UNITED STATES DISTRICT COURT
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-CV-12237WGY **ORAL ARGUMENT REQUESTED**

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 '698 AND '868 PATENTS

Defendants F. Hoffmann-La Roche, Ltd, Roche Diagnostics GmbH, and Hoffmann-La Roche, Inc. (collectively "Roche") submit the following statement of undisputed material facts, pursuant to Local Rule 56.1, in support of their motion for summary judgment that Amgen is estopped from asserting infringement under the doctrine of equivalents of claims 1 and 2 of U.S. Patent No. 5,441,868 (the '868 patent)[1] and claims 4-9 of U.S. Patent No. 5,618,698 (the '698 patent)[2].

[1] Ex. 1, U.S. Patent No. 5,441,868. All Exhibits cited herein are attached to the Declaration of Nicole A. Rizzo 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 '698 and '868 Patents.

[2] Ex. 2, U.S. Patent No. 5,618,698.

1. In this action, Plaintiff Amgen Inc. ("Amgen") alleges that Roche infringes, *inter alia*, claims 1-2 of the '868 patent and claims 4-9 of the '698 patent. (Ex. 15, Plaintiffs' Supp. Response to Defendants First Set of Interrogatories at pp. 3-4).

This Court's Claim Construction

2. This Court has construed the term "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." (7/3/07 Order, Docket No. 613 at 15; Ex. 7, Markman Hearing Transcript, 4/17/07 at 27:8-10, 34:7-10).

The Asserted Claims of the '698 Patent

3. Claims 4-9 of the '698 patent recite processes for producing "glycosylated erythropoietin polypeptide[s]" using "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6." The independent claims are claims 4 and 6:

> 4. A process for the production of *a glycosylated erythropoietin polypeptide* having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to *DNA encoding the mature erythropoietin amino acid sequence of FIG. 6*; and
>
> b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.
>
> * * *
>
> 6. A process for the production of *a glycosylated erythropoietin polypeptide* having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified *DNA encoding the mature erythropoietin amino acid sequence of FIG. 6*; and

> b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

(Ex. 2 (emphasis added)).

The Asserted Claims of the '868 Patent

Amgen alleges that Roche infringes claims 1 and 2 of the '868 patent which claim processes for producing a glycosylated erythropoietin polypeptide as follows:

> 1. A process for the production of a ***glycosylated erythropoietin polypeptide*** having the ***in vivo*** biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> (a) growing, under suitable nutrient conditions, mammalian host cells transformed or transfected with ***an isolated DNA sequence encoding human erythropoietin***; and
>
> (b) isolating said glycosylated erythropoietin polypeptide therefrom.
>
> 2. The process according to claim 1 wherein said host cells are CHO cells.

(Ex. 1 (emphasis added)).

Relevant Prosecution History of U.S. Patent No. 4,703,008

4. Each of the patents-in-suit claims priority to expired U.S. Patent No. 4,703,008 ("the '008 patent") and, through the parent application of the '008 patent, claims a priority date of December 13, 1983. The application that yielded '008 patent was filed on November 30, 1984. The '008 patent issued on October 27, 1987, and expired in 2004.

5. During prosecution of the application for the '008 patent, the examiner rejected claims to a DNA sequence for use in expressing "a polypeptide having part or all of the primary structural conformation" of naturally occurring EPO and to a DNA sequence "coding for a polypeptide fragment or polypeptide analog" of naturally-occurring EPO. (Ex. 3, '008 patent file

history, Paper 13, 2/5/87 Office Action; see also Ex. 4, Ser. No. 675,298 at pp. 99-100). In rejecting the claims as not enabled, the examiner stated:

> [T]he disclosure is enabling only for claims limited to the DNA sequence coding for erythropoietin. The recitation "of fragments thereof" the recitation of and/or "having at least a part of the primary structural conformation and one or more of the biological activities of naturally-occurring erythropoietin" permits the claims to read on proteins and peptides completely unrelated to erythropoietin.

(Ex. 3 at 3).

6. The application was then amended; the amended claims described "a polypeptide product having at least a part of the primary structural conformation" of naturally-occurring EPO and a "a polypeptide fragment or polypeptide analog of naturally-occurring erythropoietin." (Ex. 5, '008 patent file history, Paper 15, Amendment and Reply at 1-2, 4-5).

7. The examiner again rejected the claims under § 112 as not enabled, noting that the claims "appear to embrace substantially all known DNA sequences since the isolated DNA sequence is not designated as encoding erythropoietin. One that encodes for a protein having 'a' therapeutic activity of erythropoietin is not the same thing." (Ex. 6, '008 patent file history, Paper 17, 6/18/87 Office Action at 3).

8. The '008 patent issued with one claim – claim 7 – that had language similar to language that had been rejected, *i.e.*, "a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin."

9. Claim 7 of the '008 patent was later held invalid. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213-14 (Fed. Cir. 1991).

10. A June 6, 1995 preliminary amendment to the application for the '080 patent added claims which "broadly encompassed an isolated human EPO product." *Amgen IV*, 457 F.3d at 1310. A second preliminary amendment "claimed an EPO product made using the amino

acid sequence for EPO set out in Figure 6 'or a fragment thereof.'" *Id.* A third amendment "deleted claims for an EPO product made using 'a fragment of the amino acid sequence of Figure 6. Instead, as of the third preliminary amendment, the . . . application claimed only a human EPO product having the complete amino acid sequence of Figure 6." *Id.*

11. The Federal Circuit thus concluded that the third preliminary amendment "may have been central to overcoming a double patenting rejection in light of claim 1 of the '933 patent." *Id.* at 1315. Indeed, the applicant argued that the added claims "all differ in scope from glycoprotein claim 1 of U.S. 5,547,933 in specifying that the claimed subject matter comprises the mature human erythropoietin sequence of Figure 6." (Ex. 12, '080 patent file history, Paper 6, 12/20/96 Third Preliminary Amendment).

Relevant Prosecution History of the U.S. Patent No. 5,441,868

12. The application for the '698 patent was a continuation of the application which resulted in the issuance of the '868 patent.

13. The application for the '868 patent initially added claims (numbered 61, 62 and 64) to processes for the production of "a polypeptide having part or all of the primary structural conformation" of naturally-occurring EPO which used the DNA sequences of Figures 5 and 6 of the specification and DNA sequences which hybridize to those sequences, a DNA sequence consisting essentially of a DNA sequence encoding human EPO, and a DNA sequence encoding a polypeptide having a primary structural conformation sufficiently duplicative of that of EPO. (Ex. 8, '868 patent file history, Paper 7, 10/23/87 Preliminary Amendment at 5-7).

14. In a second preliminary amendment, the applicant replaced those claims with a claim (number 65) to a process for producing "an *in vivo* biologically active glycosylated polypeptide" using a DNA sequence "encoding a polypeptide having a primary structural

conformation sufficiently duplicative of that of naturally occurring human erythropoietin." (Ex. 9, '868 patent file history, Paper 8, 5/24/88 Second Preliminary Amendment at 3-4).

15. Ultimately, application claim 65 was rejected on the grounds that a claim to any "*in vivo* biologically active glycosylated polypeptide" was unsupported by a process involving only DNA encoding EPO. (Ex. 10, '868 patent file history, Paper 29, 9/1/93 at 5-6).

16. The examiner stated that "the disclosure is enabling only for claims limited to preparation of human EPO" and that the rejection could be overcome "by amending the claim to recite 'a process for the preparation of a biologically active glycosylated human erythropoietin.'" (*Id*. at 9-10).

17. The applicant cancelled the claim in response and filed the claim that issued as claim 1:

> A process for the production of a ***glycosylated erythropoietin polypeptide*** having the ***in vivo*** biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> (a) growing, under suitable nutrient conditions, mammalian host cells transformed or transfected with ***an isolated DNA sequence encoding human erythropoietin***; and
>
> (b) isolating said glycosylated erythropoietin polypeptide therefrom.

(Emphasis added).

The disclosure of "human erythropoietin" set forth in the '868 patent is a 166 amino acid sequence. The patent disclosure specifically explains to one of skill in the art that the sequence of "FIG. 6 thus serves to identify the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues (estimated M.W. = 18,399)." (Ex. 1, at col. 22:6-9; *see also* Fig. 9 & col. 20:30-38, 22:9-13, 36:44-51).

18. Amgen has admitted to this Court in prior litigation that "when the written description of Amgen's specification was drafted and submitted [in 1984], the specification did not expressly recite an EPO having the 1-165 sequence." (Ex. 14, Amgen's Post-Hearing Memo. at 5 (AM-ITC 00852567)). Amgen also admitted that the 165 amino acid sequence of EPO isolated from human urine would constitute "new matter" and this Court acknowledged that Lin would have been required to file a continuation-in-part application to claim the amino acid sequence. *Amgen v. Hoechst Marion Roussel, Inc.*, 287 F. Supp. 2d 126, 144 & fn.22 (D. Mass. 2003), *aff'd in relevant part*, 457 F.3d 1293 (Fed. Cir. 2006).

Relevant Prosecution and Litigation History of the '698 Patent

19. The application which resulted in the issuance of the '698 patent was a continuation of the application that resulted in the '868 patent and was filed on June 6, 1995. Subsequent to the August 15, 1995 issuance of the '868 patent, applicant proposed to the Patent Office adding claims in the '698 patent with the phrase "DNA encoding the mature erythropoietin amino acid sequence of Figure 6" to avoid a double patenting rejection in light of the '868 patent's "an isolated DNA sequence encoding human erythropoietin."

20. The claims that issued as claims 4 and 6 of the '698 patent were added after a December 11, 1996 patent office interview and were among five proposed claims – all of which employed the term "the mature erythropoietin amino acid sequence of Figure 6" – that were discussed with the examiner. The summary of the patent office interview included in the '698 patent file history reflects that the applicant agreed to add the claims, that the applicant agreed to file a terminal disclaimer with respect to the '868 patent and that the examiner was "favorably impressed." (Ex. 11, '698 patent file history, Paper 7, 12/11/96 Interview Summary).

21. The phrase "mature erythropoietin amino acid sequence of FIG. 6" also appears in Amgen's U.S. Patent No. 5,621,080 ("the '080 patent") which shares the specification of the '698 patent.

22. The reference to the "mature erythropoietin amino acid sequence of FIG. 6" was added to the application for the '080 patent for patentability reasons as a result of the same patent office interview referenced in the file history of the '698 patent. (Ex. 13, '080 patent file history, Paper 4, 12/11/96 Interview Summary)

23. This Court has held that the term "mature erythropoietin amino acid sequence of FIG. 6" means that the polypeptide of the claims "must contain an erythropoietin glycoprotein comprising the fully realized erythropoietin amino acid sequence of Figure 6 which depicts 166 amino acids." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 100 (D. Mass. 2001) (*Amgen I*).

24. The '080 patent claims were amended to add the term "mature erythropoietin amino acid sequence of Figure 6" to distinguish them over the '933 patent. *Amgen I*, 126 F. Supp. 2d at 135; *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 287 F. Supp. 2d 126, 151-53 (D. Mass. 2003) ("*Amgen III*").

25. The Federal Circuit has held that Amgen was foreclosed, under the doctrine of prosecution history estoppel, from maintaining that the "mature erythropoietin amino acid sequence of Fig. 6" limitation in the claims of '080 patent could cover an EPO product containing a 165 amino acid sequence under the doctrine of equivalents. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1316 (Fed. Cir. 2006). (*Amgen IV*).

26. The Court pointed out in *Amgen IV* that when the term "mature erythropoietin amino acid sequence of Figure 6" was added to the claims of the '080 patent "the 165 amino acid EPO equivalent was foreseeable." 457 F.3d at 1316.

27. This Court has stated that the phrase "mature erythropoietin amino acid sequence of FIG. 6" "should have the same meaning in both" the '080 and '698 patents. *Amgen I*, 126 F. Supp. 2d at 86.

28. The Federal Circuit has observed that Amgen amended the claims knowing of the 165 amino acid sequence, and still "chose to limit the claims to the 166 amino acid sequence depicted in Figure 6" of the '080 patent specification. *Id*. at 1316. The Federal Circuit stated: "[W]e think that if the patentee had wished to limit the claims to human EPO, the patentee could have done so by continuing to use the adjective 'human' when referring to EPO in the third preliminary amendment; instead the patentee chose to further narrow the claims in the third preliminary amendment by making reference to the specific sequence in Figure 6 rather than human EPO." *Id*. at 1315.

29. The third preliminary amendment of the application for the '080 patent followed the December 11, 1996 patent office interview which was also a part of the prosecution history of the '698 patent. The applicant and the examiner discussed five proposed claims, all of which included the phrase "the mature erythropoietin amino acid sequence of Figure 6." (Ex. 13). The interview summary which appears in the '080 patent file history reflects that two of the 5 proposed claims – which issued as claims 1 and 2 of the '080 patent – would be added via a preliminary amendment, that a terminal disclaimer would be filed with respect to the '933 patent and that the examiner was "favorably impressed." *Id.*

DATED: Boston, Massachusetts
July 3, 2007

Respectfully submitted,

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

By their Attorneys,

/s/ Nicole A. Rizzo
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
nrizzo@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*)
Peter Fratangelo (BBO# 639775)
KAYE SCHOLER LLP
425 Park Avenue
New York, NY 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/ Nicole A. Rizzo
Nicole A. Rizzo

03099/00501 698414.1