IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

AMGEN, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 05-12237 WGY
	)	
F. HOFFMANN-LA ROCHE LTD., ROCHE DIAGNOSTICS GmbH, HOFFMANN-LA ROCHE INC.,	)	
	)	
Defendants.	)	

AMGEN'S OPPOSITION TO ROCHE'S MOTION FOR SUMMARY JUDGMENT THAT CLAIM 7 OF THE '349 PATENT IS INVALID UNDER 35 U.S.C. § 112 AND IS NOT INFRINGED

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I. INTRODUCTION

Plaintiff Amgen Inc. ("Amgen") submits this Memorandum of Law in opposition to "Roche's Motion For Summary Judgment That Claim 7 Of Patent No. 5,756,349 Is Invalid Under 35 U.S.C. § 112 And Is Not Infringed" (Docket No. 539) (hereinafter "Roche's Motion").

Roche makes three arguments that the term "U of erythropoietin . . . as determined by radioimmunoassay" in '349 claims 1-6 renders '349 claim 7 invalid as indefinite,[1] not described and not enabled.[2] None of those arguments has merit.[3]

Roche's first argument about this term, that the claim is invalid because "RIA measures more than 'erythropoietin,'" should be rejected because it is based solely on attorney argument and speculation. Roche has not pointed to ***any*** evidence that a radioimmunoassay that would have been used by one of ordinary skill in 1983-84 to measure EPO produced by cells growing in culture according to '349 claim 7 would have detected "non-EPO molecules" produced by those cells, and ***no*** evidence that one of ordinary skill would not have understood the scope of '349 claim 7.

Roche's second argument, that a "Unit" of EPO should be construed as referring only to the *in vivo* biological activity of a sample of EPO, should be rejected as an untimely claim construction argument that is contradicted by virtually every prior-art publication discussing

[1] All of Roche's arguments about the purported indefiniteness of "U of erythropoietin . . . as determined by radioimmunoassay" and "capable of" in the '349 claims should be rejected on procedural grounds as untimely. Roche had every opportunity to request that these claim terms be construed during the *Markman* proceedings in this case, but did not do so. Roche should not be permitted to raise these issues of claim construction for the first time at this late date, in the guise of a motion for summary judgment.

[2] Roche says that '349 claim 7 lacks written description and is not enabled for the same reasons that it argues the claim is indefinite. These assertions cannot justify summary judgment for the same reasons.

[3] Roche's arguments that the "U of erythropoietin . . . as determined by radioimmunoassay" limitation is indefinite are particularly disingenuous in light of the fact that Roche offered to stipulate that its cells satisfy this limitation of the '349 claims. *See* Exh. 29.

EPO radioimmunoassays (including the publications by Roche's retained expert witnesses Drs. Zaroulis, Fisher, Gaylis and Shouval), as well as the '349 patent itself. All of these used the term "Units" to describe the amount of EPO determined by radioimmunoassay. There is ***no*** evidence whatsoever that one of ordinary skill in 1983-84 would have understood "Units" to refer only to the *in vivo* biological activity of EPO.

Roche's third argument, that "claims 1-6 are hopelessly indefinite for failing to disclose a particular standard to use in the RIA specified by the claim," likewise is absolutely contradicted by the prior-art scientific literature that discussed the use of radioimmunoassays to measure EPO. As Roche admits, there were multiple EPO preparations available to one of ordinary skill in 1983, and as is evident from the prior-art scientific literature, virtually any of those preparations could have been used as a standard in the radioimmunoassay called for by the '349 claims. Roche tries to rely on Amgen documents to support its argument, but those documents do not contain even a single suggestion that the results of a radioimmunoassay of an unknown sample containing EPO would differ depending on the standard used in the assay.

Roche also attacks the term "capable" in '349 claims 1-6 as rendering claim 7 indefinite because according to Roche, saying that the cells of claims 1-6 are "capable" of producing certain amounts of EPO means that "claim 7 thus covers production of 'erythropoietin' without regard to how much is actually being produced, as along as the vertebrate cells employed will produce, ***under some set of conditions***, the 'U of erythropoietin' recited in claims 1-6" (emphasis added). This argument is incorrect because it ignores the fact that '349 claim 7 is directed to "a ***process for producing erythropoietin*** comprising the step of culturing, under

suitable nutrient conditions," the cells of claims 1-6 (emphasis added).[4] As Roche's expert Dr. Kadesch admitted in his deposition, and as Amgen's expert Dr. Lodish has stated in his expert report, the plain language of claim 7 requires that the "vertebrate cells" of claims 1-6 must be "capable" of producing the recited amounts of EPO ***when used in the process of claim 7***, not when used "under some set of conditions."[5]

Finally, Roche says that Amgen cannot prove infringement of '349 claim 7 because Amgen's expert, Dr. Kolodner, did not grow Roche's cells under the conditions used by Roche to produce the EPO in its peg-EPO product. Amgen's expert witnesses, Dr. Kolodner (who grew Roche's cells in culture), Dr. McLawhon (who determined the amount of EPO produced by those cells using an FDA-approved radioimmunoassay) and Dr. Lodish (who analyzed the procedures and results provided by Drs. Kolodner and McLawhon, as well as Roche's submissions to the FDA), have provided and rely upon substantial evidence showing that the process Roche uses to produce the human EPO in its peg-EPO product satisfies all of the limitations of '349 claim 7. Roche has not submitted ***any*** actual evidence to counter the findings of Drs. Kolodner, McLawhon, and Lodish. The most Roche has done is to offer conclusory attorney arguments based on nothing more than speculation (including by its retained expert Dr. Kadesch, who by his own admission has ***no*** experience with radioimmunoassays of any kind). As a matter of law, that cannot be sufficient to justify grant of summary judgment of non-infringement.

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[4] Claims 1-6 in turn recite "vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of [100/500/1000] U of erythropoietin . . . as determined by radioimmunoassay . . ." (claims 1-3) or "which upon growth in culture are capable of producing . . . in excess of [100/500/1000] U of erythropoietin . . . as determined by radioimmunoassay" (claims 4-6).

[5] Roche also argues that "the 'capable of' language is not a patentable limitation." (Roche's Motion at 17). It is impossible to know what Roche means by "patentable limitation," but obviously the Patent Office determined that this was a valid limitation when it issued the '349 claims.

II. ARGUMENT

A. '349 claim 7 is not indefinite

1. The legal standards for indefiniteness

The second paragraph of 35 U.S.C. § 112 provides that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." As the Federal Circuit has explained, "if the claims, read in light of the specification, *reasonably* apprise those skilled in the art both of the utilization and scope of the invention, and if the *language is as precise as the subject matter permits*, the courts can demand no more."[6] The '349 claims are presumed valid,[7] so Roche must establish indefiniteness by clear and convincing evidence,[8] a burden made even greater here on a motion for summary judgment.

2. The '349 claims at issue

Amgen is asserting '349 claim 7 against Roche. Claim 7 recites:

> A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5, or 6.[9]

Claim 7 depends from any of claims 1-6. Two of those claims, claims 1 and 4, are

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[6] *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986), quoting *Shatterproof Glass Corp. v. Libbey-Owens Ford Co*., 758 F.2d 613, 624 (Fed. Cir. 1985) (emphasis added) (reversing holding of indefiniteness of patent for immunoassays where district court's basis was that "there is no standard set of experimental conditions which are used to estimate [the antibody] affinities [recited in the claims]"). *See also Miles Laboratories, Inc. v. Shandon Inc.*, 997 F.2d 870, 874 (Fed. Cir. 1993) (Section 112 is satisfied where a claim has "a clear and definite meaning when construed in the light of the complete patent document.").

[7] The claims of an issued patent "shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim. . . . The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." 35 U.S.C. § 282.

[8] *See*, *e.g.*, *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 148 (D. Mass. 2001) ("*Amgen I*").

[9] Exh. 2 at Col. 38, lines 34–36.

independent claims. Claim 1 recites:

> Vertebrate cells which can be propagated *in vitro* and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin.[10]

The other independent claim, claim 4, recites:

> Vertebrate cells which can be propagated *in vitro* which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours.[11]

3. Roche's speculation about "fragments" and "non-EPO" materials cannot render '349 claim 7 indefinite

Roche's Motion should be denied because the claim phrase "U of erythropoietin . . . as determined by radioimmunoassay" had a clear and definite meaning to one of ordinary skill in the art in 1983-84 when read in the light of Dr. Lin's '349 patent specification.

Roche asserts that '349 claim 7 is indefinite because a radioimmunoassay "measures more than 'erythropoietin'" and can measure "other materials like EPO fragments that bind to anti-EPO antibodies."[12] Yet Roche offers absolutely no ***evidence*** that establishes this point. Without any actual ***evidence*** that makes its point,[13] Roche resorts to mischaracterizing the testimony of Amgen's experts. Roche says that during his deposition Dr. McLawhon admitted

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[10] Exh. 2 at Col. 38, lines 8–14. Claims 2 and 3 depend from Claim 1 and recite higher EPO production rates: "in excess of 500 U of erythropoietin per 10^6 cells in 48 hours" for Claim 2 and "in excess of 1000 U of erythropoietin per 10^6 cells in 48 hours" for Claim 3.

[11] *Id*. at Col. 38, lines 21–27. As for Claims 2 and 3, Claims 5 and 6 recite EPO production rates in excess of 500 U (Claim 5) or 1000 U (Claim 6) per million cells in 48 hours.

[12] Roche's Motion at 7-8.

[13] *See* Exh. 41 at 203:6 to 206:14, 209:11 to 210:15, and 213:24 to 227:20; Exh. 42 at 119:21 to 126:24; 129:16 to 130:24; 162:10 to 169:12; 234:7 to 235:2; 238:18 to 239:19; 243:17–21; 245:13 to 248:6; 262:8 to 263:13; and Exh. 43 at 64:21 to 71:10; 154:15–21; 156:2–15; 273:12–20. All exhibits cited herein are attached to the Declaration of Cullen N. Pendleton in Support of Amgen Inc.'s Opposition filed concurrently herewith.

that an EPO radioimmunoassay will measure EPO fragments or other "non-EPO" molecules. He did not. In fact, he explicitly refused to speculate as to whether an anti-EPO antibody used in a radioimmunoassay will measure "fragments."[14] Roche says that during his deposition Dr. Goldwasser admitted that an EPO radioimmunoassay measures EPO fragments. He did not. Rather, he merely related what he would have done in a hypothetical situation.[15] Roche points to one of Dr. Goldwasser's published articles to support its argument, but the discussion in that article relates only to a possible theoretical explanation for experimental observations. Moreover, Roche omits the fact that Dr. Goldwasser and his co-authors later submitted a retraction of that theoretical explanation. Although Dr. Goldwasser could not discount the possibility that he had observed fragments in his published study, he offered the retraction because the data was unreliable.[16]

Roche points to statements in the '349 patent about monoclonal antibodies that recognize peptides as well as EPO. But these references are irrelevant to the issue of whether "U of erythropoietin . . . as determined by radioimmunoassay" is indefinite, because Roche does not and cannot establish that one of ordinary skill in 1983 would have used these antibodies in an radioimmunoassay to measure the amount of EPO produced by cells claimed in the '349 patent.

Even if there were evidence that Roche's cells produced the "EPO fragments" postulated by Roche (and there is absolutely no evidence to even suggest that they do), Roche has made ***no***

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[14] *See* Exh. 7 at 220:4–7 ("Q: So it doesn't necessarily have to be the entire hormone that's reacting with the antibody? It could be a fragment? A: That's speculation.").

[15] *See* Exh. 19 at 49:14 to 50:2 ("Q: But the RIA itself couldn't tell you whether it was a fragment or whether it was the entire epo protein? A: Well, if you put in something of small molecular size, the RIA would tell you there was an immunologically reactive material that was not called epo.").

[16] *See* Exh. 9 (Goldwasser *et al*. (1991), *Endocrinology* 128(1):440) ("In an earlier paper . . . . It was suggested the difference [between the results of bioassay and RIA of serum samples for EPO] might be accounted for by the presence of biologically inactive, immunoreactive, fragments of erythropoietin . . . . We now find that those results were artefactual.").

factual showing regarding the expected effect of such "EPO fragments" on the number of units of EPO determined by radioimmunoassay. Roche's argument consists solely of a ***hypothesis*** that unidentified EPO "fragments" of unspecified origin might react with an anti-EPO antibody in a radioimmunoassay to produce incorrect results. In order to prevail on summary judgment, however, Roche must do more than merely hypothesize the existence of "EPO fragments": it must establish that there is no genuine issue of material fact regarding the existence and effect of such fragments in an EPO RIA. Roche has presented ***no*** evidence of this whatsoever. Likewise, Roche's repeated assertion that "cross-reactive impurities" and "other substances" could react with an anti-EPO antibody to produce false results in a radioimmunoassay is simply baseless speculation: Roche neither identifies any such "impurities" or "other substances," nor does it offer one iota of evidence that any such substance is produced by cells in culture, much less that the scope of claim 7 would be rendered indefinite as a consequence.[17]

There is really no question that one can use a radioimmunoassay to measure the amount of EPO in a biological sample. Roche admitted as much in its Motion,[18] in its proposed stipulation that its process satisfies this limitation of the '349 claims,[19] and in its BLA submission to the FDA.[20]

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[17] Dr. McLawhon testified that he has never encountered any substance that interferes with an EPO radioimmunoassay throughout his long experience. *See* Exh. 7 at 180:18 to 181:11. Moreover, the instruction manual for the EPO radioimmunoassay kit used by Dr. McLawhon to measure the amount of EPO produced by Roche's DN2-3α3 cells supports Dr. McLawhon's experience. That manual reports that there was no cross-reactivity with any of the proteins tested and that a search of a protein database found no proteins with substantial sequence homology to EPO. *See* Exh. 21 at 12. In light of this evidence, and drawing all reasonable inferences in Amgen's favor, Roche cannot meet its burden to obtain summary judgment of invalidity.

[18] Roche's Motion at 8.

[19] *See* Exh. 29.

[20] *See* Exh. 18 at, *e.g.*, R005312695, R005312714–16, R005312772–74; Exh. 5 at ¶¶ 36–40.

4. The claim phrase "U of erythropoietin . . . as determined by radioimmunoassay" is not indefinite

Roche argues that the claim term "U of erythropoietin . . . as determined by radioimmunoassay" in '349 claims 1-6 should be construed to mean that a radioimmunoassay is used to determine the *in vivo* biological activity of the EPO produced by the cells. This proposed construction should be rejected because it is untimely and because it is inconsistent with the language of the claim and with the intrinsic record, with this Court's previous findings, and with the plain, ordinary meaning of the claim phrase to one of ordinary skill in 1983-84.

Roche erroneously focuses only on the term "U of erythropoietin," insisting that because a "Unit" of EPO was originally coined to refer to the *in vivo* biological activity of EPO, a "Unit" necessarily bears that same meaning in all contexts at all times. It does not. The claim language itself, the intrinsic record, and the prior art all establish that the phrase "U of erythropoietin . . . ***as determined by radioimmunoassay***" would have been understood by one of ordinary skill to mean exactly what it says: that the number of Units of EPO produced by the recited cells in the process of claim 7 is to be determined by an appropriately conducted radioimmunoassay.[21]

First, claim 7 itself says nothing about measuring *in vivo* biological activity of the EPO produced by the recited cells, whether by radioimmunoassay or any other method.

Second, Dr. Lin's patent specification contradicts Roche's proposed construction. The '349 patent separately and expressly describes three types of assays for measuring the amount of EPO produced by Dr. Lin's genetically engineered cells grown in culture: a radioimmunoassay (or "RIA"), an *in vitro* cellular assay, and *in vivo* animal assays.[22] The '349 patent never refers to the determination of *in vivo* biological activity using a radioimmunoassay. To the contrary, the

[21] *See* Exh. 6 at ¶ 119, 187; Exh. 5 at ¶¶ 30–33.

[22] *See* Exh. 2 at Col. 16 line 40 to Col. 17 line 8 (radioimmunoassay) and Col. 25 lines 1–15 (*in vitro* and *in vivo* assays).

‘349 specification consistently distinguishes immunological activity determined by RIA with *in vivo* biological activity determined using an *in vivo* bioassay.[23] One of ordinary skill reading the ‘349 claim language in light of the specification could not have concluded that the claims required the determination of *in vivo* biological activity by radioimmunoassay.

This claim construction is also confirmed by the prior-art scientific literature that discussed the use of radioimmunoassays to measure EPO. Neither Roche’s Motion, nor the Expert Report of Dr. Kadesch on which it relies, cites a single scientific publication that reports the results of an EPO radioimmunoassay in any terms other than “units” of EPO. This is not surprising, because ***all*** of the prior-art publications discussing EPO radioimmunoassays, including publications by Roche’s retained experts Drs. Shouval, Fisher, Gaylis, and Zaroulis, uniformly reported the results of EPO radioimmunoassays in “Units,” “U/ml” (*i.e.*, Units of erythropoietin per milliliter of sample), or similar terms.[24] Indeed, Roche itself reported the results of EPO radioimmunoassays in terms of Units (“mU/ml”) in its own submissions to the FDA seeking approval for its peg-EPO product.[25]

All of this evidence leads to the inescapable conclusion that the claim phrase “U of erythropoietin . . . as determined by radioimmunoassay” in ‘349 claim 7 would have had a clear

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[23] *See* Exh. 2 at Col. 13:45–54 (distinguishing “immunological” properties from “*in vivo* and *in vitro* biological activities of EPO”); 14:66 to 15:12 (same); 25:65 to 26:5 (discussing “immunological properties” of EPO determined by radioimmunoassay); 27:59–67 (presenting results of radioimmunoassay, *in vitro*, and *in vivo* assays together, all in terms of “U/ml”).

[24] *See* Exh. 10 (Sherwood & Goldwasser (1979)) at, *e.g.*, 891 (Tables 2 & 3); Exh. 24 (Garcia *et al.* (1979)) at, *e.g.*, 412 (Table I and accompanying text); Exh. 23 (Zaroulis *et al*. (1981)) at, *e.g.*, 89 (Fig. 2; Tables I & II); Exh. 8 (Goldwasser and Sherwood (1981)) at, *e.g.*, 359; Exh. 28 (Rege *et al*. (1982)) at, *e.g.*, 836 (Table IV); Exh. 30 (Koeffler & Goldwasser (1981)) at, *e.g.*, 46 (Table I); Exh. 25 (Cotes *et al*. (1982)) at, *e.g.*, 430 (Table I); Exh. 31 (Thomas *et al*. (1983)) at, *e.g.*, 798 (Table 3); Exh. 32 (Garcia (1974)) at, *e.g.*, 280 (Table I); Exh. 35 (Lertora *et al*. (1975)) at, *e.g.*, 146 (Table 4); Exh. 33 (Goldwasser *et al*. (1975)) at, *e.g.*, 322 (Table 6); and Exh. 34 (Lange *et al*. (1980)) at 206–207 (Table 1).

[25] Exh. 18 at R005312695, R005312714–16, R005312772–74; Exh. 5 at ¶ 36–40.

and definite meaning to one of ordinary skill in 1983: that the claimed vertebrate cells must produce the recited amounts (expressed as a number of Units) of EPO "as determined by radioimmunoassay." Under this claim construction, '349 claim 7 is definite, enabled, and supported by an adequate written description.

5. '349 claim 7 does not require the measurement of biological activity

Roche's argument that Claim 7 is indefinite because "RIA does not measure biological activity" depends completely on Roche's untimely and incorrect "straw man" claim construction. Roche's argument ignores the fact that the phrase "U of erythropoietin" is qualified in the '349 claims by the subsequent phrase "as determined by radioimmunoassay." As discussed above, this means that the EPO production rate of the claimed vertebrate cells is to be measured using radioimmunoassay, with the results reported in Units. Claim 7 does not mention "biological activity," nor does it require that it be measured, whether by radioimmunoassay or any other assay. The claim phrase would have been so understood by one of ordinary skill, as it reflected the use of the terms in all of the prior-art scientific publications discussing radioimmunoassays for EPO, including publications by Roche's own experts,[26] and on reading the '349 patent, which distinguishes the results of radioimmunoassays and assays for *in vivo* biological activity.[27]

6. The results of an EPO radioimmunoassay do not depend on the standard used

Roche argues that Claim 7 is indefinite because "different EPO standards would produce different results in RIA," making the EPO production levels recited in the '349 claims "a moving target." This argument is incorrect for several reasons. First, Roche's legal assumption that claim 7 should be construed to require the determination of *in vivo* biological activity by

[26] *See* n.24, *supra*.

[27] *Compare* Exh. 2 at Col. 16, line 39 - Col. 17, line 9 *to* Col. 25, lines 1–15; *see also* Col. 27, lines 44–48, 59–60, and 64–65.

radioimmunoassay is incorrect, for the reasons discussed above. Second, Roche's factual assumption is incorrect because one of ordinary skill would have obtained the same results in an EPO radioimmunoassay using any properly calibrated standard.[28] The very nature and purpose of a ***standard*** is to permit laboratories to compare results over time despite differences in their samples, techniques, and reagents.[29]

Given this, it is not surprising that the prior art uniformly refutes Roche's argument. For example, Roche's expert regarding radioimmunoassays in this case, Dr. Charles Zaroulis, published a scientific article in 1981 describing the use of a radioimmunoassay to measure EPO concentrations in human serum samples. In that paper, Dr. Zaroulis and his colleagues stated that "[o]ur normal EP concentrations were similar to those reported by Sherwood and Goldwasser [26] and Garcia, Sherwood, and Goldwasser [25]."[30] In the radioimmunoassays reported in his paper, Dr. Zaroulis used a standard with a specific activity of 62 U/mg, while Drs. Sherwood and Goldwasser used a standard having a specific activity of 70,400 U/mg,[31] and Drs. Garcia, Sherwood, & Goldwasser used a standard having a specific activity of 5 U/mg.[32] Despite the fact that the three groups used three different EPO preparations as standards, preparations whose specific activities differed by as much as 14,000-fold, Dr. Zaroulis was perfectly comfortable comparing the RIA results found with each of the three standards, reporting that all of the studies

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[28] *See*, *e.g.*, Exh. 22 at 10-11 (describing calibration of successive international EPO reference standards in terms of the activity of the preceding standard); *see also* Exh. 6 at ¶¶ 128, 140, 144–50, 168, 177–78, & 183; Exh. 5 at ¶¶ 60, 83, 88, 94, & 100.

[29] *See* Exh. 6 at ¶ 144; *see also* Exh. 4 at 179:16–20.

[30] *See* Exh. 23 at 81.

[31] *See* Exh. 10 at 885 (reporting the specific activity of the pure urinary EPO used as the EPO standard as "70,400 U/mg protein, based on the activity of the [1st] International Reference Preparation").

[32] *See* Exh. 24 at 409 ("The second International Reference Preparation of human erythropoietin was used as a standard [in the reported RIA analyses].").

found "similar" EPO concentrations in the sera of normal individuals.[33]

The Cotes (1982) paper relied upon by Dr. Kadesch also compared the results of its radioimmunoassay determinations of serum EPO concentrations with the results reported in the Garcia *et al.* and Sherwood & Goldwasser papers. Dr. Cotes reported that the EPO values determined by radioimmunoassay in her study were almost identical to those reported in the previous papers, despite the fact that each group used a different EPO preparation as a standard.[34]

7. The limitation "capable of" does not render '349 claim 7 indefinite

Roche contends that the limitation "capable of" renders Claim 7 indefinite because "[c]laim 7 thus covers production of 'erythropoietin' without regard to how much is actually being produced, as long as the vertebrate cells employed will produce, under some set of conditions, the 'U of erythropoietin' recited in claims 1-6." Once again, Roche is merely attempting to set up a claim construction "straw man." Because '349 claim 7 recites a process for producing EPO using the vertebrate cells recited in any of claims 1-6, one of ordinary skill would understand the claim to require that the vertebrate cells be "capable of" producing the amounts of EPO recited in claims 1-6 ***when used in the process of '349 claim 7***. Roche's expert Dr. Kadesch admitted this during his deposition.[35] There is simply no basis for concluding that a potential infringer would be incapable of using a radioimmunoassay to determine whether, under

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[33] *See* Exh. 6 at ¶¶ 177, 183.

[34] *See* Exh. 25 at 428–29 (using 1st and 2nd IRPs as EPO standards in RIA and reporting their specific activity as 1 and 5 U/mg of protein, respectively). In addition, a 1987 paper by Egrie *et al.* reported "similar estimates of potency" and "remarkable consistency" when comparing RIAs that used different antibodies and different EPO standards. *See* Exh. 26 at 240. *See also* Exh. 6 at ¶¶ 174, 183–187. These prior-art papers also demonstrate the falsity of Roche's assertion that determining "U of erythropoietin" by RIA requires assumptions about the specific activity of the standard relative to the sample (Roche does not cite any evidence to substantiate this assertion).

[35] *See* Exh. 43 at 134:21 to 135:22.

the conditions used in his process for making EPO, the cells being used in that process were producing the amounts of EPO recited in the '349 claims. The express language of claim 7 requires no more than this.

Contrary to Roche's assertion, the "capable of" limitation is not inherently indefinite or an "unpatentable limitation."[36] The use of terms like "capable of" does not render a claim indefinite.[37] Indeed, a search of the United States Patent Office website reveals over 229,000 patents issued since 1976 containing claims that use the term "capable of," and 307 issued patents containing claims using the term "capable upon."[38]

Roche's argument that '349 claim 7 is indefinite because the claim phrase "under suitable nutrient conditions" would require one to investigate an "infinite number" of nutrient conditions to determine whether a process infringes the claim is contradicted by the plain and ordinary meaning of the phrase, and by the teachings in the '349 patent itself. The '349 patent does not suggest that one should engage in such an exercise. Rather, the patent teaches that one should use "standard cell culture conditions."[39]

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[36] Indeed, in its original answers to Amgen's interrogatories seeking Roche's invalidity contentions, Roche showed it has no difficulty understanding exactly what "capable of" means in the '349 claims. *See, e.g.,* Exh. 20 at 60 ("The claims require that claimed cells produce a specified number of 'U of erythropoietin' either 100, 500 or 1000 per 100,000 [*sic*: 10^6] cells in 48 hours.").

[37] *See*, *e.g.*, *Arlington Indus., Inc. v. Bridgeport Fittings, Inc.*, 345 F.3d 1318, 1326–27 (Fed. Cir. 2003) (construing "capable of flexing" and concluding that its simple, ordinary meaning "capable of bending" was an operative limitation). Biotechnology patent claims containing similar language have also been successfully construed (*see*, *e.g.*, *Genentech, Inc. v. Inamed Inc.*, 436 F. Supp. 2d 1080, 1084–85 (N.D. Cal. 2006) (construing "[a] process for producing human IGF-I comprising preparing a replicable expression vector ***capable of*** expressing the DNA sequence encoding human IGF-I in a prokaryotic host cell") (emphasis added).

[38] *See* Exh. 44. In particular, *see* Exh. 27 (U.S. Patent No. 4,353,982, issued to Hoffmann-La Roche Inc., wherein claim 1 is directed to a process for determining the amount of an enzyme, creatine kinase, in a sample using an antibody "***capable of*** immuno-reactively binding selectively one of the B or M subunits of the creatine kinase in the sample") (emphasis added).

[39] *See* Exh. 2 at Col. 27, lines 5–6.

Roche's final indefiniteness argument, that the purported indefiniteness of '349 claim 7 is "exacerbated" because Dr. Lin did not specify when the "48 hours" period recited in claims 1-6 is to occur is objectively baseless.[40] In his specification, Dr. Lin provided a clear description of how the period is to be measured.[41]

B. The '349 patent adequately describes and enables the process of '349 claim 7

The claims of an issued patent are presumed to be described and enabled by the specification, and Roche must prove otherwise by clear and convincing evidence.[42] Roche's Motion fails to establish that '349 claim 7 is not described or enabled by the '349 patent specification.

Adequate written description under the first paragraph of 35 U.S.C. § 112 exists where "persons of ordinary skill in the art [can] recognize that [the inventor] invented what is claimed."[43] Roche has not and cannot satisfy its burden of proving invalidity of '349 claim 7 under § 112 because the '349 patent contains an adequate written description of the process recited in claim 7. After an exhaustive analysis of the detailed written description in the '349 patent, this Court held that the '349 patent "provides sufficient description of the claimed inventions to give notice to one of ordinary skill that Dr. Lin actually possessed the invention."[44] This Court's holding was affirmed by the Federal Circuit.[45]

There can be no legitimate dispute that Example 10 of the '349 patent includes a written

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[40] Roche's arguments about written description in its instant motion, to the extent that Roche makes such arguments, should be rejected on procedural grounds because Roche ***never*** raised those arguments prior to the filing of its instant motion.

[41] *See* Exh. 2 at Col. 26, lines 35–52.

[42] *Amgen II* at 1334.

[43] *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997).

[44] *Amgen I* at 152–54.

[45] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1330–34 (Fed. Cir. 2003) ("*Amgen II*").

description of the process of claim 7.[46] The patent describes a process for producing EPO comprising the step of culturing, under suitable nutrient conditions,[47] the cell line "CHO pDSVL-gHuEPO," which is a vertebrate cell line comprising non-human DNA sequences that control transcription of DNA encoding human EPO.[48] Example 10 teaches that these cells were grown in cell culture medium for 24 hours; the medium was changed; "EPO was allowed to accumulate for 48 hours in the serum-free media," and "the media was collected for RIA assay."[49] During this 48-hour period, the EPO production rate of the cells exceeded that recited in either of claims 1 or 4.[50] Because the '349 patent contains an explicit description of the process of Claim 7 using vertebrate cells according to any of claims 1-6, the written description requirement of 35 U.S.C. § 112, first paragraph, is satisfied and Roche's argument regarding lack of written description should be rejected.

Roche's argument[51] that claim 7 is not enabled because the '349 patent does not specify a particular EPO standard to employ in the radioimmunoassay recited in the '349 claims does not come close to satisfying Roche's burden on summary judgment. Indeed, Roche's argument is irrelevant to enablement because, as the Federal Circuit has explained, "patent documents need not include subject matter that is known in the field of the invention and is in the prior art . . . ." *S3 Inc. v. nVIDIA Corp*., 259 F.3d 1364, 1371 (Fed. Cir. 2001). "The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if,

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[46] *See* Exh. 2 at Col. 26, line 66 to Col. 27, line 41.

[47] *See* Exh. 2 at Col. 26, lines 40–43.

[48] *See* Exh. 2 at Col. 24, lines 1–3 and Col. 26, lines 30–33.

[49] *See* Exh. 2 at Col. 26, lines 43–45.

[50] *See* Exh. 2 at Col. 26, lines 50–52 ("The effective production rates for these culture conditions were thus 1264 and 2167 U/10^6 cells/48 hours.").

[51] Roche's other assertions of lack of enablement are based entirely on its incorrect claim construction, which fails for the reasons discussed *supra*.

given what they already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.'"[52]

Roche admits that one of ordinary skill in the art could select, obtain, and employ an EPO preparation for use as a standard in a radioimmunoassay.[53] Drs. McLawhon and Goldwasser agree that one of ordinary skill in the art would have been aware that multiple EPO standards existed, and as they stated in their expert reports, one of ordinary skill would have known how to obtain, for example, a suitable International Reference Preparation ("IRP") standard, or to calibrate an "in-house" EPO preparation for use as a standard, and would have expected to obtain similar results for a given sample in a radioimmunoassay regardless of the standard used.[54] Their conclusions are supported by the prior-art scientific literature addressing this issue. For example, Roche's experts Drs. Zaroulis and Kadesch both rely on the Cotes (1982) publication, which lists no fewer than 5 EPO preparations that could have been (and were) used by those of skill as standards in radioimmunoassays.[55] The prior-art literature described the 2nd International Reference Preparation ("IRP"),[56] a purified urinary EPO preparation,[57] and other EPO

[52] *Amgen II* at 1334 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). Roche does not discuss any of the *Wands* factors in its instant motion.

[53] Roche's Motion at 12 ("At the time of the invention, though, there were a variety of EPO standards that could be used in RIA testing . . . .")

[54] *See* Exh. 5 at, *e.g.*, ¶¶ 44–45, 47, 51, 57, 60, 66, and 82–83; Exh. 6 at, *e.g.*, ¶¶ 137, 144–50, 183–87.

[55] *See* Exh. 25 at 428 (reporting the specific activity of the 1st and 2nd IRPs of erythropoietin as 1 and 5 U/mg of protein, respectively).

[56] *See* Exh. 24 at 409 ("The second International Reference Preparation of human erythropoietin was used as a standard [in the reported RIA analyses].").

[57] *See* Exh. 10 at 885 ("This preparation [of pure urinary EPO] was used for radiolabeling and as standard [in the reported RIA analyses]."). The authors also reported the specific activity of the pure urinary EPO as "70,400 U/mg protein, based on the activity of the [1st] International Reference Preparation."

preparations[58] as suitable RIA standards. Whether or not Dr. Lin identified a particular EPO preparation as the standard used in the RIA analyses described in the '349 patent is therefore irrelevant to the question of enablement, because the '349 patent does not have to expressly describe subject matter that was already known to one of ordinary skill.

C. Roche's conclusory attorney arguments cannot support summary judgment of non-infringement of '349 claim 7

Roche asserts that "as a result of the infirmities of RIA and its use as claimed in the '349 patent, Amgen cannot show – as it must to prove infringement – that Roche uses cells capable of producing the specified number of 'U of erythropoietin . . . as determined by radioimmunoassay'" because "RIA does not measure Units of biological activity and will measure materials in a test sample such as EPO fragments" and "[c]laim 7 of the '349 patent is, therefore, meaningless . . . ." This argument for non-infringement is, obviously, wholly dependent on Roche's arguments concerning the invalidity of '349 claim 7, and it fails for the same reasons discussed *supra*.

Roche says that it does not use RIA to measure Units of EPO production by its DN2-3α3 cells. However, Roche's BLA submission to the FDA for its peg-EPO product makes clear that Roche ***does*** use, and rely on, radioimmunoassays to measure EPO (and peg-EPO) concentrations in biological samples.[59] And Roche's argument that its data is expressed in "International Units" rather than "Units," and that "'U of erythropoietin' is not defined in the '349 patent as meaning International Units," is a red herring. In the prior art, the terms "Units" and "International Units"

[58] *See, e.g.,* Exh. 23 at 87 ("An aliquot of human urinary EP (62 U/mg) was used as the standard for the [radio]immunoassay."); Exh. 28 at 830 ("Human urinary Ep preparations with a specific activity of 69 and 80 U/mg were made from the urine of patients with hookworm anemia and aplastic anemia, respectively.").

[59] *See* Exh. 18 at, *e.g.*, R005312695, R005312714–16, and R005312772–74; Exh. 5 at ¶¶ 36–40. Roche's statement in its Motion that "almost all" of the other Roche data relied on by Amgen's experts does not employ a radioimmunoassay is telling in this regard.

were used interchangeably with respect to EPO.[60]

Roche argues that "Amgen's proffered evidence of infringement is fatally flawed because the ***nutrient conditions*** Roche ***employs in the accused process*** was not specifically tested." In support of this argument, Roche offers nothing more than attorney argument that Amgen's expert, Dr. Kolodner, "employed different nutrient and cell culture conditions than Amgen accuses Roche of using," that "he took samples from cells for analysis during a stage in their maintenance that Roche does not practice," and that "cell death occurred shortly after culturing began." Roche offers absolutely ***no evidence*** that any of this is true (despite having had all of the materials they would possibly need to do so since before the inception of this case); rather, its lawyers simply say it. The only exhibit Roche cites is an excerpt from Dr. Kolodner's expert report in which he explains how he grew Roche's cells. Roche does not point to ***any*** evidence establishing just how Roche actually grows its cells, or how it believes that its growth conditions differ from those used by Dr. Kolodner.

Moreover, Roche's assertions are contradicted by the evidence. For example, Roche asserts that "Dr. Kolodner's procedures specified that he took samples from cells for analysis during a stage in their maintenance that Roche does not practice."[61] In fact, "Dr. Kolodner's procedures" are part of Roche's manufacturing process for recombinant erythropoietin, according to the documents provided by Roche along with the cells sent to Dr. Kolodner.[62] Dr. Kolodner followed these procedures in culturing Roche's cells and used cell culture medium that did not differ in any way that is material to the question of infringement,[63] as admitted by

[60] For example, *compare* Exh. 24 at 409 (discussing the 2nd IRP in terms of Units) *with* Exh. 25 at 428 (discussing the 2nd IRP in terms of International Units).
[61] Roche's Motion at 19.
[62] Exh. 47; Exh. 48 (PDF images of the documents attached to Exh. 47).
[63] *See* Exh. 49 at ¶¶ 5–10; Exh. 50.

Roche's expert, Dr. Flintoff, during his deposition,[64] and as established by Drs. Lodish and McLawhon.[65]

Consequently, Roche has not established that Dr. Kolodner deviated in any materially significant way from the conditions for growing DN2-3α3 cells that are recited in Roche's BLA. Roche's self-serving, conclusory, unsupported attorney argument does not and cannot satisfy Roche's burden under Fed. R. Civ. P. 56 to show non-infringement.

There can be no legitimate dispute that the DN2-3α3 cells produce more than 100 Units of EPO per million cells in 48 hours, as required by '349 claim 7. Indeed, Roche offered to stipulate that its DN2-3α3 cells are capable of producing in excess of 100 U of EPO per million cells in 48 hours.[66] This is sufficient in itself to create a genuine issue of material fact that precludes summary judgment of invalidity and non-infringement of '349 claim 7.

Amgen has presented substantial evidence establishing that Roche's DN2-3α3 cells produce the amounts of EPO recited in the '349 claims when grown under conditions that Roche uses in its process for manufacturing the EPO in its peg-EPO product. Dr. McLawhon's testing of the DN2-3α3 cell-conditioned medium obtained from Dr. Kolodner using an FDA-approved, commercially available EPO radioimmunoassay shows that Roche's DN2-3α3 cells produce in excess of the claimed amounts of EPO.[67] Any difference between the growth conditions that Dr. Kolodner used and the conditions used by Roche to grow its cells as part of its manufacturing process is immaterial to the question of infringement, because Roche has not and cannot show that any such difference could possibly alter the results of the radioimmunoassay conducted by

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[64] *See* Exh. 42 at 191:20 to 193:12; 202:7 to 232:20.

[65] *See* Exh. 51; Exh. 52 at ¶¶ 63–68; Exh. 11 at ¶ 24.

[66] *See* Exh. 29.

[67] *See* Exh. 11 at ¶ 32–35. Roche's own documents establish that Roche's cells produce recombinant EPO. *See, e.g.*, Exh. 53.

Dr. McLawhon. Moreover, in his expert report on infringement, Dr. Lodish presented substantial evidence from data reported by Roche and its wholly-owned subsidiary, Chugai, that indicates that Roche's DN2-3α3 cells are capable of producing the amounts of EPO recited in the '349 claims.[68]

III. CONCLUSION

As demonstrated above, none of the arguments in Roche's Motion are supported by the documents and testimony cited by Roche, and many of them are in fact contradicted by the evidence in this case. Roche's unsubstantiated attorney arguments and mischaracterizations of the evidence cannot substitute for a lack of evidence to support its positions. Consequently, its request for summary judgment that '349 claim 7 is invalid and not infringed should be denied.

[68] *See* Exh. 45 at ¶¶ 145–54; Exh. 36 at ITC-R-BLA-00005073; Exh. 40 at ITC-R-BLA-00002375–78; Exh. 37 at ITC-R-BLA- 00005581; Exh. 38 at AM ITC-00187104; Exh. 39 at A140563; and Exh. 46 at R001402763–784.

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Respectfully Submitted,

AMGEN INC.,
By its attorneys,

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 91320-1789
(805) 447-5000

/s/ Michael R. Gottfried
D. Dennis Allegretti (BBO#545511)
Michael R. Gottfried (BBO# 542156)
Patricia R. Rich (BBO# 640578)
DUANE MORRIS LLP
470 Atlantic Avenue, Suite 500
Boston, MA 02210
Telephone: (857) 488-4204
Facsimile: (857) 488-4201

Lloyd R. Day, Jr. (*pro hac vice*)
DAY CASEBEER, MADRID & BATCHELDER LLP
20300 Stevens Creek Boulevard, Suite 400
Cupertino, CA 95014
Telephone: (408) 873-0110
Facsimile: (408) 873-0220

William G. Gaede, III (*pro hac vice*)
McDERMOTT WILL & EMERY
3150 Porter Drive
Palo Alto, CA 94304
Telephone: (650) 813-5000
Facsimile: (650) 813-5100

Kevin M. Flowers (*pro hac vice*)
MARSHALL, GERSTEIN & BORUN LLP
233 South Wacker Drive
6300 Sears Tower
Chicago, IL 60606
Telephone: (312) 474-6300
Facsimile: (312) 474-0448

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/s/ Michael R. Gottfried
Michael R. Gottfried