

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opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Box Interference

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

ANTHONY J. BRAKE
Junior Party¹
v.

ARJUN SINGH
Senior Party²

Patent Interference 102,728

Before: ELLIS, Administrative Patent Judge, MCKELVEY, Senior Administrative Patent Judge and GARDNER-LANE, Administrative Patent Judge.

ELLIS, Administrative Patent Judge

¹ Patent 4,870,008, granted September 26, 1989, based on Application 07/081,302, filed August 3, 1987. Accorded the benefit of Application 06/522,909, filed August 12, 1983; Application 06/457,325, filed January 12, 1983, both abandoned.

² Application 07/522,719, filed July 16, 1990. Accorded benefit of U.S. Application 06/506,098, filed June 20, 1983.

FINAL DECISION ON REMAND

I. Prosecution History

1. In 1991, this interference was declared between then senior party Singh and junior party Brake.

2. During the preliminary motion phase of the interference, Brake's Preliminary Motion 2 for benefit, for the purpose of priority, of the January 12, 1983 filing date of U.S. Application 06/457,325, was granted.

3. The granting of this preliminary motion resulted in Brake becoming senior party.

4. Oral argument at final hearing was held before a merits panel of the Board of Patent Appeals and Interferences (hereinafter, the Board) on May 11, 1998, and final judgment was issued in favor of Brake on August 31, 1998.

5. Singh appealed the Board's final judgment to the Court of Appeals for the Federal Circuit arguing that the merits panel had erred in concluding that Singh had failed to prove conception of the subject matter of the count prior to the effective filing date accorded to Brake and that the Board should have reconsidered Brake's Preliminary Motion 2 for benefit.

6. The Federal Circuit held, inter alia, that the Board "erred in rejecting Singh's argument that the 24-mer^[3] order on December 1 [1982] had no corroborating

³ We direct attention to the discussions of the 24-mer on pp. 45-46, 53 and 55, infra. Briefly, the 24-mer is an oligonucleotide consisting of 24 nucleotides which is said to have been ordered by Dr. Singh on December 1, 1982. The nucleotide sequence of the 24-mer is AGGGAGATCACATCTTTTATCCAA. Singh Exhibit 3, p. 126. According

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value because it had no other ‘substantial use’ than to obtain the claimed construct.^[4]”

Singh v. Brake, 222 F.3d 1362, 1370, 55 USPQ2d 1673, 1679 (Fed. Cir. 2000).

7. Accordingly, the Federal Circuit vacated and remanded (i) “to reconsider Singh’s ‘substantial use’ argument,” and (ii) “to reevaluate the totality of the corroborative evidence.” Singh v. Brake, 1362 F.3d at 1370, 55 USPQ2d at 1679.

8. The Federal Circuit also remanded “for a determination of those issues that were properly raised during the earlier proceedings.” Singh v. Brake, 222 F.3d at 1371, 55 USPQ2d at 1679.

9. The mandate from the Federal Circuit was received by the Board on September 14, 2000. Paper No. 170.

10. On September 19, 2000, an order was entered inviting the parties to file briefs addressing the issue of (i) whether Brake sustained its burden of proof in its preliminary motion to be accorded the benefit of its Application 06/457,325, filed January 12, 1983; and (ii) Singh’s priority. Paper No. 171.

II. Background

Alpha (α) factor is a protein twelve to thirteen amino acids in length which is secreted by the yeast, Saccharomyces cerevisiae. Singh, Paper No. 28, Exhibit 15

to Singh, the 24-mer was employed to construct an invention within the scope of the count. Singh Brief, Paper No. 180, pp. 8-9.

⁴ We direct attention to the description of the count, infra. Claim 1 of Brake is the same as Count 1, the sole count in the interference.

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(Kurjan, U.S. Patent No. 4,546,082), col. 3, lines 7-10. The α factor protein controls mating between yeast cells which have the opposite mating type. Id., lines 32-35.

Important, for purposes of this interference, however, are the elements of the α -factor protein which enable it to be secreted.

Alpha factor is synthesized as a large, precursor molecule which contains several tandem copies of the α factor protein. Id., col. 4, lines 8-10. The copies of the α factor protein are separated from one another by a spacer region of six (6) amino acids which (from the N-terminus to C-terminus) are: lys-arg-glu-ala-glu-ala- .⁵ Id., lines 17-18. The amino acids of the spacer sequence are substrates for two yeast enzymes, KEX2 (which cleaves the spacer sequence after the arg residue), and dipeptidylaminopeptidase A (DPAP A- which cleaves after each ala residue). Brake Brief, Paper No. 190, pp. 9-10. This cleavage by the yeast enzymes results in the release of mature α factor protein.⁶ Id. In addition, the precursor molecule contains a "leader sequence which allows for transport of the α factor proteins through the outer cell membrane [of the yeast cell] and into the surrounding environment." Id., p. 8. Thus, simply stated, the structure of the precursor molecule in yeast is as follows:

Leader- [lys-arg-glu-ala-glu-ala]- α factor- [lys-arg-glu-ala-glu-ala]- α factor ...

⁵ A.k.a., lysine-arginine-glutamine-alanine-glutamine-alanine-.

⁶ A "mature" protein is one which lacks any extraneous amino acids. Thus, the cleavage of the spacer sequence with KEX2 and DPAP A results in the production of "pure" α factor. We note that there is a third enzyme which cleaves following the final amino acid of the α factor protein which is necessary to release mature α factor. Brake Brief, Paper No. 190, pp. 9-10. However, as pointed out by Brake, this enzyme is not relevant to the invention of this interference. Id.

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This interference concerns a DNA construct which comprises a sequence encoding an α -factor leader sequence derived from the yeast genus, Saccharomyces, followed by a codon which encodes a lysine (lys) or an arginine (arg) residue and a second codon which encodes an arginine.⁷ The second arg codon is directly linked to a DNA sequence which encodes a polypeptide which is foreign to Saccharomyces (designated as Gene* in Count 1). Thus, the DNA construct of the count lacks the sequence which encodes the “glu-ala” portion of the α factor spacer sequence. The formula of the count is directed to a DNA construct which comprises a nucleotide sequence which encodes:

Leader - lys-arg- Gene*

or

Leader - arg-arg- Gene*

The DNA construct is said to be useful for the expression and secretion of heterologous (i.e., foreign) proteins in yeast. This is because the aforementioned combination of amino acids; i.e., lys/arg and arg/arg, are recognized and cleaved by the yeast enzyme, KEX2. Such cleavage results in the release of a mature, biologically active protein

⁷ For purposes of background, we point out that DNA is a polymer composed of four (4) different mononucleotides; deoxyadenylate (A), deoxyguanylate (G), deoxycytidylate (C) and thymidylate (T). Amino acids are encoded by groups of nucleotides known as codons which are composed of three adjacent nucleotides. Thus, if a group of three nucleotides encodes a single amino acid, then theoretically (ignoring stop codons) 64 or (4^3) different amino acids could be formed. However, there are only twenty (20) different naturally-occurring amino acids. Therefore, most amino acids are coded for by more than one codon. This phenomenon is known as codon degeneracy or redundancy.

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which can then be recovered from the supernatant of the yeast cell culture using routine purification techniques.

III. The count

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

Count 1

A DNA construct comprising a sequence of the following formula:



where:

L encodes a Saccharomyces alpha-factor leader sequence recognized by a yeast host for secretion;

S encodes a spacer sequence providing processing signals resulting in the enzymatic processing by said yeast host of a precursor polypeptide encoded by L-S-Gene* into the polypeptide encoded by Gene*, S containing the sequence 5'-R₁-R₂-3' immediately adjacent to the sequence Gene*, R₁ being a codon for lysine or arginine, R₂ being codon for arginine, with the proviso that S not contain the sequence 5'-R₃-R₄-X-3', where R₃=R₁, R₄=R₂, and X encodes a processing signal for dipeptidylaminopeptidase A; and

Gene* encodes a polypeptide foreign to Saccharomyces.

The claims of the parties which correspond to count 1 are:

Singh: Claims 8 and 19 through 21.

Brake: Claims 1 through 37.

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IV. Issues for decision

1. Whether Singh has established that an Administrative Patent Judge (APJ) erred in granting Brake's Preliminary Motion 2 for benefit under 37 C.F.R. § 1.633(f).

If not,

2. Whether Singh has established, by a preponderance of the evidence, that Singh conceived of the invention of the count prior to the effective date accorded Brake; and, if so

3. Whether Singh has established, by a preponderance of the evidence, reasonable diligence from a time prior to Brake's effective date to an actual or constructive reduction to practice.

V. Brake's Preliminary Motion 2 for Benefit Pursuant to 37 C.F.R. § 1.633(f)

1. During the preliminary motion stage of this interference Brake filed eleven (11) preliminary motions. Brake Preliminary Motion 2 requested that it be accorded the benefit, for purposes of priority, of the January 12, 1983 filing date of Application 06/457,325 (the '325 application or Brake 1). Paper No. 15.

2. Singh opposed the preliminary motion (Paper No. 30), and a reply was filed (Paper No. 44).

3. In Preliminary Motion 2, Brake argued that the '325 Application satisfies the written description requirement of 35 U.S.C. § 112, first paragraph. Paper No. 15, pp. 5-7 and 8-10.

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4. Brake, inter alia, pointed to the disclosure at p. 3, line 30- p. 4, line 27, and original claim 5. Paper No. 15, pp. 6-7 and 9.

5. The '325 Application (pp. 3-4) states:

The constructs of the subject invention will have at least the following formula defining a pro-polypeptide:



wherein:

R is CGX or AZZ, the codons coding for lysine and arginine, each of the Rs being the same or different;

r is an integer of from 2 to 4, usually 2 to 3, preferably 2;

X is any of the four nucleotides, T, G, C, or A;

Y is G or C;

y is an integer of at least one and usually not more than 10, or usually not more than four, providing for monomers and multimers;

Z is A or G; and

Gene* is a gene other than α -factor, usually foreign to a yeast host, usually a heterologous gene, desirably a plant or mammalian gene;

n is 0 or an integer which will generally vary from 1 to 4, usually 2 to 3.

The pro-polypeptide has an N-terminal processing signal for peptidase removal of the amino acids preceding the amino acids coded for by the Gene*.

For the most part, the constructs of the subject invention will have at least the following formula:



defining a pre-pro-polypeptide, wherein all the symbols except L and S have been defined, S having the same definition as R, there being 1R and 1S, and L is a leader sequence providing for secretion of the pre-polypeptide. ... [emphasis added].

6. Original claim 5 of the '325 Application reads as follows:

A DNA construct comprising a sequence of the following formula:



wherein:

L is a leader sequence recognized by yeast for secretion;

R and S are codons coding for arginine and lysine;

X is any nucleotide;

Y is guanosine or cytosine;

y is an integer of from about 1 to 10;

Gene* is a gene foreign to yeast; and

n is 0 or 1 to 4.

7. Brake pointed out that when $n=0$ and $y=1$, the formula in the '325 Application corresponds to the count; viz.,



wherein R represents a codon for Lys or Arg and S represents a codon for Arg. Paper No. 15, p. 7.

8. Brake relied on a first declaration of Dr. Patricia Tekamp-Olson (para. 3) and Dr. Anthony J. Brake, to establish that the '325 Application expressly discloses and, thus, would have reasonably conveyed to one skilled in the art that Dr. Brake was in possession of, the $n=0$ construct required by the count. Paper No. 15, p. 10.

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9. We find the following testimony by Dr. Tekamp-Olson credible:

3. Based upon my review of the Brake 1 patent application it clearly discloses Saccharomyces α -factor constructs for secretory expression of heterologous genes which constructs lack a dipeptidylaminopeptidase A (“DPAP A”) site. This is disclosed in Brake 1 on page 3, line 33 to page 4, line 14; and in the claims page 16, lines 22 and 32. In particular, the fact that “n” can be zero in the formulae tells me (as well as those of ordinary skill as of 1983), that the DPAP A site is optional and can be deleted. Tekamp-Olson declaration, p. 2, para. 3.

10. Brake argued that one skilled in the art would have been able to make and use the n=0 construct disclosed in the ‘325 Application using the well-known technique of site-directed mutagenesis (a.k.a. in vitro or oligonucleotide mutagenesis), at the time the application was filed. Paper No. 15, pp. 10-12.

11. Brake relied, inter alia, on the declaration testimony of Dr. Patricia Tekamp-Olson (para. 5a) to establish that the site-directed mutagenesis technique was available and known to those skilled in the art by January, 1983. Paper No. 15, pp. 11-12.

12. Dr. Tekamp-Olson credibly states:

5. For example, such constructs could have been made using in vitro mutagenesis, a technique extensively used by January 1983 to modify DNA. This technique could have been performed on the construct exemplified in the Brake 1 application. The in vitro mutagenesis procedure disclosed in Brake 2 was available in January 1983. It would have been apparent to one of ordinary skill in January 1983 to apply the technique to the material disclosed in Brake 1 to produce a construct of the count, namely a construct lacking the DPAP A site.

a. To perform in vitro mutagenesis on the construct py α EGF-21 or according to the Brake 1, pYEGF-8 disclosed in Brake 1 it would have been apparent and within the level of ordinary skill in 1983 to (1) digest the construct with BamHI; (2) subclone the BamHI digest into an M13 vector; (3) mutagenized [sic, mutagenize] the M13 vector with a primer lacking the DPAP A site; (4) screen the mutagenized M13 vector with the primer to isolate a clone lacking the

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DPAP A site; (5) sequence the clone; (6) reinsert the mutagenized BamHI fragment into pC1/1 as disclosed in Brake 1.

13. Brake argued that other techniques for making the n=0 construct disclosed in the '325 Application were also known by those skilled in the art by January, 1983. Paper No. 15, p. 12.

14. Brake relied on the following declaration testimony of Dr. Tekamp-Olson (para. 5b) for support:

b. An alternative technique, which also would have been within the level of ordinary skill in January 1983 would have been to digest the disclosed vector in Brake 1 (e.g., pAB112) with the restriction endonucleases EcoRI and Hind III. Doing this would have isolated a fragment containing the α -factor leader and promoter, including the DPAP A site. This fragment would then be treated to a limited digestion with Bal 31 to remove the DPAP A site, e.g., to Serine 81 in the α -factor fragment. This would result in a blunt fragment, the α -factor promoter/leader fragment shortened on both the promoter and on the processing site of the leader. This fragment would be digested with Bgl II to generate a Bgl II sticky end at the promoter end of the fragment and gel isolated.

The EGF-fragment is generated by HgaI digestion of an EcoRI EGF fragment as described on p. 13, lines 3-6. This fragment was ligated to a blunt-Hga linker as follows (assumes screening for a Bal 31 fragment which includes Ser81 coding sequence):

CTAGATAAAAAGA

GATCTATTTTCTTTGAG as well as the Hga-Sal linker disclosed on p. 13, lines 14, 15. This EGF fragment would be gel isolated.

The Bgl II-blunt α -factor promoter fragment, the blunt Sal EGF fragment and pAB112, digested with Bgl II and Sal I would be ligated together and clones screened for the appropriate insert. One would then screen for clones in which the DPAP A site had been removed by screening with an oligonucleotide which spanned the Lys-Arg of the α -factor and the N-terminus of the EGF gene. This, combined with the teaching in Brake 1 would easily have led one of ordinary skill in the art in January 1983 to generate the spacerless construct of the Count.

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VI. Decision on Brake's Preliminary Motion 2

A. Preliminary matters

1. Return of briefs

In response to the mandate from the Federal Circuit, the parties were invited to file (i) two (2) briefs which were to separately address the written description and enablement issues raised in Brake's Preliminary Motion 2 and whether Brake had sustained its burden of proof to be accorded the benefit of its Application 06/457,325, filed January 12, 1983, and (ii) one brief addressing Singh's case for priority. See the Order Setting Times for Taking Action, Paper No. 171. Singh filed three briefs on November 3, 2000 and three reply briefs on January 9, 2001. Brake filed three briefs on December 27, 2000. We point out, however, that this permission to file new briefs did not exempt the parties from complying with the rules which govern interference practice before the Board. In particular, we direct attention to:

37 C.F.R. § 1.655(a) which states, in relevant part:

In rendering a final decision, the Board may consider any properly raised issue, including ... whether an interlocutory order should be modified. The burden of showing that an interlocutory order should be modified shall be on the party attacking the order. The abuse of discretion standard shall apply only to procedural matters [emphases added].

We further direct attention to:

37 C.F.R. § 1.655 (b) which states, in relevant part:

A party shall not be entitled to raise for consideration at final hearing any matter which properly could have been raised by a motion under § 1.633 or 1.634 unless the matter was properly raised in a motion that was timely filed by the party under § 1.633 or 1.634 and the motion

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was denied or deferred to final hearing, the matter was properly raised by the party in a timely filed opposition to a motion under § 1.633 or 1.634 and the motion was granted over the opposition or deferred to final hearing, or the party shows good cause why the issue was not properly raised by a timely filed motion or oppositions [emphases added].

Thus, in order to be entitled to reversal of the decision of the APJ granting Brake's Preliminary Motion 2, Singh has the burden of showing that the interlocutory order should be modified. 37 C.F.R. § 1.655(a). However, the availability of review does not entitle Singh to present new arguments which could have been raised in his original opposition to Brake's motion. 37 C.F.R. § 1.655 (b).

Turning to the briefs on the issues of written description and enablement provided by Singh subsequent to the Order for Setting Times for Taking Action (Paper No. 171), we find that Singh has ignored the requirement that it has the burden of showing that the interlocutory order should be modified. 37 C.F.R. § 1.655(a). We also find, in spite of our explicit reminder in our Final Decision of August 31, 1998, that only issues which were properly raised in the original opposition were entitled to review at final hearing,⁸ Singh has used the opportunity of filing new briefs to present new arguments. See also, Singh v. Brake, 222 F.3d at 1371, 55 USPQ2d at 1679 ("we remand to the Board for a determination of those issues that were properly raised

⁸ In its final decision, the Board stated that

Singh is presenting additional arguments that could have been made in his original opposition to Brake's motion, but he did not do so [Paper No. 164, p. 11, fn. 8].

Pointing to 37 C.F.R. § 1.655(b), the Board further stated that it would not consider these arguments. Id.

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during the earlier proceeding”). Accordingly, we return Singh’s briefs⁹ on the issues of written description and enablement, for failing to comply with 37 C.F.R. § 1.655(a) and (b). Thus, in this decision, we rely on Singh’s original briefs, Paper No. 151, filed April 2, 1996, and Paper No. 160, filed June 7, 1996, for written description and enablement purposes and will only consider those arguments which are properly raised.

2. Proper arguments

The court observed in Singh v. Brake, 222 F.3d at 1366, n.6, 55 USPQ2d at 1675, n.6, that the United States Patent and Trademark Office (USPTO) amended 37 C.F.R. § 1.655(a) to its current form in 1999. Thus, the present standard of review differs from the previous standard applied by the Board in entering the final judgment issued on August 31, 1998.¹⁰ This merits panel will apply the new standard.

Under 37 C.F.R. § 1.655(a), review at final hearing of a substantive decision by a single APJ granting or denying a preliminary motion means that the merits panel does not accord any deference to the single APJ on fact or legal issues. In addition, this panel will consider only those issues which were properly raised in timely-filed motions

⁹ Concordantly, Brake’s briefs filed subsequent to the Federal Circuit’s mandate on the issues of written description and enablement are also being returned with this decision.

¹⁰ The amendment to § 1.655(a) affords a full hearing of any properly-raised, dispositive issue by a three-judge panel and, thus, provides “the public with more certainty as to how matters will be considered... [and] make[s] practice within the Board more uniform.” Interim Rule, 37 C.F.R. § 1.655(a), 64 Federal Register 12900, 12901 (1999).

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and oppositions. 37 C.F.R. § 1.655(b). Review of a decision on a preliminary motion at final hearing is not a tool which a party can employ to reopen prosecution and present new arguments. We direct attention to our discussion above that the interference rules state that if an issue could have been raised in a preliminary motion and was not-- a party is not entitled to raise the issue at final hearing. 37 C.F.R. § 1.655(b). The rules are designed to provide orderly procedure and the parties are entitled to rely on their being followed. Myers v. Fegelman, 455 F.2d 596, 601, 172 USPQ 580, 584 (CCPA 1972). Waiver of the rules, absent compelling circumstances, would defeat the purpose of the rules and substantially confuse interference practice. Id. Thus, it is not appropriate for a party to file a motion or opposition, wait until after an APJ has rendered an adverse decision, and then present a new theory to support its position at final hearing. Motions and oppositions are not to be filed piecemeal, they must be completed within the set time. 37 C.F.R. §§ 1.637(a) and 1.638(a). As discussed above, because Singh's briefs, filed November 3, 2000, contain, almost exclusively, new arguments, and lack the required showing that Preliminary Motion 2 should be modified (37 C.F.R. § 1.655(a)), they are being returned. For purposes of this decision, we have limited our consideration only to those issues that were properly raised in Singh's briefs filed in Paper Nos. 151 and 160.

To eliminate any doubt as to respective arguments each of the parties made during the motions period concerning Brake's Preliminary Motion 2 for benefit, we have attached Brake's Preliminary Motion 2, Singh's Opposition and Brake's Reply to the Opposition, as Appendices 1-3, to this opinion.

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B. Brake's Preliminary Motion 2 for Benefit Pursuant to 37 C.F.R. § 1.633(f)

1. Singh's arguments for review of APJ's Decision

In the final decision of August 31, 1998, the original merits panel noted that Singh provided two reasons as to why the APJ's decision to grant Brake's Preliminary Motion 2 for benefit should be modified. 37 C.F.R. § 1.655(a). For example, the original merits panel (Final Decision, Paper No. 164, p. 6) stated:

Singh argues that Brake made misleading statements to the APJ with respect to the sufficiency of the written disclosure of the Brake 1 application, 06/457,325. Singh Brief, p. 45, last para. According to Singh, Brake "improperly imported information from the claims of the issued Brake patent, U.S. Patent 4,870,008, to support its arguments regarding the sufficiency of disclosure present in the Brake 1 Application." *Id.* Specifically, Singh refers to Brake's statement in Motion (2) that claims 3 and 4 are directed to "n=0" constructs wherein the Saccharomyces α -factor spacer includes only Arg-Arg or Lys-Arg. Singh Brief, p. 49, first complete para.

Here, we find that Brake's statements were not misleading. See also, Final Decision, Paper No. 164, p. 10. In Preliminary Motion 2, Brake was discussing where in the Brake 1 specification there was written descriptive support for patent claims 3 and 4. Paper No. 15, p. 9. Brake distinguished the patent claims from the claim of the '325 Application by referring to the latter as original claim 5. Brake Brief, Exhibit 5, pp. 67-68.

We further find that "assuming arguendo, Singh had found the referenced statements misleading, he could have, and should have, raised this issue in his opposition to Brake Motion (2). ... Not having done so, it is improper for Singh to raise this issue now." See also, Final Decision, Paper No. 164, p. 10.

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The original merits panel also noted Singh's argument that

in support of its Motion (2) and its Reply to Singh Opposition to Motion (2), Brake submitted a total of eight declarations. At the time of submission, Singh did not have the opportunity to cross-examine these declarants regarding their supporting declarations. The APJ, inter alia, in view of these supporting declarations granted Brakes [sic, Brake's] Motion (2) over Singh's timely filed opposition. After the APJ's ruling, Brake withdrew four of these supporting declarations, including two submitted by Dr. Brake, the inventor. The Board should reconsider the APJ's decision in light of Brake's withdrawal of these declarations from its case in chief [Brief, p. 45].

Like the original merits panel we, too, find this objection puzzling. Final Decision, Paper No. 164, pp. 7-8. We note that Brake elected to rely solely on the declarations of Drs. Tekamp-Olson (2), Johnson (1) and Schekman (1) for its case-in-chief. See Brake Notice Pursuant to 37 CFR § 1.671(e), submitted in Paper No. 130. Thus, although Singh does not indicate which declarations it is objecting to the "removal" of, it appears that Singh is referring to the declarations of Drs. Brake (2) and Mullenbach (2).¹¹ Paper No. 151, p. 45.

To that end we are in agreement with the original merits panel's statement (Final Decision, Paper No. 164, pp. 7-8) that:

... it is not clear whether Singh is objecting to the "removal" of the declarations of Dr. Brake, and/or Dr. Mullenbach, because he had intended to

¹¹ We note Singh's statement on p. 54 of its Brief (Paper No. 151) that the declarations of Drs. Schekman and Tekamp-Olsen are the only declarations submitted to support Brake's position that the '325 Application provides an adequate written description of a species within the scope of the count. Singh does not mention the declarations of Drs. Johnson and Mullenbach. As we understand it, Dr. Johnson's declaration was relied upon by Brake for its case-in-chief.

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rely on information or evidence presented therein, for his case-in-chief. If so, then the burden was on Singh to give his own notification under 37 CFR § 1.671(e). That is, if the Brake and Mullenbach declarations contained information which was crucial for Singh, he should not have assumed that Brake would rely on these declarations but, rather, he should have acted in the first instance, to make the information a part of his own record.

However, not having availed himself of the preemptory opportunity to obtain testimony from Drs. Brake and Mullenbach, Singh still was not without recourse. Subsequent to Brake's Notification Pursuant to 37 CFR § 1.671(e) (Paper No. 130), Singh could have filed an additional motion under 37 CFR § 1.635 requesting entry of the declarations, but did not do so. Thus, not having pursued either of the routes available for obtaining information or testimony, Singh is in a poor position to argue that he was denied the benefit of "cross examining" a witness.

On the other hand, if Singh did not intend to rely on information in the Brake declaration for his case-in-chief, and only wanted to cross-examine the declarants with respect to inaccurate or offensive statements made therein, then Singh should have no objection to the removal of such information by the senior party [footnote omitted]. Clearly, if Brake is no longer relying on evidence which Singh believed to be objectionable, there is no need for cross-examination.

Accordingly, in our consideration of Brake's Preliminary Motion 2 below, we consider only the Tekamp-Olson, Johnson and Schekman declarations.

2. Our Findings with Respect to Preliminary Motion 2

Turning to Brake's Preliminary Motion 2, we point out that the burden is on Singh, as the attacking party, to establish that the APJ erred in granting the referenced motion. 37 C.F.R. § 1.637(a).

We are not satisfied that Singh has sustained its burden of showing that the APJ erred in holding that the '325 Application constitutes a constructive reduction to practice of the subject matter of the count. Accordingly, the decision to grant Brake's Preliminary Motion 2 will not be overturned. Our reasons follow.

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a. Written description

In order to obtain benefit, for purposes of priority, the Brake '325 Application "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought," Brake was in possession of the invention defined by the count. Cf. Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Singh maintains that the APJ erred in according benefit to Brake. However, we agree with Brake that at least two sections of the '325 Application (a.k.a. Brake 1) provide adequate written descriptive support of an invention within the scope of the count; viz., pp. 3-4, and original claim 5.¹² Paper No. 15, pp. 6-7 and 9-10.

Turning first to the compound [L-(R-S-(GAXYCX)_n - Gene *)_y] set forth on page 4, line 21, of the '325 Application and comparing it to the compound set forth in Count 1 [5' - L-S-Gene*], we find the following.

The count requires that the DNA construct described therein comprise a sequence wherein "L" encodes a Saccharomyces α-factor leader sequence recognized by a yeast host for secretion. To that end, we find that the Brake 1 specification discloses that the "L" embodiment encodes a leader sequence providing for secretion of the mature protein encoded by Gene*. The '325 Application, p. 4, lines 24-26. The Brake 1 specification further discloses that "[o]f particular interest" is the Saccharomyces α-factor leader sequence. Id., lines 33-34. Thus, we find, and indeed

¹² Original claims are part of the written description of an invention. In re Koller, 613 F.2d 819, 823, 204 USPQ 702, 706 (CCPA 1980); In re Gardner, 475 F.2d 1389, 1391, 177 USPQ 396, 397 (CCPA 1973).

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the parties do not seem to dispute, that the relevant formulae in the Brake specification describe a DNA construct wherein “L” encodes the Saccharomyces α -factor leader sequence.

As to the “S” embodiment of the DNA construct described in Count 1, the count requires that “S,” contain the sequence “R₁ - R₂” wherein R₁ is a codon for lys or arg and R₂ is a codon for arg. Accordingly, an invention within the scope of Count 1 requires a DNA construct which comprises a sequence encoding a Saccharomyces α -factor leader sequence followed by codons which encode either lys-arg or arg-arg. Here, we find that the Brake ‘325 Application discloses that the “R-S” embodiment of the DNA construct designates codons which code for lys or arg. The ‘325 Application, p. 3, lines 35-36, and p. 4, lines 23-24. Thus, the “R-S” embodiment disclosed in the ‘325 Application can be lys-arg; arg-arg; arg-lys; or lys-lys. Accordingly, we find that the Brake 1 specification provides written descriptive support for a DNA construct which encodes a Saccharomyces α -factor leader sequence followed by codons which code for either lys-arg or arg-arg.

As to the “(GAXYCX)_n” portion of the formula in Brake 1, we find that the specification discloses that “GAX” and “YCX” are codons which encode, inter alia, glu (glutamine) and ala (alanine), respectively.¹³ The Brake 1 specification further discloses

¹³ In this case, Brake 1 uses the designation “GAX” and “YCX” to demonstrate that, when present; i.e., when $n \geq 1$, it is immaterial (i) which nucleotides are present in the third position delineated as “X,” and (ii) whether a “G” or “C” is present in the position designated by “Y.” That is, Brake 1 states that “X” can be any of the four nucleotides “T,” “G,” “C” or “A.” The ‘325 Application, p. 4, lines 3-4. Thus, with respect to the first codon in the formula, “GAX,” we find that one skilled in the art would have

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that “n” is “0” or an integer which will generally vary from 1 to 4, usually 2 to 3. The ‘325 Application, p. 4, lines 13-14. In the DNA construct described in Count 1, the codons which encode the “glu-ala” portion of the α -factor leader sequence have been

understood that it was immaterial whether the amino acid encoded by “GAT_I,” “GAG” or “GAC” or “GAA” was present. To confirm this finding, we turn to a genetic dictionary (see, e.g., BX 25), and we further find that “GAG” and “GAA” code for the same amino acid. That is, both codons code for glutamine (glu). Doing the same for “GAT_I” and “GAC,” we find that both codons code for aspartic acid (asp). Thus, we find that the first codon “GAX” can only encode two (2) amino acids, glu and asp.

As to the second codon in the formula (YCX), we find that Brake 1 states that “Y” can be “G” or “C.” “X” is as defined in the paragraph immediately above. Here, we find that the second codon can be “GCX” or “CCX,” with “X” being any of the four nucleotides. Turning to our genetic dictionary we find that “GCX,” i.e., “GCA,” “GCC,” “GCG” and “GCT,” all code for the same amino acid- alanine (ala). Doing the same for “CCX,” we find that all four possible codons, “CCA,” “CCC,” “CCG” and “CCT,” code for the same amino acid- proline (pro). Thus, we find that the second codon “YCX” can only code for two (2) amino acids, ala and pro.

Putting this altogether, we find one pair of the amino acids encoded by (GAXYCX) to be quite familiar, i.e., the “glu-ala” pair which is discussed extensively throughout this decision, as the recognition site in the α factor spacer sequence for the DPAP A enzyme. Our next inquiry was to determine the significance of the remaining two (2) amino acids, asp and pro. To that end, we find that Brake 1 discloses that the DPAP A enzyme recognizes both X-ala and X-pro amino acid sequences. The ‘325 Application, p. 10, lines 10-17. Accordingly, it reasonably follows that it is immaterial whether (GAXYCX) encodes “glu-ala” or “glu-pro.” Similarly, it reasonably follows that it is immaterial whether (GAXYCX) encodes “asp-ala” or “asp-pro.” All four possible amino acids sequences are functional equivalents because the DPAP A enzyme recognizes each and every one of them.

We point out that in our analysis we find that “GAXYCX” can encode four possible amino acid sequences when “ $n \geq 1$.” However, according to Singh, one skilled in the art would have understood this nucleotide sequence to encode only two amino acid sequences (glu-ala or asp-ala). Singh Opposition, Paper No. 30, p. 14. Assuming, arguendo, that Singh is correct, this would indicate that those skilled in the art would have understood the Brake 1 formula to encode a very small number of possible amino acid combinations.

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eliminated. Therefore, in the DNA construct described in the count, “n” is “0.”¹⁴

Accordingly, we find that like Count 1, the Brake 1 specification discloses a DNA construct which (i) comprises a sequence encoding a Saccharomyces α -factor leader sequence followed by codons which encode either lys-arg or arg-arg, and (ii) lacks codons which encode “glu-ala.”

Count 1 requires that “Gene*” encode a polypeptide which is foreign to Saccharomyces. We find that the ‘325 Application discloses that “Gene* is a gene other than α -factor, usually foreign to a yeast host cell, usually a heterologous gene.” The ‘325 Application, p. 4, lines 10-11.

Finally, the Brake 1 specification further discloses that “y” is an integer of at least one and usually not more than 10.” Id., p. 4, lines 6-7. Thus, we find, and Singh does not seem to dispute, that Brake 1 discloses a formula wherein “Gene*,” like “Gene*” of the count is “1.” The Brake 1 specification further discloses that

Gene* may encode any type of polypeptide of interest ... such as growth hormone, somatomedins, epidermal growth factor, the endocrine secretions, such as luteinizing hormone, thyroid stimulating hormone, oxytocin, insulin, vasopressin, renin, calcitonin, follicle stimulating hormone, prolactin, etc; hematopoietic factors, e.g. erythropoietin, colony stimulating factor, etc.; lymphokines; globins; globulins, e.g. immunoglobulins; albumins, interferons, such as α , β and γ ; repressors; enzymes; endorphins e.g. β -endorphin, enkephalin, dynorphin, etc. [The ‘325 Application, p. 10, line 34- p. 11, line 15].

Thus, we find written descriptive support for the Gene* limitation of the count in Brake 1.

¹⁴ Hereinafter, we refer to a DNA construct which lacks the codons coding for the “glu-ala” amino acids of the α -factor spacer sequence as an “n=0” construct.

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The same analysis applies to the formula set forth in claim 5 of the '325 Application.

We note that Brake points to paragraph 3 of the declaration of Dr. Tekamp-Olsen¹⁵ to establish that those of ordinary skill in the art would have understood the '325 Application to describe a compound wherein "n" is "0." Paper No. 15, p. 10; see also, para. 9 on p. 10, above. We find the declaration credible and consistent with the plain meaning of the words in the Brake 1 specification.

Accordingly, in view of the foregoing, we find that the compound [L-(R-S-(GAXYCX)_n - Gene *)_y] set forth on page 4, line 21, and claim 5, of Brake 1 expressly describe a DNA construct which lacks the codons which encode the "glu-ala" residues of the α factor spacer sequence when "n=0." Thus, we find that Brake 1 "conveys with reasonable clarity to those skilled in the art that, as of the filing date sought," Brake was in possession of a species within the scope of Count 1. Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1117.

b. Enablement

Since we find that Brake 1 provides adequate written descriptive support for a DNA construct within the scope of Count 1, the issue now becomes whether the '325 Application disclosure, in combination with knowledge generally available in the art,

¹⁵ As discussed above, Singh argues that Brake "withdrew" four of the declarations supporting Preliminary Motion 2 (Paper No. 15) and the Reply (Paper No. 44). Thus, we have only considered those declarations which are not contested. To that end, in our consideration of Brake's preliminary motion, we have found it necessary to rely only on the declaration of Dr. Tekamp-Olson.

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would have enabled one skilled in the art “to make and use” said construct at the time the application was filed. Scripps Clinic v. Genentech Inc., 927 F.2d 1565, 1571, 18 USPQ2d 1001, 1006 (Fed. Cir. 1991); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

Brake acknowledges that the ‘325 Application does not explicitly disclose how “to make” an “n=0” DNA construct. Paper No. 15, p. 11. However, it points out that “the reagents and techniques needed to make such a DNA molecule were routine [in the art] by January 1983.” Id. Brake argues, and provides the declaration of Dr. Tekamp-Olson¹⁶ to support its position, that site-directed mutagenesis (a.k.a. in vitro and oligonucleotide mutagenesis) and other DNA-modifying techniques were known in the art by January, 1983. Id., pp. 11-12. Thus, Brake contends that the disclosure of the “n=0” DNA construct in the ‘325 Application, in combination with knowledge generally available in the art, would have enabled one skilled in the art “to make” an invention within the scope of Count 1, without undue experimentation, at the time the application was filed. Id. We agree.

Enablement does not require that the specification disclose that which is well known in the art. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1384, 231 USPQ at 94. Brake’s witness, Dr. Tekamp-Olson, testified that in vitro mutagenesis was known and used extensively to modify DNA by those skilled in the art in January,

¹⁶ As noted in footnote 15, supra, we have not considered Dr. Brake’s declaration.

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1983. Declaration, p. 3, para. 5. Dr. Tekamp-Olson credibly describes how this technique would have been employed by such persons, at the time the application was filed, to make the “n=0” DNA construct described in Brake 1. Dr. Tekamp-Olson testified that one skilled in the art would have mutagenized (modified) the DNA construct pYEGF-8 (Brake 1, p. 14, line 13),¹⁷ using an oligonucleotide primer which lacks the sequence encoding the DPAP A (the glu-ala residues in the α -factor spacer sequence) site to make the construct of the count.¹⁸ Id., p. 3, para. 5a.

We find credible Dr. Tekamp-Olson’s testimony that given the Brake 1 disclosure and general knowledge in the art, one skilled in the art would have been able “to make” a DNA construct within the scope of Count 1 at the time the Brake 1 application was filed. That is, we find that the technique of in vitro mutagenesis described by Dr. Tekamp-Olson involves digesting the DNA construct described in Brake 1 with a well-known restriction enzyme (BamHI), subcloning the digested DNA into a well-known

¹⁷ pYEGF-8 is the same as pY α EGF-21 of Brake 2.

¹⁸ We note that in its Opposition, Singh does not challenge this method of making the invention of the count. We further note that two of Singh’s declarants, Dr. Singh and Dr. Hitzeman, testify that site-directed mutagenesis was well known in the art by 1982. To that end Dr. Singh testified:

During the period 1982 to 1983 site directed deletion mutagenesis was a known technique. As set forth in Sambrook, et al. “Molecular Cloning” 2nd Edition (1989) at pages 15.51 and 15.52 (Singh Exhibit 36, Bates Nos. 000564-000566), this technique was known in the early 1970’s and had developed into an established methodology by 1982. SR 0568, para. 58.

Dr. Hitzeman’s statement is identical to that of Dr. Singh. SR 0168-0169, para. 9. Thus, we find Dr. Singh’s declarants agree with Dr. Tekamp-Olson’s statements.

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vector (M13), modifying the DNA-containing vector with an oligonucleotide primer which lacks the codons encoding the glu-ala residues of the α factor spacer region, screening the vectors with the oligonucleotide primer to isolate a clone having desired modification, and sequencing said clone. These were all routine and predictable procedures in genetic engineering.¹⁹ In addition, we find that the level of skill in the field of molecular genetics at the relevant time was very high and that those having ordinary skill in the art would have been able to use techniques then known in the art to make Brake's described n=0 construct. Thus, we find that the disclosure of the "n=0" DNA construct in Brake 1, in combination with routine techniques and knowledge generally available in the art, would have enabled those skilled in the art of genetic engineering to make a species within the scope of Count 1 without undue experimentation at the time the application was filed.

Dr. Tekamp-Olson describes a known alternative method for making a species within the scope of the count which involves the use of the enzyme Bal 31 to remove the sequence encoding the DPAP A (the glu-ala residues of the α factor spacer sequence) site from a vector (pAB112) disclosed in Brake 1. Tekamp-Olson Declaration, pp. 3-4, para. 5b; see also, para. 14 on p. 11, above. According to Dr. Tekamp-Olson, this method of modifying DNA was known by those skilled in the art in January, 1983. Id.

¹⁹ We point out that several of the techniques described by Dr. Tekamp-Olson; viz., digestion of DNA with known restriction enzymes, subcloning into a vector, screening with a synthetic oligonucleotide, are described on pp. 12-15 of Brake 1.

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We find no reason to disbelieve Dr. Tekamp-Olson's testimony; in fact, we find her testimony credible and useful. The technique described in her testimony involves digesting a DNA vector described in Brake 1 with known restriction enzymes (EcoRI and HindIII), subjecting the digested DNA to limited digestion with another enzyme (Bal 31), digesting again with another restriction enzyme, adding linkers to insert the digested DNA into a known vector, and screening for clones lacking the codons encoding the glu-ala residues of the α -factor spacer sequence. Again, these appear to have been routine procedures in genetic engineering and all these techniques, with the exception of the Bal 31 digest, are described on pp. 12-15 of Brake 1. In fact, the only aspect of this procedure which Singh challenges in its Opposition is the regulation of the DNA digestion with the Bal 31 enzyme. Opposition, Paper No. 30, p. 14. However, since Brake presents the Bal 31 digestion procedure as an alternative method of making a species within the scope of the count, we need not reach this issue. Accordingly, although we find no error in Dr. Tekamp-Olson's statements in both the declaration submitted to support Preliminary Motion (2) (Paper No. 15) as well as in the declaration submitted to support Brake's Reply to Singh's Opposition (Paper No. 44), we pass on the merits of the Bal 31 digestion procedure issue.

Nevertheless, in weighing the evidence as a whole, we hold that Brake has met its burden of proving, by a preponderance of the evidence, that the '325 Application, in combination with knowledge generally available in the art, would have enabled one skilled in the art "to make and use" a DNA construct within the scope of the count without undue experimentation at the time the application was filed. That is, on this

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record, we hold that a preponderance of the evidence establishes that the Brake 1 application constitutes an enabling disclosure of the invention of Count 1. Weil v. Fritz, 572 F.2d at 856, 865 n.16, 196 USPQ 600, 608 n.16 (CCPA 1978).

3. Singh's Opposition

Singh's Opposition (Paper No. 30) is not a model of clarity. For example, Singh does not distinguish statements of fact from arguments as to why Brake's preliminary motion should be denied. See 37 C.F.R. § 1.638. See also, Paper No. 30, pp. 1-8, section entitled "Facts and Reasons in Opposition." As we understand it, Singh makes four arguments (1)-(4). Specifically, Singh argues that the preliminary motion should have been denied because

(1) Brake did not correctly identify the only fully disclosed gene in the application, (2) Brake has failed to overcome the presumption that the revised sequences which it tried to enter during the prosecution of the later abandoned original Brake 1 application were new matter, (3) it had not been determined which other genes might be operative at the time of the January 12, 1983 filing, and (4) the original Brake application taught away from having n=0 such that there would be no Glu-Ala sequences." Paper No. 30, p. 8.

We point out, however, that Singh does not indicate whether these arguments are directed to written description or enablement. In fact, the only mention Singh makes of § 112, in the entire opposition, is in the discussion concerning Penwalt Corp v. Akzon Inc., 740 F.2d 1573, 222 USPQ 833 (Fed. Cir. 1984), on p. 12 of the Opposition. Enablement and undue experimentation are mentioned on p. 13 in the discussion of Dr. Mullenbach's testimony.²⁰ We remind Singh that the rules require an

²⁰ We direct attention to our discussion on p. 33, below, wherein, we find Singh's reliance on Dr. Mullenbach's testimony from Interference No. 102,208, to be improper.

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opposition to identify any material fact in the motion which is in dispute. 37 C.F.R.

§ 1.638. It is not the responsibility of this Board to “pour over” a document to extract the relevant information. Clintec Nutrition Co. v. Baxa Corp., 44 USPQ2d 1719, 1723 n.16 (N.D. 1997), citing United States v. Dunkel, 927 F.2d 955, 956 (7th Cir. 1991).

Rather, the burden was on Singh to demonstrate that the Brake 1 application fails to satisfy the written description and/or enablement requirement(s) of § 112, first paragraph. Nevertheless, for purposes of this review, we have interpreted Singh’s arguments (1) and (2) as being directed to the issue of written description and arguments (3) and (4), as being directed to the issue of enablement.

a. Written description

Singh does not seem to contest that Brake 1 (the ‘325 Application) describes a DNA construct wherein the value of “n=0.” Paper No. 30, p. 5, lines 17-19; p. 6, lines 21-22, Dr. Falkinham’s Declaration, p. 3, para. 9. However, Singh argues that Brake 1 incorrectly designated the nucleotide sequence for human epidermal growth factor (EGF). Paper No. 30, pp. 1-2 and 8-10. Singh points out that when Brake filed an amendment to correct the sequence in the specification (Paper No. 6), the examiner rejected all the pending claims on the grounds that the amendment to the specification was “new matter” (Paper No. 7). Id., pp. 2-3. We find this argument lacks merit.

First and foremost, the relevant issue here is whether the ‘325 Application satisfies the requirements of § 112, first paragraph, for the invention of the count. We

Thus, because this argument in the Opposition is not properly before us, it has not been considered by the merits panel.

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point out that Count 1 does not require “Gene*” to encode any particular polypeptide, including EGF. Count 1 simply states that “Gene* encodes any polypeptide foreign to Saccharomyces.”²¹ Accordingly, we find that all of Singh’s arguments with respect to the EGF nucleotide sequence fail to address a limitation present in the count.

Second, to clarify the record, we point out that the examiner erred in making the new matter rejection. The ‘325 Application, Paper No. 7, p. 2.

The examiner erred procedurally by rejecting claims, not one of which was directed to a DNA construct having the EGF nucleotide sequence, as being based on a specification which contains new matter. The ‘325 Application, Paper No. 7, p. 2. Thus, even if we assume, arguendo, which we do not, that Brake’s amendment to the EGF nucleotide sequence in the specification contained “new matter,” it was improper to reject claims which do not contain the new matter under 35 U.S.C. § 112, first paragraph. In re Rasmussen, 650 F.2d 1212, 1214, 211 USPQ 323, 325-326 (CCPA 1981). When “new matter” is added only to the specification, and not to the claims, the proper course of action is for the examiner to object to the specification under 35 U.S.C. § 132.

More importantly, the examiner erred substantively in not permitting Brake to amend the EGF sequence. The ‘325 Application, Paper No. 7, p. 2. It is well

²¹ We direct attention to our discussion on p. 22, above, wherein we find that the Brake 1 specification discloses that in the formula L-(R-S-GAXYCX)_n-Gene*), Gene* is a gene other than α-factor, usually foreign to a yeast host, usually a heterologous gene... ” [emphases added]. The ‘325 Application, p. 4, lines 10-11; p. 10, line 34-p. 11, line 15.

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established that obvious errors and appropriate corrections thereto that would have been recognized by one skilled in the art can be corrected by an amendment to the specification. In re Oda, 443 F.2d 1200, 1204, 170 USPQ 268, 271 (CCPA 1971); M.P.E.P. § 2163.07. Brake explained to the examiner that a word processing, format error occurred which shifted the two strands in the original sequence so that they were not complementary. The '325 Application, Paper No. 6, p. 4; Brake Brief, Paper No. 157, p. 63. Brake's proposed amendment to the specification did not add or delete data, or alter the nucleotide sequence in any way, it simply corrected the alignment of the nucleotide sequence data already disclosed therein. The '325 Application, Paper No. 6, p. 4. In our view, since Brake 1 discloses that the contested nucleotide sequence was based on the known amino acid sequence of EGF,²² one skilled in the art would have recognized the error and known how to correct it using a conventional genetic dictionary to compare the nucleotide coding triplets (codons) disclosed in Brake 1 to the known EGF amino acid sequence. See Brake Reply, Paper No. 44, Johnson Declaration, pp. 4-7; Tekamp-Olson Declaration 2, pp. 3-5, para. 6; Brake Exhibit 25.

We note Singh's argument that due to the degeneracy of the genetic code one cannot unambiguously determine a nucleotide sequence from an amino acid sequence (Paper No. 30, p. 9), however, we point out that codon degeneracy is not an issue in

²² The Brake 1 specification discloses that:

A synthetic sequence for human epidermal growth factor (EGF) based on the amino acid sequence of EGF reported by H. Gregory and B. M. Preston[,] *Int. J. Peptide Protein Res.* 9, 107-118 (1977) was prepared... [the '325 Application, p. 12, lines 18-21].

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this instance since Brake 1 discloses the nucleotide sequence. Tekamp-Olson Declaration 2, p. 4, para. 6c. One skilled in the art need only compare manually, or using a known computer program, the disclosed EGF nucleotide sequence with the known amino acid sequence to correct the alignment. Johnson Declaration, pp. 6-7; Tekamp-Olson Declaration 2, p. 4, para. 6b.

Singh argues that (i) one skilled in the art would not have recognized the nucleotide sequence in Brake 1 as EGF and would not have tried “to find two complementary sequences in what appeared to be a single 5' to 3' strand” (Singh Opposition, Paper No. 30, p. 9); (ii) because Brake filed a continuation-in-part (CIP) of Brake 1 which contained the amended EGF nucleotide sequence, Brake is estopped from arguing that the new information in the second application was inherent in Brake 1 (id., p. 10); and (iii) if Brake had believed they were entitled to the benefit of Brake 1 they would have continued to prosecute that application rather than acquiescing to the examiner’s rejection (id., pp. 10-11). Singh relies on the declaration of Dr. Falkinham to support many of these arguments. We do not credit Dr. Falkinham’s testimony and find these arguments unpersuasive.

As discussed above Count 1 does not require a nucleotide sequence encoding EGF. Gene* encodes any non-Saccharomyces polypeptide. Accordingly, we find that each of these arguments fails to address a limitation present in the count.

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b. Enablement

Singh argues that it had not been determined what genes, other than EGF, might have been operative in the DNA construct disclosed in Brake 1 by the January, 1983, filing date (Singh argument (3), on p. 28, above). Paper No. 30, pp. 3-5. Singh relies on the testimony of Dr. Mullenbach for support. Id. We find this argument lacks merit.

Singh's reliance on testimony from another interference at the time the Opposition was filed was improper. We direct attention to 37 C.F.R. § 1.683(a)(1991) which at the relevant time then required

... a party to file a motion (§1.635) for leave to use in an interference testimony of a witness from another interference, proceeding, or action involving the same parties, subject to such conditions as may be deemed appropriate by an examiner-in-chief. The motion shall specify with particularity the exact testimony to be used and shall demonstrate its relevance.

This Singh did not do.²³ Thus, we sustain Brake's objection to the admission of this testimony set forth in the Reply pursuant to § 1.683(b)²⁴ and shall not consider those arguments in the Opposition which rely on Dr. Mullenbach's testimony. Moreover, we note that Singh did not repeat this argument in its brief (Paper No. 151). Accordingly, we consider this issue to be abandoned.

²³ We find that Singh was aware of its burden with respect to this regulation. Singh argues that 37 C.F.R. § 1.601 defines a "party" as including the assignee of a patentee involved in an interference. Paper No. 30, p.4, n.3. According to Singh, since Dr. Mullenbach is an employee of Chiron, the assignee of the Brake patent, "it is appropriate to cite Dr. Mullenbach's testimony in this interference." Id. We find this argument to be disingenuous. Chiron is the real party of interest in the interference, not Dr. Mullenbach.

²⁴ Paper No. 44, p. 4, n.2.

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Singh argues that the Brake 1 specification “teaches away” from an “n=0” construct. Paper No. 30, pp. 13-14. According to Singh, the Brake 1 specification

clearly states that the “useful DNA sequences which can be used for cassettes for expression,” having the formula:

TR-L-(R-R(GAXYCX)_n-W-(Gene*)_d)_y
contain an n’ which “will generally range from 1 to 3, more usually from 2 to 3” [id., p. 14].

Therefore, one skilled in the art would determine that the “glu-ala” or “asp-ala”²⁵ sequences would be necessary for expression. Id. Singh relies on paragraph 9 of Dr. Falkinham’s declaration for support.²⁶ Id. We find this argument unpersuasive.

First, Singh has confused the factors used to demonstrate that a disclosure is non-enabling (35 U.S.C. § 112) with the factors used to demonstrate the nonobviousness of an invention (35 U.S.C. § 103). That is, a prior art reference which is said to “teach away” from the claimed invention, is a factor which is considered when

²⁵ Although Singh does not explain, the significance of the “asp-ala” sequence, we find from a genetic dictionary (BX 25) that the (GAXYCX) sequence of Brake 1 formula can encode glu-ala or asp-ala. We further find from Brake 1 that both amino acid combinations are recognized by the DPAP A enzyme. The ‘325 Application, p. 10, lines 10-17. We point out that this finding is in agreement with our discussion in footnote 13, supra.

²⁶ Dr. Falkinham states:

9. Although there was a theoretical presentation of the n=0 construct in the Brake 1 application, there was a clear statement that “n” in the construct was “preferably 2 or 3” (column 3, line 25) or “usually 2 or 3” (column 2, line 68). In addition, the only example described in the Brake 1 application, pYEGF-8, produced not an n=0 construct, but a construct which would produce Glu-Ala-EGF. One skilled in the art would have determined from the Brake specification that the n=0 construct was not desirable [emphases added] [Falkinham declaration, p. 3, para. 9].

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determining obviousness. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir. 1983). The issue here, however, is enablement and whether one skilled in the art would have been able to “make and use” the invention defined by the count without undue experimentation at the time the application was filed. The factors to be considered in determining whether a disclosure would require undue experimentation were set forth by the court more than four (4) years prior to the filing of Singh’s Opposition in In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Those factors include

(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

We find that Singh’s Opposition conspicuously lacks any analysis of the Brake 1 application in view of the Wand’s factors.

Second, we find Dr. Falkinham’s declaration insufficient to support Singh’s position that based on the formula $TR-L-(R-R(GAXYCX)_n-W-(Gene^*)_d)_y$, one skilled in the art would have determined that a construct which included two to three “glu-ala” or “asp-ala” sequences was preferred over one lacking these sequences. It is not clear where Dr. Falkinham mentions the referenced formula in his declaration. In fact, it is not clear to us, which formula he is discussing in the paragraph (para. 9) of his declaration relied upon by Singh.

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In addition, we find that in para. 9 of his declaration, Dr. Falkinham cites to column 2, line 68, and column 3, line 25.²⁷ Thus, we agree with Brake that Dr. Falkinham is discussing the Brake patent which is based on Brake's continuation-in-part, Application 06/522,909 (Brake 2), filed August 12, 1983. Accordingly, we find that Dr. Falkinham's conclusion that "[o]ne skilled in the art would have determined from the Brake specification that the n=0 construct was not desirable," is inconsistent with the evidence of record. That is, the Brake specification from which Dr. Falkinham draws his conclusion that the "n=0" construct is not desirable is the very specification which contains the claim which is the subject matter of this interference. Claim 1 of the Brake patent (Brake 2) is identical to Count 1 of this interference.

Singh further argues that modifying genetic constructs was unpredictable at the time the Brake 1 application was filed. Paper No. 30, p. 14. Singh relies on paragraph 10 of Dr. Falkinham's declaration for support. Dr. Falkinham states:

Brake attested to this unpredictability at page 14 of the 06/522,909 application, where "Surprisingly, a deletion occurred where the codon for the 3rd and 5th amino acids for EGF, asp and ser, were deleted with the remainder of the EGF being retained" [emphasis added] [Falkinham declaration, pp. 3-4, para. 10].

We find this argument unconvincing.

It is not clear to us, and Dr. Falkinham does not explain, how this section of the Brake 2 specification, which describes the addition of synthetic linkers to a DNA

²⁷ Brake points out that Dr. Falkinham has misunderstood the teachings at column 3, line 25, of the Brake patent. Brake Reply, Paper No. 44, p. 13. The referenced section of the patent provides that l' is "2 to 4, preferably 2 or 4" when "n is 0." Id. We find that unreliable testimony, such as this, undermines Dr. Falkinham's credibility as an expert witness.

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fragment encoding epidermal growth factor (EGF), demonstrates the unpredictability of modifying the pYEGF-8 construct described in the Brake 1 specification using the techniques of oligonucleotide mutagenesis or Bal 31 digestion described in Dr. Tekamp-Olson's declaration (attached to Brake Motion 2, Paper No. 15). That is, Dr. Falkinham does not explain how the spontaneous deletion of two amino acids in a DNA fragment encoding EGF demonstrates the unpredictability of making the "n=0" DNA construct described in Brake 1 which requires the deletion of four amino acids from the α factor spacer sequence using a different technique; i.e., either the oligonucleotide mutagenesis or Bal 31 digestion technique.

Singh still further argues that the early DNA mutagenesis techniques would have required undue experimentation by those skilled in the art. Paper No. 30, p. 14. Singh relies on paragraphs eleven (11) through thirteen (13) of Dr. Falkinham's declaration for support. Id. We find this argument to be unconvincing.

Turning first to paragraph 11 of the declaration, we find that Dr. Falkinham states:

11. It is my opinion that the construction of the n=0 construct using oligonucleotide mutagenesis could not have been accomplished without undue experimentation based upon the vague disclosure of the Brake application. Brake contends that an oligonucleotide could be employed to make the deletion of the Glu-Ala sequences and to screen for potential mutants. However, this oligonucleotide would bind to both the $n \geq 1$ and the n=0 constructs. Therefore, one who attempted to use this oligonucleotide to identify mutants (i.e., the n=0 construct) would have to know how to modify the hybridization conditions to distinguish the binding to the starting $n \geq 1$ construct and the n=0 construct. Brake does not provide any disclosure or suggestion of these conditions [emphases added].

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We decline to credit Dr. Falkinham's opinion that construction of the n=0 DNA construct using oligonucleotide mutagenesis could not have been accomplished without undue experimentation in view of the allegedly vague disclosure of the Brake 1 application. Brake acknowledges that the Brake 1 specification does not disclose the synthesis of a DNA construct wherein the "glu-ala" sequence of the α -factor spacer sequence has been removed, i.e., the n=0 construct required by Count 1. However, as we discussed above, it is well established that a specification need not describe that which is well known in the art. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1385, 231 USPQ at 94, 480 U.S. 947 (1986). Moreover, as further discussed above, the evidence of record indicates that oligonucleotide (site-directed) mutagenesis was well known in the art by 1982. See Dr. Tekamp-Olson's Declaration 1, pp. 2-4, paras. 4-5; Singh Declaration, SR 568, para. 58; Hitzeman Declaration, SR 168-169, para. 9.²⁸ Thus, we find Dr. Falkinham's testimony to be inconsistent with the testimony of three (3) other declarants of record, including, arguably, two of Singh's declarants.

In addition, we find that although Dr. Falkinham states that the making of an n=0 construct using an oligonucleotide to delete the "glu-ala" sequence of the α -factor spacer sequence could not have been accomplished without undue experimentation, the only "difficulty" he discusses is that of screening for an n=0 construct once it has been made. Thus, we find that Dr. Falkinham's opinion is based on his concern that

²⁸ The Singh and Brake record will be referred to as SR and BR, respectively, followed by the appropriate page number. Similarly, the Singh and Brake exhibits will be referred to as SX and BX, followed by the page number.

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the Brake 1 application does not disclose or suggest any screening conditions for detecting an “n=0” construct. We point out, however, that screening for the appropriate clones using a synthetic oligonucleotide is simply one of the steps in the well-known oligonucleotide mutagenesis procedure. Dr. Tekamp-Olson’s Declaration 1, pp. 2-4, paras. 4-5; Singh Declaration, SR 568, para. 58; Hitzeman Declaration, SR 168-169, para. 9. Therefore, it reasonably follows that the screening aspect of the procedure would have been well-known by one skilled in the art at the time the Brake 1 application was filed. Accordingly, we again find Dr. Falkinham’s testimony to be inconsistent with the testimony of three declarants of record, including Singh’s declarants, Drs. Singh and Hitzeman.

Moreover, Dr. Falkinham has not explained how an oligonucleotide primer which lacks the nucleotide sequence encoding the “glu-ala” portion of the α factor spacer sequence can bind to a construct which has that sequence. An oligonucleotide probe can only bind when the nucleotide sequence to which it is complementary is present. An oligonucleotide probe without the sequence encoding the “glu-ala” residues can only form a completely-matched duplex with an “n=0” construct. See, the Johnson Declaration, p. 10, para. 10; Tekamp-Olson’s Declaration 2, pp. 6-7, para. 8. Since only a portion of the probe (either the 5' end which is complementary to the sequence encoding the “lys-arg” residues remaining in the spacer sequence or the 3' end which is complementary to the nucleotide sequence encoding the initial amino acids of EGF sequence) will bind to an “n \geq 1” construct, only a partial duplex will be formed. Id. Thus, we agree with Brake that those skilled in the art would have recognized that

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under stringent “wash” conditions routine in the art in 1983, “n=0” constructs could have been identified. Id.; see also Brake Exhibit 28 attached to Paper No. 44.

In paragraph 12 of his declaration Dr. Falkinham argues that the success of the oligonucleotide mutagenesis technique was unpredictable. Falkinham declaration, p. 4, para. 12. Dr. Falkinham points to a twelve (12)- page review article by Fritz which is said to state that “It is therefore not surprising that the conventional protocol typically gives rise to marker yields of only about 5%,” to support his position. Id.

Here, we agree with Brake that Dr. Falkinham has misinterpreted the referenced section of the Fritz publication. That is, Dr. Falkinham has interpreted the obtention of a 5% yield as meaning that oligonucleotide mutagenesis is an unpredictable technique. However, as pointed out by Drs. Johnson and Tekamp-Olson, the Fritz article is referring to the efficiency of the procedure, not the predictability. Johnson Declaration, p. 11, para. 10b, Tekamp-Olson Declaration 2, pp. 7-8, para. 9. Thus, we find that those skilled in the art would have understood the Fritz publication to mean that for every 100 colonies screened, five would be positive. Id. Accordingly, since screening hundreds of colonies was routine in the art in January, 1983, we further find that those skilled in the art would have reasonably expected 5% of the colonies to be positive. Id.

Finally, Dr. Falkinham urges that the Bal 31 method of making the n=0 constructs described by Dr. Tekamp-Olson (Tekamp-Olson declaration, pp. 3-4, para. 5b) “would require undue experimentation.” Declaration of Dr. Falkinham, p. 5, para. 13. According to Dr. Falkinham:

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13. Brake also alleged that a second method, using Bal 31 nuclease, could be used to make the n=0 construct. This method is also very unpredictable due to the following difficulties: (1) the need to closely monitor the Bal 31 reaction, as the reaction rate of this enzyme is high; (2) the need to isolate, purify and ligate the fragments resulting from this digestion to a suitable vector for sequencing to identify the desired construct; and (3) the fact that only a fraction of the DNA molecules in the reaction mixture at any one time will have blunt ends that are suitable for ligation. Therefore, without any disclosure of the appropriate conditions and manipulations, this method would require undue experimentation. Falkinham declaration, para. 13.

Even if we assume, arguendo, that Dr. Falkinham is correct that the Bal 31 procedure is unpredictable, we agree with Brake that this was presented as an alternative technique to the site-directed mutagenesis method initially described by Dr. Tekamp-Olson. Tekamp-Olson declaration, pp. 3-4, para. 5(b). Accordingly, since both Brake's declarant, Dr. Tekamp-Olson, and Singh's declarants, Drs. Singh and Hitzeman, agree that site-directed mutagenesis was an established technique in the art by 1982, we need not reach the merits of the Bal 31 procedure argument.

4. Singh's Brief, Paper No. 151

As discussed above, we are returning Singh's briefs on the issues of written description and enablement, filed November 3, 2000, for failure to comply with 37 C.F.R. § 1.655(a) and (b). Here, we will consider only those § 112 issues which were properly raised in Singh's original brief (Paper No. 151), filed April 8, 1996. Turning to Singh's arguments set forth therein, we find the following.

a. Written description

It is readily apparent from the Opposition to Brake's Motion (2) (Paper No. 30), attached as Appendix 2, that Singh did not raise any arguments with respect to written

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description. Therefore, we will not consider any of Singh's arguments (Paper No. 151, pp. 46-60) that the Brake 1 application fails to provide an adequate written description of the count since they were not timely filed. 37 C.F.R. § 1.655(b). To that end, we direct attention to our discussion on pp. 14-15, above, that review of a preliminary motion at final hearing is not a means of reopening prosecution and presenting new arguments. There, we pointed out that the rules governing interferences provide an orderly procedure and that the parties are entitled to rely on their being enforced by the Board. Myers v. Fegelman, 455 F.2d at 601, 172 USPQ at 584. If the Board does not follow and enforce PTO rules, then the parties might be tempted to ignore them too, as Singh has done here.

Moreover, consideration of Singh's new arguments would be grossly unfair to Brake. Such action would permit Singh, in effect, to file a new Opposition, without extending the same courtesy to Brake. Thus, Brake would have been limited exclusively to the arguments it made in the preliminary motion in the first instance, without placing similar limitations on Singh.

Accordingly, the arguments set forth on pp. 46-60 of Singh's brief (Paper No. 151) are herein DISMISSED.

b. Enablement

As we pointed out on p. 28, above, Singh did not discuss whether Brake 1 satisfies the enablement requirements of the first paragraph of § 112 in the Opposition filed in Paper No. 30. We considered some of Singh arguments as intending to demonstrate that the teachings of Brake 1 would not have enabled one skilled in the art

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“to make” a DNA construct within the scope of the count at the time the application was filed, but we find that most of the arguments on pages 60-77 of Singh’s brief bear little resemblance to those arguments.²⁹ See Paper No. 151. In fact, we find the majority of the arguments made in the referenced pages of Singh’s brief bear so little resemblance to the arguments in the Opposition that we consider them to be new arguments.

Therefore, we will not consider the new arguments, on their merits, since they were not timely filed. 37 C.F.R. § 1.655(a). Accordingly, the arguments set forth on pages 60-70 and 72-77 are herein DISMISSED.

c. Brake’s acquiescence to a new matter rejection

Singh argues that Brake’s abandonment of the Brake 1 application indicates that it [Brake] acquiesced to a rejection made by the examiner under § 112, first paragraph, concerning an amendment to the specification and, thus, Brake conceded the filing date of the Brake 1 application. Paper No. 151, pp. 77-83.

We note that these arguments were raised in Singh’s Opposition (Paper No. 30) to Brake’s Motion (2). In our discussion concerning said Opposition on pp. 29-31, above, we considered these arguments to be directed to the written description requirement of § 112, first paragraph, and found that they did not address a limitation present in the count. However, since Singh’s discussion is provided in a separate

²⁹ We acknowledge that Singh’s arguments on page 71, with respect to the unpredictability of the oligonucleotide mutagenesis technique and the problems with the Bal 31 digestion procedure were presented in the Opposition. Paper No. 30, p. 14. However, since we discussed these arguments on pp. 40-41, above, we need not address them here.

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section of the brief, it appears that Singh is still unable to determine whether this alleged “new matter” issue concerns written description or enablement, which are the relevant issues here. Given that four (4) years have passed between the filing of the Opposition and the brief, and Singh still has not directed these arguments to an appropriate section of § 112, we will not again speculate as to Singh’s intentions.

Rather, we dismiss these remarks as mere arguments of counsel to which we accord no evidentiary weight. In re Payne, 606 at 315, 203 USPQ at 256; Meitzner v. Mindick, 549 F.2d at 782, 193 USPQ at 22; In re Lindner, 457 F.2d at 508, 173 USPQ at 358.

VII. Singh’s Case-in-Chief

A. Background

In the brief filed April 2, 1996, in Paper No. 151, Singh argued that “The invention was first conceived by Dr. Singh and disclosed to another on or about October 1, 1982. From that date forward to an actual reduction to practice on February 10, 1983, Dr. Singh was said to have exercised reasonable diligence to an actual reduction to practice.” Paper No. 151, p. 14. See also the Preliminary Statement, Paper No. 12, p. 2. The Board decision pointed out that Singh had also argued that by December 1, 1982, Dr. Singh had a plan to delete the “glu-ala” portion of the α factor spacer sequence from the yeast vector, p60, which encoded, inter alia, the complete α factor spacer sequence, four additional amino acids (leu-glu-phe-met), and interferon D (IFN-D). Paper No. 151, pp. 85-87. Thus, in our view, Singh could not have conceived of the invention on October 1, 1982, as alleged. As an alternative

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position, Singh appeared to urge that Dr. Singh's conception occurred sometime before Brake's January 12, 1983, filing date. Id., p. 88

As to the events which were said to have occurred between December 1, 1982, and January 12, 1983, Singh argued (Paper No. 151, pp. 85-87):

By December 1, 1982, Dr. Singh had devised a plan to delete from the DNA construct contained in p60, the DNA encoding "Gh [sic, Glu] -Ala-Glu-Ala-Leu-Glu-Phe-Met." The resulting construct would conform to the Count. Dr. Singh's solution was to use a new methodology developed by his Genentech co-workers called "loop-deletion mutagenesis."

The loop-deletion mutagenesis process utilized methodology that was developed at Genentech late in 1982 and was first published late in 1983 by several Genentech scientists which included Mr. Vasser. (Vasser, SR 1059-1060; SX 53). As shown and described in the article, the DNA to be deleted was looped-out by the annealing of a synthetic oligodeoxyribonucleotide to the coding strand of the gene contained on the single stranded form of the recombinant phage M13mp8 DNA. The resulting heteroduplex structure was then stabilized using primer-directed *in vitro* DNA synthesis in the presence of T4 DNA ligase. On transformation of *E. coli*, the heteroduplex DNAs yield phage whose genomes contained either the original or the partially deleted gene, and genotypes were distinguished by *in situ* plaque hybridization with synthetic oligonucleotide probes.

On December 1, 1982, Dr. Singh requested the synthesis of an oligonucleotide 24 nucleotides in length to be used in his loop-deletion mutagenesis process. This is corroborated by Mr. Ng (Ng, SR 478, 516-517). This request was verified by the signatures of Mr. Vasser dated December 1, 1982 and Mr. Ng dated December 20, 1982. The request was also corroborated by other records kept by the DNA Synthesis department. (Ng, SR 478; SX 6, Bates No. 186; SX 7, Bates No. 192). Mr. Ng also verified that the synthesis was completed December 20, 1982 (Ng, SR 478). Dr. Singh and his co-workers subsequently used that methodology, and those materials, to successfully complete the reduction to practice.

Thus, on this record, the merits panel concluded that Singh had not met its burden of proving, by a preponderance of the evidence, that it had conceived of the invention of Count 1 on either October 1, or prior to January 12, 1983.

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Singh appealed to the Federal Circuit. Singh v. Brake, 222 F.3d 1366, 55 USPQ2d 1673, 1677 (Fed. Cir. 2000). There, the Court found that the Board had overlooked

two crucial pieces of evidence: first, a ‘Synthetic DNA Request’ form, dated December 1, 1982, in which Singh requested a 24-mer to carry out the loop deletion experiment, and second, a notation adjacent to the order explaining Singh’s intended use for the 24-mer^[30] [Singh v. Brake, 222 F.3d at 1368-69, 55 USPQ2d at 1677].

The Court also, noted that

the Board makes no mention of the facts that the 24-mer is of precisely the same length and of the precise complementarity needed to accomplish the loop deletion, and thereby obtain the claimed construct; indeed, that oligonucleotide is one of 2.8×10^{14} possible 24-mers that Singh could have ordered [Singh v. Brake, 222 F.3d at 1369, 55 USPQ2d at 1678].^[31]

³⁰ The Court noted that “the Board completely overlooked Singh’s notation adjacent to the DNA request form that clearly specified that the 24-mer was to be used for accomplishing the necessary loop deletion.” Singh v. Brake, 222 F.3d at 1369, 55 USPQ2d at 1678. To that end, we direct attention to Singh’s argument, above, wherein neither SX 3, Bates No. 126, nor the notation thereon, was mentioned. The Board cannot overlook that which was not argued. Nor does the Board have clairvoyant foresight to predict what the parties will argue on appeal. Keebler Co. v. Murray Bakery Products, 866, F.2d 1386, 1388, 9 USPQ2d 1736, 1738 (Fed. Cir. 1989)(“Prescience is not a required characteristic of the board. Thus, the board need not divine all possible afterthoughts of counsel that might be asserted for the first time on appeal”).

³¹ Again, we direct attention to Singh’s arguments above. We point out that Singh did not argue that the 24-mer Dr. Singh ordered on December 1, 1982, is of precisely the same length and of the precise complementarity need to accomplish the loop deletion. Nor did Singh argue that the referenced oligonucleotide is one of 2.8×10^{14} possible 24-mers that Singh could have ordered. The Board cannot consider arguments which are not made.

The Court stated that “the Board erred in rejecting Singh’s argument that the 24-mer had no other ‘substantial use’ than to accomplish the loop deletion.”³² Singh v. Brake, 222 F.3d at 1369, 55 USPQ2d at 1678.

The Court vacated the Board’s holding with respect to conception and remanded the case for the Board (i) “to consider the evidence in the December 21 entry, (ii) to reconsider Singh’s ‘substantial use’ argument, and (iii) to reevaluate the totality of the corroborative evidence on remand.” Singh v. Brake, 222 F.3d at 1369, 55 USPQ2d at 1679.

In order to ensure that the decision of this merits panel would be based on the same facts which were before the Federal Circuit, the parties were invited to re-brief the issue of Singh’s case for priority. Paper No. 171, Order Setting Times for Taking Action, pp. 2-4. Since we cannot make findings of facts on evidence not before us, the Order specifically asked the parties to address several of the issues raised by the Federal Circuit and to indicate the section(s) of the record which support their positions with respect to said issues.

³² Singh did not argue in its original Brief (Paper No. 151) that there was no other “substantial use” for the 24-mer. Rather, Singh presented this argument in its original Reply Brief (Paper No. 160, pp. 44-46). New arguments in a Reply Brief are improper and are not considered by the Board because the opposing party has no opportunity to respond. Photis v. Lunkenheimer, 225 USPQ 948, 950 (Bd. Pat. App. & Int. 1984).

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B. Conception

Conception is the touchstone of inventorship, the completion of the mental part of invention. Sewall v. Walters, 21 F.3d 411, 415, 30 USPQ2d 1356, 1358-59 (Fed. Cir. 1994). It is the “formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice.” Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1376, 231 USPQ at 87; Coleman v. Dines, 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir. 1985). Because it is a mental act, our appellate reviewing court has required corroborating evidence of a contemporaneous disclosure that would enable one skilled in the art to make the invention.” Kridl v. McCormick, 105 F.3d 1446, 1449, 41 USPQ2d 1686, 1689 (Fed. Cir. 1997); Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d 1223, 1227-28, 32 USPQ2d 1915, 1919; Coleman v. Dines, 745 F.2d at 359, 224 USPQ at 862. Moreover, with respect to corroboration of conception, the Court said in Price v. Symsek, 988 F.2d 1187, 1189, 26 USPQ2d 1031, 1036 (Fed. Cir. 1993) that “throughout the history of the determination of patent rights, oral testimony by an alleged inventor asserting priority over a patentee’s rights is regarded with skepticism, see Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 60 (1923); Deering v. Winona Harvester Works, 155 U.S. 286, 300-01 (1894); Barbed Wire Patent, 143 U.S. 275, 285 (1892), and as a result, such inventor testimony must be supported by some type of corroborating evidence.” In Price v. Symsek, 988 F.2d at 1189, 26 USPQ2d at 1036, the Court further stated:

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an inventor's testimony, standing alone, is insufficient to prove conception - some form of corroboration must be shown. Amax Fly Ash Corp., 514 F.2d [1041] at 1047, 182 USPQ [210] at 215 [Ct. Cl. 1975]. This rule is not new to patent law:

[C]onception by an inventor, for the purpose of establishing priority, can not be proved by his mere allegation nor by his unsupported testimony where there has been no disclosure to others or embodiment of the invention in some clearly perceptible form, such as drawings or model with sufficient proof of identity in point of time. For otherwise[,] such facile means of establishing priority of invention would, in many cases, offer great temptation to perjury, and would have the effect of virtually precluding the adverse party from the possibility of rebutting such evidence. Hence it has been ruled in many cases that the mere unsupported evidence of the alleged inventor, on an issue of priority, as to ... conception and the time thereof, can not be received as sufficient proof of ... prior conception [emphasis added].

A "rule of reason" applies to determine whether the inventor's conception testimony has been sufficiently corroborated, but it does not dispense with the requirement for some independent corroboration. Price v. Symsek, 988 F.2d at 1189, 26 USPQ2d at 1037; Coleman v. Dines, 754 F.2d at 360, 224 USPQ at 862. The "rule of reason" simply means that "[a]n evaluation of all pertinent evidence must be made so that a sound determination of the credibility of the inventor's story may be reached." Price v. Symsek, 988 F.2d at 1189, 26 USPQ2d at 1037. In other words, the "rule of reason" applies to corroboration, not to conception.

It is well established that conception consists of two parts: (1) the idea of the result to be accomplished, and (2) the knowledge of the means for effectively carrying out that idea. Rivise and Caesar, Interference Law and Practice, Vol. 1, § 110 (p. 319)(Michie Co. 1943). Thus, "conception of an invention is not the perception of or realization of the desirability of producing a certain result, but is rather the perception or

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realization of the means by which the result is produced.” Id., § 119, p. 350. Until the inventor has in mind the means as well as the desired result, he has not achieved complete conception. Land v. Dreyer, 155 F.2d 383, 386, 69 USPQ 602, 605 (CCPA 1946); Mergenthaler v. Scudder, 11 App. D.C. 264, 277 (D.C. Cir. 1897). Conception of a chemical invention requires both the idea of the compound plus a means of how to make and use it. Burroughs Wellcome Co. v. Barr Labs, Inc., 40 F.3d at 1227-28, 32 USPQ2d at 1919; Fiers v. Revel, 984 F.2d 1164, 1169; 25 USPQ2d 1601, 1604 (Fed. Cir. 1993); Oka v. Youssefye, 849 F.2d 581, 7 USPQ2d 1169 (Fed. Cir. 1988), citing Coleman v. Dines 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir. 1985); Alpert v. Slatin, 305 F.2d 891, 894, 134 USPQ 296, 299 (CCPA 1962).

“[T]he test for conception is whether the inventor had an idea that was definite and permanent enough that one skilled in art could understand the invention; the inventor must prove his conception by corroborating evidence, preferably by showing a contemporaneous disclosure. An idea is definite and permanent when the inventor has a specific settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue” [emphasis added]. Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d at 1227-28, 32 USPQ2d at 1919.

C. Burden of proof

Singh, as the junior party, whose application was copending with senior party Brake’s application, has the burden of proving its case for priority by a preponderance of the evidence. 37 C.F.R. § 1.657(b).

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D. Singh's case for priority

In view of its brevity, Singh's argument with respect to conception is reproduced in its entirety:

Singh respectfully submits that there can be no argument, in the wake of the decision of the Court in this case reflected at 55 USPQ2d 1673 (Fed. Cir. 2000) that Singh in fact had conception of the invention, including "the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention" no later than December 1, 1982. 55 USPQ2d at 1676, citing Kridl v. McCormick, 105 F.3d 1446, 1449, 41 USPQ2d 1686, 1689 (Fed. Cir. 1997). That specific and definite formation of the invention was the use of the 24-mer oligonucleotide ordered by Singh on December 1, 1982, whose order was corroborated, for use in the loop deletion method earlier developed. Although there are a variety of points of proof that may be relied on for corroboration, including the notebooks, the synthesis request, Singh's notation on the intended use of the synthesis request, all relied upon by the Court, the most compelling piece of evidence is the nature of the 24-mer itself. The 24-mer is the specific and complete oligonucleotide, having the necessary complementarity, to "loop out" the undesired sequences otherwise expressed by the α factor [Paper No. 180, pp. 9-10].

Contrary to our intention, Singh has failed to provide us with the arguments and citations to the record, that it apparently provided to the Court in Singh v. Brake, 222 F.3d 1362, 55 USPQ2d 1673 (Fed. Cir. 2000). When there is no citation to the record, it is very difficult, for us "to consider the evidence in the December 21 entry, to reconsider Singh's 'substantial use' argument, and to reevaluate the totality of the corroborative evidence on remand." Singh v. Brake, 222 F.3d at 1370, 55 USPQ2d at 1679. We cannot consider arguments which are not made and evidence which is not provided. Given the lack of citations to the record by Singh, it is not clear whether Singh intends to rely on (i) the arguments and evidence provided in its original brief i.e.,

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Paper No. 151, or (ii) the arguments made to the Court in Singh v. Brake.³³ With respect to the latter point, we find that Singh's arguments in the briefs before the PTO are not the same as the arguments made before the Court. To that end, we remind Singh that it is not the burden of this Board to scour the record and serve generally as an advocate for a party. Compare Ernst Haas Studio Inc. v. Palm Press Inc., 164 F.3d 110, 112, 49 USPQ2d 1377, 1379 (2d Cir. 1999). This would not be fair to the opposing party. Since we can only make findings of fact on the record before us, for purposes of this appeal, we have considered Singh's responses to two of the questions set forth in the Order Setting Times for Taking Action (Paper No. 171), as best representing its case for priority. These arguments appear to resemble the arguments made before the Court in Singh v. Brake, 222 F.3d at 1362, 55 USPQ2d at 1673, and are arguments to which Brake now has had an opportunity to respond. Accordingly, we direct attention to Paper No. 180, pp. 12-14, wherein Singh argues:

It is undisputed that Dr. Singh wished to remove the DNA encoding eight codons at the junction between the alpha factor lys-arg sequence and the beginning of the interferon gene and in doing so remove DNA that encoded the glu-ala sequences. He would carry out this deletion mutagenesis process utilizing a synthetic oligonucleotide. He drew such a plan in his notebook and

³³ We note that in Singh v. Brake, 222 F.3d at 1366, 55 USPQ2d at 1676, the Court states that

Specifically, Singh argues that the combination of the November 24 and December 21, 1982 notebook entries, the December 1, 1982 oligonucleotide order, and the testimony of DNA chemist Ng sufficiently corroborate his conception. Moreover, Singh contends that there was no use for the 24-mer ordered on December 1 other than to accomplish the desired loop deletion further corroborates his testimony.

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discussed the objective with his supervisor as well as at a meeting of his co-workers. Singh SR564:50, SX3:#108, Hitzeman SR158:8 [sic], SX 25:#483.

As recorded in his notebook verbatim, at the end of November he decided that he “will do in a different way and w/o without changing codons” SX3:#108. That “different way,” without changing codons, was indeed employed. A 24mer oligonucleotide was made for Dr. Singh’s own use in December 1982. The DNA molecules had a DNA sequence complementary to the unchanged codons, matching exactly the sequence complementary to four codons on each side of the site to

TTG GAT AAA AGA - TGT GAT CTC CCT SX3:#108 line 3 “sequence that the junction”

AAC CTA TTT TCT - ACA CTA GAG GGA 5' SX3:#126 the 24 mer in reverse sequence.

And, Paper No. 180, pp. 15-16:

... The reagents he [Dr. Singh] required were themselves extremely unique. A 24mer oligonucleotide (Singh SR564:47, SX3:#126), and the single strand DNA template made from a DNA fragment that, like his “p60” vector, had the site to be deleted encoded within it (e.g. the undesired Glu-Ala sequences). Singh SR566:52, SX3:#131-132. The existence of these two reagents, and further his corroborators conformation that they were in Dr. Singh’s possession in December of 1982 (Ng SR478:11, Lugovoy SR470-471:8), can only mean one thing - it is reasonable to conclude that he indeed formulated in December 1982, the very deletion method he used to carry out his idea in January 1983. Thus, the notation conforms with his direct testimony, and it is consistent with the problem he was known to be resolving. Singh SR564:47, SX3:#126.

E. Opinion on Priority

Count 1 is directed to a chemical compound, thus, as discussed above, “[c]onception requires (1) the idea of the structure of the chemical compound, and (2) possession of an operative method of making it.” Oka v. Youssefyeh, 849 F.2d at 581, 7 USPQ2d at 1171. “The idea must be definite and permanent in the sense that it

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involves a specific approach to the particular problem at hand. It must also be sufficiently precise that a skilled artisan could carry out the invention without undue experimentation” [emphasis added]. Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d at 1229-30, 32 USPQ2d at 1921.

Singh now shifts its argument and alleges that Dr. Singh had conception of a DNA construct within the scope of Count 1, and a novel method of making said compound by the “loop deletion” method on December 1, 1982. According to Singh, the “loop deletion” technique was a new method developed by researchers at Genentech in late 1982 and was published late in 1983. Paper No. 151, pp. 85-86. Paper No. 180, p. 9. We recognize that when a method of making a compound with conventional techniques is a matter of routine knowledge among those in the art, a compound may be conceived when it is described. Oka v. Youssefyeh, 849 F.2d at 581, 7 USPQ2d at 1171. Here, however, Singh acknowledges that “loop deletion” mutagenesis was not a conventional technique and was not a matter of routine knowledge among those skilled in the art on December 1, 1982. Thus, the relevant issue is: when did Dr. Singh have conception of a definite and permanent idea of the “loop deletion” approach to the problem of eliminating the nucleotide sequence encoding the “glu-ala” residues of the α factor spacer sequence present in the yeast

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plasmid p60?³⁴ Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d at 1229, 32 USPQ2d at 1921; Oka v. Youssefyeh, 849 F.2d at 581, 7 USPQ2d at 1171.

1. Dr. Singh's testimony with respect to his "plan"

Singh relies on Dr. Singh's testimony (SR 564, paras. 47 and 50 of his declaration), wherein he states [emphasis added]:

47. On December 1, 1982, I prepared a synthetic DNA request for a 24mer. This oligonucleotide was to be used for making the inframe deletion of the junction of α -factor pro sequence and interferon instead of the oligonucleotide discussed at paragraph 45. The 24mer requested was AGGGAGATCACATCTTTTATCCAA. A copy of this Synthetic DNA Request as well as a Synthetic DNA Specification form is shown at Notebook 1249, page 77 (Singh Exhibit 3, Bates No. 000126). As indicated on the Synthetic DNA Specifications, the purification of this 24mer was completed on December 20, 1982. (Singh Exhibit 3, Notebook 1249, Bates No. 000126).

And,

50. On December 14, 1982 I presented my results to the Research Review Group (RRG). Yeast secretion was discussed by myself and Ronald Hitzeman. Singh Exhibit 25 (Bates Nos. 000455-000487) includes a summary of the meeting and the documents I presented at the Meeting. In this Exhibit all but the pertinent information has been blocked out. At this meeting I described the α -factor gene organization and its structure including the spacer having the sequence lys arg followed by glu ala's. I also described that my future work would include removal of sequences from the interferon D expression plasmid with site directed deletion mutagenesis and construction of expression plasmids with a restriction site following the α -factor prepro sequence. (Singh Exhibit 25, Bates Nos. 000455-000487).

³⁴ p60 is a yeast plasmid which comprises a nucleotide sequence which encodes, 5' → 3', the α factor leader, the α factor spacer sequence (lys-arg-glu-ala-glu-ala), the amino acids leu, glu, phe, met, and interferon D (IFN-D).

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First, we point out that Dr. Singh is the sole inventor of the invention claimed in the Singh application involved in the interference and, as such, his testimony requires independent corroboration. Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d at 1229, 32 USPQ2d at 1921; Price v. Symsek, 988 F.2d at 1189, 26 USPQ2d at 1036-37.

Second, we find that Dr. Singh states that on December 1, 1982, he ordered a 24 mer for making an “inframe deletion of the junction of α factor prosequence and interferon.” However, an “inframe deletion” is a generic term which simply refers to any type of deletion wherein the reading frame of the nucleotides remains unchanged. Thus, we find that Dr. Singh’s statement reflects a goal that he hoped to achieve, rather than a specific and definite plan for performing the novel “loop deletion” mutagenesis technique. In fact, we find no mention of “loop deletion” mutagenesis in the sections of Dr. Singh’s testimony relied upon by Singh. Nor do we find that Dr. Singh testifies to having had any discussions with Genentech scientists, including Mr. Vasser, who were said to be involved with the development of this process (Paper No. 180, pp. 8-20).

2. Dr. Singh’s Notebooks as Corroborating Evidence

To demonstrate Dr. Singh’s conception of “loop deletion” mutagenesis Singh points to his [Dr. Singh’s] laboratory notebooks:

a. SX 3 Bates No. 108

SX 3, Bates No. 108, is said to be a page from Dr. Singh’s notebook. The page contains a handwritten date of recordation of “11/24/82.” The page contains a handwritten date of witnessing of “6/13/86.” The page reads as follows:

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b. SX 3 Bates No. 126

SX 3, Bates No. 126 is a page which is said to be from Dr. Singh's notebook. As an initial matter, we point out that the evidence before us is only a photocopy of what is said to be the original notebook page.³⁵ The page includes a "Synthetic DNA Request" for an oligonucleotide which is a 24-mer ("5' AGGGAGATCACATCTTTTATCCAA"). The requestor is listed as Arjun Singh. The order has been approved by Mark P. Vasser, and dated "12-1-82." According to Brake, and Singh does not disagree, the Synthetic DNA Request form shown on the page has been taped into the notebook.

In the upper left corner of the notebook page is an undated, handwritten notation which reads "oligonucleotide for making in-frame deletion of α pro-IFN-D junction." At the bottom of the page is a handwritten date "12/21/82" recorded by Dr. Singh. The witnessing was done three and one half years later; i.e., "6/13/86."

Singh urges that because the 24-mer shown on the laboratory notebook page dated "12/21/82" (SX 3, Bates No. 126) is complementary to the four (4) codons on each side of the glu-ala sequence indicated on the laboratory notebook page dated "11/24/82" (SX 3, Bates No. 108) that Dr. Singh conceived of the "loop deletion" mutagenesis technique for removing the glu-ala sequence of the α factor spacer

³⁵ We note Brake's belated submission of three (3) declarations; i.e., the declarations of Ms. Debra A. Shetka (Paper No. 187), Dr. Catherine M. Polizza (Paper No. 188) and Dr. Michael R. Ward (Paper No. 189), which discuss the different colors of ink present on Dr. Singh's laboratory notebook page, SX 3, Bates No. 126. See also, Brake Brief, Paper No. 190, pp. 70-71. We point out that the filing of these declarations is improper. To enter new evidence at this point, Brake's only recourse is to file a motion to reopen testimony. 37 C.F.R. § 1.687. This Brake did not do and, thus, the declarations have not been considered by this merits panel.

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sequence on December 1, 1982, the date the 24-mer was ordered. Paper No. 180, pp. 13-14.

In first considering the notebook pages alone, we point out that an inventor's notebooks generally do not constitute independent corroboration of an inventor's work. Rivise and Caesar, Interference Law and Practice, Vol. 1, §§ 126 and 127, pp. 126-128. Nevertheless, we find that Dr. Singh ordered the synthetic 24-mer on December 1, 1982. We make this finding because the order and the synthesis of the oligonucleotide are corroborated by Mr. Ng.³⁶ Thus, with respect to Dr. Singh's laboratory notebook page, SX 3, Bates No. 126, the order form and Mr. Ng's testimony corroborate Dr. Singh's ordering of the oligonucleotide. However, the order form does not corroborate the handwritten notation on the notebook page. Dr. Singh's notation stands uncorroborated.³⁷ Price v. Symsek, 988 F.2d at 1189, 26 USPQ2d at 1036 ("an

³⁶ Mr. Peter Ng states [SR 478, para. 11]:

11. On December 16, 1982, Arjun Singh requested the synthesis of a 24mer α -factor sequence, AGGGAGATCACATCTTTTATCCAA. The reference number was D1253-54. Column 7 of the Log Book shows that I completed the purification on December 20, 1982. (Singh Exhibit 6, Log Book, Bates No. 000186). (Singh Exhibit 7, Notebook 1301, Bates No. 000192). The synthetic DNA request form shows that I completed the purification of the oligonucleotide on December 20, 1982. (Singh Exhibit 3, Notebook 1249, Bates No. 000126).

³⁷ All of the pages in Dr. Singh's notebook on which Singh relies to establish conception were witnessed on "6/13/86" by Mr. Henner. To that end, we direct attention to Brake's arguments that Mr. Henner did not have first hand knowledge of Dr. Singh's work in December of 1982. Paper No. 190, p. 61. Brake points out that Dr. Singh did not explain the contents of his notebooks to Mr. Henner, but merely handed them to him for signing three and one half years after the work was said to have been performed. Id., pp. 61-62. Thus, although the page was eventually witnessed, Mr. Henner's signature does not corroborate the formation in Dr. Singh's mind of a "definite

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inventor's testimony, standing alone is insufficient to prove conception -- some form of corroboration must be shown"). On the record before us, we find it very disconcerting that Singh has not pointed to any evidence which establishes when the notation was written on the notebook page.

We recognize that physical exhibits, such as drawings, or in this case is an oligonucleotide, can be relied upon, as evidence of conception of the invention; however, "they must show a complete conception, free from ambiguity or doubt, and such as would enable the inventor or others skilled in the art to reduce the conception to practice without any further exercise of inventive skill." Gould v. Schawlow, 363 F.2d 908, 916, 150 USPQ 634, 641 (CCPA 1966), quoting Mergenthaler v. Scudder, 11 App. D.C. 264. That is, the exhibit must be sufficiently clear so as to enable those skilled in the art to understand it. Price v. Symsek, 988 F.2d at 1189, 26 USPQ2d at 1037. Here, we agree with Brake, that the notation in the laboratory notebook fails to provide a protocol or an outline of the "loop deletion" mutagenesis procedure. Paper No. 190, p. 57. The notation does not set forth Dr. Singh's plan as to how he intended to reduce his invention to practice. Thus, we find the notation insufficient to establish Dr. Singh's

and permanent idea of the complete and operative invention," as it was thereafter to be applied in practice by December 1, 1982. Burroughs Wellcome Co. v. Barr Laboratories Inc., 40 F.3d at 1228, 35 USPQ2d at 1919; Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1376, 231 USPQ at 87. Mr. Henner's signature indicating that he read and understood the notebook pages only establishes that the pages existed on the date signed. Mr. Henner's signature does not corroborate the statements made on those pages. Hahn v. Wong, 892 F.2d 1028, 1032, 13 USPQ2d 1313, 1317 (Fed. Cir. 1989).

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complete conception of this novel method of making a compound within the scope of the count using the ordered 24-mer.

Moreover, we find that, at best, the notation states a goal which Dr. Singh hopes to achieve; i.e., an in-frame deletion of the “ α pro-IFN-D junction.” As discussed above, an in-frame deletion is a generic term which refers to a deletion of nucleotides, by any method, wherein the reading frame remains unchanged. “Loop deletion” mutagenesis is species which falls within the genus of in-frame deletions. The notation does not describe the loop deletion mutagenesis means by which it is said that Dr. Singh planned to achieve his result. See Rivise and Caesar, Interference Law and Practice, Vol. I, § 110, p. 317 (“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”). Thus, even if we assume, arguendo, that the notation on the December 21, 1982, notebook page does not require independent corroboration, we find that the notation does not express a definite and permanent idea as to how to employ the 24-mer in the “loop deletion” mutagenesis procedure to accomplish that goal.

We further point out that even if we assume, arguendo, that the notation does not require independent corroboration, there are additional reasons as to why we find that it [the notation] fails to establish that Dr. Singh had a definite and permanent idea of the specific approach of using the novel Genentech “loop deletion” mutagenesis technique prior to January 12, 1983.

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First, we agree with Brake that Singh has not pointed to any evidence which shows when the “loop deletion” method was actually developed by researchers at Genentech. Paper No. 190, p. 59. The record shows that a description of the method may have been submitted for publication on April 4, 1983, and that a description was published in September, 1983. Paper No. 190, p. 14; SX 53. Thus, on the record before us, we have only attorney argument that the loop deletion mutagenesis technique was known at Genentech in late 1982. Paper No. 151, pp. 85-86; Paper No. 180, p. 9. It is well established that attorney argument cannot take the place of objective evidence. In re Payne, 606 F.2d at 315, 203 USPQ at 256; Meitzner v. Mindick, 549 F.2d at 782, 193 USPQ at 22; In re Lindner, 457 F.2d at 508, 173 USPQ at 358. In addition, it is not clear when or how Dr. Singh became aware of this technique. We find no mention of the loop deletion mutagenesis technique or reference to date(s) of discussions with the Genentech researchers who developed the technique, such as Mr. Vasser,³⁸ in the sections of Dr. Singh’s declaration relied upon by Singh.

³⁸ Mr. Vasser is listed as a co-author on the Genentech publication which describes the loop deletion mutagenesis technique. SX 53, Bates No. 703. However, Singh only relies on Mr. Vasser’s testimony to corroborate the ordering of the 24-mer on December 1, 1982. Paper No. 180, p. 14. Mr. Vasser states (SR 1059, para. 4):

4. At the request of counsel, Mr. Ng and I searched for and have retrieved from our files the Synthetic DNA Request forms for all eight of the DNA synthesis requests which are discussed in Mr. Ng’s declaration. The eight DNA sequences discussed in Mr. Ng’s declaration are requested on six Synthetic DNA Request forms. I have reviewed the six Synthetic DNA Request forms and recognize my signature and Mr. Ng’s signature on these forms. Five of the copies are the “pink” copies. These have been in our possession since the original requests were given to us and are in the original condition with no alterations. We also located and retrieved the sixth form, numbered 02478,

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Second, Brake points out the loop deletion method described in the September, 1983, Genentech paper (SX 53) mandates the use of two (2) unique oligonucleotide primers.³⁹ Paper No. 190, p. 52. An additional primer (the “LAC” primer), which is complementary to a region upstream from the site of mutagenesis, is also required. Id., SX 53, Bates No. 708, col. 2, last paragraph and Figure 3. Although it is an essential reagent for the “loop deletion” procedure, Singh does not point to any evidence which indicates that Dr. Singh ordered or possessed the LAC primer on December 1, 1982, or understood the need to order or possess said primer prior to January 12, 1983.

which is a photocopy of the original “pink” file copy. Written on it, in the top right hand corner, is a note in Mr. Ng’s handwriting, which I recognize, which states as follows: “legal got original, Peter 2/27/92.” That particular form has been maintained in our possession as a part of these files since that date. The original pink copy was maintained in our possession from the date of the request until 2/27/92. Copies of the original “pink” copies and one photocopy are shown and Singh Exhibit 54, Bates No. 000714-000719.

Thus, we find that Mr. Vasser does not mention the loop deletion mutagenesis technique, let alone testify as to his awareness that Dr. Singh intended to employ the 24-mer to make a compound within the scope of the count using said technique.

³⁹ Brake directs attention to the teachings of the Genentech article which describes the differences between the new loop deletion procedure and prior mutagenesis techniques. Paper No. 190, pp. 58-59. The teachings are, in relevant part:

Similar in vitro mutagenesis protocols involving a single primer ... have been used by others. In such a single primer approach, heteroduplex structures are stabilized by eventually joining the 3' end of the in vitro-synthesized DNA to its own 5' end after synthesis of one full-length complement of the template DNA. To obtain heteroduplex stability after short times of DNA synthesis, we used an additional primer (“LAC”) complementary to a region upstream from the site of mutagenesis [SX 53, Bates No. 708].

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Conception of a complete and definite method of making the DNA construct using “loop deletion” mutagenesis requires a showing that Dr. Singh planned to employ both the 24-mer and the LAC primer prior to January 12, 1983. This Singh has not done.

Hybritech Inc. v. Monoclonal Antibodies, Inc.

We note the Court’s comments that belated witnessing of laboratory notebooks does not undermine all the corroborative value of the entries therein. Singh v. Brake, 222 F.3d at 1369, 55 USPQ at 1678. The Court directs our attention to Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1378, 231 USPQ at 89 (Fed. Cir. 1986), and points out that “Hybritech indicates that in some cases, conception may be proved solely on the basis of laboratory notebook entries witnessed subsequent to their entry.” Id. We have considered the referenced section of Hybritech, however, we find that there are crucial differences between the facts of this case and the facts in Hybritech which justify a different outcome.

First, the Hybritech Court found that the inventor’s (Dr. David’s) January, 1979, notebook provided a detailed description of a nylon apparatus which could be used for performing a sandwich assay using monoclonal antibodies. Hybritech, 802 F.2d at 1377, 231 USPQ at 88. The Court further found that the notebook described

the procedure for detecting an antibody “(a-x)” to an antigen “(x)” complete with diagrams and text, both illuminated by Dr. David at trial. The notebook further states, “Alternatively, if one wished to quantitate an antigen, y, the identical procedure would be followed, except that reagents would be reversed, i.e., the reaction would be:” and there follows a clear illustration of an antibody attached to a solid carrier reacting with an antigen to form a complex, and that complex reacting with a second labelled [sic, labeled] antibody. The notebook was signed

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by Dr. David on January 4, 1979, and witnessed and signed on January 30 of the same year by Dr. Curry, the first cell biologist hired at Hybritech to set up the hybridoma production program [emphases added].

The Court found the inventor's testimony was corroborated by later notebook entries which disclosed experimental data such as counts per minute of the labeled antibody (August, 1979), and results confirmed by a dose response curve (September 21, 1979).

In our view, an order for one oligonucleotide (the 24-mer) and a single notation ("oligonucleotide for making in-frame deletion of α pre-IFN-D junction"), in Dr. Singh's notebook are not equivalent to the descriptive level found by the Court in Hybritech when it stated that conception may be found on the basis of an inventor's unwitnessed notebooks. Here, in Dr. Singh's notebooks, we find only an order for a 24-mer (one of two oligonucleotides needed to perform loop deletion mutagenesis) and a notation which indicates a goal that Dr. Singh hopes to achieve using the 24-mer, not a game plan for its (the 24-mer) use. A Hybritech equivalent to Dr. Singh's order for the 24-mer and notation as to its intended use, would be if the inventors in Hybritech only provided an order for one reagent, such as a monoclonal antibody, and a notation in a notebook stating "antibody for use in an immunoassay." Had the Hybritech inventors then appeared at trial with complete diagrams and text of the sandwich assay which was actually performed, we venture to say that the outcome would have been different -- as it should be here.

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Moreover, descriptive support is especially critical in this case since Singh acknowledges that the loop deletion mutagenesis procedure conceived by Dr. Singh was not publicly available; i.e., it was a novel technique unknown to those skilled in the art on December 1, 1982. Thus, we find an order for only one of two oligonucleotides needed to perform the referenced procedure, and an uncorroborated notation which generically refers to any method of in-frame deletion, insufficient to corroborate Dr. Singh's conception of "a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice." Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d at 1228, 32 USPQ2d at 1919.

Second, although the laboratory notebooks in Hybritech were not witnessed contemporaneously, they were nevertheless witnessed within a few months to one year of their writing; i.e., by May, 1980. Since the Court found that the other researchers in the field (La Jolla Cancer Research Foundation) could not demonstrate a prima facie reduction to practice before Hybritech's August 4, 1980, filing date, this meant that Hybritech's laboratory notebooks were witnessed before the critical date. Thus, the date was not critical in Hybritech; here it is.

Accordingly, in view of the foregoing, unlike Hybritech, we find Dr. Singh's uncorroborated notation in his laboratory notebook (SX 3, Bates No. 126), insufficient to establish his conception of a specific and settled plan to perform the novel loop deletion technique using both the 24-mer and the LAC primer. Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d at 1228, 32 USPQ2d at 1919.

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3. Other corroborating evidence relied upon by Singh

a. “Hitzeman SR158:8” and SX 25, Bates No. 483

Singh argues that Dr. Singh discussed his objective with his supervisor and at a meeting with his coworkers. Paper No. 180, p. 12. Singh relies on “Hitzeman SR158:8” and SX 25, Bates No. 483 for support. *Id.* at pp. 12, 17, 19.

Singh’s reliance throughout its brief (Paper No. 180) on “SR158:8,”⁴⁰ i.e.,

⁴⁰ We note that in its original brief, Singh relied on the declaration of Dr. Hitzeman (SR 168, para. 8). Dr. Hitzeman states:

8. On December 14, 1982, I gave a presentation on yeast secretion to the RRG. In addition to myself, Arjun Singh presented his work on α -factor yeast secretion. As evidenced by the Research Summary of this meeting (Document GP530002489-2521) (Singh Exhibit 25, Bates Nos. 000455-000487, in which all but the pertinent information has been blocked out), Arjun Singh describes the α -factor gene organization and the structure of the spacer including the lys arg glu ala glu ala construct at this meeting. Arjun also indicated at this meeting that his future work would include the removal of these sequences from the interferon D expression plasmid using site directed mutagenesis and the construction of expression plasmids with a restriction following the α -factor preprosequence.

However, even if we assume, *arguendo*, that Singh intended to rely on Dr. Hitzeman’s declaration, we find that it fails to corroborate the claim that Dr. Singh had formulated a definite and permanent idea to employ the new loop deletion mutagenesis method to remove the nucleotide sequence encoding the glu-ala residues of the α factor spacer sequence present in the interferon D expression plasmid on December 1, 1982. Dr. Hitzeman not only fails to specify which amino acids would be removed, but he also fails to mention the technique of loop deletion mutagenesis. To the contrary, Dr. Hitzeman only mentions site-directed mutagenesis which is further described in paragraph 9 of his declaration. According to Dr. Hitzeman:

9. During the period 1982 to 1983, site-directed deletion mutagenesis was a known technique. As set forth in Sambrook, et al. “Molecular Cloning, “ 2nd Edition (1989) at pages 15.51 and 15.52 (Singh Exhibit 26, Bates Nos. 000564-566), this technique was known in the early 1970’s and had developed into an established methodology by 1982.

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paragraph 8 of the declaration of Dr. Audrey Goddard, is unclear. The declaration reads as follows:

8. The C-track of clones 4, 6 and 9 are identical. The position of C's in the autoradiograph for clones 4, 6 and 9 corresponds to the expected positions from original nucleotides 220 to 290 of the original sequence if a deletion of nucleotides 256-279 (inclusive) have occurred in these clones at the anticipated deletion site. (Singh Exhibit No. 4, Notebook 1576, Bates Nos. 000148-000152).

We find Dr. Goddard's testimony insufficient to corroborate Dr. Singh's complete conception of the loop deletion mutagenesis method to construct a species within the scope of the count. Dr. Goddard appears to be discussing some partial nucleotide sequencing reactions which were performed in February, 1983; it is not apparent where there is any mention of Dr. Singh's alleged December, 1982 plan to employ the 24-mer in the loop deletion mutagenesis procedure. Thus, Dr. Goddard's testimony is irrelevant both in terms of subject matter and time. Accordingly, we find that Dr. Goddard's testimony fails to corroborate Dr. Singh's claim that he conceived of a "definite and permanent idea of the complete and operative invention," using loop deletion mutagenesis on December 1, 1982, or prior to January 12, 1983. Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d at 1228, 32 USPQ2d at 1919.

Thus, we find Dr. Hitzeman's testimony does not adequately support Singh's position that Dr. Singh conceived of a definite and permanent plan to employ loop deletion mutagenesis to remove the nucleotide sequence encoding the glu-ala residues from the α factor spacer sequence in the interferon D expression plasmid (p60).

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As to SX 25, Bates No. 483, we find that it is a page in what is said to be a Research Summary presented by Drs. Singh and Hitzeman on December 14, 1982.

Page 483 is entitled "Future Work" and reads as follows:

Future Work

1. Determination of processing signals.
 - A. Removal of sequences from the interferon D expression plasmid - M13 cloning, site-directed deletion mutagenesis.
 - B. Construction of expression plasmids with restriction site followed by the alpha-factor "pre-pro" sequence.
 - C. Use of an aminopeptidase?
2. Portable α -factor signals sequence for use with another promoter.
3. Construction of a promoter fragment [undated, handwritten notation which states: "from α -factor gene"]
4. Cellular location of non-secreted heterologous proteins.
5. Determination of mRNA levels.
6. Screening of strains for better secretion.

Here, although presented two weeks after Dr. Singh ordered the 24-mer, we find no mention of the oligonucleotide, loop deletion mutagenesis, or a plan to delete the nucleotide sequence encoding the glu-ala residues of the α factor spacer sequence from the interferon D expression plasmid. The "Future Work" does not indicate which sequences are to be removed from the interferon D expression plasmid, and the only technique mentioned with respect to the removal of the undisclosed sequences is site-directed mutagenesis.⁴¹ Thus, we find the Research Summary insufficient to

⁴¹ As discussed on pp. 38-39 and footnote 40, above, Drs. Singh and Hitzeman have both testified that site-directed mutagenesis is a different technique. SR 168,

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corroborate Singh's position that Dr. Singh conceived of complete plan to employ loop deletion mutagenesis to construct a species within the scope of the count on December 1, 1982, or prior to January 12, 1983.

b. Lugovoy SR470-471, para. 8

Singh argues that Dr. June Lugovoy's declaration establishes that Dr. Singh was in possession of the 24-mer and a single strand DNA template in December of 1982.

Paper No. 180, p. 15. Dr. Lugovoy's states:

8. On September 7, 1982, I constructed plasmid p60, as shown in Notebook 1269, page 18 (Singh Exhibit 21, Bates No. 000428). My notes at the bottom of Notebook 861 page 22 (Singh Exhibit 20, Bates No. 000418) indicate that p60 was derived from plasmid p58 by partial cutting with RI to isolate a DNA fragment having the promoter presequence of alpha-factor in the LEUKD gene, and then put this DNA fragment into YEp9T cut with RI. The restriction map of p60 is shown in Notebook 861, page 22 (Singh Exhibit 20, Bates No. 000418). My description of p60 indicates that it contained the alpha-factor promoter presequence in the LEUKD sequence, in a high copy number plasmid. The confirmation of the construct of p60 is shown in Notebook 1269, page 20 (Singh Exhibit 21, Bates No. 000429). Plasmid p65 was constructed between September 7, 1982 (the date p60 was constructed) and September 9, 1982 (the date p66 was constructed) as shown in Notebook 861 page 21 (Singh Exhibit 20, Bates No. 000420) which references Notebook 1269 page 23 (Singh Exhibit 21, Bates No. 000430) which shows construction on September 9, 1982.

We find the section of Dr. Lugovoy's declaration relied upon by Singh to be irrelevant both in subject matter and point in time. Dr. Lugovoy's statements are directed to events which occurred in September, 1982, and thus are insufficient to corroborate Dr. Singh's conception of a definite and permanent plan to employ the loop

para. 9; SR 568, para. 58.

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deletion mutagenesis technique to construct an invention within the scope of the count on December 1, 1982, or prior to January 12, 1983.

c. The nature of the 24-mer

According to Singh, “It is blatantly apparent to anyone who can follow the base-pairing rules that the 24-mer ordered on December 1, 1982 was of the precise length and complementarity to the flanking sequence which was set forth in the November 24 entry noted by the Federal Circuit.” Paper No. 180, p. 16.

Singh argues (Paper No. 180, p. 17) that the evidence in the record which supports

... the facts [sic] that the 24-mer is of precisely the same length and of the precise complementarity needed to accomplish the loop deletion [is]: (1) The synthetic DNA order form has the DNA sequence of the oligonucleotide in question. SX3:#126. If one counts the number of nucleotides listed on the form it is indeed 24. (2) The sequence of the site at the junction to be deleted is correctly set forth in Dr. Singh’s notes as are the flanking 12 nucleotides sequences which are indeed complementary to the 24-mer oligonucleotide. SX3:#108, #126.

TTG GAT AAA AGA- TGT GAT CTC CCT SX3:#108 line 3 “sequence at the junction”

AAC CTA TTT TCT- ACA CTA GAG GGA 5' SX3:#126 the 24mer in reverse sequence

Dr. Singh testified regarding this work. Singh SR564: 47, 52 (4). Dr. Singh’s direct testimony explaining this work is corroborated by not only these documents, but also by the testimony of Mr. Ng SR478:11, Ms. Lugovoy SR470-471:8, and Dr. Hitzeman SR158:8.

We agree that the 24-mer is complementary to the nucleotide sequence which encodes “leu-asp-lys-arg-cys-asp-leu-pro” as shown in SX 3, Bates No.108 and thus, could be used in the loop deletion method described in the Adelman publication (SX 53- see Figure 3); however, we find this insufficient to establish that Dr. Singh had “a

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definite and permanent idea of the complete and operative invention”; i.e., that Dr. Singh had a definite and permanent realization of the loop deletion method of making an “n=0” DNA construct within the scope of Count 1, on December 1, 1982. Burroughs Wellcome Co. v. Barr Laboratories Inc., 40 F.3d at 1228, 32 USPQ2d at 1919; Oka v. Youssefyeh, 849 F.2d at 581, 7 USPQ2d at 1171.

First, we agree with Brake that Singh has not pointed to any evidence which demonstrates when the loop deletion mutagenesis technique was developed at Genentech. Paper No. 190, p. 59. On the record before us, we seem to have only argument of counsel that the method was available, and known to Dr. Singh, in late 1982. As discussed above, we accord arguments of counsel little, or no, evidentiary weight. In re Payne, 606 F.2d at 315, 203 USPQ at 256; Meitzner v. Mindick, 549 F.2d at 782, 193 USPQ at 22; In re Lindner, 457 F.2d at 508, 173 USPQ at 358.

Second, the loop deletion mutagenesis procedure requires the use of two unique oligonucleotides; one which is complementary to the region which is to be mutagenized and one which is complementary to a region upstream of the site of mutagenesis (the “LAC” primer). SX 53, p. 188, col. 2, last para. At best, Singh has established that Dr. Singh may have been in possession of one of two oligonucleotides which ultimately would be required to perform loop deletion mutagenesis. Singh has not pointed to any evidence which demonstrates that Dr. Singh contemplated or knew of the need for the second oligonucleotide prior to January 12, 1983. To that end, our only finding of Dr. Singh’s awareness of the need for the “LAC” primer in the loop deletion mutagenesis procedure is a notation in his laboratory notebook (SX 3) at Bates No. 136, dated

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January 21, 1983. However, this is after Brake's critical date; i.e., after January 12, 1983.

Third, contrary to Singh's argument, we find no mention in Dr. Singh's testimony ("Singh SR564:47, 52") that the 24-mer ordered on December 1, 1982 is of the precise length and complementarity needed to accomplish the loop deletion. We direct attention to our discussion of Dr. Singh's testimony at SR 654, Bates No. 47, on p.55-56, above. As to paragraph 52 of his declaration, we find that Dr. Singh states:

52. On December 18, 1982, I isolated the 1800 based pair complete α -factor promoter prepro/spacer-interferon D sequence from p60 and inserted the fragment into the plasmid M13mp8 for deletion mutagenesis, as shown at Notebook 1249, page 75. (Singh Exhibit 3, Bates No. 00124).^[42]

There is no mention of the 24-mer in paragraph 52 of Dr. Singh's testimony.

As to the testimony of Mr. Ng SR 478, para. 11, Dr. Lugovoy SR 470- 471, para. 8, and "Hitzeman SR158: 8" [sic], we direct attention to our discussions on pp. 59, 67 and 70-71, above. Contrary to Singh's arguments, we have not found where these

⁴² As to Singh Exhibit 3, Bates No. 00124, we find a handwritten notation which reads in its entirety:

Isolate 1800 bp α f promoter - prepro - IFN-D gene
from p60 - partial RI digest-
Clone in RI site of M13mp8
Determine orientation

The page contains a handwritten date of "12/18/82," and a handwritten date of witnessing of "6/13/86." We find no mention of the 24-mer and its being of the precise length and complementarity needed to accomplish the loop deletion mutagenesis technique.

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declarants mention that the 24-mer is of the precise length and complementarity needed to perform loop deletion mutagenesis.

Singh argues that the “oligonucleotide is one of 2.8×10^{14} possible 24-mers that Dr. Singh could have ordered.”⁴³ Paper No. 180, p. 18. According to Singh, the:

⁴³ Singh’s argument is not clear. That is, it is not clear whether Singh intends to argue that if Dr. Singh were to make (i) any 24-mer oligonucleotide that there are 2.8×10^{14} possible nucleotide combinations, or (ii) a 24-mer which is complementary to the eight (8) amino acids at the junction (SX 3, Bates No. 108) that there are 2.8×10^{14} possible nucleotide combinations. We address the former argument on p. 76, wherein we state that there is only one oligonucleotide sequence which is an exact complement of the junction region.

However, if Singh intends to argue the latter, we point out that the mathematical calculation wherein there are said to be four (4) possible nucleotides for all 24 nucleotides (8 codons) comprising an oligonucleotide (a 24-mer) which complements the eight (8) amino acids at the junction (i.e., leu-asp-lys-arg-cys-asp-leu-pro), is incorrect. Degeneracy of the genetic code does not involve each nucleotide in the codon. The degeneracy usually occurs with the third nucleotide codon, and with the eight (8) amino acids under consideration here, never in all three positions. For example, if we consider the amino acid “lys” which occurs once in the series of amino acids at the junction, and use a genetic dictionary (BX 25), we find that it is encoded by “AAA” or “AAG.” Thus, there are only two (2) possible codons for this amino acid or, conversely, only two codons which will complement the nucleotide sequence. However, according to Singh’s method of calculating there would be 4 to the 3rd power (4^3) or 64 possibilities. We point out that of the eight (8) amino acids at the junction, “leu” and “arg” are encoded by the greatest number of codons; i.e., “leu” and “arg” are each encoded by six (6) different codons. For example “leu” is encoded by “TTA,” “TTG,” “CTT,” “CTC,” “CTA” and “CTG.” However, according to Singh’s method of calculating, “leu” (and “arg”) would be encoded by 4 to the 3rd power (4^3) or 64 possible codons. Continue this faulty method of calculating for the remaining codons, and the problem becomes greatly exaggerated, as it has been here. Thus, we find that only attorney argument could turn a sequence of eight (8) amino acids into a sequence which is encoded (or complemented) by 2.8×10^{14} possible oligonucleotides. Accordingly, it is with good reason the Court has held on numerous occasions that arguments of counsel cannot take the place of objective evidence. In re Payne, 606 F.2d at 315, 203 USPQ at 256; Meitzner v. Mindick, 549 F.2d at 782, 193 USPQ at 22; In re Lindner, 457 F.2d at 508, 173 USPQ at 358. While we have taken the time to point out the error in this argument, we nevertheless adhere to our original position, i.e., if Dr. Singh wanted an oligonucleotide which was complementary to the eight (8) amino acids at the junction,

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Evidence in the record supports this calculation: (1) the oligonucleotide is indeed 24 units in length SX3:#126, and (2) 4 to the 24th power is indeed 2.8 times 10¹⁴.

Evidence supports the fact that it was possible that Dr. Singh could have ordered any one of these many different 24 mers: (1) Dr. Singh's testimony is that he prepared the synthetic DNA request (Singh SR564:47), and (2) Mr. Ng and Mr. Vasser filled the request ordered by Dr. Singh as well as numerous other requests made by him at other times. Ng SR478:11, Vasser SR1059:4. There is nothing in the record that suggests that Dr. Singh was not free to order any DNA he wanted.

The number of units (nucleotides) in an oligonucleotide and a mathematical calculation generated therefrom are not evidence that the 24-mer is one of 2.8 X 10¹⁴ possible oligonucleotides Dr. Singh could have ordered. Rather, we find that the calculation is nothing more than unsupported argument of counsel to which we accord, little, or no, evidentiary weight. In re Payne, 606 F.2d at 315, 203 USPQ at 256; Meitzner v. Mindick, 549 F.2d at 782, 193 USPQ at 22; In re Lindner, 457 F.2d at 508, 173 USPQ at 358.

Moreover, we find Singh's argument that we should consider all of the possible oligonucleotides that Dr. Singh could have ordered to be misdirected. If we go down that road, then we should also consider that Dr. Singh could have ordered a 20-mer, a 30-mer, and an oligonucleotide of any other length above, below and in between, and include these oligonucleotides in the calculation. We would soon find that there would be nearly an infinite number of possibilities as to what Dr. Singh could have done. However, this method of reasoning could be applied in every case and with every

for any reason, there was only one oligonucleotide possible.

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inventor. That is, an inventor could always have been doing something else, but instead, performed Experiment X, ordered reagent Y, etc. If we were to apply this method of reasoning, it would mean that whenever any work of an inventor is offered that it should be accepted as evidence of conception, diligence, etc., because the inventor could have been doing something else. It would be impossible to determine priority, or resolve other issues, if each time we considered what the inventors could have otherwise have been doing, as opposed to what they did do? In our view, our fact-finding duty is best discharged when we consider what an inventor has done, and based on the evidence provided, determine whether a party has met its burden of proof for the issue at hand.

To that end, when we consider the 24-mer itself, and not what oligonucleotides could have been ordered, we agree with Brake, that if Dr. Singh wanted an oligonucleotide which was complementary to the “sequence at the junction” (SX 3, Bates No. 108), for any purpose, he had a choice of only one oligonucleotide due to natural base-pairing laws. Paper No. 190, p. 66. We are not aware of any other possibilities.

As to Singh’s reliance on the testimony of Dr. Singh (SR 564, para. 47), Mr. Ng (SR 478, para. 11), and Mr. Vasser (SR 1059, para. 4), to support its position with respect to the possible number of oligonucleotides Dr. Singh could have ordered, we direct attention to our discussions of these declarations above. Contrary to Singh’s argument, we find no mention of the mathematical calculation, or of the 24-mer being one of 2.8×10^{14} possible 24-mers that Dr. Singh could have ordered. Thus, on the

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record before us, we find Singh's contention that the 24-mer is one of 2.8×10^{14} possible 24-mers that Singh could have ordered to be attorney argument. As discussed above, we accord such argument little, if no, evidentiary weight. In re Payne, 606 F.2d at 315, 203 USPQ at 256; Meitzner v. Mindick, 549 F.2d at 782, 193 USPQ at 22; In re Lindner, 457 F.2d at 508, 173 USPQ at 358.

d. No other substantial use for the 24-mer

Singh argues (Paper No. 180, p. 20) that :

... Because of the unique DNA sequence of the 24-mer oligonucleotide and the M13 template, there is no other use for these materials. The first four codons are from the alpha factor (leu-asp-ly [sic, lys]-arg), and the next four codons are from the interferon (cys-asp-leu-pro), and the target sequence for his deletion mutagenesis is present on the single strand template. SX3:#108, #126, #131-132[.] The "no other use" test is a more stringent test than required.

Here, Singh points to several pages in Dr. Singh's laboratory notebook to support its position that there is no other use for the 24-mer and "the M13 template."⁴⁴ We have discussed notebook pages Bates Nos. 108 and 126, above, and we agree that the latter page contains a DNA Synthesis Request form for the 24-mer which was

⁴⁴ Singh does not explain what is meant by "the M13 template." If we assume, arguendo, that by "the M13 template," Singh means the published M13mp8 vector shown on Bates No. 131, then it appears from the published restriction map of the M13 template that it is not unique to Dr. Singh's work concerning loop deletion mutagenesis. Rather, M13 is a well-known vector for cloning and sequencing DNA. Alternatively, if we assume, arguendo, that by "the M13 template" Singh means that Dr. Singh inserted the same DNA sequence encoding the Saccharomyces α factor promoter, leader sequence, spacer sequence and human interferon D contained in p60 into M13mp8, this simply means that he has placed said DNA in a different vector. Absent evidence to the contrary, this does not indicate or suggest that there is no other use for "the M13 template" other than for loop deletion mutagenesis, any more than would the presence of said DNA in another vector, or p60 itself.

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ordered on December 1, 1982. However, we find no mention on the referenced page that there is no other use for the oligonucleotide other than for loop deletion mutagenesis. As to the former page (Bates No. 108), we agree that the 24-mer is complementary to the nucleotide sequence of the four amino acids at each end of the “sequence at the junction.” However, we find no mention of the 24-mer on this notebook page (probably because it was not ordered until a week later), and thus, no mention that there is no other use for the oligonucleotide. It is not clear to us, and Singh has not explained, how the combination of these two pages establishes that there is no other use for the 24-mer other than for loop deletion mutagenesis.

Turning to notebook pages Bates Nos. 131-132, we find two handwritten notebook pages from Dr. Singh’s notebook dated “1/5/83” and witnessed on “6/13/86.” The upper right hand corner of Bates No. 131 contains an insert from an undisclosed publication which is entitled “RESTRICTION MAP OF M13mp 8.” As to the two handwritten pages, we point out that documents do not speak for themselves; they must be explained. See 37 C.F.R. § 1.671(f)⁴⁵ which requires a witness to explain the

⁴⁵ 37 C.F.R. § 1.671 (f) states “[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.”

Here, because of the complexity of the biotechnology art, and the uniqueness of its terminology, it is important that a witness’s explanation as to the content of a document be sufficiently clear and detailed as to the specific entries in the exhibit(s) relied upon 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

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entries on the various pages of the notebooks/exhibits. This Singh has not done, and in our review we find nothing on the two notebook pages which suggests that the 24-mer oligonucleotide ordered on December 1, 1982, and “the M13 template” have no other use other than for loop deletion mutagenesis.

Here, we agree with Brake that a reagent’s suitability for one purpose is not probative of the number of uses to which it can be put. Paper No. 190, p. 67. We point out that the burden is on Singh to prove, by a preponderance of the evidence, that there is no other reasonable use for the 24-mer other than for loop deletion mutagenesis. Here, however, Singh has not pointed to any testimony from Dr. Singh, or other investigators at Genentech, to demonstrate that there was no other use for the oligonucleotide. Rather, we find that Singh is attempting to shift the burden to Brake, and possibly this merits panel, to establish that there were other uses for the 24-mer other than the loop deletion mutagenesis technique performed by Dr. Singh. This is not the proper legal standard. Since Singh has failed to point to any evidence on which we are able to determine that there is no other use for the 24-mer, we find its position to be based solely on arguments of counsel.⁴⁶ Since such arguments cannot take the place

notes or notebooks attached to the affidavit or declaration. It is not the burden of the Board to try to read the exhibits and correlate allegations made in the brief or testimony with specific entries. Amoss v. McKinley, 195 USPQ 452, 453-54 (Bd. Pat. Int. 1977).

⁴⁶ We point out that counsel’s arguments are inconsistent with the record in this case. Singh discloses that the 24-mer can be used in the method relied upon for constructive reduction to practice. See Application 06/506,098, p. 26 and Figure 11. Singh’s application discloses a method wherein the 24-mer is employed “to modify the junction between the factor ‘pre-pro’ sequence and the IFN- α_1 gene such that the removal of the modified ‘pre-pro’ sequence will result in the release of a mature

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of objective evidence, we accord arguments of counsel little, or no, evidentiary weight.

In re Payne, 606 F.2d at 315, 206 USPQ at 256; Meitzner v. Mindick, 549 F.2d at 782, 193 USPQ at 22; In re Lindner, 457 F.2d at 508, 173 USPQ at 358.

We are mindful of the Court's concern that the no other "substantial use" rule set forth in Berges v. Gottstein, 618 F.2d 771, 774-75, 205 USPQ 691, 694 (CCPA 1980), may be applicable to the facts of this case. Singh v. Brake, 222 F.3d at 1369, 55 USPQ2d at 1678. However, we agree with Brake that there are many facts which distinguish the present case from Berges and thus preclude Singh from coming within Berges.

First, the issue in Berges, was whether the inventor's own evidence of an actual reduction to practice of a compound within the scope of the count was adequately corroborated. Berges v. Gottstein, 618 F.2d at 772, 205 USPQ at 692.

Here, the issue is conception and whether the inventor's own evidence adequately corroborates completion of the mental part of the invention. Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d at 1228, 32 USPQ2d at 1919. That is, whether Dr. Singh's notebooks and an order for one of two unique reagents needed to perform a novel method are sufficient to establish conception of (i) a compound within the scope of the count, and (ii) an operative method of making it. Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d at 1229-30, 32 USPQ2d at 1921; Fiers v. Revel,

interferon molecule containing the natural N-terminus." Application No. 06/506,098, p. 26, lines 3-6. We find no mention of loop deletion mutagenesis or the use of the LAC primer in Singh's application. We note that Singh does argue conception plus diligence of the method relied upon to establish constructive reduction to practice.

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984 F.2d at 1169, 25 USPQ2d at 1604;. Oka v. Youssefyeh, 849 F.2d at 583, 7 USPQ2d at 1171.

Second, in Berges, the primary investigator was a member of a highly organized research team whose objective was to make the compounds of the count. Berges v. Gottstein, 618 F.2d at 775, 205 USPQ at 694. As pointed out by Brake, in addition to the highly complex reagents provided to Berges by two members of the team there was a large body of independent corroborating evidence of Berges' synthesis of the relevant compound.⁴⁷ Paper No. 190, p. 64. Thus, in Berges, various members of the team testified as to having received samples of the compound [of the count] and that they performed in vitro and in vivo tests at various stages for purposes of evaluation. In addition, Berges' supervisor testified that he received a "legal sample"⁴⁸ of the compound [of the count], a copy of the in vitro evaluation, and a report on the in vivo

⁴⁷ The Court stated that:

Equally relevant to the issue of corroboration of an actual reduction to practice are the routine pathways by which knowledge of ongoing research was disseminated throughout the cephalosporin research team. Berges did not simply decide by himself to synthesize a compound from the available precursors received from Taggart and DeMarinis. He was involved in a supervised research program directed toward [the compounds of the count]. Berges v. Gottstein, 681 F.2d at 775, 205 USPQ at 695.

⁴⁸ The Court found that

A "legal sample" refers to the portion of a supposedly novel compound which is recorded and stored by a designated custodian at a SK & F depository. An affidavit by Bacino confirms the receipt of a legal sample of the ...[compound of the count]... from Berges on March 28. Berges v. Gottstein, 681 F.2d at 773, n.1, 205 USPQ at 693, n.1.

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testing of said compound. Therefore, the lack of a witness who actually observed Berges combining the reagents to make the compound of the count was outweighed by the amount of corroborating evidence in support of the inventor's statements.

In the present case, however, Dr. Singh has not established that he was a member of a Berges-like team effort. To the contrary, it appears that he worked independently on the project to synthesize a compound within the scope of the count. Moreover, the 24-mer is not one part of a large body of independent corroborating evidence of Dr. Singh's conception of a "complete and definite idea of the complete and operative invention, as it was thereafter to be applied in practice"; rather, as pointed out by Brake, it appears to be the only meaningful evidence. Paper No. 190, p. 64. In addition, the only declarant who makes any statement with regard to Dr. Singh's plans in December, 1982, is Dr. Hitzeman. SR 168, paras. 8 and 9. To that end, we direct attention to our discussion above (footnote 40), that Dr. Hitzeman does not mention the 24-mer or loop deletion mutagenesis. To the contrary, Dr. Hitzeman testifies that Dr. Singh discussed using another method of mutagenesis at a meeting on December 14, 1982. SR 168, para. 8.

Third, in Berges, two members of the research team prepared two highly specific reagents found by the Court to have no substantial use other than synthesize the compound of the count. Each of these investigators testified that when they gave the reagents to Berges, they were aware of its intended use. That is, they were aware that Berges intended to use the reagents to make the compound of the count.

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Singh, on the other hand, has not provided any testimony from Mr. Ng, the scientist who synthesized the 24-mer, that he was aware of Dr. Singh's intended use of the compound. That is, Mr. Ng has not testified that he was aware that Dr. Singh was going to use the 24-mer in the loop deletion mutagenesis procedure to synthesize a compound within the scope of the count. In fact, Singh has not pointed to one declarant who has testified that Dr. Singh discussed his plan to employ the 24-mer in the loop deletion mutagenesis procedure. Burroughs v. Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d at 1228, 32 USPQ2d at 1919 ("The conception analysis necessarily turns on the inventor's ability to describe his invention with particularity. Until he can do so, he cannot prove possession of the complete mental picture of the invention").

Thus, in Berges the Court found that a reasonable analysis of all the evidence established the existence of the compound of the count. The Court's holding of an actual reduction to practice of the invention did not rest solely on the finding that the two reagents used to make the invention had no other substantial use except for the research team's stated goal. Here, however, since Singh has only provided as evidence of conception, the order of one of two reagents needed to perform the loop deletion mutagenesis procedure, i.e., the 24-mer, but no evidence that the 24-mer cannot be used for other procedures, we find the facts of this case insufficient to substantiate the application of the Berges "no other substantial use" for a reagent rule.

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4. Conclusion

Singh argues that Dr. Singh's conception of making a compound within the scope of the count involved a method which was not a matter of routine knowledge among those skilled in the art; i.e., the loop deletion mutagenesis method. Singh does not rely on the disclosure by Dr. Singh of an operative method of making the referenced compound using this novel method of mutagenesis to others. Rather, we find that Singh's entire case for conception rests on the order of a 24-mer and an uncorroborated notation in a corner of Dr. Singh's notebook ("oligonucleotide for making in-frame deletion of α pro-IFN-D junction"). SX 3, Bates No. 126. We also find Singh's arguments that (i) the 24-mer is one of 2.8×10^{14} possible oligonucleotides that Dr. Singh could have ordered, and (ii) there is no other use for the 24-mer other than for loop deletion mutagenesis, to be based only on attorney argument to which we accord little, or no, evidentiary weight.

Conception requires that Dr. Singh have a "specific and settled idea, ... not just a general goal or research plan he hopes to pursue." Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d at 1228, 32 USPQ2d at 1919. Moreover, an inventor must have an idea that is "definite and permanent enough that one skilled in the art could understand the invention." Id. at 1228, 32 USPQ at 1919.

Even if we assume, arguendo, that Singh's notation does not require independent corroboration, we find that it refers generically to any method of making an in-frame deletion and not specifically to the loop deletion mutagenesis procedure described in the Adelman publication (SX 53). We acknowledge that the 24-mer is of

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the exact complementarity needed to accomplish the loop deletion method; however, we hold that Singh has failed to satisfy its burden of proof, by a preponderance of the evidence, that Dr. Singh conceived of the complete and operative loop deletion method prior to January 12, 1983, because Singh has (i) not provided any evidence which establishes when the loop deletion method was actually developed, and that Dr. Singh knew of this method, and (ii) only demonstrated that Dr. Singh ordered or knew of one of the two oligonucleotide primers needed to perform loop deletion mutagenesis, prior to the critical date. The loop deletion mutagenesis technique requires a second primer, the LAC primer. Singh has not pointed to any evidence which demonstrates that Dr. Singh understood the need for the LAC primer prior to January 12, 1983.

Accordingly, in view of the foregoing, we hold that Singh has failed to prove, by a preponderance of the evidence, that Dr. Singh had complete conception of an invention within the scope of the count prior to Brake's critical date of January 12, 1983.

VIII. Diligence

Since we hold that Singh did not conceive of an invention within the scope of the count prior to Brake's effective filing date of January 12, 1983, the issue of diligence of the inventor to a reduction to practice is moot.

However, even if we assume, arguendo, that the Singh record establishes conception of the subject matter of the count, then we would hold that said record does not establish reasonable diligence from a time just prior to Brake's entry into the field.

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Our reasons follow.⁴⁹

⁴⁹ For purposes of clarification we address two of Singh's arguments.

1. We note Singh's argument that "At page 26 of the Decision on final hearing, this Board found that the work 'performed by Dr. Singh on January 21, 1983' provided a reduction to practice of the subject matter of the Count." Paper No. 180, p. 21. This is incorrect. Rather, the Board stated that the experiments in the laboratory notebook on the referenced day were the only evidence of record which appeared to corroborate Dr. Singh's statement that he had a plan to employ the 24-mer in the loop deletion procedure. That is, Dr. Singh's laboratory notebook page (SX3 at Bates Nos. 136-137) appeared to corroborate Dr. Singh's conception of a method of making an invention within the scope of the count. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1378, 231 USPQ at 89. The Board made no findings with respect to the criteria necessary to establish an actual reduction to practice. To that end, we point out that the Court recently held in Estee Lauder Inc. v. L'Oreal, S.A., 129 F.3d 588, 592, 44 USPQ2d 1610, 1613 (Fed. Cir. 1997), that prove an actual reduction to practice

. . . an inventor must establish that he "actually prepared the composition and knew it would work." Hahn v. Wong, 892 F.2d 1028, 1032, 13 USPQ2d 1313, 1317 (Fed. Cir. 1989) (quoting Mikus v. Wachtel [II], 542 F.2d 1157, 1159, 191 USPQ 571, 573 (CCPA 1976)); see also Burroughs Wellcome Co. v. Barr Lab., Inc., 40 F.3d 1223, 1228, 32 USPQ2d 1915, 1919 (Fed. Cir. 1994) (reduction to practice requires "the discovery that an invention actually works"); see also Standard Oil Co. (Indiana) v. Montedison, S.p.A., 494 F. Supp. 370, 206 USPQ 676 (D. Del. 1980), aff'd, 664 F.2d 356, 212 USPQ 327 (3d Cir. 1981) (reduction to practice requires a showing of three elements: (i) production of a composition of matter satisfying the limitations of the count, (ii) recognition of the composition of matter, and (iii) recognition of a specific practical utility for the composition).

In addition, an actual reduction to practice must be corroborated by facts and circumstances 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 1981). Thus, since the Board made no findings with respect to the criteria necessary to establish an actual reduction to practice, we find Singh's arguments in this regard to highly presumptuous.

2. Singh argues that the APJ's Order, dated September 19, 2000 (Paper No. 171), requires a showing of diligence for "each and every day" from a date just prior to Brake's January 12, 1983 filing date until Singh's reduction to practice and, thus, is improper. Paper No. 180, pp. 23-24. According to Singh, the case law does not require that activity must be accounted for on each day of the critical period; only a

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IX. Opinion on Diligence

It is well established that priority of invention goes to the first to reduce the invention of the count to practice unless the other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing the invention to practice. Cooper v. Goldfarb, 154 F.3d 1321, 1326, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998); Revise and Caesar, Interference Law and Practice, § 173, pp. 537-38. Reasonably continuous activity must be shown from a time prior to the opponent's entry into the field, which in this case would be a date prior to Brake's January 12, 1983 filing date, to a reduction to practice, either constructive or actual, of the invention of the count. The testimony and self-serving documentation of the inventor are not sufficient to establish diligence. The acts relied upon to establish diligence must be corroborated. Rieser v. Williams, 255 F.2d 419, 424 118 USPQ 96, 101 (CCPA 1958); Kendall v. Searles, 173 F.2d 986, 992, 81 USPQ 363, 368 (CCPA 1949).

showing of reasonable diligence is necessary.

In our view, the Order is not inconsistent with the prevailing case law with respect to a showing of reasonable diligence. In fact, the Order is silent with respect to the legal requirements for diligence. Moreover, we direct attention to Singh's original brief, Paper No. 151, Appendix 1, wherein a calendar is provided which is filled in with asterisks which purportedly represent Dr. Singh's day-to-day activities. The Order simply requested that Singh explain the work performed on the alleged dates. When provided with that information the Board would then be in a position to determine whether Singh had exercised reasonable diligence in reducing the invention of the count to practice.

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Turning first to the Singh's showing of diligence during the period prior to Brake's date of entry into the field, we find that Singh begins with the activities which Dr. Singh is said to have performed on December 16, 1982. But see, Scharmann v. Kassel, 179 F.2d 991, 997, 84 USPQ 472, 477 (CCPA 1950) (A memo written approximately one month before, and not immediately prior to, opposing party's date of entry into the field, held not to establish diligence for the one month period). We find that Singh's evidence of diligence primarily consists of various pages from Dr. Singh's laboratory notebook which are (i) unexplained as to content⁵⁰ and relevance⁵¹ to the invention of the count, and (ii) uncorroborated. The only activity we find relevant to the invention of the count, and which has been independently corroborated, is the construction and purification of the 24-mer oligonucleotide which was completed by Mr. Ng by December 20, 1982. See Mr. Ng's testimony in footnote 36, above. We find this single activity, which was completed more than 3 weeks prior to Brake's effective filing date of January 12, 1983, to be insufficient to satisfy the reasonable diligence requirement of 35 U.S.C. § 102(g).

⁵⁰ We direct attention to our discussion on pp. 78-79, above, that documents do not speak for themselves. 37 C.F.R. § 1.671 (f). It is not sufficient to allege that certain work was done by simply citing to notebook pages. The burden is on Singh to explain the entries in the notebook(s) and how they demonstrate diligence towards reducing the invention of the count to practice.

⁵¹ To establish diligence, Singh must demonstrate that the activities performed on the various dates alleged are specifically directed to the reduction to practice of the invention of the count. Naber v. Cricchi, 567 F.2d 382, 384, 196 USPQ 294, 296 (CCPA 1977). Mere work does not constitute diligence. Here, for example, we do not find, and Singh has not provided any evidence which establishes, that the activities associated with the restriction test, the "alpha factor pre-pro human serum albumin" and the "bovine interferon alpha-factor vector" which were said to have been performed on January 8-12, 1983, were required to develop the invention of the count.

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Thus, we hold that Singh has failed to establish diligence from (i) a date prior to Brake's critical date, and (ii) to Singh's subsequent reduction to practice.

In view of our holding, we need not consider Singh's remaining evidence of diligence and reduction to practice.

X. JUDGMENT

In view of the foregoing, judgment as to the subject matter of the count is hereby awarded to BRAKE, the senior party.

Accordingly, on the present record, SINGH is not entitled to a patent containing his claims 8 and 19 through 21, corresponding to the count.

JOAN ELLIS)
Administrative Patent Judge)
)
)
) BOARD OF PATENT
FRED MCKELVEY) APPEALS AND
Senior Administrative Patent Judge) INTERFERENCES
)
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