinguished its invention from the prior art based on the size of both types of particles. Acusphere cannot now argue that these amendments had no effect. *E.g.*, *ACCO Brands, Inc. v. Micro Sec. Devices, Inc.*, 346 F.3d 1075, 1078 (Fed. Cir. 2003) ("Statements made during prosecution which clearly disclaim a particular claim interpretation will limit the scope of the claims."); *Owen Mumford USA, Inc. v. SurgiLance, Inc*., 137 Fed. Appx. 342, 348–49 (Fed. Cir. 2005) ("We reject this argument because it would require us to read the claim language in dispute as superfluous. Indeed, reading the [added language] out of the claim would be particularly problematic in

this case because that language was added in response to a rejection by the examiner." (citation omitted)).

Nor can Acusphere escape the prosecution history by labeling its amendments as mere "clarifications." This Court confirmed this bedrock principle over fifteen years ago. In *Bai v. L & L Wings, Inc*., 160 F.3d 1350 (Fed. Cir. 1998), the applicant claimed that it added a term ("hemispherical") after a prior-art rejection merely to "clarify" the invention. This Court dismissed the argument, observing that "there was no lack of clarity, and no rejection under *Section 112*. Prior art was the problem." *Id*. at 1355 (emphasis in original); *see also Loral Fairchild Corp. v. Sony Corp*., 181 F.3d 1313, 1326 (Fed. Cir. 1999) ("An applicant may not avoid the conclusion that an amendment was made in response to prior art by discussing the amendment under the rubric of a clarification due to a § 112 indefiniteness rejection."); *Norian Corp. v. Stryker Corp*., 432 F.3d 1356, 1358–62 (Fed. Cir. 2005). Prior art—Hanes and Desai—was the problem here, too.

In sum: Acusphere limited the scope of the '493 patent by repeatedly distinguishing "nanoparticles" and "microparticles" by their size in order to overcome prior art. It cannot now argue that those distinct terms mean the same thing. "A patent may not, like a 'nose of wax,' be twisted one way to avoid anticipation and another to find infringement." *Amazon.com, Inc. v. Barnesandnoble.com, Inc*., 239 F.3d 1343, 1351 (Fed. Cir. 2001) (quoting *Sterner*

Lighting, Inc. v. Allied Elec. Supply, Inc., 431 F.2d 539, 544 (5th Cir. 1970), in turn quoting *White v. Dunbar*, 119 U.S. 47 (1886)).

4. Acusphere's proposed constructions for the terms "nanoparticles" and "microparticles" violate basic canons of claim construction.

Finally, Acusphere's position contravenes many of the most basic claim-construction rules, including: (1) all limitations of a claim must be considered meaningful, *Lantech, Inc. v. Keip Mach. Co.*, 32 F.3d 542 (Fed. Cir. 1994); (2) different terms in a claim have presumptively different meanings, *Bd. of Regents of the Univ. of Tex. Sys. v. BENQ Am. Corp*., 533 F.3d 1362, 1371 (Fed. Cir. 2008); and (3) constructions that render other claim terms redundant or superfluous should be avoided, *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1354 (Fed. Cir. 2012). By lumping the terms "nanoparticles" and "microparticles" together, and treating them as though they were a single claim term with the same meaning, while ignoring other express limitations in the claims, Acusphere violates each of these bedrock tenets.

To start, Acusphere's proposed constructions would erase the claims' requirement that there be two different types of particles—nanoparticles "and" microparticles. Acusphere's proposal would render the terms superfluous, or rewrite the claim from "nanoparticles *and* microparticles" to "nanoparticles *or* microparticles" (or just "particles"). *Superguide Corp. v. DirecTV Enterprises,*

Inc., 358 F.3d 870, 886 (Fed. Cir. 2004) ("[P]atentee used the term 'and' to separate the categories of criteria, which connotes a conjunctive list."). Acusphere's own expert, Dr. Langer, confirmed that under Acusphere's proposed construction, one could remove the term "nanoparticles" from the claim without changing the scope of the claim. A3147:7–10 ("Q: Did the addition of the term "nanoparticles" change the scope of the claims in any way, under your understanding? A: No. . . ."); A3152:4–21 ("Q: And so, under your proposed constructions, if I remove the term 'nanoparticles' from claim 1, does that change the scope of the claims? . . . A: . . . [I]t would not change the scope.").

Furthermore, Acusphere's proposed construction ignores the fact that the claims contain the separate, additional limitation that the claimed nanoparticles and microparticles "have a mean diameter between about 0.01 and 5 μm." A43, cl. 1. To illustrate the point, inserting Acusphere's proposed construction into claim 1 would cause it to read:

> A pharmaceutical composition comprising a porous matrix formed of a hydrophilic excipient, a wetting agent and *particles of a taxane having a mean diameter between about 0.01 and 5 μm, wherein the particles have a mean diameter between about 0.01 and 5 μm . . . .*

Such superfluity is not tolerated. *Digital-Vending Servs. Intl., LLC v. Univ. of Phoenix, Inc*., 672 F.3d 1270, 1275 (Fed. Cir. 2012) (if term "registration server" were construed to require the server to be "free of content," the additional limitation that required the server to be "free of content" would be superfluous).

In the words of a recent decision from this Court, Acusphere's proposed construction "violates nearly every tenet of claim construction and amounts to a wholesale judicial rewriting of the claim." *Source Vagabond Sys. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014) (quoting district court). That was enough to sustain Rule 11 sanctions for "frivolous claim construction arguments" in *Source Vagabond*; suffice it to say that here, Acusphere's arguments fall far short of the standard for appellate reversal.

5. Claim 6 of the '493 patent is consistent with the District Court's claim constructions.

Claim 6 of the '493 patent, which claims "[t]he composition of claim 1 wherein the mean diameter of the taxane microparticles is between about 0.50 and 5 μm," is—contrary to Acusphere's argument (AcuBr. 23–25)—harmonious with the District Court's claim constructions. As an initial matter, the District Court addressed this argument and found that any inconsistency "is a product of Acusphere's at times seemingly random omission of the term 'nanoparticles' in the patent." A9 n.2. That finding is not clearly erroneous. Indeed, the phrase "nanoparticles and microparticles" appears throughout the specification and claims, but "nanoparticles," which was added as an additional limitation during prosecution, is missing in random places. *See*, *e.g.*, A38, 1:65–2:5; A39, 3:3,15.

But even assuming that Acusphere's omission of "nanoparticles" from claim 6 had been intentional, Acusphere ignores the undisputed fact that to a person of

ordinary skill, the term "mean diameter" does not refer to a simple arithmetic average of the diameters of the individual particles. Rather, there are numerous types of "mean diameters" used in the art (including "volume mean diameter," which is how the District Court construed the term), and each are calculated using complex mathematical formulas in which the resulting values are a function not just of the particles' individual diameters, but also of other measured characteristics, such as the particles' mass, volume, intensity, or aerodynamic qualities, each of which are "weighted" differently depending on the formula used. *See infra* section II.B.1 (discussing the various types of mean diameters and measurement techniques and demonstrating that these ambiguities render the claims indefinite). Further, as Acusphere's expert explained:

> [T]o give you at a high level, of different mean diameters, you can weight something where everything, all numbers are weighted equally, or you could weight things where, say, the bigger numbers are weighted more. So there's different kinds of diameters, the way you can make the calculations. Some are just added and some are squared and so forth.

A3158:2–10. Accordingly, "[b]ecause each of the different types of mean diameter takes into account different physical characteristics, or projected characteristics, of the particles they are likely to result in vastly different 'mean diameter' values for the same set of particles." A2787; *see also* A2564–65; A2786–87; A3161:18–24; A3162:4–16; A3163:1–18; A3164:4–13. Acusphere, however, has presented no evidence that under the District Court's construction of

"microparticles," a population of microparticles can never have a *volume* mean diameter "between about 0.50 and 5 μm."[6]

Finally, even if there was an inconsistency between claim 6 and the District Court's constructions, this Court has made clear that "a court may not rewrite a claim even if giving a disputed claim its plain meaning would lead to a 'nonsensical result.'" *Source Vagabond*, 753 F.3d at 130 (citing *Chef Am., Inc. v. Lamb-Weston, Inc*., 358 F.3d 1371, 1373 (Fed. Cir. 2004)); *see also Hill-Rom Servs. v. Stryker Corp*., 2014 U.S. App. LEXIS 12105, 13–14 (Fed. Cir. June 27, 2014) ("Where the meaning of a claim term is clear, as it is here, we do not rewrite the claim to preserve its validity."). Acusphere "had the ability to draft the claim [a different] way but did not. It cannot correct that failure by adding words to otherwise unambiguous claim language." *Source Vagabond*, 753 F.3d at 1300.

6. Celgene objects to the portions of Acusphere's argument that rely on extrinsic materials not part of the record on appeal.

To support its argument that the District Court's constructions of "nanoparticles" and "microparticles" are not universally accepted, Acusphere impermissibly cites to pages and chapters from a voluminous textbook that are not in the record on appeal—and, as a result, makes arguments that were never made

[6] Contrary to Acusphere's misrepresentation, the District Court did not "acknowledge[] that its constructions are *impossible* to reconcile with the language of Claim 6." AcuBr. 13 (emphasis in original). Rather, the District Court merely recited that Acusphere believed that to be the case. A9 n.2.

before the District Court. AcuBr. 37–38. The Court should strike those arguments and authorities under its Rule 27(e).

In the District Court, the parties presented only limited portions of a 550-page textbook, *Microparticulate Systems for the Delivery of Proteins and Vaccines*, and the parties and their experts argued the weight that those excerpts should be given in the context of claim construction. On appeal, Acusphere cites to different pages and chapters from the textbook, and even provides snippets of quotes, that were never presented or argued to the District Court. *Id.*[7] This is impermissible.

Federal Rule of Appellate Procedure 10(a) limits the record on appeal to three categories of materials: "(1) the original papers and exhibits filed in the district court; (2) the transcript of proceedings, if any; and (3) a certified copy of the docket entries prepared by the district court." Fed. R. App. P. 10(a). The materials at issue were never "filed in the district court," nor do they fall within categories (2) or (3). Celgene thus requests that any references to these extra-record materials in Acusphere's brief and any arguments in reliance on them be

[7] They include: (1) the statement on page 12 of Acusphere's brief, which carries over to the top of page 13, which recites: "which is of minimal relevance given that several other chapters in the same book used completely different definitions"; (2) the entire middle paragraph on page 37 of Acusphere's brief, which purports to quote from page 61 of the *Microparticulate Systems* textbook; and (3) the entire final paragraph on page 37, carrying over to the top of page 38, which references and purports to quote from pages 105, 115, 214, 237, 366, and 392 of the *Microparticulate Systems* textbook.

struck. *E.g.*, *Sky Techs. LLC v. SAP AG*, 576 F.3d 1374, 1377 n.4 (Fed. Cir. 2009) ("[T]he [document] was never presented to the district court and, therefore, is an improper part of the appellate record."); *Chem. Eng'g Corp. v. Essef Indus., Inc.*, 795 F.2d 1565, 1572 (Fed. Cir. 1986) ("Our appellate review is based on the record—on evidence *actually* presented—not on assorted evidentiary might-have-beens." (emphasis in original)); *Am. Standard, Inc. v. Pfizer Inc.*, 828 F.2d 734, 746 (Fed. Cir. 1987).

Acusphere's conduct is especially egregious given that Celgene informed Acusphere of this defect, and, worse, given that Acusphere has acknowledged that the materials are not in the record on appeal. Initially, Acusphere unilaterally designated and assigned appendix page numbers to the entirety of this book, notwithstanding the fact that just a few pages of that book had been presented to the District Court. Its original opening brief (Dkt. No. 23) contained "A___" citations to the previously uncited materials listed in footnote 7, above. In a letter (lodged on the docket in advance of the filing of this brief), Celgene wrote Acusphere promptly after receiving Acusphere's opening brief, explained Acusphere's violation of the Rules, and requested that Acusphere submit a corrected brief omitting any reference to the improperly cited materials. Dkt. No. 31, Ex. A. Celgene also requested that Acusphere not include the new materials in the joint appendix. *Id.*

Almost a week later, Acusphere responded. It acknowledged that the disputed materials were not part of the record on appeal. *Id.*, Ex. B. But instead of omitting the materials (and the corresponding arguments) from its brief, Acusphere took the position that simply replacing the "A___" citations with citations to the page numbers of the textbook avoided the violation. *Id.*; Dkt No. 27 ¶ 3. Thus, Acusphere's "corrected" brief (Dkt. No. 29) now cites—as evidence in support of reversal—to page numbers of the *Microparticulate Systems* textbook. But changing the citation format does not alter the fact that these materials were not made a part of the district court record, and that the arguments based thereon were never made to or considered by the District Court.

According to Acusphere, the parties are "free to argue the weight to which these additional authorities are entitled." *Id.* This position is truly exceptional. The new materials being offered by Acusphere are in service of an argument captioned "The district court's reliance on extrinsic evidence was flawed and improper." AcuBr. 36. Ironically, Acusphere offers the offending argument—and the new extra-record materials—in an effort to demonstrate the District Court's supposed error. But the District Court cannot be accused of error for failing to consider an argument that Acusphere did not make—based on materials that Acusphere did not make a part of the record. That is the reason behind the black letter law that an "appellate court may consider only the record as it was made

before the district court." *E.g.*, *Ballard Medical Products v. Wright*, 821 F.2d 642, 643 (Fed. Cir. 1987). This sideshow constitutes "a substantial waste of the time and limited resources of the court and reflect[s] an absence of respect for the judicial process expected of officers of the court." *See id.* Celgene thus requests that the portions of Acusphere's brief that reference and rely on extra-record materials be struck.

B. The District Court Properly Construed "nanoparticles and microparticles of a taxane."

1. The District Court's construction of "nanoparticles and microparticles of a taxane" is compelled by the plain language of the claims.

Each of the claims require that the nanoparticles and microparticles that form the matrix be particles "of a taxane." A43, cl. 1. That is, the nanoparticles and microparticles forming the matrix are "particles formed of only a taxane drug" and do not include the other components that form the matrix—the hydrophilic excipient and the wetting agent. A17. This construction is compelled by the plain language of the claims, which recite "nanoparticles and microparticles of a taxane" without anything more, and refers to the "nanoparticles and microparticles of a taxane" as being *distinct* components from the hydrophilic excipient and the wetting agent. A43, cl. 1. Had Acusphere intended for the nanoparticles and microparticles of a taxane to include the hydrophilic excipient or the wetting agent, it could have drafted the claims to do so. It did not.

2. The specification consistently describes the "nanoparticles and microparticles of a taxane" as separate and distinct components from the hydrophilic excipient and wetting agent.

Without exception, the specification describes the active ingredient, i.e., the nanoparticles and microparticles of a taxane, as being separate and distinct from the hydrophilic excipient and wetting agent, and describes the nanoparticles and microparticles of a taxane as being left or remaining after the hydrophilic excipient and wetting are exposed to an aqueous medium. For example:

> 1. Paclitaxel
>
> As generally used in the description herein, "paclitaxel" includes taxanes and derivatives thereof, including paclitaxel and docetaxel, which have anticancer or antiangiogenic activity. Paclitaxel was specifically used in the examples which follow.
>
> 2. Excipients
>
> The matrices may contain hydrophilic excipients, such as water soluble polymers or sugars, which can serve as bulking agents or as wetting agents, wetting agents such as surfactants or sugars, and tonicity agents. 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.* The total surface area of the *resultant* low aqueous solubility paclitaxel microparticles is increased relative to the unprocessed paclitaxel and the dissolution rate of the paclitaxel is increased.

A39, 3:44–61 (emphases added); *see also* A38, 1:66–2:1 ("Paclitaxel is provided in a porous matrix form which forms nanoparticles and microparticles of paclitaxel when the matrix is contacted with an aqueous medium"); A39, 3:1–3 ("The

compositions are porous dry powders, which upon the addition of an aqueous medium form a suspension of paclitaxel nanoparticles and microparticles"); A39, 3:9–14 ("The porous paclitaxel matrix is at least 1 to 95%, preferably at least about 10%, and more preferably between about 10 and 70%, paclitaxel by weight. The matrices also may contain hydrophilic excipients such as water soluble polymers or sugars, wetting agents such as surfactants, and tonicity agents."); A39, 3:15–16 ("The matrix must yield microparticles of paclitaxel, upon contact with an aqueous medium . . . .").

Because the specification consistently describes the nanoparticles and microparticles of a taxane as being separate and distinct from the hydrophilic excipient and wetting agent, a person of ordinary skill would necessarily understand that the claimed "nanoparticles and microparticles of a taxane" are formed of taxane drug alone and do not encompass the hydrophilic excipient and wetting agent, which are the other components used to form the matrix. A2171 ¶ 69; A2543–44 ¶ 10.

3. During prosecution, Acusphere disclaimed its proposed construction that "nanoparticles and microparticles of a taxane" could encompass the hydrophilic excipient or wetting agent.

The prosecution history confirms "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. This is particularly so here.

During prosecution, the examiner rejected the originally drafted claims in view of Desai and Hanes. In general, Desai discloses pharmaceutical compositions in the form of paclitaxel nanoparticles that are stabilized or encapsulated by a polymer, such as albumin. A3269, 6:9–25. Likewise, Hanes teaches drug particles incorporating on their surface either a surfactant (a form of wetting agent), or a polymer together with a surfactant, to promote the controlled release of the drug in the body. A3290, 5:16–25, 5:64–67, 6:52–59. In response to the examiner's rejection in view of Desai and Hanes, Acusphere amended claims 1 and 17 to add, among other things, the limitation that "wherein upon exposure to an aqueous medium, the matrix dissolves *to leave* the taxane nanoparticles and microparticles." A1016–19 (emphasis added). In its remarks accompanying the amendment, in an attempt to distinguish the newly amended claims from Hanes, Acusphere argued:

> Hanes discloses a formulation that has two embodiments, one formed of a biodegradable hydrophobic, non-water-soluble *polymer encapsulating drug, which can include a surfactant* such as DPPC, and the other *just of drug and surfactant* . . . . There are no nanoparticles, *nor is there a matrix formed of a hydrophilic excipient that dissolves upon contact with water, to release nanoparticles and microparticles of a taxane.*

A1021 (emphases added).

Likewise, in an attempt to distinguish the newly amended claims from Desai, Acusphere argued: "Desai discloses *controlled release, polymer encapsulated formulations*," in contrast to the claimed composition that would "release *drug* in particulate form." A1021 (emphases added). Acusphere further argued that, in contrast to the compositions in Desai and Hanes, the amended claims "now clearly define" that

> the claimed composition is a taxane formulation comprising taxane nanoparticles and microparticles in a matrix formed of a hydrophilic excipient and wetting agent. The matrix is rapidly dissolved upon contact with an aqueous solution, yielding nanoparticles and microparticles of the taxane, *no longer associated with the matrix*.

A1020–21 (emphases added). Because the claims—in Acusphere's own words—require nanoparticles and microparticles of taxane "no longer associated with the matrix," a composition in which the particles of taxane still contain the other components of the matrix cannot be contemplated by the claims. In other words, Acusphere disclaimed its proposed construction that "nanoparticles and microparticles of a taxane" can encompass or be encapsulated by the hydrophilic excipient or wetting agent.

Even after these distinctions, the examiner rejected the claims, causing Acusphere to reiterate that "Desai discloses controlled release, polymer encapsulated formulations," as distinguished from the particles in the '493 patent. A1045. Acusphere argued that "[t]he combination of Desai and Hanes would not

lead one skilled in the art to a form a porous matrix which dissolves immediately upon exposure to an aqueous medium *to release nanoparticles and microparticles of a taxane*." A1046 (emphasis added). Thus, a person of ordinary skill would understand from Acusphere's statements that the claimed nanoparticles and microparticles of a taxane do not read on particles that are encapsulated by substances such as a polymer of albumin (Desai and Abraxane®) or a surfactant (Hanes). Rather, the prosecution history makes clear that the hydrophilic excipient and wetting agent are separate components, which, along with the nanoparticles and microparticles of a taxane, form the matrix, and which upon exposure to an aqueous medium must "dissolve immediately" so as to "release *drug* in particulate form." A1021; *see also* A2173–74 ¶ 72; A2546–47 ¶ 13.

The District Court was exactly right: "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." A16.

4. Acusphere has not shown that magnesium aluminum silicate when incorporated into a matrix will not dissolve in an aqueous medium, and, even if so, it would not affect the District Court's claim construction.

In the face of this overwhelming intrinsic evidence, Acusphere can only point to a single example, magnesium aluminum silicate, from a laundry list of

potential "wetting agents" cataloged in the '493 patent (A39, 4:48–65), which it contends will not dissolve in water. AcuBr. 43. Whether or not magnesium aluminum silicate in isolation will dissolve in water, however, is irrelevant. The claims specify that "upon exposure to an *aqueous medium*, the *matrix* dissolves." A43, cl. 1 (emphases added). Acusphere has presented no evidence that magnesium aluminum silicate would not dissolve upon exposure to an aqueous medium other than water, such as physiological saline and T80/PBS solution,[8] much less that it would not dissolve in any aqueous medium when formulated in a matrix along with a hydrophilic excipient.

Even had Acusphere presented evidence that magnesium aluminum silicate when formulated as part of the claimed matrix would not dissolve in an aqueous medium, it would not necessarily follow, as Acusphere contends, that "the 'taxane nanoparticles and microparticles' left in suspension after the matrix dissolves are not necessarily pure taxane." AcuBr. 43. Rather, any undissolved magnesium aluminum silicate could exist in suspension as a separate component, unattached from the taxane nanoparticles and microparticles. And, contrary to Acusphere's

[8] Indeed, before the District Court, in response to Celgene's assertion that the claims were indefinite because, *inter alia*, they "did not specify 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," Acusphere pointed to the examples of aqueous media in the specification, such as "physiological saline" and the "T80/PBS solution disclosed in Example 3" and contended that "the patent only requires assessing infringement in the given aqueous medium and volume used as the reconstitution medium." A25.

misstatements, the District Court's construction merely requires that when the matrix dissolves, the particles of only taxane drug "are *no longer associated* with either the hydrophilic excipient or the wetting agent." A26 (emphasis added). The District Court's construction does not exclude the possibility that the wetting agent (e.g., magnesium aluminum silicate) might not fully dissolve. The construction simply precludes the hydrophilic excipient and wetting agent from being "attach[ed] to the taxane drug." A25–26. Thus, Acusphere's argument in this regard is wholly irrelevant.[9]

5. Acusphere's argument based on pegylated excipients has been waived and, in any event, is irrelevant.

To manufacture an argument on appeal, Acusphere raises for the first time an assertion that Celgene's proposed construction (which the District Court adopted) excludes pegylated excipients, which it contends is a preferred embodiment.[10] Neither Acusphere nor its expert raised this argument in the

[9] Equally irrelevant is Acusphere's unsupported contention that the only testing method disclosed in the intrinsic evidence, a Coulter Counter, purportedly cannot measure whether "taxane is all that is present." AcuBr. 45. As an initial matter, Acusphere's citation to ¶ 41 of Dr. Langer's responsive expert report does not even remotely support Acusphere's position. AcuBr. 45; A1571. And furthermore, nothing in the claims requires that only a Coulter Counter be used to the exclusion of other analytical techniques.

[10] Nowhere in the specification of the '493 patent is a matrix having a "pegylated excipient" described as being a "preferred" embodiment, even though elsewhere Acusphere distinguished between embodiments that were "preferred" and those that were not. A38, 2:43 ("In one embodiment . . . ."); A38, 2:47 ("In a preferred embodiment . . . .").

District Court; accordingly, it has been waived.[11] *Butamax(TM) Advanced Biofuels LLC v. Gevo, Inc.*, 746 F.3d 1302, 1314 (Fed. Cir. 2014) ("This court declines to consider what appears to be a new claim construction argument raised for the first time on appeal."); *Conoco, Inc. v. Energy & Envtl. Int'l, L.C.*, 460 F.3d 1349, 1358 (Fed. Cir. 2006).

That Acusphere did not raise this argument before is unsurprising, since it is entirely irrelevant to this case. There is no allegation that the accused Abraxane® product includes a pegylated excipient, because it does not. Accordingly, whether "nanoparticles and microparticles of a taxane" could be construed in a way to permit the inclusion of pegylated excipients in some manner is a question that this Court need not and should not address. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (claim terms need only be construed "to the extent necessary to resolve the controversy"); *U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997) ("Claim construction is a matter of

[11] It would be unfairly prejudicial for the Court to consider Acusphere's argument raised for the first time on appeal, particularly without Celgene having the ability to present expert testimony and evidence regarding the scientific meaning of the statement in the specification to which Acusphere refers, i.e., that "pegylated excipient beneficially envelops or shields the paclitaxel from macrophage uptake." AcuBr. 44. It is worth noting, however, that it is obvious, as even Acusphere admits, that this statement in the specification refers to a biological event that takes place in a patient's body, *id.*, and is not a description of whether the claimed "nanoparticles and microparticles of taxane" themselves can comprise pegylated excipients.

resolution of disputed meanings and technical scope . . . for use in the determination of infringement.").

C. The District Court properly construed "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles."

The District Court relied on its correct construction of "nanoparticles and microparticles of a taxane" to properly construe the term "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles." The reasons justifying both constructions are set forth above. *See supra* I.B.1.–1.B.5. Two points, however, bear reiteration. First, Acusphere unequivocally represented to the examiner that "[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*." A1021 (emphasis added). Thus, Acusphere disclaimed any composition in which, after the matrix dissolves, the particles of taxane are still associated with the other components of the matrix.

Second, during prosecution, Acusphere repeatedly distinguished its invention from taxane particles encapsulated by an albumin polymer shell as taught in Desai. Acusphere took the position that the prior art did not teach "a matrix formed of a hydrophilic excipient that dissolves upon contact with water," and went so far as to say that the "polymer encapsulated formulations" in Desai "teach[] away from anything that would dissolve immediately upon administration

to release drug in particulate form." A1021. Yet, in the present case, Acusphere is attempting to read its claims on Celgene's Abraxane® product—a product that consists of the same albumin polymer encapsulated formulations Acusphere disclaimed during prosecution. Acusphere cannot recapture what it expressly disclaimed during prosecution. *Omega Eng'g*, 334 F.3d at 1323 (citing *Schriber-Schroth Co. v. Cleveland Trust Co*., 311 U.S. 211 (1940).

In sum, this is a straightforward case of applying well-settled law. For these reasons, the District Court correctly construed the terms "nanoparticles," "microparticles," "nanoparticles and microparticles of a taxane," and "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles." If even one of these constructions is affirmed, the judgment of noninfringement should also be affirmed.

BRIEF ON CELGENE'S CROSS-APPEAL

II. THE CLAIMS OF THE '493 PATENT ARE INDEFINITE.

The District Court decided the issue of indefiniteness on December 3, 2013, under the old, now rejected standard that a claim is not indefinite so long as it is "subject to construction, i.e., it is not insolubly ambiguous." A2039 (quoting *Bancorp Servs., L.L.C. v. Hartford Life Ins. Co*., 359 F.3d 1367, 1371 (Fed. Cir. 2004)). On June 2, 2014, the Supreme Court displaced that standard and held that

"a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, *with reasonable certainty*, those skilled in the art about the scope of the invention." *Nautilus*, 134 S. Ct. at 2124 (emphasis added). Anything short of reasonable certainty would, the Court held, "diminish the definiteness requirement's public-notice function and foster the innovation-discouraging 'zone of uncertainty.'" *Id.* at 2130 (quoting *United Carbon v. Binney & Smith Co.*, 317 U.S. 228, 236 (1942)). While the '493 patent claims are indefinite even under the previous "insolubly ambiguous" standard, there is no question the claims are indefinite under *Nautilus*.

A. The Claim Limitation "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles" Renders the Claims Indefinite.

Although Celgene agrees that the District Court's construction of the limitation "wherein upon exposure to an aqueous medium, the matrix dissolves to leave the taxane nanoparticles and microparticles" is the proper construction to the extent this limitation can be construed, in the context of the claimed invention this limitation renders the claims nonsensical and indefinite. This limitation was added by amendment to each of the claims during prosecution in an effort to overcome rejections based on Desai and Hanes. A1016–19. As explained below, this claim limitation is nonsensical, and the fact that the applicant convinced the examiner

that the prior art does not teach this nonsensical limitation was due in no small part to the scientific impossibility of this limitation.

1. The claim limitation is nonsensical.

First, the claim limitation is nonsensical because the claims specify that the nanoparticles and microparticles of a taxane, along with the hydrophilic excipient and the wetting agent, form the matrix. The claims go on to require that "the matrix dissolves to leave the taxane nanoparticles and microparticles." Something that dissolves, by definition, goes into solution, like sugar dissolves into water.[12] The nanoparticles and microparticles of a taxane cannot simultaneously form the object (the matrix) that dissolves into the solution, and also be left intact, undissolved, outside the solution. This nonsensical claim limitation accordingly "fail[s] to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus*, 134 S. Ct. at 2124; *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993).

2. The claim limitation is scientifically impossible.

Another reason the claims are indefinite is that uncontroverted expert testimony established that it is scientifically impossible for the components of the matrix that are not nanoparticles and microparticles of taxane to dissolve and "leave" the nanoparticles and microparticles behind. As Celgene's expert, Dr.

[12] Both sides agree that "dissolve" means to go into solution. A3259–60; *see also* A2801 n.3; A3170:8–18; A3174:9–15.

Mansoor Amiji, testified: "[Y]ou cannot have [the] matrix dissolve without dissolution of the nanoparticles and microparticles. You are going to have the whole system dissolve at once." A3233:8–12; A3231:11–A3232:5. This testimony was unrebutted.

Dr. Amiji further explained that Example 3 of the '493 patent confirms this simultaneous dissolution:

> [T]hat's what you see in example 3, that when the matrix is dissolving, the drug is dissolving at the same time. It is not a biphasic pattern. You don't get the biphasic dissolution profile [where] you are going to have a condition at which just the matrix dissolves and another condition where the drug will start to dissolve. The evidence in this patent both in the specification and in the example shows that the drug is dissolving the minute you put water in, aqueous medium in.

A3232:17–A3233:3. Indeed, the entire "essence of the invention" is to speed the dissolution rate of the nanoparticles and microparticles of taxane. A3111:4–8. For example, the specification identifies that an "object of the present invention [is] to provide compositions providing enhanced dissolution of paclitaxel," A38, 1:55–56, and further explains that "[w]etting agents can be used to facilitate water ingress into the matrix and wetting of the paclitaxel particles in order to facilitate dissolution," A39, 4:45–47. Likewise, in the prosecution history, Acusphere distinguished Hanes and Desai on the basis that they did not teach "nanoparticles and microparticles of a taxane that have a high surface area and dissolve rapidly," A1046, in contrast to the patented invention, which "yields taxane that dissolves at

a rate that may be 1000 times shorter than for bulk taxane." A1047. Acusphere further emphasized that "[n]one 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." A1046 (emphasis in original). Indeed, Acusphere explicitly distinguished Desai on the basis that its particles, upon exposure to an aqueous medium, remain in suspension, rather than immediately dissolve:

> Although Desai acknowledges that the matrix material dissolves in contact with water. 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). . . . Accordingly, Desai teaches away from a formulation of taxane which dissolves.

A1046. Dr. Amiji thus concluded: "You look at all the evidence. . . . One skilled in the art would not be able to differentiate" such a claimed biphasic dissolution state. A3112:11–19.

3. There is no known test for determining whether the matrix has dissolved to leave the nanoparticles and microparticles of taxane.

Not surprisingly, there is no known test for determining—or example provided in the '493 patent demonstrating how a person of ordinary skill could determine—whether the matrix dissolves to leave the nanoparticles and microparticles of taxane. Acusphere admitted in the prosecution history, and both experts agreed, that Example 3 of the '493 patent, titled "In Vitro Dissolution of Porous Paclitaxel Matrices," is the *only* example in the patent purporting to provide

an assay to test the limitation "the matrix dissolves." A2598–99; A3175:19–22 (Acusphere's expert confirming that Example 3 is the test for whether the matrix dissolves); A2800; A1047 ("The examiner's attention is drawn to example 3 of the application . . . Applicants' claimed process yields taxane that dissolves at a rate that may be 1000 times shorter than for bulk taxane."); A42, 10:12–56. Yet, as both experts further agreed, and as Acusphere asserted during prosecution, this assay actually measures only the dissolution of the nanoparticles and microparticles of taxane, not whether the matrix has dissolved to leave the nanoparticles and microparticles of taxane. A1047; A3173:12–18; A3174:9–15 ("Q. So in order to determine whether or not the porous paclitaxel matrix has dissolved, the example 3 provides you the test, and the test is to look at whether or not the taxane has gone into solution. Is that correct? A. That's what I've been saying like the last 15 minutes.").

The District Court held that the claim limitation is not indefinite based on its conclusion that the patent 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." A24 (quoting Pl's Reply Br. at 20). The District Court cited to several portions of the prosecution history that

supposedly confirm this two-step approach. A24. However, none of the cited material refers to any such two-step process. Rather, the cited sections show that, in response to the examiner's prior-art rejections, the patentee emphasized the increased dissolution rate of the nanoparticles and microparticles of taxane in its claimed invention. *E.g.*, A1047 ("Applicants' claimed process yields taxane that dissolves at a rate that may be 1000 times shorter than for bulk taxane."). It is precisely due to this increased dissolution rate of the taxane that, as Dr. Amiji explained, results in the whole of the matrix, including the nanoparticles and microparticles of a taxane, dissolving at once. A3233:8–12.

Moreover, the District Court's approach cannot be reconciled with Acusphere's arguments made during prosecution to distinguish Desai. Even though in prosecution Acusphere admitted that the matrix material taught by Desai dissolves, Acusphere argued that Desai's taxane particles "are stable for at least three days," upon "reconstitution" in an aqueous medium, and that, therefore, "Desai teaches away from a formulation which dissolves." A1046. In other words, Acusphere distinguished Desai on the basis that the Desai taxane particles do not dissolve immediately upon *reconstitution*. Acusphere did not assert that the Desai taxane particles would remain stable (i.e., undissolved) upon the addition of a larger volume of aqueous medium or upon administration to the patient (which, for the Desai formulation to be efficacious, could not be the case). Thus, the

District Court's attempt to avoid the apparent indefiniteness of the claims by concluding that the patent contemplates the dissolution of the nanoparticles and microparticles of taxane, not upon reconstitution in an aqueous medium, but only in some second step in which a larger volume of aqueous medium is added or once administered to the patient, is inconsistent with the prosecution history.

Additionally, the District Court's two-step approach ignores the unrebutted evidence, discussed above, demonstrating that such a two-step process is scientifically impossible in the context of the claimed invention because all of the components forming the matrix, including the nanoparticles and microparticles of a taxane, will dissolve together at the same time.

Further, even if such a two-step process were possible in the context of the claimed invention, the District Court's opinion fails to address the patent's failure to disclose how one of skill in the art could ever determine if such a condition existed (i.e., whether a matrix is dissolved but any nanoparticles and microparticles of a taxane remain) such that competitors trying to practice or design around the invention would be able to discern the bounds of the patent right.

The District Court should have concluded that such a two-step process is neither demonstrated in the patent, nor scientifically possible or testable, and, as a result, that the claims, the specification, and the prosecution history fail to inform, with reasonable certainty, those skilled in the art how to determine the existence of

any such condition in order to practice or design around the claimed invention. *See Nautilus*, 134 S. Ct. at 2130; *Honeywell Int'l, Inc. v. ITC*, 341 F.3d 1332, 1341 (Fed. Cir. 2003) (holding claims invalid for indefiniteness because "[c]ompetitors trying to practice the invention or to design around it would be unable to discern the bounds of the invention").

In sum: The claim term is indefinite for three different reasons: *First*, it is logically impossible: The nanoparticles and microparticles of a taxane cannot simultaneously be part of the matrix yet remain behind after the matrix has dissolved. *Second*, it is scientifically impossible: As a matter of unrebutted scientific fact, all components of the matrix, including the taxane nanoparticles and microparticles, dissolve at the same time, making it scientifically impossible for the matrix to dissolve but leave the taxane nanoparticles and microparticles. *Third*, it is untestable: There is no assay available for determining when a matrix has dissolved to leave the nanoparticles and microparticles of taxane, and the assay specified in the patent for purportedly measuring the dissolution of the porous matrix actually measures only the dissolution of the taxane nanoparticles and microparticles. Accordingly, this Court should reverse and hold the claims indefinite.

B. The Claim Term "mean diameter" is Indefinite.

1. Numerous types of "mean diameters" and measurement techniques were used in the art that result in substantially different values.

Each claim requires that "the nanoparticles and microparticles have a *mean diameter* between about 0.01 and 5 μm." A43, cl. 1 (emphasis added). There is no dispute that, to a person of ordinary skill at the time of invention, the term "mean diameter" did not refer to a simple arithmetic average of the diameters of the individual particles (as a layman might expect). A2785–88; A2790–93 ¶¶ 15–19; A3161:18–24; A3163:14–18. Instead, the term encompassed numerous, different, and complex methods and mathematical formulas, known by different names. Acusphere's own patents that share common inventors as the '493 patent, as well as publications by Acusphere's expert and others in the field, discuss some of the various types of mean diameters used in the art, such as the number mean diameter, intensity weighted mean diameter, aerodynamic mean diameter, and the Stokes mean diameter. A2790–93 ¶¶ 15–19; A2431–32 ("discussing "number average particle size" (i.e., number mean diameter), "volume average diameter" (i.e., volume mean diameter), "longest axis diameter," and "aerodynamic diameter"); A2875, 8:30–34 (reporting results as a "number mean diameter" and "volume mean diameter"); A2847; A2879, 16:5–7; A2883–89; A2893; A2900; A2908; A2916; A2992 ¶ 261; A3004; A3017, Table 1; A3028; A3037–40; A3047;

A3061–62; A2819, A2828. "Each type of mean diameter is calculated or weighted based on different characteristics of the particles being measured, such as the number, surface area, volume, length in one or more dimensions, intensity characteristics, hydrodynamic characteristics, or aerodynamic characteristics of the particles" A2786–88 ¶ 9; A3158:2–10. As a result, the values for each of the different types of "mean diameter" that can be calculated are likely to be vastly different for the same set of particles. A2786–88 ¶ 9; A3161:18–24; A3162:4–11; A3163:1–18; A3164:4–13.

Furthermore, before a skilled artisan could even attempt to calculate a particular type of "mean diameter," she would first need to measure one or more size-related characteristics of the particles of interest. A2794 ¶ 22; A2628–29; A2658; A2750; A2773. It is undisputed that, at the time of invention, there were numerous different techniques used for measuring those characteristics. Such techniques included various optical methods (e.g., electron microscopy techniques), electrozone sensing (coulter counter), laser diffraction, and inertial, electrical, and diffusional techniques. A2794–95 ¶¶ 23–24; A2628–29; A2750; A2773–75; A2565–66 ¶ 43; A2627–A2634. Those techniques rely on different characteristics of the particles as a bases for measurement, such as the particles' 2-D length across one of several possible chosen planes, volume, weight, number, or

aerodynamic characteristics. A2795–96 ¶ 26; A2628–29; A2639; A2749–50; A2565–66 ¶ 43; A2627–A2634; A2773–75.

Critically, as even Acusphere's expert admitted, the resulting mean diameter values for the same set of particles can vary greatly depending on the type of mean diameter calculated and the measurement technique used, such that one can arrive at a value that is either within the scope of the claims or outside the scope of the claims. A3161:18–24; A3162:4–16; A3163:1–18; A3164:4–13; A2786–88 ¶ 9; A2629; A2664; A2742; A2751; A2766; A2773; A2760; A2849 ¶ 67. Indeed, Acusphere's related patents provide examples where the mean diameter value for the same set of particles varies within and outside the scope of the "between about 0.01 and 5 μm" claim limitation depending on the type of mean diameter selected. A3076, 1:39–42 ("The particle diameters ranged from 1–10 microns when sized on a Coulter counter with a number average mean of 2.0 microns and a volume average mean of 5.2 microns."). Accordingly, if a particular type of mean diameter and the technique that is to be used as the basis for measurement are not specified, then the term "mean diameter" lacks a definitive meaning, particularly in the context of determining the scope of the patent.

2. The specification and prosecution history fail to inform a person of skill the type of mean diameter or measurement techniques to be used.

It is undisputed that there is no industry-standard type of "mean diameter," nor is there an industry-standard technique for measuring size-related characteristics of particles. A2789–93 ¶¶ 14–19; A3161:18–24; A3163:14–18. And neither the claims nor the specification of the '493 patent specify a type of "mean diameter" or disclose any particular technique for measuring the size-related characteristics of particles. A2796 ¶ 27; A2565–66 ¶ 43. Nor were any particular types of mean diameter or related measurement techniques discussed during the prosecution history of the '493 patent. This is not a case where the disclosure is vague or ambiguous—there is simply no disclosure, and, therefore, no way for a person of skill to discern with reasonable certainty the type of mean diameter or measurement techniques that should be used to assess the scope of the claims. *Nautilus*, 134 S. Ct. at 2124.

This Court has frequently held such patents invalid, even under the old "insolubly ambiguous" standard. In *Teva v. Sandoz*, the patent failed to specify which type of "molecular weight" should be used to measure copolymers having "a molecular weight of about 5 to 9 kilodaltons." *Teva Pharms. USA, Inc. v. Sandoz, Inc*., 723 F.3d 1363, 1367 (Fed. Cir. 2013). Three types of "molecular weight" were used in the art—peak average molecular weight, number average

molecular weight, and weight average molecular weight. *Id.* at 1367. And, depending on what type of molecular weight was used, the resulting value varied. *Id.* at 1368. Because the scope of the claims varied significantly depending on which type of molecular weight was used, the claims were indefinite. *Id.*

Similarly, in *Honeywell*, the claim required that the "melting point elevation" or "MPE" of an industrial yarn be within a specified range during the manufacturing process. *Honeywell*, 341 F.3d at 1339. The patent identified the particular machine to be used for measuring MPE, but not which of four prior-art preparation methods should be used. As here, the different methods did not produce identical or even "essentially identical results." *Id*. at 1341. Without any guidance from the patent document as to which preparation method(s) should be used, the *Honeywell* claims, too, were held indefinite.

The '493 patent suffers from both of the indefiniteness problems identified in *Teva* and *Honeywell*—the absence of a defined metric, and the absence of a defined measurement method. The '493 patent fails to inform a person of ordinary skill of either the type of mean diameter or the measurement technique that should be used for measuring the physical properties of the claimed nanoparticles and microparticles. Depending on the mean diameter type and the measurement technique chosen, the resulting values for a set of particles might fall within, or outside, the scope of the claims. This is precisely the forbidden "zone of

uncertainty which enterprise and experimentation may enter only at the risk of infringement." *Nautilus,* 134 S. Ct. at 2130 (quoting *United Carbon*, 317 U.S. at 236). Because the "claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention," the '493 patent claims are indefinite. *Id.* at 2124.

3. The District Court improperly relied on a prior-art disclosure to save the claims' definiteness.

The District Court, however, held that the term "mean diameter" was sufficiently definite solely because a prior-art reference that was distinguished by Acusphere during prosecution (Hanes), discusses "mass mean diameter"[13] and teaches that "the mass mean diameter of the particles can be measured using a Coulter Multisizer II."[14] A21. The District Court reasoned that because Hanes was cited as a prior-art reference and distinguished, the examiner and Acusphere subjectively understood "that the volume mean diameter defined the particle size for the '493 patent as well." A21. The District Court reached this conclusion even though neither the examiner nor Acusphere ever mentioned "volume mean diameter" anywhere in the prosecution history.

[13] "Mass mean diameter" is synonymous with "volume mean diameter." A21.

[14] The District Court overlooked the fact that Hanes also discloses that the mean aerodynamic diameter can be determined for such particles. A3292, 9:28–36.

But whatever technique a prior-art reference may have used—and whatever the examiner and Acusphere may have subjectively understood—is irrelevant to the § 112 inquiry, especially after *Nautilus*. *Nautilus* requires that "the specification and prosecution history[] inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus*, 134 S. Ct. at 2139. Here, the District Court merely relied on the fact that one type of mean diameter, out of the many types used in the art, was discussed in a single prior-art reference, and did not even address whether a person of skill would understand with reasonable certainty that the scope of the claims were limited to this one particular type of mean diameter. Had this type of mean diameter and measurement been required by the '493 patent, the applicants needed to—at a minimum—incorporate Hanes and its discussion of the "volume mean diameter" by reference. 37 C.F.R. 1.57(d)(2) (requiring "essential material"—defined as material that is necessary to: . . . [d]escribe the claimed invention in terms that particularly point out and distinctly claim the invention as required by 35 U.S.C. 112(b)"—to be incorporated by reference into a patent). It was not.

Were the rule as the District Court reasoned, a person of skill would be required to look up every reference cited and distinguished during prosecution, as well as venture into what the examiner and patentee might have subjectively understood, in order to guess at the claims' scope. (Even this relatively short

patent lists over 150 patents and publications on its face. A33–36.) This contravenes "the definiteness requirement's public-notice function," *Nautilus*, 134 S. Ct. at 2130, and places the onus on the public—as opposed to "the patent drafter [who] is in the best position to resolve the ambiguity in . . . patent claims," *id.* (quoting *Halliburton Energy Servs., Inc. v. M–I LLC*, 514 F. 3d 1244, 1255 (Fed. Cir. 2008)); *see also Pressure Prods. Med. Supplies v. Greatbatch Ltd*., 599 F.3d 1308, 1318 (Fed. Cir. 2010) ("The trial court erroneously used structures from the prior art references listed in the patent to provide a definition for [the claim term] encompassing structures not disclosed expressly in the patent specification.").

In sum: If Acusphere intended to limit "mean diameter" to a specific type of mean diameter, it needed to make that intent manifestly and objectively clear, just as it did in other of its patent applications. A2431 at ¶ 63 ("The terms 'size' or 'diameter' in reference to particles refers to the number average particle size, unless otherwise specified.").

CONCLUSION

For these reasons, the Court should affirm the District Court's judgment of non-infringement on Acusphere's appeal (No. 2014-1411). On Celgene's appeal (No. 2014-1442), the Court should reverse and hold the claims invalid as indefinite.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on August 18, 2014, I caused the foregoing BRIEF FOR DEFENDANTS-CROSS-APPELLANTS to be filed via CM/ECF with the Clerk of the Court, thereby electronically serving it on all counsel of record in this matter.

Dated: August 18, 2014

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 28.1(e), because it contains 16,384 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and Federal Rule of Appellate Procedure 28.1(e), and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6), because it has been prepared in a proportionally spaced typeface using Microsoft Word 2007 in Times New Roman 14 point font.

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