# United States Court of Appeals for the Federal Circuit

**AVENTIS PHARMACEUTICALS INC.,**
*Plaintiff-Appellant,*

**AND**

**AMR TECHNOLOGY, INC.,**
(now known as Albany Molecular Research, Inc.),
*Plaintiff-Appellant,*

**v.**

**AMINO CHEMICALS LTD., DIPHARMA FRANCIS, SR.L., AND DIPHARMA SPA,**
*Defendants-Appellees,*

**AND**

**MYLAN PHARMACEUTICALS INC.,**
*Defendant.*

- - - - - - - - - - - - - - - - - - -

**AVENTIS PHARMACEUTICALS INC.,**
*Plaintiff-Appellant,*

**AND**

**AMR TECHNOLOGY, INC.,**
(now known as Albany Molecular Research, Inc.),
*Plaintiff-Appellant,*

**v.**

**TEVA PHARMACEUTICALS USA, INC.,**
*Defendants,*

**AND**

**AMINO CHEMICALS LTD., DIPHARMA FRANCIS, SR.L., AND DIPHARMA SPA,**
*Defendants-Appellees.*

---

2011-1335,-1336

---

Appeals from the United States District Court for the District of New Jersey in Nos. 04-CV-1077, and 04-CV-1078, Chief Judge Garrett E. Brown Jr.

---

Decided: May 20, 2013

---

PAUL H. BERGHOFF, McDonnell Boehnen Hulbert & Berghoff LLP, of Chicago, Illinois, argued for plaintiffs-appellants, Aventis Pharmaceuticals Inc. and AMR Technology, Inc. With him on the brief were JAMES C. GUMINA, JEREMY E. NOE and PAULA S. FRITSCH. Of counsel on the brief were LIZA M. WALSH, Connell Foley LLP, of Roseland, New Jersey; ANDREW P. ZAPPIA, RICHARD A. MCGUIRK, WENDELL W. HARRIS, TATE T. TISCHNER and SHELLEY A. JONES, Leclairryan, Rochester, New York.

ANTHONY W. SHAW, Arent Fox LLP, of Washington, DC, argued for defendants-appellees, Amino Chemicals Ltd., et al. Of counsel on the brief was JOERG-UWE SZIPL, Griffin & Szipl PC, of Arlington, Virginia.

---

Before NEWMAN, BRYSON,* and REYNA, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* REYNA.

Dissenting opinion filed by *Circuit Judge* BRYSON.

REYNA, *Circuit Judge*.

Aventis Pharmaceuticals, Inc. and Albany Molecular Research, Inc. (AMRI) (collectively "Appellants") appeal a stipulated judgment of noninfringement entered by the U.S. District Court for the District of New Jersey. The parties stipulated to noninfringement following the district court's *Markman* opinion of January 13, 2011, which consolidated numerous patent infringement cases and construed terms of AMRI's U.S. Patent No. 5,750,703 ("the '703 patent"), among others.[1] Because we conclude

---

* Circuit Judge Bryson assumed senior status on January 7, 2013.

[1] Two cases were originally before this court, though they were both appealed from the same *Markman* Opinion and Order of January 13, 2011. The first case, *Albany Molecular Research, Inc. v. Dr. Reddy's Labs, Ltd.*, No. 2011-1232, was heard by the above panel on December 5, 2011, and relates to the district court's claim construction of U.S. Patent No. 7,390,906. The second case, *Aventis Pharmaceuticals, Inc. v. Dr. Reddy's Labs, Inc.*, No. 2011-1334, -1335, -1336, was heard by the same panel on March 15, 2012, and relates to the district court's claim construction of the '703 patent. Subsequent to the March 15 oral argument, Dr. Reddy's Labs and AMRI engaged in protracted settlement negotiations, finally culminating in settlement of all pending matters involv-

that the district court's *Markman* opinion misinterpreted claim terms of the '703 patent, we *reverse* and *remand*.

## I. BACKGROUND

This case concerns the processes used to make various piperidine derivatives, which are commonly used as active ingredients in antihistamines. Dr. Thomas E. D'Ambra, AMRI's president, found the prior art processes for making piperidine derivatives inefficient. Because one goal of Dr. D'Ambra's work was to obtain substantially pure piperidine derivative compounds—ultimately required for pharmaceutical-grade end products; that is, end products with greater than 98% purity—he recognized that the reduced purity achieved through known teachings meant additional purification steps were required after the piperidine derivative was fully formed, leading to low yields. The prior art processes, in short, were costly and time consuming.

Dr. D'Ambra's invention overcame the deficiencies in the prior art by synthesizing piperidine derivatives using piperidine and cyclopropylketone ("CPK") intermediates at an earlier stage in the reaction. The processes developed by Dr. D'Ambra have the stated advantage of more readily separating out a substantially pure piperidine derivative end product, if desired. Dr. D'Ambra claimed these novel methods in his '703 patent.[2] Fexofenadine, a

---

ing Dr. Reddy's on February 4, 2013. The settlement terminated the 2011-1232 and -1334 appeals. Only the 2011-1335 and -1336 appeals remain pending before this court.

[2] The application for the '703 patent, U.S. Patent Application No. 382,649, was filed on Feb. 2, 1995. The '703 patent, entitled "Piperidine Derivatives and Process

specific piperidine derivative, can be synthesized using these methods. *See* '703 patent col. 26 ll. 17–33 (claim 7).

Dr. D'Ambra eventually assigned the '703 patent to AMRI.[3] Sanofi-Aventis U.S., the exclusive licensee, uses the patented processes to produce large quantities of fexofenadine, which is the active ingredient in its antihistamines marketed under the brand name Allegra® and Allegra-D® 24 Hour. The issues relevant to this appeal gravitate around claims 1, 6, and 7 of the '703 patent.

## A. Technical Background

### 1. Independent Claim 1 of the '703 Patent

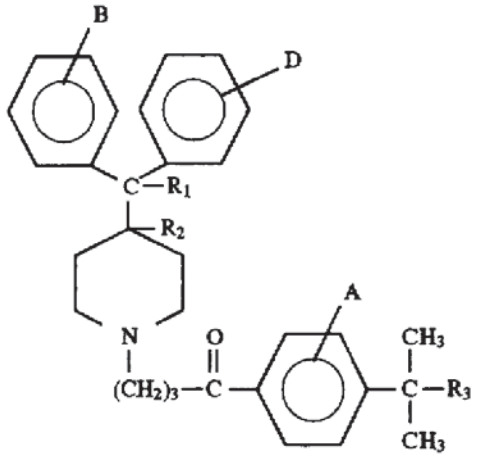
#### a. The Patented Process Generally

As its title suggests, the '703 patent describes processes for synthesizing piperidine derivatives. *See supra* note 2. Claim 1 of the '703, the only independent claim in suit, describes a process of preparing a piperidine derivative using a CPK intermediate and a piperidine intermediate. The structure of the piperidine derivative to be prepared as an end product is provided in claim 1 of the '703 patent as:

---

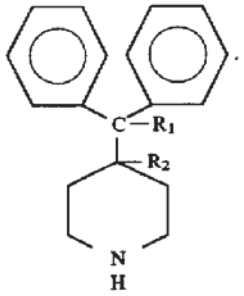
for Their Production," issued on May 12, 1998. The '703 patent is a divisional of U.S. Patent Application No. 08/083,102 ("the '102 application"), which was filed on June 24, 1993.

[3] AMRI was formerly known as AMR Technology, Inc.



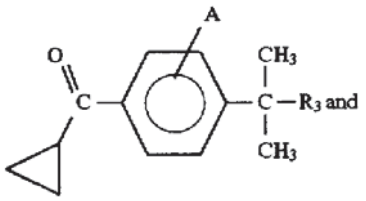

'703 patent col. 23 ll. 47–61. In the above depiction, $R_1$ is a hydrogen or hydroxyl group, $R_2$ is a hydrogen group,[4] $R_3$ is a –COOH (carboxylic acid) or –$COOR_4$ (carboxylic acid ester) group, and $R_4$ is a hydrocarbon chain with one-to-six carbon atoms.

The patented process of claim 1 generally involves the reaction of a piperidine compound like this




with a CPK intermediate of the general structure

[4] Alternatively, $R_1$ and $R_2$ can form a double bond between the carbon atoms bearing $R_1$ and $R_2$.




,

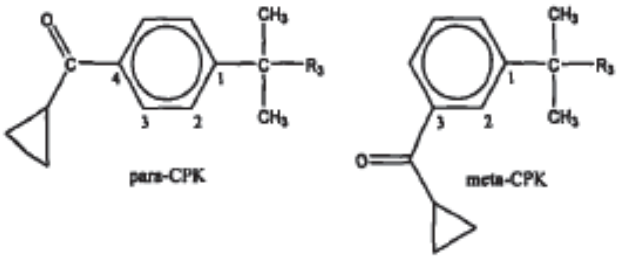
where A, $R_1$, $R_2$, and $R_3$ are defined as described for the piperidine derivative product. *See, e.g.*, '703 patent col. 24 ll. 10–17, 22–34.

The CPK intermediate exists in one of two predominant regioisomeric states:[5] either para-CPK or meta-CPK.[6] The para-CPK intermediate regioisomer has the two aromatic ring substituents located on carbons 1 and 4, on directly opposite sides of the aromatic ring. The meta-CPK intermediate regioisomer has the two aromatic ring substituents located on carbons 1 and 3, in a non-linear orientation. The different regioisomeric forms are depicted below.

---

[5] Regioisomers are chemical compounds with the same molecular formula, but with different bonding orders.

[6] The CPK intermediate can also exist in an ortho-structure, with the aromatic ring substituents adjacent to each other. However, ortho-CPK is rarely produced and of little biological efficacy, so it is ignored for the remainder of this discussion.

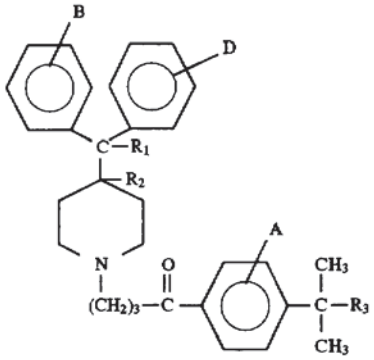



The difference between these regioisomeric arrangements of constituents on both the CPK intermediate and piperidine derivative product appears slight, but is biologically significant—the piperidine derivative produced using the para-CPK structure is biologically active, while the piperidine derivative produced using the meta-CPK structure is biologically inactive. The '703 patent extensively criticizes the prior art processes because each stage of the synthesis yields an impure mixture of meta- *and* para-regioisomers. But the new process invented by Dr. D'Ambra using a CPK intermediate means that the para/meta CPK regioisomeric mixture is more readily separable to obtain para-CPK, resulting in a substantially pure para-piperidine derivative end product.

b. "Substantially Pure"

Claim 1 of the '703 patent reads in its entirety:

> 1. A process of preparing a piperidine derivative compound of the formula:




wherein

$R_1$ is hydrogen or hydroxyl;

$R_2$ is hydrogen;

or $R_1$ and $R_2$ taken together form a second bond between the carbon atoms bearing $R_1$ and $R_2$;

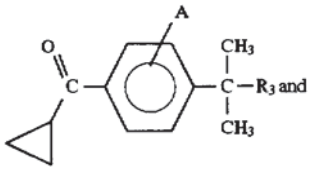
$R_3$ is –COOH or –$COOR_4$;

$R_4$ has 1 to 6 carbon atoms;

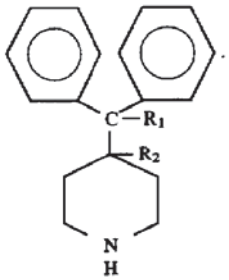
A, B, and D are the substituents of their aromatic rings, each of which may be different or the same, and are selected from the group consisting of hydrogen, halogens, alkyl, hydroxyl, alkoxy, or other substituents,

said process comprising;

providing a *substantially pure* regioisomer of the following formula:




converting the *substantially pure* regioisomer to the piperidine derivative compound with a piperidine compound of the formula:




'703 patent col. 23 l. 45 to col. 24 l. 35 (claim 1) (emphases added). There are two notable features of claim 1 of the '703 patent. First, the piperidine derivative end product synthesized through the claimed process covers a broad range of potential piperidine derivatives as components A, B, and D—substituents of the aromatic rings—that can be selected from groups such as hydrogen, halogens, alkyl, hydroxyl, alkoxy or other groups. '703 patent col. 23 ll. 45 to col. 24 l. 6. Second, and more importantly, the '703 patent refers to a "substantially pure regioisomer" of a specific formula. '703 patent col. 24 l. 8. Notwithstanding, the term "substantially pure" is not defined anywhere in the specification, as noted by the district court.

c. The "Providing" and "Converting" Steps

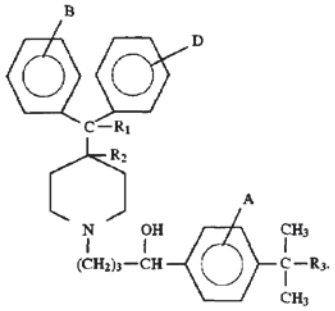
The "providing" and "converting" steps of the method in claim 1 of the '703 patent are illuminated by dependent claims 2, 3, 4, and 5, as well as the patent specification. The dependent claims and the specification examples teach multiple methods for "providing" the para-CPK intermediate, both as a substantially pure para-CPK product or as a mixture of para-CPK and meta-CPK products. *See, e.g.*, '703 patent col. 12 l. 65 to col. 19 l. 35 (specification); col. 24 l. 35 to col. 25 l. 62 (claims 2-5). For example, dependent claims 2 and 3 describe an acylation and purification process that results in the recovery of the para-CPK intermediate from a "second mixture of regioisomers". '703 patent col. 24 l. 35 to col. 25 l. 53 (claims 2-3). Example 2 of the specification, on the other hand, describes another "providing" teaching, producing a "crude product" that is a mixture of para-CPK and meta-CPK that could be further purified to predominantly para-CPK. '703 patent col. 19 l. 65 to col. 20 l. 19. Example 2, however, never requires further regioisomeric purification to a specific level. *See id.* In fact, nowhere in the specification is any numeric value attached to the purity of the CPK intermediate.

"Converting" is the coupling reaction of the para-CPK to azacyclonol to create the end-product piperidine derivative. Again, the specification describes multiple processes for performing the claimed step of "converting" the CPK intermediate to a piperidine derivative compound. *See* '703 patent col. 16 l. 31 to 18 l. 67. As with "providing" the CPK intermediate, the "converting" step does not indicate that the CPK intermediate must be in a substantially pure form, or even provide any required level of purity.

2. Claim 6 of the Patents-in-Suit

While claim 1 describes a process for producing piperidine derivatives through use of a CPK intermediate generally, claims 6 and 7 further specify the piperidine derivative end product synthesized by the patented process. Dependent claim 6 describes:

> 6. A process according to claim 1 further comprising:
>
> reducing the piperidine derivative under conditions effective to form a hydroxylated piperidine derivative of the formula:

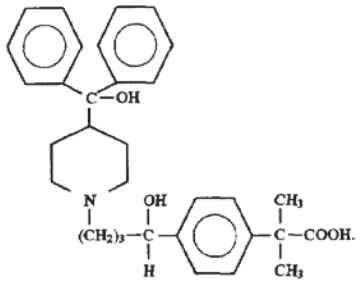



'703 patent col. 25 l. 63 to col. 26 l. 15 (Claim 6).

3. Claim 7 of the Patents-in-Suit

Dependent claim 7 further specifies the type of hydroxylated piperidine derivative end product of claim 6—fexofenadine:

> 7. A process according to claim 6, wherein the hydroxylated piperedine derivative has the formula:



'703 patent col. 26 ll. 16–33 (Claim 7). Thus, Claim 7 of the '703 patent produces an important active pharmaceutical ingredient and was the claim asserted against the generic manufacturers' accused antihistamines.

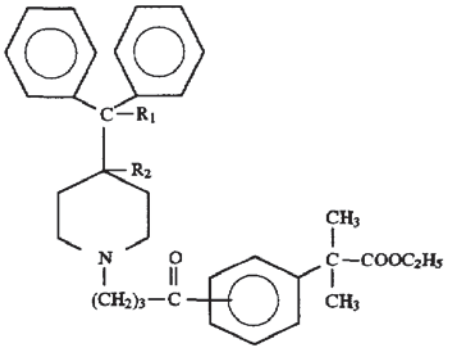
4. Prior Art Processes

The Background section of the '703 patent discusses in detail the prior art processes for making piperidine derivatives. The patented process claimed in the '703 patent represented a significant improvement over these prior art processes, in particular the method taught in U.S. Patent No. 4,254,129 ("the '129 patent"), which issued on March 3, 1981.

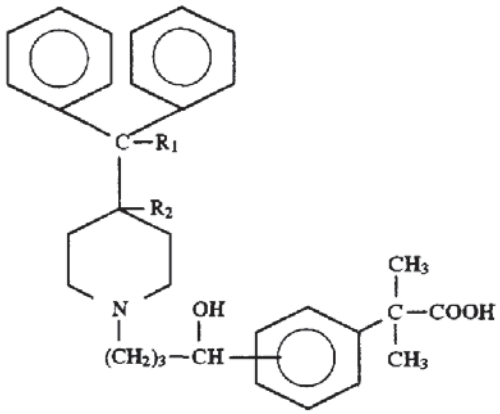
The process disclosed in the '129 patent used a "Friedel-Crafts" reaction to arrive at a piperidine derivative. *See* '703 patent col. 2 ll. 27–41. The Friedel-Crafts reaction produced a statistical admixture, termed the "second mixture of aromatic regioisomers" by the '703 patent, containing 67% meta-isomer of the piperidine derivative end product and 33% para-isomer of the piperidine derivative end product:[7]

---

[7] The illustrated bond extending into the lower aromatic ring indicates a mixture of para- and meta-isomers. *See* '703 patent col. 3 ll. 15–30.



*See, e.g.*, '703 patent col. 2 l. 42 to col. 4 l. 25. The "second mixture of aromatic regioisomers" could then be converted to a "third mixture of regioisomers" of the following formula:



'703 patent, col. 3 l. 65 to col. 4 l. 25.

Dr. D'Ambra discovered in the course of attempting to replicate the teaching of the '129 patent that it was practically impossible to completely separate the para-isomer of the piperidine derivative product to pharmaceutical purity when using the '129 patent's process. In order to improve the regioisomeric purity more easily at an earlier stage in the reaction, D'Ambra developed the patented

process discussed above; in particular, he discovered the novel use of the para-CPK intermediate. By using his unique starting material, a purer regioisomeric form of the CPK intermediate, the regioisomeric purity of the end product could be much higher than the 33% para-CPK produced by the '129 patent's process. Dr. D'Ambra discovered a different process of synthesizing a piperidine derivative product to higher regioisomeric purity; then by using recrystallization and other purification techniques, he could attain pharmaceutical-grade fexofenadine at a much lower expense.

## B. Procedural Background

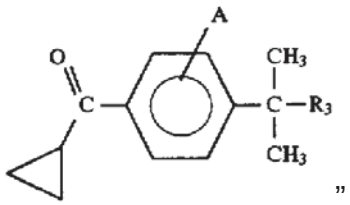
The larger procedural history is complex, involving dozens of parties in twenty cases. It suffices to limit the discussion to Defendant-Appellees, Amino Chemicals Ltd., Dipharma Francis, Sr.L., and Dipharma Spa (collectively "Appellees"). Appellees are generic drug manufacturers. Amino Chemicals had filed a Drug Master File that was referenced in Abbreviated New Drug Applications ("ANDAs") of two former parties, Mylan Pharmaceutical Inc. and Teva Pharmaceuticals USA, Inc., which had sought Food and Drug Administration ("FDA") approval to market antihistamines containing fexofenadine. Similarly, Dipharma Francis and Dipharma Spa are bulk-manufacture suppliers of Mylan and Teva. Upon submission of the ANDAs to the FDA, Appellants timely brought several suits against the generic drug manufacturers in the New Jersey district court, alleging, *inter alia*, infringement of the '703 patent.

The district court performed a tentative claim construction in connection with a September 20, 2005 motion for a preliminary injunction filed after Teva began marketing a generic fexofenadine drug. Judge Greenaway's January 30, 2006 opinion denied the preliminary injunc-

tion request, and set forth an initial claim construction of the '703 patent's disputed claim term "substantially pure." *See Aventis Pharms., Inc. v. Barr Labs., Inc.*, 411 F. Supp. 2d 490, 509 (D.N.J. 2006). The district court found that the '703 patent's specification used the phrase "substantially pure" to describe *both* the piperidine derivative end products and the CPK intermediate. *Id.* at 498-99. The district court also relied on statements from the prosecution history regarding the purity of the piperidine derivative end products to reach a tentative claim construction that the phrase "substantially pure" in the asserted claims of the '703 patent means "of greater than 95% purity." *Id.* at 502–03. The court extended this to describe not only the purity level necessary of end products, but also the CPK intermediate compound. *Id.* In declining to institute a preliminary injunction based on the '703 patent, the district court did not reach the issue of whether "substantially pure" describes overall chemical purity as to everything in the compound or whether the term is limited to regioisomeric purity, i.e., the purity only of the para-isomer relative to unwanted meta-isomer. *Id.* at 508.

The parties thereafter filed opening and responsive claim construction briefs, and on November 10, 2010, a *Markman* hearing was held before Chief Judge Brown. The *Markman* Opinion issued on January 13, 2010, construing two terms from the '703 patent relevant here. Joint App'x 41; *see also Aventis Pharms., Inc. v. Impax Labs., Inc.*, Nos. 02-1322, 03-1179, 03-1180, 03-5108, 03-5829, 04-1075, 04-1076, 04-1077, 04-1078, 04-2305, 04-3194, 05-4255, 06-5463, 07-5054, 07-5180, 09-0325, 09-4638, 09-5179, 10-1471, 2011 WL 2175928, at *1 (D.N.J. Jan. 31, 2011) (publically available *Markman* opinion).

From claim 1 of the '703 patent, the district court construed the terms "substantially pure regioisomer of the following formula




"

and "substantially pure." The district court held that neither the claims nor the specification give sufficient specific guidance as to the meaning of either claim term. The trial court found, however, that the specification "indiscriminately" equates the purity of the intermediates and final products to such an extent that there is no justification to differentiate between "substantially pure" para-CPK intermediates and "substantially pure" piperidine derivative end products. According to the court: "[B]ecause the specification uses the same term consistently for both intermediates and derivatives, the Court finds that what 'substantially pure' means when it modifies the piperidine derivative applies equally to its context in the claims' 'substantially pure regioisomer of the formula.'" Joint App'x 49; *see also Aventis*, 2011 WL 2175928, at *5.

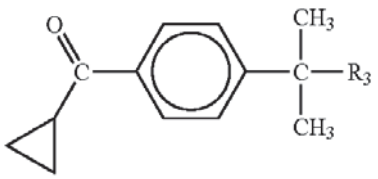
Regarding what "substantially pure" actually means when applied to both the CPK intermediate and piperidine derivative end product, the district court was forced to rely on the prosecution history of the '703 patent, as well as the prosecution history of the related U.S. Patent No. 5,578,610 (filed June 24, 1993) ("the '610 patent"), which is another divisional descended from the parent 08/083,102 application. The district court determined through the prosecution history that "the inventor understood the term 'substantially pure' to mean 98% purity

and that the inventor clearly and unambiguously disavowed any other claim scope." Joint App'x 52; *see* also Aventis, 2011 WL 2175928, at *7.

To arrive at this particularly high level of purity, the district court cited to a statement made by Dr. D'Ambra during the '610 patent interference in 1997. There, Dr. D'Ambra allegedly stated several times that "substantially pure" meant pharmaceutical-grade, or 98%, purity of end products for consumption. From this—despite acknowledging that the statements were likely only describing end-products—the district court concluded that "it is clear that by 'substantially pure' the patentee meant pharmaceutical-grade purity, which requires an impurity level no greater than 2%. These statements both explain the meaning the patentee assigned to 'substantially pure' and represent a clear disclaimer of patent scope for his patent." Joint App'x 54; *see also Aventis*, 2011 WL 2175928, at *8. Thus, by virtue of the specification's nondiscrimination between intermediates and end products, a 98% purity requirement was extended to the para-CPK intermediate as well.

Finally, with regard to "substantially pure," the court held that 98% purity refers to chemical impurities of any kind present in the product, not just regioisomeric impurity. Joint App'x 55 ("The plain language of the term 'substantially pure' is relative to all impurities—a solution of 25% para-CPK, 0.2% meta-CPK, and 74.8% dirt would not be substantially pure."); *see also Aventis*, 2011 WL 2175928, at *8.

In sum, the district court construed the relevant terms at issue from the '703 patent so that (1) "substantially pure" means "at least 98% purity with respect to all impurities" and (2) "providing regioisomer of the following formula




"

means "the regioisomer having the structure shown in the formula is present in at least 98% purity with respect to all impurities." Joint App'x 65; *see also Aventis*, 2011 WL 2175928, at *13. In light of this claim construction, Appellants stipulated that they could no longer prove infringement, and the district court entered final judgment in favor of Appellees in both cases. Appellants timely appealed the disputed claim construction of the '703 patent to this court. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

## II. DISCUSSION

Claim construction is an issue of law since *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 981 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). This court reviews district court claim constructions *de novo*. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc).

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). There is a heavy presumption that claim terms are to be given their ordinary and customary meaning. *Id.* at 1312–13; *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Courts are required therefore to "look to the words of the claims themselves . . . to define the scope of the patented

invention." *Id.*; *see also Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299 (Fed. Cir. 1999).

Claims, however, must be construed in light of the appropriate context in which the claim term is used. *See Toro*, 199 F.3d at 1299. The written description and other parts of the specification, for example, may shed contextual light on the plain and ordinary meaning; however, they cannot be used to narrow a claim term to deviate from the plain and ordinary meaning unless the inventor acted as his own lexicographer or intentionally disclaimed or disavowed claim scope. *Id.* at 1316; *cf. Markman*, 52 F.3d at 980 ("[T]he written description part of the specification itself does not delimit the right to exclude. That is the function and purpose of claims."). The prosecution history too, as part of the intrinsic record, has an important role in claim construction by supplying context to the claim language. While the prosecution history "lacks the clarity of the specification and thus is less useful for claim construction purposes", *Phillips*, 415 F.3d at 1317, it still provides evidence of how the inventor intended the term to be construed. *See Lemelson v. Gen. Mills, Inc.*, 968 F.2d 1202, 1206 (Fed. Cir. 1992).

### A. "Substantially Pure"

Claims 1, 6, and 7 of the '703 patent explicitly include the term "substantially pure regioisomer." The district court construed this language to require "at least 98% purity with respect to all impurities." This construction, however, conflates the purity required for the piperidine end product with that of the CPK intermediate.

1. CPK Intermediate Versus Piperidine End Product

We agree with both parties that the claims themselves are insufficient to define the term "substantially pure." Therefore, we must turn to other sources of intrinsic evidence to determine "what the inventors actually invented and intended to envelop with the claim." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). The specification provides the "best source" for construing a claim term and determining the inventor's intent regarding use. *Multiform Dessicants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998); *see also Vitronics*, 90 F.3d at 1582.

In this case, the specification does not provide an explicit definition of the term "substantially pure" or "substantially pure regioisomer." The district court determined that because the term "substantially pure" is used indiscriminately with regards to the CPK intermediate and the piperidine derivative end product throughout the specification, "substantially pure" should have only one construction throughout the patent. The "one construction throughout the patent" rule adopted by the district court is incorrect.

We have previously held that the same claim term can have different constructions depending upon the context of how the term is used within the claims and specification. *See Microprocessor Enhancement Corp. v. Tex. Instruments, Inc.*, 520 F.3d 1367, 1375 (Fed. Cir. 2008) (holding that, while there is a presumption that a claim term will be construed consistently when used throughout the claims, there is no requirement that a claim term be construed uniformly, particularly if it would lead to a "nonsensical reading"). In *Epcon Gas Systems, Inc. v. Bauer Compressors, Inc.*, 279 F.3d 1022

(Fed. Cir. 2002), for example, we construed the term "substantially" to have different interpretations based on a "subtle but significant difference" in context and usage. *Id*. at 1030–31.

While "substantially pure" refers to both the CPK intermediate and the piperidine derivative end product in the specification, the term "substantially pure" is used only in reference to the CPK intermediate in relevant claims 1, 6, and 7. And unlike other patents in the family, there is no explicit "substantially pure" limitation placed on the piperidine derivative end product in the relevant claims of the '703 patent. The lack of any "substantially pure" limitation on the piperidine derivative end products in claims 1, 6, and 7 obviates any explicit requirement to apply a construction of "substantially pure" that is consistent for both the CPK intermediate and the piperidine derivative end product.

Further, a person of ordinary skill in the art would recognize that an intermediate of the claimed chemical reaction would not be required to have the same purity as the end product. As mentioned in the specification, both in reference to the prior art '129 patent and also throughout the examples, various crystallization and purification processes are available to purify the piperidine derivative end product to reach pharmaceutical-grade purity after synthesis. The '703 patent represents an improvement over the prior art processes. The improvement was not that the patented technique could guarantee a piperidine derivative of pharmaceutical purity absent further purification; the improvement was that the patented technique could provide a piperidine derivative end product of higher regioisomeric purity requiring less extensive purification than the end product derived by the process

of the '129 patent.[8] Reading "substantially pure" to require a consistent construction for the CPK intermediate and piperidine derivative end product ignores the distinct contexts in which these terms are used.

Appellees argue that reading a common term to have different meanings in different contexts does not apply here to the interpretation of "substantially pure." They distinguish *Epcon* and *Microprocessor* because the patents in those cases contained intrinsic records which clearly and expressly supported multiple interpretations for a single claim term. Appellees maintain that no such clear and express support is found in the '703 patent specification at issue. But this ignores that we must always construe the specification in light of the knowledge of one of ordinary skill in the art. *Phillips*, 415 F.3d 1313. Through basic knowledge of chemical reactions and purification schemes, a skilled artisan would recognize that the purity of an intermediate compound in a reaction is often not equivalent to the purity of the end product, especially when further, common physical purification steps may be necessary. Interpreting this specification in light of the knowledge of a person of ordinary skill in the art, we hold that a proper construction requires different interpretations of "substantially pure" when applied to the CPK intermediate and piperidine derivative end product.

The "one-size-fits-all" construction adopted by the district court incorrectly construes "substantially pure" separate from the very next word--"regioisomer." The

---

[8] The process described in the '129 patent did not appear to be able to reach a purity of greater than 95% without resorting to exceptionally difficult and cost-ineffective techniques. *See supra* Part I.A.4.

district court's artificial truncation of the claim term for the expediency of a single interpretation across different contexts was error. Outside of the description of the prior art process from the '129 patent, the specification almost exclusively uses the term "regioisomer" to refer to the CPK intermediate. Further, the full term, "substantially pure regioisomer," is used *only* in reference to the CPK intermediate. *See* '703 patent col. 5 ll. 11–12, 23, 40–41; col. 12 ll. 32–33, 43, 62–66; col. 13 ll. 55–56; col. 13 l. 67 to col. 14 ll. 37–38, 51, 53; col. 15 ll. 13–14, 51–52, 54; col. 16 ll. 21–22, 25–26, 31–32, 34–35, 49; col. 18 ll. 4–5, 7–8. Such uniform use of "substantially pure regioisomer," taken as a whole, exposes the error of the district court: by decoupling the modifier "substantially pure" from "regioisomer" for purposes of claim construction, the district court imposed a single interpretation even though that context requires separate definitions of "substantially pure" when applied to the CPK intermediate as opposed to the piperidine derivative end product. We thus conclude that the district court erred in requiring that "substantially pure" have the same interpretation when applied to the CPK intermediate and the piperidine derivative end product.

2. Construction of "Substantially Pure Regioisomer"

Although it was error for the district court to limit the construed term to encompass both the CPK intermediate and the piperidine derivative end product, the proper term to construe, "substantially pure regioisomer," still requires claim construction. The presumption is that claim terms should be given their "ordinary and customary meaning," *Vitronics*, 90 F.3d at 1582, and not a restrictive construction unless there is clear evidence to support it in the intrinsic evidence, or a broader meaning is specifically disclaimed during prosecution. *See Saunders Grp., Inc. v. Comfortrac, Inc.*, 492 F.3d 1326, 1331

(Fed. Cir. 2007). A court can look to the prosecution history of related patents for guidance in claim construction. *See Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1314 (Fed. Cir. 2007).

The district court interpreted "substantially pure" in isolation to mean "at least 98% purity with respect to all impurities" based in large part on the prosecution history of the related '610 patent. The district court looked to statements made during the '610 patent's interference proceedings before the U.S. Patent and Trademark Office (PTO), where the patentee stated that a person of ordinary skill in the art would understand "substantially pure" in claims 1-17 to refer to pharmaceutical-grade purity. Claims 1-17 include claims, such as claim 12, where "substantially pure" modifies only the CPK intermediate. On that basis, the district court concluded here that "substantially pure" as applied to the CPK intermediate required "at least 98% purity with respect to all impurities."

In analyzing the claims of the '703 patent, we find statements made in the '610 patent's interference proceedings of little help. The patentee and the PTO both explicitly noted that the focus of the '610 patent's interference was limited to interpreting the claims in reference to the piperidine end product. Even the statements made by Dr. D'Ambra[9] were made specifically in regards to the "subject compound" of the interference, which was only the end product. At most, the construction of "substan-

---

[9] The statements made by Dr. D'Ambra during the '610 patent's interference proceedings were the focal point of the district court's and defendant's application of "at least 98% purity with respect to all impurities" to the CPK intermediate.

tially pure" derived from the '610 patent's interference applies to the piperidine derivative end product, not the CPK intermediate at issue in this case. Since we have found that "substantially pure" has different constructions when applied to the CPK intermediate and the piperidine end product in the '703 patent, there is no justification for applying the definition of "substantially pure" from the '610 patent's interference to "substantially pure regioisomer" in the '703 patent.

In determining the scope of the claim term "pure," the district court further assumed that "substantially pure" must apply to all impurities present in solution, not just regioisomeric purity. The district court reasoned that the plain language of "substantially pure" must involve all impurities, because "a solution of 25% para-CPK, 0.2% meta-CPK, and 74.8% dirt would not be substantially pure." Joint App'x 55; *see also Aventis*, 2011 WL 2175928, at *8. This flawed analysis again does not consider the appropriate frame of reference for claim construction. A person of ordinary skill in the art would recognize that the '703 patent improved the regioisomeric purity of the end product that results from the claimed reaction as compared to the Friedel-Crafts acylation disclosed in the '129 patent. For example, in the district court's hypothetical mixture "of 25% para-CPK, 0.2% meta-CPK, and 74.8% dirt," the patented reaction could very well produce 25% para-piperidine derivative end product, 0.2% meta-piperidine derivative end product, and 74.8% "dirt." The "dirt" could then be removed through simple purification processes, such as crystallization, leaving 99.2% para-piperidine derivative end product and 0.8% meta-piperidine derivative end product. Such an end product mixture would arrive at the standard for pharmaceutical-grade purity even though the "dirt" represented a substantial impurity in the early stages of the reaction. Again, the weakness in the '129 patent was its inability to

produce an end product with a 125:1 ratio[10] of para- to meta-piperidine derivative, or even anything approaching such a ratio. It was this inherent deficiency of the '129 patent's process in regioisomeric purity that the '703 patent improved upon. Further, the processes disclosed in the '129 and'703 patents consider the need for further purification steps after the claimed reactions. While these purification steps will help improve the ratio of para- to meta-piperidine product, they will also remove other reaction impurities. Therefore, the general purity of other reaction components in the CPK-mixture is largely irrelevant at the intermediate stage. The district court actually recognized this point to a lesser extent, noting that "with respect to all impurities" does not include "intended elements of solutions, such as solvents, catalysts and other compounds." We hold that the modifier "substantially pure," when construed in light of a person of ordinary skill in the art and in view of the claimed improvements over the prior art, only applies regioisomeric impurities, not all impurities.

3. Appellants' Construction

With no explicit construction of the term "substantially pure" in the claims, specification, or prosecution history, we apply the "ordinary and customary" definition to the claim term. In other contexts, this court has interpreted "substantially" as a non-specific term of approximation that avoids a numerical boundary. *See, e.g.*, *Playtex Prods., Inc. v. Procter & Gamble Co.*, 400 F.3d 901, 907 (Fed. Cir. 2005); *Liquid Dynamics Corp. v. Vaughan Co.*, 355 F.3d 1361, 1368 (Fed. Cir. 2004) ("The term 'substantial' is a meaningful modifier implying

[10] 25% para-piperidine derivative end product to 0.2% meta-piperidine derivative end product.

'approximate,' rather than 'perfect.'"); *Cordis Corp. v. Medtronic Ave, Inc.*, 339 F.3d 1352, 1360 (Fed. Cir. 2003); *Ecolab, Inc. v. Envirochem, Inc.*, 264 F.3d 1358, 1366–67 (Fed. Cir. 2001).

In the context of "substantially pure" as applied to a CPK intermediate, "substantially" would also not be amenable to a numerical boundary. The '703 patent implies that the regioisomeric purity should be greater than 67%, '703 patent col. 4 ll. 15–25, but the patent specification tellingly does not list any necessary minimum purity for the CPK intermediate in order to produce a desired piperidine derivative end product with pharmaceutical-grade purity. As described in the patent, a piperidine derivative end product with a regioisomeric purity below 98% can be purified through crystallization or other physical techniques to reach pharmaceutical-grade purity, showing that the CPK intermediate does not itself need to be at a regioisomeric purity of 98% or higher. '703 patent col. 13 l. 55 to col. 14 l. 14.

Appellants propose that "substantially pure regioisomer of the following formula" should be construed as "largely but not wholly the para regioisomer of the intermediate of the structure shown, as compared to the meta isomer." Appellants' Br. 10. This construction of "substantially" was previously applied with approval in *Ecolab*, 264 F.3d at 1366 (noting that Webster's Ninth New Collegiate Dictionary, 1176 (9th ed. 1983), defines "substantially" to mean "largely but not wholly that which is specified"). "Largely but not wholly" is consistent with a flexible approach to regioisomeric purity for an intermediate, is faithful to the specification's silence regarding numerical precision and, most importantly, is not arbitrarily tied to the FDA standard for pharmaceutical-grade end products. No one ingests the intermediate compound, so there is no reason to impose end-product purity on it.

Therefore, we adopt the Appellants' proposed construction of "substantially pure regioisomer of the following formula" as used in the '703 patent and construe the term to mean "largely but not wholly the para regioisomer of the intermediate of the structure shown, as compared to the meta isomer."

## III. CONCLUSION

Because the district court erred in construing "substantially pure" as used in the '703 patent, we *reverse* and *remand*.

**REVERSED AND REMANDED**

## COSTS

No costs.

# United States Court of Appeals for the Federal Circuit

**AVENTIS PHARMACEUTICALS INC.,**
*Plaintiff-Appellant,*

**AND**

**AMR TECHNOLOGY, INC.,**
(now known as Albany Molecular Research, Inc.),
*Plaintiff-Appellant,*

**v.**

**AMINO CHEMICALS LTD., DIPHARMA FRANCIS, SR.L., AND DIPHARMA SPA,**
*Defendants-Appellees,*

**AND**

**MYLAN PHARMACEUTICALS INC.,**
*Defendant.*

- - - - - - - - - - - - - - - - - - -

**AVENTIS PHARMACEUTICALS INC.,**
*Plaintiff-Appellant,*

**AND**

**AMR TECHNOLOGY, INC.,**
(now known as Albany Molecular Research, Inc.),
*Plaintiff-Appellant,*

**v.**

**TEVA PHARMACEUTICALS USA, INC.,**
*Defendants,*

**AND**

**AMINO CHEMICALS LTD., DIPHARMA FRANCIS, SR.L., AND DIPHARMA SPA,**
*Defendants-Appellees.*

---

2011-1335,-1336

---

Appeals from the United States District Court for the District of New Jersey in Nos. 04-CV-1075, 04-CV-1077, and 04-CV-1078, Chief Judge Garrett E. Brown Jr.

---

BRYSON, *Circuit Judge*, dissenting.

The majority concludes that the district court erred in its construction of the term "substantially pure" in claim 1 of U.S. Patent No. 5,750,703 ("the '703 patent") and therefore reverses the district court's judgment. I would uphold the district court's construction of that term, and I therefore respectfully dissent.

I

The district court construed the term "substantially pure" to mean "at least 98% purity with respect to all impurities." In arriving at that construction, the court first determined that "substantially pure" has the same meaning whether it refers to the piperidine derivative end product or the para-CPK intermediate. The court noted

that the "inventor uses the phrases 'substantially pure' and 'substantially pure regioisomers' indiscriminately to refer to both final products and intermediates. There is no evidence that the inventor intended the term to mean different things." Based on the prosecution histories of the '703 patent and related U.S. Patent No. 5,578,610 ("the '610 patent"),[1] the court then held that the term "substantially pure" refers to pharmaceutical grade purity, i.e., 98% pure. Finally, the court determined that the required purity level was to be measured with respect to all impurities, not just the unwanted meta-CPK, except that the 98% purity level did not include "intended elements of solutions such as solvents, catalysts, or other compounds that are not considered impurities."

Aventis's primary argument on appeal is that the term "substantially pure" should be given a different meaning when it refers to the para-CPK intermediate, which the claim describes as a "substantially pure regioisomer" of CPK, than when it refers to the piperidine derivative end product. Aventis essentially concedes that if the term at issue were "substantially pure end product," 98% purity with respect to all impurities would be an accurate construction. But since the term "substantially pure" is used in claim 1 to refer to the "substantially pure regioisomer"—i.e., the para-CPK intermediate—Aventis argues that a different construction is required. Aventis contends that the evidence relied upon by the district court pertained only to the purity of the end product, and that the term "substantially pure" has a different meaning when used to refer to intermediates than when used

---

[1] The application that issued as the '610 patent was filed as a division of the application that issued as the '703 patent, and the two specifications are essentially the same.

to refer to end products. As used in reference to the regioisomer, Aventis argues that the term "substantially pure" means "largely but not wholly [para-CPK], as compared to [meta-CPK]."

The majority embraces Aventis's proposed construction, holding that the patent gives the term "substantially pure" different meanings when referring to the terms "substantially pure regioisomer" and "substantially pure piperidine derivative." As the district court ruled, however, the intrinsic evidence does not distinguish between the way "substantially pure" is used with respect to those two terms, and for that reason I would uphold the district court's claim construction.

In seeking to distinguish between the meaning of the term "substantially pure" when it is applied to the intermediate regioisomer as opposed to when it is applied to the piperidine derivative end product, Aventis relies on the argument that one of ordinary skill in the art would know that the purity of intermediates may be different from the purity of end products, and it offers expert testimony in support of that proposition. But even if a person of ordinary skill in the art would not necessarily regard purity as meaning the same thing for an intermediate as for an end product, the analysis does not end there.

In at least two places, the intrinsic record uses the term "substantially pure" in the same way with regard to the regioisomer and the end product. First, the specification states:

> Although the second mixture of regioisomers [an intermediate] and the third mixture of regioisomers [the final piperidine derivative product] can be analyzed by HPLC experiments, a practical

> separation to obtain gram quantities of substantially pure regioisomers has not been achieved.
>
> Each mixture (including the first [also an intermediate]), would be expected to contain 33% of the para isomer and 67% of the meta isomer. Since these components are inseparable, it has not been possible to obtain either of the regioisomers in each [first, second, and third] mixture in *substantially pure* form.

'703 patent at col. 4 ll. 16-24 (emphasis added). Second, in an interference involving the related '610 patent, the patentee wrote:

> When read in light of the specification, one skilled in the art would have understood that the phrase "substantially pure", as used in claims 1-17 of the D'Ambra Patent [the '610 patent], to mean that the subject compound has pharmaceutical grade purity and is in a form purer than that attained by the prior art (e.g., U.S. Patent Nos. 4,254,129, 4,254,130, 4,285,957, and 4,285,958 to Carr (collectively, "the Carr Patents"). As demonstrated, infra, those skilled in the art recognized that pharmaceutical grade purity requires an impurity level no greater than 2%, and the Carr Patents were unable to achieve such purity.

Importantly, that response refers to claims 1-17 of the '610 patent; one of those claims, claim 12, recites, "a piperidine derivative compound produced by a process comprising: providing *a substantially pure regioisomer* . . . ." (emphasis added).

Aventis concedes that in the first passage the patentee failed to distinguish between the use of "substantially

pure" as applied to an intermediate and to an end product, but it claims that the passage is irrelevant because it concerns the prior art Carr process. In fact, however, both the discussion of the prior art and the discussion of the claimed invention use the term "substantially pure" when referring to regioisomers; one of the "mixture[s]" referenced in the second paragraph is CPK, while another is the piperidine end product. Thus, the patentee fails to distinguish between "substantially pure regioisomer" and "substantially pure [end product]," and in fact affirmatively suggests that the meaning of "substantially pure" does not turn on whether it modifies "regioisomer" or "piperidine derivative [end product]."

Regarding the second reference, Aventis argues that it is clear in context that the passage concerns the purity of the end product. Aventis also argues that the "subject compound" described in that passage is the end product, making clear that the discussion of "substantially pure" in that passage applies only to the end product. The problem with Aventis's position is that the quoted language expressly refers to "'substantially pure' . . . as used in claims 1-17," and claim 12 of the '610 patent refers to a "substantially pure regioisomer." Thus, "'substantially pure' . . . as used in claims 1-17" unequivocally includes "substantially pure regioisomer." That reference thus rebuts Aventis's claim that the patentee was careful to distinguish between "substantially pure regioisomer" and "substantially pure piperidine derivative [end product]." The patentee could have written "'substantially pure *piperidine derivative*' . . . as used in claims 1-17," but it chose not to, referring only to "'substantially pure' . . . as used in claims 1-17." Those two examples show that the patentee did not intend for the term "substantially pure" to have a different meaning depending on whether it was describing an intermediate or an end product.

Beyond those two passages, the intrinsic record provides little else of help in construing the term "substantially pure." However, general principles of claim construction are instructive here. "[W]e presume, unless otherwise compelled, that the same claim term in the same patent or related patents carries the same construed meaning." *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1334 (Fed. Cir. 2003); *see also Paragon Solutions, LLC v. Timex Corp.*, 566 F.3d 1075, 1087 (Fed. Cir. 2009) ("We apply a presumption that the same terms appearing in different portions of the claims should be given the same meaning unless it is clear from the specification and prosecution history that the terms have different meanings at different portions of the claims."). Starting with the presumption that "substantially pure" means the same thing when describing "regioisomer" as it does when describing "piperidine derivative," it is clear that Aventis has not put forth "compell[ing]" evidence to the contrary.[2] Indeed, as noted above, the intrinsic record supports the district court's finding that "substantially pure" has the same meaning throughout the patent, and Aventis has pointed to nothing compelling in the record to suggest

---

[2] The majority cites two of our cases for the proposition that the same term in a patent can have different meanings—*Microprocessor Enhancement Corp. v. Tex. Instruments Inc.*, 520 F.3d 1367, 1376 (Fed. Cir. 2008), and *Epcon Gas Sys., Inc. v. Bauer Compressors, Inc.*, 279 F.3d 1022, 1030-31 (Fed. Cir. 2002). In both of those cases, however, there was a clear basis in the intrinsic record for applying different meanings to the same term. By contrast, there is no compelling evidence that "substantially pure" was intended to mean different things with respect to "regioisomer" and "piperidine derivative."

otherwise.[3] Aventis's reliance on expert testimony that one of ordinary skill in the art would know that "substantially pure" can mean different things when describing intermediates than when describing end products is not enough to overcome the persuasive intrinsic record in this case. *See Kara Tech. Inc. v. Stamps.com Inc.*, 582 F.3d 1341, 1348 (Fed. Cir. 2009) ("While helpful, extrinsic sources like expert testimony cannot overcome more persuasive intrinsic evidence.").

Aventis's expert testimony does not indicate that "substantially pure regioisomer" is a term of art that connotes a specific level of purity relative to that of the end product. Thus, although "substantially pure" certainly could have different meanings in different contexts, there is no evidence indicating that it must mean something different when used to describe a regioisomer as opposed to an end product. The majority bases its construction of the term "substantially pure regioisomer" on the general definition of the term "substantially," which is taken from an unrelated case that in turn cites a general dictionary definition. That appeal to extrinsic evidence from outside the art underscores the fact that Aventis has offered nothing in the intrinsic record, or even in the state of the art, to define the term that is the focus of the

---

[3] The majority also suggests the presumption of consistent claim construction does not apply in this case because "there is no explicit 'substantially pure' limitation placed on the piperidine derivative end product in the relevant claims of the '703 patent." However, the term "substantially pure" limits the claimed end product in the related '610 patent, so the presumption applies here. *See Omega Eng'g, Inc.*, 334 F.3d at 1334 (applying presumption of consistency to "the same claim term in . . . related patents").

parties' dispute. Instead of resorting to extrinsic evidence as to the general meaning of the term "substantially" standing on its own, we should interpret the claim term that Aventis did define: "substantially pure."

There is no basis for ignoring the intrinsic record and the presumption that "substantially pure" is a discrete claim term with a consistent meaning throughout the patent. Aventis apparently believes that for "substantially pure" to be construed to have the same meaning each time it is used in the patent, the patentee would have to explicitly "link" the purity of the para-CPK intermediate to that of the end product. But Aventis has it backwards: If the patentee wanted "substantially pure" to have different meanings when applied to different elements, it needed to explicitly "unlink" them.

## II

Aventis's other arguments are easily disposed of. It is clear (and essentially undisputed) that "substantially pure" means "at least 98% pure" when describing end product. In the prosecution history of the '703 patent, the applicant equated substantially pure piperidine derivative with "a purity level suitable for pharmaceutical use." The district court found that "[i]t is essentially undisputed that pharmaceutically acceptable purity is 98%." The patentee's statements made in the course of an interference proceeding involving the '610 patent also support the district court's conclusion that the term "substantially pure," as used in the '906 patent and its relatives, means "at least 98% pure." In that interference proceeding, the patentee equated the term "substantially pure" with "pharmaceutical grade purity" and expressly agreed that "pharmaceutical grade purity requires an impurity level no greater than 2%." The prosecution histories also support the district court's conclusion that the required

purity level referred to purity with respect to all impurities, not just with respect to a single other component, such as meta-CPK.

Aventis argues that this evidence is irrelevant because it pertains to the purity level of the end product. But because the patent does not distinguish between the meaning of "substantially pure" as applied to an end product and as applied to an intermediate, it follows that if a "substantially pure [end product]" means a product that is at least 98% pure with respect to all impurities, then the same meaning attaches to "substantially pure [para-CPK]."

The cases that Aventis cites in support of its position are unhelpful to it. Aventis cites several cases for the proposition that the term "substantially" need not have a strict numerical boundary. *E.g.*, *Playtex Prods., Inc. v. Procter & Gamble Co.*, 400 F.3d 901, 907 (Fed. Cir. 2005); *Anchor Wall Sys. v. Rockwood Retaining Walls, Inc.*, 340 F.3d 1298, 1310-11 (Fed. Cir. 2003); *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1360 (Fed. Cir. 2003); *Ecolab, Inc. v. Envirochem, Inc.*, 264 F.3d 1358, 1366 (Fed. Cir. 2001). Those cases have no application here, however, because in this case the intrinsic evidence establishes that the term "substantially pure" was given a strict numerical meaning, as the district court found.

In sum, I conclude that "substantially pure" means "at least 98% purity with respect to all impurities" and that it has that meaning with respect to both regioisomers and the end product. I would therefore affirm the district court's judgment.