

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 57

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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SHMUEL CABILLY, HERBERT L. HEYNEKER,  
WILLIAM E. HOLMES, ARTHUR D. RIGGS  
and RONALD B. WETZEL  
Junior party<sup>1</sup>

v.

MICHAEL A. BOSS, JOHN H. KENTEN,  
JOHN S. EMTAGE and CLIVE R. WOOD  
Senior party<sup>2</sup>

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Patent Interference No. 102,572

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<sup>1</sup> Application 08/205,419, filed June 10, 1988. According benefit of Application 06/483,457, filed April 8, 1983, now patent No. 4,816,567, issued March 28, 1989. Assignee for Genentech, Inc., South San Francisco, CA, A California Corporation.

<sup>2</sup> Application 06/672,265, filed November 14, 1984, now Patent No. 4,816,397, issued March 28, 1989. Accorded benefit of PCT application, PCT/GB84/00094, filed March 23, 1984 and UK application No. 83/08235, filed March 25, 1983. Assignee for Celltech Limited, Berkshire SL1 4DY, U.K., A British Company.

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Before RONALD H. SMITH, DOWNEY and SCHAFFER,<sup>3</sup> Administrative Patent Judges.

DOWNEY, Administrative Patent Judge.

### FINAL DECISION

The interference concerns a two step process for producing either an immunoglobulin (Ig) molecule or an immunologically functional Ig fragment comprising at least the variable domains of the Ig heavy and light chains in a single host cell.

The subject matter at issue is defined by a single count, which count is identical to claim 1 of the Boss et al. patent. The count reads as follows:

#### Count 1

A process for producing an Ig molecule or an immunologically functional Ig fragment comprising at least the variable domains of the Ig heavy and light chains, in a single host cell, comprising the steps of:

- (i) transforming said single host cell with a first DNA sequence encoding at least the variable domain of the Ig heavy chain and a second DNA sequence encoding at least the variable domain of the Ig light chain, and
- (ii) independently expressing said first DNA sequence and said second DNA sequence so that said Ig heavy and light chains are produced as separate molecules in said transformed single host cell.

Boss et al. claims 1-18 and Cabilly et al. claims 101-120 correspond to the count.

During the preliminary motion stage of this proceeding, the administrative patent

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<sup>3</sup> APJ Schafer has been substituted for APJ Pellman who has retired. *In re Bose*, 772 F.2d 866, 868-869, 227 USPQ 1, 2-4 (Fed. Cir. 1985).

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judge (APJ), granted the Boss et al. motion for benefit of the March 25, 1983 and March 23, 1984, filing dates of their United Kingdom application, No. 83/08235 and PCT application, PCT/GB84/00094, respectively. With the granting of the motion for benefit, party Boss et al. became senior party in this interference.

Boss et al. took no testimony and thus stand on their March 25, 1983, filing date accorded them during the motion period.

Junior party Cabilly et al. raise the following issues in their brief (Brief, page 3):

(1) does the record establish that Cabilly et al. actually reduced to practice the invention of the count prior to the March 25, 1983, effective filing date accorded Boss et al., and if not, then,

(2) does the record establish that Cabilly et al. conceived of the invention of the count prior to the March 25, 1983, filing date accorded Boss et al. and proceeded with reasonable diligence to either an actual or constructive reduction to practice (April 8, 1983) from a time prior to conception of Boss et al. (March 25, 1983).

In addition, we have before us, a Cabilly et al. motion, pursuant to 37 CFR § 1.635, to have certain Cabilly et al. pages, 224-231 attached to exhibit 8 and page 993 attached to Exhibit 20, entered into the record (Paper No. 49). The motion stands opposed (Paper No. 50); and a reply was filed (Paper No. 51).

The following issues have not been raised by the parties:

(1) a question of no interference-in-fact;

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(2) a question of separate patentability of any claim(s);

(3) a question of whether Cabilly et al. claims are unpatentable. Boss et al. filed a motion for judgment against Cabilly et al. claims during the motion stage, which motion was denied; Boss et al. do not seek review of this motion at final hearing; and

(4) a question of whether Cabilly et al. rely upon attorney diligence for their priority case. Cabilly et al. allege priority based on conception coupled with reasonable diligence to filing of their application. Cabilly et al. could have but did not offer any evidence relating to attorney diligence in preparing and filing the Cabilly et al. patent application during the critical period.

Cabilly et al. filed a record (CR) consisting of exhibits 1-20 (CX) <sup>4</sup> and the declarations of coinventors: Arthur D. Riggs, Ph.D, (Riggs) and Shmuel Cabilly (Cabilly), employees of City of Hope; William E. Holmes (Holmes) and Ronald B. Wetzel, Ph.D., (Wetzel), employees of Genentech, Inc.; and corroborators Paul J.

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<sup>4</sup> The record and exhibits will be referred to as CR and CX followed by the appropriate number.

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Carter, Ph.D (Carter)<sup>5</sup>, Michael B. Mumford (Mumford), L. Jeanne Perry (Perry), Michael W. Rey (Rey), all employees of Genentech and John E. Shively, Ph.D., (Shively), an employee of City of Hope. Boss et al. did not cross examine any of the witnesses.

Both parties filed briefs and appeared through counsel at final hearing.

I.

Cabilly et al. motion to correct the record

With their reply brief, Cabilly et al. filed a motion to have entered into the record certain pages which were referred to and relied upon in various declarations but were omitted from the record when it was filed and served upon Boss et al. The omission was first realized when Boss et al. noted, in their brief, that the pages were not in the Cabilly et al. record.

The motion is granted. In view of the fact that Cabilly et al. referred to CX-8, pages 224-231 in the Wetzel and Perry declarations and CX-20, page 993 in the declaration, we find the failure to file these pages with their respective exhibits an oversight on the part of Cabilly et al.

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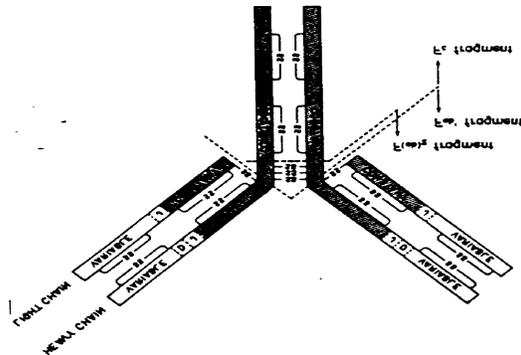
<sup>5</sup> The Carter testimony was submitted in response to the Boss et al. motion for judgment; as noted the motion is not being reviewed at final hearing and thus the Carter testimony is not relevant to the issues before us and has not been considered in rendering this decision.

The Boss et al. arguments are without merit. It is true that the present rules do not require Boss et al. to notify Cabilly et al. of the oversight. As a matter of courtesy, Boss et al. could have notified Cabilly et al. of the omission when the exhibits were served. We find no prejudice to Boss et al. by entering the omitted exhibits into the record.

II.

Background:

Immunoglobulins (Ig), also called antibodies, are protein molecules produced in vertebrates by B cells in response to foreign antigenic agents. (Boss et al. patent, column 1, lines 60-64, Cabilly et al. specification, page 1). The basic structure of all immunoglobulin molecules is a unit consisting of two identical light (L) polypeptide chains of molecular weight of approximately 23,000 daltons and two identical heavy (H) polypeptide chains of molecular weight 53,000-70,000 daltons, shaped to form a Y:



Each H and L chain is held together by disulfide bonds to form a monomer, and the two

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monomers are linked by disulfide bonds to form the basic dimeric structure of the molecule (Cabilly et al. specification, page 5). There are five classes or types of H chains, gamma, mu, alpha, delta, or epsilon which characterize an individual Ig as an IgG, IgM, IgA, IgD or IgE, respectively; and two classes of L chains, kappa (6) and lambda (8) (Cabilly et al. specification, page 5). Each antibody chain contains a variable region (V) and a constant region. The variable region is about 100 amino acids in length and is specific for the antigen which elicited it. (Cabilly et al. specification, page 6). The constant region does not take part in the binding of any antigenic determinant but does serve to link the antibody to other participants in the immune defenses, e.g. to fix complement, and thus makes an antibody bifunctional. The variable region of the H and L chain interact closely and when correctly folded form a three dimensional site at each branch of the Y for binding to a particular portion or epitope of the specific antigen which elicited the antibody (Cabilly et al. specification, page 5-6, and Boss et al. patent, column 1, line 60-column 2, line 47).

Kohler and Milstein developed a technique that made it possible to produce monoclonal antibodies, i.e., homogenous antibodies of a single class and single specificity, by the use of hybridoma technology. Monoclonal antibodies are produced in

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a laboratory by a hybridoma cell line, created by injecting the mouse with antigen, harvesting its spleen cells and fusing the same with cells from an immortal cancer cell line. Monoclonal antibodies are specific to one antigen which may have multiple determinants or epitopes. Antibodies have the ability to detect and bind to antigens. The strength of the antibody-antigen binding is referred to as specificity and is quantitatively measured by an affinity value.

### III.

#### THE COUNT

It is well-settled that, absent ambiguity, a count in an interference is to be given the broadest reasonable interpretation that the language of the count permits without resort to either party's disclosure. DeGeorge v. Bernier, 768 F.2d 1318, 1322, 226 USPQ 758, 761 (Fed. Cir. 1985); Fontijn v. Okamoto, 518 F.2d 610, 618, 186 USPQ 97, 103-104 (CCPA 1975); Lamont v. Berguer, 7 USPQ2d 1580, 1582 (Bd. Pat. App. & Int. 1988). We find the count is clear and unambiguous.

Accordingly, we construe the count as being directed to a two step process for the production of either an Ig molecule or an immunologically functional Ig fragment encoding at least the variable domains of the Ig heavy and light chains. The first step comprises transforming a single host cell (e.g., *E.coli*) with first and second DNA sequences encoding at least the variable regions of both the heavy chain and light chain and the second step comprises expressing, in the transformed host cell, the respective heavy and

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light chains as separate molecules.

The count is broad enough to include adding a single plasmid or vector containing both the DNA sequences encoding for at least the variable regions of the heavy and light chains to the host cell or by adding two plasmids to the host cell each containing said DNA sequences individually. The count does not require that the expression step directly result in the production in the host cell of an Ig molecule or an immunological functional fragment of Ig containing at least the variable regions of the heavy and light chains. If the process results in the production of inclusion bodies,<sup>6</sup> then in order to show that a useful product was produced it would be necessary to reassociate or refold after extraction of the inclusion bodies and denaturing its contents. Hence, while the count does not set forth any additional steps it is clear that the count does not exclude other process steps because the count utilizes the open-ended term "comprising". In re Baxter, 656 F.2d 679, 686-687, 210 USPQ 795, 802-803 (CCPA 1981).

#### IV.

#### THE PARTIES BRIEFS

The requirements for the parties briefs are set forth in 37 CFR § 1.656(b). In particular, 37 CFR § 1.656(b)(4) requires:

[a]n argument, which may be preceded by a summary, which shall contain

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<sup>6</sup> Inclusion bodies are also known as refractile bodies. They are insoluble particles which require cell lysis and solubilization in denaturant to permit recovery. (Cabilly et al. specification, page 23, lines 18-21).

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the contentions of the party with respect to the issues to be decided, and the reasons therefor, with citations to the cases, statutes, other authorities, and part of the record relied on. (Emphasis added)

Conclusions of fact and law made without appropriate citation to the record or citation of authority will be taken as attorney argument. Compare Ex parte McCullough, 7 USPQ2d 1889, 1891 (Bd. Pat. App. & Int. 1988); Ex parte Myer, 6 USPQ2d 1966, 1968 (Bd. Pat. App. & Int. 1988); In re Mehta, 347 F.2d 859, 863-864, 146 USPQ 284, 286 (CCPA 1965). Attorney argument cannot take the place of evidence lacking in the record. Meitzner v. Mindick, 549 F.2d 775, 782, 193 USPQ2d 17, 22 (CCPA), cert. denied, 434 U.S. 854 (1977).

V.

The Cabilly et al. Case for Priority (as set forth in their brief):

(1) Coinventor Riggs testified that during the period of July 1980 through September 1980 he was at Genentech on sabbatical from City of Hope. It was his intention to explore the possibility of producing antibodies in bacteria. According to Riggs, after returning to City of Hope, he submitted a proposal (CX-2) to Genentech on October 5, 1981, which was based in part on conversations he had with Dr. Heyneker<sup>7</sup> and Cabilly. Riggs contended that he proposed the use of a single bacterial strain for coexpression of the heavy and light chain genes. Riggs, ¶ 3. Riggs stated that he discussed this project

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<sup>7</sup> Dr. Herbert Heyneker, a coinventor of the Cabilly et al. application, is said to be a senior scientist from Genentech; he did not testify in this proceeding.

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with Shively who was involved in the study of human anti-CEA<sup>8</sup> antibodies and that he requested and received from Shively, on or about February, 1981, a mouse hybridoma cell line, CEA.66-E3, said to express anti-CEA antibodies. Riggs, ¶¶ 3-5 (CR-15-16).

(2) Shively testified that he had conversations with Riggs regarding the project and that upon request from Riggs he supplied Riggs with the cells requested on or about February, 1981. Shively, ¶ 5 (CR-17).

(3) Cabilly, a post doctoral fellow in Riggs' laboratory at City of Hope, testified that in September 1981, he received CEA.66-E3 cells from Shively and that he used these cells to extract total RNA. The polyA mRNA was purified from the total RNA by using an oligo-dT cellulose column. Following the isolation of the mRNA, Cabilly testified that he gave a sample of it to Holmes at Genentech for the preparation of an *E. coli* colony cDNA library. Cabilly ¶ 4 (CR-39).

(4) Coinventor Holmes testified that on July 12, 1982 he began working on the project to express antibodies directed against human CEA in *E. coli*. Holmes, ¶ 3. Holmes testified that he received a sample of polyA mRNA from City of Hope and prepared cDNA which was incorporated into plasmids to make a *E. coli* colony library. Holmes, ¶ 4. He testified that he inoculated colonies into microliter plates and the cultures

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<sup>8</sup> Carcinoembryonic antigen (CEA) is an antigen unique to humans and is found mainly in intestinal tumors. (CX-2, page 2).

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therefrom were stamped onto agar plates and allowed to grow. Holmes, ¶ 5 (CR-29).

(5) Rey, a research assistant at Genentech reporting to Heyneker, testified that he began work on the project in July 1982 when he received microliter dishes with cultures containing cDNA from the hybridoma cell line CEA.66-E3. He transferred these cultures to agar plates and allowed them to grow and later transferred the colonies to nitrocellulose filters, layered them onto agar plates and allowed them to grow. Once grown, he lysed the colonies on the filters and treated them for subsequent probing. Rey, ¶ 3 (CR-33).

(6) Holmes used oligonucleotides from the Organic Chemistry Department at Genentech to prepare light and heavy chain oligonucleotide probes to hybridize with the filters. After exposure to X-ray film, he picked several colonies which hybridized to the light or heavy chain oligonucleotide probes, characterized the colonies by *Pst* restriction endonuclease digestion<sup>9</sup> and fractionation by [sodium dodecylsulfate(SDS)] polyacrylamide [gel] electrophoresis (PAGE)<sup>10</sup>. Several colonies which hybridized to the heavy chain probe were also digested with both *Pst*I and *Nco*I and analyzed by PAGE. Holmes subcloned these DNA sequences into M13 vectors. Holmes, ¶ 6, ¶ 7 (CR-30).

(7) Rey testified that he assisted in the sequencing of the heavy chain cDNA by

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<sup>9</sup> Restriction digestion is a process involving the use of enzymes which recognize different DNA sequences and cleave the DNA backbone at the site recognized forming either blunt or stick ends.

<sup>10</sup> SDS-PAGE stands for sodium dodecylsulfate-polyacrylamide gel electrophoresis which is a technique which separates various species of proteins or polynucleotides of different sizes in an electric field.

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subcloning DNA into M13 vectors, preparing single-stranded template and carrying out the sequencing reactions. Rey also testified that he assisted in the sequencing of the heavy and light chain cDNA's. Rey, ¶ 4 (CR-33).

(8) Holmes testified that he and Heyneker analyzed the sequences and found that the entire coding region of the light chain was found in the cDNA insert of pK17G4 and that portions of the nucleotide sequence of the heavy chain were found in two isolated plasmids: pGamma298 and pGamma11. Holmes, ¶ 7.

(9) Holmes indicated that the plasmid, pKCEAInt 2, for direct expression of the anti-CEA light chain gene was prepared from five DNA fragments, 1-5. According to Holmes, fragment 1 was prepared by digesting pHGH207-1\* with *EcoRI*, filling in<sup>11</sup> and digesting with *BamHI*. Following purification of this fragment, Holmes stated that he treated the DNA with bacterial alkaline phosphatase (BAP). The large fragment (fragment 1) was purified by PAGE. Holmes, ¶ 8 (CR-30). For fragment 2, Holmes testified that he digested pK17G4 DNA with *PstI*, purified the fragment by PAGE, digested with *Avall* and isolated the 333 bp *PstI-Avall* fragment by PAGE; he used the *PstI-Avall* fragment and an oligonucleotide primer in a primer repair reaction to introduce the initiation codon to the light chain gene. Following the primer repair, Rey sequenced a *PstI* to *Avall* DNA fragment of the light chain. Rey, ¶ 5 (CR-34). Holmes indicated that he and Heyneker analyzed the

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<sup>11</sup> The Cabilly et al. brief (page 11) alleges that the "filling in" was done with DNA polymerase I large fragment. No one testified as to how the filling in was done. Meitzner, 549 F.2d at 782, 193 USPQ at 22.

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sequencing results . Holmes, ¶ 9 (CR-30). The fragment was purified by PAGE, cleaved with *Sau3A* and the 182 bp fragment isolated by PAGE (fragment 2). Holmes, ¶ 9 . Thereafter, fragments 1 and 2 were ligated together and the ligation reaction transformed into *E. coli*. The resultant transformants were analyzed by restriction digestion and sequencing to confirm the construction of pKCEAInt1.<sup>12</sup> Holmes, ¶ 10. To prepare fragment 3, Holmes testified that he digested pK17G4 DNA with *PstI* and purified the fragment by PAGE. This fragment was partially digested with *Avall*, filled in and purified by PAGE. This fragment was subsequently digested with *HpaII* and the 497 bp fragment isolated by PAGE (fragment 3). Holmes, ¶ 11 (CR-31). For fragment 4, Holmes testified that he digested the plasmid pKCEAInt1 with *AvaI*, filled in and digested with *XbaI*. The large fragment was treated with BAP and isolated by PAGE (fragment 4). Holmes, ¶ 12. The small fragment was digested with *HpaII* and the 169 bp fragment isolated by PAGE (fragment 5). Holmes, ¶ 12 (CR-31). Fragments 3, 4 and 5 were ligated and the ligation reaction transformed into *E.coli*. Resultant transformants were analyzed by restriction digestion to confirm the construction of pKCEAInt2. Holmes, ¶ 13 (CR-31).

(10) Cabilly testified that he modified plasmid pKCEAtrp207-1\* by cleaving out the *PstI-PvuI* fragment from the ampicillin resistance gene, filling it in and relegating the blunt ends to yield plasmid pKCEAtrp207-1\*delta which is resistant to tetracycline but sensitive

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<sup>12</sup> The Cabilly et al. brief (page 11, first paragraph) alleges that this analysis and isolation of pKCEAInt1 was done on or about October 30, 1982. No one testified as to this date. *id.*

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to ampicillin. Cabilly ¶ 5 (CR-39).

(11) According to Holmes, six fragments, A-F, had to be isolated to make the heavy chain expression plasmid, pGammaCEAInt2. To make the first fragment, Holmes digested pHGH207-1\* with *Ava*I, filled in, digested with *Bam*HI, treated with BAP and purified the large fragment by PAGE (fragment A). Holmes, ¶ 14. He digested pGamma11 with *Pst*I, the fragment was purified by PAGE, digested with *Av*all, filled in, and digested with *Taq*I. The 375 bp fragment was isolated by PAGE (fragment B). Holmes, ¶ 15. He digested pGamma298 with *Taq*I, *Bam*HI, and isolated the 496 bp fragment by PAGE (fragment C). Holmes, ¶ 16. Holmes ligated fragments A, B and C and transformed the ligation reaction into *E. coli*. The resultant transformants were analyzed by restriction digestion to confirm the construction of pGammaCEAInt1. Holmes, ¶17 (CR-31). Holmes used a 15 nucleotide DNA primer in a primer repair reaction to introduce the initiation codon into an *Alu*I to *Rsa*I fragment of pGamma 298 (fragment D). Holmes, ¶ 18 (CR-31). He digested pGamma298 with *Pst*I, *Bam*HI, *Hpa*II and purified the fragment by PAGE (Fragment E). Holmes, ¶ 18 (CR-31). He digested pGammaCEAInt1 with *Eco*RI, filled in, and digested with *Bam*HI. The then treated this fragment with BAP and purified the fragment by PAGE (Fragment F). Holmes, ¶ 18. He then ligated fragments D, E and F and transformed the ligation reaction into *E. coli*. The plasmid, pGammaCEAInt2 was said to be confirmed by restriction analysis and sequencing. Holmes, ¶ 18 (CR-31).

(12) Holmes stated that he prepared the expression plasmid pGammaCEAtrp207-

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1\* when he digested plasmid pBR322(Xap) with *EcoRI*, filled in, digested with *PstI*, and purified by PAGE. He isolated a 1543 bp fragment by treating pGammaCEAInt2 with *PstI* followed by *BamHI* and purification by PAGE. He also isolated a 869 bp fragment from pGammaCEAInt2 by digestion with *AvaI*, filling in, cleaving with *BamHI* and subsequent PAGE purification. He then ligated these fragments, transformed the ligation reaction into *E. coli* and analyzed the resultant colonies by restriction analysis to confirm pGammaCEAtrp207-1\*.<sup>13</sup> Holmes, ¶ 19 (CR-31-32).

(13) Accordingly to Cabilly he transformed competent *E. coli* cells with pKCEAtrp207-1\*delta and retransformed the successful *E. coli* cells with pGammaCEAInt2 which confers resistance to ampicillin but not to tetracycline. Cabilly, ¶ 6 (CR-39-40). He grew the cotransformed cells in minimal media containing ampicillin and tetracycline and induced the cultures with indoleacrylic acid (IAA) to make refractile body preparations. Cabilly testified that he gave a sample to Jeanne Perry for SDS-PAGE analysis. Cabilly indicated that he analyzed several samples by SDS-PAGE; subsequently these were silver stained or subjected to Western blot using anti-mouse IgG for the identification of light and heavy chain protein.<sup>14</sup> Cabilly, ¶ 7 (CR-

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<sup>13</sup> The Cabilly et al. brief (page 13) argues that this work was done by December 8, 1982. This argument is also not supported by any testimony. id.

<sup>14</sup> The Cabilly et al. brief (page 14, sec. 4) alleges that the Western Blot used rabbit anti-mouse primary antibodies and <sup>125</sup>I-labeled protein A. This is attorney argument.

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40).

(14) Perry indicated that the first sample she analyzed from a "cotransformed refractile body preparation" was supplied to her by Cabilly. She analyzed this sample by PAGE. Perry, ¶ 12 (CR-26).

(15) Cabilly testified that he also constructed pGammaCEAFABtrp207-1\*, a plasmid vector for the direct expression of the FAB fragment of the heavy chain gene. (CR-40). Accordingly to Cabilly, he digested pBR322 with *HindIII*, filled in, digested with *PstI* and treated with BAP. He isolated the vector fragment by PAGE (fragment I). Cabilly, ¶ 9. Cabilly indicates that he received a sample of pGammaCEAtrp207-1\* from Holmes, he digested this plasmid with *BamHI* and *PstI* and isolated the fragment by PAGE (fragment II). Another sample of this plasmid was digested with *NcoI* and *NdeI*, he isolated the 260 bp DNA by PAGE. He used a 13 bp oligonucleotide primer in a primer repair reaction in order to introduce a termination codon. The fragment was then digested with *BamHI*, the 179 bp fragment isolated by PAGE, filled in (fragment III). Fragments I, II and III were ligated and transformed into *E. coli*. Cabilly, ¶ 9. These transformants were said to be analyzed by Rey, Holmes and Cabilly by restriction cleavage analysis and sequencing.<sup>15</sup> Cabilly, ¶ 9, Holmes, ¶ 20 and Rey, ¶ 7 (CR-40-41).

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id.

<sup>15</sup> The Cabilly et al. brief (page 14) alleges that this analysis was performed on or about January 22, 1983. No one testified as to this date for the analysis. id.

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(16) Cabilly testified that he conducted a refolding experiment with the material from the cotransformed heavy and light chain *E. coli* cells. He grew the cotransformants, lysed them by sonication, solubilized the pellet with guanidine hydrochloride and incubated this material overnight at room temperature. He then, dialyzed the reaction mixture against urea buffer at room temperature followed by dialysis into phosphate buffered saline (PBS). Cabilly testified that he performed an assay to detect active anti-CEA antibody. He indicated that he found the heavy chain and light chain protein had recombined to yield antigen binding activity significantly higher than background. Cabilly, ¶ 8 (CR-40).

(17) Mumford, an employee of Genentech, was responsible for microbial fermentation optimization of gene products. Mumford, ¶ 2 (CR-35) . The record shows that on three occasions between December 13, 1982 to March 25, 1983, he or someone in his lab received and recorded receipt of labeled microbial samples. Mumford, ¶¶ 5-7 (CR-36). Of specific interest is the receipt on February 2, 1983 of W3110/p10<sub>2</sub> and W3110/p6<sub>2</sub> from Heyneker's laboratory. Mumford, ¶ 7. Mumford recorded:

[T]hese two organisms are *E. coli* strains, which had been co-transformed with two plasmids for the co-expression of heavy and light chain of an anti-CEA antibody. These samples were used to prepare the DMSO stocks 1246-31 and 1246-32, respectively. (¶ 7) (CR-36)

(18) Fermentations were run on these two stock solutions.<sup>16</sup> Thereafter, on February 14, 1983, Mumford recorded the fermentations in CX-18. Mumford, ¶ 13

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<sup>16</sup> The Cabilly et al. brief (page 16) alleges that the fermentations occurred on Feb. 8, 1983. Rey did not give any specific run dates for these fermentations. id.

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(CR-38).

(19) Coinventor Wetzel, a senior scientist at Genentech, testified that he had some success in folding other recombinant proteins and his help was enlisted on the project. Wetzel, ¶ 5 (CR 19-20). He and Perry, a research associate in his lab, began working on the project in January, 1983. Wetzel, ¶ 6 (CR-20) , and Perry, ¶ 2 (CR-21-22 ). Initially they attempted to isolate and purify the heavy and light chains produced in two different *E. coli* strains from cell pastes received by Mumford. Wetzel, ¶7 (CR-20).

(20) Perry<sup>17</sup> testified that their strategy to refold the heavy and light chains from singly transformed bacteria was to first purify the refractile bodies from the bacteria, solubilize the protein in denaturant, followed by sulfitolysis. The chains would then be further purified by S300 gel filtration chromatography and possibly DEAE ion-exchange chromatography. The plan was to then reconstitute the antibodies by folding the heavy chain first, adding it to the light chain, allowing both chains to fold together and then oxidize the disulfide bonds. Perry, ¶ 3 (CR-22). She testified that they tried this strategy and found a loss of heavy chain protein after the removal of the denaturant by dialysis into native buffer. In order to alleviate proteolysis, they tried adding PMSF, EDTA, EGTA, and altering pH and temperature. Protease was found to be inactivated by addition of PMSF,

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<sup>17</sup> Other than referring to January, 1983, Perry, in her testimony, does not set forth any date for the work she did or observed.

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Perry, ¶ 7 (CR-23-24), and protease could be removed by DEAE ion exchange chromatography. Perry, ¶ 8 (CR-24).

(21) The strategy to reconstitute immunoglobulin chains also included the comparison of the refolding results of heavy and light chains from the anti-CEA antibodies produced from hybridoma cells. Perry, ¶ 10. The antibodies were said to be supplied by Cabilly. Optimal conditions were determined and used.<sup>18</sup> Perry, ¶ 10.

(22) Perry stated that later they found that they could isolate the heavy and light chains from both single and cotransformed bacteria by guanidine solubilization of refractile body preparations without any further purification by column chromatography. These samples could then be used directly in the refolding reactions. The final conditions involved a mixture of sulfitolized heavy chain and an extract of light chain cells. The chains were reconstituted using the same conditions as the optimal conditions for the reconstitution of antibody chains produced in hybridoma cells. Perry, ¶ 11 (CR-26) .

(23) Wetzel testified that he recorded in his notebook the results of a Western blot of SDS-PAGE run by Perry. He testified that from the blot they noted production of heavy and light chain protein product in the co-transformed *E.coli* cells and that they were able to estimate the level of expression (%) from cell paste from Mumford. Wetzel testified that the results were used to calculate the theoretical maximum possible yield which were in turn

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<sup>18</sup> The Cabilly et al. brief (page 19, last 5 lines-page 20, line 1) lists a number of conditions not identified by Perry in her testimony. id.

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used to calculate % yield. Wetzel, ¶ 9 (CR-25).

(24) Perry testified that she performed a refolding experiment on the cotransformed cell paste received from Mumford. The paste was sonicated and centrifuged to isolate the refractile bodies. Perry analyzed the refractile body preparations by SDS-PAGE. The sample was resuspended in urea, dialyzed, and then assayed. Later Perry analyzed another reconstitution experiment from denaturant solubilized refractile body preparations of cotransformed cells. Perry found that the heavy and light chains were insoluble, and that dialysis into urea was necessary to obtain activity. She stated “[T]he reconstitution of cotransformed cell extracts utilizing the optimal conditions for the reconstitution of hybridoma cell produced antibody chains was significantly higher than the background”. Perry, ¶ 13 (CR26-27).

(25) Wetzel testified that he and Perry, between March 18, and March 24, 1983, performed an experiment in which CEA-binding activity was generated after refolding. He testified that the results showed a refolding yield of 0.76% starting from a cotransformed cellular extract and a yield of 0.32% starting from a mixture of a heavy chain S-sulfonate and the urea-solubilize crude extract of light chain producing cells. The value of 1580 ng/ml in the cotransformed refolding reaction was significantly higher than the background levels of apparent activity obtained from controls of either heavy chain alone (441ng/ml) or light chain alone (108ng/ml); these latter values are said to arise from the non-specific binding to CEA in the assay. Wetzel concluded that this data shows “that heavy and light chain

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recombine in the refolding reaction to generate antigen binding activity". Wetzel, ¶ 11 (CR-20A).

## VI.

### The Boss et al. position

Boss et al. argue that Cabilly et al. have not established (A) prior conception or (B) an actual reduction to practice of the subject matter of the count. Boss et al. argue that the Cabilly et al. record is deficient because (1) there is no corroborated evidence of the preparation and identification of the starting DNA sequences, the expression plasmids, and the end product produced or verified dates for these activities; (2) there is no corroboration of the inventor's work; (3) the exhibits are unauthenticated as to author, content and date and are mostly illegible, and not sufficiently explained; and (4) binding activity does not establish a practical utility for the unidentified end product. Boss et al. assert that the Cabilly et al. case for priority falls within the doctrine of simultaneous conception and reduction to practice, citing Smith v. Bousquet, 111 F.2d 157, 160, 45 USPQ 347, 348 (CCPA 1940); Alpert v. Slatin, 305 F.2d 891, 894, 134 USPQ 296, 299 (CCPA 1962); Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1217, 18 USPQ2d 1016, 1021 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991); and Colbert v. Lofdahl, 21 USPQ2d 1068, 1071 (Bd. Pat. App. & Int. 1991).

## VII.

BURDEN OF PROOF

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Cabilly et al. as the junior party, whose application was copending with the Boss et al. patent, bears the burden of proving their case for priority by a preponderance of the evidence. Bosies v. Benedict, 27 F.3d 539, 541-542, 30 USPQ2d 1862, 1864 (Fed. Cir. 1994); See also Peeler v. Miller, 535 F.2d 647, 651 n.5, 190 USPQ 117, 120 n.5 (CCPA 1976); Linkow v. Linkow, 517 F.2d 1370, 1373, 186 USPQ 223, 225 (CCPA 1975); Frilette v. Kimberlin, 412 F.2d 1390, 1391, 162 USPQ 148, 149 (CCPA 1969) cert. denied, 396 U.S. 1002 (1970). See also 37 CFR § 1.657(b)[1995].<sup>19</sup>

#### REDUCTION TO PRACTICE

The issue of reduction to practice is a question of law. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1376, 231 USPQ 81, 87 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). To establish a reduction to practice of a method count, a party must show that each step of the method was performed. Szekely v. Metcalf, 455 F.2d 1393, 1396, 173 USPQ 116, 119 (CCPA 1972) . All limitations of the count have to be satisfied. Id. Such performance may be made by the inventor or someone on his behalf. A party must show that the method produced the product of the count. Blicke v. Treves, 241 F.2d 718, 720-721, 112 USPQ 472, 475 (CCPA 1957). Where the objective of the process is to produce a product having particular properties, the product must be tested to show that it has the desired properties, and that the product is satisfactory for its intended purpose,

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<sup>19</sup> 37 CFR § 1.657(b), as now amended, states that: [I]n an interference involving copending applications or involving a patent and an application having an effective filing date on or before the date the patent issued, a junior party shall have the burden of establishing priority by a preponderance of the evidence.

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which in some cases requires testing of the product. Birmingham v. Randall, 171 F.2d 957, 958-959, 80 USPQ 371, 372 (CCPA 1948). Whether a product must be tested in order to establish a reduction to practice, and if so, what tests are necessary is a question which must be decided on the basis of the facts of the particular case involved. Blicke, 241 F.2d at 720-21, 112 USPQ at 475. The character of testing varies with the character of invention and the problem it solves. Scott v. Finney, 34 F.3d 1058, 1061-1062, 32 USPQ2d 1115, 1118 (Fed. Cir. 1994). Complex inventions require laboratory tests that “accurately duplicate actual working condition in practical use” Id. When complex inventions are involved, a correlation between the test conditions and actual use conditions must be shown Id. When reviewing the sufficiency of evidence for reduction to practice a “reasonableness” standard is applied. Holmwood v. Sugavanam, 948 F.2d 1236, 1238, 20 USPQ2d 1712, 1714 (Fed. Cir. 1991). Lastly, there must be an appreciation of the existence of an embodiment of the invention and the operability of the embodiment. Estee Lauder v. L’Oreal, 129 F.3d 588, 595-595, 44 USPQ2d 1610, 1615 (Fed. Cir. 1997); Silvestri v. Grant, 496 F.2d 593, 597, 181 USPQ 706, 706 (CCPA 1974), cert. denied, 420 U.S. 928 (1975); Heard v. Burton, 333 F.2d 239, 243, 142 USPQ 97, 100 (CCPA 1964). See also, D. Chisum Int. Law & Practice §10.06[2](1995).

The reduction to practice must be corroborated in point of time. An inventor must provide independent corroborating evidence in addition to his own statements and documents. Hahn v. Wong, 892 F.2d 1028, 1032, 13 USPQ2d 1313, 1317 (Fed. Cir.

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1989); Lacotte v. Thomas, 758 F.2d 611, 613, 225 USPQ 633, 634 (Fed. Cir. 1985). Such evidence “may consist of testimony of a witness, other than an inventor, to the actual reduction to practice or it may consist of evidence of surrounding facts and circumstances independent of information received from the inventor” (our emphasis). Hahn, 892 F.2d at 1032-33, 13 USPQ2d at 1317; Reese v. Hurst, 661 F.2d 1222, 1225, 211 USPQ 936, 940 (CCPA 1981) . The purpose of the rule requiring corroboration is to prevent fraud. Berry v Webb, 412 F.2d 261, 267, 162 USPQ 170, 174 (CCPA 1969). A rule of reason applies to determine whether the inventor's testimony has been sufficiently corroborated. Price v. Symsek, 988 F.2d 1187, 1192, 26 USPQ2d 1031, 1036-1037 (Fed. Cir. 1993). The “rule of reason” involves an examination, analysis and evaluation of the record as a whole to the end that a reasoned determination as to the credibility of the inventor’s story may be reached. Berges v. Gottstein, 618 F.2d 771, 776, 205 USPQ 691, 695 (CCPA 1980); Mann v. Werner , 347 F.2d 636, 640, 146 USPQ 199, 202 (CCPA 1965). There is no single formula that must be followed in proving corroboration. Whether an actual reduction to practice has been corroborated must be decided on the facts of each particular case. Berges, 618 F.2d at 776, 205 USPQ at 695. Nonetheless, adoption of the “rule of reason” has not dispensed with the requirement that corroborative evidence must not depend solely from the inventor himself but must be independent of information received from the inventor. Coleman v. Dines, 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir. 1985); Reese v. Hurst, 661 F.2d 1222, 1225, 211 USPQ 936, 940 (CCPA

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1981); Mikus. Wachtel , 542 F.2d 1157, 1159, 191 USPQ 571, 573 (CCPA 1976). Thus where, as here, the process is carried out by the inventors, there must be corroborated evidence that all the limitations as to materials, properties, steps and results required by the count were present in the work performed. Land v. Regan, 342 F.2d 92, 101, 144 USPQ 661, 669 (CCPA 1965) ; Vandenberg v. Reynolds, 268 F.2d 744, 747, 122 USPQ 381, 383 (CCPA 1959).

#### VIII.

#### OPINION ON PRIORITY

We find that based on the record before us, Cabilly et al. have not proved, by a preponderance of evidence, an actual reduction to practice of the invention in issue prior to March 25, 1983.

#### A. Exhibits

As noted previously, Boss et al. have challenged the Cabilly et al. exhibits on the basis of lack of authentication as to author, date, and content.

Authentication is defined as “genuineness” and is said to be established, when it is proved to be the thing it is supposed or represented to be. Rivise & Caesar, 1940, Vol IV, §563, page 2418; see also FRE 901. An exhibit may be authenticated by oral testimony of a witness but not by the uncorroborated testimony of the party on whose behalf it is offered in evidence. Hence, a witness must properly identify the exhibit<sup>20</sup> as to what it is

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<sup>20</sup> Extrinsic evidence of authenticity as a condition precedent to admissibility is not required for self-authenticating evidence. See FRE 902.

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as well as to explain the witness' relationship to the document in question. In addition, authenticity of an exhibit must be established both as to subject matter (content) and time.

Rivise & Caesar, Vol IV, § 563, page 2418.

Documents do not speak for themselves.<sup>21</sup> They must be explained even if they contain a label and a date. Further, 37 C.F.R. § 1.671(f)<sup>22</sup> requires a witness to explain the entries on the various pages of the notebooks/exhibits. This explanation provides the opponent

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<sup>21</sup> Amoss v. McKinley, 195 USPQ 452, 453-454 (Bd. Pat. Int. 1977). The extent to which an exhibit is explained depends on the simplicity or complexity of the subject matter as well as technical background of tribunal hearing the case. Rivise and Caesar Vol. III, § 435, page 1891. Herein, because of the complexity and the terminology used in the biotechnical arena, it is most imperative that a witness' explanation as to authorship and content of a document be sufficiently clear and detailed as to the specific entries in the exhibits relied upon by a witness in order for the Board to make a proper analysis of the record. It is not sufficient to provide a bare allegation that certain work was done citing certain pages of notes or notebooks attached to the affidavit or declaration. It is not the burden of the Board to try to read the exhibits and to correlate allegations made in the testimony with specific entries. Amoss, citing Gipstein v. Contois, 191 USPQ 688, 690 (Bd. Pat. Int. 1975); and Golota v. Strom, 489 F.2d 1287, 1292-1293, 180 USPQ 396, 400-401 (Bd. Pat. Int. 1975); Triplett v. Steinmayer, 129 F.2d 869, 871-872, 54 USPQ 409, 411-412 (CCPA 1942); Chandler v. Mock, 150 F.2d 563, 567-568, 66 USPQ 209, 213-214 (CCPA 1945); Teel v. Cotton, 151 USPQ 428, 430-431 (Bd. Pat. Int. 1966); Popoff v. Orchin, 144 USPQ 762, 763 (Bd. Pat. Int. 1963); and In re Borkowski, 505 F.2d 713, 194 USPQ 29 (CCPA 1974).

<sup>22</sup> C.F.R. § 1.671(f) states that "[T]he significance of documentary and other exhibits shall be discussed with particularity by a witness during oral deposition or in an affidavit." See Notice of Final Rule at 48447, col. 3, 1050 Off. Gaz. Pat. Office at 416, in 1984 the rules were amended to require the particularized explanation of material in non-self authenticating documents. The commentary explained that "[B]y providing in the rules that documentary evidence must be explained, the PTO hopes to save both parties and the Board considerable difficulty in presenting and evaluating evidence."

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party and the Board a basis to determine whether the witness' testimony is supported by contemporaneous documentation or whether a party is relying upon the witness' oral testimony.

While the record index, page v, refers to CX-20 as Cabilly's notebook,<sup>23</sup> Cabilly himself provides no testimony regarding the identity of the exhibit, the specific entries in the exhibit or any date the work was done except for his initial statement of when he received the cells. No other declarant identifies this exhibit. Our review of CX-20 shows that it consists of a series of loose-leaf pages that are unsigned and unwitnessed. The entries on the pages are either pasted in or handwritten<sup>24</sup> and are difficult to read and understand because of legibility as well as the extensive use of abbreviations and acronyms. While a few pages appear to bear dates, the dates on the pages are not in chronological order. (See for example Feb. 8, 83 (Bates page 991) and Jan. 21, 83 (Bates Page 998). We find CX-20 unauthenticated and of no probative value.

The record index, pages iv and v, identifies CX-11 and CX-13 as Holmes' notebook and CX-12 as Wetzel's notebook. Wetzel does not identify CX-12 as his notebook and makes no mention of this exhibit in his declaration. Holmes parenthetically refers to CX-11, 12 and 13 in his declaration but never identifies these documents as his

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<sup>23</sup> Notebooks are not self-authenticating. FRE 902.

<sup>24</sup> Where a party submits a handwritten exhibit, the Board should not be expected to decipher it. If the exhibit is a handwritten document, a typed copy of the document should be provided on a separate piece of paper and attached to the exhibit. Cf. Latimer v. Wetmore, 231 USPQ 131 (Bd. Pat. App. & Int. 1985).

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notebooks. Our review of CX-11 shows it to be a notebook No. 1446 issued to Holmes consisting of unwitnessed pages with mostly illegible handwritten entries, abbreviations and acronyms, along with a number of attachments. Our review of CX-12 and CX-13 shows them to consist of spiral bound notebooks containing a series of pages of mostly illegible handwritten entries containing deletions, abbreviations and acronyms, and with a number of attachments. The pages are unsigned and unwitnessed. The dates that do appear on various pages of CX-12 are not in chronological order. CX-11, 12 and 13 are non-probative.

CX-6 is identified by Wetzel as one of three notebooks (CX-6, CX-8 and CX-9) that he reviewed in reconstructing the work he and Perry did on this project. Our review of the CX-6 shows it to be a notebook issued to Wetzel, and consists of handwritten entries, mostly illegible, unsigned, unwitnessed and undated except for Bate page Nos. 64 and 87. CX-2 is identified by Riggs as a proposal he wrote. CX-2 and CX-6 have been identified as to author. However, questions as to content and date as well as corroboration remain.

Both Perry and Rey indicate that it was their practice to date their notebooks and then parenthetically refer to CX-8 and CX-15, respectively. Perry does not identify CX-9 as her notebook. Mumford testifies that he or someone under his supervision recorded receipt of cultures and fermentations of the same into CX-17 and CX-18. Even assuming arguendo that CX's-8, 9, 15, 17 and 18 have been adequately identified as the corroborator's notebooks, the issue of whether these exhibits have been adequately

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explained as to content and date remain.

Cabilly et al. allege that the parties had a stipulation that in the event that verification of information such as the dating of notebooks was necessary, the original would be furnished. (Reply brief, page 9) Contrary thereto, the stipulation (Record, vi-ix) does not reflect any agreement with respect to dates on the exhibits.

Cabilly et al. also allege that Boss et al. failed to cross-examine the witnesses. However, we will draw no adverse inference from Boss et al.'s failure to cross-examine because it is fundamental that after the junior party has made its case-in-chief that if a senior party upon examination thereof is of the opinion that the record made by the junior party is not sufficient to establish priority, there is no compulsion upon senior party to present any evidence whatsoever. Senior party has the right to stand on its position that junior party has failed to make his case. Teter v. Kearlby, 169 F.2d 808, 814, 79 USPQ 65, 70 (CCPA 1948); and Cf. Boises v. Benedict, 27 F.3d at 541-542, 30 USPQ2d at 1864 (Fed. Cir. 1994); citing Linkow, 517 F.2d at 1373, 186 USPQ at 225.

#### B. Essential Limitations of the Count

In the Cabilly et al. proofs, Cabilly et al. focus upon the production of an IgG molecule containing the heavy (Gamma) chain and light chain of CEA.66-E3 antibody. In order for Cabilly et al. to prove priority based upon an actual reduction to practice of the process count, Cabilly et al. must prove by a preponderance of the evidence that they carried out each step of the process and that the process actually results in the production

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of an IgG molecule comprising the heavy and light chain of the CEA.66-E3 antibody, and that such product is useful.

We find that Cabilly et al. have failed to show the essential elements of the count, to wit: (1) the first and second DNA sequences of the heavy and light chain of CEA.66-E3 antibody, and (2) that the separate molecules expressed contain the heavy and light chain of CEA.66-E3 antibody. In addition, Cabilly et al. have failed to show production of the IgG molecule of CEA.66-E3 antibody and that such product is useful.

Cabilly et al. argue that the heavy and light chains of the anti-CEA antibody were cloned and sequenced by the end of October, 1982, citing CR-30 and CR-33. In support of this argument, Cabilly et al. rely upon Holmes' testimony that Rey sequenced both the light chain and heavy chain DNA inserts. Holmes' testimony requires corroboration. A review of Rey's testimony indicates that he only assisted in sequencing of the heavy and light chain cDNA's. Rey has not explained what he meant by "assisted", what the results were from such alleged sequencing and when such work was done. CX-15 contains various attachments as well as handwritten entries which are not at all legible. This notebook, CX-15, as best that we can review it, does not appear to contain DNA sequences for the heavy and light chain of CEA.66-E3 antibody. Rey's parenthetical reference to certain pages of CX-15 in his declaration are deemed insufficient to explain the entries on the pages or when this work was done. In our view, Rey's testimony, some nine years after the alleged activities, and his alleged notebook are insufficient to identify

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or corroborate the identity of the DNA sequences encoding for the heavy and light chain of CEA.66-E3. Corroboration must consist of factual evidence as to what was done, not of broad generalizations or conclusions. Murphy v. Eiseman, 166 USPQ 149, 150-151 (Bd. Pat. Int. 1970); Azar v. Burns, 188 USPQ 601, 605 (Bd. Pat. Int. 1975).

Cabilly et al. contend that the heavy and light chain sequences were confirmed by Holmes and Rey (Brief, page 24) . The Cabilly et al. contention that Rey confirmed the sequences is unsupported by Rey. Holmes testified that he and Heyneker analyzed the sequences.<sup>25</sup> This testimony requires corroboration and none is offered.

On this record, Cabilly et al. point to no evidence which identifies the first and second DNA sequences encoding the heavy and light chains of CEA.66-E3 antibody and thus such argument is but attorney argument. Meitzner, 549 F.2d at 782, 193 USPQ at 22.

As to the separate molecules expressed, Cabilly et al. argue that Perry analyzed by SDS-PAGE the cotransformed cell culture she received. While it is true that Perry testified that she analyzed a sample supplied to her by Cabilly, this record does not establish that the sample was labeled, how it was transferred between City of Hope and Genentech, what the results of the run were with respect to the unlabeled sample and the meaning, if any, of such results. Perry reference to CX-8, pages 149-151 for contemporaneous documentation is deemed inadequate in view of the fact that the entries on the pages and

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<sup>25</sup> The Cabilly et al. Brief (page 10, sec. 3) alleges that the work on the light chain was done on or about October 28, 1982 and for the heavy chain on or about October 18, 1982. This is an unsupported allegation. Meitzner, 549 F.2d at 782, 193 USPQ at 22.

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time of work are not fully explained. These pages are illegible and also contain unexplained attachments.

Cabilly et al., in their brief, page 16, argue that the SDS-PAGE gel run by Mumford showed that each of these transformants, GGLH-1 and GGLH-2, was expressing both heavy and light chains. (our emphasis). They also argue in their reply brief, page 17, that Mumford testified that:

“Analysis by SDS-polyacrylamide gel electrophoresis (PAGE) show[ed] a band in the 55kD region which is the expected molecular weight of the heavy chain product,” (Mumford, CR-37, ¶10) “ SDS-PAGE analysis indicated product expression at the 23.5kD molecular weight range which was expected for light chain product,” (Mumford, CR37-38, ¶12) and then finally that SDS-PAGE showed that the cotransformed cells expressed both the heavy and light chain of the antiCEA-antibody.(our emphasis)

Initially we note that this record never identifies the origin of GGLH-1 and GGLH-2, that is, who made them, the process used to make them, and what DNA they contained. Contrary to the Cabilly et al. arguments, Mumford never testified that the SDS-PAGE gel of GGLH-1 and GGLH-2 showed expression of both the heavy and light chain(our emphasis). Mumford testified to an expectation <sup>26</sup> and not to what he actually found.<sup>27</sup> The

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<sup>26</sup>Mumford actually stated: [T]he products that were expected from these fermentation runs were both the light and heavy chain of an anti-CEA antibody. SDS-PAGE shows protein expression from the time course samples. I recorded that the fermentation run No. GGLH-1 was harvested and that the 80 grams of wet biomass paste was given to Dr. Ron Wetzel. Fermentation GGLH-1 demonstrated refractile bodies upon microscopic analysis. (¶ 13). (CR-38).

<sup>27</sup>Mumford’s entry in his notebook No. 18, at page 31 (Bates 730) actually appears to contradict the Cabilly et al. arguments. Mumford states (as best that we can read the (continued...)

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analysis of the cultures noted by Mumford at CR-37, ¶ 10 and at CR-37-38, ¶ 12 are those of the heavy chain or light chain transformed cells and are not of cotransformed cells.

SDS-PAGE of refractile body preparations does not and cannot identify and verify the production of the intended product because the refractile body preparations made by *E.coli* require lysis and solubilization to permit recovery and then refolding of the recovered heavy and light chains. Cabilly et al. offered no evidence to identify and verify the refolded product as the intended protein product of the count.

A demonstration of binding activity in an assay does not establish that all of the steps of the process have been performed and that the intended product was produced. No declarant asserted that a conclusion as to the chemical composition or structure could be drawn from the binding activity data. Schendel v. Curtis, 83 F.3d 1399, 1403-1404, 38 USPQ2d 1743, 1747 (Fed. Cir. 1996); Colbert, 21 USPQ2d at 1071. Because the intended product has not been identified and verified there can be no appreciation of the existence or operability of the intended product.

While the question of utility is actually moot, we add the following comments for completeness. Herein, the count does not set forth a particular utility for the intended product of the count. Evidence of substantial utility for any purpose is sufficient to prove

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<sup>27</sup>(...continued)  
entry): “[T]he gels are shown on [the] following pages. No real strong product bands could be seen on either gel. It is possible that trace metal contamination would have occurred in the new fermentors due to condensation pick-up during sterilization.”

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reduction to practice. Cabilly et al. have chosen to rely upon a difference between an assay value of an alleged reformed product and an antigen and the background values of the heavy and light chain individually. Cabilly et al. conclude that such data shows recombination and utility. Cabilly et al. urge that binding activity to the antigen which binds the known hybridoma antibody is sufficient to prove the utility of the recombinantly produced antibodies.

We disagree with Cabilly et al. that such testing establishes practical utility.

This record does not identify the antigen used in the binding assay and its relationship to the original source of immunoglobulin cDNA.

Cabilly et al. have provided no testimony which explains how a comparison of an assay value of an allegedly reformed antibody of CEA.66-E3 bound to an unidentified antigen and the background values of the individual unfolded chains is indicative of practical utility. Practical utility is a shorthand way of attributing "real world" value to the claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public. Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980). We acknowledge that assays, in general, are useful for immunological diagnostic testing to detect or quantitate antigens or antibodies in solution. Antibodies and antigens bind; how they bind, that is, how complementary the antibody and antigen are to one another and the strength of the bond between the antibody and antigen is determinative of the specificity of the antibody-antigen

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reaction. If in an assay, an antibody is used to detect the presence of or quantity of the antigen which elicited the initial response of the antibody-producing cell used in producing the hybridoma cell line, practical utility may be shown because the antibody and antigen which elicited it have a unique relationship and the specificity and sensitivity of that relationship would be known and used as a control. Where an antigen other than that which elicited the antibody is used, binding may occur, however such binding, that is, cross-reactivity is not indicative of practical utility but may lead to false positives in diagnostic testing. Thus, any assay to be reliable requires investigation of the sensitivity and specificity of the antibody-antigen reaction. On this record, we are unable to conclude that the testing is adequate since neither a correlation between the test conditions and actual use conditions is established nor is the sensitivity and specificity of the recombinantly produced antibody with regard to any antigen and the reformed product and same antigen established.

Cabilly et al. allege that the authenticity and identity of the cell line from which the known anti-CEA antibodies and recombinant Ig molecules were derived was attested to by Shively and his reference to Cabilly et al. CX-4. We do not find this argument persuasive. Shively provided no specific testimony with respect to CX-4 other than to provide a statement that a mouse hybridoma cell line was generated, CEA.66-E3, which secretes antibodies directed against human carcinoembryonic antigen and to parenthetically refer to CX-4 in that statement. Our review of CX-4 shows it to be an article entitled

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“Monoclonal Antibodies for Carcinoembryonic Antigen and Related Antigens as a Model System: A Systematic Approach for the Determination of Epitope Specificities of Monoclonal Antibodies,” authored by several persons including Shively, published in May, 1983, after the date accorded to Boss et al. The significance of this document with respect to the cells made and given to Riggs in February 1981 has never been explained. Moreover and contrary to Cabilly et al. allegations (brief, page 9<sup>28</sup> and reply brief page 12), no one gave detailed testimony explaining exactly how the cell line, CEA.66-E3, was prepared, how the antibodies produced therefrom were characterized, and what, if any, epitope specificity the antibody has. Statements in the brief cannot take the place of evidence in the record. Meitzner, 549 F.2d at 782, 193 USPQ at 22.

In addition to not having established all the steps of the process, the production and appreciation of the intended product and the usefulness of the same, we find after a reasoned examination, analysis and evaluation of all the pertinent evidence relied upon by Cabilly et al. that the work allegedly done by inventors stands uncorroborated.

Cabilly alleges that he received the cell line, CEA.66-E3, from Shively in September of 1981 and extracted the mRNA therefrom. Cabilly’s oral testimony regarding the obtention of the cell line is not confirmed by Shively.

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<sup>28</sup> Cabilly et al., in their brief (page 9), argue that the CEA.66-E3 cell line prepared by Shively and given to Riggs in February 1981, was produced by polyethylene glycol (PEG) fusion of cells from a myeloma cell line Sp2/0-Ag 14 with splenocytes from female BALB/c mice which had been immunized with CEA, at a ratio of 1:3, citing Shively CR-17 and CX-4.

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While Cabilly indicates that he sent the mRNA to Holmes, Holmes' testimony indicates that the mRNA was from an unnamed source at City of Hope. And while Cabilly et al. would have us accept that Holmes received the cell line from Cabilly based on Cabilly's testimony, it is well settled that joint inventors cannot be corroborators. Kendall v. Dickinson, 195 USPQ 605, 614 (Bd. Pat. Int. 1975). It should be noted that the record never establishes that these inventors were working in the same laboratory; note that City of Hope is said to be in Duarte, California, and Genentech in San Francisco, California. Moreover, here, as well as throughout this record, samples made are not labeled and no chain of transfer of the samples between the declarants is ever established. id.

Holmes testifies that he prepared an *E.coli* cDNA library. Cabilly et al. (RB-13) alleges that Holmes gave the cells on agar plates to Rey. Rey is identified as a research assistant at Genentech who reported to Heyneker not Holmes. There is no testimony that the cultures received were labeled and Rey never testified when he got or from whom he got the cultures or to whom he gave the filters. Moreover, Rey never testified that he analyzed the cultures and thus there is no independent corroboration as to the content of the cultures.

Holmes alleges that he received from the Genentech lab oligonucleotides which he used to prepare light and heavy chain oligonucleotide probes to hybridize with the filters. On this record, the oligonucleotides are not identified. Holmes did not testify as to how he

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designed the probes.<sup>29</sup> And no one corroborated the oligonucleotide request, what the actual request was, and the making of such probes and the transfer of such probes to Holmes. Cabilly et al. argue that it is irrelevant that Holmes (1) did not identify from whom in the lab he received oligonucleotides and (2) did not examine the sequence of oligonucleotides he received because he used the oligonucleotides for its intended purpose and sequenced the resulting clones. We disagree. Holmes testimony requires corroboration. Corroboration may be by a witness or by

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<sup>29</sup> Prior to 1983, there were only three approaches to designing oligonucleotide probes to screen libraries. Amgen Inc. v. Chugai Pharmaceutical Co., 13 USPQ2d 1737 (D. Mass. 1989) .

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circumstantial evidence independent of the inventor. We find neither. The count requires the use of specific DNA encoding an Ig molecule [herein CEA.66-E3 antibody] These sequences are material limitations in the count. The question is how one obtains and verifies such materials.<sup>30</sup> In order to isolate a gene of interest from a cDNA library, the library is first denatured and then screened with a probe which may bind or hybridize under specific conditions with a complementary strand. In addition, the probe must not bind with identical portions of a gene for other proteins thereby resulting in the retrieval of a gene other than the one of interest. Thus, the identity of the DNA sequence that complexes with the probe and forms the hybridized product is directly related to the identity of the oligonucleotides used as probes and to the conditions used. Holmes also alleges that he sequenced the resulting clones. Such allegation stands uncorroborated. There is no evidence of record to indicate that the first and second DNA molecules used were ever obtained, identified and verified.

Cabilly et al., in their brief (page 24), asserts that the expression plasmids for the heavy and light chains, pKCEAtrp207-1\*delta and pGammaCEAInt2, respectively, were constructed by Cabilly and Holmes and confirmed with the assistance of Rey by about December, 8, 1982. Reduction to practice must be completely corroborated in point of

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<sup>30</sup> Cabilly et al. alleged that the DNA sequence encoding various Ig heavy and light chains were known by 1981. (CS Brief, p. 2) There is no evidence in this record to support this allegation. Meitzner, 549 F.2d at 782, 193 USPQ at 22.

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time. Neither inventors Cabilly and Holmes nor corroborator Rey testified to when the alleged constructions and confirmations were done. Meitzner, 549 F.2d at 782, 193 USPQ at 22. Cabilly's and Holmes' testimony with respect to the making and confirming the constructs requires corroboration. Holmes indicates that he made pGammaCEAInt2, an expression plasmid said to contain the heavy chain of CEA.66-E3 antibody. He does not indicate what he did with this expression plasmid after making it. Cabilly et al. in their brief, allege that his work was done on or about December 2, 1982. This allegation is unsupported. The process involved a series of complex steps. See Cabilly et al. case, ¶ 11, supra. Cabilly indicates that he made pKCEAtrp207-1\*delta, an expression plasmid said to contain the light chain of CEA.66-E3 antibody, by initially modifying pKCEAtrp207-1.\* Cabilly et al., in their brief, have not presented any citation to the record or argument as to who made pKCEAtrp207-1,\* how it was made, what DNA sequence it contained or how Cabilly got it.

Rey's limited testimony that he sequenced a fragment of the light chain following a primer repair reaction (Cabilly et al. case, ¶ 9, supra, Rey ¶ 5, CR-34) does not and can not corroborate the making or confirmation of both of these two expression plasmids or the identity of the first and second DNA sequence of the count. Hence, Holmes' and Cabilly's testimony with respect to the making and confirmation of the expression plasmids said to contain the heavy and light chain of CEA.66-E3 antibody stands uncorroborated. An inventor's statements are self-serving and have no corroborative value. The record before

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us does not show or confirm the structure of the expression plasmids.

Cabilly testified that he cotransformed *E.coli* with pKCEAtrp207-1\*delta and pGammaCEAInt2 and expressed refractile bodies. Cabilly et al. allege in their brief (page 14, sec. 4) that this work was done on or about January 21, 1983. Cabilly did not provide any dates with respect to this work. Therefore, the Cabilly et al. allegation as to when this work was done is but attorney argument. Id. Cabilly's testimony requires corroboration.

For corroboration, Cabilly et al. allege that Perry received a sample of cotransformants from Cabilly and that she analyzed these transformants by SDS-PAGE.<sup>31</sup> While it is true that Perry testified that she received a sample from Cabilly neither Cabilly nor Perry testified as to the label on the sample and the chain of transfer between the City of Hope and Genentech. SDS-PAGE analysis by Perry was performed on an unlabeled and unidentified sample. Perry's testimony, in our view is insufficient to corroborate Cabilly's alleged work, since she did not have first-hand knowledge of how the sample was made or whether it was made according to the process recited in the count. Her analysis by SDS-PAGE of such sample would not establish how the sample was made or whether it was produced by the process of the count and produced the intended Ig molecule of CEA.66-E3. It would appear that she derived all of her information with respect to the sample from Cabilly. The burden is on Cabilly et al. to prove that information was not

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<sup>31</sup> The Cabilly et al. brief (page 17) alleges that the SDS-PAGE was run on January 21, 1983. Perry did not provide any date for this run.

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derived from the inventor. Zoiss v. Nix, 185 USPQ 419, 421-422 (Bd. Pat. Int. 1974).

Further, since SDS-PAGE is but a technique to separate proteins or nucleotides by size and the sample allegedly contained refractile bodies, neither Perry nor any other witness explained the results of this run, what such analysis would establish or how one would know from the data of the run that the process of the count had been successfully performed and the intended product made.

Cabilly et al. also allege that Mumford received these cotransformed cells on February 2, 1983. This allegation is not corroborated by Mumford. Mumford testified that he received from Heyneker's lab, on February 2, 1983, samples labeled W3110/ p10<sub>2</sub> and W3110/p6<sub>2</sub> said to contain the heavy and light chain of CEA.66-E3 antibody. There is no indication in this record that Cabilly labeled his sample(s) as W3110/ p10<sub>2</sub> and W3110/p6<sub>2</sub> and transmitted them from City of Hope to Mumford at Genentech. Mumford provides no first hand knowledge as to who made these samples, whether the samples were made according to the process of the count, and whether the samples contained the separate molecules of the heavy and light chain of CEA.66-E3 antibody. Id. Mumford's testimony (CR-36, ¶ 7, and ¶ 17 of case in chief) identifying these two organisms as E.coli strains that had been cotransformed with two plasmids for coexpression of heavy and light chain of an anti-CEA antibody is not independent of the inventor. Hahn, 892 F.2d at 1032, 13 USPQ2d at 1317; Reese, 661 F.2d at 1225, 211 USPQ at 940.

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Cabilly indicates that he refolded the material obtained from the refractile bodies and assayed the refolded protein in an assay to detect active anti-CEA antibody. Cabilly et al. brief (page 21) alleges that this was done on February 8, 1983. There is no testimony with regard to the date of this work. Meitzner, 549 F.2d at 782, 193 USPQ at 22. There is no testimony or evidence to corroborate the Cabilly's testimony regard this testing. Cabilly et al. allege that the assay demonstrated effective refolding of the heavy and light chains which produced antibody that bound antigen at a level significantly higher than background. However, the testimony of an inventor is not by itself effective to prove reduction to practice in the absence of corroboration. White v. Habenstein, 219 USPQ 1213, 1217 (Bd. Pat. Int. 1983). Cabilly's testimony stands uncorroborated and does not establish that Cabilly et al. identified a product of the count or its usefulness.

Cabilly et al. urge that we need look no further than the Wetzel and Perry tests demonstrating immunological activity for the refolded antibody to determine that Cabilly et al. have proven actual reduction to practice. We disagree. There is no testimony that a demonstration of binding activity of an unidentified product would establish an actual reduction to practice of the process of the count. Without explaining the entries on pages 87-88 of CX-6, Wetzel testified that he and Perry conducted an experiment in which "CEA-binding activity was generated after refolding" and that they found refolding yield percentages and binding levels. He concluded that "the data shows that the heavy chain and light chain recombine in the refolding reaction to generate antigen binding activity.

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(CR-20A, ¶ 11, see also ¶ 25, supra, in Cabilly et al. case). However, he did not explain exactly what sample was tested, how it was tested, and what antigen was used. Further he did not explain how this test and the results of such test establish practical utility. Further, Wetzel's testimony and documentation are self-serving and require corroboration.

Perry does not identify the sample tested, the test performed, the results of any testing or when the tests were performed. Corroboration must be independent of the inventor and must be to point in time. She simply states at various places that "samples" were assayed. (CR-27, ¶ 13). She also did not explain how this testing established a practical utility. Further, Perry does not corroborate Wetzels' testimony regarding refolding yield percentages, the value of the refolding process and the levels of chains allegedly expressed in the transformations.

Cabilly et al. argue that they have shown that there was a well defined "network" of researchers involved in this project, who maintained reasonable records of their activities and who worked together to achieve an actual reduction to practice of the invention. We do not find the Cabilly et al. argument persuasive. As noted, supra, not all of the researchers were employed by Genentech nor did they maintain reasonable records. The researchers did not label their samples nor provide a chain of custody for transferring the samples between the two companies in different cities. In addition, we cannot conclude that Cabilly et al. maintained reasonable records because of the lack of authentication and explanation of the exhibits.

Lastly, Cabilly et al. argue in their reply brief (page 16) that Cabilly testified that he ligated fragments I, II and III and transformed them into *E.coli* and that he later retransformed these cells to get cotransformed cells potentially expressing both the heavy and light chains; that Rey corroborates this testimony because he analyzed these transformants by restriction analysis and sequencing before Boss et al.' March 25, 1983 filing date. Cabilly et al. in their brief set forth their scenario for priority and included the work of Cabilly et al. in ligating fragments I, II and III to prepare pGammaCEAFABtrp207-1\* (identified by Cabilly et al. as a plasmid vector for the direct expression of the FAB fragment of the heavy chain gene) (see ¶ 15, Cabilly et al. case). However, they did not rely upon Cabilly's testimony that he later retransformed these cells potentially expressing both heavy and light chains. Moreover, there are no arguments in the Cabilly et al. brief directed to the work of Cabilly et al. in the preparation of pGammaCEAFABtrp207-1\* transforming these into *E.coli* nor to the cotransformation of this heavy chain with a light chain. Hence, both of these new arguments are not entitled to any consideration.<sup>32</sup>

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<sup>32</sup> Even assuming arguendo that Cabilly et al. relied upon this testimony and made such an argument in their brief, such testimony would not be deemed sufficient to establish an actual reduction to practice as now alleged because an inventor's testimony and documentation are self-serving and have no corroborative value. Moreover, while Rey testified that he analyzed the transformant pGammaCEAFABtrp207-1\*, there is no corroborating evidence of record with respect to Cabilly's alleged work on any cotransformation involving pGammaCEAFABtrp207-1\*. There is no evidence proffered to establish (1) what Rey found upon sequencing the heavy chain transformant, (2) whether Rey sequenced a light chain transformant; (3) whether Rey analyzed a cotransformant containing plasmid(s) containing the heavy and light chains of CEA.66-E3 antibody; and  
(continued...)

II.

**Conception**

We find that the Cabilly et al. record does not establish a complete conception of the count in issue prior to the March 25, 1983, date accorded to Boss et al. Without an earlier conception than the date accorded Boss et al., the issue of reasonable diligence by the inventors to a reduction to practice is moot and the evidence relating to diligence has not been considered herein.

Conception is a question of law. Kridl v. McCormick, 105 F.3d 1446, 1449, 41 USPQ2d 1686, 1688-1689 (Fed. Cir. 1997); Bosies v. Benedict, 27 F.3d at 542, 30 USPQ2d at 1864; and Fiers v. Revel, 984 F.2d 1164, 1168-1169, 25 USPQ2d 1601, 1604 (Fed. Cir. 1993). Conception is defined as the formation “in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice.” Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1376, 231 USPQ at 87-88 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987) ( citing 1 Robinson on Patents 532 (1890), Coleman, 754 F.2d at 359, 224 USPQ at 862; (quoting Gunter v. Stream, 573 F.2d 77, 80, 197 USPQ 482, 484 (CCPA 1978)). By this definition, conception consists of two parts, the idea and the means to carry out the idea.

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(...continued)

(4) what the DNA sequence analysis results of the individual transformants were, what product was produced on expression, what product was produced after refolding, and whether there was utility testing for the product.

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Conception must include every feature or limitation in the count, and every limitation must have been known to the inventor at the time of the alleged conception. Coleman, 754 F.2d at 359, 224 USPQ at 862. Conception of an inventive process involves proof of mental possession of the steps of an operative process and, if necessary, of means to carry it out to such a degree that nothing remains but routine skill for effectuation thereof. Alpert v. Slatin, 305 F.2d 891, 894, 134 USPQ 296, 299 (CCPA 1962). Since, conception takes place in the mind of the inventor, additionally there must be disclosure to and corroboration by a third party. For it is well settled that the inventor's testimony standing alone, is insufficient to prove conception Price, 988 F.2d at 1193-1194, 26 USPQ2d at 1036. In evaluating whether there is conception, a rule of reason is applied, the rule does not however dispense with the requirement of some evidence of independent corroboration. Coleman, 754 F.2d 360, 224 USPQ at 862.

For conception, Cabilly et al. rely upon Riggs' testimony, on CX-2 and also upon discussions that Riggs is said to have had with Shively regarding the strategy for bacterial expression of immunogloblins.

The conception analysis necessarily turns on the inventor's ability to describe his invention with particularity. Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d 1223, 1227-1228, 32 USPQ2d 1915, 1919 (Fed. Cir. 1994). Coinventor Riggs, in his testimony, testified that he formulated a proposal which suggested that a "single bacterial strain could be constructed which contained both heavy and light chain genes for co-

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expression...”; and submitted the proposal to Genentech on October 5, 1981 (citing CX-2 and Bates page 922). While Riggs’, in his testimony identifies CX-2 as a proposal he formulated and forwarded to Genentech on October 5, 1981, his testimony is insufficient to establish a complete conception since he does not explain what specific passage(s) of Bates page 922 support his conclusory statement or how any part of Bates page 922 “contains all the elements of Count 1” as alleged in their brief. (CB-24, first paragraph) Amoss, 195 USPQ at 453-454. Exhibits do not speak for themselves. We find no explanation as to how the statement “a single bacterial strain could be constructed which contained both heavy and light chain genes for co-expression” satisfies the terms of the count and shows that every limitation of the count was known by the inventor at the time of the alleged conception. Coleman, 754 F.2d at 359, 224 USPQ at 862. Each express limitation of the count is considered material and cannot be disregarded. Schur v. Muller, 372 F.2d 546, 551, 152 USPQ 605, 609 (CCPA 1967). The count requires employing a first and second DNA sequence encoding for at least the variable regions of the heavy and light chain of an Ig molecule. In addition, the process requires the production of specific product. There is no evidence in this record that establishes that the inventors were in possession of the DNA encoding for the heavy and light chains of the IgG antibody produced by CEA.66-E3 cell line or any other antibody and the means for producing an active antibody product. Hence, the idea is not so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without

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extensive research or experimentation. Burroughs, 40 F.3d at 1230, 32 USPQ2d 1921. Riggs' testimony and exhibit are also deficient, in that there is no corroboration independent of the inventor. Herein, no third party testified regarding receipt of CX-2.

For conception, Cabilly et al. also rely upon a conversation between Riggs and Shively as to the Riggs' proposal. We also do not find Riggs' testimony that he discussed the proposed project with Shively and Shively's testimony that he recalled having some conversations "regarding the cotransformation of E.coli with plasmids containing heavy and light chain genes " sufficient to establish corroborated conception of the count in this interference. There is no testimony as to when and where this conversation took place, who was present, and exactly what the conversation was and how such alleged conversations satisfy all the limitations of the count. The testimony by both of these witnesses regarding the alleged conversation is conclusory and it fails to explain how Riggs' discussion and corroborator's Shively's vague recollection of some earlier conversations establish a complete conception of the subject matter of the count. We find Riggs' and Shively's oral testimony, given some nine years after an alleged conversation, unsupported by any contemporaneous documentation or physical evidence, unreliable and of little probative value.

Boss et al. urges in his brief, that this case is one which comes under the doctrine of conception and simultaneous reduction to practice because of the unpredictability of the technology. Smith, 111 F.2d at 160, 45 USPQ at 348; Alpert, 305 F.2d at 894, 134

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USPQ at 299; Amgen, 927 F.2d at 1217, 18 USPQ2d at 1021; and Colbert, 21 USPQ2d at 1071. If after the claimed conception date extensive research was found necessary before achieving minimum satisfactory performance obviously the mental embodiment of that date was a mere hope or expectation, a statement of a problem, but not an inventive conception Alpert, supra.

We agree with Boss et al. that on the record before us, this case is one where conception and reduction to practice must be concurrent. The record shows that by March 25, 1983 it was known, at least theoretically, that the recombinant DNA approach may be applied to the production of any heterologous polypeptide or protein in a suitable host cell, provided that appropriate DNA coding sequences can be identified and used to transform the host cell. And that indeed a number of heterologous protein were produced by bacteria however all of these were single chain polypeptides or proteins. (Boss et al. patent col. 1, lines 15-65) Thus the construction of plasmids, the transformation of cells and expression of single chain genes in a single cell were routine. However, there is no evidence that immunoglobulins, multiple chains proteins, had been produced by recombinant DNA techniques from a single host cell prior to March 25, 1983. (See Boss et al. patent, column 1).

Rather the evidence of record establishes that Riggs had but a research plan. He testified that he intended "to explore the possibility of producing antibodies in bacteria." and suggested that "a single bacterial strain could be constructed which contained both

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heavy and light chain genes for co-expression” (emphasis added) (CR-15, ¶ 3). The written proposal indicates that Cabilly et al. would construct a strain carrying both heavy and light chain genes and “try to get in vivo assembly of active antibody” (emphasis added) (CX-2, Bates No. 922). In addition, Wetzel testified (CR-20, ¶ 4-5) that a major hurdle as to expression of immunoglobulin in *E.coli* was expected to be in the folding of the protein.<sup>33</sup>

Riggs' and Wetzel's testimony as well as CX-2 provide a clear indication that the contemplated process was not a complete idea of the process of the subject matter of the count which would allow the skilled worker to carry out the process of the count in issue. Herein, the evidence indicates that Cabilly et al. had but a hope or wish to produce active antibodies in bacteria; and, there is no supporting evidence to establish the development of the means to accomplish that result or evidence of a disclosure to a third party of a complete conception. Conception is not the perception or realization of the desirability of producing a certain result; rather it is the perception or realization of the means by which the result can be produced. *Rivise & Caesar Vol. I, § 110, page 317*. Accordingly, Cabilly et al. were unable to establish conception until Cabilly et al. reduced the invention to practice through a successful experiment.

Cabilly et al. continually argue that they established conception when the genes encoding the Ig heavy and light chains were isolated and sequenced by Holmes and Rey

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<sup>33</sup>The Cabilly et al. specification (pages 24-25) supports this view in indicating that attempts to reconstitute active antibodies from native IgG had been largely unsuccessful.

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by the end of October 1982. There is no evidence in this record that the DNA sequences encoding of the Ig heavy and light chains of CEA.66-E3 or any other immunoglobulin DNA were known at any time before the Boss et al. filing date.

#### Decision

In view of the foregoing, judgment is entered against Shmuel Cabilly et al., Herbert L. Heyneker, William E. Holmes, Arthur D. Riggs, and Ronald B. Wetzel, the junior party, who are not entitled to a patent containing claims 101 through 120 corresponding to the count.

On this record, judgment is entered in favor of Michael A. Boss et al., John K. Kenten, John S. Emtage and Clive R. Wood, the senior party, who are entitled to their

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patent containing claims 1 through 18 corresponding to the count

RONALD H. SMITH	)	)
Administrative Patent Judge	)	)
	)	)
	)	) BOARD OF PATENT
MARY F. DOWNEY	)	) APPEALS AND
Administrative Patent Judge	)	)
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