UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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| AMGEN INC.,<br><br>Plaintiff,<br><br>v.<br><br>F. HOFFMANN-LAROCHE LTD., a Swiss Company, ROCHE DIAGNOSTICS GmbH, a German Company and HOFFMANN LAROCHE INC., a New Jersey Corporation,<br><br>Defendants. | Civil Action No.: 05-12237 WGY |

**AMGEN INC.'S RESPONSE TO**
**DEFENDANTS' CLAIM CONSTRUCTION BRIEF**

610006_1

# TABLE OF CONTENTS

**Page**

# TABLE OF AUTHORITIES

**Page**

**Cases**

**TABLE OF AUTHORITIES (continued)**

**Page**

## TABLE OF AUTHORITIES (continued)

**Page**

## I. INTRODUCTION

The parties appear to be in substantial agreement as to the meaning of the forty-four claim terms that were previously asserted by Defendants to require construction.[1] As presented in Defendants' Opening Memorandum in Support of their Proposed Claim Construction (Docket No. 311) (hereinafter "Defendants' Brief"), the only points still in dispute are:

(1) whether "***human erythropoietin***" and "***glycosylated erythropoietin polypeptide***" should be construed to graft on narrow structural limitations that are inconsistent with the meaning of the claim terms themselves and are expressly addressed more broadly elsewhere in the claims or in the specification;

(2) whether "***adjuvant, diluent, or carrier***" ('422 and '933 claims) should be construed to require an entity that is separate from the claimed human erythropoietin or glycosylated erythropoietin polypeptide;

(3) whether "***CHO cell***" should be construed to include limitations that are not recited in the claim or stated in the specification;

(4) whether "***therapeutically effective amount***" ('422 and '080 claims) and "***effective amount [of product] effective for erythropoietin therapy***" ('933 claims) should be construed to have identical meanings;

(5) whether "***host cell transformed and transfected with an isolated DNA sequence encoding human erythropoietin***" ('868 claims) should be construed to require within the claimed process the separate step of introducing only EPO DNA into a cell; and

(6) whether "***isolating said glycosylated erythropoietin polypeptide expressed by said***

[1] Amgen provided to Defendants its construction for each of the asserted claims on January 9, 2007. *See generally* Docket No. 252, Exh. C (at Exhibit A therein). With this construction in hand, Defendants, through discovery, had asserted that over 44 terms set forth in the patents-in-suit would need to be construed by the Court. Amgen's Claim Construction Brief (Docket No. 312) (hereinafter "Amgen's Brief"), Exhibit 13 at 15-18. Having chosen to raise only 11 terms for construction in their Brief, it appears that Defendants agree with Amgen's other proposed constructions, as first set forth in its

***cells/therefrom***" should be construed to imply an activity limitation.

The crux of the dispute is clear. Defendants seek to lay a foundation to avoid infringement by narrowly construing Dr. Lin's product claims. They do so by arguing that Dr. Lin's claims should be construed to exclude the attachment of structures other than glycosylation to the erythropoietin products recited in the claims. Alternatively, they argue that Dr. Lin's product claims should be construed so as to limit the glycosylation of his claimed products to the precise structures produced by the cells exemplified in the preferred embodiment of his specification. Unless there is an express disclaimer in the intrinsic record that would preclude the addition of such structures or subsequent variations in them, Dr. Lin's claims should not be construed to preclude them.[2]

The same is true for Dr. Lin's process claims. Defendants seek to construe Dr. Lin's process claims as excluding the performance of steps beyond those expressly recited in his claims. But absent an express disclaimer of such additional steps, Dr. Lin's process claims cannot be construed to exclude the performance of steps beyond those recited in his claims.[3]

## II. DEFENDANTS SEEK TO IMPROPERLY NARROW THE CLAIMS TO AVOID INFRINGEMENT

Claim construction is a question of law for the Court.[4] The Federal Circuit's framework for claim construction favors intrinsic evidence, whereby the claims, specification and prosecution history are considered in preference to extrinsic evidence, such as expert testimony.[5] Under this framework, the first step is to look to the totality of the claim language, including

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interrogatory responses and again at Appendix A to Amgen's Brief.

[2] *Northern Telecom v. Samsung*, 215 F.3d 1281, 1296-97 (Fed. Cir. 2000). *See also A.B. Dick Co. v. Burroughs Corp.*, 713 F.2d 700, 703 (Fed Cir. 1983).

[3] *Amstar Corp. v. Envirotech Corp.*, 730 F.2d 1476, 1481-82 (Fed. Cir. 1984) (stating that the presence of the extra step in the accused process was "simply and totally irrelevant" to the infringement analysis). *See also ACCO Brands, Inc. v. Micro Sec. Devices, Inc.*, 346 F.3d 1075, 1081-82 (Fed. Cir. 2003).

[4] *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (*en banc*); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

both the disputed and undisputed claim terms, and then to construe the meaning of the claim language in light of the other claims, the specification, and the prosecution history of the patent, all in accordance with the understanding of one skilled in the art at the time of the invention.[6]

Defendants' proposed constructions seek to narrow the scope of Dr. Lin's claimed inventions by importing limitations that are not required by, and often conflict with, Dr. Lin's claim language and specification. In many instances, the limiting constructions that Defendants seek to impose are designed to exclude the presence of additional structures or the performance of additional process steps beyond those expressly recited in the claims. In other instances, the Defendants' limiting constructions seek to read into the claims specific structural requirements beyond those recited in the claims. But the law of claim construction is clear — an express disclaimer in the intrinsic record is required before claim terms can be construed in such a restrictive manner:

> [I]f a patent requires A, and the accused device or process uses A *and* B, infringement will be avoided only if the patent's definition of A excludes the possibility of B. . . . Statements simply noting a distinction between A and B are thus unhelpful: what matters is not that the patent describes A and B as different, but whether, according to the patent, A and B must be mutually exclusive. [7]

Because patent claims are examined and allowed by reference to the limitations that are expressly recited in the claims, it is improper to read into a claim term limitations that are not expressly recited in the claims themselves. That is why a disclaimer is rarely, if ever, based on claim language alone. Rather, disclaimers are most commonly based on an express statement in the specification whereby the inventor defines a claim term by reference to certain elements or properties that are excluded from the invention, or by the absence of variation in those elements

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[5] *Phillips v. AWH Corp.*, 415 F.3d 1303, 1318 (Fed. Cir. 2005) (*en banc*); *Vitronics*, 90 F.3d at 1583.

[6] *Id*. at 1582; *Masco Corp. v. United States*, 303 F.3d 1316, 1329 (Fed. Cir. 2002); *see also Phillips*, 415 F.3d at 1312 ("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.'") (citations omitted); *id.* at 1314.

[7] *Northern Telecom*, 215 F.3d at 1296-97.

that are recited in the claim.[8]

Likewise, prosecution history disclaimer must also be express.[9] As recently articulated by the Federal Circuit:

> Where the patentee has unequivocally disavowed a certain meaning to obtain his patent, the doctrine of prosecution disclaimer attaches and narrows the ordinary meaning of the claim congruent with the scope of surrender. . . . Such use of the prosecution history ensures that the claims are not construed one way in order to obtain allowance and a different way against potential infringers.[10]

Statements that suggest a disclaimer, but do not clearly and unambiguously disclaim subject matter, do not give rise to prosecution history disclaimer. For example, simply extolling the virtue of a particular product without unambiguously disclaiming other embodiments will not give rise to disclaimer.[11] Similarly, claim amendments and cancellations that are unnecessary[12] or broader than necessary to distinguish over the prior art do not constitute a disclaimer of subject matter.[13] Silence in response to statements by the examiner is also insufficient to serve as a clear disavowal of claim scope.[14] Finally, statements by an applicant during prosecution that

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[8] *Id*. at 1294-96; *Invitrogen v. Biocrest Mfg'g*, 327 F.3d 1364, 1369 (Fed. Cir. 2003); *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1177-78 (Fed. Cir. 1991).

[9] *Omega Eng'g Co. v. Raytek Corp.*, 334 F.3d 1314, 1326 n.1 (Fed. Cir. 2003), *citing Schriber-Schroth Co. v. Cleveland Trust Co.*, 311 U.S. 211, 220-21 (1940); *Graham v. John Deere Co.*, 383 U.S. 1, 33 (1966); *see also Chimie v. PPG Indus. Inc.*, 402 F.3d 1371, 1374 (Fed. Cir. 2005); *Spectrum Int'l. v. Sterilite Corp*., 164 F.3d 1372 (Fed. Cir. 1998); *Southwall Tech. Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995).

[10] *Chimie*, 402 F.3d at 1384, *citing Omega*, 334 F.3d at 1324. Conceptually, prosecution history estoppel and prosecution history disclaimer are similar. *Id*. at 1326 n.1 ("just as prosecution history estoppel may act to estop an equivalence argument under the doctrine of equivalents, positions taken before the PTO may bar an inconsistent position on claim construction"). But it is prosecution history disclaimer, not prosecution history estoppel, that applies in the context of literal infringement. *Invitrogen Corp. v. Biocrest Mfg'g*, 327 F.3d 1364, 1367 (Fed. Cir. 2003).

[11] *Vanguard Prods. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372 (Fed. Cir. 2000).

[12] *Pickholtz v. Rainbow Tech*., Inc., 284 F.3d 1365, 1373 (Fed. Cir. 2002).

[13] *3M Innovative Prods. v. Avery Dennison*, 350 F.3d 1365, 1373-74 (Fed. Cir. 2003).

[14] *Id.* at 1373-74; *see also Middleton, Inc. v. Minnesota Mining and Manufacturing Co.*, 311 F.3d. 1384, 1388 (Fed. Cir. 2003); *Schwing GmbH v. Putzmeister Aktiengesellschaft*, 305 F.3d 1318, 1324-25 (Fed. Cir. 2002).

are later found to be in error do not necessarily narrow the scope of the claims.[15]

## III. DEFENDANTS' PROPOSED CONSTRUCTIONS ARE CONTRARY TO THE INTRINSIC RECORD

### A. DEFENDANTS' CONSTRUCTION OF "HUMAN ERYTHROPOIETIN" WOULD IMPROPERLY READ LIMITATIONS INTO THE CLAIMS AND IGNORE THE PLAIN LANGUAGE OF THE CLAIMS, THE SPECIFICATION AND THE PROSECUTION HISTORY

The salient differences between Amgen's and Defendants' proposed construction of "human erythropoietin" are highlighted in yellow below:

| ***"human erythropoietin"***<br>'422 claim 1, '933 claims 3, 7-9, 11-12, and 14<br>'868 claim 1, '349 claim 7 | |
|---|---|
| *Amgen's Proposed Construction* | *Defendants' Proposed Construction* |
| A protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine | a glycoprotein having the amino acid sequence of erythropoietin isolated from human urine having the structure that would be produced in mammalian cells as of the invention date |

The construction proposed by Defendants would not only require the claimed "human erythropoietin" to be a "glycosylated" human erythropoietin, but also would require that it have (1) ***the*** structure, (2) that is produced ***in*** a mammalian cell, (3) as of the date of the invention. In other words, not only would the human erythropoietin have to be glycosylated, but its glycosylation would have to be identical to the glycosylation originally attached to the protein by the cell: that glycosylation could not thereafter be altered in any way (*e.g.*, as a result of purification processes or post-expression chemical or enzymatic modification of the carbohydrates that are attached to the protein). Nor could the glycoprotein be produced in those mammalian cells that were adapted for growth in culture after the date of Lin's inventions. While human EPO produced in mammalian cells will be glycosylated (unless steps are taken to

[15] *Storage Technology Corp. v. Cisco Systems, Inc.*, 329 F.3d 823, 832 (Fed. Cir. 2003).

alter the cells or the protein),[16] the errors in Defendants' proposed construction are manifest.

First, Lin's claims elsewhere refer to a "glycosylated" erythropoietin product, and do so expressly. For example, unasserted '933 claim 4 recites "human erythropoietin glycoprotein."[17] Defendants' proposed construction of "human erythropoietin," which includes a requirement for glycosylation, would render the "glycoprotein" limitation in '933 claim 4 meaningless, thereby violating long-settled claim construction principles.[18]

Defendants' proposed construction is also inconsistent with use of the term "human erythropoietin" in the '933, '868, and '349 claims which refer to a DNA sequence that encodes "human erythropoietin." If "human erythropoietin" were construed to include the "39 to 40 percent polysaccharides" as Defendants' proposed construction would require,[19] the "DNA encoding" limitation in the '933, '868 and '349 claims would be rendered nonsensical — a DNA sequence can only encode a sequence of amino acid residues comprising a polypeptide. It does not encode moieties that may be attached to the peptide backbone, such as carbohydrate molecules (*i.e.*, glycosylation) or the sulfates that may be attached to these molecules.[20]

Likewise, '422 claim 1 imposes a limitation on the structure of the recited "human erythropoietin" beyond the required amino acid sequence, by reciting that the "human erythropoietin" must be "purified from mammalian cells grown in culture" and be "therapeutically effective." It is the source limitation "purified from mammalian cells grown in

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[16] Exhibit 1 at ¶ 33 (3/19/07 Declaration of Harvey Lodish in Support of Amgen's Reply Brief ("Lodish Dec."), ¶ 33).

[17] *See* Amgen's Brief, Appendix B, '933 claim 4.

[18] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 90-91 (D. Mass. 2001), *aff'd in part, rev'd in part, vacated in part*, 314 F.3d 1313 (Fed. Cir. 2003), *on remand*, 339 F. Supp. 2d 202 (D. Mass. 2004), *aff'd in part, rev'd in part, vacated in part*, 457 F.3d 1293 (Fed. Cir. 2006) ("a claim will not be construed as containing a limitation that is expressed in other claims . . . Similarly, '[a]ll the limitations of a claim must be considered meaningful' . . . and if two separate and distinct limitations are construed as synonymous, the claim recitation of both limitations is redundant and superfluous.") (citations omitted).

[19] *See* Defendants' Brief at 6-7.

[20] Exhibit 1 at ¶ 26 (Lodish Dec., ¶ 26).

culture," not "human erythropoietin," that defines the carbohydrate structures (*i.e.*, glycosylation) that may be attached to the sequence of amino acid residues that constitute "human erythropoietin." Moreover, once the claimed "human erythropoietin" is "purified from mammalian cells grown in culture" (whether the purification is from the cell culture medium or the cells themselves), there is no further limitation in '422 claim 1 that excludes further changes in the structure of the protein (so long as it is still "therapeutically effective").

Second, Dr. Lin's specification makes clear that the term "human erythropoietin" is defined by a sequence of amino acid residues, not by the presence or absence of glycosylation.[21] The specification also expressly contemplates "human erythropoietin" products that are not glycosylated (for example, human erythropoietin manufactured by *E. coli* cells — cells which do not glycosylate a protein)[22] and to which additional molecules can be attached (for example, human erythropoietins to which an additional amino acid, methionine, or a leader sequence has been attached)[23].

Finally, the prosecution history similarly states that "[h]uman erythropoietin is understood ***to include any*** polypeptide having the amino acid sequence of EPO isolated from human urine and ***may*** be produced in human cells or in other mammalian cells."[24] This express description of "human erythropoietin" requires only that the claimed polypeptide include the sequence of amino acid residues found in EPO isolated from human urine and recognizes that the product is not limited to some restricted set of carbohydrate molecules added to the amino acid

[21] Amgen's Brief, Appendix B at 13:50-53; 10:9-15. *See also* Exhibit 1 at ¶¶ 30-31 (Lodish Dec., ¶¶ 30-31).

[22] Amgen's Brief, Appendix B at Examples 11, 12, Exhibit 1 at ¶¶ 30-31 (Lodish Dec., ¶¶ 30-31).

[23] Amgen's Brief, Appendix B at 10:28-33; 29:26-29; 20:39-45; Exhibit 1 at ¶¶ 32-33 (Lodish Dec., ¶¶ 32-33).

[24] Amgen's Brief, Exhibit 8 at AM-ITC-00899474 (U.S. Appln. 100,197 File History, 4/28/99 Amendment (Paper 33) at 5); *see also* Amgen's Brief, Appendix B at 21:11-19; 35:10-20; 35:27-39 (providing that "human erythropoietin" includes any naturally occurring allelic variations in human EPO's amino acid sequence).

backbone. Defendants recognize the import of this portion of the prosecution history, as they too cite it in their brief. However, Defendants do not acknowledge the expressly open-ended nature of this statement or its lack of any reference to glycosylation.

Rather, Defendants point to the "Background of the Invention" section of Dr. Lin's specification and to Dr. Goldwasser's testimony about the definition of EPO. But these descriptions of prior art naturally occurring EPO as a 34,000 dalton glycoprotein do not alter how Dr. Lin's inventions are described in his "Summary of the Invention" and "Detailed Description of the Invention." Indeed, Dr. Lin describes the products of his inventions as including deglycosylated and unglycosylated human EPO polypeptides, whose molecular weight would differ substantially from 34,000 daltons.[25] Likewise, he describes products that are made synthetically,[26] as well as those that have been chemically modified.[27]

In contrast to Defendants' effort to read an additional "glycosylation" limitation into the claim term "human erythropoietin," Defendants ask this Court to ignore the explicit meaning and significance of the term "purified from mammalian cells grown in culture," an expressly recited source limitation.

| ***"purified from mammalian cells grown in culture"*** | |
|---|---|
| *Amgen's Proposed Construction* | *Defendants' Proposed Construction* |
| wherein the protein is obtained in substantially homogeneous form from mammalian cells grown in culture, such that it originates in mammalian cells, but need not be taken directly out of the interior of the cells | obtained in substantially homogeneous form from mammalian cells, using the word "from" in the sense that it originates in mammalian cells, without limitation to it only taking it directly out of the interior of the cells, which have been grown in the in vitro culture<br><br>*This limitation cannot define the structure of* |

[25] *Id., see also id.* at col. 21:5-6 (describing the molecular weight of the mature EPO polypeptide as including an amino acid sequence weighing 18,399 daltons); *id*. at col. 10:28-33.

[26] *See* Amgen's Brief, Appendix B at 10:50-64.

[27] *See* Amgen's Brief, Appendix B at 12:8-21.

| *"purified from mammalian cells grown in culture"* | |
|---|---|
| *Amgen's Proposed Construction* | *Defendants' Proposed Construction* |
| | *the claimed product*. |

Instead, in an attempt to buttress their invalidity defense, Defendants contend that because the term is a source limitation, it does not define the claimed product. But Defendants cannot simply eliminate a claim limitation that distinguishes the structure of the claimed product over the prior art.

As long recognized by the Federal Circuit and its predecessor court, such source or process limitations can and do serve to define the structure of a claimed product where such limitations are the best means to distinguish a claimed product over the prior art.[28] This is especially true where, as here, a patentee has relied on the source from which his claimed product is obtained to establish its novelty over the prior art.[29] In this context, Defendants' citation to *SmithKline Beecham Corp. v. Apotex Corp.*[30] is misleading[31] since it omits the very next passage, which recognizes that process limitations may impart novel structure to a product claim: "If those product-by-process claims produced a different product than that disclosed by the *'723 patent*, there would be an argument that the *'723 patent* disclosure did not anticipate."[32]

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[28] *In re Luck*, 476 F.2d 650, 653 (C.C.P.A. 1973) (*citing In re Brown*, 459 F.2d 531, 535 (C.C.P.A. 1972)) ("Product claims may include process steps to wholly or partially define the claimed product. To the extent that *these* process limitations distinguish the product over the prior art, they must be given the same consideration as traditional product characteristics.").

[29] Amgen's Brief, Exhibit 8 at AM-ITC-00899474 (U.S. Appln. 100,197 File History, 4/28/99 Amendment (Paper 33) at 5 (in contrasting '422 claims 1 and 2, Amgen provided that "purified from mammalian cells in culture" is a source limitation and relied on the recombinant process by which Amgen made EPO to structurally distinguish rEPO from uEPO)); Amgen's Brief, Exhibit 9 at AM-ITC-00899180 (U.S. Appln. 100,197 File History, 3/2/95 Amendment (Paper 25) at 2).

[30] 439 F.3d 1312 (Fed. Cir. 2006).

[31] *See* Defendants' Brief at 9-10.

[32] *Id*. at 1319 (citing *In re Luck*). Defendants' reference to this Court's previous finding of indefiniteness regarding unasserted (and now cancelled) '933 claims 1 and 2 (*see* Defendants' Brief at 10-11) similarly misses the point. While this Court has previously found that reference to the molecular weight of urinary EPO is a "standardless standard," this does not address whether a specific prior art urinary EPO

### B. DEFENDANTS' CONSTRUCTION OF THE OBJECT OF THE '933 CLAIMS IGNORES THE INTRINSIC RECORD

The important differences between Amgen's and Defendants' proposed constructions of "a non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin" are highlighted in yellow below:

| ***"a non-naturally occurring[33] glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin"[34]*** '933 claims 3, 7-9, 11-12 and 14 | |
|---|---|
| **Amgen's Proposed Construction** | **Defendants' Proposed Construction** |
| A glycoprotein product not occurring in nature that is expressed in a mammalian cell from a DNA sequence that does not originate in the genome of the host and comprises a DNA sequence encoding human erythropoietin | a protein [not occurring in nature] that is the expression product of the mammalian host cell having the amino acid sequence of human erythropoietin which is glycosylated naturally by the host cell at specific amino acids |

Defendants' construction defines the recited "non-naturally occurring" glycoprotein product as "having":[35] (a) the amino acid sequence of human EPO, (b) glycosylation as is added by the host cell, and (c) glycosylation only at specified amino acid residues.

While the disputed limitation incorporates a DNA encoding human EPO, the claim language is actually broader as it recites that the product is expressed by "exogenous" DNA comprising a DNA encoding human EPO, thus expressly indicating that the "exogenous DNA"

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preparation (Dr. Goldwasser's urinary EPO preparation) differs from Amgen's claimed products.

[33] Defendants' construction does not include the term "non-naturally occurring," as this term modifies the "glycoprotein product." *See* Amgen's Brief, Appendix B at '933 claim 3. There does not appear to be any dispute over the construction of this adjective. *See* Amgen's Brief, Exhibit 10 at 2). For the sake of completeness, Amgen includes the full term here.

[34] Defendants offer a similar construction for '080 claim 3, as offered for '933 claim 3. As set forth in Amgen's Brief, Amgen does not seek construction of the asserted '080 claims until such time as the Federal Circuit's decision regarding the applicability of prosecution history estoppel is reversed. Resolution regarding construction of the terms in dispute, as they pertain to the '933 and '422 claims will also resolve the parties' apparent dispute regarding the asserted '080 claims.

[35] Amgen understands Roche's use of the open-ended word "having" to mean that they agree that the

can also comprise additional DNA, including DNA encoding additional amino acids, *e.g.*, DNA that encodes the signal peptide shown in Figure 6. Nothing in the claim language precludes the DNA from which the claimed product is produced from encoding amino acids in addition to, and different from, the sequence of amino acid residues in human EPO, so long as it also encodes the sequence of amino acid residues in human EPO.[36]

Nor does anything in the claim language or the specification require that the recited protein must be glycosylated at specific amino acid residues and not at others. The portion of Dr. Lin's specification to which Defendants refer, concerning sites for glycosylation, uses the permissive language "potential."[37] While Dr. Lin identified three consensus sequence sites in the deduced amino acid sequence of Figure 6 which could allow for attachment of N-linked glycosylation by a cell, nothing in the intrinsic record restricts "glycoprotein products" to products having glycosylation at these sites. Indeed, the products of Example 10 of the specification include glycoprotein products with O-linked glycosylation at the serine amino acid residue at position 126.

Finally, Defendants' proposal that the recited glycosylation be "naturally" attached by the cell that produces the product is ambiguous and is contradicted by the express language of the claim. First, the production of a glycoprotein product by a genetically engineered cell is anything but "natural." Moreover, use of "non-naturally occurring" contradicts the notion that only "naturally-occurring" glycosylation be allowed.

In support of their proposed construction, Defendants point to passages in Dr. Lin's specification that refer to production of the products of the invention by cells. None of these passages, however, refer to specific sites of glycosylation, or specific types of post-translational

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glycoprotein may have other structures.

[36] *Amgen v. Hoechst Marion Roussel*, 339 F. Supp. 2d at 251-252.

[37] Amgen's Brief, Appendix B at 21:10-11.

modifications.[38] To the contrary, these passages all refer to products of the expression of specified exogenous DNA and these products may have varying degrees of glycosylation.[39] Likewise, the specification also specifically contemplates additions to the amino acid residues making up the claimed polypeptides by other chemical entities, such as additional amino acids or detectable labels.[40] Nothing in the intrinsic record imposes a requirement by Dr. Lin that the products of his invention be glycosylated by a host cell at specific amino acids, or a suggestion that he was disclaiming glycoprotein products that include amino acids in addition to those constituting human erythropoietin.

Rather, for the reasons set forth in Amgen's Brief, the term "glycoprotein product" should be construed simply to mean "a protein not occurring in nature having carbohydrate groups attached to the polypeptide." Based on this Court's past constructions of the terms "DNA sequence encoding"[41] and "mammalian cells,"[42] the full term should be read to mean "a glycoprotein not occurring in nature wherein said product is produced by a mammalian cell transformed or transfected with a DNA sequence that does not have its origin from the genome of the host and which contains at least the genetic instructions for human erythropoietin."[43]

### C. DEFENDANTS' CONSTRUCTION OF "PHARMACEUTICAL COMPOSITION COMPRISING . . . A PHARMACEUTICALLY ACCEPTABLE DILUENT, ADJUVANT OR CARRIER" IGNORES THE CLAIM LANGUAGE AND ITS PLAIN MEANING TO ONE OF ORDINARY SKILL IN THE ART

The important differences between Amgen's and Defendants' proposed construction of "pharmaceutical composition comprising . . . a pharmaceutically acceptable diluent, adjuvant or carrier" are highlighted in yellow below:

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[38] *See generally* Amgen's Brief, Appendix B at 10:15-20.

[39] Amgen's Brief, Appendix B at 10:28-33, Examples 11 and 12.

[40] Amgen's Brief, Appendix B at 10:28-33, 29:27-29, 12:8-12.

[41] *Amgen v. Hoechst Marion Roussel*, 339 F. Supp. 2d at 251.

[42] *Amgen v. Hoechst Marion Roussel*, 126 F. Supp. 2d at 86.

| ***"a pharmaceutical composition comprising. . . a pharmaceutically acceptable diluent, adjuvant or carrier"*** ‘422 claim 1, ‘933 claims 9 and 12 | |
|---|---|
| *Amgen's Proposed Construction* | *Defendants' Proposed Construction* |
| a composition suitable for administration to humans containing at least a diluent, adjuvant or carrier | a mixture having in addition to the active ingredient (as defined in the claim), an additional distinct and separate ingredient that acts as a diluent, an adjuvant or a carrier |

The construction proposed by Defendants would require that only one "diluent, adjuvant or carrier" [44] could be present in the composition, and would further require that it somehow be kept "distinct and separate" from the "human erythropoietin" in the claimed composition. Neither the term's plain meaning nor the intrinsic record supports such a contorted reading.

First, Defendants' contention that the claim term "comprising" should be construed to require ***either*** (a) a diluent, ***or*** (b) an adjuvant, ***or*** (c) a carrier is inconsistent with the well-established open-ended meaning of "comprising," which expressly allows for the inclusion of elements other than the recited elements.[45] The specification expressly confirms this "open" construction:

> Also comprehended by the invention are pharmaceutical compositions comprising effective amounts of polypeptide products of the invention together with suitable diluents, adjuvants ***and/or*** carriers . . .[46]

Likewise, nothing in the claim language or specification requires the recited diluents, adjuvants, or carriers to be "distinct and separate" from the recited "human erythropoietin." Rather, the specification exemplifies diluents, adjuvants, or carriers that interact with and bond to the recited "human erythropoietin" "active ingredient." For example, saline, albumin and many

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[43] Amgen's Brief, Appendix A at 19-20 (citing to intrinsic record supporting proposed construction).

[44] *See* Defendants' Brief at 8.

[45] Amgen's Brief at 19 (in the context of Amgen's claims); *see also Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1572 (Fed. Cir. 1997) ("comprising" "permits inclusion of other moieties.").

[46] Amgen's Brief, Appendix B at 12:1-4 (emphasis added).

proteins listed as adjuvants in the specification may or may not be separate and distinct from the recited human erythropoietin.[47] Defendants' reliance on their construction of "composition" to denote a "mixture" does not remedy these scientific facts, since, as the Supreme Court found in *Diamond v. Chakabarty*, a "composition" includes "all compositions of two or more substances ***and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders, or solids***."[48]

### D. THE "CHO CELLS" USED TO PRODUCE EPO NEED NOT BE IDENTICAL TO THE CELLS FOUND IN A CHINESE HAMSTER OVARY

Defendants also appear to ask this Court to read unstated limitations into Lin's claimed use of Chinese Hamster Ovary cells to produce EPO.

| ***"wherein said cells are CHO cells"*** ‘868 Claim 2, ‘933 claim 8 | |
|---|---|
| *Amgen's Proposed Construction* | *Defendants' Proposed Construction* |
| A cell derived from the ovary of a Chinese hamster. | A cell from the ovary of a Chinese hamster. |

According to Defendants' Brief, a "cell" "in common parlance … contains a diploid or full complement of paired chromosomes."[49] If this is intended to require that the "CHO cells" of Dr. Lin's claims must be found in the ovary of a living Chinese hamster, there is no basis in the intrinsic record to justify such limitation.[50] Rather, it is yet another unjustifiable attempt to

[47] Exihibit 2 at ¶¶ 33, 35 (Declaration of Vladamir Torchilin in Support of Amgen's Reply Brief ("Torchilin Dec.") at ¶¶ 33, 35 (providing that, *inter* alia, saline forms ionic bonds with EPO, albumin can be covalently bound to EPO, and albumin and the described adjuvant proteins can bind to EPO through ionic, hydrophobic and van der Waals interactions)).

[48] 447 US 303, 206 USPQ 193, 196-197 (1980) (emphasis added). Defendants rely heavily on *PIN/NIP, Inc. v. Platte Chemical Corp*., 304 F.3d 1235, 1243-44 (Fed. Cir. 2002). However, the *PIN/NIP* Court did not state that a composition must exist as "separate and distinct components. To the contrary, the Court stated that the term composition recognizes that "the components are present *together* at some point in time." PIN/*NIP*, 304 F.3d at 1244.

[49] Defendants' Brief at 13.

[50] *See* Amgen's Brief, Appendix B at 25:46-51(describing the use of CHO cells that have been modified

restrict the meaning and scope of Dr. Lin's issued claims.

### E. "THERAPEUTICALLY EFFECTIVE AMOUNT" AND "AMOUNT . . . EFFECTIVE FOR ERYTHROPOIETIN THERAPY" DO NOT HAVE THE IDENTICAL MEANING

Defendants adopt the Federal Circuit's recent construction of "therapeutically effective amount" as the construction for a different claim term,[51] and then ask this Court to construe "effective for erythropoietin therapy" and "therapeutically effective" to have the identical meaning.[52]

| ***"effective amount of a glycoprotein product effective for erythropoietin therapy"*** **'933 Claims 9, 10 and 11** | |
|---|---|
| *Amgen's Proposed Construction* | *Defendants' Proposed Construction* |
| A quantity of a glycoprotein product according to claim 1, 2, 3, 4, 5 or 6 that produces a result that in and of itself helps to heal or cure a patient in the class of patients listed in the specification, column 33 lines 31 through 36: patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like | A therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22, stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals |

The term "erythropoietin therapy" is expressly set forth in the specification at column 12, line 5 and column 33, lines 22, 37-38, and 44. In each instance, the term is used in the context of treating anemia patients and patients in need of blood transfusions as confirmed from the perspective of how one of ordinary skill in the art at the time of the invention would have

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to delete DNA encoding DHFR) and 27:17-29 (describing these cells, after they have been further manipulated to include EPO DNA, as "CHO cells").

[51] Amgen is currently petitioning the Supreme Court for a writ of certiorari to review both the Federal Circuit's construction of "therapeutically effective amount" and its determination that Amgen failed to rebut the presumption of estoppel resulting from its amendment of the '080 claims during prosecution.

[52] Defendants' Brief at 14.

understood the specification.[53]

The prosecution history supports this meaning, as well. During prosecution, the Examiner rejected the pending claim to "a pharmaceutical composition comprising an effective amount of a glycoprotein product . . ." as indefinite for failing to identify the effect of the composition.[54] In response, Amgen amended its claims to include the term "an effective amount . . . effective for erythropoietin therapy," and argued that the amendment mooted the rejection specifying the therapies provided to a patient.[55]

Under these circumstances, the term "effective amount [of product] effective for erythropoietin therapy" means "a quantity of a glycoprotein that produces a result that in and of itself helps to heal or cure a patient in the class of patients listed in the specification at column 33, lines 31-36 (patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like)."

### F. DR. LIN'S PROCESS CLAIMS DO NOT EXCLUDE PROCESSES HAVING ADDITIONAL STEPS

At bottom, Defendants' proposed constructions are an attempt to avoid literal infringement by unduly limiting Dr. Lin's asserted process claims to products directly resulting from the recited process steps without allowing any further processing or modifications:

[53] Exhibit 3 at 649:25-667:10 (excerpt from the 11/3/03 trial testimony of Dr. Joseph Eschbach in *Amgen Inc. v. Hoecht Marion Roussel*, Civil Action No. 97-10814-WGY).

[54] Exhibit 11 at AM-ITC-00941460 (U.S. Appln. 487,774 File History, 8/16/94 Office Action (Paper No. 38) at 5).

[55] Exhibit 12 at AM-ITC-00941511, -516 (U.S. Appln. 487,774, 2/22/95 Amendment and Request for Reconsideration (Paper No. 42) at 4, 9).

| ***"process for the production of a glycosylated erythropoietin polypeptide . . . comprising the steps of"*** '868 claims 1 and 2, '698 claims 4-9 | |
|---|---|
| *Amgen's Proposed Construction* | *Defendants' Proposed Construction* |
| a process for the production of an erythropoietin polypeptide having one or more carbohydrate groups attached to the polypeptide . . . containing at least the following steps | process for the production of a glycosylated erythropoietin polypeptide having the amino acid sequence and carbohydrate modifications obtainable through process steps (a) and (b) of these claims |
| ***"process for producing erythropoietin comprising the step of"*** '349 claim 7[56] | |
| *Amgen's Proposed Construction* | *Defendants' Proposed Construction* |
| a process for producing erythropoietin containing at least the step | process for producing a glycoprotein having the amino acid sequence and glycosylation structure of a naturally occurring hormone that is produced in a cell and secreted from that cell, and that controls the formation of red blood cells in bone marrow |
| ***"cells transformed or transfected with an isolated DNA sequence encoding human erythropoitein"*** '868 claims 1 and 2 | |
| *Amgen's Proposed Construction* | *Defendants' Proposed Construction* |
| cells receiving purified genetic instructions for human erythropoietin | introduction of purified exogenous DNA molecules encoding the genetic instructions for human erythropoietin into a host cell |
| ***"isolating said glycosylated erythropoietin polypeptide expressed by said cells/therefrom"*** '868 claims 1 and 2, '698 claims 4-9 | |
| *Amgen's Proposed Construction* | *Defendants' Proposed Construction* |
| recovering in pure form said glycosylated erythropoietin polypeptide | separating the glycosylated erythropoietin polypeptide having the defined activity from the growth medium, cellular lysates or cellular membrane fractions of the cells that produce it |

[56] Defendants incorrectly assert that Amgen has only asserted '349 claim 7, as it depends on '349 claim 1. Defendants' Brief at 5, n. 2. As set forth in Amgen's infringement chart (Appendix A to Amgen's Brief), while Amgen provides only an infringement chart for '349 claim 7 (as it depends on claim 1) for purposes of its *Markman* submission, Amgen will rely on each of '349 claims 1-6 to support dependent claim 7.

Insofar as Defendants' proposed constructions seek to exclude any further alteration or modification of the product obtained by means of Lin's claimed processes, they find no support in the intrinsic record or the law. As the Federal Circuit held in the context of Amgen's claims, "comprising" is "a term of art used in claim language which means that the named elements are essential, ***but other elements may be added and still form a construct within the scope of the claim***."[57] Thus, the asserted process claims cover processes that include additional steps.

Dr. Lin's specification is consistent with this plain meaning. It discloses additional process steps for making Dr. Lin's EPO products that are not recited in his process claims. For example, Example 10 includes the precursor step of actually transforming the cells used in the claimed process with EPO DNA, as well as amplifying such DNA.[58] At the other end of the process, the specification describes steps that follow the isolation of the expression product. For example, the specification describes the step of formulating an isolated product into a pharmaceutical composition.[59] It further identifies the step of labeling the expressed product by the covalent association of a detectable marker substance to EPO after its isolation.[60] Finally, there is no basis in either the terms' plain meaning or the intrinsic record to limit the terms "erythropoietin" and "glycosylated erythropoietin polypeptide" to exclude EPOs to which an additional molecule has been attached.

Amgen also disagrees with two limitations that Defendants seek to add to the term "cells transformed and transfected with an isolated DNA sequence encoding human erythropoietin" by their construction. Specifically, Defendants' offered construction requires: (1) that the DNA

[57] *Amgen v. Hoechst Marion Roussel*, 314 F.3d at 1344-45 (emphasis added).

[58] Amgen's Brief, Appendix B at 25:39-26-65.

[59] Amgen's Brief, Appendix B at 33:60 to 34:27.

[60] Amgen's Brief, Appendix B at 12:8-12. The file histories for these patents are silent as to this issue and thus do not change the claims' plain meaning, as supported by the specification.

introduced into the cell "must be isolated and not be introduced with other genetic material;[61] and (2) that the step of transforming a cell with EPO DNA is a process step that limits Dr. Lin's '868 process claims.[62]

As taught by Dr. Lin's specification, EPO DNA, as well as transcription control DNA (*e.g.*, promoter DNA) and DNA used to amplify EPO, can be inserted into vectors (which also comprise DNA).[63] These vectors are then used to transform or transfect the cell used in the claimed process.[64] Defendants' construction, which would preclude any other genetic material from being introduced with the EPO DNA, flies in the face of this teaching. Likewise, there is no basis for asserting that the step of "transforming or transfecting" a cell should be read into a claim which plainly only requires two steps: "growing" and "isolating."[65] The claim requires a "cell [that has been] transformed or transfected" — not a separate transforming step.

Finally, the sole distinction of "isolating said . . ." is whether the isolation step, without reference to any other claim term, is limited to the isolation of a product having a specific "activity." Assuming that Defendants' reference to "defined activity" means the activity recited in the claims' preambles ("in vivo biological property of causing red blood cells to increase the production of reticulocytes and red blood cells"), there is no meaningful difference between the parties' proposed constructions.

## IV. CONCLUSION

For the reasons set forth above, Amgen's constructions, as set forth in its March 5, 2007

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[61] *See* Defendants' Brief at 19.

[62] *Id.* at 18 (citing passages from Dr. Lin's specification describing "transformation and transfection techniques").

[63] Amgen's Brief, Appendix B at Figs. 2-4, 11:19-41, Examples 6, 7, 10.

[64] *Id.*

[65] Defendants' motive for reading this additional step into the claims as an express limitation is obvious. Defendants, using the exact same cell line that had been previously held to be infringing, transformed that line before Amgen's asserted process claims had issued. *See* Amgen's Brief at 8-9 (providing that Defendants' current process for making EPO uses the same cells that had been found to infringe Amgen's

Claims Construction Brief at Appendix A (Docket No. 312) should be adopted.

Respectfully Submitted,

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'008 patent).

**CERTIFICATE OF SERVICE**

I hereby certify that this document, filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of electronic filing and paper copies will be sent to those indicated as non-registered participants on March 19, 2007.

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