United States District Court,
C.D. California.

AVENTIS PHARMS S.A. and,
v.
AMPHASTAR PHARMACEUTICALS, INC. and USA.

Nos. ED CV 03-887 RT (SGLX), ED CV 04-333 RT (SGLX)

Oct. 22, 2004.

Allen M. Sokal, Esther H. Lim, Don Ridge, for Plaintiffs.

Lee J. Papageorge, Jan P. Weir, Francis C. Lynch, Steven M. Hanle, Laurie Gill, for Defendants.

PRESENT: ROBERT J. TIMLIN**. Judge.**

Lenora Pulliam, Courtroom Clerk.

Theresa Lanza, Court Reporter.

PROCEEDINGS: COURT'S CONSTRUCTION OF CERTAIN CLAIMS IN U.S. PATENT NO. 5,389,618

The court, Judge Robert J. Timlin, has read and considered plaintiffs Aventis Pharma S.A. and Aventis Pharmaceuticals Inc. (collectively, "Aventis"), and defendants Amphastar Pharmaceuticals, Inc. ("Amphastar") and Teva Pharmaceuticals, Inc. ("Teva") (collectively, "Defendants")'s opening claim construction briefs for construction of the patent in suit, U.S. Patent No. 5,389,618 (' "618 patent"), each party's opposition to the opening claim construction briefs, and each party's reply brief to those oppositions.

On October 1, 2004, the court presided over a hearing pursuant to Markman v. Westview Instruments, Inc., 517 U.S. 370 (1996), *aff'g* 52 F.3d 967 (Fed.Cir.1995) (en banc), concerning the proper construction of certain claims of the '618 patent. The parties were represented at the hearing by counsel, and the court heard oral argument. Based on consideration of the written briefs, supporting evidence, and counsel's oral argument, the court concludes as follows:

I.

BACKGROUND

Aventis is a pharmaceutical company that manufactures Lovenox. Lovenox is a blood thinner that inhibits the formation of certain venous blood clots called thromboses. Lovenox is derived from heparin. Heparin is a mixture of long polysaccharide molecules obtained from the internal organs of animals such as pigs and cattle. Through a chemical process, heparin's longer molecules can be broken down into shorter molecules.

A group of these shorter molecules are called low molecular weight heparins ("LMWHs"). The ' 618 patent covers a range of defined LMWHs, including Lovenox, and their administration to patients who are susceptible to blood clots.

On August 4, 2003, Aventis filed an action in this court against Amphastar and Teva for infringement of the '618 patent. Defendants dispute infringement and claim that the '618 patent is invalid and unenforceable. Defendants also have filed related counterclaims against Aventis.

Before the court for claim construction are 6 terms or phrases contained in certain claims of the '618 patent.

II.

APPLICABLE LAW

The construction of a patent claim is a matter of law for the court. Markman, 517 U.S. at 372. To determine the meaning of a patent claim, the court considers three sources: the claims, the specification, and the prosecution history. Markman, 52 F.3d at 979.

First, the court looks at the words of the claims. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996). "[T]he analytical focus must begin and remain centered on the language of the claims themselves, for it is that language that the patentee chose to use to particularly point out and distinctly claim the subject matter which the patentee regards as his invention." Texas Digital Systems, Inc. v. Telegenix, Inc., 308 F.3d 1193, 1201-02 (Fed.Cir.2002) (internal quotations and citations omitted). The Federal Circuit imposes a "heavy presumption that the claim term carries its ordinary and customary meaning." CCS Fitness, Inc. v. Brunswick Corp., 288 F.3d 1359, 1366 (Fed.Cir.2002); Nellcor Puritan Bennett, Inc. v. Masimo Corp., 300 F.Supp.2d 923, 928 (C.D.Cal.2004). Dictionaries, encyclopedias, and treatises are "particularly useful resources to assist the court in determining the ordinary and customary meanings of claim terms." Texas Digital, 308 F.3d at 1202.

Second, it is always necessary to review the specification to determine if the presumption of ordinary and customary meaning is rebutted. Texas Digital, 308 F.3d at 1204. The presumption is only rebutted in situations where "the inventor (1) acting as his own lexicographer, clearly sets forth an 'explicit definition' of the term that is different from its ordinary meaning; or (2) has disavowed or disclaimed scope of coverage by using words of 'manifest exclusion or restriction....' " Stephen Key Design, LLC v. Lego Systems, Inc., 261 F.Supp.2d 1196, 1198 (N.D.Cal.2003) (*citing* Texas Digital, 308 F.3d at 1204). However, "if the meaning of the words themselves would not have been understood to persons of skill in the art to be limited only to the examples or embodiments described in the specification, reading the words in such a confined way would mandate the wrong result and would violate our proscription of not reading limitations from the specification into the claims." *Id*.

Third, the court may consider the prosecution history of the patent, if in evidence. Vitronics, 90 F.3d at 1582. "Although the prosecution history can and should be used to understand the language used in the claims, it too cannot enlarge, diminish, or vary the limitations in the claims." Markman, 52 F.3d at 980 (internal quotations and citations omitted).

Extrinsic evidence should be used in claim construction only if needed to assist in determining the meaning or scope of technical terms in the claims, and may not be used to vary or contradict the terms of the claims. Stephen Key Design., 261 F.Supp.2d at 1198; Markman, 52 F.3d at 981. The court is free to consult

reference materials, such as dictionaries, for assistance in determining the ordinary meaning of a claim term and such sources are not considered extrinsic evidence. Texas Digital, 308 F.3d at 1202-03.

Finally, "[t]he subjective intent of the inventor when he used a particular term is of little or no probative weight in determining the scope of a claim (except as documented in the prosecution history)." Markman, 52 F.3d at 985 (citation omitted). "Rather the focus is on the objective test of what one of ordinary skill in the art at the time of the invention would have understood the term to mean." Id. at 986.

III.

CLAIM CONSTRUCTION

Applying the applicable law as stated above, the court hereby construes as a matter of law the following terms and phrases in the claims for which claim construction is sought by the parties.

A. Admixture

Aventis and Amphastar request construction of the term "admixture" which appears in claims 1, 2, 3, 4, 5, 6, 7, 23, 24, 25, 27, 28, 30, 31, and 32 of the '618 patent. FN1 Amphastar asserts that the common meaning of "admixture" is "the compound formed by mixing different substances together." Webster's Revised Unabridged Dictionary (1998). Using the same dictionary, Aventis claims that the common meaning of "admixture" is simply "mixture." Id.

FN1. Claim 1, representative of all claims referencing "admixture," is as follows:
A heterogeneous intimate admixture of sulfated heparinic polysaccharides, such sulfated polysaccharides having a weight average molecular weight less than that of heparin and said admixture consisting essentially of

from 9% to 20% of polysaccharide chains having a molecular weight less than 2,000 daltons

from 5% to 20% of polysaccharide chains having a molecular weight greater than 8,000 daltons, and

from 60-86% of polysaccharide chains having a molecular weight of between 2,000 and 8,000 daltons,

the ratio between the weight average molecular weight and the number average molecular weight thereof ranging from 1.3 to 1.6

said admixture (i) exhibiting a bioavailability and antithrombotic activity greater than heparin and (ii)

having an average molecular weight of between approximately 3,500 and 5,500 daltons.

When a claim term has two plain and ordinary meanings, "intrinsic evidence is the most reliable guide to help the court determine which of the possible meanings of the terms in question was intended by the inventor to particularly point out and distinctly claim the invention." Texas Digital, 308 F.3d at 1203-04 (*citing* Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1250 (Fed.Cir.1998)). There is nothing in the claim language that limits that "admixture" to a compound formed by different substances. The language of claim 1 specifies that "said admixture" consists essentially of various percentages of polysaccharide chains having various weights. There is no reference to a different substance. There is nothing in the specification that rebuts the presumption of Aventis' construction which is one of arguably two ordinary and customary meanings of the term "admixture ." *See* Texas Digital, 308 F.3d at 1204. The court is not convinced that Aventis defined "admixture" as requiring two different substances in the prosecution history. Thus, because Aventis' definition stays true to the claim language and "most naturally aligns with the patent's description of the invention," the court finds that it is the correct construction. Texas Digital, 308 F.3d at 1203-04 (*citing* Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1250 (Fed.Cir.1998) ("The construction that stays true to the claim language and most naturally in the end, the correct construction.")).

Thus, the court construes "admixture" which appears in claims 1, 2, 3, 4, 5, 6, 7, 23, 24, 25, 27, 28, 30, 31, and 32, as follows: "A mixture of sulfated heparinic polysaccharides having a variety of molecular weights, regardless of how the mixture was prepared."

B. Bioavailability

Aventis and Amphastar request construction of the phrase "bioavailability ... greater than heaparin" which appears in claims 1, 31, and 32 of the '618 patent. Aventis contends that the term "bioavailability" should be given its ordinary meaning to those skilled in the art. It asserts that the ordinary meaning of bioavailability is "a percentage, based on subcutaneous ("S.C.") anti-Xa activity over time divided by intravenous ("I.V.") anti-Xa activity over time," greater than heparin. Amphastar contends that the term is indefinite under Section 112 of Title 35 of the United States Code.

Generally, "bioavailibility" is defined as "the degree to which or rate at which a drug or other substance is absorbed or becomes available at the site of physiological activity after administration." American Heritage Dictionary (4th ed.2000); *see also* Merriam-Webster Medical Dictionary (2002) (defining bioavailability as the degree and rate at which a substance is absorbed into a living system or is made available at the site of physiological activity). As evidenced by the general definition of bioavailability which uses rates and degrees and as indicated by both parties' briefs, "bioavailability" needs to be construed because it must be measured in relation to some other activity. In the case of heparin, it is measured in relation to a biological activity. Thus, because the meaning of "bioavailability" is not conspicuous from the ' 618's claim language, the court will consider the specification. "For claim construction purposes, the description may act as a sort of dictionary, which explains the invention and may define terms used in the claims." Markman, 52 F.3d at 979-80; *see also* Bell Atl. Network Servs., Inc. v. Covad Communs, Group, Inc., 262 F.3d 1258, 1268 (Fed.Cir.2001) (stating that the specification may define claim terms "by implication" such that the meaning may be "found in or ascertained by a reading of the patent documents").

The reference to bioavailability in the '618 patent specification is in the "Summary of the Invention" section. It states, "[I]n humans, the mixtures of the invention display excellent bioavailability, as measured by the anti-Xa activity. Thus, this value is approximately 30 IU for heparin, but is approximately 90 IU for the mixtures of this invention." '618 patent, cols. 2-3. The first sentence of this reference supports Aventis' construction. It specifically refers to anti-Xa activity. However, the second sentence frustrates Aventis' construction because it quantifies bioavailability for heparin as "30 IU" and for the '618 patent as "90 IU." "IU" is an abbreviation for international unit. An international unit is an amount of a substance that produces a specific effect as defined by an international body. *See, e.g.,* Webster's II New Riverside Dictionary (1994); *see also,* American Heritage Dictionary (4th ed.2000) (defining IU as the "quantity of a biologically active substance, such as a hormone or vitamin, required to produce a specific response"). This is a barrier to Aventis' construction because Aventis argues that "bioavailability" should be construed as a percentage; however, the specification describes the value of bioavailability in its specification in IUs.

Aventis advances that the patent specification was mistakenly altered during prosecution. As a result of this mistake, Aventis claims the specification contained the reported anti-Xa values expressed in IUs. Aventis argues that this error is "readily apparent" because heparin's anti-Xa activity per se was widely known to be around 160 to 180 IU, about six times more than the 30 IU figure described in the specification.

Aventis cites Biotec Biologische Naturverpackungen GmbH v. Biocorp, Inc., 249 F.3d 1341 (Fed.Cir.2001), for the proposition that errors apparent to those skilled in the art should not alter the ordinary meaning of claims. In *Biotec,* the Federal Circuit stated that a court may ignore an error made by an attorney during patent prosecution if "a person of reasonable intelligence would not be misled into relying on [the] erroneous statement." *Id.* at 1348. However, the *Biotec* court also noted that in the case before it, the error was clear because "the statement was contrary to the plain language of the claims and specification as well as other statements in the same document." *Id.*

The court concludes that applying *Biotec* to Aventis' proposed construction goes beyond the limits set by *Biotec,* First, unlike *Biotec,* the error extends beyond a single statement in the prosecution history. *See id.* (characterizing the mistake as "an isolated statement and manifestly contradicted by the rest of the prosecution history."). Both the prosecuting patent attorney and PTO examiner, presumably individuals of "reasonable intelligence", agreed on the IU term of measurement. The patent examiner objected to the specification because it "[F]ail[ed] to adequately define the manner of describing anti-Xa activity by employing a percentage." In response, the prosecuting attorney seems to have agreed and explicitly requested that the PTO "change '30%' to-30 IU-and '90%' tp-90 IU-". The "IU" term then goes from the prosecution history directly into the specification of the '618 patent. Finally, the IU term is not self-evidently contrary to the plain language of the claim because, as described above, at least with reference to which biological activity, the plain language of the claim requires interpretation at least to the extent of defining the biological activity used to measure bioavailability.

Aventis also argues Novo Indus-L.P. v. Micro Molds Corp., 350 F.3d 1348 (Fed.Cir.2003), supports its argument that the court can correct its error. In *Novo,* the Federal Circuit held that "a district court can act to correct an error in a patent by interpretation of the patent where no certificate of correction has been issued ... only if (1) the correction is not subject to reasonable debate based on consideration of the claim language and the specification and (2) the prosecution history does not suggest a different interpretation of the claims." *Id.* at 1354. Notwithstanding the first part of the *Novo* test, the second part precludes its application. As discussed above, the prosecution history explicitly advances an interpretation in international units. Thus, the prosecution history does suggest an interpretation different than what Aventis proposes. This precludes

application of *Novo*.

The court refuses to correct the purported error in the '618 patent and to adopt Aventis' construction of "bioavailability." The term "bioavailability" has various meanings. The specification refers to bioavailability in terms of international units. The patent history shows the patent examiner objected to percentages because of its lack of definition. As a result, the prosecuting patent attorney apparently agreed and affirmatively adopted international units. With respect to the reissue proceeding, the court is not persuaded that the reissue examiner's silence is sufficient to overcome the intrinsic evidence of the patent. Thus, the court concludes the term bioavailability is indefinite. FN2

FN2. The court wants to make clear that this conclusion pertains only to the word "bioavailability" and only to claim construction. It does not imply indefiniteness or invalidity with respect to any claim as a whole or to any other part of the '618 patent.

C. Antithrombotic Activity Greater than Heparin

Aventis and Amphastar request construction of the phrase "antithromobic activity ... greater than heaparin" which appears in claims 1, 31, and 32 of the '618 patent. Aventis urges that this phrase should be construed as, "the claimed substance prevents the growth of thrombi better than heparin in at least one *in vivo* setting." Amphastar argues that antithrombotic activity should be construed either as "anti-Xa activity, measured as described in Tien" or as indefinite.

Generally, "antithrombotic" is defined as "preventing or interfering with the formation of thrombi." Dorlands Illustrated Medical Dictionary (28th ed. 1994) "Thrombi" are defined as "an aggregation of blood factors ... frequently causing vascular obstruction at the point of its formation." Id. Aventis' proposed construction comports with the plain and ordinary meaning of "antithrombotic" because it refers to preventing growth of thrombi. Moreover, the definition of "thrombi" supports the " *in vivo* " portion of the proposed definition because thrombus formation is a biological activity. Finally, the specification itself supports the " *in vivo* " portion of the proposed definition because it refers to the following which implies an *in vivo* construction: "thrombotic episodes in a human patient," '618 patent, abstract, "useful therapeutic compositions for the prevention of venous thromboses in patient risk situations," '618 patent, 6 :24-26, and "orthopedic surgery," '618 patent, 6:29-30.

Amphastar asserts that the specification defines "antithrombotic" as *in vitro*. In particular, Amphastar cites a passage which states, "The anti-factor Xa (antithrombotic) activity was measured by the amidolytic method on a chromogenic substrate, described by Tien et al ... using the Primary International Standard for low molecular weight heparin." '618 patent, 7 :10. Amphastar argues that this scientific measurement favors an *in vitro* construction because it was conducted in an artificial environment. However, one reference to prior art which the rest of the patent contradicts does not "provide reasonable clarity, deliberateness, and precision sufficient to narrow the definition of the claim term in the manner urged." Abbott Labs. v. Syntron Bioresearch, Inc., 334 F.3d 1343, 1355 (Fed.Cir.2003). While the court recognizes that Aventis may act as its own lexicographer, the court is not convinced that Aventis redefined "antithrombotic" by this reference to *Tien*.

The court adopts Aventis' construction. It is consistent with the plain and ordinary meaning of "antithrombotic." It is reinforced by the specification which has repeated *in vivo* references. It is not

redefined by one *in vitro* reference in the patent specification. Thus, the court construes "antithrombotic" as: "the claimed substance prevents the growth of thrombi better than heparin in at least one *in vivo* setting."

D. Esterifying the Salt ... to a Degree of Esterification Ranging from 9.5% to 14%

Aventis and Amphastar request construction of the phrase, "Esterifying the salt ... to a degree of esterification ranging from 9.5% to 14%." This phrase is used in subpart (b) part of claim 7 which claims a three-step process. Specifically, claim 7 is a "process for the preparation of the heterogeneous polysaccharide admixture as defined by claim 1, comprising (a) salifying a heparin with a long-chain quaternary ammonium salt in an aqueous medium, (b) esterifying the salt thus produced to a degree of esterification ranging from 9.5% to 14%, and then (c) depolymerizing such ester having a degree of esterification ranging from 9.5% to 14%."

Amphastar contends that claim 7 requires a fourth step which measures the degree of esterification before depolymerizing. Amphastar's support for this measuring step is through one example included in the specification of the ' 618 patent. In example 5, Aventis illustrated "the preparation of a mixture not in accordance with the invention" because the degree of esterification fell outside the limits of the claim. '618 patent, 8 :55-9 :31. Amphastar claims that this constitutes a disclaimer of example 5's admixture and establishes the requirement of the fourth measuring step. Even assuming Aventis disclaimed the particular admixture not made in accordance with the claims process, an issue that is beyond the scope of this inquiry, there is simply no basis for reading a fourth measuring step into the claim language. The plain language of the claim does not contain a fourth step. The summary of the invention and preferred embodiments do not require the fourth step. Example 5 of the '618 patent does not require the fourth step. Finally, the prosecution history does not suggest a measuring step.

Thus, the court construes "Esterifying the salt ... to a degree of esterification ranging from 9.5% to 14%" as not requiring a measuring step.

E. Numerical Limitations for Molecular Weight Ranges, the Polydispersity Range, and the Degree of Esterification Range

Aventis and Teva request construction of various numerical limitations within the patent and particularly claims 1, 28, 31, and 32. Aventis argues that the court should construe numerical limitations strictly. Teva argues these numerical limitations should be construed to include values stated to one or more decimal places that can be rounded to that same whole number. FN3

FN3. For example, Teva proposes that the limitation "from 9% to 20% of polysaccharide chains having a molecular weight less than 2000 daltons" should be construed to include products having between 8.6% and 20.4% of the polysaccharide chains with a molecular weight less than 2000 daltons.

Aventis cites Jeneric/Pentron, Inc. v. Dillon Co., 205 F.3d 1377, 1381 (Fed.Cir.2000) to support its position. In *Jeneric,* the Federal Circuit held that claim terms not modified by a term of approximation should be strictly construed. *Id.* "Assigning numerical precision to composition ranges[ ] is particularly appropriate when other variables in the same claims explicitly use qualifying language." *Id.* Aventis points out that the '618 patent, like *Jeneric,* uses qualifying language in other parts of '618's claims. For example, claim 1 recites an "average molecular weight of between approximately 3,500 and 5,500 daltons." '618 patent, 10:24-25. Claim 28 recites "an anti-Xa activity of about 100 IU." '618 patent, 11:50-51.

In addition, like *Jeneric,* the '618 patent uses ranges and degrees. Aventis argues that these ranges and degrees reinforce the use of precise values because the patentee repeatedly emphasized the criticality of the claimed ranges to overcome prior art rejections. FN4 Thus, Aventis concludes that the intrinsic evidence supports strict interpretation of the numerical limitations.

FN4. For example, *Lopez,* a prior art reference, claimed 4.3% of its polysaccharides greater than 8000 daltons. In contrast, the '618 patent claimed 5% to 20% of its polysaccharides greater than 8000 daltons.

Teva cites two cases to support its position that '618's numerical limitations should be construed to include values stated to one or more decimal places that can be rounded to that same whole number. The court finds that neither of these cases undermines the applicability of *Jeneric*. The first, San Huan New Materials High Tech v. ITC., 161 F.3d 1347 (Fed.Cir.1998), is incongruous because it implemented rounding with respect to the factual inquiry of infringement, not claim construction. The second, Viskase Corp. v. American Nat'l Can Co., 261 F.3d 1316, is less on point than *Jeneric* because it recognized that rounding is "a standard scientific convention when a number has not been carried to the next mathematically significant figure" with respect to a term modified by a term of approximation. Because some terms in the '618 patent are so modified and others are not, and the numerical terms at issue are not modified by a term of approximation, the court finds *Viskase* less persuasive than *Jeneric*.

Thus, the court construes the numerical limitations of the '618 patent strictly and the numbers are as stated with no modifications by approximation or otherwise. The underlined portions below should not be construed to include values stated to one or more decimal places that can be rounded to that same whole number:

1) from *9% to 20%* of polysaccharide chains having a molecular weight less than 2,000 daltons

2) from *5% to 20%* of polysaccharide chains having a molecular weight greater than 8,000 daltons,

3) from *60-86%* of polysaccharide chains having a molecular weight of between 2,000 and 8,000 daltons,

4) the ratio between the weight average molecular weight and the number average molecular weight thereof ranging from *1.3 to 1.6*

5) esterifying the salt thus produced to a degree of esterification ranging from *9.5% to 14*.

F. About 100 IU

Aventis and Teva request construction of "about 100 IU" in claim 28 of the ' 618 patent. '618 patent, 11:50-51. Aventis urges that the court not limit the phrase to a precise construction. Teva posits that the phrase should be construed to encompass range values from 90 IU to 122 IU, the lowest and highest values reported in the examples contained in the '618 patent.

"About" is defined as "approximately" or "near." Webster's II New Riverside University Dictionary (1994). It has been interpreted as meaning "reasonably close to." CellNet Data Systems, Inc. v. Itron, Inc., 17 F.Supp.2d 1100, 1114 (N.D.Cal.1998). Based on this plain and ordinary meaning, the court declines to limit

the phrase "about" to a precise construction. Taking limitations from patent examples and importing them as claim limitations is in direct contravention to Federal Circuit precedent. *See* Unitherm Food Sys. v. Swift-Eckrich, Inc., 375 F.3d 1341, 1351 (Fed.Cir.2004); Jeneric, 205 F.3d at 1381. The court does agree with Teva that it would be inappropriate to construe "about 100 IUs" to recognize only variability above 100 IU and ignore the variability below that value. Thus, the court construes "about 100 IU" as follows: from some reasonably close number below 100 IU to some reasonably close number above 100 IU.

IV.

DISPOSITION

ACCORDINGLY, IT IS ORDERED that the claim language of the '618 patent as stated above shall be interpreted as set forth in the portion of the order, entitled "Claim Construction."

C.D.Cal.,2004.
Aventis Pharms S.A. v. Amphastar Pharmaceuticals, Inc.