EXHIBIT A

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

AMGEN'S [PROPOSED] REPLY TO ROCHE'S OPPOSITION TO AMGEN'S BENCH MEMORANDUM REGARDING EVIDENCE OF INFRINGEMENT OF '349 CLAIM 7

Roche's opposition (D.I.1361) to Amgen's bench memorandum regarding evidence of infringement of claim 7 of the '349 patent (D.I.1339) only reinforces the sufficiency of the evidence of record establishing that Roche's commercial cell line meets the minimum EPO production requirements recited in the '349 patent claims. Dr. Lodish's testimony, based on Roche's own documents, provides three separate and sufficient bases for a finding of infringement of '349 claim 7:

1. Dr. Lodish's opinion that Roche's cells are capable upon growth in culture of producing EPO in excess of 100 U per 10^6 cells in 48 hours based upon his

review of and reliance upon radioimmunoassay tests performed by Dr. McLawhon on Roche's cells grown in culture by Dr. Kolodner.[1]

2. Dr. Lodish's calculation based on data reported in Roche's BLA (Ex. 52) that Roche's commercial cells produce "in round numbers 1,500 units of EPO per million cells in 48 hours." This calculation was based upon an ELISA assay reported in the BLA which Dr. Lodish described as "a similar assay" to a radioimmunoassay – "both assays use an antibody to EPO which binds specifically to EPO to measure how much EPO is in the culture fluid" – and the results "would be very similar, if not identical."[2]
3. Roche's BLA shows that Roche follows the teachings of Example 10 in Dr. Lin's patents to make the EPO component of peg-EPO. Using these steps, the same cells described in Dr. Lin's Example 10 produced EPO well in excess of the production levels recited in the '349 claims.[3] Since Roche follows these same steps, it would be more than reasonable for the jury to conclude that Roche's cells are capable of achieving the same "high level of expression of EPO" as Dr. Lin's cells.

Against this compelling evidence, Roche offers only unsupported attorney argument criticizing Dr. Lodish's testimony regarding the EPO production rate of Roche's commercial cell line. But Roche's attorney argument is not evidence and cannot undermine the testimony and documentary evidence of record. Roche argues that in doing his calculation based on the ELISA assay data in Roche's BLA, Dr. Lodish misapplied the specific activity number for the EPO in

[1] Trial Tr. 2452:19 – 2455:11.

[2] Trial Tr. 2449:23 -2451:15.

[3] Trial Ex. 1, Col. 26, lines 43 – 65; Col. 28, lines 6-10.

peg-EPO because that number was measured using an *in vivo* mouse bioassay, while ELISA is an *in vitro* assay. Roche complains that "Dr. Lodish mixes apples and oranges." But there is no evidence that using specific activity in this way is inaccurate. Dr. Lodish is an expert with "extensive experience" in reading and interpreting ELISA and radioimmunoassay results.[4] He testified that the specific activity number "allows one to convert micrograms to international units, which is another measure of EPO that is spelled out in the patent."[5] Roche could have raised this issue on cross-examination of Dr. Lodish, but did not. Consequently, Roche's attorney argument about Dr. Lodish's calculation is completely unsupported by the evidence of record.[6]

Based on ELISA data from Roche's BLA, Dr. Lodish calculated that Roche's commercial cell line, the DN2-3α3 cells, produce 7.4 micrograms of EPO per 10^6 cells in 48 hours.[7] Dr. Lodish identified where Roche admitted in its BLA that the EPO produced by Roche's cells in the medium of their growth has an activity of 207 units per microgram.[8] Dr. Lodish then testified that he was "able to calculate [the number of international units of EPO per 10^6 cells for 48 hours]" based on these numbers in the BLA and testified that by his calculation

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[4] Trial Tr. 2450:16 -21.

[5] Trial Tr. 2447:22 -24.

[6] Indeed, Dr. Lodish's method, far from being "unorthodox," as Roche asserts, is consistent with other evidence of record in this case. For example, in the Miyake *et al.* (1977) paper, Dr. Goldwasser reported that his purified urinary EPO preparation had an activity of 70,400 U/mg of protein as determined by the "fasted rat method of bioassay." Exh. 2002 at 5558. In his 1979 paper, Dr Goldwasser reported that this "preparation of pure erythropoietin . . . [with] a potency of 70,400 U/mg protein" was used as a standard to calculate the results from his *in vitro* EPO radioimmunoassays. Exh. 2082 at 885. Thus, skilled workers like Dr. Goldwasser use the activity of an EPO preparation determined in an *in vivo* assay to calculate results from *in vitro* assays such as a radioimmunoassay.

[7] Trial Transcript, 2443:10–2446:19. The Roche BLA contains ELISA data showing that Roche's cells produce 3.7 micrograms of erythropoietin per million cells in 24 hours.

[8] *Id*. at 2448:4–2448:16.

the Roche cells are capable of producing "in round numbers 1,500 units of EPO per million cells in 48 hours."[9]

Roche likewise offers only attorney argument, rather than any actual evidence, in an attempt to rebut Dr. Lodish's testimony that, based on his extensive experience with both radioimmunoassay (RIA) and ELISA procedures, the two assays are very similar[10] and would therefore be expected to give very similar, if not identical, results.[11] Dr. Lodish explained why the two assays yield comparable results:

> [B]oth assays use an antibody to EPO which binds specifically to EPO to measure how much EPO is in the culture fluids. In a radioimmunoassay one uses radioactive tracers to monitor how much antibody is bound to EPO. In ELISA, it's a similar assay except one uses an enzyme attached to the antibody as a measure. …
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> Both assays use a purified standard of erythropoietin as an internal control. So one is measuring the reactivity of an unknown substance to the reactivity of a known amount of EPO, and it s very simple then to calculate how much EPO there is in this unknown sample. And since they're both antibody-based assays, use similar antibodies, the results should be very similar if not identical, as they are.[12]

Roche's expert Dr. Flavell has admitted that the two assays work in similar ways to determine the concentration of EPO in a sample.[13] Further, as pointed out in Amgen's bench memorandum, this Court has previously recognized the comparability of results from ELISA and RIA assays.[14]

Based solely on Dr. Lodish's unrefuted expert testimony and the admissions in the Roche BLA, a reasonable juror could conclude that Roche's DN2-3α3 cells are capable of producing

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[9] *Id*. at 2450:1-9.

[10] *Id*. at 2443:25–2444:1; 2450:11–2451:16.

[11] *Id*. at 2451:21–2452:16.

[12] Trial Tr. 2451:9 -2452:16

[13] Non-Infringement Expert Report of Richard A. Flavell, Ph.D. at ¶ 129.

[14] *Amgen, Inc. v. Hoechst Marion Roussel, Inc*., 126 F. Supp. 2d 69, 120 (D. Mass. 2001).

erythropoietin at the rate recited in '349 claim 1 when grown in a process for producing erythropoietin as recited in '349 claim 7.

In its Opposition, Roche attempts to make a mountain out of an evidentiary molehill in criticizing Dr. Lodish's reliance upon the radioimmunoassay results from Dr. McLawhon.[15] In fact, the Court's refusal to admit the test results is perfectly compatible with Dr. Lodish's testimony regarding those results. Fed. R. Evid. 703 specifically provides that "the facts or data [relied upon by an expert in forming opinions or inferences] need not be admissible in evidence in order for the opinion or inference to be admitted."[16] Having reviewed the reports of Drs. Kolodner and McLawhon, Dr. Lodish testified that their results further supported his opinion regarding infringement.[17] A reasonable juror is entitled to credit that testimony, regardless of whether the results themselves are ultimately admitted.[18]

As noted above, the third basis upon which a reasonable jury could conclude that Roche's commercial cell line meets the requirements of the '349 claims is that Roche followed the teachings of Example 10 in Dr. Lin's patents in producing human EPO. As Dr. Lodish testified, and as Roche's BLA demonstrates, Roche makes its recombinant human erythropoietin by using the same starting CHO cell line containing a viral promoter, using methotrexate to create

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[15] Contrary to Roche's hyperbolic and unsubstantiated assertion, Dr. McLawhon ***never*** stated in his deposition (or anywhere else) that the radioimmunoassay tests in his report were "fundamentally flawed."

[16] As the Court stated in sidebar, "[Dr. Lodish] can give us his opinion based on those [EPO radioimmunoassay] results. But he can't give us the results. That's how 702 works." Trial Tr. at 2453:10-13.

[17] Trial Transcript at 2452:18–2453:3; 2454:11–2455:11.

[18] Roche's position here in attacking an expert's opinion testimony is in stark contrast to its position on its own experts, who against the higher clear and convincing standard gave unsupported opinion testimony regarding the purported obviousness and invalidity of the patent claims.

amplified EPO DNA in the cells, and growing the cells in suitable culture medium, all as Dr. Lin described and claimed in his patent.

Roche uses the same CHO cell line (DuX-B11) as Dr. Lin described in Example 10[19]; Roche inserted human EPO DNA with a viral promoter/SV40 enhancer and the DHFR gene into that CHO cell line, as described in the patent[20]; Roche used the same method of gene amplification by increasing levels of methotrexate to achieve "high level expression of EPO"[21]; and grew the cells in a suitable culture medium.[22] Using these same steps, the cells described in Dr. Lin's Example 10 produced EPO well in excess of the production levels recited in the '349 claims.[23] Since Roche followed these same steps, it would be more than reasonable for the jury to conclude that Roche's cells would achieve the same "high level of expression of EPO" so as to satisfy the '349 patent claims.

Finally, Roche criticizes Amgen's arguments concerning infringement based on the doctrine of equivalents. Based on an out-of-context quote from *Genentech, Inc. v. Boehringer Mannheim GmbH,* 47 F. Supp. 2d 91, 107 (D. Mass. 1999),[24] Roche contends that infringement under 35 U.S.C. § 271(g) requires a showing of literal infringement. It does not. Rather, § 271(g)

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[19] Trial Tr. 2409:3 -20.

[20] Trial Tr. 2408:9 -25; 2455:12 – 2456:7. Cf. Trial Ex. 1, Col. 24:12 -14; Col. 25:45-60.

[21] Trial Tr. 2409:23 -2410:7; Trial Ex. 52, p. 4723. *Cf.* Trial Tr. 1962:14 -1963:18; Trial Ex. 1, Col. 26, lines 19-65.

[22] Trial Tr. 2417:16 -22.

[23] Trial Ex. 1, Col. 26, lines 43 – 65; Col. 28, lines 6-10.

[24] Because the doctrine of equivalents was not at issue in *Genentech*, the defendant having conceded literal infringement, any such language would be, at best, *dicta*.

requires a showing of **direct** infringement, either literally or under the doctrine of equivalents.[25] Dr. Lodish's testimony quoted above regarding the nature of the two assays – ELISA and radioimmunoassay – provides more than adequate basis for a finding of infringement under the doctrine of equivalents (if literal infringement is not found).

Conclusion

Dr. Lodish's testimony, based on Roche's own documents as well as the reports from Drs. Kolodner and McLawhon, provides three separate and sufficient bases for finding infringement of '349 claim 7. Roche's opposition to Amgen's Bench Memorandum merely reinforces the sufficiency of this evidence in establishing that Roche's accused cells are capable of producing EPO at the rate required by '349 claim 7. Roche's criticisms of Dr. Lodish's testimony consist of mere attorney argument, not evidence, and should be rejected.

[25] *Trustees of Columbia Univ. in City of New York v. Roche Diagnostics GmbH*, 272 F. Supp. 2d 90, 100–103 (D. Mass. 2002) (explaining, at p. 100, that "[i]f the product shipped by Roche into the United States was made by a process that did not **directly** infringe upon Columbia's patents, then Roche cannot have violated Section 271(g)," and going on to analyze whether Genetics Institute, on which Roche's liability depended, infringed the patents-in-suit either literally or under the doctrine of equivalents, at p. 100–103).

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Respectfully Submitted,

AMGEN INC.,
By its attorneys,

/s/ Michael R. Gottfried

D. DENNIS ALLEGRETTI (BBO#545511)
MICHAEL R. GOTTFRIED (BBO#542156)
DUANE MORRIS LLP
470 Atlantic Avenue, Suite 500
Boston, MA 02210
Telephone: (857) 488-4200
Facsimile: (857) 488-4201

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

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

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

Of Counsel:

STUART L. WATT
WENDY A. WHITEFORD
MONIQUE L. CORDRAY
DARRELL G. DOTSON
KIMBERLIN L. MORLEY
ERICA S. OLSON
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, CA 91320-1889
(805) 447-5000

CERTIFICATE OF SERVICE

I hereby certify that this document, filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of electronic filing and paper copies will be sent to those indicated as non-registered participants on October 14, 2007.

/s/ Michael R. Gottfried
Michael R. Gottfried