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 CV 12237 WGY U.S. District Judge William G. Young **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 '933 AND '422 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 3, 7-9, 11-12 and 14 of U.S. Patent No. 5,547,933 (the '933 patent) and claim 1 of U.S. Patent No. 5,955,422 (the '422 patent). In this action, Plaintiff Amgen Inc. ("Amgen") alleges that Roche infringes, *inter alia*, claims 3, 7-9, 11-12 and 14 of the '933 patent and claim 1 of the '422 patent. (Ex. 20, Plaintiff's Supp. Responses to Defs.' First Set of Interrogatories at pp. 3-4).[1]

[1] All Exhibits cited herein are attached to the Declaration of Keith E. Toms in Support of Defendants' Motion For Summary Judgment That Amgen Is Estopped From Asserting
(continued...)

This Court's Claim Construction

1. 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." (Ex. 21, Markman Hearing Transcript, 4/17/07 at 27:8-10, 34:7-10).

The Asserted Claims of the '933 Patent

2. Claim 3 of the '933 patent is an independent claim directed to a non-naturally occurring glycoprotein product:

> 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.

(Ex. 18, '933 patent col. 38 ll. 26-31).

3. Claims 7 and 8 of the '933 patent also are directed to non-naturally occurring glycoprotein products. Both are dependent on claim 3 (among other claims), and they further purport to limit the mammalian host cell of that claim. They provide:

> The glycoprotein product according to Claim 3, 4, 5 or 6 wherein the host cell is a non-human mammalian cell.
>
> The glycoprotein product of claim 7 wherein the non-human mammalian cell is a CHO cell.

Id. at col. 38, ll. 64-67.

4. Claims 9 and 12 of the '933 patent are directed to pharmaceutical compositions that include as an active ingredient the glycoprotein product of claims 3 and 7:

Infringement Under The Doctrine Of Equivalents Of The Asserted Claims Of The '933 And '422 Patents.

> A pharmaceutical composition comprising an effective amount of a glycoprotein product for erythropoietin therapy according to claim 1, 2, 3, 4, 5 or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.
>
> A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 7 and a pharmaceutically acceptable diluent, adjuvant or carrier.

Id. at col. 39 ll. 1-4, 12-13.

5. Claim 14 is a method of treatment claim which depends from claim 12:

> A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 12 in an amount effective to increase the hematocrit level of said product.

Id. at col. 40 ll. 7-11

Relevant Prosecution and Litigation History of the '933 Patent

6. The application for the '933 patent Ser. No. 487,774 (the '774 application), filed June 7, 1995, was a continuation of Serial Nos. 202,874, (the '874 application) and 113,178 (the '178 application).

7. During prosecution of the applications that led to the '933 patent, the applicant first sought claims to:

> 1. A purified and isolated polypeptide *having part or all of the primary structural conformation* and one or more of the biological properties *of naturally-occurring erythropoietin* and characterized by being the product of procaryotic or eukaryotic expression of an exogenous DNA sequence.
>
> 7. A polypeptide according to claim 1 possessing *part or all of the primary structural conformation of human erythropoietin as set forth in Table VI [Figure 6] or any naturally occurring allelic variant thereof*.
>
> 41. A glycoprotein product having a *primary structural conformation sufficiently duplicative of that of a naturally-occurring human erythropoietin* to allow possession of one or more of the biological properties thereof and having an average carbohydrate composition

> which differs from that of naturally-occurring human erythropoietin.
>
> 48. A *synthetic polypeptide having part or all of the amino acid sequence set forth in Figure 6*, other than a sequence of residues entirely within the sequence numbered 1 through 20, and having a biological property of naturally-occurring human erythropoietin.

(Ex. 1, '178 application file history, application claims at 97, 101, 102 (emphasis added)).

8. The examiner rejected these claims as indefinite and not enabled stating:

> The terms "part or all of" [and] "sufficiently duplicative of" . . . do not particularly nor adequately point out the distinctions from native erythropoietin (EPO) . . . [T]he "parts" of EPO which are contemplated and supported by the disclosure (in terms of amino acid sequence) . . . should be pointed out.
>
> * * *
>
> The claims must particularly point out the essential aspects of the disclosed 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.

(Ex. 5, '178 application file history, Paper 4, 6/2/86 Office Action at 3-5).

9. The examiner further stated:

> *Claims to "synthetic polypeptides" are not enabled by this disclosure*. "Synthetic," as opposed to "recombinant," is an art recognized term which indicates a chemically derived rather than genetically engineered protein. *No support for chemical synthesis of EPO or EPO fragments is shown by this disclosure.*

Id. at 5 (emphasis added).

10. In addition, the examiner rejected application claims 1, 7 and 49 in view of prior art. The examiner stated that the prior art showed production of "human EPO in substantially purified form having EPO activity" which was "inherently identical to the claimed EPO." *Id*. at 6.

11. In response, the applicant canceled claims 1, 7 and 48 (as well as other claims). (Ex. 6, '178 application File History, Paper 6, 12/1/88 Amendment and Reply at 3). The applicant also amended claim 41 to read:

> A glycoprotein 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.

Id.

12. After failing to overcome the examiner's § 112 rejection (***See*** Ex. 7, '178 Application File History, Paper 9, 2/10/89 Office Action), the applicant canceled claim 41 without prejudice, and submitted new claim 67:

> A glycoprotein product of the expression of an exogenous DNA sequence in a eucaryotic host cell, said 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.

(Ex. 2, '178 Application File History, Paper 11, 6/2/89 Amendment at 1 (emphasis added)). The applicant explained that "[a]ll product claims in the subject application are now product-by-process claims. . . . These product-by-process claims are presented . . . 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.***" *Id.* at 3.

13. The examiner maintained his rejection under §112 as to the use of the term "sufficiently duplicative" of human erythropoietin:

> *Claim 67 to 75 are rejected under 35 U.S.C. 112, first and second paragraphs*. . . . The claim as presented remain deficient under 35 USC 112 first and second paragraphs. The following modifications are suggested to overcome this rejection.
>
> 1. In claim 67, line 3, the phrase "a primary structural conformation" should be changed to "a primary structure and conformation ...". *This modification makes it clear that the recombinant protein possess the primary structure (e.g. the amino acid sequence of naturally occurring human EPO)* and the tertiary or spatial conformation of human EPO to the extent that the recombinant EPO retains the biological activity of the human EPO in vivo.
>
> 2. The claim must be limited to recombinant *human* erythropoietin. *As presented, a non human analog which possesses enough similarity to native human erythropoietin is encompassed by the claims. This breadth is not supported by the disclosure.* Applicant may recite that the exogenous DNA sequence codes for human erythropoietin.

(Ex. 13, '178 application file history, Paper 13, 6/14/89 Office Action at 3).

14. The Applicant ultimately canceled claim 67 in favor of application claim 76 which did not include the "sufficiently duplicative" language:

> A non-naturally occurring glycoprotein product of the expression in a non-human eucaryotic host cell of an exogenous DNA sequence consisting essentially of *a DNA sequence encoding human erythropoietin* said product possessing the in vivo biological property of causing human 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.

(Ex. 4, '178 application file history, Paper 19, 1/10/90 Amendment at 1 (emphasis added)).

15. Applicant noted that new claims 76-83 were "similar" to the cancelled claims, but "specify that the DNA sequences encode human erythropoietin." *Id.* at 5.

16. Applicant noted that application claim 76 was drafted to parallel claim 2 of the '008 patent that had been held valid in *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, No. 87-2617-Y, 1989 U.S. Dist. LEXIS 16110 (D. Mass. Dec. 11, 1989), *aff'd in part, rev'd in part*, 927

F.2d 1200 (Fed. Cir. 1991). *Id.* at *250. Claim 2 of the '008 patent claimed: "A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin." (Ex. 4 at 6). Based on the validity of claim 2 of the '008 patent, the applicant for the '933 patent argued:

> In determining that claims 2 and 4 of the Lin '008 patent are valid, the Court recognized that Lin is the first inventor of the DNA sequence encoding human erythropoietin and of the use thereof in a host cell to make recombinant erythropoietin . . . .
>
> * * *
>
> [I]t is submitted that if Lin was the first to invent the DNA encoding erythropoietin, and the use of that DNA in a host cell to produce recombinant erythropoietin, then clearly he was the first to invent a recombinant erythropoietin product produced using such a host cell.

Id. (emphasis omitted).

17. The decision in *Chugai* held issued claim 7 of the '008 patent (and its dependent claims) invalid under § 112 for lack of enablement. 1989 U.S. Dist. LEXIS 16110, at *164. Claim 7 of the '008 reads:

> A purified and isolated DNA sequence consisting essentially of a DNA sequence *encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin* to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

(Ex. 17, '008 patent, claim 7 (emphasis added)). The Court found that the "sufficiently duplicative" language did not comply with § 112. *Chugai*, 1989 U.S. Dist. LEXIS 16110, at *152-164. Citing the "lack of predictability in the art," the Court noted that "the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 . . . without undue experimentation." *Id.* at *164.

18. The Federal Circuit affirmed that claim 7 of the '008 was invalid under § 112, stating:

> [M]ore is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity.

Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200, 1214 (Fed. Cir. 1991).

19. Application claim 76 was eventually cancelled. (Ex. 14, '874 application file history, Paper 37, 6/13/94 Preliminary Amendment).

20. The applicant then added claims which described a biologically active human erythropoietin glycoprotein product produced by "mammalian host cells." The examiner rejected the claims, saying that "it is not evident that the process of production defined the product." (Ex. 15, '874 application file history, Paper 38, 8/16/94 Office Action at 9). In response, the applicant argued that "it is in fact 'evident that the process of production defines the product.'" (Ex. 16, '874 application file history, Paper 42, 2/16/95 Amendment and Request for Reconsideration at 11).

21. The claim which issued as claim 3 of the '933 patent was added to the '774 application in a Second Preliminary Amendment dated December 20, 1995. (Ex. 13, '774 Application File History, 6/20/95 Second Preliminary Amendment and Remarks).

22. The asserted claims of the '933 patent all contain, either directly (claim 3) or by dependence (claims 7-9, 11-12 and 14), the term "an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin."

23. The '933 patent discloses "human erythropoietin" as 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. 19, '422 patent, col. 20:66-21:2; *see also id.* Fig. 9 & col. 19:28-36, 21:2-5, 35:4-11).

24. Amgen further 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. 22, Amgen's Post-Hearing Memo. at 1 (AM-ITC 00852563)). 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, Inc. v. Hoechst Marion Roussel, Inc.*, 287 F. Supp. 2d 126, 144 n.22 (D. Mass. 2003), *aff'd in relevant part*, 457 F.3d 1293 (Fed. Cir. 2006).

The Asserted Claim of the '422 patent

25. Amgen alleges that Roche infringes claim 1 of the '422 patent which provides:

> A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, *wherein said erythropoietin is purified from mammalian cells grown in culture.*

(Ex. 19, '422 patent (emphasis added)).

Relevant Prosecution History of the '422 Patent

26. During the prosecution of the '422 patent, application claim 63 (a dependent claim written below in independent form) was presented by Amgen:

> An erythropoietin-containing, pharmaceutically acceptable composition] containing a therapeutically effective amount of recombinant erythropoietin.

(Ex. 11, '422 patent file history, Paper 2, 11/6/90 Preliminary Amendment at p. 9).

27. In rejecting this claim over the prior art the examiner cited the following disclosure in the specification:

> The present invention provides . . . isolated polypeptide products having part or all of the primary structural conformation . . . and one or more of the biological properties (e.g. immunological properties and The present invention provides . . . isolated polypeptide products having part or all of the primary structural conformation . . . and one or more of the biological properties (e.g. immunological properties and in vivo and in vitro biological activity of naturally occurring erythropoietin . . . These polypeptides are also uniquely characterized by being the product of prokaryotic or eukaryotic host expression . . . of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis . . . Depending on the host employed, polypeptides of the invention may be glycosylated with mammalian or other eukaryotic carbohydrates or may be non-glycosylated.

(Ex. 12, '422 patent file history, Paper 20, 5/26/94 Office Action at 4).

28. The examiner concluded:

> [I]t is apparent that the claimed erythropoietin (EPO) compositions read on any erythropoietin molecule regardless of its source. In particular, the specification indicates that glycosylated erythropoietin that exhibits the characteristic amino acid squence4 and biological properties of naturally occurring erythropoietin is envisioned. Therefore, the EPO recited the claims reads directly upon natural isolates and the basics of the instant rejection as explained above properly established that the claimed invention would have been *prima facie* obvious.

Id.

29. The examiner further found claim 63 to be indefinite in using "recombinant" on the basis that it was unclear how that limitation would "modify the physical erythropoietin composition." *Id.* at 2. The examiner "deemed unpersuasive" a declaration submitted by Dr. Richard Cummings purportedly showing that recombinant EPO and urinary EPO are structurally distinct. (Ex. 9, '422 patent file history, Paper 26, 3/31/95 Patent Office Communication; AM-ITC 00899419).

30. In the face of these continued rejections, claim 63 was cancelled and replaced with the claim that issued as '422 claim 1. Acknowledging that the phrase "purified from mammalian cells grown in culture" limited the "source of the EPO," the applicant stated that the intent was to "include any EPO produced by mammalian cells (human, CHO, COS etc.) that are grown in culture, which means in vitro." (Ex. 8, '422 patent file history, Paper 33, 4/20/99 Amendment at 5).

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Respectfully submitted,

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