

Appendix B. Rejections Faced in the '179 that were Not Disclosed in the '178

<u>Date</u>	<u>'178 Line of Prosecution</u>	<u>Examiner in the '178 Line</u>	<u>'179 Line of Prosecution</u>	<u>Examiner in the '179 Line</u>
10/23/87	Application filed		Application filed	
5/24/88		Ex. Kushan	<p>Amgen files preliminary amendment adding new claims 65-69, directed to a process for the preparation of an <i>in vivo</i> biologically active polypeptide. (R. Ex. 10 (AM-ITC 00953207-08)).</p> <p>Claim 65: a process for the preparation of an <i>in vivo</i> biologically active glycosylated polypeptide comprising the steps of:</p> <p>(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 <u><i>in vivo</i></u> 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,</p> <p>(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;</p>	Ex. Tanenholtz

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			<p>(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;</p> <p>(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</p> <p>(b) isolating the glycosylated polypeptide so produced.</p>	
8/3/88		Ex. Kushan	Examiner Tanenholtz rejected claims 65-69 as obvious and unpatentable over Yokota and Gething. Yokota taught and claimed the production of a glycosylated product.	Ex. Tanenholtz
9/27/88		Ex. Kushan	Odre argued that the claims were directed to a "novel series of process steps wherein a mammalian host cell capable of glycosylating the expressed polypeptide is first transformed or transfected with a DNA sequence encoding a	Ex. Tanenholtz

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			specifically delineated polypeptide, i.e., one having a sufficient amino acid sequence homology to natural human erythropoietin to allow it to qualify ... for potential in vivo biological activity.” This shows that Odre viewed the '178 claims as the inherent product of the '179 claims. (R. Ex. 38 (AM-ITC 00953272-78)).	
12/1/88	Amgen filed an amendment, amending claims 41, 55, and 56 and adding new claims 61-66. Claim 41 was directed to a glycoprotein product having the primary structural conformation and glyc. sufficiently duplicative of naturally occurring EPO.... Amgen did not disclose the August 1988 rejection to Examiner Kushan. (R. Ex. 96 (AM-ITC 00941105-18)).	Examiner Kushan		Examiner Tanenholtz
2/10/89	Kushan rejected the pending claims of the '178 over concerns that the particular glycosylation of rEPO and uEPO was not sufficiently defined. (R. Ex. 109 (AM-ITC 00941147-60)).	Ex. Kushan		Ex. Tanenholtz

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6/2/89	Amgen cancelled all claims and added new claims 67-75, product-by-process claims, defined as the "glycoprotein product of the expression of an exogenous DNA sequence in a eucaryotic host cell..." Applicant did not inform Examiner Kushan of Tanenholtz's August 1988 rejection, even when making the claims product-by-process. (R. Ex. 86 (AM-ITC 00941164-72)).	Ex. Kushan		Ex. Tanenholtz
7/11/89	Applicant amended claim 67 to limit the host cell to a "non-human eukaryotic host cell" to avoid a rejection over Sugimoto. Applicant did not inform the Examiner of the prior rejection in the '179. (R. Ex. 97 (AM-ITC 00941187-97)).	Ex. Kushan		Ex. Tanenholtz
1/10/90	Applicant cancelled claims 67-75 and added new claims 76-83 (product-by-process), noting that "[t]hese new claims parallel claim 2 of U.S. Patent No. 4,703,008" confirming that applicant regarded the applications as part of the same overall invention. Furthermore,	Ex. Kushan or Ex. Schain		Ex. Tanenholtz

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	<p>Applicant argued that the priority determinations of the different applications rise and fall together (i.e. if Lin was first to invent DNA encoding EPO and the use of that DNA in a host cell, then clearly he was the first to invent the product). Nonetheless, Applicant never disclosed the rejection in the co-pending '179. (R. Ex. 75 (AM-ITC 00941211-20)).</p> <p>Claim 76: A non-naturally occurring glycoprotein product of the expression in a non-human eukaryotic host cell of an exogenous DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin, said product possessing the <i>in vivo</i> 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.</p>			
2/9/90	<p>Schain sent communication to Borun indicating that Applicant's arguments were sufficient to overcome rejections based on §112, but upheld double patenting rejection over Lai. (R. Ex. 249 (AM-ITC 00941224-27)). The '334 interference was</p>	Ex. Schain		Ex. Tanenholtz

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	subsequently declared.			
12/29/93	Fitzgerald issued an Office Action allowing claims 76-83, but Borun opted to continue prosecution via the '874 application. (R. Ex. 4 (AM-ITC 00941410-15)).	Ex. Fitzgerald		Ex. Hodges
2/28/94	'874 application filed	Ex. Fitzgerald		Ex. Hodges
4/8/94	Borun filed an IDS listing 394 references, including references of record from both lines of applications. Among the references cited as being of record from the '179 application were Yokota and Gething. However, their significance was not disclosed. (Ex. 25).	Ex. Fitzgerald		Ex. Hodges
6/13/94	Applicant filed an amendment, adding new claims 84-94. New claim 86, a product-by-process claim, read "growing...mammalian host cells transformed or transfected with an isolated DNA sequence encoding the human erythropoietin amino acid sequence...." The '179 rejection from August 1988 was never disclosed. (R. Ex.	Ex. Fitzgerald		Ex. Hodges

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	81 (AM-ITC 00941451-54)).			
August 1994	Martinell takes over prosecution	Ex. Martinell		Ex. Martinell
8/16/94	Martinell rejected claims 87 and 89-97 for indefiniteness and claims 87-94 under §102(b) or §103 based on differences in glycosylation and carbohydrate composition between uEPO and rEPO.	Ex. Martinell		Ex. Martinell
9/7/94	Martinell sits for an interview (discusses Sugimoto)	Ex. Martinell	Martinell sits for an interview (discusses Yokota and Gething)	Ex. Martinell
2/6/95		Ex. Martinell	Martinell issues notice of allowability	Ex. Martinell
5/17/95	Martinell issues a Final Office Action, rejecting all pending claims	Ex. Martinell		Ex. Martinell
6/7/95	Applicant files '774 continuation application	Ex. Martinell		Ex. Martinell
3/15/96	Martinell issues a notice of allowability	Ex. Martinell		Ex. Martinell

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