Fritsch et al persist in characterizing the invention of the count as a strategy for isolating the EPO gene, which strategy was allegedly conceived by Edward Fritsch or by Fritsch et al at some time prior to Lin.[17] The Federal Circuit's ruling completely disposes of this argument (18 USPQ2d at page 1021):

> *Fritsch had a goal of obtaining the isolated EPO gene, whatever its identity, and even had an idea of a possible method of obtaining it, but he did not conceive a purified and isolated DNA sequence encoding EPO and a viable method for obtaining it until after Lin. It is important to recognize that neither Fritsch nor Lin invented EPO or the EPO gene. The subject matter of claim 2 was the novel purified and isolated sequence which codes for EPO, and neither Fritsch nor Lin knew the structure or physical characteristics of it and had a viable method of obtaining that subject matter until it was actually obtained and characterized.* Underscoring added.)

The Court disagreed completely with Fritsch's argument that Fritsch was the first inventor because of his probing strategy. Thus, the Court stated:

> *Defendants further argue that because the trial court found that the probing and screening method employed by Lin is what distinguished the invention of the '008 patent over the prior art, Fritsch's strategy in 1981 had priority over Lin's use of that strategy. We disagree. The trial court found that Fritsch's alleged conception in 1981 of an approach that might result in cloning the gene was mere speculation. Conception of a generalized approach for screening a DNA library that might be used to identify and clone the EPO gene of then unknown constitution is not conception of a "purified and isolated DNA sequence" encoding human EPO. It is not "a definite and permanent idea of the complete and operative invention". Fritsch's conception of a process had to be sufficiently specific that one skilled in the relevant art would succeed in cloning the EPO gene. See, Coleman, 754 F.2d at 359, 224 USPQ at 862. Clearly, he did not have that conception because he did not know the structure of EPO or the EPO gene.*

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[17] The Fritsch et al brief (page 20) actually invites the Board to pick from among five dates for completeness of the Fritsch et al cloning strategy.

Commenting further on the inadequacy of the Fritsch et al position, the Federal Circuit held that (pages 1021-1022):

> *The record indicates that several companies, as well as Amgen and GI, were unsuccessful using Fritsch's approach. As the trial court correctly summarized:*
>
> > *'Given the utter lack of experience in probing genomic libraries with fully degenerate probes and the crudeness of the techniques available in 1981, it would have been mere speculation or at most a probable deduction from facts then known by Dr. Fritsch that his generalized approach would result in cloning the EPO gene.' 13 USPQ2d at 1760.*
>
> *As expert testimony from both sides indicated, success in cloning the EPO gene was not assured until the gene was in fact isolated and its sequence known. Based on the uncertainties of the method and lack of information concerning the amino acid sequence of the EPO protein, the trial court was correct in concluding that neither party had an adequate conception of the DNA sequence until reduction to practice had been achieved; Lin was first to accomplish that goal.*
>
> *Defendants also argue that the court failed to consider that 1983, just prior to Lin's conception, was the relevant time for determining the completeness of Fritsch's conception, not 1981. However, the record shows that the court did consider what occurred in 1983. Moreover, Fritsch had no more of a conception in 1983 than he did in 1981, because he did not then know the sequence of the gene encoding EPO.* (Underscoring added.)

This means that all of the evidence from the District Court proceedings, which Fritsch et al have reintroduced into these proceedings, including his alleged strategy involving a possible method of probing suitable for cloning the DNA sequence, is of no consequence and can be dismissed as irrelevant to priority. According to the Federal Circuit decision, Fritsch et al could not have a conception of the DNA sequence until they had actually reduced to practice the DNA sequence. By that time, according

to the undisputed facts, Lin had not only purified and isolated the DNA sequence but he or others at his request had used it to produce in vivo biologically active recombinant human EPO.

While the foregoing is believed to be dispositive of the priority issue as between Fritsch et al and Lin, it is useful to separately set out the District Court's undisputed findings as to the work done by Lin and Fritsch in reducing the invention to practice as this serves to underscore Lin's priority position. Thus, the District Court found, the Federal Circuit did not question, and Fritsch et al have not challenged, the following findings of facts as to Lin's work (at page 1748, 13 USPQ2d):

> *The successful cloning of the EPO gene took place in September or early October 1983. (Tr. 4, 64-66; 5, 123-124). This was the first time that Lin ever designed, ordered and used two sets of probes, both fully degenerate, from two different regions of the EPO gene to screen a genomic library. (Tr. 5, 91, 124). Amgen (someone other than Dr. Lin) sequenced the gene to confirm it was the EPO gene (Tr. 4,74).*
>
> *In late October, 1983, Lin cloned the monkey cDNA EPO sequence. (Tr. 4, 72). On December 3, 1983, Lin also hybridized the human EPO gene to monkey EPO cDNA so that he could determine from an electron micrograph which area of the human DNA consisted of introns, and what the sizes of the exons and introns were. (Tr. 4, 68-72; PX 63-38).*
>
> * * * * * * * * * * * * * * *
>
> *By January 10, 1984, Amgen had expressed human EPO in human embryonic kidney cells called "293" cells and in COS cells, which are monkey kidney cells. (Tr. 4-75-77; PX 63-39; PX 63-41). Someone other than Dr. Lin did the work with the mammalian expression system. (Tr. 5, 51-52). Lin was personally involved in the E. Coli expression of EPO. (Tr. 5,52). On February 13 and 14, 1984, Amgen conducted experiments to show that the*

> *recombinant human EPO produced in the COS cell was biologically active. (Tr. 4, 80).'*
>
> * * * * * * * * * * * * * * *
>
> *From March 1-9, 1984, Amgen conducted an in vivo bioassay and determined that the recombinant EPO was biologically active. (Tr. 4, 82-83).*
>
> *On March 15, 1984, Lin obtained the human full length EPO cDNA gene. (Tr. 4, 83; 5, 28).*
>
> * * * * * * * * * * * * * * *
>
> *By May 2, 1984, human rEPO had been expressed in CHO cells. (Tr. 4, 86). Jeff Browne and Ralph Smalling worked together on the EPO project team, which Lin continued to head through 1984...*

As for Fritsch et al, the District Court noted that Fritsch et al were unsuccessful in cloning the EPO gene prior to August, 1984 summarizing the Fritsch et al position as follows (page 1751):

> *On May 30, 1984, the genomic library for isolating the EPO gene was plated and hybridized using two sets of probes, both fully degenerate, from different regions of the amino acid sequence. (Tr. 26, 96-98). This process resulted in the identification of two clones in July, 1984, both of which were the full gene for EPO. (Tr. 26, 100-102). This was the first time that GI used two sets of fully degenerate probes based on the correct amino acid sequence for EPO. (Tr. 31, 46). Also, Dr. Fritsch used a hybridization solution called TMAC, which had not been used by Dr. Lin when he cloned the EPO gene. (Tr. 7, 101; 26, 86).*
>
> *The positive clones were then used to construct a single long probe to screen a cDNA library constructed from human fetal liver, and on August 6, 1984, cDNA clones were successfully isolated. (Tr. 26, 104-106). GI transfected a CHO cell with a cDNA clone for EPO; this was the expression system with which GI was most familiar. (Tr. 26, 107).*

The District Court's uncontested factual findings can thus be summarized in the following chronology:

ACTIVITY	DATE
Lin clones human EPO gene	Sept.-Oct. 1983
Amgen (for Lin) confirms EPO gene by sequencing	Sept.-Oct. 1983
Lin clones monkey EPO gene	Late Oct. 1983
Amgen (for Lin) expresses human EPO gene in 293 and COS cells	Jan. 10, 1984
Amgen (for Lin) determines biological activity of recombinant human EPO gene expression product	Feb. 13-14, 1984
Amgen (for Lin) determines in vivo biological activity of recombinant human EPO gene expression product	March 1-9, 1984
Amgen (for Lin) expresses human EPO gene in CHO cells	May 2, 1984
Fritsch identifies two clones	July 1984
Fritsch expresses human EPO gene in CHO cells	after Aug. 1984

The above undisputed factual summary from the District Court decision thus clearly and unequivocally shows that Lin made the invention at issue, i.e., he expressed in vivo biologically active recombinant human EPO by a process involving culturing (or growing) a mammalian host cell transformed with the isolated EPO DNA

sequence and isolating an in vivo biologically active expression product, before Fritsch et al even conceived of the essential DNA sequence[18].

It is appreciated that the Court decisions use shorthand language (e.g. "expressed") concerning the preparation process rather than reciting the specific language of the present count. However, there can be no distinction between Lin's expression of in vivo biologically active recombinant human EPO using 293, COS cells and CHO cells and the determination of its activity as found by the Courts and the specific language of the count. Glycosylation is necessary to provide in vivo biological activity. This is art-recognized and the Examiner-in-Chief has noted that Fritsch et al have not challenged this. See Paper No. 44, sentence bridging pages 2-3. Transforming or transfecting a mammalian host cell (e.g. 293, COS or CHO) with the DNA sequence of the Lin '008 patent and growing (or culturing) this transformed cell under nutrient condition necessarily and inherently involves transcription, translation and glycosylation as specified in steps (a)(i)(ii)(iii) of the Count to provide the in vivo biologically active recombinant EPO. Fritsch et al cannot challenge this as their claims corresponding to the Count simply recite culturing and isolating. Furthermore, they recognized the identity of the respectively claimed processes by not bringing a motion urging no interference in fact. This leave step (b) for consideration and Lin notes that determination of the in vivo biological activity obviously requires isolation (b) of the product from the host cells.

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[18]While it is not necessary to do so in view of the Federal Circuit's simultaneous conception/reduction to practice position, it is noted that the District Court also found that Lin conceived the probing method in October, 1981, i.e. before Fritsch et al (13 USPQ2d at 1763). Hence, as noted earlier, Fritsch et al could not prevail even if, in theory, conception could occur prior to reduction to practice on the basis of the probing method.

Fritsch et al cannot validly argue the contrary. The isolation step (b) means nothing more than separating the expressed product from the cells (LR 229) and would obviously be necessary to determine the in vivo biological activity of the expression product. Any effort by Fritsch et al to argue that the isolation step of the Count means purification is nothing more than an afterthought which is inconsistent with Fritsch et al's own disclosure, as noted earlier.

Manifestly, the Lin evidence shows that Browne carried out the process of the count using COS cells transfected with Lin's isolated human EPO encoding gene and that Dukes should that the expressed product to be in vivo biologically active by March 1984 (expression products E3 and E7) and that Browne's CHO cell expressed human EPO (H3 and B11) was found to have in vivo activity by June 1984. All of this is prior to Fritsch et al's conception date.

Furthermore, it is noted that Fritsch et al have not proven an actual reduction to practice as they have not established that their expression product had in vivo biological activity. See discussion under "The Fritsch Priority Evidence".

In view of the foregoing, it is submitted that Lin is entitled to priority as to the count.

(c) Lin Has Satisfied Best Mode Requirements

The Fritsch et al argument (FB 35-44) that Lin has failed to meet best mode requirements is nothing more than a re-hash of the arguments which were met head on by Lin before the District Court and Federal Circuit and on which these Courts ruled

favorably for Lin. No new evidence has been adduced by Fritsch et al in this proceeding. Fritsch et al sought no discovery on this issue when their motion I was deferred for final hearing. The same record which prompted the District Court to observe that:

> *[T]here is no evidence that Dr. Lin knew of a better mode which he failed to disclose at all...*

and thus

> *those of ordinary skill in the art could produce mammalian cells with similar levels of [EPO] production identified in Example 10...*

is presented to the Board. The attempt by Fritsch et al to secure a different result from the Board must fail.

In affirming the District Court on best mode with respect to the same arguments as now urged by Fritsch, the Federal Circuit decision states (18 USPQ 2d at page 1023):

> *Defendants argue that the district court erred in failing to hold the '008 patent invalid under 35 U.S.C. §112, asserting that Lin failed to disclose the best mammalian host cells known to him as of November 30, 1984, the date he filed his fourth patent application.*
>
> *The district court found that the "best mode" of practicing the claimed invention was by use of a specific genetically-heterogeneous strain of Chinese hamster ovary (CHO) cells, which produced EPO at a rate greater than that of other cells. It further found that this strain was disclosed in Example 10 and that Lin knew of no better mode. GI argues that Lin's best mode was not adequately disclosed in Example 10 because one skilled in the art could not duplicate Lin's best mode without his having first deposited a sample of the specific cells in a public depository. The issue before us therefore is whether the district court erred in concluding that Example 10 of the '008 patent satisfied the best mode requirement as to the invention of the challenged claims and that a deposit of the preferred CHO cells was not necessary.*

After commenting on the relevant case law, the Court went on to state:

> *We agree that the district court did not err in finding that defendants have not met their burden of proving a best mode violation.*
>
> *As noted above, the district court found that the best mode of making the CHO cells was set forth in Example 10. As the district court stated, while it was not clear which of two possible strains Lin considered to be the best, the cell strain subjected to 1000 nanomolar MTX (methotrexate) or that subjected to 100 nanomolar MTX, the best mode was disclosed because both were disclosed.*[6] *Defendants argue that this disclosure is not enough, that a deposit of the cells was required.*
>
> * * * * *
>
> *The district court found that the claims at issue require the use of biological materials that were capable of being prepared in the laboratory from readily available biological cells, using the description in Example 10. The court also found that there were no starting materials that were not publicly available, that were not described, or that required undue experimentation for their preparation in order to carry out the best mode. The court noted that Lin testified that the isolation of the preferred strain was a "routine limited dilution cloning procedure[]" well known in the art. Dr. Simonsen, GI's own expert, testified that the disclosed procedures were "standard" and that: with the vectors and the sequences shown in Example 10, I have no doubt that someone eventually could reproduce -- well, could generate cell lines [sic, strains] making some level of EPO, and they could be better, they could be worse in terms of EPO production.*

The district court relied on this testimony, and, upon review, we agree with its determination. The testimony accurately reflects that the invention, as it relates to the best mode host cells, could be practiced by one skilled in the art following Example 10. Thus, the best mode was disclosed and it was adequately enabled.

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6 In its opinion, the district court stated that "the best way to express EPO was from mammalian cells ... and that a cell line derived from 11 possible clones from the CHO B11, 3.1 cell strain was to be used for Amgen's master working cell bank, which was expected to be started on November

> 26, 1984". 13 USPQ 2d at 1772. At another point, the court stated that Amgen "did disclose the best mode in Example 10 of the invention, when it described the production rates of the 100 nanomolar-amplified cells (the B11 3.1 cell strain) and one micromolar-treated cells." Id.

The Court then went on to distinguish the case from the situation where biological cells were obtained from unique soil samples, noting at page 1025:

> *On the other hand, when, as is the case here, the organism is created by insertion of genetic material into a cell obtained from generally available sources, then all that is required is a description of the best mode and an adequate description, not deposit of the cells. If the cells can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required. See Feldman v. Aunstrup, 517 F.2d 1351, 1354, 186 USPQ 108, 111 (CCPA 1975), ("No problem exists when the microorganisms used are known and readily available to the public".), cert. denied, 424 U.S. 912 [188 USPQ 720] (1976). Since the court found that that is the case here, we therefore hold that there is no failure to comply with the best mode requirement for lack of a deposit of the CHO cells, when the best mode of preparing the cells has been disclosed and the best mode cells have been enabled, i.e., they can be prepared by one skilled in the art from known materials using the description in the specification.*

The Court also dealt with the Fritsch argument regarding the possibility of "duplicating" Lin's example (at 1026-1027) as follows:

> *Defendants also assert that the record shows that scientists were unable to duplicate Lin's genetically-heterogeneous best mode cell strain. However, we have long held that the issue is whether the disclosure is "adequate", not that an exact duplication is necessary. Indeed, the district court stated that*
>
> > *[t]he testimony is clear that no scientist could ever duplicate exactly the best mode used by Amgen, but that those of ordinary skill in the art could produce mammalian host cell strains or lines with similar levels of production identified in Example 10.*
>
> *13 USPQ 2d at 1774. What is required is an adequate disclosure of the best mode, not a guarantee that every aspect of the specification*