UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, vs. F. HOFFMANN-LA ROCHE LTD; ROCHE DIAGNOSTICS GmbH; and HOFFMANN-LA ROCHE INC. Defendants.	CIVIL ACTION No.: 05-CV-12237WGY

EXHIBIT I TO DECLARATION OF HOWARD S. SUH IN SUPPORT OF ROCHE'S MOTION FOR SUMMARY JUDGMENT THAT THE ASSERTED CLAIMS OF THE '933 PATENT ARE INVALID FOR INDEFINITENESS AND LACK OF WRITTEN DESCRIPTION

Dated: June 15, 2007
Boston, Massachusetts

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

By their attorneys,

/s/ Nicole A. Rizzo
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EXHIBIT I

UNITED STATES DISTRICT COURT
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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

EXPERT REPORT OF HARVEY F. LODISH, Ph.D. REGARDING INFRINGEMENT

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EPO polypeptide contains four potential sites ("glycosylation sites") at which chains of carbohydrates can be attached – three N-linked glycosylation sites (where a carbohydrate structure is attached to an asparagine amino acid residue) and one O-linked glycosylation site (where a carbohydrate structure is attached to a serine amino acid residue).[7] These carbohydrate structures (called "oligosaccharides") comprise many different structures and can be attached in a variety of different ways. For example, at each of the N-linked glycosylation sites, the oligosaccharide can have two branches ("bi-antennary"), three branches ("tri-antennary"), or four branches ("tetra-antennary"). A detailed overview of the cellular processes for building oligosaccharide chains of glycoproteins is set forth in my textbook, *Molecular Cell Biology*, at pp. 673-75, which I incorporate by reference.

31. For human EPO produced in mammalian cells, as for other glycoproteins, there is considerable heterogeneity in the carbohydrate structures at any given glycosylation site. The heterogeneity takes two forms: the number of branches (or "antennae") in the chain, which as noted above can be 2, 3, or 4, and the number and nature of the carbohydrate residues which make up the branches. In particular, a negatively charged carbohydrate residue, sialic acid (also called N-acetyl neuraminic acid) may or may not be present at the end of each branch. The maximum total number of sialic acid residues that may be present on the carbohydrate chains on each human EPO molecule is 14 (*i.e.*, one sialic acid attached to the end of each of the four branches of each of the three N-linked chains (a total of 12), and one sialic acid residue attached to each of the two branches of the single O-linked chain (a total of two).

32. The different forms of EPO glycoprotein having different overall carbohydrate structures are called "isoforms" or "glycoforms." EPO produced by a single cell typically

[7] Figure 6 of the Lin specification identifies the N-linked glycosylation sites at positions +24,

consists of a heterogeneous mixture of different isoforms, which all share the same amino acid backbone, but differ in their glycosylation patterns. Because each EPO isoform can have different numbers of sialic acid residues (from 0 to 14), they also differ in charge. Attached as Exhibit I are three-dimensional representations of various isoforms or glycoforms of human EPO. Exhibit I1 depicts representations of EPO isoforms with sialic acid contents of 9, 12, 13, and 14 and Exhibit I2 shows the sialic acids in purple.

33. Isoforms of EPO that are more highly sialylated (*i.e.*, those that have more tri- and tetra-antennary structures in which most of the branches end in sialic acid) exhibit a longer half-life in the body, lower binding affinity to the EPO receptor, and greater biological activity than do isoforms of EPO glycoprotein which are less sialylated.

34. Despite the fact that these isoforms of EPO are structurally distinct molecules with different molecular weights, different binding affinities, different half-lives in the body, and different degrees of biological activity, scientists in the fields of molecular biology and biochemistry today (as well as in 1983-84) consider each of these molecules to be human erythropoietin because each shares the same polypeptide "backbone" comprised of the same amino acid sequence.[8]

35. Given the natural microheterogeneity of EPO isoforms, a single graphic cannot depict all of the possible variations of the attached carbohydrate structure. Moreover, unlike the EPO polypeptide backbone which can be imaged via x-ray crystallography, the structure of the carbohydrate chains on EPO molecules cannot be visualized using such techniques. But given

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+38, and +83 with asterisks. (Exh. 104 at Col. 21:10-11).

[8] Lin's patent specification teaches that human EPO is not limited to glycosylated human EPO, but also includes non-glycosylated human EPO, including non-glycosylated EPO produced in *E. coli* cells. (Exh. 104 at Cols. 10:25-33, 29-32).

products – activating EPO receptors to initiate the JAK2/STAT5 signaling pathway. Neither peg-EPO's increased half-life in the bloodstream nor its reduced binding affinity represent a significant difference or fundamental change in principle with respect to how peg-EPO functions. MIRCERA™ is also a pharmaceutical composition that is not changed in principle from, performs the same function as, and achieves the same result in substantially the same way as the pharmaceutical compositions claimed in the Amgen Patents, because it contains the glycosylated human EPO polypeptide that functions in the same way to achieve the same result as the human EPO claimed in the Amgen Patents.

Executed this 6th day of April, 2007 at Boston, Massachusetts.

HARVEY F. LODISH, PH.D.