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

U.S. District Judge William G. Young

ROCHE'S PRE-TRIAL BRIEF

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Defendants F. Hoffman-La Roche, Ltd, Roche Diagnostics GmbH and Hoffman-La Roche Inc. (collectively "Roche") submit this pre-trial brief outlining for the Court what the evidence adduced at trial will show. For years Roche has been a leader in the anemia treatment field, selling its own erythropoietin product Neorecorman®, worldwide outside the U.S. Roche developed MIRCERA™ as a new anemia drug to provide patients with improved treatment. MIRCERA™ is not human erythropoietin.[1] It is a new chemical entity (as recognized by the United States FDA) and has significant medical advantages including allowing once monthly dosing as compared to 2-3 times weekly for currently available erythropoietin products, fewer injections for patients leading to a better quality of life, and essentially more choice for physicians in treating seriously ill patients. Just recently patients outside the U.S. gained access to this drug and are now enjoying the significant benefits that it offers.

I. ROCHE'S ACCUSED MIRCERA™ PRODUCT

MIRCERA™ represents the culmination of nearly a decade of intensive scientific research by Roche scientists aimed at creating improved treatments for anemia. The U.S. Patent Office (PTO) recognized Roche's achievement in 2003, awarding Roche U.S. Patent No. 6,882,272. The MIRCERA™ that Roche plans to sell in the U.S. will be manufactured in

[1] During the July 17, 2007 summary judgment hearing, the Court asked Amgen's counsel "what is the structure of human erythopoietin?" Amgen has yet to respond to that question in this case. However, just days ago, in the *HMR/TKT* case, in which Amgen is attempting to narrow the meaning of claim 1 of the '422 patent in order to avoid invalidating prior art, Amgen ascribes *inter alia*, specific structural distinctions purportedly possessed by human erythropoietin "purified from mammalian cells grown in culture." (Amgen's Brief on Remand Concerning Whether Goldwasser Anticipates '422 Claim 1, Document 863, *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, Civil Action No. 97-10814-WG4). Amgen has provided no evidence whatsoever that MIRCERA™ has *any* of these structural characteristics.

Europe. MIRCERA™ has not yet been approved for sale in the United States, although the FDA issued an "approvable" letter in May 2007.[2] The European Commission approved the sale of MIRCERA in Europe in July 2007.

The active ingredient in MIRCERA™ is CERA -- an acronym for Continuous Erythropoiesis Receptor Activator. CERA is an erythropoiesis stimulating agent (ESA) that is synthesized by chemically reacting two starting materials: a specific activated polyethylene glycol reagent and Epoetin beta.[3]

Roche makes Epoetin beta by fermenting cells that are genetically altered with DNA that codes for the 193 amino acid residues that make up pre-erythropoietin. The cells Roche uses were originally created by a process known as "protoplast fusion." Bacteria transformed with plasmids containing DNA coding for the pre-erythropoietin amino acid sequence were "smushed" with mammalian cells so that DNA from the bacteria was introduced into the mammalian cells without isolation. The resulting cells are grown up in fermentation tanks under controlled conditions. The cells express various proteins, including a 166 amino acid residue glycoprotein which the cells proteolytically cleave to yield a 165 amino acid glycoprotein.

Roche then harvests (separates from the cells) a crude isolate containing a heterogeneous collection of proteins, impurities and byproducts. That therapeutically useless mixture is transformed into Epoetin beta via a patented process which includes five distinct

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[2] Roche has produced substantial evidence that MIRCERA™ is not being used for any purposes that fall outside the exemption provided by 271(e)(1). Therefore, in addition to the non-infringement grounds detailed herein, Roche does not infringe any of the asserted claims because all of Roche's activities with CERA are protected from infringement by the safe harbor exemption. 35 U.S.C. §271(e)(1).

[3] Recombinant human erythropoietins are known as "epoetins." Amgen's product is denominated Epoetin alfa.

chromatography steps. Although erythropoietin molecules found in the crude isolate from mammalian host cells ordinarily exist as fourteen different charged forms (isoforms) of erythropoietin, Roche's purification process yields a product having predominantly only six isoforms. That product is Epoetin beta.

Roche synthesizes CERA by reacting Epoetin beta with an activated PEG reagent -- *N*-hydroxysuccinimidyl ester of methoxy poly(ethylene glycol)-butanoic acid (mPEG-SBA). A covalent bond forms between the mPEG-SBA and a free amino group on Epoetin beta. Hydrogen is removed from Epoetin beta and N-hydroxysuccinimide is released. The mPEG-SBA reacts productively with the Epoetin beta at any one of nine locations on the Epoetin beta molecule and, following chromotography, yields a heterogeneous preparation of CERA. The chemical reaction changes either an internal lysine residue to a PEG-amido-2-aminocaproic acid (PEG-AACA) residue or the N-terminal alanine to a PEG-amido propionic acid (PEG-APA) residue.

CERA is a new chemical entity which is a substantially different molecule from the Epoetin beta and mPEG-SBA starting materials. For example:

- The molecular weight of CERA is approximately double (60kDa) that of Epoetin beta (30kDa).
- The binding affinity of CERA to the EPO receptor on cell surfaces is 50- to 100-fold lower than the binding affinity of Epoetin beta to the EPO receptor.
- CERA has been found to be metabolized by cells more quickly than Epoetin alpha.
- CERA has a substantially longer half-life *in vivo* than Epoetin beta.
- CERA exhibits substantially greater potency than Epoetin beta both *in vitro* and *in vivo*.
- CERA and Epoetin beta have demonstrated different intracellular signaling properties.

II. AMGEN CANNOT MEET ITS BURDEN OF PROVING THAT ROCHE INFRINGES THE ASSERTED CLAIMS[4]

A. Amgen's Burden Of Proving Infringement

As patentee, Amgen has the "burden of proving infringement by a preponderance of the evidence." *Centricut, LLC v. Esab Group, Inc.*, 390 F.3d 1361, 1367 (Fed. Cir. 2004). "If the accused product meets each of the limitations contained in a claim" as properly construed, "then the product literally infringes that claim. If, however, even one limitation is not met, then the product does not literally infringe." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 117 (D. Mass. 2001) ("*Amgen I*").

A product "which does not infringe a patent claim literally may still infringe the claim under the doctrine of equivalents if each and every limitation of the claim is literally or equivalently presented." *Id.* As this Court explained: "A claim limitation is equivalently present in an accused product if there are only 'insubstantial differences' between the limitation and the corresponding aspects of the product. 'The usual test of the substantiality of the differences is whether the element in the accused composition performs substantially the same function in substantially the same way to obtain substantially the same result as the claimed element.'" *Id.* (citations omitted).

The Court further observed that "application of infringement by equivalents . . . is limited by the doctrine of prosecution history estoppel." *Id.* According to the Federal Circuit "[t]he doctrine of prosecution history estoppel acts as a 'legal limitation on the doctrine of equivalents.'

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[4] The "asserted claims" refers to claims 1 and 2 of the '868 Patent; claims 4-9 of the '698 Patent; claim 7 of the '349 Patent; claim 1 of the '422 Patent; and claims 3, 7-9, 11-12 and 14 of the '933 Patent. By letter from R. Day to L. Ben-Ami, dated August 2, 2007, Amgen represented that it would not assert claims 4 and 5 of the '698 patent at trial. Nonetheless, Roche maintains its invalidity counterclaims with respect to those claims.

'[P]rosecution history estoppel limits the range of equivalents available to a patentee by preventing recapture of subject matter surrendered during prosecution of the patent.'" *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 2007 WL 1932269, *6 (Fed. Cir. 2007).

The Supreme Court has "made clear that a 'presumption' of prosecution history estoppel arises when an amendment is made to secure the patent and the amendment narrows its scope." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 287 F. Supp. 2d 126, 131 (D. Mass. 2003) ("*Amgen III*") (citing *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 736 (2002)). "The inventor can overcome the 'presumption' by showing that the amendment does not surrender the particular equivalent in question." *Id*.

B. Amgen Cannot Prove That Roche Will Infringe Any Of The Asserted Claims of the '933 Patent

1. The Asserted Claims Of The '933 Patent.

Amgen asserts claims 3, 7, 8, 9, 11, 12 and 14 of the '933 patent in this action.

Claim 3 is an independent product-by-process claim directed to a non-naturally occurring glycoprotein product:

> "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells."

Claims 7 and 8 also are product-by-process claims directed to non-naturally occurring glycoprotein products. Both are dependent on claim 3 (among other claims) and further limit the mammalian host cell of that claim:

> 7. The glycoprotein product according to Claim 3, 4, 5 or 6 wherein the host cell is a non-human mammalian cell.
>
> 8. The glycoprotein product of claim 7 wherein the non-human mammalian cell is a CHO cell.

Claims 9 and 12 of the '933 patent are directed to pharmaceutical compositions that include, as an active ingredient, the glycoprotein product of claims 3 and 7:

> 9. A pharmaceutical composition comprising an effective amount of a glycoprotein product for erythropoietin therapy according to claim 1, 2, 3, 4, 5 or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.
>
> 12. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 7 and a pharmaceutically acceptable diluent, adjuvant or carrier.

Claims 11 and 14 are method of treatment claims which depend from claims 9 and 12, respectively:

> 11. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 9 in an amount effective to increase the hematocrit level of said patient.
>
> 14. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 12 in an amount effective to increase the hematocrit level of said product.

Thus, the asserted claims of the '933 patent include, directly or by dependence, reference to "non-naturally occurring glycoprotein" products which are the "product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin."

2. "Product Of The Expression In A Mammalian Host Cell."

In June 1989, during prosecution of the '933 patent, Amgen asserted that the claims of the application were "product-by-process claims" which define each of the claimed products "by the process by which it is produced," *i.e.*, "expression in a mammalian cell." ('178 Application File History 116, Paper 11, Amendment Under Rule 116 at 3-4). This Court has construed the

term "expression" to mean that "the glycoprotein was produced in a cell and recovered from the cell culture." (Mem. and Order, 7/3/07 at p. 32 n.3).

Plainly, Roche's CERA is literally non-infringing because it is not a "product of . . . expression in a mammalian host cell," even under the broadest interpretation of a product-by-process claim. *See Scripps Clinic & Research Found. v. Genenech, Inc.*, 927 F.2d 1565, 1583 (Fed. Cir. 1991) ("the correct reading of product-by-process claims is that they are not limited to product prepared by the process set forth in the claims"). Rather, CERA is a chemically synthesized compound that is created in the laboratory. CERA is not and cannot be produced by living cells and is substantially different in structure and function from a product of the recited process. CERA is distinct from the Epoetin beta and mPEG-SBA starting materials and CERA cannot be broken down into the starting materials. CERA differs from an erythropoietin glycoprotein product of a mammalian host cell not only in its structure but also in its resulting physiochemical, biological and clinical properties.[5]

Nor does Roche infringe under the doctrine of equivalents. As referenced above, during prosecution of the application for the '933 patent, the applicant added a claim which recited a "glycoprotein product of the expression of an exogenous DNA sequence" and represented to the PTO: "All product claims in the subject application are now product-by-process claims. . . . These product-by-process claims are presented. . . . to further define the product of the subject invention since the recombinant erythropoietin claim cannot be precisely defined except by the process by which it is produced." ('178 Application File History, paper 11, 6/2/89 Amendment

[5] While the initial step in producing Epoetin beta involves expression in a mammalian host cell, Epoetin beta is made and used by Roche only outside of the United States in synthesizing CERA. Thus, Roche does not make, use, sell or offer to sell Epoetin beta in the United States.

at 1, 3-4). Having thus narrowed its claims by introducing the phrase "product of the expression," Amgen should be estopped, under the Supreme Court's decision in *Festo*, from arguing that the term is satisfied under the doctrine of equivalents.

In any event, CERA is not the equivalent of a "product of . . . expression in a mammalian host cell." Indeed, as cited above, there are profound physical and biological differences between Epoetin beta, the purified therapeutically active protein extracted through a series of steps from material expressed by a mammalian host cell, and CERA.

Furthermore, during prosecution Amgen argued to the PTO that human erythropoietin is an "obligate glycoprotein," a term Amgen coined to mean that EPO must be properly glycosylated to possess *in vivo* activity. ('179 Application File History, Paper 8, 5/24/88 Second Preliminary Amendment at 6.) Amgen stated that the claimed processes were "believed to constitute one of the first instances (if not the first instance) of recombinant production of an *in vivo biologically active obligate human glycoprotein*." *Id*. (emphasis in original). By contrast, experimental data indicates that CERA is not an "obligate glycoprotein" in that its *in vivo* biological activity persists even after N-deglycosylation.

These differences reflect that CERA is structurally very different from human EPO and interacts with the body's EPO receptors in a substantially different way than does EPO to effect an increase in hemoglobin. As a practical matter, CERA and EPO yield different results in patients in that CERA requires less frequent dosing than Epoetin beta. Hence, even if infringement under the doctrine of equivalents were not barred by prosecution history estoppel, CERA is not the equivalent of a "product of . . . expression in a mammalian cell."

3. "Non-Naturally Occurring Glycoprotein."

Amgen also cannot prove the "non-naturally occurring glycoprotein" element which, directly or by dependence, is a requirement of each of the asserted claims of the '933 patent.

This Court has construed the words "non-naturally occurring" to mean "not occurring in nature." (Mem. and Order, 7/3/07 at 32). Thus, in order to prevail on infringement, Amgen has to prove that the allegedly infringing glycoprotein has structure that is different than the erythropoietin glycoproteins that occur in nature.

In the course of prosecution, the applicant introduced the "non-naturally occurring" limitation in what issued as claim 3 in order to "distinguish the subject matter claimed from all prior art reference relating to erythropoietin isolates." (12/20/95 Second Preliminary Amendment, Ser. No. 08/487,774, p. 7.) The applicant stated that in a PTO interview with the examiner "it was agreed that the negative limitation 'non-naturally occurring' would, when combined with the notation of glycosylation differences in [what became claims 1 and 5], meet Section 112 specificity requirements." (*Id*. at p. 6).

In order to overcome the prior art and distinguish the claimed glycoproteins from any that occur in nature, the addition of the term "non-naturally occurring" to the claims of the '933 patent had to reflect a physical difference. Stated otherwise, a protein that is not distinguishable from naturally occurring proteins is not a protein that does not occur in nature -- whatever the source. Indeed, the examiner's rejections which gave rise to the amendment (8/16/94 Office Action, pp. 6-9; 5/16/95 Office Action, pp. 4-6) had cited *In re Brown*, 459 F.2d 531, 535 (C.C.P.A. 1972), where the court stated that "the lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since . . . *it is the patentability of the product claimed and not of the recited process steps which must be established*." (Emphasis added). In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003) (*Amgen II*), the Federal Circuit similarly stated that "a claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition

of source or process limitations." *See also General Electric Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938) ("a patentee who does not distinguish his product from what is old except by reference, express or constructive, to the process by which he produced it, cannot secure a monopoly on the product by whatever means produced").

The only supposed physical distinction between naturally occurring EPO glycoproteins and the EPO glycoproteins described in the specification of the '933 patent is their glycosylation:

> Novel glycoprotein products of the invention include those having a primary structural conformation sufficiently duplicative of that of a naturally-occurring (*e.g.*, 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 (*e.g.*, human) erythropoietin.

('933 patent, col. 10: 29-40).

Given that the Court has already held that the glycosylation of naturally occurring EPO is so variable as to be an "unascertainable" standard, Amgen cannot prove -- as it erroneously attempts to do -- that the glycosylation of Epoetin beta is structurally distinct from the glycosylation of naturally occurring EPO.[6] In other words, Amgen cannot show that Epoetin

[6] Amgen is foreclosed, under the doctrine of collateral estoppel, from relitigating of whether the glycosylation of naturally occurring EPO is a definite standard. In patent cases, the Federal Circuit applies the issue preclusion law of the regional circuit. *Vardon Golf Co. v. Karsten Mfg. Corp.*, 294 F.3d 1330, 1332 (Fed. Cir. 2002). In the First Circuit, courts look for five essential elements in applying collateral estoppel: "(1) the issue sought to be precluded must be the same as that involved in the prior action; (2) the issues must have been actually litigated; (3) the issue must have been determined by a valid and binding final judgment; and, (4) the determination of the issue must have been essential to the judgment; and (5) the party to the second action must be the same as or in privity with the parties in the first action." *Boston Sci. Corp. v. SciMed Life Sys., Inc.*, 983 F. Supp. 245, 255 (D. Mass. 1997). Here, all of the requirements of issue preclusion are met: Whether glycosylation would allow a potential infringer to distinguish between naturally occurring and non-naturally occurring EPO was actually at issue in the prior Amgen litigation. That question was fully litigated by Amgen in the district court and the indefiniteness holding was essential to the final judgment holding claims 1, 2 and 9 of the '933 patent invalid. The judgment was affirmed on appeal.

beta has glycosylation that physically distinguishes it as a product having a structure that does not occur in nature. Although the accused product here is CERA, not the Epoetin beta starting material Amgen ignores the significant differences between the two products and bases most of its evidence on the features of Epoetin beta.

Nor can Amgen show that CERA satisfies the "non-naturally occurring" term under the doctrine of equivalents. Given that Amgen added the words "non-naturally occurring" to the claims of the '933 patent to overcome prior art, Amgen should be estopped, pursuant to *Festo*, from arguing that the term "non-naturally occurring" can somehow be satisfied under the doctrine of equivalents.

4. Amgen Cannot Show That Roche Induces Infringement Of Claims 11 And 14.

Claims 11 and 14 of the '933 patent recite methods for treating kidney dialysis patients with the pharmaceutical compositions of claims 9 and 12, respectively. Even assuming, contrary to fact, that Roche does infringe claims 9 and 12, it does not infringe claims 11 and 14.

Given that Roche sells -- but does not administer -- pharmaceuticals, Roche indisputably does not directly infringe claims 11 and 14 under 35 U.S.C. § 271. *See Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 n. 7 (Fed. Cir. 2003) ("[P]harmaceutical companies do not generally treat diseases; rather, they sell drugs to wholesalers or pharmacists, who in turn sell the drugs to patients possessing prescriptions from physicians. Pharmaceutical companies also occasionally give samples of drugs to doctors and hospitals. In none of these cases, however, does the company itself treat the diseases").

Roche also does not induce infringement by others, under 35 U.S.C. § 271(b), because Roche lacks the requisite specific intent. As explained by the Federal Circuit: "'It must be established that the defendant possessed specific intent to encourage another's infringement and

not merely that the defendant had knowledge of the acts alleged to constitute inducement.'. . . . Accordingly, inducement requires evidence of culpable conduct, directed to encouraging another's infringement, not merely that the inducer had knowledge of the direct infringer's activities." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006). In *DSU*, the court upheld a jury verdict of no inducement, where the record contained evidence that the party accused of inducing infringement "did not believe its [product] infringed. Therefore, it had no intent to infringe." *Id*. at 1307.

Here, Roche is proceeding with a good faith belief that treating patients with MIRCERA™ is non-infringing. Consequently, Roche lacks the intent necessary to induce infringement.

C. Amgen Cannot Prove That Roche Will Infringe The Asserted Claims Of The '868 Patent

1. The Asserted Claims Of The '868 Patent.

Amgen alleges that Roche infringes claims 1 and 2 of the '868 patent which claim processes for producing a glycosylated erythropoietin polypeptide as follows:

> 1. A process for the production of a glycosylated erythropoietin polypeptide having the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> > (a) growing, under suitable nutrient conditions, mammalian host cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin; and
> >
> > (b) isolating said glycosylated erythropoietin polypeptide therefrom.
>
> 2. The process according to claim 1 wherein said host cells are CHO cells.

2. Roche Does Not Practice The Claimed Process In The United States.

The asserted claims of the '868 patent describe processes for producing "a glycosylated erythropoietin polypeptide" using mammalian host cells which are "transformed or transfected with an isolated DNA sequence encoding human erythropoietin." Given that Roche makes MIRCERA™ in Europe, Roche plainly does not practice the process claims of the '868 patent "within the United States," per 35 U.S.C. § 271(a). Process claims are only infringed if the entire process is carried out in the U.S.

3. "Cells Transformed Or Transfected With An Isolated DNA Sequence."

Even outside of the U.S., Roche does not transform or transfect cells with what the claims pointedly describe as "an *isolated* DNA sequence encoding human erythropoietin." (Emphasis added).

This Court has construed the claims to recite "cells that have been genetically modified with isolated DNA containing genetic instructions for human erythropoietin or later generations of these cells that have inherited those instructions." At the time of the application, DNA-mediated gene transfer techniques, such as calcium phosphate precipitation, electroporation and, microinjection, were available for transferring isolated and purified DNA fragments into host cells. In fact, the specification of the Amgen patents discloses several examples of host cell transformation and transfection with an isolated DNA sequence, including introduction of purified and isolated DNA into COS cells (Examples 6 and 7), CHO cells (Example 8) and *E. Coli* (Example 12) via DNA mediated gene transfer. As explained above, however, the protoplast fusion method used to create Roche's production cell bank, in which cells are "smushed" together, does not involve the transfer of *isolated* DNA. Simply stated, Roche's cells are not themselves, nor are they later generations of cells, that were transformed or transfected

with an "isolated" DNA sequence, as required by the claims, or even with an insubstantially different equivalent thereof.

Furthermore, infringement under the doctrine of equivalents of the phrase "transformed or transfected with an isolated DNA sequence encoding human erythropoietin" is barred by the doctrine of prosecution history estoppel. During prosecution of U.S. Patent No. 4,703,008 (the '008 patent) -- the parent of the '868 patent -- the applicant distinguished over the prior art Sugimoto patent (U.S. Pat. No. 4,377,513), telling the PTO that "[u]nder no circumstances can the claims be urged to 'read on' non-isolated DNA" of the Sugimoto reference. ('298 Application File History, Paper 12, 10/2/86 Amendment and Reply at 13). Therefore, the claims cannot cover non-isolated DNA by equivalence. Moreover, because *literal* infringement is a predicate for liability under 271(g), *Genentech, Inc. v. Boehringer Mannheim GmbH*, 47 F. Supp. 2d 91, 107 (D. Mass. 1999), the doctrine of equivalents is irrelevant with respect to Roche's manufacture of CERA outside the U.S.

4. "Isolating Said Glycosylated Polypeptide."

The concluding step of the processes of the claims of the '868 patent is "isolating said glycosylated erythropoietin polypeptide" from the cells which produce the protein. In securing its patents in the PTO, Amgen asserted that the term "isolating" means "nothing more than separating the expressed product from the cell," flatly denying that the step of "isolating" includes "purification." (Interf. No. 102,097, Brief for the Senior Party Lin at 48, 58). At the Markman hearing in this case, the Court acknowledged the binding effect of Amgen's statements and held that the term "isolating said glycosylated erythropoietin polypeptide" means separating said glycosylated erythropoietin polypeptide. Hence, the final product of the process recited in the claims, which ends with isolation, is the "crude isolate" -- the unpurified expression product that is "isolated" from the cells. Amgen has no evidence at all, however, that Roche's crude

isolate -- in contrast to CERA or purified Epoetin beta -- has "the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells." Because Amgen cannot prove that the unpurified product of Roche's process has the *in vivo* biological activity recited in the '868 patent claims, Amgen cannot prevail on the issue of literal infringement.

5. Roche Does Not Infringe Under 35 U.S.C. § 271(g) Because The Isolated Glycoprotein Is "Materially Changed."

Even assuming, *arguendo*, that Roche practices the claims of the '868 patent outside of the United States, Amgen can establish infringement of the claims of the '868 patent, under 35 U.S.C. § 271(g) if, but only if, it demonstrates that Roche imports the product of the claimed process without it having been "materially changed by subsequent processes."

In *Eli Lilly & Co. v. American Cyanamid Co.*, 82 F.3d 1568 (Fed. Cir. 1996), the Federal Circuit stated that § 271(g) "permits the importation of an item that is derived from a product made by a patented process as long as that product is 'materially changed' in the course of its conversion into the imported item." *Id*. at 1572. The court explained that the issue under § 271(g) is "the substantiality of the change between the product of the patented process and the product that is being imported." *Id*. at 1573. "In the chemical context, a 'material' change in a compound is most naturally viewed as a significant change in the compound's structure and properties." *Id*. The patentee "bears the burden of proof on the issue of material change" under § 271(g). *Genentech*, 47 F. Supp. 2d at 108.

The *Lilly* case concerned a claim to a method for making an intermediate compound that the defendants there used in synthesizing the antibiotic cefaclor which they, in turn, imported into the United States. Both the intermediate and cefaclor had the same nucleus, but the intermediate had to be changed at three positions to create cefaclor. In denying a motion for a

preliminary injunction, the court there held that the product of the claimed process was "likely to be found to have been 'materially changed' in the process of its conversion into cefaclor" such that the importation or sale of the final product was "not likely to be held to infringe." *Id*. at 1578. Ultimately, the district court granted summary judgment finding a material change based, at least in part, on "ease of dosing," despite evidence presented that the product of the patented process had antibiotic utility like the imported product.

Roche does not infringe under § 271(g) because, even if Roche practiced the process of claims 1 and 2 of the '868 patent outside of the U.S., the product of that process is "materially changed" before it is imported as MIRCERA™. Roche materially changes the crude isolate recovered from cells by performing a series of patented purification steps to remove potentially harmful chemicals. The purification process converts a therapeutically useless composition—the crude isolate—into a useful therapeutic product Epoetin beta. While EPO produced by a single mammalian cell can consist of a heterogeneous mixture of different isoforms having from zero to 14 sialic acid residues and, as a result, different electrical charges, Roche's purification method materially changes the recovered product by selecting out predominantly six isoforms. Amgen has made much of the fact that the isoform composition of EPO impacts its *in vivo* biological activity.

Roche makes a further, more drastic, material change by chemically reacting the Epoetin beta with an activated polythylene glycol molecule to create CERA. As made clear above, CERA differs from the Epoetin beta starting material in terms of structure and function as well as in terms of pharmacodynamic and pharmacokinetic properties. This Court has pointed to the same sorts of differences between the imported product and the product of the patented process, in finding material change under § 271(g). *Genentech*, 47 F. Supp. 2d at 113-20.

Amgen argues that the pegylation reaction between Epoetin beta and mPEG-SBA that yields CERA is a "conventional process" which, according to Amgen, does not effect a material change. However, as mentioned, pegylation is not the only material change that occurs in the process of transforming the crude isolate to make MIRCERA™. Prior to the pegylation reaction, the crude isolate is subjected to a patented purification process and after the pegylation reaction the CERA must be formulated to make MIRCERA™. Furthermore, in *Lilly*, the Federal Circuit concluded that there likely was a material change even though steps involved in changing the intermediate to the final cefaclor product were all "relatively routine chemical reactions." 82 F.3d at 1573.

In any event, the pegylation of Epoetin beta was far from routine—particularly at the time of the priority date of the '868 patent in the early 1980s. Pegylation reactions are complex chemical reactions, requiring the evaluation of numerous variables and yielding new molecules with unpredictable physiochemical and biological properties. Pegylation procedures employed during the late 1970s and 1980s were plagued by difficulties, including restriction to PEGs with low molecular weights, relatively unstable activated PEGs and lack of selectivity in protein modification. As of 1992, the experience with pegylation technology was limited and rather unsatisfactory. When asked in this case about the predictability of pegylation, Amgen's inventor, Dr. Lin, testified:

> "For any particular procedure, you had to do it yourself to see if the end product that you modified -- the way you did it -- would be active or not. You had to check it out experimentally.

(Lin Tr. (3/28/07) at 100:18-22).

The notion that pegylation of a particular protein was routine is at odds with the fact that (i) Roche's MIRCERA is the product of nearly a decade of research and experimentation toward the development of a new erythropoiesis stimulating agent; and (ii) between 1985 and

approximately 2000, Amgen attempted unsuccessfully to develop a new product by reacting PEG and EPO.

Amgen maintains that Roche has no commercially viable alternatives to the patented process. The evidence however, is to the contrary. A DNA sequence encoding an analog of erythropoietin with an amino acid other than arginine at position 166 is not a DNA sequence encoding human erythropoietin. Host cells transformed or transfected with such a DNA sequence would ultimately produce a glycoprotein having the 165 amino acid residues of Epoetin beta because of the activity of cellular carboxypeptidases which leave the amino acid at position 166. In the alternative, the crude isolate from these cells could be purified and treated with a carboxypeptidase *in vitro* to remove the C-terminal amino acid. In this way one could make what is essentially the Epoetin beta starting material for CERA without practicing any of the claimed methods. Another example of a viable alternative would be to use non-mammalian host cells to produce the products of the claimed process.

In sum, even if Roche were to practice the process of claims 1 and 2 of the '868 patent outside of the U.S., the MIRCERA™ that Roche will be importing is materially changed from the product of the processes claimed in the '868 patent. Therefore, Roche does not infringe under 35 U.S.C. § 271(g).

D. Amgen Cannot Prove That Roche Will Infringe The Asserted Claim Of The '698 Patent

1. The Asserted Claims Of The '698 Patent.

Amgen alleges that Roche infringes claims 6-9 of the '698 patent[7]. Similar to the asserted claims of the '868 patent, claims 6-9 of the '698 patent recite processes for the

[7] Amgen has indicated, by letter from R. Day to L. Ben-Ami, dated August 2, 2007, that it would not assert claims 4 and 5 at trial.

production of a glycosylated erythropoietin polypeptide involving growing cells with DNA encoding "the mature erythropoietin amino acid sequence of FIG. 6" and "isolating said glycosylated erythropoietin polypeptide expressed by said cells." Independent claim 6 provides:

> 6. A process for the production of *a glycosylated erythropoietin polypeptide* having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified *DNA encoding the mature erythropoietin amino acid sequence of FIG. 6*; and
>
> b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

(Emphasis added).

2. Roche Does Not Infringe Under § 271(a) Because Roche Does Not Make MIRCERA™ In The U.S.

As explained above in connection with the '868 patent, Roche does not make CERA or MIRCERA™ in the United States and, therefore, does not infringe under 35 U.S.C. § 271(a).

3. Amgen Cannot Prove That Roche Practices The Patented Process.

As in the case of the '868 patent, the product of the claimed process is the crude isolate -- the product of the process which concludes with "isolating said glycosylated erythropoietin polypeptide" expressed by said cells -- not purified Epoetin beta. The court decided that "expressed" means produced by a cell and recovered from a cell. However, there is no evidence that Roche's crude isolate has the claimed "*in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells." Additionally, the claims of the '698 patent require DNA encoding the mature erythropoietin amino acid sequence of Fig. 6 which as explained above Roche's cells do not have.

4. Roche Does Not Infringe Under § 271(g) Because The Crude Isolate Is "Materially Changed" Before Importation.

Even if Roche were to practice the claimed processes outside of the United States, Roche would not infringe, under 35 U.S.C. § 271(g), because, as detailed above, the crude isolate produced by Roche is materially changed in the course of being purified, reacted with mPEG-SBA and then formulated into MIRCERA™ before importation into the U.S.

E. Amgen Cannot Prove That Roche Will Infringe The Asserted Claim Of The '349 Patent

1. The Asserted Claim Of The '349 Patent.

Amgen claims that Roche infringes one claim of the '349 patent -- claim 7 -- which states:

> "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**."**

According to Amgen, Roche infringes claim 7 by using cells according to claims 1, 2 and 3 of the patent. (Plaintiff's Supp. Resp. to Defs. First Set of Interrogs, Ex. A thereto, p. 21). Claims 1-3 read as follows:

> 1. 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.
>
> 2. Vertebrate cells according to claim **1** capable of producing in excess of 500 U erythropoietin per 10^6 cells in 48 hours.
>
> 3. Vertebrate cells according to claim **1** capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.

Thus, asserted claim 7 recites a process which employs vertebrate cells that are "capable of" producing 100, 500 and 1000 "U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay." The term "U of erythropoietin" is not defined in the patent.

2. Roche Does Not Practice The Claimed Process In The U.S.

Again, Roche does not infringe, under 35 U.S.C. § 271(a), because claim 7 of the '349 patent is a process claim and Roche makes MIRCERA™ outside of the U.S.

3. Roche Does Not Infringe Because The Product Of Roche's Cells Is "Materially Changed" Prior To Importation.

Even assuming, *arguendo*, that Roche does practice the claimed process abroad, Roche does not infringe, under 35 U.S.C. § 271(g), because, as recited above, the product of the cells described in the claims of the '349 patent (which does not even include the "isolating" step of the '868 and '698 claims) is materially changed -- being isolated from the cells, purified, reacted with mPEG-SBA and formulated -- in making MIRCERA™.

4. Amgen Cannot Show That Roche Uses Cells That Have The Required Protein Production Capability.

Amgen cannot prove that Roche infringes the '349 patent because Amgen cannot show that in the process used by Roche, the cells produce the claimed "U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay." Evidence regarding the level of EPO produced by Roche's cells under conditions different from those used by Roche is irrelevant.

Furthermore, the term "U of erythropoietin" means units of erythropoietin biological activity which, in this context, refers to the ability to stimulate the formation of new red blood cells in an assay animal. However, radioimmunoassay -- the mode of measurement prescribed by the claim -- does not measure biological activity. Rather, RIA measures immunological activity, *i.e.*, binding to an anti-EPO antibody.

RIA is a competitive binding assay which determines the extent to which an unknown sample competes with radioactively labeled EPO to bind with an anti-EPO antibody. Anything in the test sample that binds to the antibody displaces labeled EPO by taking its place at the binding site on the antibody. Because the radio-labeled EPO bound to the antibody can be quantified (based on its radioactivity), the amount of unlabeled EPO in the sample that is bound to the antibodies is also determinable.

The first step in conducting an RIA is to generate a standard curve by running a competitive binding assay using radio-labeled EPO and an EPO standard having a known concentration which typically is expressed in "units" (or "milliunits") of biological activity per ml. The percentage of the labeled EPO that binds to the antibody is plotted versus various concentrations of the EPO standard. The standard curve thus reflects the "units" of EPO necessary to inhibit binding of a fixed amount of labeled EPO to a fixed amount of anti-EPO antibody. The amount of EPO in the test sample is then calculated by repeating the competitive binding assay using the labeled EPO and the unknown sample. The amount of the unknown is determined by measuring the percent of the labeled EPO that is bound in competition with the unknown sample and then identifying the location on the standard curve corresponding to that point. The amount of EPO determined by the RIA is expressed in "units" based on known biological activity of the EPO standard.

However, a radioimmunoassay does not always distinguish between erythropoietin and other non-erythropoietin substances that cross react with the antibody. For example RIA will register fragments and precursors of EPO as EPO if the fragments have the epitope which is recognized by the antibody. In that case, the RIA will identify EPO fragments that bind to the antibody as being biologically active EPO.

Hence, in any given serum sample, it is possible that precursors of EPO and degradation products of EPO will compete with radio-labeled EPO for the anti-EPO antibody, even though they are not EPO and do not have EPO-activity. RIA may, therefore, report the presence of EPO even if some of what is being measured is EPO which lacks biological activity or is less than a complete EPO molecule. Even if the RIA result is expressed in "units" – based on the known biological activity of the standard – the RIA does not prove whether the sample -- which is measured in the RIA based on immunological activity -- actually has that level of biological activity. Accordingly, even if the RIA indicates that the sample contains 100, 500 or 1,000 units, that, in fact, does not show that the sample has 100, 500 or 1,000 units of EPO biological activity as required by the claims of the '349 patent.

Moreover, the RIA simply assumes that amounts of the standard and the sample that have the same immunological activity also have the same biological activity. In fact, though, there is no single standard for use in measuring EPO. Individual laboratories standardize preparations of their own against primary standards. A standard used in an RIA may be calibrated in a bioassay and then used in an RIA. However, two standards calibrated based on biological activity may have the same biological activity, yet have different immunological activities. Consequently, a single sample of EPO could yield different results in two RIAs if it is tested against two standards having different immunological activities. Yet, neither the claims nor the specification of the '349 patent specify a particular standard to use in conducting the RIAs of the claim.

In sum, Amgen cannot prove that Roche's process uses cells which produce at the levels mandated by claim 7 of the '349 patent or the equivalent.

F. Under the Reverse Doctrine Of Equivalents, Roche Should Be Found Not To Infringe Any Of The Claims Asserted By Amgen.

Even if Roche were deemed to satisfy literally each and every element of any of the asserted claims of the patents-in-suit, Roche would not infringe, pursuant to the reverse doctrine of equivalents. As this Court has stated, "[t]he reverse doctrine of equivalents is an equitable doctrine that a court applies when it finds that the accused device literally infringes a patented invention, but is so fundamentally different from the patented invention that a judgment of infringement would in inappropriate." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202, 283 (D. Mass. 2004) (*Amgen IV*). "[T]he purpose of the 'reverse' doctrine is to prevent unwarranted extension of the claims beyond a fair scope of the patentee's invention." *Scripps Clinic & Research Found v. Genentech Inc.*, 927 F.2d 1565, 1581 (Fed. Cir. 1991). "[T]he Court must determine the originally intended scope, the 'spirit and intent' of the claims, [*Boyden Power-Brake Co. v. Westinghouse*, 170 U.S. 537, 568 (1898)], based on the context of the patent, the prior art, and the particular circumstances of the case, [*Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 609 (1950)]." *Amgen IV*, 339 F. Supp. 2d at 285. As the Supreme Court explained in *Westinghouse*:

> The patentee may bring the defendant within the letter of his claims, but if the letter has so far changed the principle of the device that the claims of the patent, literally construed, have ceased to represent his *actual invention*, he is as little subject to be adjudged an infringer as one who has violated the letter of a statute has to be convicted, when he has done nothing in conflict with its spirit and intent.

170 U.S. at 568 (emphasis added). "[A]fter the alleged infringer makes a prima facie showing that its process is so far changed in principle from the claimed processes that the patentee, 'who retains the burden of persuasion on infringement,' must rebut." *Amgen IV*, 339 F. Supp. 2d at 284 n. 97 (citations omitted).

Here, the patents-in-suit and their prosecution histories reflect that the "spirit and intent" of the claimed inventions was the production of glycoproteins using host cells and DNA. As recited in the specification, the polypeptides of the invention are "uniquely characterized by being the product of procaryotic or eucaryotic host expression . . . of exogenous DNA sequences." ('933 patent, col. 10:16-19). The inventor's expressed idea was to use "the existing machinery for expression in . . . 'transformed' or 'transfected' microbial host cells . . . to construct the desired product." (*Id*. at 2:28-31).

As explained above, however, CERA is not what Dr. Lin, the inventor of the patents-in-suit had in mind. Amgen tried to produce a substance similar to CERA and failed to develop anything close. The PTO granted Roche a patent on its novel and nonobvious product which "may aid in making a *prima facie* case in support of the reverse doctrine of equivalents." *Amgen IV*, 339 F. Supp. 2d at 300. CERA is not a protein expressed by host cells. Rather, CERA is synthesized outside of cells via a chemical reaction. The resulting product is a unique glycoprotein that is substantially changed in principle from the invention of the patents. CERA differs dramatically from human erythropoietin in size and shape. Moreover, the pronounced biological differences between CERA and human erythropoietin -- such as the dramatically lower affinity that CERA has for the EPO receptor -- reflect that CERA and EPO interact with EPO receptors and stimulate bone marrow cells to increase red blood cell and reticulocyte production" in fundamentally different ways. CERA is not an obligate glycoprotein. The prolonged half-life of CERA translates into a result that will make a significant difference to patients. Accordingly, it would be wholly inequitable to hold Roche liable for infringement even if one or more of the asserted claims can somehow be read to cover Roche's product or method of making it.

III. THE ASSERTED PATENT CLAIMS ARE INVALID

Roche will demonstrate below that the claims asserted in this case by Amgen are invalid for anticipation under 35 U.S.C. § 102; for obviousness under § 103; under the judicially-made doctrine of obviousness type double-patenting; and for lack of written description, non-enablement and/or indefiniteness under § 112. Roche will establish invalidity, as it must, by clear and convincing evidence.

A. The Legal Grounds For Invalidity

1. Anticipation Under 35 U.S.C. § 102.

Invalidity for anticipation, under 35 U.S.C. § 102, "requires disclosure of each and every claim limitation in a single prior art reference, either explicitly or inherently." *Astra Aktiebolag v. Andrx Pharms., Inc.*, 483 F.3d 1364, 1371 (Fed. Cir. 2007). An anticipation analysis involves "a comparison of the construed claim to the prior art." *Id.*

2. Obviousness Under 35 U.S.C. § 103.

Pursuant to 35 U.S.C. § 103, a patent may not be obtained "if the difference between the subject matter sought to be patented and the prior art are such that the subject as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."

3. Prior Invention Under 35 U.S.C. § 102(g).

35 U.S.C. § 102(g)(2) provides in pertinent part that a person shall be entitled to a patent unless "before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it." Therefore, "if a patentee's invention has been made by another, prior inventor who has not abandoned, suppressed or concealed the invention, § 102(g) will invalidate that patent." *Apotex USA, Inc. v. Merck & Co.*, 254 F.3d 1031, 1035 (Fed. Cir. 2001). "Prior invention by another invalidates a

claimed invention under section 102(g)(2) if the prior inventor either reduced the invention to practice first, or conceived of the invention first and subsequently reduced the invention to practice." *Rosco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373, 1381 (Fed. Cir. 2002).

4. Derivation Under 35 U.S.C. § 102(f).

Section 102(f) provides that a person shall be entitled to a patent unless "he did not himself invent the subject matter sought to be patented." "This is a derivation provision, which provides that one may not obtain a patent on that which is obtained from someone else whose possession of the subject matter is inherently 'prior.'" *Oddzon Prods., Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1401 (Fed. Cir. 1997). "To prove derivation under § 102(f), 'the party asserting invalidity must prove both prior conception of the invention by another and communication of that conception to the patentee by clear and convincing evidence." *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1344 (Fed. Cir. 2003).

5. The Doctrine Of Obviousness-Type Double Patenting.

"Obviousness-type double patenting is a judge-made doctrine that prevents an extension of the patent right beyond the statutory time limit. It requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent. Its purpose is to prevent an unjustified extension of the term of the right to exclude granted by a patent by allowing a second patent claiming an obvious variant of the same invention to issue to the same owner later." *In re Berg*, 140 F.3d 1428, 1431-32 (Fed. Cir. 1998). (citations omitted).

"Generally, a 'one-way' test has been applied to determine obviousness-type double patenting. Under that test, the examiner asks whether the application claims are obvious over the patent claims." *Berg*, 140 F.3d at 1432.

6. Indefiniteness Under 35 U.S.C. § 112.

Paragraph 2 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." According to the Federal Circuit, the "requirement of claim definiteness set out in § 112 ¶ 2 assures that claims in a patent are 'sufficiently precise to permit a potential competitor to determine whether or not he is infringing.'" *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1342 (Fed. Cir. 2003) ("*Amgen II*") (*quoting Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993)). *See also Oakley, Inc. v. Sunglass Hut, Int'l*, 316 F.3d 1331, 1340 (Fed. Cir. 2003) ("The primary purpose of the definiteness requirement is to ensure that the claims are written in such a way that they give notice to the public of the extent of the legal protection afforded by the patent, so that interested members of the public, *e.g.*, competitors of the patent owner, can determine whether or not they infringe").

As this Court stated in *Amgen I*, "[d]etermining whether a claim is definite requires an analysis of 'whether one skilled in the art would understand the bounds of the claim when read in light of the specification.'" 126 F. Supp. 2d at 156 (quoting *Personalized Media Communications, LLC v. Int'l Trade Comm'n*, 161 F.3d 696, 705 (Fed. Cir. 1998)). "The focus of the inquiry . . . is on the clarity of the claim terms and the extent to which such terms, viewed from the perspective of one of ordinary skill in the art, sufficiently identify the actual invention." *Id.* This notice defines the boundary at which infringement begins so that others can freely experiment and invent outside of those bounds. *Athletic Alternatives, Inc. v. Prince Manufacturing, Inc.*, 73 F.3d 1573, 1581 (Fed. Cir. 1996). Indefiniteness is a question of law to be determined by the court. *Personalized Media Communications, LLC. v. Int'l Trade Com'n*, 161 F.3d 696, 702 (Fed. Cir. 1998).

7. Lack Of Written Description Under 35 U.S.C. § 112.

35 U.S.C. § 112 ¶ 1 requires that each claim be supported by a "written description of the invention." In order to satisfy the requirements of § 112 ¶ 1, "the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). "[I]t is in the patent specification where the written description requirement must be met." *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927 (Fed. Cir. 2004) (affirming summary judgment on written description grounds).

8. Lack Of Enablement Under 35 U.S.C. § 112.

35 U.S.C. § 112 ¶ 1 further requires that the specification enable one of skill in the art to make and use the claimed invention. The test for enablement is whether one reasonably skilled in the art could make or use the invention based on the written disclosures of the patent coupled with information known in the art, without undue experimentation. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999). "In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970). The Federal Circuit has found that claims lacked enablement when the patent's specification taught only how to approximate the claimed result. Donald S. Chisum, (2007) Chisum on Patents, Vol. 3, § 7.03(4)(b); *see Nat'l Recovery Techs., Inc. v. Magnetic Separations Sys., Inc.*, 166 F.3d 1190, 1196-98 (Fed. Cir. 1999).

B. The Asserted Claims Of The '933 Patent Are Invalid

1. The Asserted Claims Of The '933 Patent Are Invalid As Anticipated Under 35 U.S.C. § 102(a).

The glycoforms of recombinant human erythropoietin expressed in at least some mammalian host cells are indistinguishable from some of the naturally occurring glycoforms

found in human urinary erythropoietin. Therefore, claim 3 of the '933 patent, is anticipated by prior art describing urinary EPO preparations made from different sources and using different purification schemes, for example: Chiba et al., U.S. Patent 4,465,624; Dukes, P.P. (1982) (abs.); Espada (1982) (abs. 5192); Lange (1984); Takaji Miyake, Charles Kung, and Eugene Goldwasser, "Purification of Human Erythropoietin," *J. Biol. Chem.*, 252, 5558-64 (1977); Miyake (1977); Spivak et al., "Use of Immobilized Lectins and Other Ligands for the Partial Purification of Erythropoietin," *Blood* 52(6):1178-88 (1978); Webber and Clemens, "Purification of Erythropoietin from Human Urine," Fed. Proceed, 42(7):1872 (1983); Yanagawa et al., "Isolation of human erythropoietin with monoclonal antibodies," *J. Biol. Chem.*, 259(5):2707-10 (1984).

At the time of the November 1984 filing of the applications which resulted in the Lin patents, no evidence existed establishing any conclusive difference between the glycoforms of rEPO (recombinant EPO) and uEPO (urinary EPO). In the late 1980s and early 1990s, more comprehensive analyses were conducted to characterize the representative glycoforms of uEPO and rEPO, including sequence analyses of particular glycan structures found on these molecules. These studies pointed to one conclusion: every glycan identified in rEPO was also observed in uEPO. In short, defining a human erythropoietin product as a recombinant product of the expression of a mammalian host cells fails to impart any structural or chemical difference that distinguishes such a product from a human erythropoietin product that either existed naturally or could have been derived from a human urinary source.

In the late 1980s, a number of studies were conducted to analyze the glycans in uEPO and rEPO. Sasaki (1987) and Takeuchi (1988) used purified human uEPO prepared according to the procedure described by Miyake (1977), which was compared against rEPO produced in

recombinant CHO cells. Their data too demonstrated that every glycan identified in rEPO was also observed in uEPO.

That finding has since been confirmed by various Amgen studies as well as the testimony of Amgen scientists. In 1987, recombinant human erythropoietin was being developed for use as a therapeutic in a joint development program by Amgen in the United States and Kirin Brewery Co. in Japan. Kirin and Amgen both used the same cell culture, purification process and "Master Working Cell Bank" of recombinant CHO cells to produce recombinant human EPO products, and made every effort to produce equivalent products. To confirm the equivalence of the Kirin and Amgen produced material, Amgen obtained and assayed the Kirin material using established analytical methods. Within the error of the method of analysis, the Amgen produced material and the Kirin produced material had the same carbohydrate composition. A presentation at a Kirin-Amgen Board meeting in 1990 indicated that the carbohydrate structure of the Kirin-produced rEPO was the "same as urinary EPO."

In short, a recombinant product of the expression of a mammalian host cell does not exhibit any structural, chemical or biological difference that distinguishes such a product from a human erythropoietin product that either existed naturally, or could have been derived from a human urinary source. If claim 3 of the '933 patent covers a recombinant human erythropoietin product, such as Amgen's CHO cell produced product, then the claim is invalid as anticipated by the prior art describing purification and use of uEPO. Claims 7 and 8 of the '933 patent are similarly anticipated.

The further limitations in the other asserted claims of the '933 patent (claims 9, 11, 12, 14), which all depend on claim 3, add no novel or inventive elements to the claimed inventions. It would have been obvious in 1983 to use the recombinant EPO in a pharmaceutical

composition and to administer that pharmaceutical composition to kidney dialysis patients. The fact that the '933 patent has claims directed specifically to pharmaceutical compositions and the treatment of kidney dialysis patients, notwithstanding that the patent specification provides no examples of pharmaceutical compositions or methods for treating kidney dialysis patients, and at most includes only a cursory reference to preparing or using EPO for these purposes, reflects that these additional limitations were obvious.

2. The Inventions Of The Asserted Claims Of The '933 Patent Would Have Been Obvious To One Of Skill In The Art In October 1983.[8]

At trial, Roche will also demonstrate, based on expert testimony and documentary support, that, in October 1983, non-naturally occurring glycoprotein products of the '933 patent claims would have been obvious to one of ordinary skill in the art.

The Federal Circuit has stated that "subject matter derived from another not only is itself unpatentable to the party who derived it under §102(f), but, when combined with other prior art, may make a resulting obvious invention unpatentable to that party under a combination of §§102(f) and 103." *Oddzon Products, Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1403-04 (Fed. Cir. 1997). The evidence will show that Dr. Eugene Goldwasser used government funds to obtain and purify EPO which he then provided exclusively to Amgen. Without the amounts of purified EPO and EPO fragments provided by Dr. Goldwasser to Amgen, Dr. Lin would not have been able to obtain the sequence information needed to clone EPO. Dr. Goldwasser's EPO, though not generally available, was thus § 102(f) prior art as against Amgen and, in combination with the rest of the prior art, would have made Dr. Lin's invention obvious.

[8] For purposes of its prior art analysis Roche uses this date but does not concede that any of Amgen's claims are entitled to this priority date.

If quantities of purified EPO had been made available to others of skill in the art in 1983, they could have obtained the amino acid sequence. Given that sequence, it would have been obvious to one of skill in the art to use cDNA cloning or DNA synthesis to obtain a gene encoding human EPO and to use one of a number of widely available mammalian host cell expression systems, such as the COS cell line or the CHO cell line, to express human EPO as a glycosylated recombinant protein. Indeed, as of October 1983, cloned DNA was routinely used for transforming mammalian and other vertebrate cells. Expression vectors for use with various host cells were well known. The prior art had described the successful expression of human and other mammalian glycoproteins in a functional and biologically active form using non-human mammalian cells, including CHO and COS cells.

Based on the experience in the art expressing other proteins in CHO and COS cells, one of skill in the art would have had a reasonable expectation that they would succeed in using non-human mammalian host cells, including CHO cells and COS cells, to express a recombinant human glycoprotein having *in vivo* biological activity. Accordingly, the use of a non-human mammalian host cell to produce the human erythropoietin glycoprotein product of claims 3, 7 and 8 of the ‘933 patent would have been obvious to one of skill in the art as of October 1983.

Having expressed and isolated recombinant human EPO for the purpose of making a therapeutic, it would have been obvious to use the glycoproteins of claims 3, 7 and 8 in combination with a diluent, adjuvant or carrier to make the pharmaceutical compositions of claims 9 and 12 of the ‘933 patent. Suitable diluents, adjuvants and carriers were well known in the art and were described in standard treatises.

In addition, it was already widely recognized by October 1983 that chronic renal failure requiring dialysis was associated with refractory anemia due to insufficient renal production of

EPO and that human EPO could be important for therapeutic use. Thus, it would have been obvious to use the pharmaceutical compositions of claims 9 and 12 to practice the methods of claims 11 and 14 by treating kidney dialysis patients to increase hematocrit levels.

3. Claims 3, 7, 8, 9, 11, 12 and 14 Of The '933 Patent Are Invalid For Obviousness-Type Double Patenting Over the Claims of The '868 or '698 Patents

The asserted claims of the '933 patent are nothing more than obvious variants of the '868 patent claims to processes for producing a glycosylated erythropoietin polypeptide. The '933 claims are product-by- process claims directed to the product produced when the processes of the '868 claims are carried out. Thus, the product of claims 3, 7 and 8 is simply the natural result of the '868 processes. Further as described above, it would have been obvious to formulate the product as a therapeutic according to claims 9 and 12 to practice the methods of claims 11 and 14.

Finally, 35 U.S.C. § 121 affords the claims of the '933 patent no protection from obviousness-type double patenting because the applications for the '868 patent were not filed "as a result of" the 1986 restriction requirement. The claims of the '179 application, which led to the issuance of the '868 patent, were process claims that were voluntarily cancelled from the '298 application ('008 patent) even though they could have been prosecuted in the '298 application consistent with the 1986 restriction requirement.

C. The Asserted Claim Of The '422 Patent Is Invalid

1. Claim 1 Of The '422 Patent Is Anticipated Or Made Obvious By Prior Art Relating To Purification Of Human Urinary EPO.

Claim 1 of the '422 patent is directed to a "pharmaceutical composition" comprising "a therapeutically effective amount of human erythropoietin," which is "purified from mammalian cells grown in culture," as well as a "pharmaceutically accepted diluent, adjuvant or carrier."

Thus, the claim encompasses composition containing urinary EPO, EPO produced by cultured tumor cells and/or recombinant EPO. As mentioned above, though, the source alone does not connote a distinctive structure. *See Amgen II*, 314 F.3d at 1354. The claimed pharmaceutical composition would have been anticipated or obvious in view of the same prior art that would have made obvious '933 patent, dependent claims 9 and 12. In 1983-1984, it would have been anticipated or obvious to use purified EPO in a pharmaceutical composition and to use that pharmaceutical composition in treating a kidney dialysis patient.

As early as 1971, it was appreciated that human EPO could be important for "possible therapeutic use in some types of refractory anemia." (Goldwasser 1971). Amgen admits that that the uEPO preparation purified by Drs. Miyake and Goldwasser, as described in Miyake (1977), "caused increased hemoglobin synthesis after *in vivo* administration to mice." (Amgen's Response to Defendant's Third Set of Requests for Admission No. 32). Moreover, Dr. Eschbach demonstrated a dose-dependent correction of anemia in uremic sheep by parenteral administration of erythropoietin-enriched plasma, confirming that chronic renal failure, which typically requires dialysis, is associated with a refractory anemia due to insufficient renal production of erythropoietin. (Eschbach (1984) (original submission date July 5, 1983; published August 1984)). Thus, by 1983-1984, the desirability of treating dialysis patients with human EPO was widely recognized and appreciated.

As discussed above, by all means available 1983-1984, uEPO was indistinguishable in terms of its immunological, biological and physical properties from CHO cell produced rEPO. Therefore, it would have been obvious to use rEPO in the claimed pharmaceutical composition of the '422 patent, and to use that composition for treating a kidney dialysis patient. Such pharmaceutical compositions could also be used in animals.

In sum, claim 1 of the '422 patent would have been anticipated or obvious in light of by the prior art describing purification and use of EPO.

2. Claim 1 Of The '422 Patent Would Have Been Obvious Given The State of The Art With Respect to Recombinant Proteins.

In construing the claim term "therapeutically effective amount," this Court adopted the Federal Circuit's construction as meaning an amount that merely "elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals." (Mem. and Order, 7/3/07, p. 23). No disease cure is required.

As described above, in October 1983, it would have been obvious, assuming one had quantities of Dr. Goldwasser's purified EPO, to obtain the amino acid sequence, to obtain the gene encoding human erythropoietin, to insert the gene into a suitable expression vector, to introduce the vector into one of several mammalian cells routinely used for recombinant expression of glycoproteins, such as a COS or CHO cells, and to express the encoded human erythropoietin protein with expectation that the expressed recombinant human erythropoietin would exhibit the *in vivo* biological activity of the naturally occurring glycoprotein. In addition, it would have been obvious to use methods for amplification -- *i.e.*, expression vectors encoding marker genes such as DHFR -- to express human erythropoietin in quantities sufficient to elicit any one or all of the effects often associated with *in vivo* biological activity of natural EPO, in either an animal or a human subject. Using routine methods for protein purification, it would

have been obvious to isolate the biologically active erythropoietin from the transformed mammalian host cell cultures.

The further limitation of '422 patent, claim 1, that the pharmaceutical composition comprise a pharmaceutically acceptable diluent, adjuvant or carrier, would have been obvious and routine. Suitable pharmaceutical vehicles -- diluents, adjuvants and carriers -- were well known in the art and described in standard treatises.

In sum, much of the interest in recombinant DNA technology in 1983 was to produce recombinant human proteins in useful quantities in order to initiate and conduct animal and clinical testing. Having expressed and isolated recombinant human erythropoietin, it would have been obvious to formulate a suitable pharmaceutical composition containing a recombinant human glycoprotein, such as human erythropoietin, and a well known suitable diluent, adjuvant or carrier for use in an animal or human subject.

3. Claim 1 Of The '422 Patent Is Anticipated By The Baron Clinical Study.

Claim 1 of the '422 patent is anticipated by a clinical study conducted by Dr. Joseph Baron in 1979-80 using human EPO. Dr. Baron used a pharmaceutical composition that satisfied the elements of claim 1.

The Baron clinical study disclosed a "therapeutically effective amount of human erythropoietin" as that term has been construed by the Federal Circuit. Furthermore, Baron's IND application disclosed a "pharmaceutical composition" and a "pharmaceutically acceptable diluent, adjuvant, or carrier," stating:

> Human erythropoietin (H-EPO) has been prepared from the urine of patients with aplastic anemia….The hormone is diluted in Normal Serum Albumin (Human) USP (Albuspan®, Parke Davis) at a concentration of 276 units/ml (80,000 units/H-EPO protein) to maintain stability and permit appropriate volume for administration.

Although claim 1 of the '422 patent further provides that the erythropoietin in the claimed pharmaceutical composition is "purified from mammalian cells grown in culture," that source or process limitation, as mentioned above, does not add a patentable distinction to the claims of the '422 patent and is irrelevant for validity purposes. In any event, the prior art discloses purified urinary EPO that is ultimately derived from mammalian kidney cells. *See* Miyake *et al.*, 1977.

The Baron clinical study data showed that the pharmaceutical composition was administered to three renal anemia patients and was effective in stimulating erythropoietic activity. Because the Baron study discloses a pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin the study anticipates claim 1 of the '422 patent.

4. The Baron Clinical Study Is A Prior Invention That Invalidates Claim 1 Of The '422 Patent Under 35 U.S.C. §§ 102(g), 102(f).

Claim 1 of the '422 patent is also invalid under 35 U.S.C. § 102(g) because the pharmaceutical composition used in the Baron study is the pharmaceutical composition of claim 1 of the '422 patent. In other words, Dr. Lin's supposed invention of the '422 patent was previously "made in this country by another inventor." According to the documents associated with Baron's IND, the prior inventors were diligent in pursuing their invention, and did not abandon, suppress, or conceal their work as evidenced by their repeated attempts to obtain additional material to continue their studies and share their findings.

Claim 1 of the '422 patent is also invalid under 35 U.S.C. § 102(f), under which "'the party asserting invalidity must prove both prior conception of the invention by another and communication of that conception to the patentee' by clear and convincing evidence." *Eaton Corp. v. Rockwell Intl' Corp.*, 323 F.3d 1332, 1344 (Fed. Cir. 2003). The evidence will show that Dr. Goldwasser conceived and reduced to practice a pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier. Moreover, in developing the pharmaceutical composition of the '422 patent claims, Amgen knew of and relied on the Baron clinical study.

5. Claim 1 Of The '422 Patent Is Anticipated Or Rendered Obvious By The Essers EPO-Rich Plasma Studies.

Claim 1 of the '422 patent is also anticipated or rendered obvious by studies conducted in the 1970s by Dr. Ursula Essers, who used EPO-rich blood fractions to treat renal insufficiency. The Essers studies involved a "therapeutically effective amount of human erythropoietin," as that term has been construed by the Federal Circuit, together with a diluent, adjuvant, or carrier, as required by claim 1 of the '422 patent. The studies demonstrate that an increase in reticulocytes followed administration of EPO-rich plasma, a pharmaceutical composition according to claim 1. The claim 1 limitation "wherein said erythropoietin is purified from mammalian cells grown in culture" is a source or process limitation which, as explained above, is irrelevant for determining whether a piece of prior art anticipates a patent claim. In any event, Essers discloses enriched plasma containing EPO that was ultimately derived from mammalian kidney cells.

6. Claim 1 Of The '422 Patent Is Anticipated Or Rendered Obvious By The Eschbach EPO-Rich Plasma Study.

Claim 1 of the '422 patent is also anticipated or rendered obvious by a study that Dr. Joseph Eschbach conducted in 1984. Dr. Eschbach treated a dialysis patient suffering from anemia with a pharmaceutical composition of EPO-rich plasma that contained a "therapeutically

effective amount of human erythropoietin," as that term has been construed by the Federal Circuit, along with a diluent, adjuvant, or carrier. The patient showed an increase in reticulocyte count and plasma iron turnover -- indications of red blood cell production. Again, the claim 1 limitation "wherein said erythropoietin is purified from mammalian cells grown in culture" is a source or process limitation that is irrelevant for determining whether a piece of prior art anticipates a patent claim. Nevertheless, Eschbach discloses enriched plasma containing EPO that is ultimately derived from mammalian kidney cells.

7. Claim 1 Of The '422 Patent Is Anticipated Or Rendered Obvious By The Baron And Goldwasser Hamster Study.

In 1978, Drs. Baron and Goldwasser conducted a toxicology study on hamsters to measure the general effects of large doses of a pharmaceutical composition comprising purified human urinary EPO. The study, though very small, showed that the EPO was therapeutically effective, producing a significant increase in hematocrit.

The EPO that Baron and Goldwasser administered to the hamsters was the same pharmaceutical composition, comprising urinary EPO and human serum albumin (a pharmaceutically acceptable diluent), that was administered in the Baron Clinical Study. Thus, in 1978, the Goldwasser and Baron hamster study disclosed every element of claim 1 of the '422 patent in 1978 -- a pharmaceutical composition, suitable for administration in humans, containing a therapeutically effective amount of human erythropoietin, and a pharmaceutically acceptable diluent adjuvant or carrier. Based on the results of the Goldwasser and Baron hamster study, it also would have been obvious to one skilled in the art in 1983 to administer to a human a pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier.

8. Claim 1 of the '422 Patent Is Invalid For Obviousness-Type Double Patenting Over

the Claims of The ‘868 or ‘698 Patents

Claim 1 of the ‘422 patent is nothing more than an obvious variant of the ‘868 and ‘698 patent claims to processes for producing a glycosylated erythropoietin polypeptide. Claim 1 of the ‘422 patent is directed to a therapeutic composition of human erythropoietin. By following the processes of the 868 and ‘698 claims recombinant human erythropoietin would be produced. Having expressed and isolated a glycosylated erythropoietin polypeptide in accordance with the claims of the ‘868 or ‘698 patents, it would have been obvious to purify the product for use in combination with a diluent, adjuvant or carrier to make the pharmaceutical composition of claim 1.

Finally, 35 U.S.C. § 121 affords the claims of the ‘422 patent no protection from obviousness-type double patenting because the applications for the ‘868 and ‘698 patents were not filed “as a result of” the 1986 restriction requirement. The claims of the ‘179 application, which led to the issuance of the ‘868 and ‘698 patents, were process claims that were voluntarily cancelled from the ‘298 application (‘008 patent) even though they could have been prosecuted in the ‘298 application consistent with the 1986 restriction requirement.

9. Claim 1 Of The ‘422 Patent Is Invalid Under 35 U.S.C. § 112.

The patent specification points to FIG. 6 of the patent as serving “to identify the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues.” (‘422 patent, 20:66-21:1). In fact, human EPO is thought today to have only 165 amino acids, though the correct amino acid sequence was published by others (not Amgen) only after the filing of the patents-in-suit. If the claim term “human erythropoietin” is understood to mean the 165 amino acid sequence of naturally occurring human erythropoietin, then the 166 amino acid sequence recited in the patents-in-suit does not provide the required written description of the invention. The Court’s claim construction provides that human

erythropoietin is a protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine. There is no written description of the sequence of human urinary EPO in the patent or prior art.

D. The Asserted Claims Of The '868 Patent Are Invalid

1. Claims 1 and 2 Of The '868 Patent Would Have Been Obvious In View Of The Prior Art.

Claim 1 of the '868 patent is directed to "a process for the production of a glycosylated erythropoietin" comprising two steps: (1) "growing . . . mammalian host cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin" and (2) "isolating said glycosylated erythropoietin polypeptide therefrom." The glycosylated erythropoietin is the to have "in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells." Dependent claim 2 is directed to the process of claim 1 where "said host cells are CHO cells."

In essence, the '868 patent claims a process for producing the glycoprotein product of the '933 patent using the transformed or transfected cells of the '008 patent. Accordingly, the process claims of the '868 patent -- like the glycoprotein products of the '933 patent -- were obvious in October 1983 in view of the state of the art with respect to art relating to synthesizing and/or cloning of DNA, the expression of biologically active proteins with transformed mammalian host cells, and the isolation of the desired protein product. The limitation to using CHO cells according to claim 2 provides no non-obvious distinction over such a method as CHO cells would have been an obvious choice to use for recombinant expression of human glycoproteins.

2. Claims 1 and 2 Of The '868 Patent Are Invalid For Obviousness-Type Double Patenting Over Claims 2, 4, 6, 7, 25 And 27 Of The '008 Patent.

The processes of the '868 patent represent nothing more than obvious variants of the '008 patent claims to cells transformed or transfected with EPO DNA for the purpose of expressing biologically active EPO. The claims of the '868 patent present no patentable distinction over the '008 patent. It would have been obvious to one of skill in the art to grow mammalian host cells, as recited by '008 patent, claim 25, or CHO host cells, as recited by '008 patent, claim 27, to produce a biologically active glycosylated erythropoietin according to the process of '868 patent claims 1 or 2. Moreover, it would have been routine for one of skill in the art to isolate the biologically active erythropoietin from the host cells of claims 25 and 27 of the '008 patent and thereby carry out the second and final required step in the process of the '868 patent, claims 1 and 2.

Furthermore, there is no patentable distinction between claim 2 of the '008 patent to a DNA sequence "consisting essentially of a DNA sequence encoding human erythropoietin," and the claimed process as recited by '868 patent claims 1 or 2, comprising the use of host cells to produce a biologically active glycosylated erythropoietin capable of causing bone marrow cells to increase production of reticulocytes and red blood cells.

Finally, 35 U.S.C. § 121 affords the claims of the '868 patent no protection from obviousness-type double patenting because the application for the '868 patent plainly was not filed "as a result of" the 1986 restriction requirement. The claims of the '179 application, which led to the issuance of the '868 patent, were process claims that were voluntarily cancelled from the '298 application ('008 patent) even though they could have been prosecuted in the '298 application consistent with the 1986 restriction requirement.

E. The Asserted Claims Of The '698 Patent Are Invalid

1. Claims 4-9 of the '698 Patent Would Have Been Obvious.

Much like the asserted claims of the '868 patent, claims 4 and 6 of the '698 patent are directed to a process for the production of a biologically active glycosylated erythropoietin polypeptide comprising two steps: (1) "growing . . . vertebrate cells" comprising certain DNA sequences; and (2) "isolating said glycosylated erythropoietin polypeptide expressed by said cells." The '698 patent claims specify that the cells comprise "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6." Claim 4 of the '698 patent states that the cells contain "promoter DNA, other than human EPO promoter DNA;" claim 6 of the '698 patent requires that the EPO DNA be "amplified."

The processes of the '698 patent -- like the processes of the '868 patent -- were obvious, in October 1983, in view of the state of the art with respect to the cloning of DNA, the expression of biologically active proteins using transformed mammalian host cells, and the isolation of the desired protein product. In particular, in October 1983, given quantities of Dr. Goldwasser's purified EPO, it would have been obvious, in accord with claims 4 and 6 of the '698 patent, to obtain the gene encoding human erythropoietin through cDNA cloning or chemical synthesis; to use one of several amplifiable expression vectors in which the DNA sequence encoding human erythropoietin is operably linked to suitable non-human erythropoietin promoter DNA sequences, such as SV40 or other viral promoters; to introduce such an expression vector into one of several mammalian cells (a class of vertebrates) routinely used for recombinant expression of glycoproteins, such as a COS or CHO cells, using routine and well described methodology for transformation of mammalian host cells, including transfection and infection; to grow such mammalian host cells under suitable nutrient conditions to produce a

biologically active EPO product; and to isolate the biologically active erythropoietin from the transformed mammalian host cell cultures.

Dependent claim 5 of the '698 patent further limits the process of claim 4 by specifying the promoter DNA be "viral promoter DNA." Dependent claim 7 limits the process of claim 6 to using vertebrate cells that "further comprise amplified marker gene DNA." Dependent claim 8 further limits claim 7 by specifying that the amplified marker gene DNA is "Dihydrofolate reductase (DHFR) gene DNA." Dependent claim 9 is directed to the process of claims 4 and 6 where "said cells" used in the process "are mammalian." The evidence will show that these further limitations to the processes recited by '698 claims 4 or 6 would all have been obvious and routine.

Prior to October 1983, some viral promoters were known and those of skill in the art would position such promoters in an expression vector to drive transcription of an adjacent coding sequence. It would have been obvious to use a selectable marker, such as a gene for DHFR, to select cells having amplified DNA and thereby generate cells that express the recombinant human erythropoietin protein at high levels. Lastly, as also noted above, use of mammalian host cells, such as COS or CHO cells would have been an obvious choice for expressing a recombinant human glycoprotein. Thus, claims 5, 7, 8 and 9 of the'698 patent would also have been obvious.

2. Claims 4-9 Of The '698 Patent Are Invalid For Obviousness-Type Double Patenting Over Claims 2, 4, 6, 7, 25 Or 27 Of The '008 Patent.

As in the case of the claims of the '868 patent, the processes of the '698 patent are merely obvious, non-patentable variations of the inventions of the now expired '008 parent of the patents-in-suit. There is no patentable distinction between the host cell claims 25 or 27 of the '008 patent -- directed to a recombinant mammalian host cell, transformed in such a manner as to

allow the host cell to express an erythropoietin with the "biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells" -- and the processes recited by claims 4 and 6 of the '698 patent which use such cells for their intended purposes. The use of DNA encoding the amino acid sequence of Figure 6, as required by claims 4 and 6 of the '698 patent is not a patentable distinction over the '008 patent which discloses the same sequence. For the reasons discussed above with respect to the other patents-in-suit, there is also no patentable distinction between claim 2 of the '008 patent , and the processes recited by claims 4 and 6 of the '698 patent.

The use of promoter DNA other than human erythropoietin promoter DNA, in the process of '698 patent, claim 4, or more specifically a viral promoter as recited by '698 patent, claim 5, does not provide any patentable distinction over the DNA and host cell claims 2, 25 and 27 of the '008 patent. As disclosed above, the prior art described numerous examples of promoters and various expression vectors including such promoters operably linked in order to drive expression of exogenous genes. The prior art also taught the use of the viral promoters, from the SV40 virus. It would have been obvious to one of skill in the art using either the claimed DNA or host cells expressing such DNA to employ the 5V40 promoter to express DNA encoding human erythropoietin in a mammalian or other vertebrate cell, such as a COS cell or CHO cell.

Moreover, the use of cells comprising amplified marker DNA as recited by '698 patent, claim 7, and specifically, amplified marker DNA corresponding to the DHFR gene per claim 8, does not provide any patentable distinction over the DNA and host cell claims, of the '008 patent. As described above, as of October 1983, the prior art described numerous examples of using amplification for transient and stable expression of human glycoproteins in host cells, such

as COS cells or CHO cells, and expression vectors encoding various marker genes such as the DHFR gene for use in such methods. Given that claim 10 of the '016 patent expressly recites the use of mammalian cells, the process of claim 9 of the '698 patent would also have been obvious over the '016 patent.

Again, § 121 provides Amgen with no protection from obviousness-type double patenting because Amgen voluntarily filed the '698 claims separately from the claims of the '008 patent even though the '698 patent claims did properly belong in Group II, which was prosecuted in the '008 patent, pursuant to the 1986 restriction requirement.

3. Claims 4 And 5 Of The '698 Patent Are Invalid For Lack Of Written Description And Indefiniteness.

Claims 4 and 5 of the '698 patent are invalid for lack of written description and indefiniteness because the claims broadly recite "promoter DNA, other than human erythropoietin promoter DNA," but the '698 patent does not demonstrate that Dr. Lin, the inventor, was in possession of the vast genus of such "promoter DNA other than human EPO promoter DNA." In fact, there is no indication that Dr. Lin considered any non-human promoter DNA to control transcription in DNA cells other than from the SV40 virus.

In the first step of gene expression, a nucleotide sequence of DNA is "transcribed" (or copied) into an intermediate RNA molecule using a cellular component called RNA polymerase. RNA polymerase functions by binding to certain nucleotides (bases) in the DNA sequence and synthesizing an RNA copy. The resulting RNA is then spliced into a mature messenger RNA (mRNA) that carries the genetic information encoded by the DNA molecule to the elements of the cell responsible for protein synthesis.

Very generally, RNA polymerase binds to particular "promoter" sequences in the DNA. Promoters generally encompass both the binding site for RNA polymerase and any additional

DNA elements minimally required for transcription to occur. Promoters are typically located where transcription starts, at the beginning of genes, and they direct the RNA polymerase to transcribe in a particular direction (through the gene as opposed to away from it). Promoters can also, but do not necessarily, include DNA elements that regulate the rate of transcription,. Such regulatory elements are highly diverse and vary in both number and position depending on the gene. Thus, while some promoters and their associated regulatory elements are compact and simple, others are complex.

In the human genome there are approximately 30,000 genes. Each gene is thought to have its own promoter and regulatory elements. By rough approximation there are 30,000 DNA sequences which control transcription in human cells. The number of animals that are classified as vertebrates is also very large. All of the genes in all of those species have DNA sequences that control their transcription. By multiplying the number of genes by the number of vertebrate species one can estimate the number of DNA sequences which control expression naturally in vertebrate cells. A calculation based on a conservative estimate of 10,000 different vertebrate species with an average of 10,000 different DNA sequences which control transcription yields 100,000,000 different possible DNA sequences. Yet, by the early 1980's, only a handful of promoters (and enhancers) had been characterized in any detail.

The phrases "promoter DNA, other than human erythropoietin promoter DNA" and "said promoter DNA is viral promoter DNA," of claims 4 and 5, are not supported by the original specification. None of the originally filed claims recited these phrases. Neither the general disclosure defining terms of art nor the examples of Amgen's experiments identify a broad genus of non-human DNA sequences which control transcription in vertebrate cells. Further, the

specification does not provide a description of the DNA sequences that control transcription of the human erythropoietin gene.

There is nothing in the '698 patent specification that would indicate to a person of ordinary skill in the art that Dr. Lin was in possession of broad classes of DNA promoter sequences as are encompassed by the phrases in the '698 patent claims. The patent's general discussion about promoters and regulators provides background information but does not describe particular DNA sequences that serve as promoter sequences. The patent provides no practical information from which a person of the skill in the art could determine what DNA sequences Dr. Lin had possession of in 1984 for producing erythropoietin from vertebrate cells.

The only non-human DNA sequences disclosed in the '698 patent that initiate and/or regulate transcription of DNA encoding human erythropoietin in *vertebrate cells* are the sequences from SV40 virus. However, one example does not provide a written description of the large genus of all viral promoter sequences which control transcription in vertebrate cells, let alone provide a written description of a complete genus of sequences that are covered by the broader language in claim 4 of the '698 patent.

F. The Asserted Claim Of The '349 Patent Is Invalid

1. Claim 1 Of The '349 Patent Is Invalid For Obviousness.

The process of claim 7 of the '349 patent, like the processes discussed above, would have been obvious to one of skill in the art who had quantities of purified EPO from Dr. Goldwasser. As detailed above and as the evidence will show, it would have been obvious to sequence the protein, obtain the gene encoding human erythropoietin through cDNA cloning or chemical synthesis and to then use a mammalian host cell to express the encoded human erythropoietin protein having *in vivo* biological activity.

2. Claim 7 of the '349 Patent Is Invalid For Obviousness-Type Double Patenting Over the Claims of The '868 or '698 Patents

Claim 7 of the '349 patent is nothing more than an obvious variant of the '868 and '698 patent claims to processes for producing a glycosylated erythropoietin polypeptide. Claim 7 of the '349 patent is directed to a process of producing erythropoietin at a minimum production level by culturing vertebrate cells. The '868 and '698 patent claims are to processes for producing a glycosylated erythropoietin polypeptide. The minimum production level specified in '349 claim 7 is the inherent result of practicing the processes patented. For example, the use of methotrexate to amplify and increase expression had already been reported before 1983. Thus claim 7 of the '349 patent is simply an obvious variant of the '868 or '698 claims.

Finally, 35 U.S.C. § 121 affords the claims of the '349 patent no protection from obviousness-type double patenting because the applications for the '868 and '698 patents were not filed "as a result of" the 1986 restriction requirement. The claims of the '179 application, which led to the issuance of the '868 and '698 patents, were process claims that were voluntarily cancelled from the '298 application ('008 patent) even though they could have been prosecuted in the '298 application consistent with the 1986 restriction requirement.

3. The '349 Patent Claims Are Not Enabled And Lack Written Description.

Notwithstanding that there are thousands of different species of vertebrates, and many millions of different cells from those species, the '349 patent potentially describes only two cell lines, both arguably derived from mammalian species: COS and CHO cells. In 1983-84 skilled scientists knew that cells from different species, cell types, and differentiation states often had very different properties. One of skill in the art in that time period would not have considered

the two cell lines described in the '349 patent to be representative of the entire group of "vertebrate cells" claimed.

In 1984, there were only a handful of cell lines being used to express exogenous genes. A skilled artisan could not have predicted whether or not given cells could have expressed erythropoietin from an isolated DNA sequence unless that cell was known to be capable of growing in culture and being transformed with foreign DNA, and unless there were suitable regulatory sequences available. Only CHO cells and COS-1 cells are discussed in the '349 patent. Moreover, only a specialized version of CHO cells, CHO DHFR cells, is described to produce the levels of human erythropoietin claimed in the '349 patent. The patent clearly states that COS-1 cells did not produce reliable amounts of protein. *See* col. 25:31-39. The single example of a specially derived CHO cell for producing erythropoietin at the levels recited in the claims of the '349 patent would not convey to one of skill in the art methods of using all vertebrate cells to make reliable quantities of glycosylated recombinant erythropoietin.

Moreover, in 1984, only a few vertebrate and mammalian host cells had been used to express biologically active glycoproteins. Thus, there would not have been a reasonable expectation of success that a skilled artisan, reading the '349 patent in 1984, could produce biologically active forms of the erythropoietin glycoprotein in the full range of vertebrate cells encompassed by claim 7.

The technique described in the '349 patent specification, while well known for COS and CHO cells, was not predictable for non-mammalian cell lines. The literature at the time does not provide any evidence of a viable protein expression system in any cell from non-mammalian vertebrate classes of reptiles, amphibians, or fish. Therefore, one of ordinary skill in the art in

1983-84 would have had no expectation that the methods described in the examples of the '349 patent would be transferable to cells from any of these non-mammalian vertebrate classes.

Consequently, in 1984, it would have undue experimentation for one of ordinary skill in the art to practice the full scope of claim 7 of the '349 patent which encompasses expression of an exogenous DNA encoding erythropoietin in *all vertebrate host cell* systems. Thus, the claims were not enabled.

In addition, given the narrow disclosure of the '349 patent and the breadth of the claims, the claims lack written description. A person of skill in the art reading the '349 patent would not have understood Dr. Lin to have been in possession of the enormous genus of all "non-human DNA sequences which control transcription of DNA encoding human EPO" in "vertebrate cells," per the '349 patent.

4. Claim 7 Should Have Expired With The '008 Patent.

Pursuant to 35 U.S.C. § 103(b), biotechnology process patents which claim the use or production of a novel composition of matter are entitled to the benefit of a special standard -- and are deemed nonobvious -- where (1) the applicant elected to proceed under the statute; and (2) the process and composition of matter are owned by the same person and are contained in either the same application or in separate applications having the same filing date. Under the statute, where the novel product and the process that uses or produces it are contained in separate patents they must be "set to expire on the same date."

During prosecution of the '349 patent, the applicant relied on § 103(b), arguing to the PTO that "amendments to 35 U.S.C. § 103 have been effective to permit the grant of microbiological process claims involving use of novel cellular material in a patent claiming such cellular material." ('369 Application File History, Paper 8, 12/20/96 Second Preliminary Amendment at 9).

Amgen's '008 patent includes claims (23-27) to host cells which are transformed or transfected -- with a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of EPO to have the biological property of EPO -- "in a manner allowing the host cell to express said polypeptide." In other words, claim 7 describes a process which uses the host cells of claims in the '008 patent. Therefore, under 35 U.S.C. § 103(b), claim 7 of the '349 patent should have expired with the '008 patent.

IV. THE PATENTS-IN-SUIT SHOULD BE HELD UNENFORCEABLE FOR INEQUITABLE CONDUCT

Roche will demonstrate at trial that the patents-in-suit should be held unenforceable for inequitable conduct because in seeking to obtain patent protection extending its long-standing EPO monopoly, Amgen repeatedly violated its duty of candor to the PTO.

A. The Law Of Inequitable Conduct

"A patent may be [held] unenforceable for inequitable conduct if an applicant, with intent to mislead or deceive the examiner, fails to disclose material information or submits materially false information to the PTO during prosecution." *McKesson Info. Solutions, Inc. v. Bridge Med., Inc.*, 487 F.3d 897, 913 (Fed. Cir. 2007). "Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the [Patent] Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section." 37 C.F.R. § 1.56(a).

The duty of candor imposed on patent applicants "is broader than the duty to disclose material information." MPEP § 2001.04 (5th ed. Rev. 14, 1992); *Rohm & Haas Co. v. Crystal Chem. Co.*, 722 F.2d 1556, 1571 (Fed. Cir. 1983) ("Surely, a very important policy consideration is to discourage all manner of dishonest conduct in dealing with the PTO"). The PTO imposes a duty of candor, in part, because patent examiners rely upon the information and statements

submitted by an applicant in order to examine any given application in the limited time allotted them. (*See* U.S. Gen. Accounting Office, GAO-RCED-89-120BR, Biotechnology, Backlog of Patent Applications, at 20 (1989) (biotechnology examiners spent 19.3 hours per application)). Moreover, where prior art is submitted in an IDS but not described, the examiner is only responsible for cursorily reviewing the reference. (Guidelines for Reexamination Of Cases In View of *In Re Portola Packaging*, Inc., 110 F.3d 786 (Fed. Cir. 1997)); MPEP § 609 (5th ed. Aug. 2001). Accordingly, the law requires applicants and their attorneys to be candid, honest and forthcoming in their interactions with the PTO.

The Federal Circuit recognizes several materiality standards in inequitable conduct cases. *Digital Control Inc. v. Charles Machine Works*, 437 F.3d 1309, 1314-16 (Fed. Cir. 2006). Under the standard that is "most dominant" in the case law, "an inequitable conduct determination requires a showing that 'a reasonable examiner would have considered [the information] important in deciding whether to allow the parent application.'" *Id*. at 1314.

Intent to mislead the PTO, the second prong of inequitable conduct, "need not, and rarely can, be proven by direct evidence . . . .[I]n the absence of a credible explanation, intent to deceive is generally inferred from the facts and circumstances surrounding a knowing failure to disclose material information. . . .[A] patentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish subjective good faith sufficient to prevent the drawing of an inference of intent to mislead." *Ferring B.V. v. Barr Labs. Inc.*, 437 F.3d 1181, 1191 (Fed. Cir. 2006).

Mere submission of information is not a defense against inequitable conduct where an applicant buries material information or presents the information in such a manner that the examiner would likely ignore it. *See eSpeed Inc. v. Brokertec USA, L.L.C.*, 417 F. Supp. 2d 580,

598 (D. Del. 2006), *aff'd*, 480 F.3d 1129 (Fed. Cir. 2007) (inequitable conduct where information was buried in declarations and exhibits of over two thousand pages and "not pointed out to the examiner"); *Golden Valley Microwave Foods Inc. v. Weaver Popcorn Co. Inc.*, 837 F. Supp. 1444, 1477 (N.D. Ind. 1992), *aff'd*, 11 F.3d 1072 (Fed. Cir. 1993) ("it is likewise a violation of the duty of candor and fair dealing with the Patent Office for an applicant or its attorney to disclose a pertinent prior art patent reference to the examiner in such a way as to 'bury' it. . ."') (emphases added); MPEP § 2002.03 (5th ed. Rev. 3, May 1986) ("non-identification of an especially relevant passage buried in an otherwise less or non-relevant text could result in a holding of 'violation of duty of disclosure'").

Moreover, submission of information to one branch of the PTO does not satisfy the duty of disclosure as to all branches. Federal Regulations dictate that "a separate copy of every paper to be filed in a patent…must be furnished for each file to which the paper pertains, even though the contents of the papers filed in two or more files may be identical." 37 C.F.R. § 1.4(b); *see also* § 1.4(c) ("Since different matters may be considered by different branches. . . . each distinct subject, inquiry or order must be contained in a separate paper"). Accordingly, submission of information to the Board of Patent Appeals and Interferences does not fulfill an applicant's duty to disclose information to a patent examiner. *See also A.B. Dick Co. v. Burroughs Corp.*, 617 F. Supp. 1382, 1397 (N.D. Ill. 1985) ("the PTO cannot realistically be thought of as the equivalent (say) of a small law office, in which notice to one person may fairly be deemed notice to all. It is not necessarily true that the PTO Examining Division will have access to proofs filed in the course of an interference.") *aff'd*, 798 F.2d 1392 (Fed. Cir. 1986); *see also General Electric Co. v. United States*, 206 U.S.P.Q. 260, 278 (Ct. Cl. 1979) ("The attorneys . . . were familiar with the procedures in the Patent Office and should have known that the Patent

Examiners do not normally inspect the interference record after termination of an interference before the Board of Interference Examiners. Even if they had reason to believe that the Patent Examiner might review the interference record, it was incumbent upon counsel ... to call to his attention any evidence which might bear on the issue of patentability of the claims.").

Here, Roche has the burden of proving "a threshold level of materiality and intent by clear and convincing evidence." *McKesson*, 487 F.3d at 913. The Court "must then determine whether the questioned conduct amounts to inequitable conduct by balancing the levels of materiality and intent, 'with a greater showing of one factor allowing a lesser showing of the other.'" *Id*. As explained below, the evidence will show that the information withheld and misrepresented by the applicants, as well as information buried within submissions to the PTO, was clearly material and Amgen, in repeatedly violating its duty of candor, plainly acted with the requisite intent to deceive the patent examiner. Accordingly, the patents-in-suit should be held unenforceable.

B. Amgen's Misrepresentations And Omissions Aimed At Extending Its Monopoly

The key to Amgen's patent strategy with respect to EPO has been obtaining patents which effectively extend the protection initially afforded under Amgen's expired '008 patent and '016 (Lai) patents. To that end, during prosecution of the patents-in-suit, Amgen's patent attorneys -- Michael Borun, Steven Odre and Stuart Watt -- misrepresented material facts with intent to deceive the PTO and its examiners in order to overcome double patenting rejections based on Amgen's '008 and '016 patents.

In prosecuting Amgen's '179 application, which ultimately resulted in the issuance of Amgen's '868 patent, Mr. Borun misrepresented to Examiner Martinell that the Board of Patent Appeals and Interferences determined -- in connection with Interferences 102,096 ("*Fritsch I*")

and 102,097 ("*Fritsch II*") -- that the "production process subject matter claimed [in the '179 application] was patentably distinct from the DNA-related subject matter claimed in U.S. [Patent No.] 4,703,008." ('179 Application File History, Paper 43, 10/7/94 Applicant's Amendment and Remarks at 7).[9]

Not only did Mr. Borun misrepresent the position of the Board, which reached no such conclusion, Amgen chose not to inform the examiner that in the *Fritsch II* interference Amgen had taken the entirely contradictory position that its process claims were inherently part and parcel of the invention claimed in its '008 patent. As referenced above, in a brief to the PTO Board of Appeals -- which bore the names of Mr. Borun and Mr. Odre -- Amgen expressly stated in the section entitled "Summary of Lin's Positions":

> While the count is directed to a process for preparing *in vivo* biologically active EPO using a mammalian host cell transfected or transformed with an isolated DNA sequence encoding human EPO [i.e., the process patent claims], and the litigation was directed to the purified and isolated DNA sequence and host cells transfected or transformed thereby [i.e., the '008 DNA claims], *it is evident that these are only different manifestations of the same invention . . . . Clearly, the whole purpose and intent of the purified and isolated DNA sequence encoding human EPO* (and host cells transfected therewith) at issue in the litigation *was to express in vivo biologically active human EPO*. Stated otherwise, the process language of the Lin patent claims at issue in the litigation ("encoding human EPO") [see '008 patent claims] is, for all intents and purposes, a description of the present count.

(Interf. No. 102,097, Brief for the Senior Party Lin at 25-26 (AM-ITC 00337677-78) (emphasis added)).

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[9] Dr. Lin, the inventor on the '008 patent and the patents-in-suit was a party to the Interferences. In the *Fritsch I* interference, the sole count was identical to claim 2 of the '008 patent which recites a purified and isolated DNA sequence encoding human EPO. In the *Fritsch II* interference, the sole count was identical to then-pending claim 65 of the '179 application which recited a process for the preparation of an *in vivo* biologically active glycosylated polypeptide.

In the same filing, Amgen admitted that "the isolated DNA sequence is *the* novel feature of the process claims," "[t]he expression and isolation of the recombinant EPO did not involve separate inventive input" and "there is clearly nothing separately inventive" in the isolating step. (Interf. No. 102,097, Brief for the Senior Party Lin at 57-58 (AM-ITC 00337709-10) (emphasis added)). In other words, Amgen represented then that claims to the process of producing recombinant EPO were not patentably distinct from DNA sequence and host cells claims. Amgen also failed to inform the examiner that in the *Fritsch II* interference, it had similarly argued that resolving priority issues in regard to the count for the DNA sequence in the *Fritsch I* interference would necessarily determine those issues in regard to its process claims. Amgen asserted that "if Lin was the first to invent a host cell containing a DNA sequence in a manner allowing the host cell to express rEPO as determined by the Court, he is of necessity the first to invent the process of making rEPO using the host cell." (Interf. No. 102,097, 1/25/90 Lin Reply to Fritsch Motion to Terminate Interference).

Critically, the Board agreed with Amgen:

> Of the issues enumerated above, all except issue No. 8 [Lin inventorship] *are essentially identical* to the issues already considered in related Interference No. 102, 096. With regard to the issue of prior inventorship in particular, we note that Fritsch conceded at the final hearing that *priority in each of the related interferences turns on isolation of the EPO gene, i.e., determination of priority in Interference No. 102,096 is dispositive on the issue of priority in the present interference*.

Fritsch v. Lin, 21 U.S.P.Q.2d 1737, at 1738-39 (Bd. Pat. App. 1991) (emphasis added). More importantly, in rejecting Fritsch's inventorship attack under § 102(f) in favor of Lin, the Board stated "*[w]e agree with Lin*" that there is "*no evidence ... that the work done at Amgen* relating to the expression of the EPO gene in mammalian host cells and isolation of the resulting glycoprotein product involved *anything other than the exercise of ordinary skill by practitioners in that field*." *Id.* at 1739 (emphasis added).

Amgen's successful arguments to the Board of Appeals were material in the context of the '179 application in that they supported the examiner's initial rejection of the process claims as being obvious in view of the earlier '008 patent and contradicted Amgen's position in the '179 prosecution (that issued as the '868 patent). Amgen's misrepresentations during prosecution of the '179 application relating to the patentability of its pending process claims over the '008 patent are also material to the claims of the other later issued patents in the '179 family -- i.e., the '698 and '422 patent -- as well as the '349 patents that also claims a process for producing EPO.[10] Furthermore, because the '933 patent claims are product-by-process claims that necessarily rely on Lin's claimed process, Amgen's misconduct likewise affects the enforceability of that patent as well.

In prosecuting the patents asserted in this case, Amgen also failed to disclose to the PTO arguments that Amgen had made during opposition proceedings in Europe involving Genetics Institute's EP 411 678 and EP 209 539 that were similarly inconsistent with Amgen's arguments for the patentability of its '179 application process claims. Amgen acknowledged in the European proceedings that its process and the resulting biologically active erythropoietin were merely an obvious and inherent result of expressing the DNA sequence encoding human

[10] With respect to the '349 patent, Amgen also successfully extended its monopoly by misrepresenting the restriction requirement in the parent '298 application. Mr. Borun affirmatively told the examiner that the vertebrate cell claims were restricted into Group IV, yet omitted that the examiner required Lin's process claims -- such as claim 7 of the '349 patent -- to be prosecuted with the Group II claims that issued as the '008 patent. (See '369 Application File History, Paper 8, 12/20/96 Second Preliminary Amendment at 8-9). Mr. Borun also neglected to explain that predecessor claims of the '349 patent, claim 7 were filed in the application that led to the '868 process claims. As a result of this misconduct, the '349 patent issued without a terminal disclaimer over the '008 patent and does not expire until 2015, over ten years after it should have expired.

erythropoietin in a host cell. (EP 411 678 Opposition Proceedings, Statement of Grounds submitted by Amgen 10/8/1992).

Amgen further misrepresented to the PTO that it would be improper for the examiner to consider certain prior art (the Yokota 4,695,542 patent) together with the claims of the '008 patent to show that the pending '179 application claims were obvious. Amgen argued that "as noted in the decisional authorities, [double patenting] must be determined through consideration of the *claims* of the pending application and issued patent -- and not with reference to the prior art." ('179 Application File History, Paper 43, 10/7/94 Applicant's Amendment and Remarks at 10). Amgen misstated the law, which provides that consideration of prior art may be necessary to determine whether one of skill in the art would deem the later claim to be an obvious variation on the earlier one. *See* MPEP § 804, ¶ 7.25 (5th ed. Rev. 8, May 1988) and MPEP § 804 ¶¶ 8.36-8.37 (8th ed. Rev. 5, Aug. 2006) ("Claim [1] rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim [2] of U.S. Patent No. [3] in view of [4], [5].").

Furthermore, Amgen continued its pattern of misrepresentations and omissions in trying to overcome a rejection for obviousness-type double patenting over the '016 patent (Lai). During prosecution of the '179 application, pending claims 65-59 were rejected over Lai because Lai taught the production of recombinant EPO-containing fluid by the same method. ('179 Application File History, Paper 29, 9/1/93 Office Action). In response, Mr. Borun stated that the two-way test for double patenting had to be applied because the rejected claims of the '179 application were entitled to an effective filing date that was earlier than the filing date of the Lai '016 patent. ('179 Application File History, Paper 33, 1/3/94 Amendment and Remarks at 12). Mr. Borun also represented that "issuance of the claims pending in the present ['179] application

would provide no extension . . . of the protection of the Lai *et al*., much less an unjustified extension thereof." ('179 Application File History, Paper 33, 1/3/94 Amendment and Remarks at 10). Mr. Borun did not tell the examiner that Amgen expressly and voluntarily withdrew its process claims from the '298 application and waited approximately 5 months to file the '179 application. Accordingly, Amgen, and not the PTO, caused the delay, and the two-way test would, therefore, have not applied. The examiner accepted Mr. Borun's misrepresentations, noting that "while *the instantly claimed method is an obvious variation of the process of Lai et al.* it is considered that applicant is not responsible for the delay in the prosecution of the instant application which resulted in the prior patenting of a later filed application." ('179 Application File History, Paper 34, 2/15/94 Office Action at 2 (emphasis added). Had Mr. Borun disclosed the true facts surrounding the delay, the examiner would have maintained the rejection over Lai.

Accordingly, Amgen's attorneys knowingly misrepresented the facts of prior proceedings in which they participated and also misstated legal standards. This deliberate deception of the PTO was motivated by Amgen's desire to extend the life of its EPO franchise by maintaining and prosecuting applications that issued as new patents despite being obvious over the earlier-issued and now-expired '008 and '016 patents. Because Amgen had been unable to enforce its '008 patent against Chugai in both the International Trade Commission and in federal court, Amgen was well aware, at the time of its misconduct in prosecuting its continuation patents, that it needed to secure additional process and product patents to enforce against its competitors to avoid losing its U.S. monopoly. But for such misrepresentations and omissions, the patents-in-suit would not have issued, as they did, with terms exceeding those of the '008 and '016 patents. Accordingly, the patents-in-suit should be unenforceable for inequitable conduct.

C. Amgen Regularly Withheld From The PTO Examiner In One Case Material Information Regarding The Rejections Made By Another Examiner In Related Co-Pending Applications

On numerous occasions during the prosecution of the co-pending '178 and '179 lines of applications which resulted in the patents-in-suit, the examiner in one line of co-pending applications issued rejections to claims that were substantially similar to claims that Amgen was prosecuting in the other co-pending line. The existence and grounds for such rejections in one co-pending line thus constituted highly material information that Amgen had a duty to disclose to the examiners prosecuting the other co-pending line. However, in arguing in favor of the patentability of the claims in each application line, Amgen knowingly took positions inconsistent with arguments that examiners raised in rejecting the patentability of substantially similar claims in the other co-pending line of applications. Moreover, in doing so, Amgen did not disclose the arguments that had been made by the examiner in the other application line. Amgen's knowing and intentional failure to disclose to the examiner in one case the examiner's rejections in the other co-pending case was clearly inequitable conduct.

1. Rejection in the '179 Application

During prosecution of the '179 application (from which the '868, '698, '422 and '349 patents issued), in an August 3, 1988 Office Action, Examiner Tanenholtz rejected the pending claims to a host cell expression process for making a glycosylated recombinant EPO (rEPO) as obvious and unpatentable over Yokota *et al*. (U.S. Pat. No. 4,695,542) which taught "a process as claimed herein differing only in using mammalian DNA sequence that encodes a different polypeptide" and "growing a mammalian host cell which is capable of effecting post-translational glycosylation of polypeptides expressed therein." ('179 Application File History, Paper 9, Office Action at 2). The rejection was also in view of Gething *et al*. 1982 (Nature, vol. 300, pp. 598-603), which indicated "that eukaryotic cells innately possess the property of

glycosylating proteins." (*Id*.) Examiner Tanenholtz stated that "it would be expected that where one expresses the cDNA gene encoding erythropoietin using the Yokota et al. procedures the resulting erythropoietin would necessarily be glycosylated." (*Id.*)

At the same time, in the co-pending '178 application (from which the '933 patent issued), Amgen was prosecuting, before Examiner Kushan, substantially similar claims directed to the product of the process described by its pending '179 application claims. In a December 1, 1988 Amendment and Reply, Applicant argued for patentability of the '178 application claims over previous prior art rejections -- none of which was based on either Yokota and/or Gething -- stating:

> [I]t could hardly be characterized as within the reasonable expectation of an ordinarily skilled artisan (i.e., obvious) that Applicant could call into existence the glycoprotein products herein claimed -- glycoproteins which have a carbohydrate composition conspicuously different from that of human urinary erythropoietin glycoprotein isolates, but which nonetheless have sufficient amino acid sequence and glycosylation similarities to allow them to possess the essential in vivo biological activity of naturally occurring erythropoietin.

('178 Application File History, Paper 6, 12/1/88 Amendment and Reply at 12).

Undoubtedly aware of the high materiality of Examiner Tanenholtz's rejection in the '179 prosecution to the substantially similar claims then pending in the '178 prosecution, Amgen knowingly and intentionally failed to disclose that rejection, or the basis for that rejection, to Examiner Kushan in the '178 prosecution. In fact, throughout the remainder of the prosecution of the '178 application and follow-on applications, Amgen continued to argue the novelty of its product-by-process claims, knowing that its arguments for patentability were wholly inconsistent with Examiner Tanenholtz's rejection of the process claims as obvious in the context of the '179 application. Yet Amgen never brought Examiner Tanenholtz's rejection to the attention of the examiner handling the '178 application line.

Furthermore, on February 10, 1989, Examiner Kushan issued a final office action rejecting the pending claims of the '178 application over concerns that the glycosylation of recombinant erythropoietin and urinary erythropoietin were not sufficiently defined. (*See* '178 Application File History, Paper 9, 2/10/89 Office Action). In response, Amgen cancelled all the pending claims and added new claims 67-75, which were product-by-process claims. The erythropoietin of the claimed invention was newly defined as a "glycoprotein product of the expression of an exogenous DNA sequence in a eukaryotic host cell." ('178 Application File History, Paper 11, 6/2/89 Amendment Under Rule 116 at 3-4). Again, there is no evidence that Amgen informed Examiner Kushan of Examiner Tanenholtz's prior rejection of the '179 process claims over Yokota and Gething, despite transforming its "product" claims into "product-by-process" claims.

Amgen and its attorneys frequently had the opportunity and reason to disclose the Yokota and Gething rejection, but repeatedly failed to do so. In a July 11, 1989 amendment, Amgen amended claim 67 to specify that the claimed product of host cell expression was one produced through a process using a non-human host cell, in order to distinguish the claimed erythropoietin product from the erythropoietin product produced by using a human cell line in the process taught by Sugimoto. ('178 Application File History, Paper 15, 7/11/89 Amendment at 5). Amgen still did not disclose Examiner Tanenholtz's rejection.

Moreover, on January 10, 1990, Amgen cancelled claims 67-75, replacing them with new claims 76-83, which were "similar to cancelled claims 67-75, but which specify that the DNA sequences encode human erythropoietin. These new claims parallel claim 2 of U.S. Patent No. 4,703,008 (Lin '008 patent), the parent of the instant application." ('178 Application File History, Paper 19, 1/10/90 Amendment at 5). At the same time, Amgen argued against

suspending prosecution in light of pending Interferences given the decision in *Amgen v. Chugai*. Amgen argued that the decision was "fully dispositive" of any priority issue in both the '179 and '178 applications because "if Lin was the first to invent the DNA encoding erythropoietin and the use of that DNA in a host cell to produce recombinant erythropoietin, then clearly he was the first to invent a recombinant erythropoietin product produced using such a host cell." (*Id.* at 6). Acknowledging the substantial similarity between the '178 and '179 claims, Amgen nonetheless continued to withhold Examiner Tanenholtz's rejection.

2. Rejection in the '178 Application

Amgen's pattern of intentionally withholding material information from the examiners is further evidenced by its failure conversely to disclose rejections it received in the course of prosecuting claims in the '178 line of applications during its prosecution of the '179 application as well as in further continuations of the '179 application, specifically, the '741, '073 and '197 applications. The '178 application contained pharmaceutical composition claims that were substantially similar to those of the '741, '073 and '197 applications, which eventually issued as the '422 patent. In addition, as also noted above, the '178 application contained product-by-process claims that were substantially similar to the process claims of the '179 application, which led to the '868 patent.

In a June 2, 1998 Office Action, Examiner Kushan rejected all claims pending in the '178 application, including claim 55, a dependent claim directed to a pharmaceutical composition comprising an effective amount of polypeptide. Examiner Kushan rejected that claim under § 103 as being obvious over Miyake *et al.*, Takezawa *et al.*, Chiba *et al.* or Sugimoto *et al.* in view of Papayannopoulo *et al.* The examiner noted that each of the four cited references "would enable one of ordinary skill in the art to prepare biologically active, homogenous human EPO," and Papayannopoulo taught the effectiveness of EPO in a murine model. ('178 Application File

History, Paper 4, 6/2/88 Office Action at 9). According to the examiner, in view of these references, "one would find it obvious to use EPO in a treatment to restore hemoglobin concentration in vivo." (*Id.*).

However, in a November 6, 1990 Preliminary Amendment filed in connection with a continuation of the '179 application (which led to the '422 patent), Amgen sought to prosecute substantially similar claims to a pharmaceutical composition or preparation containing erythropoietin. Amgen failed to inform Examiner Nolan of the prior rejection of claim 55 of the '178 application issued by Examiner Kushan.

Amgen also failed to disclose the February 10, 1989 rejection by Examiner Kushan of 61-66 under § 103 based on the same references. (*See* '178 Application File History, Paper 9, 2/10/89 Office Action). Moreover, on June 20, 1989, Examiner Kushan issued a rejection of claims 67-73, directed, *inter alia*, to glycoprotein products and pharmaceutical compositions, for obviousness-type double patenting over Lai as well as a § 102(b) rejection over Sugimoto and a § 103 rejection over Sugimoto in view of Papayannopoulo. ('178 Application File History, Paper 13, 6/20/89 Office Action). Amgen argued for the patentability of substantially similar claims in the '179, '741, '073 and '197 applications and again failed to disclose the rejection by Examiner Kushan. ('741 Application File History, Paper 2, 11/6/90 Preliminary Amendment; '197 Application File History, Paper 18, 12/20/93 Amendment; '179 Application File History, Paper 8, 5/24/88 Second Preliminary Amendment; '179 Application File History, Paper 33, 1/3/94 Amendment and Remarks). Finally, Amgen and Mr. Borun failed to disclose a September 18, 1989 rejection by Examiner Kushan of, among others, claims 67-73, under the doctrine of obviousness-type double patenting, as being unpatentable over claims 1 to 11 of the Lai '016 patent. ('178 Application File History, Paper 16, 9/18/89 Office Action). The

examiner noted that "the recombinantly produced erythropoietin as instantly claimed, would have been a prima facie obvious modification of the claimed process of producing recombinant EPO recited in previously patented claims of Lai et al." (*Id.* at 2).

While the references forming the basis of the aforementioned rejections, including Yokota, Gething, Sugimoto, Miyake, Papayannopoulo, Takezawa and Chiba, were disclosed to the examiners of both lines of applications via IDS's, this was not sufficient to comply with the applicant's duty of candor and serves only to illustrate that Amgen knew that the claims in the co-pending line of applications were similar. Courts have made clear that a rejection is in and of itself material, apart from disclosure of the references upon which it is based. *See McKesson Info. Solutions, Inc. v. Bridge Med., Inc.*, 2006 WL 1652518, *16 (E.D. Cal. 2006) ("an adverse decision by another examiner. . . meets the materiality standard."), *aff'd*, 487 F.3d 897 (Fed. Cir. 2007).

Moreover, the fact that Examiner Martinell ultimately took over both lines of applications is of no consequence. *See McKesson*, 2006 WL 1652518, *16-*22 (fact that patents-in-suit ultimately issued from same examiner does not defeat inequitable conduct). Examiner Martinell would have been required to give full faith and credit to the prior examiners' work and, therefore, would not have substantively reconsidered the prior rejections by the previous examiners. The '178 and '179 applications are not continuations of each other, but parallel co-pending lines, and Amgen had a duty to bring to the attention of the examiner "information within [its] knowledge as to other copending United States applications which are 'material to the examination' of the application in question." MPEP § 2001.06(b) (5th ed. Rev. 3, May 1986). Amgen and its prosecuting attorneys knew of the rejections years before Examiner Martinell assumed responsibility for the applications, sat on that material information, and

exploited the fact that at least 8 different examiners were responsible for each co-pending line at some point. It would be improper for Amgen now to benefit from the happenstance that Examiner Martinell ultimately issued both lines of patents. This is improper. MPEP § 2001.06 (5th ed. Rev .3, 1986) ("The duty to disclose material information extends to information such individuals are aware of prior to or at the time of filing the application or become aware of during the prosecution thereof.")

Amgen's intent to deceive the PTO in this regard is evidenced by the fact that at least Odre and Borun were both involved throughout the prosecution of the '178 and '179 lines of applications, and were fully familiar with the proceedings in both lines of applications. Both attorneys were interested in securing issued claims for their client in order to have patents to enforce against third parties such as Genetics Institute, and to maintain and extend the patent monopoly first secured by the '008 patent. Both attorneys were experienced practitioners that surely knew, or at a minimum should have known, that the rejections in the co-pending related patents would have been important to a reasonable examiner because they could potentially support additional rejections in the applications in which they were not disclosed.

D. Amgen's Misrepresentations Regarding The Apparent Molecular Weight Of Recombinant EPO

In December 1995, late in the prosecution of what became the '933 patent, Mr. Borun added the claim that issued as claim 2, reciting a non-naturally occurring erythropoietin glycoprotein product having "a higher molecular weight than human urinary EPO as measured by SDS-PAGE." ('178 Application File History, Paper 50, 12/20/95 Second Preliminary Amendment and Remarks at 2). Dr. Lin's specification showed that human urinary EPO was a glycoprotein with an apparent molecular weight of 34,000 daltons. ('933 patent at 5:48-52). Amgen knew of substantial evidence that recombinant EPO, made in accordance with the

patents-in-suit, does not have a higher molecular weight than urinary EPO as measured by SDS-PAGE. Amgen did not disclose any of this evidence to the examiners of the '933 patent.

Roche will show at trial that in numerous publications Amgen scientists reported that recombinant human EPO and urinary EPO had identical molecular weights. These documents include the Egrie Input File, which was provided to Mr. Borun by Dr. Egrie, as well as numerous articles, abstracts and presentations by Drs. Egrie and Vapnek, all of which directly contradicted Amgen's assertion that the claimed recombinant EPO had a higher molecular weight that human urinary EPO. Moreover, Amgen's Notice of Claimed Investigational Exemption for Recombinant-Human Erythropoietin (r-HuEPO) submitted to the FDA ("1985 IND") showed an "identical" molecular weight, but was never submitted to the examiner. Also, Amgen's own Product License Application shows that Amgen's rEPO does not have a higher molecular weight than urinary EPO and explains that differences in apparent molecular weight of EPO as determined by SDS-PAGE are "not reliable." This information also was not submitted to the examiner. Finally, in various foreign patent proceedings, Amgen submitted declarations from scientists including Drs. Strickland, Heckler and Goldwasser, which showed that the molecular weight of recombinant EPO was *not* higher than the molecular weight of urinary EPO.

Amgen inexplicably never brought any of this contrary evidence to the attention of the examiner. While one of Dr. Egrie's articles and the Egrie Input File were submitted during the '334 Interference, that did not fulfill Amgen's duty of candor to the *examiner* of the '933 patent. 37 C.F.R. § 1.4(b) and (c). Moreover, even though Examiner Fitzgerald reviewed portions of the '334 Interference file in connection with his examination of the '933 patent, the evidence will show that any such review was limited in duration and scope, and focused solely on resolving a pending protest of inventorship by Dr. Lai. Accordingly, Examiner Fitzgerald would not have

seen any of Amgen's so-called "disclosures" in the Interference file pertaining to apparent molecular weight.

Another court, faced with these questions, has already found that the information disclosed in the specification regarding apparent molecular weight is not accurate because (1) Lin's COS rEPO had the same apparent molecular weight and (2) Lin's CHO rEPO had the same molecular weight as some urinary EPOs. *Hoechst Marion Roussel v. Kirin-Amgen Inc.*, [2002] EWHC 471 (Patents). Yet, Amgen failed to disclose information that directly refuted the patentability of claim 2 of the '933 patent. In short, Amgen allowed the '933 patent to issue notwithstanding that claim 2 was at odds with facts well known to Amgen.

Amgen's intent to deceive is evident from the fact that Amgen knew as early as 1989 that its rEPO had the same molecular weight as uEPO, yet Amgen filed claim 2 in December 1995. Amgen and Mr. Borun selectively submitted information regarding molecular weight that included only those experimental results that supported patentability, excluding the well-known information that would have rendered claim 2 invalid. The fact that Amgen submitted information to the Interference Board, and not the Examiner, plainly supports an inference of intent. *A.B. Dick Co.*, 798 F.2d at 1399.

In sum, Amgen knew that it needed to get product claims because it could not enforce its process claims overseas, and Amgen and its attorneys were willing to do anything to get the product claims to issue, including selective disclosure of material references.

E. Amgen's Affirmative Misrepresentations And Omissions Regarding COS rEPO

In the '178 application, Amgen included claims to glycoproteins "having an average carbohydrate composition which differs from that of naturally occurring [human] erythropoietin" and "having glycosylation that differs from that of human urinary erythropoietin." Amgen

maintained during prosecution that its independent claims covered recombinant erythropoietin expressed in a variety of host cells including both CHO and COS cells. Examiner Kushan rejected the claims and asked that "the sites and extent of glycosylation and how they 'differ' from native EPO should be pointed out." ('178 Application File History, Paper 4, 6/2/88 Office Action at 4). He explained:

> This protein is inherently identical to the claimed EPO by virtue of the same amino acid sequence (or an allelic variant thereof) and the same type of biological activity. The recombinant protein has not been shown to behave in a distinct and unobvious manner with respect to the naturally occurring EPO, and in any case the claims clearly encompass the naturally produced EPO shown by the cited art. The burden of proving the claimed rEPO distinct and unobvious over the cited prior art is shifted to the applicant.

('178 Application File History, Paper 4, 6/2/88 Office Action at 6-7).

In order to establish the differences in glycosylation, Amgen relied on a November 30, 1988 declaration of Dr. Thomas Strickland ('178 Application File History, Paper 7, 11/30/88), an Amgen scientist, who represented that his "analysis indicates that recombinant erythropoietin as described by Serial No. 113,178 has a different carbohydrate composition than naturally occurring urinary erythropoietin." (*Id.* at 15). Although Amgen and Dr. Strickland provided information comparing urinary EPO to EPO expressed in CHO cells, Amgen provided no information comparing urinary EPO to EPO expressed in COS cells. Yet, as noted above, the recombinant erythropoietin as described in the '178 application claims includes COS r-EPO. Nonetheless, Examiner Kushan accepted that Amgen had provided "proof of a distinction in the physical attributes of the naturally isolated and recombinant species is sufficient to overcome the rejections over 35 USC 102." ('178 Application File History, Paper 9, 2/10/89 Office Action at 5).

Examiner Kushan subsequently made clear that he was under the misimpression that Dr. Strickland had shown that both recombinant EPO from COS cells and recombinant EPO from CHO cells differed from urinary EPO. Examiner Kushan stated: "Applicant has proven that human EPO isolated from urine is distinct from the EPO produced recombinantly according to the instant disclosure." ('178 Application File History, Paper 13, 6/20/89 Office Action at 6).

A January 1994 expert declaration by Dr. Richard Cummings, also submitted to the PTO by Amgen, like the Strickland declaration, focused on CHO rEPO. The only mention of COS rEPO (Declaration of Cummings in Appeal Proceedings Against EP 148 607 at ¶ 6.2) was in passing and relied on information lifted directly from the Amgen patent application which, as discussed below, ignored Amgen's own test results which touted the "similarities" in glycosylation.

In a February 16, 1995 Amendment and Request for Reconsideration, the applicant argued: "As confirmed by Takeuchi article cited by the Examiner, the glycosylation of recombinant EPO products is different from that of urinary EPO." ('874 Application File History, Paper 42, Amendment and Request for Reconsideration at 8-9). However, the Takeuchi article too apparently relates to CHO rEPO, not COS rEPO. (Takeuchi *et al.*, "Comparative Study of Asparagine-linked Sugar Chains of Human Erythropoietins Purified from Urine and the Culture Medium of Recombinant Chinese Hamster Ovary Cells").

The evidence at trial will show that Amgen scientists expressed the view that the glycosylation of COS recombinant EPO was the same as that of human urinary EPO. However, the materials that Amgen submitted to the examiner distinguishing the glycosylation of recombinant EPO from that of naturally occurring EPO did not address COS rEPO. Plainly, the withheld information, including many of the same documents discussed above with respect to

apparent molecular weight, would have been material to an examiner determining the patentability of recombinant EPO products based on supposed differences in glycosylation as compared to human urinary EPO. To the extent Amgen argues that such materials were, in fact, included in the 102,334 Interference file before the PTO, that did not satisfy Amgen's duty of candor. *See* 37 C.F.R. § 1.4(b) and (c). Moreover, the materials would have been buried among thousands of pages, and Examiner Fitzgerald's review of the file, as discussed above, would have been limited to matters wholly unrelated to COS rEPO. Even if, contrary to the evidence, Examiner Fitzgerald, had reviewed the '334 Interference file for information pertaining to COS rEPO, the focus of the arguments that appear in the file was the difference between human urinary EPO and CHO recombinant EPO, not COS recombinant EPO.

Accordingly Amgen submitted to the PTO information about CHO rEPO, not COS rEPO, and was silent in the face of the Examiner's mistaken understanding that the data was not so limited. An intent to deceive is easily inferred for many of the same reasons as discussed above with respect to molecular weight. Amgen was facing repeated rejections for failing to show a difference between the claimed rEPO and uEPO and was willing to do anything to secure the much-needed product claims.

F. Amgen Made Affirmative Misrepresentations And Omissions Regarding CHO rEPO

Amgen also withheld and misrepresented information regarding CHO rEPO. Amgen's attorneys, Messrs. Borun and Odre, affirmatively told Examiner Martinell, in prosecuting what became the '933 patent, that the applicant intended to submit "declaration evidence to show that r-EPO differs in glycosylation from any of the naturally occurring EPOs known as of the effective filing date of the instant application and even from the naturally occurring EPOs known

since." ('874 Application File History, Paper 39, 2/28/94 Interview Summary). In response, Amgen submitted the Cummings Declaration.

Although Amgen had contrary data showing that there were no differences when Dr. Lin's CHO rEPO was compared to Lot 82 and Alpha Therapeutics urinary EPO, this data was not provided to the PTO in either (1) the Cummings declaration or (2) any filings submitted by the applicants in response to office actions. The Cummings declaration that Mr. Borun submitted to the PTO to support patentability mentioned "two articles by Egrie *et al.*" but did not give their citations. In fact, two Egrie articles that discuss CHO rEPO concluded that:

- "By Western analysis, *the recombinant and human urinary EPO migrate identically*."; "As seen in Figure 4, purified rHuEPO migrates identically with an apparent molecular weight of approximately 36,000 daltons, *suggesting that both molecules are glycosylated to the same extent*." Egrie *et al.*, 1986, Characterization and Biological Effects of Recombinant Human Erythropoietin, *Immunobiol*., vol. 172, pp. 213-224 (1986) (emphasis added).

- "Complete analysis of human urinary erythropoietin and recombinant human erythropoietin has demonstrated that the hormones have the same amino acid sequence. In addition, *the carbohydrate portion* and the immunologic and biologic properties *of the natural urinary and recombinant hormones are indistinguishable*." Eschbach *et al.* Correction Of The Anemia Of End-Stage Renal Disease With Recombinant Human Erythropoietin, *NEJM* 316:73-78 (1987) (Egrie, co-author) (emphasis added).

Neither of these Egrie articles was submitted to the examiner in an IDS and neither is cited on the face of the patents as a reference cited. Moreover, in describing the Egrie articles, Dr. Cummings stated that "rEPO and uEPO samples migrate to similar regions, but they do not precisely comigrate." Dr. Cumming's statement was entirely false in light of the disclosures of the Egrie articles.

Additional documents in Amgen's possession showed the same similarity between CHO rEPO and uEPO. These documents include an article by Dr. Browne, a 1984 Egrie Presentation, a Vapnek article (with Dr. Lin as a co-author) and the Egrie Input File. With the exception of the Browne article, none of these documents were disclosed to the examiner. The Browne article,

was cited in the Cummings Declaration, but its teachings were misrepresented. Dr. Cummings made a table of references that were relevant for showing a difference between rEPO and uEPO, and he conspicuously did not include the Browne reference. Browne was cited only for its relevance to another issue, misleading the examiner to believe that it had no relevance to any purported differences between rEPO and uEPO.

In order to receive approval for its CHO r-EPO drug, Amgen made statements to the FDA -- aimed at equating natural and rEPO -- that directly contradicted the positions Amgen took in arguing patentability of its EPO claims to the PTO. Again, these statements were not submitted to the Examiner of the '933 patent. (*See* AM-ITC 00092853 ("Where it is possible to compare r-HuEPO and u-HuEPO, the two materials were shown to be identical within the error of the methods."; "The most relevant findings are the overall similarity of the oligosaccharide structures and the demonstration that all of the carbohydrate structures in r-HuEPO are also found in u-HuEPO.").

Furthermore, after Amgen learned of the error in its reporting of the carbohydrate analysis of CHO rEPO and urinary EPO in Example 10 of the patents-in-suit ('933 patent, col. 28:51-67), it did not make that error known to the various examiners or the public by disclosing the mistake in any response or amendment in the file history. And even after the error became apparent, Mr. Borun and Amgen's attorneys left the erroneous information in the specification notwithstanding that the information could have been removed from later applications without losing the earlier filing dates.

Amgen's intent to deceive the PTO is evident for the same reasons discussed above with respect to apparent molecular weight and COS rEPO. In addition, Messrs. Borun, Odre and Watt specifically represented to the examiner that Amgen would submit "declaration evidence to

show that r-EPO differs in glycosylation from any of the naturally occurring EPOs known as of the effective filing date of the instant application *and even from the naturally occurring EPOs known since*." Accordingly, by selectively submitting information that showed a difference and withholding information that showed a similarity, Amgen and its attorneys knowingly and intentionally deceived the PTO. If the data showing the similarity of glycosylation between CHO rEPO and two uEPOs had been submitted to the examiner, Amgen would not have been able to rely on arguments set forth in the subsequently filed Cummings Declaration. Intent may also be inferred because Amgen never disclosed to the examiner, as required, that carbohydrate data in Example 10 was wrong, leaving incorrect data in the patent specification.

G. Amgen Concealed Information Regarding The Standard Used In RIA From The '349 Examiner

The claims of the '349 patent includes a limitation to cells capable of producing specified "U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay" ('349 patent, claims 1-7, col. 10:40-47). A protocol for conducting an RIA is set forth in Example 2 in the specification ('349 Patent, cols. 16-17). However, the protocol discloses only "an erythropoietin standard," without identifying the particular standard used by Dr. Lin and his colleagues in developing his "invention." Example 10 of the common specification further sets forth experimental results using RIA to determine "effective production rates" as "U of erythropoietin per 10^6 cells in 48 hours" ('349 patent, col. 26), but also does not disclose what standard the inventor used to conduct the RIA in support of his claims.

At the time, different urinary EPOs were available for use as standards in RIA. However, Amgen's CAT-1 standard was no longer available as of September 1984. Yet, as mentioned above, RIA results expressed in units of biological activity may vary depending on the standard used. Accordingly, information as to the EPO standard to use in performing the RIA of the

claims would have been important to the patentability of the claims under §112 (definiteness and enablement). The evidence also shows that Amgen's units ("U") are arbitrary units which do not equate to international units ("IU") accepted by those of skill in the art.

Drs. Egrie and Lin were aware that the EPO standard they used was unavailable when the '298 application was filed, and that the units of biological activity disclosed in the claims were not defined in terms of a particular EPO standard. Dr. Egrie and Mr. Borun knew, or at a minimum should have known, that the information would have been important in determining whether the claims were enabled and definite. However, Drs. Lin and Egrie and Messrs. Borun and Odre purposefully ignored the material information because Amgen needed the '349 patent to issue without difficulty for enforcement against Hoecsht Marion Roussel and TKT.

H. Non-Disclosure Of Amgen Work With The 1411 Cell Line

As discussed above, the '298 application issued as the '008 patent on October 27, 1987, and is a parent to each of the patents-in-suit. When the '298 application was pending, the examiner rejected claims over the prior art for obviousness under §103. Examiner Tanenholtz explained that "Ullrich et al and Martial teach a basic process for isolating mRNA and converting it into a cDNA library for use in cloning and expressing mammalian genes. It would be obvious to prepare erythropoietin as a fused peptide by extracting the messenger RNA for erythropoietin from kidney cells known to be rich therein and converting that mRNA to a cDNA library in the manner taught by Ullrich et al or Martial." (AM-ITC 00873694-95).

In arguing patentability over the rejection, Mr. Borun stated:

> Thus, as pointed out in Applicant's submission of October 3, 1986, there was, at the time of the invention, a serious problem securing what could be recognized as erythropoietin-producing cells, much less cells producing high levels of the protein or cells "known to be rich" in erythropoietin messenger RNA such as would provide a cDNA library with multiple copies of erythropoietin-encoding DNA.

> For the Examiner to characterize the publications of Ullrich et al. and Martial et al. as readily enabling the preparation of a library including translatable human erythropoietin cDNA by an ordinarily skilled worker is unsupported and in fact contradicted by other references comprising the totality of the art.

('298 Application File History, Paper 20, 7/10/87 Applicant's Amendment at 20). In response to Mr. Borun's statements, Examiner Tanenholtz allowed all the pending claims to issue. ('298 Application File History, Paper 21, 7/30/87 Examiner Interview Summary).

The applicant and Mr. Borun failed to disclose, however, that "cells producing high levels" of erythropoietin were, in fact, available and that supernatant from such cells was tested at Amgen. Amgen and Dr. Egrie were provided supernatant from Dr. Gaylis who had 1411 cells which produced significant amounts of erythropoietin over a prolonged period of time.

Likewise, Amgen's consultant on the erythropoietin project, Dr. Goldwasser, who also was involved with the drafting the patents-in-suit was also provided with supernatant to run assays in early 1983. (FG 000012-13) ("Subsequently we found that the cells produce significant quantities of Erythropoietin"). Moreover, published literature (which apparently was not disclosed to the examiner) related to the high producing cells plainly supported the Examiner's argument regarding obviousness.

Given Examiner Tanenholtz's prior art rejections, information regarding the 1411 cells would have strengthened the examiner's argument against patentability of the pending claims. Final rejection of the claims then pending in the '298 application would have made arguing patentability in subsequent applications (*i.e.* the patents-in-suit) much more difficult if not impossible. Accordingly, Amgen had every incentive to withhold from the PTO information regarding the 1411 cells.

I. Misrepresentations Regarding The State Of The Prior Art As To The Expression Of Biologically Active Recombinant Glcyoproteins

During the prosecution of the '179 application (which led to the '868 and '698 patents-in-suit), in a Declaration Accompanying Petition to Make Special, dated February 9, 1988, Mr. Borun represented to the Examiner:

> I have taken what I believe to be substantial steps to acquire knowledge of the prior art pertinent to the claims pending in the present application Serial No. 113,179**...**I believe myself to possess a "good knowledge of the pertinent prior art" with respect to the claimed subject matter and specifically those claims of application Serial No. 113,179 which relate to recombinant methods for production of erythropoietin.

('179 Application File History, Paper 3, Declaration Accompanying Petition to Make Special at 6). Mr. Borun also resubmitted an earlier petition to make special with respect to the '298 application in which he made similar representations regarding his knowledge of the prior art. ('179 Application File History, Paper 3, Declaration Accompanying Petition to Make Special to Ser. No. 675,298). Mr. Borun thus requested special treatment for Amgen's applications and induced reliance on his statements regarding the prior art. The Petition was approved and the special status of the '179 application continued throughout the '097 Interference and subsequent examination.

However, following approval of the Petition ('179 Application File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment), Mr. Borun misrepresented the state of the art regarding recombinant production of what Amgen termed human "obligate" proteins. In particular, Mr. Borun argued that the pending claims were patentable and would not be obvious under 35 U.S.C. §103 in light of prior art disclosing general recombinant techniques because the claimed "methods as practiced in 1983 were among the first, if not the first, instances of the successful production of an *in vivo* biologically active obligate human glycoprotein." ('179

Application File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 19; Paper 14, 9/27/88 Applicant's Reply).

Then pending claim 65 "relate[d] to a novel series of process steps wherein a mammalian host cell capable of glycosylating the expressed polypeptides is first transformed or transfected with a DNA sequence." ('179 Application File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 6). In arguing patentability, Mr. Borun stated that for an "obligate" human glycoprotein to be "provided in therapeutic quantities by recombinant means" the product would have had to be glycosylated. He stated that: "[u]nlike other human glycoproteins such as the interferons and Interleukin-2, human erythropoietin was conspicuously known to be an obligate glycoprotein and no hope at all existed for isolating in vivo active material from recombinant host cells unless, at a minimum, both the issues of required polypeptide sequence and of required glycosylation could be successfully attended to." ('179 Application File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 10).

Applicants relied on this distinction throughout the prosecution of the '868 patent claims to overcome prior art rejections. However, Mr. Borun misrepresented and omitted material information regarding the teachings and applicability of prior art recombinant processes to make proteins, including those deemed by Amgen to be "obligate" glycoproteins.

1. Amgen's Misrepresentations Regarding tPA

In the May 1988 Second Preliminary Amendment, Mr. Borun reported that in searching the prior art "[t]he only reference located which appeared to relate to recombinant production of an *in vivo biologically* active obligate human glycoprotein was Collen et al., *J. Pharm. & Expt. Therapeutics*, 231, 146-152 (1984) relating to tissue plasminogen activator." ('179 Application File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 16-17). Mr. Borun represented that the Collen reference was "accepted for publication and published

well after Applicant's initial description of COS cell expression and in vivo biological activity reported in parent application Serial Nos. 561,024 and 582,185" but that "[t]he reference does not describe how the recombinant mammalian host cell expression product was prepared." (*Id.* at 17).

Mr. Borun also cited EP 0 093 619 ("EP '619"), stating that it "contains *no* description of use of mammalian host cell expression systems for tPA production." (AM-ITC 00953222 (emphasis in original)). He represented that "[t]he only clear mention of such systems was entirely speculative and appears in the 'Summary of Invention' at page 7." ('179 Application File History, Paper 8, 5/24/88 Applicant's Second Preliminary Amendment at 18). In fact, however, the EP '619 application discloses, *inter alia*, the use of vertebrate cells and mammalian cells in producing recombinant tPA. The reference claims a "composition comprising a therapeutically effective amount of human tissue plasminogen activator according to Claims 1-5 in admixture with a pharmaceutically acceptable carrier." (EP '619, claim 11; see also claims 12-15). By 1984 -- four years before Mr. Borun submitted the '988 Second Preliminary Amendment -- public press releases showed that animal testing demonstrated that recombinant tPA had *in vivo* biological effects as disclosed by the EP '619 application, and, in 1987, the FDA approved the use of recombinant tPA.

Thus, the EP '619 reference disclosed that "obligate" human glycoproteins could be expressed through recombinant techniques, and supports the argument that one of skill in the art would have a reasonable expectation of success in applying those techniques to other obligate human glycoproteins such as erythropoietin. (35 U.S.C. §§ 102(a), 103). This directly contradicted Mr. Borun's arguments for patentability of the process claims and clearly would have been material to a reasonable examiner.

Amgen also did not disclose, U.S. Pat. No. 4,766,075, the counterpart to EP '619, which issued on August 23, 1988, during the pendency of the '179 application. The '075 patent, which was filed on April 7, 1983, claims an earliest priority date of May 5, 1982 and similarly discloses a process for recombinant production of tPA. Unlike the EP '619 application which was available under §§ 102(a), 103, an examiner could have used the '075 patent as a basis for a §§ 102(e), 103 rejection.

In addition, during the '179 prosecution, no steps were taken to correct Mr. Borun's misrepresentations regarding the state of art regarding tPA and "obligate" glycoproteins. To the contrary, in a September 27, 1988 Reply, Mr. Odre misrepresented that:

> Attached hereto as Exhibit "D" is a Table describing the proteins which are the subject of expression in the references reviewed for the purposes of Applicant's previous submission. As will be apparent from consideration of the Table, *no public reports of recombinant expression of an obligate human glycoprotein appeared before the December 13, 1983 filing of parent application* Serial No. 561,024.

('179 Application File History, Paper 14, 9/27/88 Applicant's Reply at 5) (emphasis added). Subsequent to this Reply, Examiner Tanenholtz issued a Notice of Allowability for pending process claims 65-69. ('179 Application File History, Paper 17, Notice of Allowability).

2. Amgen's Non-Disclosure Of Interferon Art

With respect to human interferon, Amgen knew of but failed to disclose McCormick *et al.*, U.S. 4,966,843 ("the '843 patent"), entitled "Expression of Interferon Genes In Chinese Hamster Ovary Cells", which, on its face, claims priority to an application filed November 1, 1982 -- a full year before the earliest priority date for the asserted Amgen patents. Furthermore, a declaration submitted during examination of the '991 priority application and then resubmitted during examination of the application that led to the '843 patent, discloses that the date of conception for the claimed invention was December 9, 1981 and that recombinant interferon was

expressed by approximately April 1982. Had the '843 patent been disclosed, in prosecuting the patents-in-suit, the Examiner would have known about the earlier priority date based on the '991 application and could have rejected the pending process claims in light of McCormick. (MPEP § 706.02 (5th ed. Rev. 6, Oct. 1987) (regarding §§ 102(e), 103)).

Both the '843 patent and the '991 priority application disclose that human interferon β is a glycoprotein which, when produced in animal host cells, was "expected to be glycosylated and in conformation closest to that of native human IFNs." ('991 Application File History at 3; '843 Patent, Cols. lns. 1:49-50 - 2:3-8). The '991 application, in fact, discloses use of mammalian cells and recombinant techniques to produce glycosylated products "substantially identical in structure, properties and confirmation to native IFNs." Moreover, the '991 application claims a method for production of interferon "wherein said interferon is glycosylated." ('991 Application File History at 19; '843 Patent claims 13-15).

The file history makes plain that, until Amgen persuaded the Examiner of its purported distinction of "obligate" glycoproteins and the state of the art, at least Examiner Tanenholtz considered the recombinant production of glycoproteins other than erythropoietin to be material to the pending process claims, and Amgen and Mr. Borun were aware of the Examiner's position. ('179 Application File History, Paper 41, 8/3/88 Office Action at 2 (citing Yokota U.S. 4,695,542 disclosing production of GM-CSF); Paper 14, 9/27/88 Applicant's Reply at 4 (characterizing Yokota as disclosing multi-CSF or IL-3 (interleukin-3)); Paper 43, 10/7/94 Applicant's Amendment at 3). Given the Examiner's rejections of the process claims based on other recombinant processes, information regarding tPA and interferon would have been important to the reasonable examiner, especially in light of Amgen's attempt to distinguish

"obligate" glycoproteins from other recombinant glycoproteins. Again, material information was withheld and misrepresented.

J. Misrepresentation Regarding The Prior Art Use Of Compositions Of EPO and Human Serum Albumin

According to Amgen, the continuation application Ser. No. 07/609,741 -- which is part of the '197 application line -- was filed for the purpose of requesting an interference with claims 1-4 of U.S. Patent No. 4,879,272 (Shimoda, assigned to Chugai). (*See also* April 6, 2007 Exp. Rep. of Michael Sofocleous, at ¶¶170, 174-175; '741 Application File History, Paper 2, 11/6/90 Preliminary Amendment at 9-10; Paper 3, Examiner Interview Summary Record). More specifically, Amgen needed to eliminate the issued Chugai patent "to protect the current clinical formulation of Epogen(R), containing human serum albumin."

The proposed count for interference with the Shimoda '272 patent was: "An erythropoietin-containing, pharmaceutically-acceptable composition wherein human serum albumin [HSA] is mixed with erythropoietin." ('741 Application File History, Paper 2, 11/6/90 Preliminary Amendment at 10; Paper 3, Examiner Interview Summary Record). During the prosecution of the applications leading to the '422 patent, the applicant similarly requested an interference with U.S. 4,806,524 (Kawaguchi *et al*., assigned to Chugai) and proposed that the count be: "An erythropoietin preparation containing one or more selected from the group consisting of bovine serum albumin, human serum albumin and gelatin." ('197 Application File History, Paper 18, 12/20/93 Amendment at 4; Paper 17, Examiner Interview Summary Record; Paper 23, 12/1/94 Request for Reconsideration). Applicant requested that file claims 61-63, the claims designated for interference with the Shimoda '272 patent, be designated as corresponding to the count. ('197 File History, Paper 18, 12/20/23 Amendment at 2; Paper 2, 11/6/90 Preliminary Amendment at 9).

Before initiating an interference with the Kawaguchi '524 patent, the Examiner rejected file claims 61-63 over the prior art, stating:

> Claims 61-63 are rejected under 35 U.S.C. § 103 as being unpatentable over any one of Miyake et al., 1977 (R), Takezawa et al., 1981 (B) or Takezawa et al., 1982 (C) in view of either applicant's admission on page 87, lines 29-31 or Bock et al. 1982 (D).
>
> The claims under instant consideration are drawn towards pharmaceutical compositions comprising [EPO] in combination with human serum albumin.
>
> * * *
>
> Since erythropoietin was a known compound with accepted therapeutic use, one of ordinary skill in the art at the time of the instant invention, would have been motivated to prepare pharmaceutical compositions comprising erythropoietin. Further, since HSA was a known and accepted pharmaceutically excipient, one would have used HSA in preparing any pharmaceutical composition. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have prepared the claimed pharmaceutical compositions comprising erythropoietin and HSA,

('197 Application File History, Paper 20, 6/1/94 Office Action at 3). Thus, the Examiner made clear that he had found no reference that expressly disclosed a composition of erythropoietin comprising human serum albumin during his search for prior art.

In response to the prior art obviousness rejections, Amgen argued:

> The Examiner has in hindsight combined references disclosing urinary erythropoietin with references which suggest the use of HSA in general in pharmaceutical compositions. This is improper. From the disclosure of Miyake and the two Takezawa patents, there is no indication that a diluent such as human serum albumin would be required to prepare a pharmaceutical composition with erythropoietin.

('197 Application File History, Paper 23, 12/1/94 Request for Reconsideration at 4-5). The §103 rejections were not maintained by the Examiner and, subsequently, the '422 patent issued after the applicant argued that two Goldwasser references "do not disclose a pharmaceutically acceptable preparation, and there is no indication that [bovine serum albumin] or other stabilizing additive would be necessary once the purified EPO was obtained." ('197 Application File History, Paper 33, 5/5/99 Amendment at 5).

Notwithstanding the representations to the examiner during the prosecution of the '422 patent, Amgen was aware of prior art that did disclose compositions with erythropoietin and human serum albumin (and erythropoietin and bovine serum albumin). A November 1, 1990 internal Amgen memorandum to Steven Odre, in-house patent counsel, who bore primary responsibility for patent prosecution, entitled "Literature Search to Support an Interference Filing Against U.S. Patent 4,879,272," reported finding that:

> Dr. J. Baron and coworkers initiated an early clinical trial of purified human erythropoietin. The physician's IND states that "the hormone [human erythropoietin] is diluted in Normal Serum Albumin (Human) (Albuspan (R), Parke Davis) (an injectible HSA preparation] at a concentration of 276 units/ml (80,000 units/mg H-EPO protein) to maintain stability and permit appropriate volume for administration" [Baron, J., D. Emmanouel, and E. Goldwasser]. Since the study began in 1979 - 1980, the IND probably dates from those years. In any case, it cannot date later than 1983, since the clinical study concluded that year. The IND clearly teaches that HSA stabilizes erythropoietin and that preparations of erythropoietin with HSA are suitable for human administration. It also demonstrates that clinical use of erythropoietin and HSA, in combination, predates U.S. patent 4,879,272. In addition, HSA is disclosed as an additive in erythropoietin preparations for parenteral administration to animals in a 1971 journal article by J. F. Garcia and J. C. Schooley. The authors dilute purified, human erythropoietin in 5% HSA prior to subcutaneous administration to polycythemic mice.

The memo also reported to Mr. Odre that "many documents describe the use of HSA (human serum albumin) or BSA (bovine serum albumin) in combination with erythropoietin," and specifically acknowledged that the compositions of erythropoietin and HSA were disclosed in the "prior art":

> The use of HSA and BSA in erythropoietin preparations is also well documented in the prior art. A physician's IND for a clinical trial of human erythropoietin, dating no later than 1983, states that erythropoietin is diluted in HSA to stabilize the protein and permit an appropriate volume for administration. This document, which predates U.S. patent 4,879,272 (including the Japanese priority date) can be considered prior art that specifically teaches the use of

> HSA to stabilize erythropoietin in preparations intended for human administration. Additionally, a paper from 1971 reports administration of a solution of HSA and erythropoietin to animals. . . .

(AM-ITC 00097010-00097011).

The Baron-Goldwasser study and the make-up of its EPO composition (EPO plus HSA) was widely known throughout Amgen, including by Drs. Lin, Egrie and Strickland and by the patent department. (AM-ITC 00245727-29; AM-ITC 00084770-80; AM-ITC 00554114-25; AM-ITC 00557514-27; AM-ITC 00573885-903; AM-ITC 00097004-18). Amgen used the results of the Baron-Goldwasser study as a guideline to determine the clinical dosing for its EPO product, and in an October 31, 1990 memorandum Dr. Egrie told Mr. Odre that "EPO was formulated in HSA for therapeutic use sometime prior to 11/15/78." (AM-ITC 00573885).

Despite these findings, the '741 application was filed on November 6, 1990. In addition, despite these findings, Amgen waited nearly 8½ years before submitting an Information Disclosure Statement during prosecution of the '422 patent and did not list disclose the Baron-Goldwasser clinical study or the 1971 Garcia reference which were cited in the 11/1/90 memo to Mr. Odre. ('197 Application File History, Paper 34, 4/28/99 IDS and PTO-1449). The IDS listed 1 article by Baron and 11 different articles by Goldwasser, but not the Baron-Goldwasser clinical study. Likewise, Applicant disclosed 3 articles by Garcia, but not the 1971 article discovered by the literature search requested by Mr. Odre.

The failure to disclose these material references is particularly egregious given the examiner's rejections over the prior art and Amgen's response that: (1) the examiner improperly "in hindsight combined references disclosing urinary erythropoietin with references which suggest the use of HSA in general in pharmaceutical" and (2) that the art of record did "not

disclose a pharmaceutically acceptable preparation, and there is no indication that BSA or other stabilizing additive would be necessary once the purified EPO was obtained."

Because Amgen was interested in filing the application to protect the clinical formulation of Epogen® containing human serum albumin by having an interference declared, Amgen had everything to gain by withholding this information to gain patent protection. As discussed above, many individuals at Amgen involved with the prosecution of the patents-in-suit, including the legal department through Mr. Odre, knew of these references yet failed to disclose the information during the extended pendency of the '422 patent. Furthermore, by 1985, individuals at Amgen had concluded that a formulation with erythropoietin and HSA would be obvious and "not worth" a patent. This information too apparently was not disclosed to the Examiner of the '422 patent.[11]

[11] Amgen's frequent and widespread misconduct infects all of the closely related claims of the patents-in-suit. *See Fox Indus., Inc. v. Structural Preservation Systems, Inc.*, 922 F.2d 801, 803-04 (Fed. Cir. 1990) ("The duty of candor extends throughout the patent's entire prosecution history. In determining inequitable conduct, a trial court may look beyond the final claims to their antecedents 'Claims are not born, and do not live, in isolation.' . . . Therefore, a breach of the duty of candor early in the prosecution may render unenforceable all claims which eventually issue from the same or a related application.").

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Boston, Massachusetts

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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 (NEF) and paper copies will be sent to those indicated as non-registered participants on the above date.

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