Appendix A. Rejections in the '178 Amgen Did Not Disclose in the '179

Date	'178 Line of Prosecution	Examiner in the '178 Line	'179 Line of Prosecution	Examiner in the '179 Line
10/23/87	Application filed		Application filed	
6/2/1988	Ex. Kushan rejected all claims pending in the '178, including claim 55, which was directed to a pharmaceutical composition comprising an effective amount of polypeptide. The rejection was under §103, as obvious over Miyake, Takezawa, Chiba or Sugimoto in view of Papayannopoulo (all disclosing uEPO). (R. Ex. 99 (AM-ITC 00941089-100). Claim 1: A purified and isolated polypeptide having all or part of the structural conformation and one or more of the biological properties of a naturally-occurring erythropoietin and characterized by being the product of an exogenous DNA sequence." Claim 55: "A pharmaceutical composition of an effective amount of a polypeptide according to claims 1, 16, 39, 40 or 41 and a pharmaceutically acceptable diluent, adjuvant or carrier."	Ex. Kushan		Ex. Tanenholtz
2/10/1989	Ex. Kushan rejected all pending claims of the '178 application, including claims 55 and 61-66 over Miyake, Chiba, Takezawa or Sugimoto in view of Papayannopoulo. (all disclosing uEPO). (R. Ex. 109 (AM-ITC 00941147-60)). Claim 41: "A 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	Ex. Kushan		Ex. Tanenholtz

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	increase production of reticulocytes and red blood cells and having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin. Claim 55: "A pharmaceutical composition comprising an effective amount of a glycoprotein product according to claim 41 and a pharmaceutically acceptable diluent, adjuvant or carrier."			
9/18/1989	Ex. Kushan rejected pending claims 67-73 due to double patenting over Lai, §102(b) over Sugimoto, and §103 over Sugimoto in view of Papayannopoulo (all disclosing uEPO). (R. Ex. 247 (AM-ITC 00941198-203)). 67. A glycoprotein product of the expression of an exogenous DNA sequence in a eucaryotic host cell, said 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 having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin. Claim 73: "A pharmaceutical composition comprising an effective amount of a glycoprotein product according to Claim 67 and a pharmaceutically acceptable diluent, adjuvant or carrier." "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 invention since the recombinant erythropoietin claimed can not be precisely defined except by the process by which it is produced." (R. Ex.	Ex. Kushan		Ex. Tanenholtx

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	86).			
9/18/1989	In a Final Office Action, Ex. Kushan once again rejected claims 67-75 due to double patenting over Lai.	Ex. Kushan		Ex. Tanenholtz
11/6/1990		Ex. Schain	Applicant sought to prosecute claims in the '741 application substantially similar to the pharmaceutical composition claims rejected on June 2, 1988, February 10, 1989, June 20, 1989 and September 18, 1989 in the '178 prosecution. Applicant did not inform Ex. Nolan of the prior rejection. Claim 61: An erythropoietin-containing, pharmaceutically acceptable composition wherein human serum albumin is mixed with erythropoietin. Claim 63: A composition according to claim 61 containing a therapeutically effective amount of recombinant erythropoietin.	Ex. Nolan ('741 application)
08/02/1993		Ex. Fitzgerald	Applicant continued to prosecute claims in the '197 application that were substantially similar to pharmaceutical composition claims rejected on June 2, 1988, February 10, 1989, June 20, 1989 and September 18, 1989 without informing Exr. Stanton of those rejections. See claims 61, 63 above.	Ex. Stanton ('197 application)
1/3/1994		Ex. Fitzgerald	Applicant added new claims 72-75 to the '179 application that were substantially	Examiner Hodges

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			similar to claims 62-66 and 68-72 in the '178 prosecution, which were rejected on February 10, 1989, June 20, 1989 and September 18, 1989. Applicant did not inform Exr. Hodges of that prior rejection. Claim 72: A process for the preparation of an in vivo biologically active glycosylated erythropoietin polypeptide 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. Mr. Borun files IDS with 375 references, including Miyake, Takezawa, Chiba, Sugimoto and Papayannopoulo which were also disclosed in '178 application.	('179 application)
8/1994	Martinell takes over prosecution of '933	Ex. Martinell	Martinell takes over prosecution of '868	Ex. Martinell
2/6/1995		Ex Martinell	Notice of Allowability for '868 patent Claim 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	Ex. Martinell ('179 application)

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			(b) isolating said glycosylated erythropoietin polypeptide therefrom.	
3/15/1996	Notice of Allowability in '933 Claim 4. A non-naturally occurring human erythropoietin glycoprotein possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells which is the product of the process comprising the steps of: (a) growing, under suitable nutrient conditions, mammalian host cells transformed or transfected with an isolated DNA sequence encoding the human erythropoietin amino acid sequence set out in FIG. 6 or a fragment thereof; and (b) isolating a glycosylated erythropoietin polypeptide therefrom.	Ex. Martinell		Ex. Martinell
4/21/99			Ex. Martinell takes over prosecution of '422	
4/28/99			Applicant adds claim which issue as '422 patent that were substantially similar to pharmaceutical composition claims rejected on June 2, 1988, February 10, 1989, June 20, 1989 and September 18, 1989 without 64. A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture. 65. A pharmaceutically-acceptable preparation containing a therapeutically effective amount of	Ex. Martinell ('197 application)

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			erythropoietin wherein human serum albumin is mixed with said erythropoietin. "The application further discloses that the glycosylation of human erythropoietin may differ depending upon the host cell used for production. Claim 64, however, excludes EPO that is isolated from human urine by the phrase "purified from mammalian cells grown in culture." This phrase is intended to include any EPO produced by mammalian cells (human, CHO, COS, etc.) that are grown in culture, which means in vitro, In contrast to Claim 64, newly added Claim 65 does not limit the source of the EPO but does specify that the EPO is mixed with human serum albumin in the preparation." (R. Ex. 200 AM-ITC 00899474).	
4/28/99			Amgen submits IDS with 392 references, including Miyake, Takezawa, Chiba, Sugimoto and Papayannopoulo,which were also disclosed in '178 application.	Ex. Martinell
5/28/99			Ex. Martinell allows '422	

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