Exhibit D, Part 1

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

REBUTTAL EXPERT REPORT OF STEPHEN G. KUNIN

(MPEP § 201.06 (8th ed. Rev. 5, Aug. 2006))

As evidenced by the written record, each of Dr. Lin's patents-in-suit meet the definition of a divisional application: (1) later applications for distinct or independent inventions; (2) carved out of a pending application; (3) disclosing and claiming only subject matter disclosed in the parent '298 application; (4) filed as a result of a restriction requirement made by the Examiner; and (5) claims the benefit of the nonprovisional '298 parent application under 35 U.S.C. 120.

XII. ROCHE'S OBVIOUSNESS-TYPE DOUBLE PATENTING DEFENSE

137. Obviousness-type double patenting is a judicially-created doctrine designed to prevent improper timewise extension of the patent right by prohibiting claims in a later patent which are not "patentably distinct" from claims in a commonly-owned earlier patent from enjoying a longer patent term. *In re Braat*, 937 F.2d 589, 592 (Fed. Cir. 1991). The underlying policy is that the public should "be able to act on the assumption that upon the *expiration* of the [earlier] patent it will be free to use not only the invention claimed in the patent but also modifications or variants which would have been *obvious* to those of ordinary skill in the art at the time the invention was made." *In re Longi*, 759 F.2d 887, 892-93 (Fed. Cir. 1985) (emphasis in original) (internal quotation omitted).

138. Obviousness-type double patenting is a question of law. *In re Berg*, 140 F.3d 1428, 1432 (Fed. Cir. 1998). As with other affirmative defenses of invalidity, the defendant bears the burden of proving obviousness-type double patenting by clear and convincing evidence, "a heavy and unshifting burden." *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1580 (Fed. Cir. 1991). Where, as here, the same allegations of obviousness-type double patenting were considered and overcome during examination of the patents-in-suit, the defendant bears an even heavier burden in proving obviousness-type double patenting. *Cf. Amgen, Inc. v.*

Hoechst Marion Roussel, Inc., 126 F.Supp.2d 69, 105 (D. Mass. 2001) ("Moreover, if the Patent Office considered a particular prior art reference, then the challenger has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job.") (internal quotation omitted).

139. Double patenting is evaluated on a claim-by-claim basis. Thus, the invalidity of one claim because of double patenting does not automatically require the invalidation of other claims in the same patent. *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 942 (Fed. Cir. 1992).

140. In determining whether or not two claims are "patentably distinct," courts (and the USPTO) have applied an obviousness analysis that parallels the analysis set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 15 (1966), and applied in the context of 35 U.S.C. § 103. *See Longi*, 759 F.2d at 892 n.4; MPEP § 804(II)(B)(1). For this reason, the "patentably distinct" analysis is often framed as a determination of whether a claim in a later patent is "obvious over" a claim in a commonly-owned earlier patent, or whether the differences between two such claims would have been "obvious" to one of ordinary skill in the art at the time the invention claimed in the later patent was made. As part of this inquiry, courts look to the factors that are pertinent when determining nonobviousness under 35 U.S.C. § 103, including whether there was a motivation to modify the prior art, *see, e.g.*, *Ortho*, 959 F.2d at 943; *In re Baird*, 348 F.2d 974, 979 (C.C.P.A. 1965), a reasonable expectation of success, *see, e.g.*, *Longi*, 759 F.2d at 896-97, and objective evidence of non-obviousness, such as long-felt need, unexpected results, etc., *see, e.g.*, *In re Emert*, 124 F.3d 1458, 1462 (Fed. Cir. 1997); *Longi*, 759 F.2d at 896-97; *In re Gladrow*, 406 F.2d 1376, 1383 (C.C.P.A. 1969). One important difference, however, is that the double-patenting analysis involves a comparison of two ***claims***, and it is impermissible to treat

the patent specification underlying one claim (or even the disclosure found in that claim) as prior art against the other claim. *See Gen. Foods. Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1281 (Fed. Cir. 1992) ("Our precedent makes clear that the disclosure of a patent cited in support of a double patenting rejection cannot be used as though it were prior art, even where the disclosure is found in the claims."); *Longi*, 759 F.2d at 892 n.4; *In re Kaplan*, 789 F.2d 1574, 1580 (Fed. Cir. 1986).[7] It is impermissible to apply the earlier commonly-owned patent's disclosure in assessing double patenting—it does not qualify under 35 U.S.C. § 102 as prior art. The reason for this is because "that disclosure is the applicant's and is not in the 'prior art.'" *Gerber Garment Tech., Inc. v. Lectra Sys., Inc.*, 916 F.2d 683, 687 (Fed. Cir. 1990).

141. Under certain circumstances where the USPTO has determined that a patent application contains claims to multiple independent and distinct inventions and has issued a requirement forcing the applicant to divide out and prosecute claims to these inventions in separate applications (i.e., a "restriction requirement"), 35 U.S.C. § 121 bars litigants and the USPTO from using the claims in one of the resulting applications (or in the patent issuing therefrom) against the claims in another for double patenting purposes. Section 121 provides in pertinent part:

> A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the

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[7] In several instances in his report, Mr. Sofocleous mistakenly overlooks this important principle when he contends that "the '008 ***patent***" is available as a double-patenting reference against the claims of Dr. Lin's patents-in-suit. *See, e.g.*, Sofocleous ¶¶ 447, 450, 457, 465, 468, 474.

[9] *Union Carbide Corp. v. Dow Chem. Co.*, 619 F. Supp. 1036, 1060 (D. Del. 1985) ("It is almost inevitable that some refinement of the claims will occur after restriction is ordered, since restriction often comes as a preliminary step before the examiner reaches the merits of the patent claims.")

> original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.

142. Congress enacted § 121 as a remedial statute to protect applicants and patentees from the unfair consequences of USPTO restriction practice. For this reason, § 121 is often described as providing a "safe harbor" for patentees. Section 121 operates by "effect[ing] a form of estoppel that shields the applicant from having to prove the correctness of the restriction requirement in order to preserve the validity of the second patent." *Studiengesellschaft Kohle mbH v. N. Petrochemical Co.*, 784 F.2d 351, 361 (Fed. Cir. 1986) (Newman, J., concurring). In so doing, § 121 "assures that the technicalities of restriction practice are not elevated from their purpose of examination convenience to a potential taint on the validity on the ensuing patents." *Applied Materials, Inc. v. Adv. Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1568 (Fed. Cir. 1996). At its most basic level, § 121 makes sense because it would be unfair to require a patentee to defend against double patenting attacks if the reason why he has multiple patents is because the Patent Office required him to separate one application into multiple applications which led to the multiple patents. *Cf. Applied Materials*, 98 F.3d at 1568 ("[W]hen the existence of multiple patents is due to the administrative requirements imposed by the Patent and Trademark Office, 35 U.S.C. § 121 provides that the inventor shall not be prejudiced by having complied with those requirements.").

143. In the litigation context, § 121 provides patentees with a defense to certain claims of invalidity based on double patenting. Although the heavy burden of proving obviousness-type double patenting remains with the party challenging the validity of the patent at all times (i.e., it never shifts to the patentee), the patentee bears the burden of proving, by a preponderance of the evidence, that the safe harbor provision of § 121 applies. *Pfizer Inc. v. Teva Pharms. USA, Inc.*, No. 04-cv-754, 2007 U.S. Dist. LEXIS 20190, at *215-16 (D.N.J. Mar.

20, 2007). The determination of whether § 121 applies is a question of law. *Bristol-Myers Squibb Co. v. Res. Corp. Techs., Inc.*, 361 F.3d 1343, 1348 n.1 (Fed. Cir. 2004); *Applied Materials*, 98 F.3d at 1567.

144. There are two fundamental elements required for proving the applicability of § 121 in a litigation context: (1) the patent-in-suit issued from an application that was filed as a result of a restriction requirement; and (2) the claims in the patent are consonant with the restriction requirement. *Gerber*, 916 F.2d at 687-88.

145. Requirement (1) is satisfied if the first application giving rise to the patent-in-suit filed after the restriction requirement contained claims drawn only to the non-elected invention or inventions (and not to the invention elected in response to the restriction requirement for examination in the parent application). *Gerber*, 916 F.2d at 687-88. This requirement makes sense because it ensures that the protections of § 121 are not extended to applicants who voluntarily file multiple patent applications, or who reclaim the invention elected for examination in the parent application.

146. Requirement (2) — "consonance" — is satisfied as long as the claims in the issued patent fall within the same group(s) as the claims in the parent application drawn to the non-elected invention or inventions and "do not cross the line of demarcation drawn around the invention elected in the restriction requirement." *Symbol Techs.*, 935 F.2d at 1579. Thus, new or amended claims in the patent-in-suit (i.e., claims that were not originally in the application filed "as a result of" the restriction requirement) also are entitled to the protections of § 121, provided they fall within the scope of the non-elected group(s) and are not drawn to the invention elected in response to the restriction requirement and prosecuted in the parent application. *Id.* This requirement makes sense because it allows for claims to be added or

amended during examination, which is "almost inevitable,"[9] but at the same time ensures that the protections of § 121 are not extended to applicants who reclaim the invention elected in the parent application during subsequent examination of the application filed as a result of the restriction requirement. *Cf. Gerber*, 916 F.2d at 688 ("A consonance requirement is consistent with the legislative purpose behind Section 121. Congress could not have intended to deny all inquiry into whether the restriction requirement established in Section 121 had been disregarded during prosecution of a divisional application."). When assessing whether claims are consonant with a restriction requirement, the proper point of reference is the actual restriction groupings (i.e., the substance of the claims in each restriction group), not the examiner's written descriptions thereof. *Texas Instruments Inc. v. ITC*, 988 F.2d 1165, 1179 (Fed. Cir. 1993).

A. THE JULY 1986 RESTRICTION REQUIREMENT

147. After an initial assessment of Dr. Lin's '298 application, on July 3, 1986, Examiners Thomas Wiseman and Joanne Giesser decided that the '298 application included claims to multiple independent and distinct inventions under 35 U.S.C. § 121 and, for the convenience of the USPTO and its examination, insisted that the claims to these inventions be examined in multiple applications. Accordingly, they issued an Office Action requiring that Amgen's counsel select one of six invention groups for further examination in Dr. Lin's '298 application and forcing Amgen's counsel to prosecute separately the claims to the other, "non-elected" inventions. The text of this "restriction requirement" read as follows:

> "Restriction to one of the following inventions is required under 35 U.S.C. 121:
>
> I. Claims 1-13, 16, 39-41, 47-54 and 59, drawn to polypeptide, classified in Class 260, subclass 112.
>
> II. Claims 14, 15, 17-36, 58 and 61-72, drawn to DNA, classified in Class 536, subclass 27.

III. Claims 37-38, drawn to plasmid, classified in Class 435, subclass 240.

IV. Claims 42-46, drawn to cells, classified in Class 435, subclass 240.

V. Claims 55-57, drawn to pharmaceutical composition, classified in Class 435, subclass 177.

VI. Claim 60, drawn to assay, classified in Class 435, subclass 6.

Inventions I and II are related as process of making and product made.

The inventions are distinct if either (1) the process as claimed can be used to make another and materially different product, or (2) the product as claimed can be made by another and materially different process. MPEP 806.05(f).

In this case, the product as claimed may be made by a materially different product, such as isolation from a naturally occurring source.

Inventions II and III are related as product and process of use.

The inventions are distinct if either (1) the process for using the product claimed can be practiced with another and materially different product, or (2) the product as claimed can be used in a materially different process of using the product. MPEP 806.05(h).

In this case, the product as claimed may be made by a materially different product, such as isolation from urine.

Inventions I and V are related as subcombinations disclosed as useable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately useable. In the instant case, invention I has separate utility such as use in an assay. See MPEP 806.05(d).

Inventions I and VI are related as subcombinations disclosed as useable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately useable. In the instant case, invention I has separate utility such as use as a pharmaceutical. See MPEP 806.05(d).

Because these inventions are distinct for the reasons given

above and have acquired a separate status in the art because of their recognized divergent subject matter restriction for examination purposes as indicated is proper."

(*See* '008 File History, Tab 8, 7/3/86 Office Action (AM-ITC 00952500)).

148. The language of the claims identified in the Examiners' restriction requirement is shown in the following chart, which I may use in connection with my testimony:

Restriction Group	Claim Language
Group I: Polypeptide	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 prokaryotic or eukaryotic expression of an exogenous DNA sequence. 2. A polypeptide according to claim 1 further characterized by being free of association with any mammalian protein. 3. A polypeptide according to claim 1 wherein the exogenous DNA sequence is a cDNA sequence. 4. A polypeptide according to claim 1 wherein the exogenous DNA sequence is a manufactured DNA sequence. 5. A polypeptide according to claim 1 wherein the exogenous DNA sequence is a genomic DNA sequence. 6. A polypeptide according to claim 1 wherein the exogenous DNA sequence is carried on an autonomous replicating circular DNA plasmid or viral vector. 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 or any naturally occurring allelic variant thereof. 8. A polypeptide according to claim 1 possessing part or all of the primary structural conformation of monkey erythropoietin as set forth in Table V or any naturally occurring allelic variant thereof. 9. A polypeptide according to claim 1 which has the immunological properties of naturally-occurring erythropoietin. 10. A polypeptide according to claim 1 which has the *in vivo* biological activity of naturally-occurring erythropoietin. 11. A polypeptide according to claim 1 which has the in vitro biological activity of naturally-occurring erythropoietin. 12. A polypeptide according to claim 1 further characterized by being covalently associated with a detectable label substance.

Restriction Group	Claim Language
	13. A polypeptide according to claim 12 wherein said detectable label is a radiolabel. 16. A polypeptide product of the expression of a DNA sequence of claim 14 in a prokaryotic or eukaryotic host. 39. A polypeptide product of the expression in a prokaryotic or eukaryotic host cell of a DNA sequence according to claims 17 or 34. 40. A glycoprotein product having a primary structural conformation sufficiently duplicative of that of a naturally-occurring 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 erythropoietin. 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. 47. A synthetic polypeptide having part of all of the amino acid sequence as set forth in Table V and having one or more of the *in vivo* or *in vitro* biological activities of naturally-occurring monkey erythropoietin. 48. A synthetic polypeptide having part of all of the amino acid sequence as 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. 49. A synthetic polypeptide having part of 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, having a biological property of naturally-occurring human erythropoietin. 50. A process for the production of a polypeptide having part of all of the primary structural conformation and one or more of the biological properties of naturally-occurring erythropoietin, said process comprising: growing, under suitable nutrient conditions, prokaryotic or eukaryotic host cells transformed or transfected with a DNA vector according to claim 37, and isolating desired polypeptide products of the expression of DNA sequences in said vector. 51. An antibody substance characterized by immunoreactivity with erythropoietin and with a synthetic polypeptide having a primary structural conformation substantially duplicative of a continuous sequence of amino acid residues extant in naturally-occurring erythropoietin except for any polypeptide comprising a sequence of amino acid residues entirely comprehended within sequence, A-P-P-R-L-I-C-D-S-R-V-L-E-R-Y-L-L-E-A-K. 52. An antibody according to claim 51, which is a monoclonal antibody. 53. An antibody according to claim 51, which is a polyclonal antibody. 54. An antibody according to claim 51, which is immunoreactive with erythropoietin

Restriction Group	Claim Language
	and a synthetic polypeptide having eh sequence selected from the sequences: V-P-D-T-K-V-N-F-Y-A-W-K-R-M-E-V-G; K-E-A-I-S-P-P-D-A-A-S-A-A; V-Y-S-N-F-L-R-G-K-L-K-L-Y-T-G-E-A-C-R-T-G-D-R. 59. A polypeptide product of the expression of a DNA sequence according to claim 58 in a prokaryotic or eukaryotic host cell.
Group II: DNA	14. A DNA sequence for use in securing expression in a prokaryotic or eukaryotic host cell of a polypeptide product having at least a part of the primary structural conformation and one or more of the biological properties of naturally-occurring erythropoietin, said DNA sequence selected from among: (a) the DNA sequence set out in Tables V and VI or their complementary strands; (b) DNA sequences which hybridize to the DNA sequences defined in (a) or fragments thereof; and (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) or (b). 15. A prokaryotic or eukaryotic host cell transformed or transfected with a DNA sequence according to claim 14 in a manner allowing the host cell to express said polypeptide product. 17. A purified and isolated DNA sequence coding for prokaryotic or eukaryotic host expression of a polypeptide having part or all of the primary structural conformation and one or more of the biological activities of erythropoietin. 18. A cDNA sequence according to claim 17. 19. A monkey species erythropoietin coding DNA sequence according to claim 18. 20. A DNA sequence according to claim 19 and including the protein coding region set forth in Figure 5. 21. A genomic DNA sequence according to claim 17. 22. A human species erythropoietin coding DNA sequence according to claim 21. 23. A DNA sequence according to claim 22 and including the protein coding region set forth in Figure 6. 24. A manufactured DNA sequence according to claim 17. 25. A manufactured DNA sequence according to claim 24 and including one or more codons preferred for expression in *E. coli* cells. 26. A manufactured DNA sequence according to claim 25, coding for expression of human species erythropoietin. 27. A manufactured DNA sequence according to claim 26 including the protein coding region set forth in Figure 7. 28. A manufactured DNA sequence according to claim 24 and including one or more

Restriction Group	Claim Language
	codons preferred for expression in yeast cells.
	29. A manufactured DNA sequence according to claim 28, coding for expression of human species erythropoietin.
	30. A manufactured DNA sequence according to claim 29 including the protein coding region set forth in Figure 8.
	31. A DNA sequence according to claim 17 covalently associated with a detectable label substance.
	32. A DNA sequence according to claim 31 wherein the detectable label is a radiolabel.
	33. A single-strand DNA sequence according to claim 31.
	34. A purified and isolated DNA sequence coding for a polypeptide fragment or polypeptide analog of naturally-occurring erythropoietin.
	35. A DNA sequence coding for $[Phe^{13}]_{hEPO}$, $[Phe^{87}]_{hEPO}$, $[Phe^{(45)}]_{hEPO}$, $[His^{7}]_{hEPO}$, [Asn^{7} des- Pro^{7} through Ile^{9}]$_{hEPO}$, [des-Thr$^{(45)}$ through Arg$^{(166)}$]$_{hEPO}$, or $[\Delta 27\text{-}55]_{hEPO}$.
	36. A DNA sequence according to claim 34 which is a manufactured sequence.
	58. A purified and isolated DNA sequence as set out in Figure 5 or 6 or a fragment thereof or the complementary strand of such a sequence or fragment.
	61. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 14.
	62. A prokaryotic or eukaryotic host cell stably transformed or transfected with a DNA vector according to claim 61.
	63. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 17.
	64. A prokaryotic or eukaryotic host cell stably transformed or transfected with a DNA vector according to claim 63.
	65. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 34.
	66. A prokaryotic or eukaryotic host cell stably transformed or transfected with a DNA vector according to claim 65.
	67. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 35.
	68. A prokaryotic or eukaryotic host cell stably transformed or transfected with a DNA vector according to claim 67.
	69. A process for the production of a polypeptide having part or all of the primary structural conformation and one or more of the biological activities of naturally-