EXHIBIT A

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

CONTAINS RESTRICTED ACCESS BLA/IND CONFIDENTIAL INFORMATION

SUBJECT TO PROTECTIVE ORDER

FOURTH EXPERT STATEMENT OF RICHARD A. FLAVELL, PH.D. IN RESPONSE TO VARIOUS ARGUMENTS RAISED BY AMGEN'S EXPERTS

originally derived from Chinese hamster ovary ("CHO") cells. Dr. Kolodner shipped aliquots of the conditioned medium to the Clinical Chemistry Laboratories at the University of Chicago Hospitals and Clinics ("University of Chicago"). Technicians at the University of Chicago ran radioimmunoassays ("RIA") on the conditioned medium using a commercial kit, designed to detect erythropoietin in serum or plasma from patients. These technicians were not directly supervised by Dr. McLawhon.

8. I have reviewed and agree with the invalidity reports submitted by Dr. Zaroulis on April 6, 2007, and Dr. Kadesch on May 24, 2007. Based on the indefiniteness of the claims of the '349 patent, I agree with the views of Dr. Zaroulis and Kadesch that one of skill in the art could not ascertain whether a particular cell line is "capable of" meeting the specified production levels. Assuming however, as Amgen's experts do, that the claims simply require measurement using radioimmunoassay under any culture conditions for any 48-hour period, for the reasons detailed below it is my opinion that the tests that Amgen conducted fail to establish that Roche's production cell line meets the limitations of any of claims 1-6 of the '349 patent. Because Roche does not employ the claimed cells, it cannot practice a process requiring their use, and therefore does not infringe asserted Claim 7. Moreover, because Amgen's tests did not replicate the exact conditions employed by Roche, these tests cannot provide evidence that Roche practiced the process of Claim 7.

A. Claim Construction for "Erythropoietin"

9. Amgen argued in its Markman brief that the term "human erythropoietin" as used in the specification "refers to polypeptides having the same amino acid sequence of amino acid

residues as naturally occurring erythropoietin."[4] This meaning of "human erythropoietin" was confirmed by Amgen's counsel at the Markman Hearing:

> Amgen's construction is a protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine. . . . Roche's construction differs. And I've highlighted on the right what is importantly different about Roche's construction. First of all, they say it's not a protein. They say it's a glycoprotein. That means that it must have glycosylation. It has the amino acid sequence of erythropoietin isolated from human urine. So they agree with us about the amino acid sequence.[5]

Further, Amgen's construction was adopted by the Court, and therefore "human erythropoietin" in the context of the claims of the patents in suit means a polypeptide having the amino acid sequence of erythropoietin isolated from human urine, which I understand to be 165 amino acids.[6] Amgen's expert Dr. Lodish agrees with my understanding.[7]

10. Although the term "erythropoietin" was not construed in isolation, the patent defines "erythropoietin" as an acidic glycoprotein of approximately 34,000 dalton molecular weight,[8] and states that the invention provides for polypeptides having the primary structural

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[4] Amgen's Markman Brief at 16 (citing specification).

[5] Markman Hearing Tr. at 27, ll. 8-23. See also Markman Hearing Tr. at 29, ll. 16-18 ("Amgen construes human erythropoietin as referring to the amino acid sequence of human erythropoietin as isolated from urine.").

[6] Markman Hearing Tr. at 39, ll. 7-10 ("Here's what we're going to do. At this stage and for these purposes we're going to adopt Amgen's proposed construction. I'll reflect on whether I'll add the glycoprotein before the word, substitute it for protein."). I have been told by counsel for Roche that other claims generally directed to fragments or analogs of erythropoietin were either not allowed by the Patent Examiner or held to be invalid by the Courts.

[7] See Expert Report of Harvey F. Lodish, Ph.D. Regarding Infringement, dated Apr. 6, 2007 (the "Lodish Report") at ¶26 ("Human EPO has a primary structure consisting of a polypeptide backbone with 165 amino acid residues. The amino acid sequence for human EPO is depicted at position +1 through +165 in Figure 6 of Amgen's patents.").

[8] '349 patent, col. 5, ll. 47-48.

concerning the standard to be used in the assay makes it impossible to determine whether, in fact, a sample contains a given number of Units of EPO using RIA.

67. Claim 7 of the '349 patent is invalid for lack of enablement for several reasons. First, the patent fails to disclose sufficient information to teach one of skill to correlate RIA results with biological assay results. The patents further fail to instruct how to determine the number of Units of erythropoietin in an unknown sample having an unknown specific activity. The limitation in the claim therefore invites one of skill to *guess* the specific activity or *assume* that it is equal to that of the standard used in the assay. Finally, Claim 7 is not enabled because there is no instruction on how to discriminate between "erythropoietin" according to the claims and erythropoietin fragments or analogs, or other materials that are not erythropoietin.

IV. MY OPINION DOES NOT CHANGE THAT THE CLAIMS LACK INDEFINITENESS AND LACK WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112

68. In his Supplemental Expert Report,[74] Dr. Lodish presents a lengthy rebuttal of the invalidity positions I raised in my Corrected Supplemental Expert Report dated May 8, 2007. Dr. Bradshaw presents similar opinions in his Rebuttal Report.[75] If I understand Amgen's experts' positions correctly, Drs. Lodish and Bradshaw believe that the patent specification provides "sufficient guidance to a person of ordinary skill in the art to understand the metes and bounds of Dr. Lin's claimed inventions."[76] For the same reasons, Amgen's experts opine that the specification adequately describes "human erythropoietin" as defined by Amgen and accepted by

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[74] Supplemental Expert Report of Harvey F. Lodish, Ph.D. dated June 4, 2007 (the "Lodish Supplemental Report").

[75] *See generally* Rebuttal Report of Ralph A. Bradshaw, Ph.D. to New Non-Infringement Arguments Raised in the Rebuttal Reports of Defendants' Experts dated June 1, 2007.

[76] Lodish Supplemental Report ¶ 13.

the Court at the April 17, 2007 Markman hearing.[77] Having read and considered Amgen's experts' respective positions, I see no reason to alter my original opinion, and therefore disagree.

69. At the outset, I am not sure that Dr. Lodish has the proper understanding of the legal bases underlying his opinions. For example, Dr. Lodish states that to satisfy the definiteness standard of ¶ 112, claims only need be "sufficiently specific" and that claims "may not be precise."[78] He further states that "[t]he claim language need only be as precise as the subject matter permits."[79] Dr. Lodish's understanding differs from mine. However, I note that the "subject matter" of the claimed invention is human erythropoietin having a specific 165 amino acid sequence. As such, I believe the specification must set forth the boundaries of the claimed invention in a clear and unambiguous manner and provide information about this exact sequence. Concerning written description, Dr. Lodish believes that the specification describes the invention as "finally claimed in the patent" demonstrating that the inventor possessed the means to make, obtain, or use the invention as claimed." Although I do not necessarily agree with this understanding of the legal basis for the written description requirement, I believe that "human erythropoietin" as claimed is not adequately described for all the reasons outlined in my previous report.

70. Dr. Lodish's belief that the patent specification discloses sufficient information to be definite and to have adequate written description is simply not supportable by the evidence he relies on. For example, Dr. Lodish's opinion that Dr. Lin deduced the correct protein sequence for human erythropoietin ignores the fact that the specification also discloses a protein sequence

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[77] Markman Hearing Tr. at 27, 39.
[78] Lodish Supplemental Report ¶ 7.
[79] *Id.*

having a different amino acid residue at a given position. In the face of conflicting information, it would be impossible for one of skill to comprehend the exact amino acid sequence of human erythropoietin.

71. Dr. Lodish relies on a portion of the specification in to support his opinion that the patent claims cover a broad "scope of useful polypeptides."[80] In my opinion, this potentially broad scope makes it even more essential that the invention *as claimed* be adequately described and definite. I also believe that claims directed to "human erythropoietin," in light of the Court's current claim construction for this term, are not adequately described by a class of polypeptides, and for the same reason, are indefinite.

72. In contrast to Dr. Lodish, I believe that a single amino acid error in the sequences provided in Table 1 of the patent specification is quite meaningful. This is especially the case in the context of a patent specification, in which an inventor is seeking to exclude others from practicing a claimed invention for the public in exchange for an accurate description of its true scope. Dr. Lodish acknowledges that the sequence for human erythropoietin was later deduced from urinary isolates.[81] In my opinion, later confirmation of ambiguous information is not evidence that the inventor was in possession of the invention at the time his application was filed. The fact that in 1983 "microsequencing of peptides had an appreciable chance of error" simply requires that the inventor should have taken additional measures to "get it right" in disclosing and claiming his invention. I disagree with Dr. Lodish's suggestion that faced with discrepancies one of skill would have focused on the DNA sequence to deduce the protein

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[80] *See id.* ¶ 15 (quoting '933 patent, col. 35, ll. 10-17).
[81] *Id.* at ¶ 16 (quoting Lai, et al. (1986) *J. Biol. Chem.*, 261:3116-21).

sequence. In my opinion, discrepancies would have suggested that additional work must be performed to conclusively determine the proper amino acid sequence of a protein.

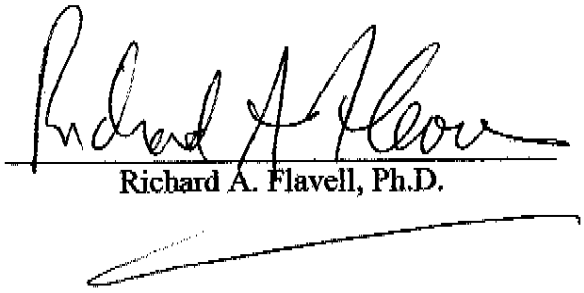
73. Dr. Lodish mentions that the patent purports to cover "allelic forms" of human EPO.[82] I do not dispute that allelic forms were known to one of skill in the art at the time of the invention. However, the polypeptides identified by Dr. Lodish as being allelic forms – one having a methionine at position 126 and the other having a serine – is not an example of an allelic form, but rather is disclosure of an error. Thanks to the Lai *et al.* paper, published well after the filing date of the Lin patents, it is clear that the disclosure of the sequence in the tryptic fragment was incorrect. In my opinion, one of skill in the art would not have automatically suspected that this discrepancy was an allelic form, but rather, a simple discrepancy that needed further clarification.

74. But even if this change was one of the "allelic forms" it wouldn't matter. Human erythropoietin according to the claims is specifically limited to the 165-amino acid polypeptide isolated from human urine. Disclosure of a broad class of polypeptides (assuming that such a class even exists, which in this case it does not) cannot suffice for specifically identifying and describing the single polypeptide covered by the claims.

75. Dr. Lodish's reliance on hemoglobin beta as an example of a protein having allelic forms is particularly interesting.[83] Only a few atoms' difference between the normal and sickle cell anemia variants of the protein is capable of producing a radically different function and a serious

[82] *Id.* at ¶¶ 17, 18.
[83] *Id.* at ¶ 18.

Dated: June 13, 2007



Richard A. Flavell, Ph.D.