UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

AMGEN'S RESPONSE TO ROCHE'S RULE 56.1 STATEMENT OF UNDISPUTED MATERIAL FACTS IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT THAT AMGEN IS ESTOPPED FROM ASSERTING INFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS OF THE ASSERTED CLAIMS OF THE '933 AND '422 PATENTS

Amgen disputes the following statements in Roche's Rule 56.1 Statement of Undisputed Facts In Support Of Defendants' Motion For Summary Judgment That Amgen Is Estopped From Asserting Infringement Under The Doctrine Of Equivalents Of The Asserted Claims Of The '933 And '422 Patents:

1. Responding to paragraph 1, the Court's construction of "human erythropoietin" is also found in the Court's July 3, 2007 Memorandum and Order at p.15 (Docket No. 613).

2. Responding to paragraph 4, contrary to Roche's characterization, claims 9 and 12 of the '933 patent do not use the term, "active ingredient."

3. Responding to paragraph 6, contrary to the implication of Roche's statement, the '774 application was not a continuation of both the '874 application and the '178 application.

Rather, the '774 application was a continuation of the '874 application, which in turn was a continuation of the '178 application.

4. Responding to and clarifying paragraph 7, application claims 1, 7, 41 and 48 were included in the '178 and '874 applications.

5. Responding to paragraph 11, Roche has misquoted the claim 41 as amended on 12/1/88, and has failed to note that the emphasis was added and is not in the original. The amended claim 41 reads:

> 41. A glycoprotein product having a primary structural conformation and glycosylation sufficiently duplicative of that of a naturally occurring human erythropoietin to allow possession of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin.[1]

6. Responding to paragraph 12, Roche fails to note that new claim 67 was a (combination) of claims 41 and 61. Claim 61, which included the "product of the process" limitation, was added by amendment dated 12/1/88, and reads:

> 61. A glycoprotein product according to claim 41 further characterized by being the product of expression of an exogenous DNA sequence in a eukaryotic host cell.[2]

7. Thus, contrary to Roche's implication, the "product of the process" limitation was not added to the application in response to the examiner's subsequent § 112 rejection of claim 41 in the 2/10/89 Office Action,[3] and did not narrow the scope of the claimed invention beyond that which was claimed in the application prior to that rejection. The examiner's sole response to

---

[1] Mammen Decl. Ex. E, '933 Patent File History, paper 6, 12/1/88 Amendment and Reply at 3).

[2] Mammen Decl. Ex. E, '933 Patent File History, paper 6, 12/1/88 Amendment and Reply at 4).

[3] Mammen Decl. Ex. F, '933 Patent File History paper 9, 2/10/89 Office Action

claim 61 was to assert that it added no limitation to the claims.[4] In response to this Office Action, the applicant "combine[d] previously pending Claims 41 and 61" into new independent claim 67, "in an effort to more particularly point out and distinctly claim the subject invention."[5] Applicant further explained, "These product-by-process claims are presented in an effort to positively recite the physical properties of recombinant erythropoietin, and to further define the product of the subject invention since the recombinant erythropoietin claimed cannot be precisely defined except by the process by which it is produced."[6] There is thus no support for Roche's position that the addition of the "product of the process" limitation was a narrowing amendment sufficient to create a presumption of prosecution history estoppel.

8. Responding to paragraphs 14 and 19, Roche fails to note that, before applicant cancelled claim 76,[7] the examiner allowed claim 76, which includes a "product of the process" limitation similar to that in issued claim 3. Specifically, allowed claim 76 reads:

> A non-naturally occurring glycoprotein product of the expression in a non-human eukaryotic host cell of an exogenous DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin …[8]

'933 Patent claim 3 reads:

> 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 …[9]

9. Responding to paragraph 20, Roche misleadingly states that, following further

---

[4] *Id.*, paper 9 at p. 8

[5] Mammen Decl. Ex. , '933 Patent File History, paper 11, 6/2/89 Amendment Under Rule 116 at 3

[6] *Id.*, paper 11 at 4.

[7] Mammen Decl. Ex. J, '933 Patent File History, paper 34, 12/29/93 Office Action at 1.

[8] Mammen Decl. Ex. H, '933 Patent File History, paper 19, 1/10/90 Amendment Under Rule 116 at 1.

[9] '933 patent claim 3.

amendment and substitution of claims, the examiner rejected "the claims" on the basis that "it is not evident that the process of production defined the product." Claim 88, which closely resembles both issued claim 3 and allowed claim 76, was not rejected on that basis. Claim 88 reads:

> A glycoprotein product of the expression in a eucaryotic host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin …[10]

Moreover, as noted above, by the time of the rejection of claims 89-94, the examiner had already allowed claim 76, which included a "product of the process" limitation.

10. Responding to paragraph 23, as the Court has ruled in its July 3, 2007 Memorandum and Order, and in prior litigation, "human erythropoietin" is not limited to a 166 amino acid sequence. This Court's construction of "human erythropoietin" is set forth in paragraph 1 of Roche's Rule 56.1 Statement, and Roche admits that it includes a 165 amino acid sequence.[11] In *Amgen, Inc. v. Hoechst Marion Roussel, Inc*., 126 F.Supp.2d 69, 93-96 (D.Mass. 2001),[12] this Court granted summary judgment of literal infringement of claim 1 of the '422 patent by TKT's accused product, which was a 165 amino acid product. Just as Roche argues here, "TKT thus [sought] to read a 166 amino acid limitation into the claim term 'human erythropoietin.' This the Court cannot do. … [T]his argument drifted far astray from the language of the claim and was therefore unpersuasive."[13] The Federal Circuit affirmed.[14] Thus, as a matter of claim construction, "human erythropoietin" literally includes a 165 amino acid

---

[10] Mammen Decl. Ex. K, '933 Patent File History, paper 37, 6/13/94 Preliminary Amendment at 1.

[11] Roche Motion at 9.

[12] *Amgen, Inc. v. Hoechst Marion Roussel, Inc*., 126 F.Supp.2d 69, 93-96 (D.Mass. 2001)

[13] *Id.* at 95.

[14] *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1347-1349, 1358 (Fed. Cir. 2003).

sequence.

11. Responding to paragraph 24, Roche misleadingly and selectively quotes sentence fragments out of context. The Amgen brief and court decisions cited in paragraph 24 pertain to the applicability of prosecution history estoppel and the doctrine of equivalents to the '080 patent claim term, "mature human erythropoietin sequence of Figure 6."[15] This term is a narrower and different claim term which was added to the '080 patent via amendment to distinguish the '080 claims from those of the '933 patent.[16] All of the partial quotations included in paragraph 24 relate to that narrower claim term, not to "human erythropoietin."[17].

12. Responding to paragraph 26, Roche confusingly paraphrases and merges independent claim 61 and dependent claim 63 of the '073 application. The claims actually read:

> 61. An erythropoietin-containing, pharmaceutically-acceptable composition wherein human serum albumin is mixed with erythropoietin.
>
> 62. A composition according to claim 61 containing a therapeutically effective amount of erythropoietin.
>
> 63. A composition according to claim 61 containing a therapeutically effective amount of recombinant erythropoietin.[18]

13. Responding to paragraph 30, Roche's allegation that claim 63 was cancelled "in the face of these continued rejections" and that it was "replaced with" the claim that issued as '422 claim 1 is nothing more than unsupported attorney argument and should be disregarded.

---

[15] Mammen Decl. Ex.L , *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, D.Mass. Case No. 97-10814-WGY, Amgen Inc.'s Post-Hearing Memorandum In Support of Its Fed. R. Civ. P. 52(c) Motion that '080 Claims 2-4 Are Infringed Under the Doctrine of Equivalents, filed 8/18/03, AM-ITC 00852559-580; *see also Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 287 F.Supp.2d 126 (D.Mass. 2003).

[16] *Id. a*t p. 10 ¶ 5.

[17] *See generally id.*

[18] Mammen Decl. Ex. M, '422 Patent File History, paper 2, 11/6/90 Preliminary Amendment at 9.

I. ADDITIONAL FACTS RELIED UPON BY AMGEN IN OPPOSITION TO ROCHE'S MOTION

A. PROSECUTION HISTORY OF THE '933 PATENT

14. Contrary to Roche's contention, Amgen did not rewrite the '933 claims to limit Lin's claimed invention to the products of a specified process. In fact, the '178 application from which the '933 patent issued always contained claims to polypeptide products of the expression of a DNA sequence encoding EPO. For example, as originally filed, claim 16 read:

> "A polypeptide product of the expression of a DNA sequence of claim 14 in a prokaryotic or eukaryotic host."[19]

Original claim 14 read:

> "A DNA sequence for use in securing expression in a prokaryotic or eukaryotic host cell of a polypeptide product having at least a part of the primary structural conformation and one or more of the biological properties of naturally occurring erythropoietin, said DNA sequence selected from among:
>
> the DNA sequences set out in Tables V and VI or their complementary strands;
>
> DNA sequences which hybridize to the DNA sequences defined in (a) or fragments thereof; and,
>
> DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences in (a) and (b)."[20]

In October 1987, prior to any action on the claims by the PTO, Amgen unilaterally amended claim 16 to an independent claim, reading as follows:

> "A polypeptide product of the expression in a prokaryotic or eukaryotic host, said DNA sequence selected from among:
>
> the DNA sequences set out in Figures 5 and 6 or their complementary strands;

---

[19] Mammen Decl. Ex. A, '933 Patent File History, paper 1, 10/23/87 '178 Application Specification at 99 (AM-ITC 00941039).

[20] *Id.* at 98 (AM-ITC 00941038).

> DNA sequences which hybridize to the DNA sequences defined in (a) or fragments thereof; and,
>
> DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences in (a) and (b)."[21]

15. In response to this amendment, the PTO issued its May 18, 1988 Office Action, in which the Examiner rejected Lin's pending claims, including claim 16, stating *inter alia*:

> "The claims must particularly point out the essential aspects of the claimed invention. The broadest limitations must also be supported by the disclosure. As currently set forth, the claims are indefinite and to an extent, non-enabled. The **particular biological activities and physical properties** which can be used to define the rEPO should be reflected in the claim language to adequately define the invention."[22]

16. Far from the misimpression Roche seeks to create, the examiner did not reject Lin's claims because they failed to limit his invention to the products of a particular process. Rather, he merely insisted that Lin's claims, including his "polypeptide product of DNA expression" claims, point out the particular biological activity and physical properties that defined the claimed polypeptides. Each of the succeeding amendments to Lin's then-pending claims was designed to address **that** concern and ultimately did so to the examiner's satisfaction. For example, immediately following the May 1988 Office Action, Amgen amended pending claim 41 and added new claim 61. As amended, claim 41 read:

> "A glycoprotein product having a primary structural conformation and glycosylation sufficiently duplicative of that of a naturally occurring human erythropoietin to allow possession of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and having an

---

[21] Mammen Decl. Ex. C, '933 Patent File History, paper 3, 02/19/88 Preliminary Amendment at 5 (AM-ITC 00941086).

[22] Mammen Decl. Ex. D, '933 Patent File History, paper 4, Office Action at 5(AM-ITC 00941094) (emphasis added).

> average carbohydrate composition which differs from that of naturally occurring human erythropoietin."[23]

New claim 61 read:

> "A glycoprotein product according to claim 41 further characterized by being the product of expression of an exogenous DNA sequence in a eucaryotic host cell."[24]

17. Because the examiner continued to object that these claims failed to define the claimed polypeptides with sufficient particularity, Amgen continued to amend Lin's "polypeptide product of DNA expression" claims, ultimately adding new claim 76, which the Examiner accepted on February 9, 1990 as overcoming his prior section 112 rejections.[25]

18. Thus, contary to the false impression Roche seeks to create, the full prosecution history reveals that Lin consistently chose to define polypeptides claimed in the '933 prosecution as the product of the expression in certain cells of DNA sequences encoding EPO. And contrary to the inference Roche asks this Court to draw, nothing in the prosecution history demonstrates that Lin's claim amendments were requested or made for the purpose of excluding compounds, such as peg-EPO, that contain polypeptide products of the expression in a mammalian cell of DNA encoding human EPO.

19. Roche also states that, following further amendment and substitution of claims, the examiner rejected "the claims" on the basis that "it is not evident that the process of production defined the product." Contrary to the misimpression Roche seeks to create, claim 88, which closely resembles both issued claim 3 and allowed claim 76, was not rejected on that

---

[23] Mammen Decl. Ex. E, '933 Patent File History, paper 6, 12/1/88 Amendment and Reply at 3 (AM-ITC 00941108).

[24] Mammen Decl. Ex. E, '933 Patent File History, paper 6, 12/1/88 Amendment and Reply at 4 (AM-ITC 00941109).

[25] Mammen Decl. Ex. I, '933 Patent File History, paper 21, 2/9/90 Office Action at 2 (AM-ITC 00941226). *See also*, Mammen Decl. Ex. J, '933 Patent File History, paper 34, 12/29/93 Office

basis.[26] Claim 88 reads:

> "A glycoprotein product of the expression in a eucaryotic host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin …."[27]

B. PROSECUTION HISTORY OF THE '422 PATENT

20. As the Court ruled in its July 3, 2007 Memorandum and Order, and in prior litigation, "human erythropoietin" is not limited to a 166 amino acid sequence. This Court's construction of "human erythropoietin" is set forth in paragraph 1 of Roche's Rule 56.1 Statement, and Roche admits that it includes a 165 amino acid sequence.[28] In *Amgen, Inc. v. Hoechst Marion Roussel, Inc*., 126 F.Supp.2d 69, 93-96 (D.Mass. 2001), this Court granted summary judgment of literal infringement of claim 1 of the '422 patent by TKT's accused product, which was a 165 amino acid product. As the Court noted in that case, TKT sought, as Roche does here, "to read a 166 amino acid limitation into the claim term 'human erythropoietin.' This the Court cannot do. … [T]his argument drifted far astray from the language of the claim and was therefore unpersuasive."[29] The Federal Circuit affirmed.[30] Thus, as a matter of claim construction, "human erythropoietin" literally includes a 165 amino acid sequence.

21. In its Rule 56.1 Statement, Roche selectively and misleadingly quotes out of

---

Action at 1 (AM-ITC 00941411-412).

[26] *See* Mammen Decl. Ex. N, '933 Patent File History, paper 38, 8/16/94 Office Action at 1, 2-6 and *passim* (AM-ITC 00941456-466).

[27] Mammen Decl. Ex. K, '933 Patent File History, paper 37, 6/13/94 Preliminary Amendment at 1 (AM-ITC 00941452).

[28] Roche Motion at 9.

[29] *Amgen, Inc. v. Hoechst Marion Roussel, Inc*., 126 F.Supp.2d 69, 95 (D.Mass. 2001).

[30] *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1347-1349, 1358 (Fed. Cir. 2003).

context sentence fragments from proceedings relating to the Court's application of the doctrine of equivalents to a different claim term in the '080 patent. The Amgen brief and court decisions cited in paragraph 24 pertain to the applicability of prosecution history estoppel and the doctrine of equivalents to the '080 patent claim term, "mature human erythropoietin sequence of FIG. 6."[31] This term is a narrower and different claim term which was added to the '080 patent via amendment to distinguish the '080 claims from those of the '933 patent.[32] All of the partial quotations included in paragraph 24 relate to that narrower claim term, not to "human erythropoietin."[33]

22. In its brief, Roche argues that the addition of the claim language "wherein said erythropoietin is purified from mammalian cells grown in culture" creates an estoppel for products that are not so made. As shown above, however, the claim language characterizing the claimed products as being expressed by particular types of cells was present in the originally filed claims down to the issued claims. Amgen did not surrender any such subject matter.

23. Roche incorrectly cites to the claims pending in the '422 application prior to the filing of the claim that issued as '422 claim 1 but rewrites dependent claim 63 in a confusing manner. Prior pending claims 61-63 actually read:

> "61. An erythropoietin-containing, pharmaceutically-acceptable composition wherein human serum albumin is mixed with erythropoietin.
>
> 62. A composition according to claim 61 containing a

---

[31] Mammen Decl. Ex. L, *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, D.Mass. Case No. 97-10814-WGY, Amgen Inc.'s Post-Hearing Memorandum In Support of Its Fed. R. Civ. P. 52(c) Motion that '080 Claims 2-4 Are Infringed Under the Doctrine of Equivalents, filed 8/18/03, AM-ITC 00852559-580; *see also Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 287 F.Supp.2d 126 (D.Mass. 2003).

[32] *Id. a*t p. 10 ¶ 5.

[33] *See generally id.*

therapeutically effective amount of erythropoietin.

63. A composition according to claim 61 containing a therapeutically effective amount of recombinant erythropoietin."[34]

Claim 1 of the '422 patent actually broadened the scope of these claims by eliminating the reference to human serum albumin. Without that specific element, Amgen rewrote the claim and included the phrase "purified from mammalian cells grown in culture."

24. Without so stating, Roche seems to argue that this amendment narrowed the claim from "recombinant erythropoietin" and creates an estoppel for the subject matter between the two terms. But the first question is whether the claim was narrowed given the redrafting of the claim as a whole and the deletion of human serum albumin from the claim. Even if this was a narrowing amendment made for purposes of patentability, Roche has not cited to any feature in its product, the source from which it is obtained, or the method of its making that falls outside the scope of erythropoietin produced by "mammalian cells" as compared to "recombinant erythropoietin." In fact, Roche produces its EPO product in mammalian cells just as described and claimed in Lin's patents.

Respectfully Submitted,

AMGEN INC.,
By its attorneys,

/s/ *Michael R. Gottfried*
D. DENNIS ALLEGRETTI (BBO#545511)
MICHAEL R. GOTTFRIED (BBO#542156)
PATRICIA R. RICH (BBO#640578)
DUANE MORRIS LLP
470 Atlantic Avenue, Suite 500
Boston, MA 02210

Of Counsel:

STUART L. WATT
WENDY A. WHITEFORD
MONIQUE L. CORDRAY
DARRELL G. DOTSON

[34] Mammen Decl. Ex. M, '422 Patent File History, paper 2, 11/6/90 Preliminary Amendment at 9 (AM-ITC 0094-2134).

KIMBERLIN L. MORLEY
ERICA S. OLSON
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, CA 91320-1789
(805) 447-5000

Telephone: (857) 488-4200
Facsimile: (857) 488-4201

LLOYD R. DAY, JR. (*pro hac vice*)
DAY CASEBEER
MADRID & BATCHELDER LLP
20300 Stevens Creek Boulevard, Suite 400
Cupertino, CA 95014
Telephone: (408) 873-0110
Facsimile: (408) 873-0220

WILLIAM GAEDE III (*pro hac vice*)
McDERMOTT WILL & EMERY
3150 Porter Drive
Palo Alto, CA 94304
Telephone: (650) 813-5000
Facsimile: (650) 813-5100

KEVIN M. FLOWERS (*pro hac vice*)
MARSHALL, GERSTEIN & BORUN LLP
233 South Wacker Drive
6300 Sears Tower
Chicago IL 60606
Telephone: (312) 474-6300
Facsimile: (312) 474-0448

Dated: July 13, 2007

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.

/s/ Michael R. Gottfried
Michael R. Gottfried