IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

AMGEN, INC., Plaintiff, v. F. HOFFMANN-LA ROCHE, LTD, ROCHE DIAGNOSTICS GMBH, and HOFFMANN-LA ROCHE INC., Defendants.	Civil Action No. 05-12237 WGY U.S. District Judge Young

DEFENDANTS' OPPOSITION TO AMGEN'S MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT OF '422 CLAIM 1, '933 CLAIM 3, AND '698 CLAIM 6

Contains Roche Restricted Access Confidential BLA/IND Information Subject to Protective Order

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I. INTRODUCTION AND STATEMENT OF FACTS

Amgen's motion requires this Court to find that each and every element of the properly construed claims is met by the accused product or process.[1] Rather than tackle infringement on an element by element basis, Amgen obfuscates the multiple fact issues raised by its motion by collapsing the claims at issue (alternatively directed to a pharmaceutical composition, a product produced by a claimed process and a process) to a single claim element—"human EPO." It is Roche's position that:

> (i) CERA is not human erythropoietin and Roche is not intending to import or sell any product that contains or comprises human erythropoietin.[2]
>
> (ii) CERA is substantially different chemically from human EPO, with very different chemical properties including, for example, twice the molecular weight and size when compared to human EPO.[3]
>
> (iii) CERA is substantially different functionally from human EPO, binding 30 to 50 times less efficiently to the EPO receptor and exhibiting greater potency, longer circulating half-life and greater stability allowing doctors to administer the drug far less frequently as compared to currently available EPO drugs.[4]
>
> (iv) Amgen is not entitled to lay claim to synthetic molecules including polypeptides, merely because they "act like EPO."[5]

The active ingredient of MIRCERA, CERA, is manufactured in Germany, through an irreversible chemical reaction of epoetin beta (purified through a complex process from crude material obtained from a proprietary cell line created by Roche in 1993) and a synthetic

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[1] *See Mass. Inst. of Tech. v. Lockheed Martin Global Telecomms., Inc.*, 251 F. Supp. 2d 1006, 1010 (D. Mass. 2003) ("To support a finding of patent infringement, the accused device or method must embody each and every element of a claim, either literally or under the doctrine of equivalents.").

[2] All citations in this brief are to 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") ¶ 52-78, 106-168. In citing to specific paragraphs of Roche's Separate Statement, Roche incorporates by reference the expert declaration paragraphs and all exhibits cited to support the specific paragraphs of Roche's Separate Statement.

[3] *Id.* ¶¶ 52-78.

[4] *Id.* ¶¶ 79-105.

[5] *Id.* ¶¶ 107-146, 169-176.

methoxy-polyethylene glycol reagent. Amgen admits that CERA contains chemically substituted amino acid residues as compared to human EPO.[6] In *Eli Lilly & Co. v. American Cyanamid Co.*, the Federal Circuit found that a chemical substitution is a change that results in a new compound.[7] Applying this same reasoning here, in addition to a number of other reasons detailed herein, CERA cannot literally infringe the asserted claims.

CERA is a stable chemical entity with markedly different chemical and physical properties when compared to currently available EPO drugs.[8] As Amgen's expert Dr. Benet succinctly stated regarding CERA, "[I]t's a different chemical."[9] These differences allow MIRCERA to be administered as infrequently as once a month as compared to two to three times weekly for Amgen's EPOGEN®.[10] As discussed herein and in the accompanying Declarations by Drs. Cords, Jorgensen, Klibanov and Longmore and Mr. Adelman, numerous genuine issues of material fact are in dispute, precluding grant of Amgen's summary judgment motion.

II. ARGUMENT

A. ROCHE'S MIRCERA DOES NOT MEET THE LIMITATIONS OF THE '422 PATENT CLAIM 1

1. The Only Therapeutically Effective Ingredient In MIRCERA Is CERA, Not Human Erythropoietin

A pharmaceutical composition, according to claim 1 of the '422 patent, must have: "human erythropoietin"; "purified from mammalian cells grown in culture";[11] present in a "therapeutically effective amount"; with either a separate "pharmaceutically acceptable diluent,

[6] *See* Amgen Inc.'s Mem. in Supp. of Its Mot. for Summ. J. of Infringement of '422 Claim 1, '933 Claim 3, & '698 Claim 6 ("Amgen's Mem.") at 18.

[7] 82 F.3d 1568, 1573 (Fed. Cir. 1996) .

[8] Roche's Separate Statement ¶¶ 52-105.

[9] *Id.* ¶ 55.

[10] *Id.* ¶ 100.

[11] Roche's position is that the language "purified from mammalian cells grown in culture" is a source limitation that does not impart any structure limitation to the term human EPO that would confer patentability over prior art human EPO.

adjuvant or carrier."[12] The only therapeutically effective ingredient in MIRCERA is CERA.[13] There can be no genuine dispute that CERA, with its unique chemical structure and properties, is not human EPO.[14] Amgen therefore improperly focuses its infringement analysis on the epoetin beta starting material which it alleges is human erythropoietin "contained in" CERA.

The Court, at Amgen's urging, has construed "human erythropoietin" to mean "[a] protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine."[15] In asserting that this claim element is met, Amgen merely concludes that "[e]poetin beta is identical [to the] amino acid sequence first disclosed and produced by Dr. Lin in Example 10 of his patent."[16]

At the outset, Amgen's analysis is misplaced. The patent does not disclose the full sequence of the protein produced in Example 10,[17] and it remains an open question.[18] Even if the Example 10 sequence was known, the Federal Circuit has "repeatedly said, it is error for a court to compare in its infringement analysis the accused product or process with the patentee's commercial embodiment or other version of the product or process; the only proper comparison is with the claims of the patent."[19]

"Human EPO" as defined by Dr. Lin has the 166 specific amino acid residues of Fig. 6

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[12] Roche has filed a separate motion for non-infringement based on this claim limitation, attached as Ex. 291 and incorporated by reference herein. All Exhibits cited herein are attached to the 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.

[13] Roche's Separate Statement ¶¶ 156-161.

[14] *Id.* ¶¶ 147-168.

[15] Ex. 233, Markman Tr. 27:8-10; *see id.* at 39:7-9 (adopting Amgen's construction).

[16] Amgen's Mem. 4.

[17] Roche's Separate Statement ¶¶ 119-139.

[18] Amgen's own expert, Dr. Harvey Lodish, has pointed out in his report that not all mammalian cells secrete the 165 amino acid fragment of human EPO. He points to a 1988 reference to support his opinion which shows that a hamster cell line comprising a gene for human EPO secretes the uncleaved mature protein of 166 amino acid residues. *See* Ex. 295 ¶ 25.

[19] *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1423 (Fed. Cir. 1994).

and has one altered residue as compared to EPO from human urine.[20] Based on this information Amgen persuaded the Patent Office to issue seven separate patents on Dr. Lin's single invention, arguing that it was Dr. Lin "who first developed knowledge of the full amino acid sequence of erythropoietin."[21] These structural elements of human EPO (166 amino acids and the altered residue) defined by Lin are not met by CERA or epoetin beta.[22] Moreover, even if epoetin beta is considered to be "human erythropoietin," Amgen's motion still fails.[23]

a. CERA Is Structurally Distinct From Human EPO

Amgen mischaracterizes the irreversible chemical synthesis that produces CERA as merely the addition of a further element in a misguided attempt to align this case with prior court decisions dealing with mechanical inventions. First, as admitted by Amgen's own experts, this is *not* a situation involving an added element. All of the amino acid residues that define human EPO are not found in CERA because hydrogen atoms have been chemically substituted on certain amino acids to create new, synthetic amino acid residues.[24] Moreover, chemical molecules are not mechanical devices. A molecule by definition does not "contain" other molecules. The unique situation posed by chemical inventions has been recognized by the courts[25] including *Lilly*. In *Lilly*, the Federal Circuit found that substitution of a hydroxy group

[20] Roche's Separate Statement ¶¶ 123-124.

[21] Ex. 10 at 8.

[22] Roche's Separate Statement ¶¶ 53-60, 106-118, 162-168.

[23] If the Court were to accept Amgen's interpretation of the construction, the claim would cover not only sequences that Dr. Lin described but also concatenated sequences, fragments of sequences, and all derivatives of the human EPO sequence. Under this view, such a claim has already been invalidated. *See Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1214 (Fed. Cir. 1991) (citing *In re Fisher*, 427 F.2d 833, 836, 839 (C.C.P.A. 1970)); *see also* Ex. 292 at 3.

[24] Roche's Separate Statement ¶ 64. Amgen acknowledges that at best "human erythropoietin contemplated by Amgen's claims" includes only "natural allelic variants." Amgen Inc.'s Opposition to Roche's Mot. For Summ. J. That Claim 1 Of The '422 Patent Is Invalid Under 35 U.S.C. § 112, at 4.

[25] *See Exxon Chem. Patents, Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1557-58 (Fed. Cir. 1995) ("[A claim to a chemical product is] not merely a recipe for making whatever product results from the use of the recipe ingredients. This conclusion respects that which is claimed, namely a chemical composition."). If a claim to a chemical composition

with a chlorine group, resulted in a new compound.[26] Similarly, the chemical reaction that produces CERA, which replaces a hydrogen atom on one of the amino acid residues that define human EPO with literally hundreds of carbon atoms and oxygen atoms is not a mere "addition," but rather, a "substitution" that creates a new compound.[27]

In a decision more applicable to this case than *A.B. Dick & Co. v. Burroughs Corp.*[28] cited by Amgen, the Federal Circuit affirmed summary judgment of non-infringement, finding that the term "alkoxy" used in the patent claim at issue, without reference to possible chemical substitutions, "must be read restrictively to exclude substituted variations."[29] As support for its decision, the court cited, *inter alia*, patentees' failure to indicate substituents for the alkoxy group while providing for substitutions of other chemical groups.[30] The accused products, which substituted hydrogen in the alkoxy group, were therefore deemed non-infringing.[31] Similarly, the Lin specification does not disclose the substitution of hydrogen from human EPO's lysine residues or N-terminal residues in any context, let alone to create new, synthetic amino acids. The only potential substitutions discussed are through natural glycosylation at specific arginine residues in the EPO molecule.

Amgen admits the amino acid residues in CERA are changed but seeks to minimize this change, asserting: *"Aside from the displacement of a single hydrogen atom . . . EPO's structure*

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does not cover products formed by reaction of the recited ingredients, it certainly should not cover reaction products of unrecited ingredients.

[26] *Lilly*, 82 F.3d at 1570.

[27] Roche's Separate Statement ¶¶ 53, 66, 69.

[28] 713 F.2d 700 (Fed. Cir. 1983).

[29] *Dow Agrosciences LLC v. Crompton Corp.*, 381 F. Supp. 2d 826, 833 (S.D. Ind. 2005), *aff'd*, 182 Fed. App'x 978 (Fed. Cir. 2006).

[30] *Id.* at 835.

[31] *Id.* at 839.

is otherwise unaffected."[32] This change, which results in the formation of a strong chemical bond and a new molecule with an altered charge and structure, cannot be dismissed as inconsequential. Even if inconsequential, this change still takes CERA out of literal infringement since every claim element must be met. Even Amgen's experts agree that the bond is essentially unbreakable and that the chemical reaction that results in CERA cannot be reversed to recover human EPO.[33] Contrary to Amgen's misleading outtakes from Roche's regulatory filings, the changes to the amino acid sequence of its starting epoetin beta material are fully disclosed. Likewise, Roche has provided the FDA with detailed information regarding glycosylation alterations to the epoetin beta starting material.[34]

As explained in Dr. Klibanov's Declaration, the statements that Amgen selectively plucks from Roche's regulatory filings do not support Amgen's infringement positions.[35] Those statements must be read in context and from the perspective of the FDA specialists to whom they are directed. In fact, just a few lines below the statements regarding the amino acid sequence of epoetin beta cited by Amgen, Roche explains precisely how the amino acids within the starting material sequence are changed by the reaction that creates CERA.[36]

b. CERA Is Functionally Distinct From Human EPO

Amgen's own experts have repeatedly acknowledged that "the function of EPO is derived

[32] Amgen's Mem. 18 (emphasis added); *see* Roche's Separate Statement ¶ 78 (listing other admissions by Amgen that CERA and EPO are structurally distinct substances).

[33] Roche's Separate Statement ¶ 154.

[34] Similarly, the snippets of Rule 30(b)(6) testimony must be viewed in context, taking into account any document that the witness may have been considering at the time. Moreover, 30(b)(6) testimony is not a judicial admission and such testimony provides no adequate basis to make a summary judgment determination. *See Indus. Hard Chrome Ltd. v. Hetran, Inc.*, 92 F. Supp. 2d 786, 791 (N.D. Ill. 2000) ("[Rule 30(b)(6)] testimony is not a judicial admission that ultimately decides an issue."); *accord* 8A Alan Wright & Arthur R. Miller, *Federal Practice and Procedure* § 2103 (2d ed. 1987).

[35] Klibanov Decl. ¶¶ 105, 108; Ex. 152; Roche's Separate Statement ¶ 57.

[36] Ex. 152; Roche's Separate Statement ¶ 57.

from its three-dimensional structure."[37] While the complexity of the CERA molecule renders actual visualization of CERA's three dimensional structure impossible,[38] differences in structure as compared to human EPO can be inferred from CERA's different functional activity.[39] While CERA does bind to the EPO receptor, that fact provides little or no information as to conformation of the amino acid residues in CERA, nor does it indicate that CERA is functionally the same as human EPO. Amgen's assertions to the contrary fail on a number of grounds.

First, "human EPO," if defined purely as an amino acid sequence, would cover material without three-dimensional structure and devoid of erythropoietin activity.[40]

In addition, the tortured prosecution and litigation history of these patents confirms that Amgen cannot lay claim to all molecules that bind to the EPO receptor.[41] As detailed in the accompanying Declaration by Mr. Adelman, the Patent Office repeatedly rejected Amgen's efforts to obtain claims to synthetic EPO molecules and fragments.[42] The Federal Circuit similarly held that Amgen is not entitled to claim all molecules with "EPO-like" activity.[43] Consistent with this is Amgen's position that its second generation erythropoiesis stimulating agent, Aranesp®, which Amgen admits activates the EPO receptor, does *not* fall within the scope of these claims.[44]

Binding cannot properly be viewed as the function of only a few amino acid residues. It

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[37] *Id.* ¶ 111.

[38] *Id.* ¶ 116.

[39] *Id.* ¶¶ 94-96, 117.

[40] *Id.* ¶¶ 120-125. Moreover, if human EPO is only defined by an amino acid sequence, surely Amgen cannot maintain its argument that its claims are patentable over erythropoietin isolated from human urine and used in prior art clinical trials.

[41] *Id.* ¶¶ 141-146.

[42] *Id.* ¶ 142.

[43] *Chugai*, 927 F.2d at 1214.

[44] Roche's Separate Statement ¶ 145.

is the overall structure and conformation of the entire molecule that dictates binding.[45] CERA's very different binding kinetics at the EPO receptor are evidence of its different structure. By Dr. Lodish's own calculations, CERA binds the EPO receptor with *30-fold lower* affinity than EPO.[46] Significantly, the amide bond in CERA (not found in human EPO) that Amgen seeks to dismiss, interrupts a specific interaction believed to be important in the EPO/receptor interaction.[47]

The functional difference between CERA and EPO is confirmed by CERA's ability to function *in vivo* after deglycosylation. Amgen distinguished prior art during prosecution of the Lin patents by emphasizing that EPO is an *obligate glycoprotein*, *i.e.*, having no *in vivo* function without glycosylation.[48] CERA is *not* an "obligate glycoprotein."[49]

Finally, CERA has a significantly longer circulating half-life when administered to patients as compared to EPO. As acknowledged by Dr. Torchilin, the half-life of CERA is increased "approximately 15-20 fold longer."[50] This longer half-life allows patients treated with CERA to be dosed as infrequently as *once per month*, as compared to *two to three times weekly* for patients treated with Amgen's EPOGEN. The impact of this difference on the quality of a patient's life cannot be dismissed lightly.[51] Even Amgen's own expert conceded this fact.[52]

2. <u>CERA Is Not Purified From Mammalian Cells Grown In Culture</u>

Seeking to avoid prior art, Amgen now asserts that the human EPO of claim 1 is limited

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[45] *Id.* ¶ 117.

[46] *Id.* ¶ 97

[47] *Id.* ¶¶ 65-67.

[48] *Id.* ¶¶ 112-113.

[49] *Id.* ¶ 81.

[50] *Id.* ¶ 97.

[51] *Id.* ¶¶ 100-101, 104-105.

[52] *Id.* ¶ 100.

to structures that are obtainable from mammalian cells grown in culture. If Amgen is correct,[53] it must prove that the structure of CERA is obtainable from mammalian cells grown in culture. CERA is a chemically synthesized product, which Dr. Lodish admitted could not be made by mammalian cells. Thus, Amgen cannot in good faith allege that CERA satisfies this claim limitation.[54]

3. MIRCERA Does Not Contain A Diluent, Adjuvant Or Carrier

Under the proper interpretation announced by the Court, a product infringes only if it can be found to be "containing a diluent, adjuvant or carrier."[55] Dr. Lodish has already admitted that Roche formulates CERA into MIRCERA "by adding a diluent and carrier,"[56] so it can hardly be undisputed that MIRCERA contains only a single diluent.

B. '933 PATENT CLAIM 3 IS NOT INFRINGED

1. Amgen Has Not Proven That Epoetin Beta Has A Structure That Does Not Occur In Nature

Claim 3 of the '933 patent is only infringed by a product that is "non-naturally occurring"; the "glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin"; possessing "the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells."

This Court has defined the term "non-naturally occurring" to mean "not occurring in nature" and found that "[b]y including this limitation, [Amgen] meant to stand clear of the

[53] Roche does not agree that such a source limitation imparts structure or makes the claim patentable over structures that existed in the prior art. Nevertheless, even as a pure source limitation, Amgen must prove the limitation is met by CERA, which it cannot do.

[54] Amgen has pointed to no evidence that *any* epoetin beta starting material is present, let alone in a "therapeutically effective" amount as required by the claim. Ex. 227 ¶ 95.

[55] Ex. 233 at 77:1-3; *see also* Ex. 292 at 4-8.

[56] Roche's Separate Statement ¶ 160.

unpatentable, naturally occurring products."[57] To meet its burden on this claim element under its flawed "it's in there" analysis, Amgen must prove that epoetin beta is distinct from EPO occurring in nature. However, there is substantial evidence that Roche's epoetin beta starting material is structurally *indistinguishable* from naturally occurring EPO.[58]

Amgen's view that "non-naturally occurring" is merely a source limitation and imparts no structural limitation is at odds with the prosecution and litigation history of the '933 patent. During patent prosecution, Amgen introduced "non-naturally occurring" to "distinguish the subject matter claimed from all prior art references relating to erythropoietin isolates."[59] Thus, "non-naturally occurring" must impart structure to be effective in distinguishing prior art structures.

That "non-naturally occurring" cannot simply be a source limitation is illustrated by comparing the actual language with a hypothetical claim that removes only the phrase "non-naturally occurring," as shown on Appendix A. One of skill in the art would understand that the product produced by expressing an exogenous DNA sequence in a mammalian host cell is EPO from a non-natural source. Therefore, the hypothetical claim lacking "non-naturally occurring" would have precisely the same scope as '933 claim 3 if, as Amgen contends, this phrase simply requires a product that is not isolated from a natural source.

Simply put, Amgen's product claims read on the prior art if "non-naturally occurring" is not construed to impart structural limitations.[60] As such, to prove infringement, Amgen must prove that Roche's product does not have a structure that occurs in nature. However, assuming

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

[58] Roche's Separate Statement ¶ 150.

[59] Ex. 33 at 7.

[60] Any structural distinctions however rely on differences in glycosylation, which Amgen is collaterally estopped from arguing is definite. Roche has filed a separate motion for indefiniteness on this topic, attached as Ex. 292 and incorporated by reference herein.

arguendo Amgen's "it's in there" argument, the evidence shows that epoetin beta is structurally indistinguishable from structures occurring in nature.[61]

2. Epoetin Beta Is Not The Product Of The Expression Of A DNA Sequence Encoding Human Erythropoietin

To meet claim 3 of the '933 patent, CERA must be the "product of the expression . . . of a DNA sequence encoding erythropoietin." "Expression," defined in the '933 patent as the process of transcription and translation, takes place in the cell. CERA is chemically synthesized in a laboratory. Importantly, in invoking a product by process format for these claims, Amgen acknowledged that the product claimed could not "be precisely defined except by the process by which it is produced."[62] The molecular structure of CERA is not made by the recited process. Even under the most expansive reading of Amgen's product-by-process claim, Amgen must prove that CERA, "regardless of how produced, [has] the same material structural and functional characteristics"[63] as the product of expression in a mammalian host cell of DNA encoding human EPO.[64]

Nor does epoetin beta allegedly "contained in" CERA meet this claim limitation. The product of transcription and translation of an exogenous DNA sequence encoding EPO in a mammalian host cell is known to be a 166 amino acid product.[65] Epoetin beta has 165 amino acid residues and is only a fragment of the product of expression. Thus, considering only the amino acid sequence purportedly "contained in" CERA, this claim element is not met. Nor, as discussed above, is CERA an "obligate glycoprotein" as required by the claims. Further, Amgen has pointed to no evidence that the product of expression in Roche's cells possesses the claimed

[61] Roche's Separate Statement ¶ 150.

[62] Ex. 2 at 4.

[63] *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1580 (Fed. Cir. 1991).

[64] *Cf. id.* at 1583-84.

[65] Ex. 262.

in vivo biological activity.

C. ROCHE DOES NOT INFRINGE CLAIM 6 OF THE '698 PATENT UNDER 35 U.S.C. § 271(g)

To prove infringement, pursuant to 35 U.S.C. § 271(g), Amgen must show that Roche practices the claimed process outside of the United States and imports into the United States the product of the claimed process without the product being materially changed. Amgen fails in both respects. At most, Amgen raises fact questions unsuited for resolution on a motion for summary judgment.

1. Roche Does Not Practice The Process Of Claim 6

The product of claim 6 is obtained by growing vertebrate cells having the DNA of "the mature erythropoietin amino acid sequence of FIG. 6" and then "isolating" the glycosylated erythropoietin polypeptide "expressed by" those cells. The "isolating" step concludes the claimed process.[66]

Amgen has asserted that the claim term "isolating" means "nothing more than separating the expressed product from the cells,"[67] flatly denying that the step of "isolating" includes "purification."[68] Thus, at the Markman Hearing, the Court's working hypothesis was that the term "isolating said glycosylated erythropoietin polypeptide" means "separating said glycosylated erythropoietin polypeptide."[69] Hence, the product of the claim 6 process is the unpurified expression product separated from the cells.

In Roche's accused process, material is harvested (separated from the cells used to

[66] Ex. 233 at 89:13-16, 90:22-23.

[67] Ex. 71, Br. for the Senior Party Lin, Interference No. 102,097 at 48.

[68] *Id.*

[69] Ex. 233 at 97:22-98:1; *see id* at 93:23-94:2 (Amgen's rejected proposed construction for isolating to mean "recovering in pure form").

express the protein), as a "crude isolate."[70] Amgen cites no evidence at all that Roche's crude isolate—in contrast to purified epoetin beta—has "the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells" or that the isolated material contains the product "expressed" by the cells. Under the first requirement of § 271(g), the absence of any such showing is fatal to Amgen's infringement claim.

2. The Expression Product Is Subsequently Materially Changed In The Manufacture Of MIRCERA

Even assuming *arguendo* that Roche does practice the process of claim 6 of the '698 patent, Roche does not infringe under § 271(g) because the MIRCERA product that Roche imports into the United States is materially changed from the crude isolate that is the product of claim 6. After harvesting the crude isolate from cells, Roche subjects the material to a patented purification process, then reacts the purified epoetin beta with an activated polyethylene glycol reagent to manufacture CERA, and, finally, formulates CERA to make MIRCERA. Amgen "bears the burden [of proof] on the issue of material change" under § 271(g).[71]

Roche materially changes the crude isolate obtained from cells by performing a series of purification steps patented by Roche.[72] The patented purification process removes potentially harmful chemicals and converts "a therapeutically useless composition"—the crude isolate—"into a useful therapeutic product."[73] Absent this complex procedure, the chemical reaction to produce CERA would be impossible.[74]

Roche's patented process materially changes the composition of the product isolated

[70] Roche's Separate Statement ¶¶ 19-28.

[71] *Genentech, Inc. v. Boehringer Mannheim GmbH*, 47 F. Supp. 2d 91, 108 (D. Mass. 1999). *See* Roche's Separate Statement ¶¶ 26-28.

[72] Roche's Separate Statement ¶ 26.

[73] *Id.* ¶¶ 26, 28.

[74] *Id.* ¶ 28.

from cells. According to Dr. Lodish, "EPO produced by a single cell consists of a heterogeneous mixture of different isoforms" having anywhere from zero to 14 sialic acid residues and, as a result, different electrical charges.[75] Roche's purification method selects out predominantly 6 isoforms,"[76] which constitutes a material change to this product isolated from cells."[77]

The significance of the distinctions among the isoforms is indisputable. Indeed, Amgen has made much of the fact that the isoform composition of EPO impacts its *in vivo* biological activity. Amgen holds a U.S. patent which is based on the crucial relationship between the relative *in vivo* specific activity of erythropoietin and the presence of specific isoforms.[78]

Furthermore, during prosecution of the Lin patents, Amgen argued the importance of the isoform distribution in its commercial product to attempt to distinguish it from prior art.[79] Dr. Lodish acknowledges that "[i]soforms of EPO that are more highly sialylated . . . exhibit a longer half-life in the body, lower binding affinity to the EPO receptor, and greater biological activity than do isoforms . . . which are less sialylated."[80]

In short, a jury could reasonably conclude that Roche's patented purification process and selection for 6 of the 14 EPO isoforms materially changes the crude isolate product of the process of claim 6. In any event, as shown below, Roche makes a further material change to epoetin beta by chemically reacting it with an activated polythylene glycol ("PEG") to create CERA, the active ingredient in Roche's MIRCERA product.[81]

CERA differs structurally and functionally from the epoetin beta starting material. One

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[75] *Id.* ¶ 108, Response to Amgen Fact Nos. 4, 14.

[76] *Id.* ¶¶ 25-26, 168, Response to Amgen Fact Nos. 4, 8, 14-15.

[77] *Id.*, Response to Amgen Fact No. 14.

[78] *See* Ex. 46.

[79] Roche's Separate Statement ¶ 110 (citing Exs. 100, 267).

[80] *Id.* ¶ 110 (citing Ex. 227 ¶ 33).

[81] *Id.* ¶ 70, Response to Amgen Fact Nos. 21, 31.

or two hydrogen atoms are replaced by hundreds of atoms not present in epoetin beta.[82] The molecular weight of CERA is approximately 60 kDa in contrast with EPO which has a molecular weight of approximately 30 kDa;[83] the glycosylation of CERA is different from that of epoetin beta;[84] CERA has a hydrodynamic radius that is twice as large as that of epoetin beta;[85] and CERA is substantially more stable than epoetin beta, facilitating ease of formulation and allowing a greater shelf life.[86]

CERA possesses markedly different pharmacodynamic and pharmacokinetic properties as compared with EPO.[87] CERA (i) has a 30 to 50 fold lower binding affinity for the body's EPO receptor than does epoetin beta;[88] (ii) has a dramatically longer half-life than epoetin beta;[89] (iii) has a "greater potency . . . meaning that the same number of CERA molecules is capable of generating a greater cellular response";[90] and (iv) allows for substantially longer clinical dosing intervals.[91]

Faced with overwhelming evidence that any product produced by Amgen's patented process is materially changed,[92] Amgen responds by citing to cartoons allegedly depicting

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[82] *Id.* ¶ 66.

[83] *Id.* ¶¶ 70, 78.

[84] *Id.* ¶ 150.

[85] *Id.* ¶ 154.

[86] *See* Longmore Decl. ¶ 126.

[87] Roche's Separate Statement ¶¶ 79-97.

[88] *Id.* ¶¶ 93, 95, 97, Response to Amgen Fact No. 33.

[89] *Id.* ¶¶ 95, 97, 103.

[90] *Id.* ¶¶ 87, 89, 90.

[91] *Id.* ¶¶ 104-05. Thus, unlike the situation in *OKI America, Inc. v. Advanced Micro Devices, Inc.*, No. C 04-03171 CRB, 2006 U.S. Dist. LEXIS 73144 (N.D. Cal. Sept. 21, 2006), which Amgen cites, where the "changes [did] not impact the product of [the patented] process," *id.* at *45, the changes here were made to the glycosylated erythropoietin polypeptide which is the product of the claimed process. CERA is not glycosylated erythropoietin polypeptide nor contains glycosylated erythropoietin polypeptide.

[92] There is a final material change when CERA is formulated into MIRCERA via a multi-step process which includes the addition of 5 other chemical substances.

human EPO with an unaltered conformation, "contained in" CERA. Amgen's own experts have acknowledged that EPO function is inextricably tied to structure. As discussed in the accompanying Declaration by Dr. Jorgensen, CERA is too complex to visualize structurally using available techniques. Nonetheless, CERA's functional differences refute Amgen's position. In finding that there was a material change, this Court has pointed to the same sorts of differences between the imported product and the product of the patented process, such as CERA's different glycosylation, a longer half-life and easier administration.[93]

Amgen's reliance on the unpublished, non-precedential decision in *OKI* is misplaced. There, the evidence showed that the product of the process was unchanged.[94] Here, through purification, isoform selection and chemical synthesis, CERA is substantially changed from the product of the '698 claim. Moreover, in *Lilly*, the Federal Circuit has held that the proper comparison is between the product of the patent process and the imported product.[95] That decision supports a finding of material change here. *Lilly* concerned a claim to a method for making an intermediate compound that the defendants there used in making the antibiotic cefaclor which they, in turn, imported into the United States.[96] Both the intermediate and cefaclor had the same nucleus, but the intermediate had to be changed at three positions to create cefaclor.[97]

The Federal Circuit observed that § 271(g) "permits the importation of an item that is derived from a product made by a patented process as long as that product is 'materially

[93] *See Genentech*¸ 47 F. Supp. 2d at 113-16, 117-20.

[94] *OKI*, 2006 U.S. Dist. LEXIS 73144, at *44-45.

[95] 82 F.3d at 1573.

[96] *Id.* at 1569-70.

[97] *Id.* at 1570.

changed' in the course of its conversion into the imported item."[98] The court stated that the issue under § 271(g) is "the substantiality of the change between the product of the patented process and the product that is being imported."[99] Thus, according to the Federal Circuit, "[i]n the chemical context, a 'material' change in a compound is most naturally viewed as a significant change in the compound's structure and properties."[100] In denying a motion for a preliminary injunction, the court held that the product of the claimed process was "likely to be found to have been 'materially changed' in the process of its conversion into cefaclor" such that the importation or sale of the final product was "not likely to be held to infringe."[101]

Here, there is ample probative evidence that the crude isolate produced by the process of claim 6 is materially changed in the process of making MIRCERA. Indeed, CERA, the active ingredient in MIRCERA, is structurally and functionally very different from the crude isolate of claim 6 and even from the later purified epoetin beta.[102] At most, therefore, the *Lilly* case proves that the issue of whether Roche's crude isolate—if it even is a product of the process of claim 6—is materially changed in making Roche's MIRCERA product, is a fact question which cannot be resolved on a motion for summary judgment.[103]

Amgen argues that the pegylation reaction that yields CERA is a "conventional process" which, therefore, does not effect a material change. However, in *Lilly*, the Federal Circuit concluded that there likely was a material change even though steps involved in changing the

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[98] *Id.* at 1572.

[99] *Id.* at 1573.

[100] *Id.*

[101] *Id.* at 1578.

[102] In fact, the *Lilly* court rejected the argument, advanced by Amgen here, that only a change to the core nucleus of a compound can constitute a material change. *Id.* at 1573.

[103] Significantly, here, as in *Lilly*, "there is at least one known commercial method for making" MIRCERA "that does not use the patented process." *Id.* at 1578; s*ee* Roche's Separate Statement ¶¶ 23-28.

intermediate to the final cefaclor product were all "relatively routine chemical reactions."[104] Following the denial of preliminary injunction, the court held on summary judgment that a material change had occurred, despite evidence by the plaintiff showing that the product of the patented process had antibiotic utility like the imported product.[105]

Pegylation is not the only material change that occurs in the process of using the crude isolate to make MIRCERA. Furthermore, it makes no sense that the question of whether the product of a chemical reaction is materially different from the starting material would turn on whether the reaction is conventional rather than on the structural and functional differences between the molecules. If material change turned on whether or not the subsequent process used were routine or conventional, the first product made using a novel process would be non-infringing and then as time passed and the procedure became routine it would then become an infringing process.

Finally, there is significant probative evidence, contrary to Amgen's position, that the pegylation of epoetin beta was far from routine—particularly at the time of the priority date of the '698 patent in the early 1980s. As of 1992, the experience with pegylation technology was limited and rather unsatisfactory. In particular, pegylation procedures employed during the late 1970s and 1980s were plagued by difficulties, including restriction to PEGs with low molecular weights, relatively unstable activated PEGs and lack of selectivity in protein modification. This gave rise to "impure and heterogeneous substances difficult to purify."[106] "[T]he reactions of molecules with activated PEG reagents [are] complex chemical reaction[s], requiring the evaluation of numerous variables and yielding new molecules with unpredictable physiochemical

[104] 82 F.3d at 1573.

[105] *Id.* at 1577-78.

[106] Roche's Separate Statement ¶ 33.

and biological properties. It is by no means predictable or trivial to create a useful therapeutic through chemical reactions with PEG reagents."[107] "[S]uccessful pegylation greatly depends on numerous factors including the protein's concentration and primary structure, as well as the activated PEG reagent's concentration, molecular weight, distribution, activation site, and structure; and also reaction time, temperature, pH and ionic strength."[108] Amgen's inventor, Dr. Lin, confirmed the unpredictability of pegylation.[109]

Amgen's view that pegylation is routine is also at odds with the fact that (i) Roche's MIRCERA is the product of nearly a decade of research and experimentation toward the development of a new erythropoietic agent; and (ii) between 1985 and approximately 2000, Amgen attempted unsuccessfully to develop a new product by reacting PEG and EPO.[110] Roche's undertaking was by no means trivial.[111]

In sum, even if Roche did practice the process of claim 6, which Amgen has not shown, as it must on this motion, no reasonable jury could conclude that CERA is materially changed from the crude isolate containing epoetin beta or even from purified epoetin beta.

D. REVERSE DOCTRINE OF EQUIVALENTS

If Amgen's claims are improperly considered to literally read on CERA, the facts here dictate application of the reverse doctrine of equivalents and a finding of non-infringement.[112]

Well over two decades ago, Amgen narrowly edged out others attempting to clone the

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[107] *Id.* ¶¶ 29-43, Response to Amgen Fact Nos. 39-40.

[108] *Id.* ¶ 31.

[109] *Id.* ¶ 39.

[110] *Id.* ¶¶ 40-41, 44-51.

[111] *Id.* ¶¶ 29-51.

[112] Reverse doctrine of equivalents is an equitable doctrine, but nevertheless requires findings of fact that preclude summary judgment. Roche has patents that cover CERA and processes used to manufacture CERA, and since all factual inferences must be made in favor of the non-movant, the existence of Roche's patent and CERA dictates that summary judgment of no reverse doctrine of equivalents be denied.

human gene encoding EPO. The '008 patent which expired in 2004 gave Amgen a full 17 years of patent protection for its accomplishment. Through a series of maneuvers that even Amgen's CEO is at a loss to explain, Amgen convinced the U.S. Patent Office to issue six more patents, all related to that single cloning success, resulting in a combined term of nearly 30 years.[113] One fact is clear: Amgen is not entitled to lay claim on any molecule that acts like EPO. Yet, if these patents cover CERA, Amgen will be given rights over a molecule with activity that is vastly *improved* over EPO. While the erythropoiesis stimulating drugs currently available to patients in the United States (all of which are made by Amgen, albeit sold by its licensee Johnson & Johnson) are useful drugs, by virtue of its long half-life, CERA provides significant medical benefits to patients. Roche's new drug, soon to be available to patients outside the U.S., should likewise be available to patients in need in this country.

III. 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.

[113] When asked how it could still have patent coverage, Kevin Sharer, Amgen's chief executive, replied: "It's an obvious question; I've had it myself." Ex. 290, Andrew Pollack, *A Biotech Battle Royal: Rivals Laying Siege to Amgen's Near Monopoly in Anemia Drugs*, N.Y. Times, Dec. 23, 2005, at C1; *see* Ex. 289, Steven Harr, M.D. et al., *Amgen: Some Setbacks for Competitors in EU*, Morgan Stanley Equity Research N. Am., Feb. 23, 2006, at 1 ("[W]e view Amgen's position in the erythropoietin market as the second best monopoly of our generation (behind Microsoft's Windows).").

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Respectfully submitted,

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/s/ Keith E. Toms
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APPENDIX A

"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 said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocyte and red blood cells."	"A glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocyte and red blood cells."