UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

DECLARATION OF MARTIN J. ADELMAN IN SUPPORT OF DEFENDANTS' OPPOSITION TO AMGEN INC.'S MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT OF '422 CLAIM 1, '933 CLAIM 3, AND '698 CLAIM 6

I, MARTIN J. ADELMAN, submit this declaration on behalf of defendants, F. Hoffmann-La Roche, Ltd, Roche Diagnostics GmbH and Hoffmann-La Roche Inc. (collectively "Roche") in support of Roche's Opposition to Amgen Inc.'s Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6.

I. Background

1. I am the Theodore and James Pedas Family Professor of Intellectual Property and Technology Law, Co-Director of the Intellectual Property Law Program, and the Co-Director of the Dean Dinwoodey Center for Intellectual Property Studies at the George Washington University Law School in Washington, D.C.

2. I received a bachelor's degree in medical science in 1958 and a master's degree in physics in 1959, both from the University of Michigan. In 1962, I received my law degree from the University of Michigan, where I was on the editorial board of the Michigan Law Review.

After graduating from law school, I served as a law clerk for Chief Judge Levin of the United States District Court for the Eastern District of Michigan.

3. Following my clerkship, I practiced law as an associate at the business law firm of Honigman, Miller, Schwartz & Cohn in Detroit until 1964, when I joined the patent department of the Burroughs Corporation in Washington, D.C. While at Burroughs, I participated in the Burroughs program for training its patent attorneys to prepare and prosecute patents before the United States Patent and Trademark Office ("USPTO" or "Patent Office"). In 1965, I became an associate in the patent firm of Barnard, McGlynn and Reising in Birmingham, Michigan, where I later became partner. During the 1968-1972 period, I was partner in charge of patent, patent-antitrust and related litigation. From 1973 until I retired from that position in 1999 to become Professor Emeritus, I was full professor at Wayne State University Law School, where I taught courses (seminars) in patent law, advanced patent law, antitrust law and law and economics.

4. In 1977-1988, I was one of the co-authors of a six volume (now eight volume) treatise on patent law and practice entitled *Patent Law Perspectives* (2d ed.), published by Matthew Bender. Since 1988, I have been solely responsible for writing the release for each of the volumes. I am also the co-author of *Cases and Materials on Patent Law,* 2d edition (with Randall R. Rader, John R. Thomas and Harold C. Wegner), published by West Group.

5. I also have written many articles on issues of patent law and practice, and have taught seminars in patent law and practice for United States District Judges and United States Magistrate Judges. I have lectured widely on patent law subjects, and within the past few years have spoken at intellectual property conferences across the United States and in Amman, Beijing, Bangalore, Berlin, Bhopal, Bonn, Bucharest, Buenos Aires, Brussels, Cairo, Calcutta, Edinburgh, Haifa, Hong Kong, Kharagpur, Maastricht, Mumbai, Munich, New Delhi, Osaka,

Paris, Parma, Phuket, Pune, Rio de Janeiro, Shenzhen, Sofia, Stockholm, Taipei, Tel Aviv, Tokyo, Trieste, Trivandrum, Utrecht, and Wuhan.

6. I have been held qualified to testify as an expert in patent law and procedures in more than 90 cases in federal court including cases relating to biotechnology, DNA, and recombinant processes.

7. A copy of my *curriculum vitae* is attached as Exhibit A. If called upon to do so, I will go through my *curriculum vitae* to discuss the contents..

II. The Current Litigation

8. I understand that this is a patent infringement action instituted by Amgen for infringement of United States Patent Nos. 5,411,868 ("the '868 patent"), 5,547,933 ("the '933 patent"), 5,618,698 ("the '698 patent"), 5,621,080 ("the '080 patent), 5,756,349 ("the '349 patent") and 5,955,422 ("the '422 patent"). I understand that each of the patents-in-suit shares a common specification with, and claims priority to, United States Patent No. 4,703,008 ("the '008 patent") which expired in 2004. The '008 patent issued from a string of four continuation-in-part applications, with the earliest application filed on December 13, 1983. I understand that the continuation-in-part applications filed on February 21, 1984 (Ser. No. 16/582,185), September 28, 1984 (Ser. No. 06/655,841) and November 30, 1984 (Ser. No. 06/675,298) all added new information to the common specification.[1]

9. I am aware that Amgen has submitted a motion for summary judgment alleging that Roche's MIRCERA™ and CERA products literally infringe claim 1 of the '422 patent, claim 3 of the '933 patent and claim 6 of the '698 patent. I have reviewed the related

[1] When citing to information set forth in the common specification, I generally cite to the '868 patent.

memorandum, statement of facts and declaration submitted by Harvey F. Lodish, Ph.D. in connection with Amgen's motion for summary judgment. As explained below, the prosecution histories of the patents-in-suit demonstrate that Amgen is not entitled to all "EPO-like" molecules, such as EPO analogs and derivatives, "synthetic polypeptides . . . having a biological property of naturally-occurring human erythropoietin," and proteins "sufficiently duplicative" of EPO.

III. Amgen Surrendered The Subject Matter That It Now Tries To Claim In Litigation

A. Amgen Surrendered Claims to DNA Sequences Encoding Analogs, "Synthetic Polypeptides" and Proteins "Sufficiently Duplicative" of EPO

10. Each of the patents-in-suit claims priority to the expired '008 patent and, through the parent applications of the '008 patent, claims a priority date of December 13, 1983. The '008 patent, entitled "DNA sequences encoding erythropoietin," issued from Ser. No. 06/675,298 ("the '298 application") which was filed on November 30, 1984. The '008 patent issued on October 27, 1987 and expired in 2004.

11. Because each of the patents-in-suit is a related continuation application claiming priority to the expired '008 patent, the prosecution histories of each of the patents-in-suit is relevant to determining: (1) what Amgen expressly claimed as its invention in the asserted claims-in-suit; and (2) what subject matter Amgen surrendered during prosecution in exchange for the Patent Office issuing its claims. Upon review of the file histories of the patents-in-suit, it is clear that Amgen's product claims do not cover all "EPO-like" molecules, such as EPO analogs and derivatives, "synthetic polypeptides . . . having a biological property of naturally-occurring human erythropoietin," and proteins "sufficiently duplicative" of EPO. During prosecution of the asserted claims, Lin expressly explained to the Examiners (and the public) what his claims did cover, cancelled claims to other potential products and processes, and was

required to surrender subject matter that Amgen is now trying to recapture in litigation. This is not permissible.

1. Prosecution of the '698 Patent

12. United States Application Serial No. 113,179 (" the '179 application"), filed October 23, 1987, led to the '868 patent (discussed below) and is also the basis for the '698 patent-in-suit. The '698 patent issued from Application Serial No. 08/468,381 ("the '381 application"), filed June 6, 1995 as a continuation of the '179 application. (Ex. 22, '381 File History, Paper 1, Application; Ex. 23, Paper 3a, 6/6/95 Continuing Application Transmittal).[2] The '698 patent includes claim 6 which issued from file claim 72:

> 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. 45, '698 patent, claim 6 (emphasis added); Ex. 26, '381 File History, Paper 9, 12/20/96 Second Preliminary Amendment at 7-8; *see also* Ex. 24, '381 File History, Paper 7, Interview Summary, Claims D and E).

13. Claim 6 of the '698 patent was first introduced into the '381 application ***after*** the Patent Office had already issued the parent '868 patent. (Ex. 24, '381 File History, Paper 7, 12/11/96 Interview Summary). Claim 6 of the '698 patent includes the limitation "DNA

[2] 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.

encoding the mature erythropoietin amino acid sequence of FIG. 6" as compared to the limitation "DNA sequence encoding human erythropoietin" of claim 1 of the '868 patent. Indeed, because the claim language is so similar between the '868 patent and the '698 patent, to consider the patentability of file claim 72, the Applicant agreed to file a terminal disclaimer over the '868 patent. (Ex. 24, '381 File History, Paper 7, 12/11/96 Interview Summary; *see also* Ex. 25, '381 File History, Paper 8, 12/20/96 Terminal Disclaimer; Ex. 26, '381 File History, Paper 9, 12/20/96 Second Preliminary Amendment at 10). Claim 6 of the '698 patent, like the claims of the '868 patent, also are limited by the '179 application prosecution history to a process for the production of a glycosylated erythropoietin polypeptide. (*See infra* ¶¶ 41-49). Thus, chemically produced products cannot literally infringe claim 6 of the '698 patent.

14. Moreover, in *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, this Court and the Federal Circuit explained that the limitation "the mature erythropoietin amino acid sequence of FIG. 6" requires that the resulting amino acid be a 166 amino acid residue. *See* 314 F.3d 1313, 1345 (Fed. Cir. 2003). I understand that Amgen asserts that CERA "contains" 165 amino acids, not 166. Therefore, even if Amgen's allegations that CERA contains EPO are credited, Roche's products cannot literally infringe claim 6 of the '698 patent.

2. Prosecution of the '422 Patent

15. On November 6, 1990, Applicant filed United States Application Serial No. 07/609,741 ("the '741 application"), entitled "Production of Erythropoietin," which eventually led to the issuance of the '422 patent after the filing of additional continuation applications Serial No. 07/957,073 ("the '073 application") and Serial No. 08/100,197 ("the '197 application"). The '741 application was filed as a continuation application under 37 C.F.R. § 1.60 of the prior '179 application (which issued as the '868 patent), and claims priority through the expired '008 patent

to a December 13, 1983 filing date. (Ex. 29,'741 File history, Paper 1, 11/6/90 Application). I also note that the '422 patent was terminally disclaimed over both the '933 patent (discussed below) and the '080 patent, as well as U.S. Patent No. 5,856,298. (Ex. 7, '178 File History, Paper 32, 4/21/99 Examiner Interview Summary; Ex. 20, Paper 33, 4/28/99 Amendment at 4; Ex. 8, '197 File History, Paper 35, Terminal Disclaimer).

16. Claim 1 of the '422 patent claims:

> 1. 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. 47, '422 patent).

17. As originally filed and prosecuted, the '741 application included claims 48 and 49:

> 48. A synthetic polypeptide having part or all of the amino acid sequence set forth in Table VI, other then a sequence of residues entirely within the sequence numbered 1 through 20, and having a biological property of naturally-occurring human erythropoietin.
>
> 49. A synthetic polypeptide having part or all of the secondary conformation of part or all of the amino acid sequence set forth in Table VI, 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. 28, '741 File History, Application Claims at 102; *see also* Ex. 31, Paper 4, 4/6/92 Office Action). I note that Table VI was subsequently redesignated as Figure 6 in the common specification. (Ex. 30, Paper 2, 11/6/90 Preliminary Amendment at 2, 4, 5, 6 and 8).

18. Applicant then added claims 61 through 63:

> 61. An erythropoietin-containing, pharmaceutically acceptable preparation wherein human serum albumin is mixed with erythropoietin.

> 62. A preparation 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.

(Ex. 17, '197 File History, Paper 2, 11/6/90 Preliminary Amendment at 8 (adding claims 61-63)).

19. With claims 1-63 pending in the application, the Examiner entered a restriction requirement where Group I included claims 48 and 49 and Group VII included claims 61-63. (Ex. 21,'197 File History, Paper 4, 4/6/92 Office Action at 2). Applicant elected Group VII, thereby removing claims to a synthetic polypeptide having part or all of the amino acid sequence set forth in Figure 6 from the instant application.

20. The Examiner then rejected each claim under §103 over several references (Miyake *et al.*, Takezawa *et al*. and Bock *et al.*) and because the Applicant admitted that "'[s]tandard diluents such as human serum albumin' may be used in the claimed pharmaceutical compositions." (Ex. 18, '197 File History, Paper 20, 6/1/94 Office Action at 3). The Examiner further explained that:

> It should be noted that the instant specification in general and claim 63 in particular is addressed towards the use of erythropoietin that is prepared using recombinant DNA technology. Within the paragraph bridging pages 18 and 19 of the specification, applicant states that.
>
> > 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 <u>in vivo</u> and <u>in vitro</u> biological activity) of naturally occurring erythropoietin. These polypeptides are also uniquely characterized by being the product of procaryotic or eucaryotic host expression ... of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis ... Depending upon the host employed, polypeptides of the invention may be glycosylated with mammalian or other eucaryotic carbohydrates or may be non-glycosylated.
>
> From this quotation, it 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 sequence and biological properties of naturally occurring erythropoietin is envisioned. Therefore, the EPO recited in the claims reads directly upon natural isolates and the basis of the instant rejection as explained above properly establishes that the claimed invention would have been ***prima facie*** obvious.

(*Id*. at 4 (ellipses in original)).

21. In response, Applicant Lin submitted arguments in an attempt to overcome the rejections. (Ex. 35, '197 File History, Paper 23, 12/1/94 Request for Reconsideration; Ex. 36, Paper 25, 3/3/95 Amendment and Declaration of Richard D. Cummings, Ph.D.). However, the Examiner dismissed the arguments explaining that:

> [T]he Declaration by Dr. Richard Cummings ... has been considered but is not deemed persuasive in regard to distinguishing the subject matter of claim 63, drawn to recombinant EPO, from that found in urine. While the declaration indicates some forms of recombinant EPO may be alternatively glycosylated, the use of the generic term "recombinant" fails to impose any definitive physical limitation on the claimed compositions.

(Ex. 19, '197 File History, Paper 26, 3/31/95 Letter (emphasis added)).

22. After a lapse in prosecution, Applicant cancelled claims 61-63 in favor of file claims 64 and 65 which eventually issued as claims 1 and 2 of the '422 patent. (Ex. 20, '197 File History, Paper 33, 4/28/99 Amendment at 3). Applicant explained that the amino acid sequence of human erythropoietin as recited in claim 64 is disclosed in Examples 1, 7 and 10 of the common specification. (*Id.* at 4-5). Admittedly, Example 1 does not disclose the full 165-amino acid sequence of human urinary EPO but only specific discrete fragments (*Id.*; Ex. 43, '868 patent, col. 16:9-40) and Examples 7 and 10 are directed to the human erythropoietin disclosed by the specification by Figure 6. However, the polypeptide disclosed by Figure 6 is a human erythropoietin with a 166-amino acid sequence. In the alternative, it also may include the two alternative translation products disclosed during the prosecution of the '008 patent.

23. To secure claim 1 of the '422 patent, the Applicant narrowed his claim from "erythropoietin" to "human erythropoietin" to overcome prior art objections and explained that the new limitation was based on examples 1, 7 and 10 – not some other product. Moreover, with respect to chemically synthesized products with amino acid sequences, Amgen cannot rebut the presumption that the subject matter was surrendered during prosecution of the applications leading to the '422 patent especially because it cancelled all claims to "synthetic polypeptide having part or all of the amino acid sequence" set forth in Figure 6 from the patent. Moreover, in the related applications as discussed above, including the direct parent application – Ser. No. 07/113,179 – Lin also surrendered subject matter to synthetic polypeptides.

3. Prosecution of the '933 Patent

24. On October 23, 1987, Applicant filed United States Application Serial No. 113,178 (" the '178 Application"), entitled "Production of Erythropoietin," which, following the filing of additional continuing applications (Ser. No. 08/202,874 ("the '874 application") and Ser. No. 08/487,774 ("the '774 application"), led to the issuance of the '933 patent. The '178 application is a continuation of the '298 application and claims priority back to December 13, 1983.

25. I understand that Amgen has asserted claim 3 of the '933 patent and dependent claims 7-9, 11-12 and 14, which incorporate each limitation of claim 3. Claim 3 recites:

> 3. 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 reticulocytes and red blood cells.

(Ex. 44, '933 patent, claim 3 (emphasis added); *see also* claims 7-9, 11-12 and 14).

26. During prosecution of the applications that led to the '933 patent, Applicant Lin 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 File History, Application Claims at 97, 101, 102 (emphasis added), *see also* File Claim 49).

27. Like Examiner Giesser during prosecution of the '024 application, Examiner Kushan rejected claims 1, 7, 41 and 48 (as well as other claims) of the application that led to the '933 patent under §112 as indefinite and not enabled stating:

> With respect to the actual physical properties, such as amino acid sequence and degree and locations of glycosylation, the actual physical characteristic in question should be presented. The terms "part or all of" [and] "sufficiently duplicative of" ... do not particularly nor adequately point out the distinctions from native erythropoietin (EPO) ... For example, the "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. 9, '178 File History, Paper 4, 6/2/86 Office Action at 3-5 (emphasis added)). The Examiner also rejected the claims under §102 and §103.

28. Examiner Kushan also held that claims to "synthetic polypeptides" were not enabled by the common specification stating:

> 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)).

29. In response, Applicant canceled claims 1, 7 and 48 (as well as other claims). (Ex. 10, '178 File History, Paper 6, 12/1/88 Amendment and Reply at 3). Lin also amended claim 41 to read:

> –41. (Amended) A glycoprotein having a primary structural conformation and glycosylation sufficiently duplicative of that of a naturally occurring human erythropoietin to allow possession of [one or more of the biological properties thereof] 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*.).[3]

30. In arguing to overcome the §112 rejections, Applicant stated that:

[3] Pursuant to Patent Office procedure when amending a claim deleted language is placed in brackets [ ] and added language is underlined. Here, the underlining and bracketing is part of the original document.

> At the time of Applicant's invention, nothing was known of the primary structural conformation (amino acid sequence) of human erythropoietin except the identity of a few of the amino acid residues. It was the present Applicant who first developed knowledge of the full amino acid sequence of erythropoietin ....
>
> Having provided the public with its first knowledge of naturally occurring erythropoietin's primary structural conformation. Applicant has provided the pubic [sic] with the wherewithal for determining the extent to which any sequence of amino acids may function, in vivo, as though it were the sequence encoded by the erythropoietin gene in the human genome. No impermissible vagueness attends claiming glycoproteins which share that amino acid sequence to an extent sufficient to allow the products to function, in vivo, as erythropoietin hematopoietic agents. Thus, the term "sufficiently duplicative of" as applied to [the] amino acid sequence needed for the specified in vivo biological activity is not violative of the requirements of the second paragraph of 35 U.S.C. §112.

(*Id*. at 8-9 (emphasis added)). As discussed above, however, the common specification discloses to the public that the "primary structural conformation (amino acid sequence) of human erythropoietin" is 166 amino acids.

31. After failing to overcome the examiner's §112 rejection (Ex. 11, '178 File History, Paper 9, 2/10/89 Office Action), Applicant canceled claim 41 without prejudice, and submitted new claim 67:

> –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 File History, Paper 11, 6/2/89 Amendment at 1 (emphasis added)). Applicant argued for patentability of file claim 67 stating:

> Claims 41, 55-57, and 61-66 were rejected under 35 U.S.C. 112, first and second paragraphs. Reconsideration is requested in view of the above-noted new claims and the remarks that follow.

> All product claims in the subject application are now product-by process claims. Independent Claim 67, and thus all the pending claims, specifically define the erythropoietin of the subject invention as a "glycoprotein product of the expression of an exogenous DNA sequence in a eucaryotic host cell ...." 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. It is submitted that the claims now pending herein fully meet the requirements of 35 USC 112.

(*Id*. at 3-4 (emphasis added)).[4] In arguing for reconsideration of the §103 rejection of claim 41 in view of new file claim 67, Applicant stated: "The claims of the subject invention relate to erythropoietin which is produced through recombinant DNA techniques." (*Id*. at 4 (emphasis in original)).

32. Despite Applicant's submission of new file claim 67 and his accompanying argument, Examiner Kushan maintained his rejection under §112 regarding the use of primary conformation sufficiently duplicative of human erythropoietin:

> Claim 67 to 75 are rejected under 35 U.S.C. 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
>
> 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

[4] A product-by-process claim is a particular form of claim permitted by the Patent Office. A product-by-process claim allows an applicant to draft a product claim that defines the claimed product in terms of the process by which it is made. (Ex. 243, MPEP §2173.05(p) (8th ed. Rev. 5, Aug. 2006); Ex. 244, MPEP §706.03(e) (5th ed. Rev. 6, Oct. 1987)). If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is not patentable even though the prior product was made by a different process. (*Id*.).

> 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. 3, '178 File History, Paper 13, 6/20/89 Office Action at 3 (emphasis added)). Thus, the Patent Office explained that Applicant was entitled only to the product (defined as a product-by-process) that had the amino acid sequence of human erythropoietin, which the common specification discloses as 166 amino acids, and that Lin was not entitled to analogs "sufficiently duplicative" of human EPO. The Examiner also rejected claim 67 under §102 and §103. (*Id*. at 5).

33. In response, claim 67 was amended to read:

> 67. (Amended) A non-naturally occurring glycoprotein product of the expression of an exogenous DNA sequence in a non-human eucaryotic host, 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 reticulocytes and red blood cells and having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin.

(Ex. 4, '178 File History, Paper 15, 7/11/89 Amendment at 1 (underline in original)). He also argued that:

> Claims 67-75 stand rejected under 35 U.S.C. §112, first and second paragraphs. Reconsideration is requested.
>
> Regarding point 1 raised by the Examiner, the phrase "a primary structural conformation" particularly points out the subject matter which applicant regards as the invention, and is defined at page 19, line 2, of the subject specification as a "continuous sequence of amino acid residues." Further, page 90, lines 10-17 state "While the deduced sequences of amino acid residues of mammalian EPO provided by the illustrative examples essentially define the primary structural

> conformation of mature EPO, it will be understood that the specific sequence of 165 amino acid residues of monkey species EPO in Figure 5 and the 166 residues of human species Epo in Figure 6 do not limit the scope of useful polypeptides provided by the invention." Thus, it can be seen that the phrase "primary structural conformation" as used in the specification and claims, relates to amino acid sequence.
>
> Regarding point 2, Claim 67 relates to a recombinant glycoprotein product having a "primary structural conformation and glycosylation sufficiently duplicative of that of naturally occurring human erythropoietin to allow possession of in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells." Applicant submits that the disclosure of the subject invention supports a claim of this breadth. Example 11, for example, relates to analogs of naturally occurring human erythropoietin, and the specification clearly enables one of skill in the art to prepare additional analogs having the properties claimed.

(*Id*. at 3-4 (emphasis added)). Accordingly, the Applicant was still arguing that human erythropoietin had 166 amino acids, but that he should be entitled to analogs of that sequence as well.

34. Subsequently, however, Applicant canceled claim 67 in favor of claim 76 which did not include the language "having a primary structural conformation":

> –76. 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. 6,'178 File History, Paper 19, 1/10/90 Amendment at 1 (emphasis added)). Applicant cancelled claims 67-75 which "stand rejected under 35 U.S.C. 112 first and second paragraphs." (*Id*. at 5; *see also* Ex. 5, Paper 17, 12/1/89 Examiner Interview Summary Record). He noted that new claims 76-83 were "similar" to the cancelled claims, but "specify that the DNA sequences

encode human erythropoietin" which the specification states is 166 amino acids. (Ex. 6, '178 File History, Paper 19, 1/10/90 Amendment at 5).

35. Applicant Lin also noted that the new claims, including file claim 76, were drafted to "parallel claim 2" of the '008 patent that had recently been held valid in *Amgen Inc. v. Chugai, Pharm. Co.*, 13 U.S.P.Q.2d 1737 (D. Mass. 1989). (*See* Ex. 6, '178 File History, Paper 19, 1/10/90 Amendment at 5). Claim 2 of the '008 patent claimed: "2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin." (*Id.* at 6). Based on the validity of claim 2 of the '008 patent, Applicant argued that:

> 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 ….
>
> * * *
>
> The decision is thought to be fully dispositive of not only the priority of the invention issues in both interferences, and any priority issue in the subject application. Therefore, it 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 changed)).

36. The *Amgen v. Chugai* decision, however, also held that claim 7 (and its dependent claims) of the '008 patent invalid under §112 for lack of enablement. Claim 7 of the '008 reads:

> 7. 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. 40, '008 patent, claim 7 (emphasis added)). Invalid claim 7 of the '008 patent has claim language similar to that of cancelled claim 67 which, as discussed above, required "a primary

structural conformation ... sufficiently duplicative of that of a naturally occurring human erythropoietin". Thus, the Court, like Examiner Kushan, found this language did not comply with §112. The Court noted that various parts of the common specification did not enable a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin. *See* 13 U.S.P.Q.2d at 1776 (citing to the '008 patent, col. 37:1-4, 11-41 (regarding, for example, "polypeptide analogs of EPO and fragments of 'mature' EPO" and "polypeptide fragments duplicating only a part of the continuous amino acids")).

37. The Federal Circuit affirmed that claim 7 of the '008 was invalid under §112 using different reasoning. *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213-14 (Fed. Cir. 1991). Like Examiner Kushan's previous rejections to claims reciting the limitation "sufficiently duplicative of" during prosecution of the application that led to the '933 patent, the Court found "that more 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." *Id.* at 1214.

38. By canceling file claim 67 which broadly claimed "a primary structural conformation ... sufficiently duplicative of that of a naturally occurring human erythropoietin" – which is similar to the broad language of claim of the '008 that attempted to not only cover human EPO but "analogs" as well – in favor of language paralleling claim 2 of the '008 patent, the Applicant narrowed the scope of his claimed invention in filing claim 76.

39. In any event, file claim 76 was also eventually cancelled from the prosecution. (Ex. 34, '874 File History, Paper 37, 6/13/94 Preliminary Amendment). Similarly, file claim 99

– which Applicants represented as having text identical to claim 76 (Ex. 32, '774 File History, Paper 45, 6/7/95 Preliminary Amendment at 2) – was also canceled in favor of different claims. (Ex. 33, '774 File History, Paper 50, 12/20/95 Second Preliminary Amendment at 2). For example, asserted claim 3 of the '933 patent issued from file claim 102 including the limitation to a "glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin." (*Id.*).

40. Review of the file history demonstrates that to overcome the Examiner's various rejections during prosecution of the '933 patent, Applicant Lin chose to prosecute the asserted claims of the '933 patent to issuance without the limitations (1) "having part or all of the primary structural conformation ... of naturally-occurring erythropoietin," (2) "part or all of the primary structural conformation of human erythropoietin as set forth in Figure 6 or any naturally occurring allelic variant thereof," (3) "primary structural conformation sufficiently duplicative of that of a naturally-occurring erythropoietin" or (4) "a synthetic polypeptide having part or all of the amino acid sequence set forth in Figure 6", which were rejected in file claims 1, 7, 41, 48 and 67. As a result of Lin's amendments and decision to cancel claims to overcome the Examiners' rejections, Amgen abandoned any potential patent coverage to the subject matter and can not now assert that the claims cover that same subject matter that they had to surrender in exchange for securing the asserted claims of the '933 patent from the Patent Office.

B. Amgen Argued to the Patent Office that EPO is an "Obligate Glycoprotein" that Requires Glycosylation for *In Vivo* Activity

1. Prosecution of the '868 Patent

41. The '179 application, filed October 23, 1987, and entitled "Production of Erythropoietin," led to the issuance of the '868 patent on August 15, 1995. (Ex. 43, '868 patent). The '179 application was filed as a continuation application under 37 C.F.R. §1.60 of the prior

'298 application filed on November 30, 1984 and claims priority through applications to December 13, 1983. (Ex. 12, '179 File History, Paper 1). In addition to leading to the '868 patent-in-suit, the '179 application also is a direct parent application to both the '698 patent and the '422 patent. (Ex. 74, Amgen Patent Tree).

42. Issued claim 1 of the '868 patent is:

> 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.

(Ex. 43, '868 patent, claim 1 (emphasis added); *see also* claim 2 (limiting the host cell to CHO cells)).

43. During prosecution, in 1988, Applicant introduced, *inter alia*, claim 65 (and dependent claims):

> –65. A process for the preparation of an in vivo biologically active glycosylated polypeptide comprising the steps of:
>
> (a) growing a mammalian host cell which is capable of effecting post-translational glycosylation of polypeptides expressed therein which is transformed or transfected with an isolated sequence encoding a polypeptide having a primary structural conformation sufficiently duplicative of that of 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, or the progeny thereof, under nutrient conditions suitable to allow, in sequence,
>
> (i) transcription within said host cell of said DNA to mRNA in the sequence of transcription reactions directed by the nucleotide sequence of said DNA;

> (ii) translation within said host cell of said mRNA to a polypeptide in the sequence of translation reactions directed by the nucleotide sequence of said transcribed mRNA;
>
> (iii) glycosylation within said host cell of said polypeptide in a pattern directed by the amino acid sequence of said translated polypeptide and sufficiently duplicative of the pattern of glycosylation of naturally occurring human erythropoietin to allow possession by the translated glycosylated polypeptide product of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells; and
>
> (b) isolating the glycosylated polypeptide so produced.

(Ex. 16, '179 File History, Paper 8, 5/24/88 Second Preliminary Amendment at 3-4 (emphasis added)).

44. In arguing for patentability of claim 65, Lin explained that the claimed invention "relates to novel methods for the production in mammalian host cells of human erythropoietin glycoprotein – the first article of human manufacture ever to possess both the amino acid sequence and glycosylation needed for in vivo erythropoietin biological activity." (*Id.*, Ex. 16 Paper 8 at 6; *see also* Ex. 13 Paper 14, 9/27/88 Reply). Lin plainly stated that the claimed invention was the process for making "human erythropoietin glycoprotein" in "mammalian host cells", not a chemical process for making a different product which is not erythropoietin.

45. For over seven (7) years Lin repeatedly defined the metes and bounds of his claimed process within the Patent Office as a method for making an *in vivo* biological human erythropoietin (as defined by the common specification). For example, during prosecution of the '868 patent Lin made the following statements regarding the scope of his process claims:

- "As set out in detail hereafter, the practice in late 1983 of processes herein claimed is believed to constitute one of the first instances (if not the first instance) of the recombinant production of an in vivo biologically active obligate human glycoprotein ...." (Ex. 16, '179 File History, Paper 8, 5/24/88 Second Preliminary Amendment at 6).

- "[I]ndependent claim 65 relates to a novel series of process steps wherein a mammalian host cell capable of glycosylating the expressed polypeptides is first transformed or transfected with a DNA sequence encoding a specifically delineated polypeptide ...." (Ex. 16, '179 File History, Paper 8, 5/24/88 Second Preliminary Amendment at 6 (footnotes omitted)).
- "The claim 65 process calls for host cell growth in culture under conditions wherein transcription, translation and glycosylation processing occurs. More particularly, the claim calls for mRNA transcript formation according to the per se unique directions provided by the recited DNA sequence." (*Id.* at 6-7).
- "Claims 65 through 69 are pending. Briefly summarized, independent claim 65 relates to a novel series of process steps wherein a mammalian host cell capable of glycosylating the expressed polypeptides is first transformed or transfected with a DNA sequence encoding a specifically delineated polypeptide ...." (Ex. 13, '179 File History, Paper 14, 9/26/88 Applicant's Reply at 2).
- "Further required by claim 65 is the glycosylation processing of the translated polypeptide at sites directed by the order of amino acids of the translated polypeptide so that the resulting product, upon isolation, will have the pattern of glycosylation which is also required for in vivo biological activity." (*Id.* at 3).
- "Applicant has disclosed the production of *in vivo* biologically active erythropoietin in mammalian cells and has specifically exemplified the production of *in vivo* biologically active monkey and human species erythropoietin in monkey (COS) and Chinese Hamster Ovary (CHO) cells." (Ex. 15, '179 File History, Paper 33, 1/3/94 Applicant's Reply at 5).

46. Similarly, to overcome prior art rejections made by the Examiner during prosecution, Lin further explained that his claims were limited to processes for isolating a specific product – the "obligate glycoprotein" human erythropoietin rather than any other product. (Ex. 16, '179 File History, Paper 8, 5/24/88 Second Preliminary Amendment at 8-10, 15-19). For example, Lin argued that:

> The skilled worker at the time of the present invention would thus have understood that if preparations of <u>in vivo</u> biologically active human erythropoietin were to be provided in therapeutic quantities by recombinant means, a method would have to be devised whereby (a) an appropriate array of glycosylation including sialic acid terminal residues and, possibly, penultimate galactose residues would be provided on (b) a polypeptide with requisite amino acid sequence homology to erythropoietin. Unlike other human glycoproteins such as the interferons and Interleukin-2, <u>human erythropoietin was conspicuously known to be an obligate glycoprotein and no hope at all existed for isolating in vivo active material from recombinant host cells unless, at a minimum, both the issues</u>

> of required polypeptide sequence and of required glycosylation could be successfully attended to.

(Ex. 16, '179 File History, Paper 8, 5/24/88 Second Preliminary Amendment at 10 (emphasis added)). Thus, the literal scope of the process claims, as explained by Lin during prosecution of the '179 application, is limited to processes for making a glycosylated human erythropoietin polypeptide not a chemically synthesized product such as Roche's MIRCERA™ and CERA products.

47. There is no question that the Patent Office was led to believe that Lin's method was limited to a process for making human erythropoietin. For example, Lin relied upon the his resulting product to overcome prior art processes and secure his method claims:

> As set out in greater detail in the PTO-1449 Statement scheduled to be submitted imminently, the references generally dealt with recombinant expression of non-human glycoproteins, or recombinant expression of human glycoproteins which are not obligate glycoproteins and do not require glycosylation for in vivo activity, or recombinant expression of fragments of human obligate glycoproteins.
>
> * * *
>
> Applicant submits that the results of the above-described searches and analysis provide a clear indication that the claimed methods as practiced in 1983 were among the first, if not the first, instances of the successful production of an in vivo biologically active obligate human glycoprotein.

(Ex. 16, '179 File History, Paper 8, 5/24/88 Second Preliminary Amendment at 16-17, 19 (emphasis added); *see also* Ex. 13, '179 File History, Paper 14, 9/26/88 Applicant's Reply at 5 ("As set forth in detail at pages 16 through 20 of the Second Preliminary Amendment, it appears that Applicant may have been the first to have successfully produced a human obligate glycoprotein by recombinant methods.").

48. Lin's continued reliance on the distinction of his end-product for years to overcome prior art rejections of his process claims in the Patent Office plainly shows what he

claimed as his invention. (Ex. 15, '179 File History, Paper 33, 1/3/94 Applicant's Amendment and Reply at 11 ("As previously maintained by Applicant, his production of in vivo biologically active glycosylated erythropoietin was among the first, if not the first, demonstrations of production of a biologically active obligate human glycoprotein."). During prosecution of his process claims Lin argued that "the core patentability issue is whether the prior art extant at the time of the present invention provided the skilled artisan with a reasonable expectation of success in securing the recombinant production of a human obligate glycoprotein..." (Ex. 13, '179 File History, Paper 14, 9/26/88 Applicant's Reply at 3-4 (emphasis added)). Thus, the patentability of Lin's process claims relies on isolating a glycosylated human erythropoietin polypeptide, not a chemically made product such as Roche's CERA.

49. Indeed, when Lin attempted to claim a process for making a product other than the human erythropoietin disclosed by the common specification, his claims were rejected and ultimately cancelled. In rejecting Lin's application claims for violation of 35 U.S.C. §112, the Examiner recognized the proper scope of Lin's claimed process acknowledging only that: "Applicant claims a process for the preparation of a biologically active glycosylated polypeptide." (Ex. 14, '179 File History, Paper 29, 9/1/93 Office Action at 9-10). The Examiner noted that "the specification provides guidance for and a working example of only the production of EPO" and that "the instantly claimed invention is critically dependent on an isolated clone of encoding a polypeptide of interest. (*Id*. at 10). Thus, the Patent Office required Lin to limit his claimed process to "a process for the preparation of biologically active glycosylated human erythropoietin" (*id*.) and rejected claims to other processes and claims for processes to make other products. Lin acquiesced to the Examiner's requirement and subsequently limited his pending claims as required by the Patent Office in exchange for his issued process claims. (Ex.

15, '179 File History, Paper 33, 1/3/94 Amendment and Response at 2; Ex. 43, '868 patent claims). As a result, Amgen cannot now broaden Lin's process claims to cover more than what the Patent Office allowed him to claim during prosecution.

2. Prosecution of the '933 Patent

50. Likewise, during prosecution of the application that led to the '933 patent, Lin made clear that the '933 claims are limited to human erythropoietin as an obligate glycoprotein -- not other products -- and relied on this distinction to overcome rejections by the examiner.

51. To overcome a rejection under 35 U.S.C. §112 Amgen argued that:

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

(Ex. 10, '178 File History, Paper 6, 12/1/88 Amendment and Reply at 9).

52. Similarly, Lin also explained that the claimed product was limited to the human erythropoietin disclosed by the specification:

> 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.

(Ex. 2, '178 File History, Paper 11, 6/2/89 Amendment at 4).

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed this 29th day of June at Southfield, Michigan.

June 29, 2007 /s/ Martin J. Adelman
Martin J. Adelman

CERTIFICATE OF SERVICE

I hereby certify that this document filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on the above date.

/s/ Keith E. Toms
Keith E. Toms

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