EXHIBIT 1
Part 2 of 3

which differs from that of human urinary erythropoietin" (*e.g.* '933 patent; AM-ITC 00941452; AM-ITC 00941511; AM-ITC 00941545), "has glycosylation which differs from that of human urinary erythropoietin" (e.g. '080 patent; AM-ITC 00868072; AM-ITC 00868083), "said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE (*e.g.* '933 patent; AM-ITC 00941545) and "having an average carbohydrate composition which differs from that of naturally occurring [human] erythropoietin." (e.g. '933 patent; AM-ITC 00941041; AM-ITC 00941108; AM-ITC 00941165; AM-ITC 00941188; AM-ITC 00941208, AM-ITC 00941212; AM-ITC 00941546).

During prosecution, like Amgen during litigation, the applicant maintained that the claimed inventions covered recombinant erythropoietin expressed in a variety of host cells including both CHO and COS cells. (e.g. AM-ITC 00941111; AM-ITC 00941548; see also AM-ITC 00953641 ("Applicant has disclosed the production of ... human species erythropoietin in monkey (COS) and Chinese Hamster Ovary (CHO) cells."). Ser. No. 113, 178 and the related continuation applications included dependent claims "wherein the host cell is a mammalian cell" or "a non-human mammalian cell" ('933 patent; AM-ITC 00941109; AM-ITC 00941166, AM-ITC 00941208; AM-ITC00941213; AM-ITC 00941453; AM-ITC 00941511; AM-ITC 00941511), "wherein the host cell is a COS cell" (AM-ITC 00941109; AM-ITC 00941166) and "wherein the host cell is a CHO cell." ('933 patent, AM-ITC 00941109; AM-ITC 00941166; AM-ITC 00941208; AM-ITC00941213; AM-ITC 00941453; AM-ITC 00941511; AM-ITC 00941546). Mr. Borun explained that dependent claims "further characterize products of the present invention in terms of their derivation from eucaryotic host cell expression ... particularly in mammalian host cells (64) such as COS (65) and CHO (66) cells" (AM-ITC 00941111). Accordingly, to support and prove patentability of the independent claims with limitations to

glycosylation, molecular weight and average carbohydrate composition, differences between human EPO and recombinant EPO from COS and CHO cells needed to be shown.*

Examiner Kushan stated that "the sites and extent of glycosylation and how they 'differ' from native EPO should be pointed out." (AM-ITC 00941093). He further explained that:

> 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.***

(AM-ITC 00941095-96 (emphasis added)).

By Amendment and Reply, Amgen stated that:

> As is apparent from consideration of independent claim 41, ***the subject matter herein claimed is seen to comprise Applicant's novel glycoprotein preparations*** having amino acid sequence characteristics in common with naturally occurring human erythropoietin isolated from urine, ***having carbohydrate composition characteristics different from those of naturally occurring erythropoietin*** and nonetheless having the glycosylation-requiring in vivo biological activity (promoting reticulocyte and red blood cell production) characteristics of naturally occurring human erythropoietin.

(AM-ITC 00941111 (emphasis added)). Furthermore it was urged that:

> Applicant was the first to provide for a glycoprotein which is both different from previously isolated urinary erythropoietin in its glycosylation and yet sufficiently like the natural product (previously isolated in the art) in terms of its glycosylation to allow it to fill the long-felt need (unsatisfiable by urinary

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* It is telling that Mr. Borun eventually dropped the dependent claim specifically claiming COS host cells without comment or explanation to the examiner, and not until after the examiner relied on the Strickland Declaration. The only conclusion is that Mr. Borun was aware of the data that showed there is no difference between COS rEPO and human urinary EPO, and abandoned the claim. Nonetheless, the omitted and misrepresented information is material because remaining claims cover rEPO expressed by COS cells. (e.g. '933 patent; '080 patent; 3/5/2007 "Amgen's Claim Construction Brief" at 6 ("Dr. Lin's specification discloses how to manipulate a range of host cells, including mammalian cells ... to produce a therapeutically effective EPO composition.")

> isolates) for life-sustaining human therapeutic agents for, e.g., the anemia associated with dialysis in renal failure patients.
>
> The precise nature of ***the differences in the carbohydrate structures of products of the present invention and urinary-derived human erythropoietin are only now starting to be understood, as evidenced by the results of the experimental procedures detailed in the attached Declaration of Thomas W. Strickland***. Briefly put, the procedures demonstrate that the urinary erythropoietin is heterogeneous in terms of glycosylation, that the same is true of recombinant erythropoietin preparations of the present invention, and that, ***most importantly, the two products are clearly distinct from each other in terms of glycosylation***.
>
> Having provided the public with its first knowledge concerning the fact that a glycoprotein can exist which is simultaneously different in carbohydrate composition from urinary source erythropoietin and yet sufficiently like it in glycosylation to allow for in vivo biological activity, no impermissible vagueness attends the recitation of these unique and readily ascertainable characteristics in a patent claim."

(AM-ITC 00941114-5 (emphasis added)). Responding to rejections under §102 and §103, Amgen stated:

> ***Confirmation of these assertions of novelty is found in the attached Declaration of Thomas Strickland*** which provides detailed description and analysis of the differences in carbohydrate structure between FDA clinical lot preparations of recombinant erythropoietin according to the present invention and human urinary erythropoietin isolates as represented by samples actually obtained by Miyake et al. in the work forming the basis for the publication, as well as urinary erythropoietin samples obtained by means of a specified modification of the Miyake et al. procedure. ...
>
> The work described in the Strickland Declaration and that of the publication cited by Strickland, as well as the results set out in the Sasaki et al. publication noted by the Examiner, ***stands as testimony to the differences between Applicant's products and those of Miyake et al***. In sum, ***Applicant's products are indeed novel.***
>
> Against a background wherein the prior art had noted the essential nature of sialic acid residues for in vivo biological activity, it 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.

(AM-ITC 00941116-17 (emphasis added); *see also* 11/23/99 Borun Depo. Tr. 125:12-126:21.)

Rather than submit information comparing the glycosylation, molecular weight and average carbohydrate composition of human urinary EPO versus recombinant EPO expressed in COS cells -- which was necessary to support the independent claims as well as dependent claims to mammalian cells and COS cells -- the Strickland Declaration disclosed information pertaining only to the comparison of human urinary EPO versus recombinant EPO expressed in CHO cells. (AM-ITC 00941121 ("The r-HuEPO for use in the experimental procedures was prepared in accordance with the general procedures described in Example 10 of USSN 113,178 ...."); see also, e.g., Strickland Depo. Tr. 155-156, 208-217, 293-311, 208:14-16 ("My declaration . . . doesn't have any information on COS-cell EPO"); 215:12-14 ("I don't think I could infer anything about COS-cell EPO from the information in [my] declaration.")).

Under Section 1001 of Title 18 of the United States Code Strickland represented that:

> 11. The above analysis of r-HuEPO and u-EPO demonstrate that the differences shown by the isoelectric focusing experiments, specifically, the more acidic nature of the u-EPO isoforms compared to the r-HuEPO isoforms, is due to the differences in carbohydrate composition, in particular carbohydrate structure, of r-HuEPO and u-EPO. ***This analysis indicates that recombinant erythropoietin as described by Serial No. 113,178 has a different carbohydrate composition than naturally occurring urinary erythropoietin.***

(AM-ITC 00941134 (emphasis added)). However, the recombinant erythropoietin as described by Ser. No. 113,178 includes COS r-EPO, which Amgen knew had not shown differences in glycosylation, molecular weight and average carbohydrate composition. The Strickland Declaration intentionally omitted this information and focused solely on supposed differences between CHO r-EPO and human urinary EPO. For example, the Strickland Declaration omitted

at least the following information regarding the similarity in glycosylation, molecular weight and average carbohydrate composition of COS rEPO compared to human urinary EPO:

- Egrie *et al.*, Characterization Of Recombinant Monkey And Human Erythropoietin, *Proc Clin Biol Res.* 1985;191:339-50: "As seen in Figure 5, recombinant human EPO produced in COS1 cells has a molecular weight of 34,000 daltons and migrates identically to the human urinary standard, suggesting that both the recombinant and native EPO are glycosylated to the same extent." (See 3/27/07 Egrie Depo. Tr.79-81, 86-90).
- Egrie *et al.*, Abstract (1984) from 10th Annual Fredrick Stohlman Memorial Symposium on Stem Cell Physiology, Boston, MA, October 2, 1984: "By Western analysis, the recombinant erythropoietin has a molecular weight of 34,000 daltons and migrates identically to the human standard erythropoietin, indicating that the expressed protein is glycosylated to the same extent as the native hormone."; "By all criteria examined, the recombinant monkey and human erythropoietin appear identical to the native hormone."
- Egrie *et al.*, Presentation (1984) from 10th Annual Fredrick Stohlman Memorial Symposium on Stem Cell Physiology, Boston, MA, October 2, 1984 (AM-ITC 01073032-42): "MW and migration of recombinant EPO is identical to EPO standard indicating recombinant EPO is glycosylated to the same extent as the native hormone."; "CONCLUSION: COS CELLS TRANSFECTED WITH THE HUMAN EPO GENE PRODUCE AND SECRETE FULLY GLYCOSYLATED EPO WHICH MIGRATES IDENTICALLY TO THE HUMAN EPO STANDARD."
- Egrie, Presentation Transcript "Cloning of Human & Monkey EPO" (1984) from Hemoglobin Switching Meeting, Airlie House, Virginia, September 1984 (AM-ITC 00557610-16; 3/27/07 Egrie Depo. Tr. 70-71, 79-81): "In order to determine the size of the recombinant erythropoietin, we characterized the COS-cell expressed EPO by Western analysis. ... This band has a MW of 34,000 daltons + migrates identically to the human EPO standard. ... These expts show that the recombinant mK + hu Erythropoietin are the same size as the native hormone which suggests that both the recombinant + native hormones are glycosylated to the same extent." (AM-ITC 00557614-15). "These sequences have been expressed in both COS + CHO cells + the expressed erythropoietin has been shown to be immunologically identical to the native hormone. It has the same MW as the native hormone [illegible] suggesting that it is glycosylated to the same extent." (AM-ITC 00557616). (See also AM-ITC 00557617-23).

The Egrie articles apparently were not submitted in any of the patents-in-suit and plainly are not listed on the face of the patents as "references cited". (e.g. AM-ITC 009414122-49*; AM-ITC 00868126-55*; '933 patent; '080 patent).

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* This IDS, which was submitted after the '344 Interference, submitted "references of record" in the parent applications of Ser. No. 07/113,178, Ser. No. 07/113,179, "references of record" in Ser. No. 07/113,178 which were not previously cited on a PTO-892 form, references from the §282 Notice and exhibits admitted in *Amgen v. Chugai* (D. Mass.) and "references of

Furthermore, prior to filing the CIP application Ser. No. 675,298, Dr. Egrie had provided laboratory notebook pages to Mr. Borun (11/10/99 Egrie Depo Tr. 335-336) -- who drafted the Lin specification (3/2/07 Borun Depo. Tr. 14:2-13; 11/23/99 Borun Depo. Tr. 21:21-23:15; 9/06/2000 Trial Tr. 2831:2-4; 2/5/2002 Borun Trial Tr. 239:12-240:9) -- that showed COS rEPO was no different than human urinary EPO. Indeed, she plainly and unequivocally concluded that "human EPO produced by COS cells have the same molecular weight as native urinary EPO (Goldwasser's EPO). This result indicates that the recombinant EPO is glycosylated to the same extent as the native protein." (AM-ITC 01072494; AM-ITC 01072497; 09/6/2000 Trial Tr. 2845:6-17). While at various times Mr. Borun has testified that he did not recall seeing the Egrie input file until years after the application was filed -- the exact time depending on which time he was asked -- (11/23/99 Borun Depo. 71:21-73:11, 90:16-91:6; 9/6/2000 Borun Trial Tr. 2848:7-22, 2853:3-4; 2863:3-8) his testimony is not credible. Mr. Borun asked for the information (9/6/00 Trial Tr. 2835:17-2836:8; 2/5/2002 Borun Trial Tr. 263:12-15; AM-ITC 01072474) and Dr. Egrie provided the information before Mr. Borun drafted and submitted the CIP application Ser. No. 675,298 (11/8/99 Borun Depo Tr. 325, 334-336; 2/5/2002 Borun Trial Tr. 264:20-270:25, 282:20-283:2, 283:20-284:3; 11/10/99 Egrie Depo. Tr. 325; AM-ITC 01072476). Mr. Borun had the Egrie data in his files. (9/6/2000 Trial Tr. 2837:22-2838:3; 2/5/2002 Borun Trial Tr. 248:3-14). It is Mr. Borun's practice to review information that he has requested. (2/5/2002 Borun Trial Tr. 248:22-249:18) and there is no legitimate reason to believe that he did not follow his normal practice. Moreover, Dr. Lin declared under oath in a submission to the PTO that the

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record" from European Opposition Proceedings regarding the foreign counterpart EP 0148 605). The Egrie articles are not included as being a "reference of record."

* This IDS also "identifies all art of record" from SN 07/113,179 and SN 08/487,774, but does not include any of the Egrie articles.

studies conducted by Dr. Egrie are set forth in Example 10 of the patent application. (AM-ITC 00295812; see also 11/23/99 Borun Depo. 65:11-21). In any event, Mr. Borun admits that he was aware of the Egrie data when the applications that led to the '933 and '080 patent were still pending. (11/23/99 Borun Depo. 83:21-85:13, 91:7-16; 9/6/2000 Borun Trial Tr. 2863:3-8). Nonetheless, the Egrie data was not submitted to the examiner in any response to an Office Action and was not included on any IDS submitted to the examiner.* (9/6/2000 Borun Trial Tr. 2864:5-8, 2865:6-14).

As a consequence of the information chosen to be disclosed by the Strickland Declaration and that which withheld, Examiner Kushan stated that:

> Applicant has shown through the declaration of Strickland and via the disclosure of Takeuchi et al [regarding CHO rEPO] that there is a difference in the overall carbohydrate composition between the naturally occurring and recombinant species. ... The 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.

(AM-ITC 00941151-52). Amgen, however, argued commercial success, long-felt need and other secondary considerations in an attempt to prove patentability under §103. (AM-ITC 00941159; AM-ITC 00941169-72; AM-ITC 00941182). Nonetheless, applicant continued to argue that "Recombinant erythropoietin is different from naturally occurring erythropoietin (for a description of the differences, see the response filed December 5, 1988)" (AM-ITC 00941168) and continued to omit material information regarding COS rEPO covered by the pending claims (AM-ITC 00941165-66; AM-ITC 00941179 ("Applicant's claim encompass erythropoietin produced recombinantly in any eucaryotic cell line which has an average carbohydrate composition which differs from naturally occurring human EPO, and which possess a particular

* Compare AM-ITC 00941422-449 submitting 2 boxes of documents purportedly including exhibits from *Amgen v. Chugai* (but not the Egrie file) with Mr. Borun's testimony that the Egrie file was an exhibit in that action. (TKT Trial Tr. at 2863:9 to 2864:4).

in vivo activity when administered to humans.")). Thus, the examiner was left with the misimpression that both recombinant EPO from COS cells and recombinant EPO from CHO cells differed from urinary EPO.

Applicant was fully aware that Examiner Kushan had relied on the partial information provided with respect to CHO rEPO in removing his then pending rejections. As Examiner Kushan explained:

> ***Applicant has proven that human EPO isolated from urine is distinct from the EPO produced recombinantly according to the instant disclosure***. ...
>
> Applicant must provide for a distinction between the lymphoblastoid derived EPO and the instantly claimed recombinant species. ***Applicant is encouraged to file a declaration in the form of the previous declaration of Strickland, which provided evidence of a distinction between the urinary and recombinant species.***

(AM-ITC 00941180-81 (emphasis added)).

Again, however, applicant did not submit the omitted information regarding COS rEPO to the examiner, instead opting to once again point to the defective Strickland Declaration to overcome a prior art rejection based on Sugimoto:

> In the response filed December 5, 1988, ***the Strickland Declaration established the difference between human produced urinary erythropoietin and the recombinant glycoprotein***. As discussed with the Examiner during the interview, urinary-derived erythropoietin-is active in vivo. There is no teaching in Sugimoto et al. that the carbohydrate composition of the product produced is different from urinary-derived erythropoietin. Nor is there any teaching that the Sugimoto et al. product is the same as the recombinant glycoprotein claimed herein."

(AM-ITC 00941192 (emphasis added)). In response, the examiner dropped his rejection.

In the following continuation application, Mr. Borun also submitted an IDS dated April 8, 1994 along with two boxes of references (AM-ITC 00941422-50). Among the 394 references submitted by Mr. Borun was WO 86/03520 ("PCT '520"), which Amgen represented was a reference of record in the parent applications of Ser. No. 113,178. (AM-ITC 00941422). There is, however, no previous IDS in the certified file histories of the parent applications that

disclosed this reference, there is no IDS in the '178 application disclosing the reference, and the reference is not listed on the earlier '008 patent as a reference cited. The reference was cited in Ser. No. 113,179 (which led to the '868 patent), but that co-pending application is not directly related to Ser. No. 113,178. Furthermore, in prosecuting Ser. No. 113,179, again, Amgen had represented that the reference was already of record in the parent applications (AM-ITC 00953609; AM-ITC 00953612), which it apparently was not.

Given Mr. Borun's misrepresentation there would be no reason for Examiner Martinell to focus on the PCT reference because it would have appeared that it was already considered by at least one other examiner and that the reference was not deemed important to patentability. (MPEP §704.01, MPEP §1214.04) (full faith and credit to the prior examiner's search)). Furthermore, given the earliest priority date, the filing date and the publication date of the PCT application, there was no reason for the examiner to give more than a cursory look past the cover sheet of the reference.

However, WO 86/03520 discloses that:

> By Western blotting, using a polyclonal anti-EPO antibody, the ***EPO produced by COS cells has a mobility on SDS-polyacrylamide gels which is identical to that of native EPO prepared from human urine*** (Example 8). Thus, the extent of glycosylation of COS-1 produced EPO may be similar to that of native EPO.

(WO 86/03520, pp. 1026-27 and Fig. 6 (emphasis added)).

Moreover, Applicant and Dr. Strickland were aware of the PCT '520 reference during the prosecution of the applications leading to the '933 and '080 patents. In February 1992, Dr. Strickland had submitted a declaration opposing EP 0 411 678 (AM-ITC 00326183-98), which has the same disclosure as PCT '520. (3/9/07 Strickland Depo. Tr. 275-277). In his declaration, Dr. Strickland addressed molecular weight and the monosaccharide content of rEPO produced by Amgen, and concluded that the "values are within the range of experimental and analytical

error". This declaration was not submitted to the PTO, nor did Dr. Strickland's earlier declaration that was submitted discuss the impact of experimental and analytical error in determining differences/similarities in glycosylation, molecular weight and average carbohydrate composition of recombinant EPO compared to human urinary EPO.

An Examiner Interview Summary Record indicated that "Applicant intends 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.***" (AM-ITC-00941497 (emphasis added)). This apparently refers to "the January, 1994 expert statement of Dr. Richard Cummings (Exhibit B herein) as submitted in proceedings before the European Patent Office in counterpart European Patent EP 0 148 605" (AM-ITC 00903254-488), which is not found in the certified file history. Once again, a declaration submitted on behalf of the applicant, omitted material information regarding COS rEPO.

The declaration, again, focuses primarily on CHO rEPO. The only mention of COS rEPO (AM-ITC 00822949 ¶6.2) is in passing and relies on information lifted directly from the Lin application which, as discussed above, ignores conflicting test results set forth by Dr. Egrie's internal work at Amgen. Dr. Cumming did not include any published literature regarding COS rEPO but directed the examiner's focus, yet again, to CHO rEPO and other references regarding EPO expressed in BHK, C127 mouse fibroblast, Namalwa and BHK-21. To the extent that Dr. Cummings mentioned "2 articles by Egrie" cited by Dr. Conradt, he does not give any identifying information such as title, publication or date so that examiner could independently obtain the articles and the articles were not attached as exhibits to his declaration (AM-ITC 00903238-448). Moreover, the Egrie articles referenced by Dr. Cummings may have related to

CHO rEPO, not COS rEPO, as discussed in more detail below. Mr. Borun also did not provide the opposing Conradt Declaration (or any other declarations opposing Amgen's viewpoint which it knew about) to the examiner.

To the extent that Dr. Cummings discussed the "2 articles by Egrie", he misrepresented the conclusions presented in those references. Although it is not clear from the submission to the PTO which of the Egrie articles Dr. Cummings referred to, as discussed above, each Egrie article concluded that COS rEPO and human urinary EPO "migrate identically." But, that is not what he and Mr. Borun told the examiner. Instead, the declaration states that:

> 17.4.2 Dr. Conradt cites to two articles by Egrie et al. which show several SDS-PAGE and Western blot analysis on rEPO and uEPO. Again, the gels in these articles show that the rEPO and uEPO samples migrate to similar regions, but they do not precisely comigrate. The gels would suggest the samples were similar but not identical, and any comments in the articles must be interpreted with the gels in view.

(AM-ITC 00903276). Obviously, however, Dr. Egrie and/or her co-authors had the "gels in view" and still made the conclusion in each paper that COS r EPO and uEPO "migrates identically" -- in direct contradiction to Dr. Cummings statements. Furthermore, neither Egrie articles were submitted to the PTO in an IDS and none is cited on the face of the patents as a reference cited.

Along with the Cummings Declaration, Mr. Borun also argued that: "As confirmed by Takeuchi article cited by the Examiner, the glycosylation of recombinant EPO products is different from that of urinary EPO." (AM-ITC-00941515-16). The Takeuchi article, however, relates to CHO rEPO, not COS rEPO. (AM-ITC 00903340-42).

When prosecution resumed after Interference 102,334, Examiner Fitzgerald allowed pending claims 76-83 (AM-ITC 00941409; AM-ITC 00941413), but Mr. Borun elected to continue prosecution without letting the claims issue. Subsequently, when Mr. Borun was

unable to get a different examiner -- Examiner Martinell -- to allow pending claims, Amgen urged that: "New claim 99 has a text identical to claim 76 of prior U.S. Application Serial No. 113,178. Claim 76 was allowed prior to filing of parent U.S. Application Serial No. 08/202,874 and its text was identical to the sole Count in Fritsch v. Lin, Interference No. 102,334." (AM-ITC-00941537; AM-ITC 00941547). However, claim 99 did not have text identical to either claim 76 or the sole Count. Furthermore, Mr. Borun added claims to "glycosylation which differs from that of human urinary erythropoietin" and "said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE." (AM-ITC 00941544-51). Mr. Borun and Amgen's in-house counsel -- who had been practicing for years -- were aware of PTO rules stating that "a claim noted as allowable shall thereafter be rejected only after the proposed rejection has been submitted to the primary examiner for consideration of all the facts and approval of the proposed action. Great care should be exercised in authorizing such a rejection". (See also MPEP §704.01 (regarding "full faith and credit")). They plainly used those rules advantageously. The Examiner allowed those claims, as well as dependent claims, to issue without further rejection. (AM-ITC 00941562-65).

Subsequently, based on the actions of applicants during prosecution of the '933 patent claims, Examiner Martinell also allowed the '080 patent to issue without rejection over any prior art, including claims to a glycoprotein that "has glycosylation which differs from that of human urinary erythropoietin". (AM-ITC 00868083-88; AM-ITC00868157-59).

To the extent that Amgen relies on the '334 Interference file to show that material information was submitted to the PTO, that does not negate the fact that those documents were buried within its interference filings, effectively withheld from the subsequent examiner(s) and, thus, material information was omitted from the prosecution file while other information

highlighting purported differences between the claims and the prior art were misrepresented to the examiner. Moreover, the IDS statements filed by Amgen after the Interference make clear that the references discussed herein were not considered "references of record".

The '344 Interference file alone comprises approximately 5,500 pages of documents focusing on CHO rEPO, and the file for the consolidated Interferences 102,096, 102,097 and 102,334 is over 18,000 pages. Any alleged statement regarding COS rEPO does not qualify as proper disclosure. Nor does it negate an intent to deceive by misdirecting the examiner from material information regarding COS rEPO to focus instead on CHO rEPO. If anything, it shows a pattern of misconduct by applicant and Amgen to hide behind the technical procedures of the PTO rather than fulfill its duty of good faith and fair dealing with the examiners here. Amgen took advantage of the limited hours that an examiner is allotted and the sheer volume of documents contained in the prosecution files (including related interferences) and forced the examiners to scour thousands of pages to rack down material information that Amgen knew about and should have brought to the forefront. Amgen also exploited the fact that multiple examiners were responsible for the examination of the applications leading to the patents-in-suit.

Furthermore, only §102 and certain sections under §112 were at issue in the ' 334 Interference, not patentability pursuant to §103. (e.g. *Fritsch v. Lin*, 21 USPQ2d 1739, 1742 (BPAI 1991); AM-ITC 00832914-15 ("The Fritsch et al motion is based on Section 102(b), not 103.")). Similarly, information submitted and allegedly considered in the '334 Interference was considered only in the context of the claim limitation "having an average carbohydrate composition which differs from that of human urinary erythropoietin" (Count 1, AM-ITC 00941235). The Interference did not substantively address the patentability of the other limitations "having glycosylation which differs from that of human urinary erythropoietin", "has

glycosylation which differs from that of human urinary erythropoietin", or "said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE. (AM-ITC 00941407 ("Claims 76-83 ... were the only claims considered by the BPAI and Court.")). Indeed, those claim limitations did not appear in any filed claims until years after the Opinion of the Board of Patent Appeals and Interferences. (AM-ITC 00941237).

Importantly, the focus of the arguments presented in the Interference file was the difference between CHO rEPO and human urinary EPO, not COS rEPO. Thus, a subsequent examiner would quickly dismiss the idea of looking closely at the Interference record for information regarding COS rEPO. For example:

- AM-ITC 00295811 (emphasis added):

> 5. My patent application involved in the subject interference indicates that recombinant human erythropoietin (rHuEPO) of my invention has an average carbohydrate composition which differs from that of EPO in a partially purified pooled source human urinary EPO preparation obtained from Dr. Goldwasser. This is based in part on the work done by Dr. Egrie with ***recombinant human EPO expressed from CHO cells*** and on other work on carbohydrate analysis done by Dr. Robert K. Yu, both acting at my request.

- AM-ITC 00295812 (emphasis added):

> 7. Dr. Egrie showed by Western blot analysis and SDS-PAGE that CHO cell produced rHuEPO migrated differently than the pooled urinary EPO present in a partially purified sample provided by Dr. Eugene Goldwasser. Studies conducted by Dr. Egrie involving digestion of the ***CHO cell produced rHuEPO*** and the pooled human urinary EPO with carbohydrate digesting enzymes indicated that the difference in migration, which is indicative of difference in apparent molecular weight, resulted from a difference in carbohydrate moieties. These studies are set forth in Example 10 of my patent application.

- AM-ITC 00295814 (emphasis added):

> The results of carbohydrate analysis provided to me by Dr. Egrie (see paragraph 7 above) and Dr. Yu, by November 30, 1984, indicated that the in vivo biologically active ***recombinant EPO product expressed by CHO cells***, had an average

carbohydrate composition which was different from the pooled human urinary EPO obtained from Dr. Goldwasser.

- AM-ITC 00295815 (emphasis added):

9. I am advised that the count of the interference in which I am involved reads as follows:

Interference No. 102,334

A non-naturally occurring glycoprotein product of the expression in a non-human eucaryotic host cell of an exogenous DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing human bone marrow cells to increase production of reticulocytes and red blood cells and having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin.

10. I confirm that the ***rHuEPO produced by CHO cells transfected with the human genomic EPO gene meets all of the limitations of the count of Interference No. 102,334.*** Dr. Browne, acting at my request, carried out the expression in CHO cells of the rHuEPO.

- AM-ITC 00339456 (emphasis added):

the Strickland Declaration unambiguously demonstrates that ***rEPO produced according to Example 10 of the Lin application and uEPO differ*** in their monosaccharide composition ...

- AM-ITC 00361603 (emphasis added):

(25) The in vivo biologically active ***rHuEPO that was expressed in CHO cells*** by May of 1984 was shown by Dr. Egrie and subsequently by others to have an average carbohydrate composition that differed from that of a partially purified pooled source human urinary EPO provided by Dr. Goldwasser. ...

- AM-ITC 00832911 (emphasis added):

The conspicuously missing "fact" is that the carbohydrate composition of the prior art urinary EPO is the same as the carbohydrate composition of Lin's recombinant EPO as exemplified by his ***Example 10 expression product of the human EPO gene in Chinese Hamster Ovary (CHO) cells.***

- AM-ITC 00832911 (emphasis added):

2. Yes, Lin submitted a declaration by Dr. Strickland under Section 132 and the 102(b) ***rejection was withdrawn upon directing the Examiner's attention to differences in carbohydrate composition between the Lin Example 10 product and the prior art product.***

- AM-ITC 00832913 (emphasis added):

> There has been no showing or representation by Fritsch et al that the average carbohydrate composition of urinary EPO and ***Lin's CHO cell-expressed recombinant EPO of Example 10*** are in fact identical in all aspects.

- AM-ITC 00832914-15 (emphasis added):

> The Fritsch et al. motion is based on Section 102(b), not 103. To bar patentability, Section 102 requires identity of subject matter, not a generalized similarity. To overcome a rejection under § 102, one need only show that the claimed subject matter is different. Lin has clearly shown this. ***Fritsch et al has submitted no evidence to show that urinary EPO and Lin's Example 10 EPO are identical***, in particular with respect to carbohydrate.

- AM-ITC 00832918 (emphasis added):

> However, it is significant that Cumming presents no evidence of his own to confirm his position that urinary EPO is identical in its carbohydrate composition to ***Lin's Example 10 EPO***.

- AM-ITC 00832919 (emphasis added):

> Finally, it is noted that the Fritsch at al argument really bypasses the fundamental point, namely, ***Lin's CHO cell-expressed recombinant human EPO as obtained in Example 10***, shows a different average carbohydrate composition from a pooled source of human urinary EPO. ... It has not been shown that Lin's Example 10 product does not meet the requirements of the Lin claims or the count. Fritsch at al have not, therefore, sustained their burden.

- AM-ITC 00832920 (emphasis added):

> The ***CHO-expressed recombinant product*** obtained by Lin as exemplified in his disclosure (for instance, Example 10) meets the claim limitation to the effect that the recombinant product is different in terms of average carbohydrate composition from naturally-occurring EPO (LR 105).

The opinion from the Board of Patent Appeals and Interferences makes plain that they -- like the examiner -- focused on CHO rEPO and not COS rEPO. (*Fritsch v. Lin*, 21 USPQ2d 1739 (BPAI 1991) (discussing purported evidence of alleged differences in "average carbohydrate

composition" including specific mention of CHO cells, Example 10, the *Takeuchi* reference and Amgen's PLA (all based on CHO rEPO))). Likewise, the opinion makes no mention of any Egrie articles or other reference regarding COS rEPO.

But for Amgen's misconduct conduct at least claims 1 and 6 of the '933 patent and claim 1 of the '080 patent would not have issued. Accordingly, the '933 patent and the related '080 patents are unenforceable for inequitable conduct.

Amgen's Affirmative Misrepresentations and Omissions Regarding CHO rEPO

In addition to the information outlined above, Amgen also withheld and misrepresented information regarding CHO rEPO. Applicant's attorneys affirmatively told the examiner that: that "Applicant intends 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.***" (AM-ITC-00941497 (emphasis added). Thus, Amgen affirmatively represented that it would provide information regarding prior art uEPO purified using the Miyake method (e.g. "Goldwasser's EPO) as well as uEPO from other sources (e.g. Lot 82 and Alpha Therapeutics). Instead, Amgen offered the Cummings Declaration as discussed above.

Dr. Egrie's data showing that there were no differences when Lin's CHO rEPO was compared to Lot 82 and Alpha Therapeutics urinary EPO was not provided in either (1) the Cummings declaration or (2) any filings submitted by the applicants in response to office actions. (AM-ITC01072481; AM-ITC 01072486 (both showing "CHO(2) + Lot 82 same size", "α Therapeutics - is same size as CHO + Lot 82"). Amgen relied solely on supposed differences between Goldwasser uEPO (AM-ITC 01072499) in drafting the language of the patent

specification and ignored the conflicting results based on comparisons to Lot 82 and Alpha Therapeutics urinary EPO. (2/5/2002 Borun Trial Tr. 298:10-299:8, 300:19-301:2).

Furthermore, the Cummings declaration cherry-picked information relied upon. As discussed above in relation to COS rEPO, Cummings hastily mentioned two articles by Egrie *et al.* but he did not give any information to identify the which of the Egrie articles he was referring to so that the examiner could independently review the articles. The two Egrie articles that discuss CHO rEPO concluded that:

- Egrie *et al.*, 1986, Characterization and Biological Effects of Recombinant Human Erythropoietin, *Immunobiol.*, vol. 172, pp. 213-224 (1986): "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."
- Eschbach *et al.* Correction Of The Anemia Of End-Stage Renal Disease With Recombinant Human Erythropoietin, *NEJM* 316:73-78 (1987) (Egrie, co-author): "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***."

However, that is not what he and Mr. Borun told the examiner. Instead, in direct contradiction to the Egrie articles, the declaration states:

> 17.4.2 Dr. Conradt cites to two articles by Egrie et al. which show several SDS-PAGE and Western blot analysis on rEPO and uEPO. Again, the gels in these articles show that the rEPO and uEPO samples migrate to similar regions, but they do not precisely comigrate. The gels would suggest the samples were similar but not identical, and any comments in the articles must be interpreted with the gels in view.

(AM-ITC 00903276). Furthermore, neither of these Egrie articles was submitted to the PTO in an IDS and none is cited on the face of the patents as a reference cited. Likewise, the 1984 Egrie Presentation (AM-ITC 01073033 ("MW and migration of recombinant EPO is identical to EPO standard indicating recombinant EPO is glycosylated to the same extent as the native hormone.")

also was not submitted to the examiner and is not cited as a reference cited or a reference of record in an IDS.

In addition, Dr. Cumming's citation to the Brown article regarding CHO rEPO is merely a passing reference with respect to O-glycosylation of EPO in support of his argument regarding the Nimtz et al (1993) reference. The articles he relied on to show differences between rEPO and uEPO were clearly summarized in table form for the examiner (AM-ITC 00903273) and did not include the Browne article, implying that the Browne article was not relevant to the main thrust of his declaration. Neither Dr. Cummings not Amgen pointed out that the Browne article undercut the arguments he was making based on other references. Important and contradictory data and conclusions set forth in Browne include:

> Human urinary EPO and CHO-cell derived r-hEPO migrate identically in SDS-polyacrylamide gels indicating that both molecules are glycosylated to a similar extent. ... The carbohydrate composition of r-hEPO was essentially the same as that of urinary EPO (T.W. Strickland et al., in prep) ...
>
> Shown in Figure 4 are the results of a deglycosylation experiment that indicates that both r-hEPO and urinary EPO contain both N-linked and O-linked carbohydrates in similar amounts. Both r-hEPO and urinary EPO were analyzed by Western blot analysis after sequential gycosylase digestion. ***Figure 4 (lanes 1 and 5) shows urinary EPO and r-hEPO, respectively, prior to treatment.*** After treatment with endoglycosidase F which removes N-linked carbohydrate, ***the apparent molecular weight of both r-hEPO and urinary EPO is shifted to approximately 19,500 with a minor band at about 18,400*** (lanes 2 and 6). Following further treatment, first with sialidase (lanes 3 and 7) and then by O-glycanase (lanes 4 and 9), which remove O-linked carbohydrate, ***both r-hEP0 and urinary EPO migrated as a single band with an apparent molecular weight of 18,400.*** Although the presence of N-acetylgalactosamine had not been detected previously (Dordal et al. 1985). These results demonstrate that urinary EPO, as well as r-hEPO contains O-linked carbohydrate. In addition, direct carbohydrate analysis of endoglycosidase-F treated r-hEPO yields galactose, sialic acid, and N-acetyl galactosamine, confirming the presence of O-linked carbohydrate (T.W. Strickland et al., in prep). As shown in Figure 4, the proportion of EPO containing O-linked carbohydrate is comparable in urinary EPO and r-hEPO.

(AM-ITC 00903452). Mr. Borun did not submit the Browne reference in the IDS which included "references of record" in the prosecution (AM-ITC00941422-449) and the article is not cited as considered by the examiner(s) in allowing the '933 patent. Furthermore, the reference is not cited on the face of the '933 patent as a reference cited ('933 patent). However, in later applications the reference was submitted indicating its materiality was appreciated by the applicants. (e.g. '080 patent). Likewise, the Board of Appeals apparently did not substantively consider or rely on the Egrie articles or the Browne article. *Fritsch v. Lin*, 21 USPQ2d 1739, 1742 (BPAI 1991).

Similarly, Amgen and its attorneys did not disclose Vapnek *et al.*, "Comparative Studies of Natural and Recombinant Erythropoietin," *Banbury Reports 29:Therapeutic Peptides and Proteins*, 241-56 (1988) (see, e.g., '933 patent and '080 patent "References Cited") which reported "no differences in structure have been observed" between CHO rEPO and urinary EPO. The article also reports that treatment with Endo F, neuraminidase and O-glycanase "demonstrate that both urinary and recombinant human Epo contain sialic acid, O-linked carbohydrate, and three N-linked carbohydrate chains. Further characterization of the fine structure of the carbohydrate chains is currently being carried out (A. Kubota et al., unpubl.). Initial results indicate that both contain oligosaccharides of the same structure."

Additionally, in order to receive approval for its CHO r-EPO drug, Amgen made statements to the FDA that directly contradict the positions Amgen took in arguing patentability of its EPO claims to the PTO. Significantly, 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-EPO."); AM-ITC 00092884; AM-ITC 00092981-83). Nor did Amgen explain to the examiner(s) that purported differences in glycosylation and carbohydrate composition were not due to differences between CHO rEPO and urinary EPO, but because of different purification techniques in certain instances and variability and error in testing techniques. These documents and information were not submitted to the examiners.

Furthermore, after Amgen learned of the error in its reporting of the carbohydrate analysis of CHO rEPO and urinary EPO in example 10 ('933 patent 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. But for Amgen's misconduct conduct at least claims 1, 2 and 6 of the '933 patent and claim 1 of the '080 patent would not have issued. Accordingly, the '933 patent and the related '080 patents are unenforceable for inequitable conduct.

Amgen's Affirmative Misrepresentations and Omissions Regarding Molecular Weight

In addition to the information outlined above regarding COS rEPO and CHO rEPO (hereby incorporated), in 1995 Mr. Borun presented for the first time a claim requiring that "said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE." (AM-ITC 00941545), and the claim was allowed without a rejection or any amendment. ('933 patent). Relevant literature, as well as Lin's specification, acknowledged that human urinary erythropoietin is a glycoprotein with a molecular weight of approximately 34,000 daltons (*e.g.* '933, col. 5:48-52 ("Erythropoietin, an acidic glycoprotein of approximately 34,000 dalton molecular weight, may occur in three forms: α, β and asialo. The α and β forms differ slightly in carbohydrate components, but have the same potency, biological activity and molecular weight."); AM-ITC 00987639-49 ("The human asialo hormone has an apparent molecular

weight of 34,000 in SDS, whereas the native form has an apparent molecular weight of 39,000.")). Dr. Egrie also had measured the molecular weight of various urinary EPOs and found that Goldwasser's uEPO "is 34,000 MW + Lot-82 EPO - ~35-36". (AM-ITC 01072482; 4/15/91 Egrie Depo. Tr. 562-565).

Dr. Strickland, however, filed a declaration in May 1994 in related foreign proceedings that showed rEPO produced in accordance with Lin's Example 10 falls between 31,000 daltons and 45,000 daltons as measured by SDS-PAGE. (AM-ITC00312260-71; 3/9/07 Strickland Depo. Tr. 277-280). Clearly 31,000 daltons is not a "higher molecular weight than human urinary EPO as measured by SDS-PAGE", yet the Amgen never submitted this information or declaration to the U.S. examiner(s). In that same proceeding, Cilag GmbH, an Opposing Party (AM-ITC 00312411) -- along with Kirin-Amgen, Inc. an assignee of the '933 patent-in-suit -- filed a declaration by Dr. Thomas Heckler ("Exhibit 4") stating that: "The molecular weight of the purified r-HuEPO band shown in Figure 5 was calculated by comparison of its migration to that of the protein standards and r-HuEPO reference standard. The r-HuEPO migrated identically to the reference standard (which had a molecular weight of 34,000 daltons) ...." (AM-ITC00311606). Dr. Goldwasser also filed a declaration ("Exhibit 1") in which he reported that the apparent molecular weight of urinary erythropoietin as measured by SDS-page was first reported as 39,000 daltons and later reported as 34,000 daltons. (1/23/93 Declaration of Eugene Goldwasser Ph.D., ¶21). Amgen "relie[d] without limitation upon Citations 1 through 7a and Exhibits 1-17 presented by Opponent I herein, Cilag GmbH." (AM-ITC 00312411-12). This information was not submitted to the U.S. patent examiners.*

* Attorneys for Cilag and Johnson & Johnson kept at least in-house Amgen attorneys, Messrs. Watt and Odre, apprised of developments in Europe. (e.g. AM-ITC 0312283; AM-ITC 0312291-92). Mr. Watt was a corporate officer of Kirin-Amgen, Inc. (e.g. AM-ITC 00898341).

Likewise, its own Product License Agreement, which was not submitted to the PTO, shows that Amgen's rEPO does not have a higher molecular weight than urinary EPO. (AM-ITC 00092870; AM-ITC 00092880). Indeed, the product label states that Amgen's rEPO product "has a molecular weight of 30,400 daltons... ." (See AM-ITC 00092249-60 (10/30/87 Proposed Package Insert); Physician's Desk Reference (44th ed. 1990) at 616; AM-ITC 00601553-60 (6/29/94 Product Label for Epogen®); 3/09/2007 Product Label for Epogen® and Procrit® available at www.accessdata.fda.gov). Neither the draft or approved Product Label was submitted to the examiner(s).

Furthermore, in September 1985, when the applications leading to the '933 patent were still pending, Amgen submitted its Notice of Claimed Investigational Exemption for Recombinant-Human Erythropoietin (r-HuEPO) to Office of Biologics Research and Review Center for Drugs and Biologics at the Food and Drug Administration (AM-ITC 00091218) in relation to seeking approval of its CHO rEPO product. The application was assigned to Amgen's attorney, Mr. Odre, who also prosecuted the applications that resulted in the '933 patent. In that document, Amgen represented that: "The r-HuEPO migrates identically to the pure urinary hormone with an apparent molecular weight of ~ 36,000 daltons" in SDS-polyacrylamide. (AM-ITC 00092135, 00092210-11). Thus, showing that Amgen's CHO rEPO covered by the '933

Indeed, Messrs. Odre, Watt and Borun, as well as Drs. Strickland, Egrie and Goldwasser attended the oral arguments for the foreign proceedings relating to EP 209 539. (AM-ITC 00312754). Additionally, written submissions by Kirin-Amgen, Inc. included confidential information provided by Amgen, Inc. (e.g. AM-ITC 00312455-73) and declarations provided by Amgen employees. (e.g. AM-ITC 00312260-71; AM-ITC 00312441-45). The Strickland, Goldwasser and Heckler declarations were all in the possession of Amgen's patent counsel at Marshall, Gerstein & Borun, including Mr. Borun. (See, e.g., February 20, 2007 Third Party Marshall, Gerstein & Borun LLP's Objections and Responses to Subpoena *Ad Testificandum* and *Duces Tecum*, Objections and Response to Request No. 1; March 27, 2007 Letter from Ross to Rycroft).

patent does not have a "higher molecular weight than human urinary EPO as measured by SDS-PAGE." Again, Amgen did not submit this information to the examiner(s).

In addition, as discussed above, Amgen and its attorneys were aware that the claim was not patentable. Dr. Egrie had concluded that "human EPO produced by COS cells have the same molecular weight as native urinary EPO (Goldwasser's EPO)" (AM-ITC 01072494; AM-ITC 01072497; 11/10/99 Egrie Depo. Tr. 340-342) and that CHO rEPO was the same as Lot 82 and Alpha Therapeutics urinary EPO. (AM-ITC 01072481-86). (*See also* 11/23/99 Borun Depo Tr. 79:3-80:7). Applicant also failed to properly submit the Egrie papers and presentation which showed that COS rEPO and CHO rEPO did not have a higher molecular weight than human urinary EPO as measured by SDS-PAGE. Likewise, as discussed above, key information from the Browne article regarding molecular weights was not properly presented to the examiner(s). Nor was Vapnek *et al.*, which concluded that "both rh-Epo and urinary Epo have an apparent molecular weight of approximately 36,000" disclosed to the examiner(s).

Omitting this information is especially egregious given applicant's representation that Amgen would submit evidence to show that r-EPO differs in glycosylation -- and, thus, apparent molecular weight -- "even from the naturally occurring EPOs known since" the filing of the patents. But for Amgen's misconduct, at least claim 2 of the '933 patent would not have issued. Accordingly, the '933 patent and the related '080 patent are unenforceable for inequitable conduct.

Amgen's Prosecution of Claims Rejected By Different Examiners

Amgen's patents-in-suit issued from one of two co-pending lines of applications, based on Ser. No. 113,178 (the '178 application) and Ser. No. 113,179 (the '179 application). The

'178 line ultimately led to the '080 and '933 patents, while the '179 line ultimately led to the '868, '698, '422 and '349 patents.

On numerous occasions during the prosecution of these co-pending lines of applications, 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 constituted highly material information that Amgen had a duty to disclose. A prior rejection of a substantially similar claim refutes, or is inconsistent with the position that those claims are patentable. An adverse decision by another examiner, therefore, is material under the Rule 56.

The patents-in-suit are unenforceable because individuals associated with the filing and prosecution of these patents, in arguing for the patentability of pending claims in one line of applications knowingly took positions inconsistent with highly material arguments that examiners raised against the patentability of substantially similar claims in the other co-pending line of applications, but nonetheless knowingly and intentionally failed to disclose those rejections.

Amgen's intent to deceive the PTO is further evidenced by the fact that at least applicant's attorneys -- Mr. Odre and Mr. Borun -- were both involved throughout the prosecution of the '178 and '179 lines of applications, and therefore, had intimate knowledge regarding the proceedings of both lines of applications. (e.g. AM-ITC 00941082-88; AM-ITC 00941146; AM-ITC 00941553; AM-ITC 00953196-202; AM-ITC 00953233-34; AM-ITC 00953689). In addition, Mr. Borun was intimately involved in and was, therefore, aware of material details of the prosecution of the parent applications which led to the '008 patent. (AM-ITC 00953135-74).

In prosecution of the '179 application, Amgen submitted a Second Preliminary Amendment (AM-ITC 00953205-25) canceling all pending claims and entering five new claims 65-69. Among these the only independent claim (65) recited "a process for the preparation of an *in vivo* biologically active glycosylated polypeptide comprising the steps of:

> (a) growing a mammalian host cell which is capable of effecting post-translational glycosylation of polypeptides expressed therein and which is transformed or transfected with an isolated DNA sequence encoding a polypeptide having a primary structural conformation sufficiently duplicative of that of naturally occurring human erythropoietin to allow possession of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, or the progeny thereof, under nutrient conditions suitable to allow, in sequence,
>
> > (i) transcription within said host cell of said DNA to mRNA in the sequence of transcription reactions directed by the nucleotide sequence of said DNA;
> >
> > (ii) translation within said host cell of said mRNA to a polypeptide in the sequence of translation reactions directed by the nucleotide sequence of said transcribed mRNA;
> >
> > (iii) glycosylation within said host cell of said polypeptide in a pattern directed by the amino acid sequence of said translated polypeptide and sufficiently duplicative of the pattern of glycosylation of naturally occurring human erythropoietin to allow possession by the translated glycosylated polypeptide product of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells; and
>
> (b) isolating the glycosylated polypeptide so produced.

(AM-ITC 00953207-08). The dependent claims further characterized the claimed process in terms of host cell expression of cDNA (68) or genomic DNA (69) sequences, particularly in a CHO cell (66) or COS cell (67). (AM-ITC 00953208).

In the first Office Action dated August 3, 1988 (AM-ITC00953227-31), 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.* (US 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 ...." (AM-ITC 00953228). He also noted the Yokata *et al.* "teach the production and in fact claim the production of a gylcosylated product." (AM-ITC 00953229). 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." (AM-ITC 00953229). Examiner Tanenholtz noted 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." (AM-ITC 0953229).

In this same time period, in the co-pending '178 application, Amgen sought to prosecute substantially similar claims directed to the product of the process described by its pending '179 application claims. Examiner Tanenholtz was not involved in the '178 prosecution, which was before Examiner Kushan. (e.g. AM-ITC 00941146). In particular, in its December 1, 1988 Amendment and Reply (AM-ITC 00941106-18), applicant amended claim 41 and added new claims 61-66 directed to a human erythropoietin glycoprotein product "having a primary structural conformation and glycosylation sufficiently duplicative of that of a naturally occurring human erythropoietin to allow possession of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells" and further characterized as a product derived "from eukaryotic host cell expression (61) of exogenous cDNA (62) or genomic DNA (63) sequences, particularly in mammalian host cells (64) such as COS (65) and CHO(66) cells." (AM-ITC 0941108-09).

Applicant argued for patentability in light of previous prior art rejections -- none of which was based on either Yokata 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.

(AM-ITC 00941117).

The substantial similarity of these pending '178 claims to the pending process claims of the '179 application (and Amgen's awareness of that fact) is plainly evident through the Reply to Examiner Tanenholtz' August 3, 1988 Office Action in the '179 prosecution. There, Amgen argued that pending claims 65-69 were directed to:

> a novel series of process steps wherein a mammalian host cell [including such non-human, non-kidney cells as COS and CHO cells as specified in claims 66 and 67] capable of glycosylating the expressed polypeptides is first transformed or transfected with a DNA sequence [including, e.g., cDNA and genomic DNA as specified in claims 68 and 69] encoding a specifically delineated polypeptide, i.e., one having a sufficient amino acid sequence homology to natural human erythropoietin to allow it to qualify, amino acid sequence-wise, for potential in vivo biological activity. (The DNA reagent employed in the transformation/transfection process is itself the novel and unobvious subject matter of claim 7 of U.S. Patent 4,703,008 and the resulting host cells are as recited in claim 24 of the Patent).

(AM-ITC 00953274).

Applicant's characterization of its pending '179 claims strikingly demonstrates that its '178 application claims were directed to nothing more than the inherent product of the '179 process claims 65-69. 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.

The failure to disclose Examiner Tanenholtz' August 3, 1988 rejection to Examiner Kushan during the prosecution of the '178 claims gained greater significance in view of Amgen's subsequent actions in the '178 prosecution and its subsequent reliance on product-by-process claims. On February 10, 1989, Examiner Kushan issued a Final Office Action rejecting all the pending claims on several grounds. (AM-ITC 00941148-58). Among the rejections, Examiner Kushan objected to the claimed description of the glycoprotein product as having "glycosylation sufficiently duplicative of that of a naturally occurring human erythropoietin" because "The manner in which applicant has attempted to characterize the degree and extent of glycosylation of the r-huEPO does not particularly point out what the actual glycosylation comprises." (AM-ITC 00941149). Notably, however, Examiner Kushan never raised the prior art arguments that Examiner Tanenholtz had raised as to the obviousness of the process used to make the claimed rEPO product, nor did he raise the Yokota or Gething references that Examiner Tanenholtz had cited.

In response, Amgen replaced all pending claims with new claims 67-75, which defined the claimed product solely through the process through which it was made. (AM-ITC 00941165-72) In particular, Amgen acknowledged that:

> All product claims in the subject application are ***now product-by-process claims***. Independent claim 67, and thus all of the pending claims, specifically ***define the erythropoietin of the subject invention as a "glycoprotein product of the expression of an exogenous DNA sequence in a eucaryotic host cell...."*** These product-by-process claims are presented in an effort to positively recite the physical properties of recombinant erythropoietin, and to further define the product of the subject invention since the recombinant erythropoietin claimed cannot be precisely defined except by the process by which it is produced.

(AM-ITC 00941167-68) (emphasis addeed). Applicant once again did not disclose that Examiner Tanenholtz had rejected the its related process claims over the prior art.

Throughout the remainder of the '178 prosecution, Amgen continued to argue the novelty of its product-by-process claims to a glycosylated erythropoietin knowing that its arguments for patentability were wholly inconsistent with Examiner Tanenholtz's rejection of the process claims as obvious and continued to hide that rejection from the attention of the '178 examiners.

In an Amendment dated July 11, 1989 (AM-ITC 00941188-97), applicant kept all its product-by-process claims pending, amending only claim 67 to specify that the claimed product of host cell expression was one produced through a process using "a non-human eucaryotic host cell" (AM-ITC 00941188), 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. (AM-ITC 00941192 ("Unlike the glycoprotein product of the subject claims, which results from the expression of an exogenous DNA sequence in a non-human eucaryotic host cell, Sugimoto et al. relates to erythropoietin assertedly produced by a human lymphoblastoid cell line.")). Once again, Amgen did not disclose the earlier rejection by Examiner Tanenholtz concerning the obviousness of the process described in the pending claims and claimed in the '179 application.

In the subsequent Amendment dated January 10, 1990 (AM-ITC 00941212-20), applicant cancelled claims 67-75, replacing them with new product-by-process claims 76-83, representing that:

> The Applicant has cancelled claims 67-75 without prejudice. These claims will be the subject of a continuation application. The Applicant has added new claims 76-83, which are 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*** [claim 2 was held valid in the District Court decision referred to herein]. The Examiners [Kushan and Schain] have indicated during the interview of December 20, 1989, that these new claims would he entered and be allowable.

(AM-ITC 00941213).