UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, vs. F. HOFFMANN-LA ROCHE LTD; ROCHE DIAGNOSTICS GmbH; and HOFFMANN-LA ROCHE INC. Defendants.	CIVIL ACTION No.: 05-CV-12237WGY

DEFENDANT'S SURREPLY IN SUPPORT OF ITS OPPOSITION TO AMGEN'S MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT OF '422 CLAIM 1, '933 CLAIM 3, AND '698 CLAIM 6

Leora Ben-Ami (pro hac vice)
Patricia A. Carson (pro hac vice)
Thomas F. Fleming (pro hac vice)
Howard S. Suh (pro hac vice)
Peter Fratangelo (BBO# 639775)
KAYE SCHOLER LLP
425 Park Avenue
New York, New York 10022
Tel. (212) 836 8000

Lee Carl Bromberg (BBO# 058480)
Julia Huston (BBO# 562160)
Keith E. Toms (BBO# 663369)
Nicole A. Rizzo (BBO# 663853)
BROMBERG & SUNSTEIN LLP
125 Summer Street
Boston, MA 02110
Tel. (617) 443-9292
ktoms@bromsun.com

Counsel for Defendants
F. Hoffman-La Roche Ltd.
Roche Diagnostics GmbH, and
Hoffman-La Roche Inc.

Dated: Boston Massachusetts
July 13, 2007

I. INTRODUCTION

Roche submits this surreply memorandum in further support of its Opposition to Amgen's Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6. Roche submitted its opposition to Amgen's motion on June 29, 2007. On July 3, 2007, the Court's Memorandum and Order on claim construction issued. Amgen therefore had the benefit of the Court's memorandum on claim construction in styling its reply. Roche submits this surreply to respond to certain new points raised in Amgen's reply, particularly in light of the Court's memorandum on claim construction.

II. ROCHE'S NON-INFRINGEMENT POSITION IS ENTIRELY CONSISTENT WITH THE COURT'S CLAIM CONSTRUCTION OF "HUMAN ERYTHROPOIETIN"

A. CERA Does Not Have the Amino Acid Sequence of "Human Erythropoietin" as Defined by the Court

Contrary to Amgen's assertions, Roche's non-infringement argument with respect to '422 claim 1 is fully consistent with this Court's claim construction of "human erythropoietin." In the Court's order dated July 3, 2007, "human erythropoietin" was defined as "[a] protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine."[1] In stating this construction, the Court expressly recognized that "a district court must interpret the claim terms as having the 'meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.'"[2]

The only information regarding the full "amino acid sequence of human EPO" available to one of skill in the art at the time that the '422 patent was filed, is the patent specification itself. Based on that disclosure, one of skill in the art would understand the amino acid sequence to be

[1] Memorandum and Order dated July 3, 2007 ("Markman Order") (Docket No. 613).

[2] *Id.* at 15 quoting *Phillips v. AWH Corp.,* 415 F. 3d 1303 at 1312-1313 (Fed. Cir. 2005) (Docket No. 613).

the 166 amino acid sequence of Figure 6 or a variant with methionine at position 126.[3] As pointed out in Roche's opposition, neither CERA nor the epoetin beta starting material have those sequence elements.[4] However, even if this difference is improperly disregarded, the amino acid sequence of CERA does not correspond to the amino acid sequence of human EPO, as it would have been understood by the skilled practitioner at the time the Lin specification was filed or even today.[5]

For example, based on the sequence disclosed in the Lin specification, one of skill in the art would have understood the amino acid residues at position 45 and 52 in human erythropoietin to be lysine residues. In fact, regardless of where one looks to define the sequence of human erythropoietin at the time of the Lin application and today, positions 45 and 52 *always* correspond to a lysine residue. CERA has amino acid residues at 45 and 52 that are not lysine residues.

In order for the Court to truly understand why the amino acids in CERA *do not* correspond to the amino acid sequence of human EPO, a brief explanation of the chemistry of amino acids is necessary. In order to view the issues in the light most favorable to Amgen, Roche relies on the textbook authored by Amgen's longtime expert, Dr. Lodish, for this explanation. There, Dr. Lodish teaches that all amino acids contain a common core structure

[3] Roche's Rule 56.1 Statement of Material Facts in Support Defendants' Opposition to Amgen's Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6 Pursuant to Local Rule 56.1 ¶ 120 (Docket No. 607).

[4] Defendants' Opposition to Amgen's Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6 ("Roche Opp.") at p. 4 (Docket No. 588).

[5] Amgen attempts to skirt the scientific facts by relying on out of context cites to Roche's regulatory filings. First, in describing the amino acid sequence of CERA in the BLA, Roche expressly points out the formation of the amide bond which changes amino acid residues where the bond is formed. Moreover, those statements are utterly irrelevant to the question at hand. Roche's BLA was written over fifteen years after the filing date of Lin's patents. Roche was clearly not using "human erythropoietin" in accordance with the understanding that one of skill in the art would have had in 1983/1984. In that time frame, at minimum one of skill in the art would have understood "human erythropoietin" was defined by what Dr. Lin disclosed, which makes it a question of fact as to what that amino acid sequence is.

"consisting of a central **alpha (α) carbon atom (Cα)** bonded to four different chemical groups; an amino (NH_2) group, a carboxylic acid or carboxyl (COOH) group (hence the name *amino* acid), a hydrogen (H) atom, and one variable group, called a **side chain** or R group."[6] This "core" structure can be graphically depicted as follows:

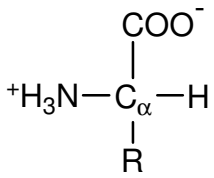
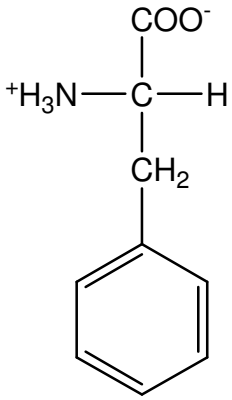
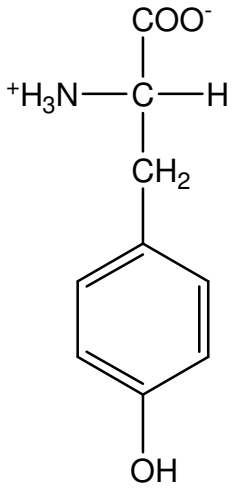


Figure 2-14 of Lodish's textbook graphically depicts the twenty common amino acids. As shown by these depictions, the *only* difference between these twenty amino acids is the side chain. For example, Dr. Lodish's text illustrates phenylalanine as follows:

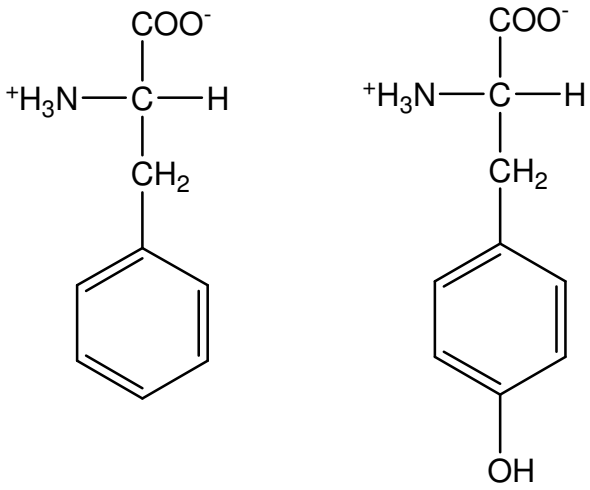


Tyrosine is depicted as follows:

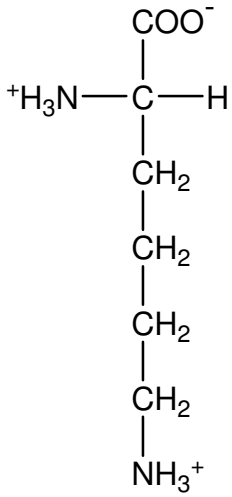
[6] Declaration of Keith E. Toms in Support of Roche's Opposition to Amgen's Motion for Summary Judgment that Dr. Lin's Asserted Claims are Definite, Adequately Described, and Enabled ("Toms Decl. I"), Ex. C, Lodish et al. *Molecular Cell Biology 6th Edition* at p. 41 (Docket No. 637).



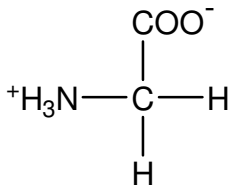
Placing these depictions side by side as shown below, it is apparent that the two molecules differ solely by the "addition" (if Amgen's view of chemistry is erroneously adopted) of an OH group. Dr. Lodish however depicts these as two distinct amino acids with distinct properties.



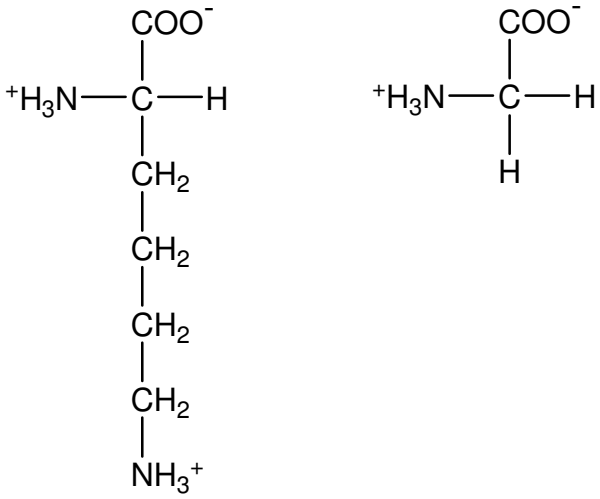
Similarly, Dr. Lodish's textbook depicts Lysine as follows:



Glycine is depicted as having the following structure:



Again, placing these depictions side by side as shown below, under Amgen's erroneous view, Lysine would simply be glycine, with additions. Yet again, as confirmed by Dr. Lodish, these are distinct chemicals with distinct properties.



What is clear from the examples above and indeed all twenty common amino acids depicted by Dr. Lodish is that it is the side chain of the amino acid that defines the amino acid. In short, the side chain is crucial.

Referring to the twenty common amino acids depicted in Figure 2-14 of his textbook Dr. Lodish states:

> Although cells use the 20 amino acids shown in Figure 2-14 in the *initial* synthesis of proteins, analysis of cellular proteins reveals that they contain upward of 100 different amino acids. Chemical modifications of the amino acids account for this difference.[7]

With this brief overview of amino acid chemistry, the significant flaws in Amgen's infringement position are evident.

First, if it is Amgen's position that "human erythropoietin" can contain any of the common amino acids or upward of 100 different chemically modified amino acid residues (or such chemical modifications that may be identified at some point in the future), Amgen's claim fails for indefiniteness. Specifically, if the claim phrase is interpreted in accordance with the understanding of one in skill in the art in 1983/1984 as this Court has indicated it should be, the finder of fact would have to decide which of the chemically modified amino acid residues were known at that time. In short, that position would convert "human erythropoietin" into a "moving target" and hence a "standardless standard for use in defining the claimed EPO product" similar to the '933 claims previously invalidated by this Court.[8]

Moreover, stretching the Court's definition of "human erythropoietin" to include any permutation of EPO, as Amgen suggests, would lead to an absurdly overbroad interpretation of

[7] *Id.* at p. 43 (emphasis added) (Docket No. 637).

[8] *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F.Supp. 2d 69, 91, 129, 155 (D. Mass. 2001).

Amgen's patent claims. The Federal Circuit's opinion in *Genentech, Inc. v. Wellcome Found. Ltd*. closely parallels the present case and is instructive on this issue.[9]

In *Genentech,* Defendants appealed a jury verdict finding infringement under the doctrine of equivalents, of three patents directed to a human protein involved in dissolving blood clots known as "tissue plasminogen activator." The court narrowly defined "human tissue plasminogen activator" as natural t-PA, i.e., the same number and sequence of amino acids. The court rejected broader and more "functional" definitions because they were "hopelessly overbroad" and included "an infinite number of permutations of natural t-PA" whose properties were "totally unpredictable." Applying the correct construction, the court found that accused product met-t-PA, a protein whose sequence differed from natural t-PA by only one substitution of methionine for valine at position 245, did not literally infringe the patent claims. The one additional atom in the methionine side chain (C_3H_7S) as compared to the valine side chain (C_3H_7) was sufficient to distinguish the amino acid sequence of t-PA from that of met-t-PA. The Court was obviously not persuaded by a simplistic Amgen-style analysis that the accused product must contain t-PA because the substance is named "met-t-PA". The Federal Circuit reversed the jury finding of infringement under the doctrine of equivalents based in part on differences in half-life and binding affinity compared to natural t-PA. The Court found that an overbroad functional definition that looked only at the enzyme's activity would not be useful because it would be "hard to imagine how any version of t-PA ... would avoid infringement under the doctrine of equivalents because t-PA, or any operative variant, would by definition necessarily perform this function in the same general way with the same general results." [10]

[9] 29 F.3d 1555 (Fed. Cir. 1994)

[10] Amgen's motion does not raise doctrine of equivalents so Roche does not address this issue.

As detailed below, CERA does not contain the amino acid sequence of human erythropoietin as interpreted by the Court. Similarly, when "human erythropoietin" is defined solely by its amino acids, those amino acids, specifically, the side chains that define those amino acids, are critically important in defining structure and cannot be disregarded in a proper infringement analysis. Like the difference between t-PA and met-t-PA, CERA contains an amino acid substitution -- a non-naturally occurring amino acid has been substituted for a naturally occurring amino acid. The substitution of one hydrogen atom for an amide group, as demonstrated by *Genentech*, is highly significant and is sufficient to exclude CERA from any literal application of Amgen's asserted claims.

In this case, lysine is defined in standard textbooks as an amino acid with an epsilon amino group that is positively charged at the pH of biological fluids.[11] The replacement of a hydrogen of the epsilon amino group of a lysine residue with a simple amide bond results in a different residue known as N-acetyllysine, an uncharged residue. Another textbook from 1985 on the chemistry and biochemistry of the amino acids characterizes N-acetyllysine as a "non-protein amino acid"[12], which is defined as an amino acid which is not found in proteins because it does "not arise by post-translational modifications".[13]

> Non-protein amino acids are those amino acids which are not found in protein main chains either for lack of a specific transfer RNA and codon triplet or because they **do not arise from protein amino acids by post-translational modifications**.

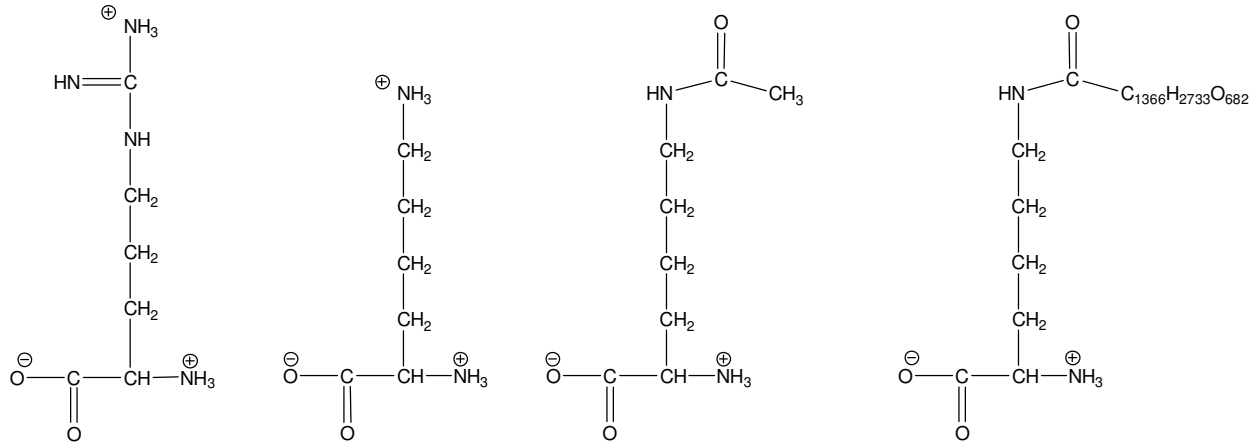
The chemical reaction to make CERA changes lysine residues of epoetin beta into different amino acid residues that are akin to *N*-acetyllysine, but with vastly increased

[11] *See*, *e.g.,* Toms Decl. I, Ex. C at p. 42, Fig. 2-14 (Docket No. 637).

[12] Declaration of Keith E. Toms in Support of Defendants' Surreply in Support of Its Opposition to Amgen's Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6 ("Toms Decl. III"), Ex. A at 71, Table 4.1(emphasis added), filed concurrently.

[13] *Id*. at 55.

complexity. Thus if *N*-acetyllysine was recognized in 1985 as being a different amino acid than lysine then the amino acid residues that are chemically changed in CERA should be recognized as different residues than lysine residues that define the sequence of human erythropoietin. The figure shown below illustrates the point. The first three structures are all recognized in the art as being different amino acids. In this case however, Amgen disputes that the fourth structure differs from lysine.



In short, CERA molecules at positions 45 and 52 have residues that are not lysine.[14] The CERA sequence has residues that do not arise from post-translational modifications and thus are "non-protein" amino acid residues. This is further explained in Dr. Klibanov's declaration submitted in support of Defendants' opposition. As Dr. Klibanov explains, amino acids can be changed to create new amino acids, including amino acids that do not occur in nature.[15] Dr. Alton Meister, a renowned authority in the field describes the synthesis of numerous amino acid analogs in his two-volume treatise on amino acid chemistry, generally regarded by protein

[14] For purposes of this surreply, Roche discusses only the lysines at positions 45 and 52. The reaction that results in CERA can occur at Lys residues 20, 45, 52, 97, 116, 140 152, 154, and at the alpha amino group of the N-terminal Ala residue. Declaration of Alexander M. Klibanov, Ph.D. in Support of Defendants' Opposition to Amgen's Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6 ("Klibanov Decl.") at ¶ 107 (Docket No. 610).

[15] Klibanov Decl. at ¶ 64 (Docket No. 610).

chemists as one of the definitive references in the field. As illustrated above for lysine, this well-known treatise refers to these molecules as synthetic amino acid analogs and by new chemical names. [16]

Similarly, in his textbook, Dr. Lodish assigns new names to amino acids that have been chemically created from other common amino acids. As previously discussed, Dr. Lodish describes the common "core" structure of amino acids and teaches that amino acids differ only by the side chain or R group.[17] When the side chains that define the twenty common amino acids are chemically modified, Dr. Lodish also recognizes that they become new amino acids and refers to such amino acids by new names. Thus, N-acetyllysine is a different chemical than lysine, analogous to the difference between fluoroacetic acid and acetic acid discussed in Dr. Klibanov's declaration.[18]

It is scientifically incorrect to view the reaction that results in the creation of CERA as simply adding a peg molecule.[19] When chemical bonds are formed between two or more chemicals, the chemicals are not literally "attached" to each other, that term is used figuratively.[20] Rather in a chemical reaction, chemical bonds are broken, atoms removed and new bonds are formed to create new molecules. In the case of the reaction that forms CERA, this reaction results in the *substitution* of a hydrogen atom for an amide group and series of ethylene oxide residues. The reaction is depicted below:

---

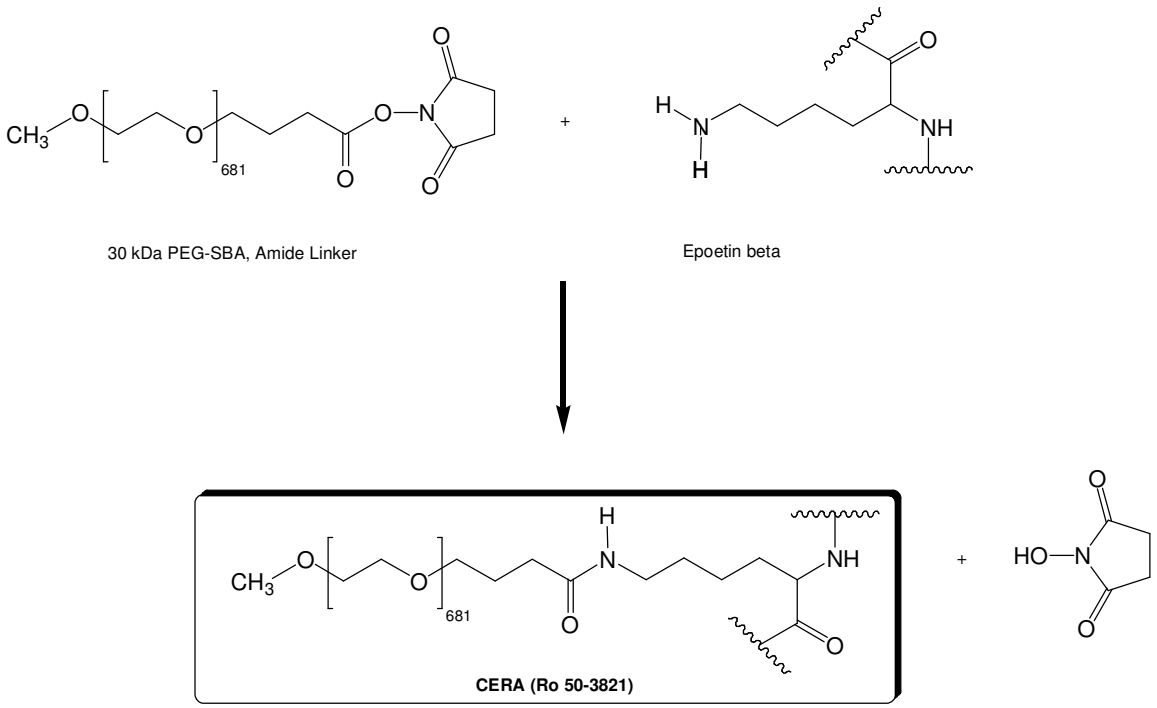
[16] Declaration of Keith E. Toms in Support of Defendants' Opposition to Amgen's Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6 ("Toms Decl. II"), Ex. 287, Alton Meister, BIOCHEMISTRY OF THE AMINO ACIDS, Preface and Chapter III (Docket No. 593).

[17] Toms Decl. I, Ex.C at p. 41 (Docket No. 637)

[18] Klibanov Decl. ¶¶ 47-48. (Docket No. 610).

[19] Amgen Inc.'s Reply in Support of Its Motion for Summary Judgment on Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6 ("Amgen Reply") at 6 (Docket No. 664).

[20] *See*, *e.g.*, Klibanov Decl. at ¶¶ 37-50 (Docket No. 610).



The *Lilly* case is instructive on this point. Although the product that the court in *Lilly* evaluated for material change involved stepwise substitutions, it recognized that a new "compound 7" was formed by a *single* substitution on "compound 6."[21] In CERA, the loss of a hydrogen atom and substitution with another group of atoms takes it outside the literal scope of "human erythropoietin" as defined by the Court.[22]

Amgen argues that "the lysine residue does not disappear."[23] Amgen's position is apparently "once a lysine always a lysine." In effect, Amgen is asking this Court to focus on the starting material that Roche uses. Claim 1 of the '422 patent however is a *product* claim. The

[21] *Eli Lilly & Co. v. American Cyanamid Co.*, 82 F.3d 1568, 1570 (Fed. Cir. 1996).

[22] Amgen completely mischaracterizes the evidence in *Lilly*. In fact, Lilly presented new scientific evidence in subsequent proceedings demonstrating that Compound 6 did in fact exhibit antibiotic activity. *Eli Lilly & Co. v. American Cynamid Co*., 66 F. Supp. 2d 924, 931 (S.D. Ind. 1999). The Court rejected Lilly's position that the only meaningful difference for 271(g) purposes is a difference in basic utility, finding that the presence of antibiotic activity in compound 6 insufficient to overcome or eliminate significant differences between compound 6 and ceflacor's chemical structures and properties. Additionally, the court acknowledged that the fact that ceflacor could be administered orally was an important difference as compared to compound 6, despite antibiotic similarities. *Id*. at 931-932.

[23] Amgen Reply at 6 (Docket No. 664).

starting materials are irrelevant to the infringement analysis. In short, disregarding the changed amino acid in CERA, is not only incorrect as a matter of law, it flies in the face of established chemical principles as articulated by the experts in the field and Amgen's own expert.

Moreover, even if in spite of the altered amino acid residue, CERA is determined to fall within the meaning of" "human erythropoietin" there remains additional significant factual dispute. Claim 1 of the '422 patent requires the presence of a "therapeutically effective amount of human erythropoietin." Amgen has provided no evidence whatsoever that the bare amino acid sequence of CERA, i.e. with missing hydrogen from lysine, has any therapeutic effect. In fact, as discussed below, Amgen's assertions made in the context of prosecuting the Lin patents indicate that the bare amino acid sequence, without glycosylation, would have *no* therapeutic effect.

In addition, claim 1 of the '422 patent requires that the claimed human erythropoietin be "purified from mammalian host cells grown in culture." The Court has defined this phrase to mean "obtained in substantially homogenous form from the mammalian cells…"[24] As hypothesized by Amgen's expert Dr. Lodish, CERA is not "substantially homogenous." Dr. Lodish testified regarding the composition of CERA as follows:

Q. Why is the binding affinity of CERA different than EPO?

...

A. I have several hypotheses. I will offer you one.

Q. Can you offer them all to me?

A. Well, let's go through one at a time.

Q. Okay.

[24] Markman Order at 19 (Docket No. 613).

> A. The first hypothesis is, **CERA is a mixture of 90 percent dead protein and 10 percent functional protein**. That is, the simplest explanation of what happens after PEGylation is, you kill, in some unknown way, roughly 90 percent of the EPO molecules. They're dead.[25]

Apparently in Dr. Lodish's view, CERA is not "substantially homogenous" but rather, is a mixture of 90% "dead" molecules and 10% active molecules.

III. PEGYLATION IS NOT ANALOGOUS TO THE ATTACHMENT OF CARBOHYDRATES TO EPO

A. Glycosylation is an integral property of human erythropoietin

Amgen asserts that pegylation is similar to the "attachment of carbohydrates" to EPO. This argument is not supported by the Court's claim construction, intrinsic evidence, or scientific texts. The glycosylation referred to in the specification is the result of post translational modifications by a cell whereas pegylation creates "non-protein" amino acid residues, as discussed above. As illustrated in Figure 6 of the specification, the only potential substitutions of the amino acid sequence are through natural glycosylation at specific asparagine residues.[26] Even if glycosylation is improperly viewed as being an "add-on" to human erythropoietin, Lin's disclosure of this natural process provides no support for synthetic chemical modifications such as pegylation.

The specification and prosecution history of the Lin patents further contradict Amgen's assertion. Reference in the specification to "polypeptides of the invention" are not describing human erythropoietin.[27] "Polypeptides of the invention" is indisputably broader than "human erythropoietin" as ultimately claimed in the '422 patent. For example, the specification indicates

---

[25] Toms Decl, III Ex. C at 123:19-124:12 (emphasis added).

[26] These residues were incorrectly referred to as "arginine" residues in Roche's Opposition. Roche Opp. at 5 (Docket No. 588).

[27] Toms Decl. II, Ex. 44 at col.10 l.9-15; 28-33 (Docket No. 593).

that such polypeptides include: "polypeptide products having part or all of the primary structural conformation (i.e., continuous sequence of amino acid residues) and one or more of the biological properties ...of naturally occurring erythropoietin...."[28] Such polypeptides are disclosed to further include "those having a primary structural conformation sufficiently duplicative of that of a naturally occurring erythropoietin..."[29] The only place the patent discusses "human erythropoietin" the glycosylation is expressly acknowledged.[30] Consistent with this, Amgen has repeatedly taken the position that glycosylation is an integral part of human erythropoietin. In prosecuting the application leading to the '933 patent, Amgen stated:

> "**At the time of the invention, the art knew that erythropoietin isolated from urine was a glycoprotein** and that treatment to remove its carbohydrate would destroy in vivo biological activity. Applicant was the first to provide for a glycoprotein which is both different from previously isolated urinary erythropoietin in its glycosylation and yet sufficiently like the natural product (previously isolated in the art) in terms of its glycosylation to allow it to fill the long-felt need (unsatisfiable by urinary isolates) for lite-sustaining human therapeutic agents for, e.g., the anemia associated with dialysis in renal failure patients."[31]

Similarly, during the prosecution of a parent application that gave rise to the '422 patent, Amgen argued:

> Unlike other human glycoproteins such as the interferons and Interleukin-2, human erythropoietin was conspicuously known to be an obligate glycoprotein and no hope at all existed for isolating in vivo active material from recombinant host cells unless, at a minimum, both the issues of required polypeptide sequence and of required glycosylation could be successfully attended to.[32]

Amgen's efforts to distinguish *Dow* are unavailing. The Lin specification cannot be read to support any and all substitutions of the amino acid side chains of human erythropoietin, based

[28] *Id.* at col.10 l.9-15 (Docket No. 593).

[29] *Id.* at col.10 l.35-37 (Docket No. 593).

[30] *Id.* at col.10 l.34-41 (Docket No. 593).

[31] Toms Decl. III, Ex. B (emphasis added).

[32] Toms Decl. II, Ex. 16 at 10 (emphasis in original) (Docket No. 593).

on the court's reasoning in *Dow*. The Lin specification expressly disclosed substitutions at specific amino acid residues and not others. Thus at best, Lin defined the human erythropoietin amino acid sequence with variation in residues at only these positions. A person of skill in the art would recognize that all other residues are defined as specific residues and not variable with substitution.[33]

Under Amgen's reasoning, "human erythropoietin" as claimed may "add-on" amino acids at either end of the sequence, as long someplace embedded in the sequence is series of 165 amino acids that correspond to human erythropoietin. Amgen's position is untenable because such a reading creates an infinite genus of structures. Moreover, as discussed in Roche's opposition papers, the Patent Office and Courts have repeatedly rejected Amgen's asserted right to lay claim to "polypeptides sufficiently duplicative" of EPO.[34]

As to the purported disclosure of adding "radioactive labels" to EPO, Amgen's own expert, Dr. Goldwasser apparently disagrees with Amgen's view that such a reaction would simply be an add-on to EPO.[35] Covalent attachment of iodine results in a molecule that is not human erythropoietin and the patent specification does not state otherwise.

IV. CERA IS NOT "THE GLYCOPROTEIN..PRODUCED IN A CELL AND RECOVERED FROM THE CELL CULTURE" AS REQUIRED BY THE '933 CLAIMS

Even if "human erythropoietin" as used in '422 claim 1 allows for an infinite number of "additions" as asserted by Amgen, the Court's interpretation of "non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence

[33] Klibanov Decl. ¶¶ 82-83 (Docket No. 610).

[34] Roche Opp. at 7 (Docket No. 588); Roche's Rule 56.1 Statement of Material Facts in Support of Defendants' Opposition to Amgen's Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6 ("Roche's Separate Statement") ¶¶ 141-146 (Docket No. 607).

[35] Dr. Goldwasser testified that a iodinated molecule has no biological activity. Toms Decl. II, Ex. 117 at 178 (Docket No. 593).

encoding human erythropoietin" does not. The Court has defined the claimed product as "a non-naturally occurring glycoprotein product of the expression in a mammalian host cell," finding that expression "means that the glycoprotein was produced in a cell and recovered from the cell culture."[36] Because the '933 claims are product-by-process claims, it is the cellular process that defines the claimed structure.[37] The CERA structure does not satisfy that requirement under the Court's construction; the structure of CERA is one that cannot be produced in a cell and isolated from a cell. Amgen argues that "nothing in claim 3 excludes the presence or absence of additional structures like peg to the claimed 'non-naturally occurring glycoprotein product'."[38] Yet, the Court's claim construction clarifying the meaning of "expression" does precisely that. The synthetic amino acid residues found in CERA are not and indeed cannot be, produced or recovered from the cell culture. Similarly, the product of the process of claim 6 of the '698 patent is a glycosylated erythropoietin polypeptide expressed by vertebrate cells. A molecule containing synthetic amino acids is not the product of the patented process. The Court pointed out that the question of material change is properly for the trier of fact.[39]

V. CONCLUSION

Based on the foregoing, Roche requests that Amgen's motion for summary judgment of infringement of '422 claim 1, '933 claim 3 and '698 claim 6 be denied.

---

[36] Markman Order at 32 (Docket No. 613).

[37] Toms Decl. II, Ex. 2 at 4 (Docket No. 593); Roche Opp. at 11 n. 63 (Docket No. 588); *Tropix v. Lumigen, Inc.*, 851 F. Supp. 25 (D. Mass. 1994).

[38] Amgen Reply at 12 (Docket No. 664).

[39] Markman Order at 28 (Docket No. 613).

Dated: July 13, 2007
Boston, Massachusetts

Respectfully submitted,

F. HOFFMANN-LA ROCHE LTD,
ROCHE DIAGNOSTICS GMBH, and
HOFFMANN-LA ROCHE INC.

By their Attorneys

/s/ Keith E. Toms
Lee Carl Bromberg (BBO# 058480)
Timothy M. Murphy (BBO# 551926)
Julia Huston (BBO# 562160)
Keith E. Toms (BBO# 663369)
Nicole A. Rizzo (BBO# 663853)
BROMBERG & SUNSTEIN LLP
125 Summer Street
Boston, MA 02110
Tel. (617) 443-9292
@bromsun.com

Leora Ben-Ami (*pro hac vice*)
Mark S. Popofsky *(pro hac vice)*
Patricia A. Carson (*pro hac vice*)
Thomas F. Fleming (*pro hac vice*)
Howard S. Suh (*pro hac vice*)
Christopher T. Jagoe (*pro hac vice*)
KAYE SCHOLER LLP
425 Park Avenue
New York, New York 10022
Tel. (212) 836-8000

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 (NEF) and paper copies will be sent to those indicated as non registered participants on the above date.

/s/ Keith E. Toms
Keith E. Toms

03099/00501 704282.1