2. Factual Distinctness of Patentability Issues herein from those of In re Durden

The decision of the C.A.F.C. in In re Durden, 226 USPQ 359-362 (1986) was noted by the Examiner as potentially relevant to patentability of claims originally presented in parent Serial No. 675,298. Applicant respectfully submits that the decision is not in any way controlling on the determination of nonobviousness of claims 65-69 under Section 103. This is so because the factual context which was the focus of the Court's deliberations in the Durden case is wholly distinct from that extant with respect to the invention claimed herein.

Here, as in Durden, method claims are in issue and practice of the claimed method involves use of patentable starting materials to obtain patentable products. It will be recalled at the outset, however, that the C.A.F.C. specifically declined to provide any "general rule" for application to all cases wherein the patentability of a method for manufacturing a novel product using a novel starting material is under consideration.

> We reiterate another principle followed in obviousness issue cases, which is to decide each case on the basis of its own particular fact situation. What we or our predecessors may have said in discussing different fact situations is not to be taken as having universal application.
>
> * * * * *
>
> We are sure that there are those who would like to have us state some clear general rule by which all cases of this nature could be decided. Some judges might be tempted to try it. But the question of obviousness under §103 arises in such an unpredictable variety of ways and in such different forms that it would be an indiscreet thing to do. Today's rule would likely be regretted in tomorrow's case. Our function is to apply, in each case, §103 as written to the facts of disputed issues, not

> to generalize or make rules for other cases which are unforeseeable. The task may sometimes be easy and sometimes difficult; and as this case shows, not all of those required to decided may agree. But such is the way of the "law".

Against this background, only a cursory examination of the facts and stipulated issues in the Durden appeal is necessary to show that the final outcome in that case has no controlling effect here.

In Durden, the claim under consideration was directed to performing a well known chemical conversion of an oxime to a carbamate ester. More specifically, the claim called for use of a novel oxime-substituted, 6-membered ring compound as a starting material. The prior art showed successful carbamate ester formation using an oxime-substituted 5-membered, ring compound as the starting material. The Examiner properly noted two structural differences between applicant's and the prior art's starting materials and requested factual input from the applicant as to whether, in view of the success achieved in the prior art, the distinct features of the new starting material might have any influence on whether a skilled worker could reasonably expect the desired carbamate ester product to be formed. As noted by the C.A.F.C., no such facts concerning any potentially unexpected results of the process were provided to the Examiner or the Board.

Given this factual background, the concisely-stated legal issue decided by the C.A.F.C. in Durden was:

> ...whether a chemical process, otherwise obvious, is patentable because either or both the specific starting material employed and the product obtained, are novel and unobvious. (id at page 360, emphasis in text.)

The facts relevant to a determination of obviousness in the present case are completely different. The subject matter of the present claims conspicuously involves myriad biological processes rather than a single chemical process. As indicated earlier, even after the host cell's biological transformation or transfection has been achieved, there remain to be performed literally thousands of complex individual cellular reactions in a specific order directed first by the novel DNA sequence, then by the mRNA transcript of the DNA, and finally by the translated polypeptide sequence, all within the infinitely complex biochemical milieu of the host cell.

The issue presented here, therefore, is not that which was before the Durden Court: whether a concededly obvious process, providing its entirely expected result, can be bootstrapped to the stature of patentable subject matter merely by calling for its application to a new starting material or by causing it to be applied to formation of a new product. In such a case, the outcome of deliberation on potential patentability is invariably negative because, by definition, merely achieving the expected cannot be patentable.

The issue here presented is the threshold issue of whether the series of processes whose practice is called for by the claims is an obvious series of processes giving rise to an expected result. Deliberation on this issue must involve consideration of the novel nature of the DNA sequence employed in the process and also must involve consideration of whether the product isolated could reasonably have been expected to come into existence by practice of the recited procedures.

The Examiner's position in Serial No. 675,298 construes the Durden decision to indicate that the C.A.F.C. has relegated evidence regarding properties of a claimed process's product to the junk heap of immateriality for purposes of determining obviousness of the process. This is simply not true. While the novelty (indeed, the patentability) of a product may not necessarily render the process for making it patentable, no deliberation on the obviousness of a series of manipulative processes can ever be made without considering the nature of the result achieved. Where the result (however "new" by virtue of use of a new starting material) is only that which the prior art would lead the skilled artisan to expect, a finding of obviousness may be appropriate. Where, as here, virtually nothing was known about precisely how naturally-occurring glycosylated human erythropoietin comes into existence in the human body and there was no substantial basis in the art for believing that the in vivo active material could be made in any recombinant system, the successful result of the practice of Applicant's claimed invention is certainly relevant and material to obviousness considerations. Alternately stated, a result cannot transform to nonobvious a process which is concededly obvious to begin with, but the fact that a process succeeds in providing a desired result in the absence of a substantial basis in the art for expecting it to succeed is highly probative on the issue of nonobviousness.

3. The Lack of Relevance of the Talmadge et al. Reference

Attached hereto as Exhibit "D" is a copy of the Talmadge et al. reference cited by the Examiner as pertinent to process claims initially presented during prosecution of the '008 Patent. The disclosures of this reference are conspicuously distinct from the subject matter herein claimed. Whatever a skilled artisan might have understood from the reference concerning E.coli processing of endogenous and exogenous "secretory" signal sequences incorporated into fusion genes and resulting in transported fusion proteins, the disclosures are entirely silent concerning recombinant production of glycoproteins. They thus provide no suggestion to practice the processes of claims 65-69, nor any reasonable expectation that the practice of such processes would succeed in providing an in vivo biologically active product.

4. Lack of Relevance of Prior Art References Disclosing Recombinant Glycoprotein Production

In an attempt to facilitate early consideration of all patentability issues, Applicant has caused a computer-assisted search to be performed in "Medline" and "Chemical Abstracts" data bases for publications which may have relevance to the recombinant preparation of human obligate glycoproteins in in vivo biologically active form.

The general format of the search involved development of four "Concepts", each of which incorporated specific alternative search terms. The concepts were combined in various ways to provide input composite search terms within the two data bases. Concept No. 1 ("Recombinant") was defined to embrace recombinant, genetic..., engineer...,

molecular cloning, cloning/cloned, rDNA, cDNA, rErythropoietin, biotechnolog..., mRNA (Medline only), DNA biosynthesis (Medline only), recombinant protein(s). Concept No. 2 ("Proteins") was defined to embrace membrane proteins, surface proteins, receptor(s), trypanosome, clathrin, fibronectin, laminin, glycoproteins, amyloid, asialoglycoproteins, avidin, csf, hemopexin, inhibin, lactoferrin, mucoprotein, mucins, peptidoglycan, haptoglobin, protein c, proteoglycans, thrombopoietin, thryoglobulin, glycosylat..., carbohydrate structure, carbohydrate conformation. Concept No. 3 ("Cell Lines") was defined to embrace CHO, chinese hamster ovar..., CV1, BSC1, BHK, COS. Concept No. 4 ("Mammalian") was defined to embrace human and mammal. Medline searches for the period 1966-1984 were conducted for the composite of the concepts "recombinant" X "proteins" X "cell lines" (revealing 62 abstracts) and "recombinant" X "proteins" X "mammalian" plus "expression" (revealing 178 abstracts). Similarly, Chemical Abstract searches for the period 1963-1984 were based on the composites "recombinant" X "protein" X "cell lines"/-"mammalian" (providing 49 abstracts) and "recombinant" X "proteins" (excluding the above 49 abstracts and in turn providing 65 abstracts).

Copies of the search reports generated are attached as Exhibit "E" hereto. On these reports, Applicant's counsel has marked with a red "X" the reference which appeared to be relevant.

As set out in greater detail in the PTO-1449 Statement scheduled to be submitted imminently, the references generally dealt with recombinant expression of non-human glycoproteins, or recombinant expression of human

glycoproteins which are not obligate glycoproteins and do not require glycosylation for in vivo activity, or recombinant expression of fragments of human obligate glycoproteins. The 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. A copy of the publication is attached hereto as Exhibit "F".

The Collen et al. article (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) describes thrombolytic in vivo biological activity versus rabbit jugular vein thrombosis for recombinant human tissue-type plasminogen activator (tPA). Naturally occurring tPA is believed by applicant to share with erythropoietin the characteristic of being an obligate human glycoprotein. The reference does not describe how the recombinant mammalian host cell expression product was prepared but rather cites to Pennica et al., Nature, 301, 214-221 (1983) for this purpose. (See page 147, Methods and Materials, line 2.) The cited Pennica et al. reference is attached as Exhibit "G" hereto. Despite its characterization in Collen et al. as providing a description of mammalian cell expression of tPA, however, the 1983 Pennica et al. reference deals exclusively with non-glycosylated E.coli expression products (see penultimate paragraph on page 220) and, of course, includes no data suggesting in vivo biological activity for the E.coli-derived products. Thus Pennica et al. contains no disclosure or suggestion of

successful practice of a process for production of an obligate human glycoprotein which might be at all analogous to that set out in claims 65-69.

In a subsequent attempt to determine whether published patent applications might exist concerning mammalian cell production of recombinant human tPA, a search was conducted for such applications in the Derwent World Patents Index data base. Three published European Patent Applications filed by Genentech were located and are attached hereto as Exhibits "H", "I" and "J".

EPO 0 093 619 was published in November, 1983 (and was ultimately based on U.S. Patent Applications dating back through May, 1982). This document, like Pennica et al., contains no description of use of mammalian host cell expression systems for tPA production. The only clear mention of such systems was entirely speculative and appears in the "Summary of the Invention" at page 7:

> In addition, depending upon the host cell, the human tissue plasminogen activator hereof may contain associated glycosylation to a greater or lesser extent compared with the native material. (Emphasis supplied)

EPO Applications 0 117 059 and 0 117 060 were assertedly based on January, 1983 U.S. filings and published in late August of 1984. These publications address the production of tPA in mammalian host cells but they contain no reference to glycosylation of the recombinant products nor to any successful assays of in vivo biological activity. Thus, the Genentech published patent applications provide no demonstration of the production of an obligate

human glycoprotein such as might give rise, by analogy, to any reasonable expectation of success in the practice of the methods of present claims 65-69.

Applicant submits that the results of the above-described searches and analysis provide a clear indication that 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. Of course, whether Applicant was in fact absolutely the first to succeed in this respect is not outcome determinative of patentability of the present claims. It is possible that an instance of successful mammalian cell expression of such an active protein might have been reported at a time prior to Applicant's work and that the report simply escaped detection in the searches described above. Whether or not this is the case, however, it must be abundantly clear that there did not exist any body of information in the art which would be at all analogous to that existing in the Durden case, providing a basis for asserting that the transformation/transfection, transcription, translation, glycosylation and isolation as described by the present claims could reasonably have been expected to succeed in yielding a human erythropoietin product having the amino acid sequence and glycosylation needed for in vivo biological activity.

Applicant respectfully submits that the processes herein claimed were in no way obvious when originally practiced by Applicant and, accordingly, that no proper basis exists for rejection of the claims under 35 U.S.C. §103. Allowance of the claims is in complete legal harmony

with the ruling of the C.A.F.C. in In re Durden because the process herein claimed could not have been expected to provide the valuable product attained.

**CONCLUSION**

The foregoing amendments and remarks are believed to establish that claims 65-69 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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May 24, 1988