United States District Court,
N.D. California.

AMERSHAM PHARMACIA BIOTECH, INC,
Plaintiff.
v.
THE PERKIN-ELMER CORPORATION,
Defendant.
AMERSHAM LIF,
AMERSHAM LIFE.
v.
PERKIN-ELMER COR,
PERKIN-ELMER CORP.

No. C 97-CV-4203 CRB

Feb. 28, 2000.

Richard Warburg, Brobeck Phleger & Harrison LLP, San Diego, CA, for Plaintiff.

Edward R. Reines, Weil Gotshal & Manges LLP, Menlo Park, CA, The Honorable Charles R. Breyer, United States District Court, San Francisco, CA, for Defendants.

Douglas E. Olsen, Richard J. Warburg, Brobeck Phleger & Harrison LLP, San Diego, California, for Plaintiff Amersham Pharmacia BioTech, Inc.

Matthew D. Powers, Edward R. Reines, Maureen K. Toohey, Weil, Gotshal & Manges LLP, Menlo Park, California, The Honorable Charles R. Breyer, United States District Court, San Francisco, CA, for Defendants The Perkin-Elmer Corporation; PE Applied Biosystems Division.

ORDER

BREYER**, J.**

AND RELATED COUNTERCLAIM

Now before the Court is defendant's motion for *de novo* determination of the Magistrate Judge's Recommended Order of February 28, 2000 construing the disputed claims of the '648 patent. After carefully considering the papers filed by the parties, including the record presented to the Magistrate Judge, having had the benefit of oral argument, and reviewing the parties' dispute *de novo,* the Court DENIES defendant's motion to submit additional evidence and ADOPTS the Magistrate Judge's recommended construction of the disputed claims as set forth in his February 28, 2000 Order for the reasons set forth in that Order.

With respect to the dispute as to the meaning of the preamble, and, in particular, whether "[a] method of identification and detection of nucleic acids in a multi-nucleic acid mixture" requires the identification of the nucleic acids to take place *while* the nucleic acids are *in* a "multi-nucleic acid mixture," the Court makes the following additional comments.

First, the phrase at issue is ambiguous. The word "in" may modify "identification and detection" as defendant urges, or it may modify "nucleic acids" so that the language means that the method (of identification and detection) is applied to the nucleic acids *that are found in a multi-nucleic acid mixture*.

Second, the latter interpretation, the one adopted by the Court, is consistent with the language of the claims and the specification.

Third, the fact that the specification describes DNA sequencing as the "best mode" of the invention does not as a matter of law compel the interpretation urged by plaintiff. The claims of a patent, properly construed, may in some circumstances exclude the preferred embodiment disclosed in the specification. In this case, however, the Court concludes that the weight of the intrinsic and extrinsic evidence compels the conclusion that the preamble language does indeed encompass DNA sequencing, the preferred embodiment.

Fourth, the "restriction requirement" imposed by the Examiner during the initial stages of the prosecution of the parent '924 application are not "legally irrelevant." The Court has considered the requirement, and the fact that it supports defendant's interpretation of the preamble, in construing the meaning of the preamble. The Court concludes, however, that the restriction when considered in context, together with the other evidence identified by defendant, do not overcome the evidence demonstrating that the preamble encompasses DNA sequencing.

IT IS SO ORDERED.

*** * CERTIFICATE OF SERVICE * ***

I, the undersigned, hereby certify that I am an employee in the Office of the Clerk, U.S. District Court, Northern District of California.

That on May 19, 2000, I SERVED a true and correct copy(ies) of the attached, by placing said copy(ies) in a postage paid envelope addressed to the person(s) hereinafter listed, by depositing said envelope in the U.S. Mail, or by placing said copy(ies) into an inter-office delivery receptacle located in the Clerk's office.

Bernard F. Rose, Esq.

Lyon & Lyon LLP

333 West San Carlos St

Ste 800

San Jose, CA 95110

Robert W. Dickerson, Esq.

Lyon & Lyon

633 W Fifth St 47th Flr

Los Angeles, CA 90017

Richard Warburg, Esq.

Brobeck Phleger & Harrison LLP

12390 El Camino Real

San Diego, CA 92130

Douglas E. Olson, Esq.

Brobeck Phleger & Harrison LLP

12390 El Camino Real

San Diego, CA 92130

Jeffrey W. Guise, Esq.

Brobeck Phleger & Harrison LLP

12390 El Camino Real

San Diego, CA 92130

John E. Peterson, Esq.

Brobeck Phleger & Harrison LLP

12390 El Camino Real

San Diego, CA 92130

Vicki G. Norton, Esq.

Lyon & Lyon LLP

4225 Executive Sq

Ste 800

La Jolla, CA 92037

Gary H. Silverstein, Esq.

Lyon & Lyon LLP

4225 Executive Sq

Ste 800

La Jolla, CA 92037

Edward R. Reines, Esq.

Weil Gotshal & Manges LLP

2882 Sand Hill Rd Ste 280

Menlo Park, CA 94025

Matthew D. Powers, Esq.

Weil Gotshal & Manges LLP

2882 Sand Hill Rd Ste 280

Menlo Park, CA 94025

ORDER CORRECTING TYPOGRAPHICAL ERROR IN MAGISTRATE JUDGE'S RECOMMENDED ORDER RE: CLAIM CONSTRUCTION OF U.S. PATENT NO. 5,688,648

INFANTE**, Magistrate J.**

(RULE 72(b), F.R.Civ.P**.)**

On February 28, 2000, the Court issued the Magistrate Judge's Recommended Order Re: Claim Construction of U.S. Patent No. 5,688,648 (Rule 72(b), F.R.Civ.P.). A typographical error was made at page 29, lines 8-9. Rule 60 of the Federal Rules of Civil Procedure provides in relevant part:

(a) Clerical Mistakes. Clerical mistakes in judgments, orders or other parts of the record and errors therein arising from oversight or omission may be corrected by the court at any time of its own initiative or on the motion of any party and after such notice, if any, as the court orders.

Rule 60(a) Fed. R. Civ. P.

Pursuant to Rule 60, the Court hereby corrects the typographical error, leaving the holding and reasoning of the Recommended Order unchanged by this clerical correction.

The sentence currently reads:

This particular example described in the specification should be read as a claim limitation to polymers or to a nucleic acid.

The corrected sentence shall now read as follows:

This particular example described in the specification should *not* be read as a claim limitation to polymers or to a nucleic acid.

The Recommended Order is hereby amended as set forth above.

IT IS SO ORDERED.

MAGISTRATE JUDGE'S RECOMMENDED ORDER RE: CLAIM CONSTRUCTION OF U.S. PATENT NO. 5,688,648

(Rule 72(b), F.R.Civ.P**.)** FN1

FN1. A recommended order is not suitable for publication.

I. INTRODUCTION

Pending before the Court is the construction of U.S. Patent No. 5,688,648 ("the '648 patent"). Following a full briefing of the claim construction issues by the parties, the Court conducted a *Markman* hearing in this matter on December 10, 1999. Each side presented the Court with an explanation of their respective claim constructions, followed by testimony from one inventor and four expert witnesses, and the submission of exhibits into evidence. FN2 In lieu of extended oral argument, the parties each submitted a supplemental brief on January 10, 2000, summarizing their arguments and the evidence supporting their positions. Having reviewed and considered all of the above, the Court now construes the disputed patent claim terms as follows.

FN2. The '648 patent came into evidence during the hearing as Exhibit 31. For purposes of this Order, the Court will cite to the '648 patent as "Patent, Col. (Column): (lines). Unless otherwise indicated, references to "Ex(s) at __" refer to document(s) entered into evidence during the hearing, by page number and by lines, or by paragraph, as appropriate. Citations to the hearing transcript are TR (at page):(lines). A deposition transcript will be cited by deponent, Dep.(Vol), at (page): (lines).

II. BACKGROUND

A. The Litigation

In its complaint for infringement, Amersham Pharmacia Biotech, Inc. ("Amersham") alleges it is the exclusive licensee to the '648 patent, issued on November 18, 1997, relating to a method of identification and detection of nucleic acids by using energy transfer coupled dyes as labels. It accuses Perkin-Elmer

Corporation ("Perkin-Elmer") of infringing its '648 patent by manufacturing and selling energy transfer dye products, including the ABI PRISM BigDye Primer Cycle Sequencing Ready Reaction Kit, and by using such products in sequencing methods covered by the '648 patent. The parties' central dispute during the claim construction phase has been whether the '648 patent claims encompass DNA sequencing processes.

B. The '648 Patent

The '648 patent is a fruit of the work of scientists at the University of California, Berkeley, with fluorescent tags to develop an improved method of identifying and quantifying components in a mixture. The inventors are Richard A. Mathies, Alexander Glazer and Jingyue Ju. The '648 patent specification describes compositions and methods for analyzing a mixture by means of labels using energy transfer coupled dyes, that is, fluorescent labels that absorb light at substantially the same wavelength and emit light at different wavelengths. These labels are comprised of (usually) two different fluorescent dyes (fluorophores) referred to as the donor and the acceptor, linked by a backbone chain to which the fluorophores are covalently bonded. FN3 The donor fluorophore is so named because it transfers the excitation energy it absorbs from a single light source of narrow bandwidth (particularly a laser) to the acceptor fluorophore. The acceptor fluorophore is able to absorb this energy because it is maintained in close proximity and in the proper orientation by the backbone chain. The acceptor emits this transferred energy at a different wavelength, which can be detected. The specification defines the range of "energy transfer" to be the transfer of from 20% to 100% of the energy absorbed by the donor to the acceptor. *See* Patent, Col.4:55-65; Joint Claim Construction Statement for U.S. Patent No. 5,688,468, at 1. Together, the donor fluorophore, the acceptor fluorophore, and the backbone chain, represent a single energy transfer dye. FN4

FN3. Covalence is a type of chemical bonding in which each combining atom contributes an electron to the bond; it is the typical sort of valence in organic compounds. *McMillian Dictionary of Measurement,* at 97.

FN4. The specification states that the user may employ more than a pair of absorbing molecules, for example, three or more molecules where energy is transferred from one molecule to the next at higher wavelengths, to greatly increase the difference in wavelength between absorption and observed emission. Patent, Col.3:28-34; 5:9-23.

The patent purports to provide novel fluorescent labels, combinations of fluorescent labels, and their use in separation systems involving the separation of a plurality of components. Patent, Col.2:62-64. The labels may be composed of a wide variety of fluoroescent dyes falling into different chemical classes (id., Col.4:2-7; 4:40-54), different chains or backbones may be employed (id., Col.3:46-53), and the distance between the fluorophores can be varied along the backbone or chain. Id., Col.3:35-59; 3:67; 4:1-2; 4:17-39; 4:66-5:8; 8:18-38.

The specification states that the labels find particular application in various separation techniques, such as electrophoresis, chromatography, or the like, where optimized spectroscopic properties, high sensitivity and comparable influence of the labels on the mobility of the components being analyzed are desired. Patent, Col.1:57-63; 4:8-16; 10:5-16. The inventors envisioned "tuning" label compositions to devise label sets, each set having distinct emission wavelengths and high emission quantum yields while retaining substantially the same excitation-light absorbance and mobility. Id., Col.4:17-39; 6:10-20; 7:56-67; 8:1-38; 10:5-16. Amersham contends that the '648 patent method has as its preferred embodiment a dramatically

improved process of DNA sequencing. Other applications for the labels are also described in the patent. FN5

FN5. The specification describes how the labels may be used in a variety of analytic contexts, for example, where different primers have been used in polymerase chain reaction ("PCR"), or in identifying isozymes, using specific antibodies, or identifying lectins using different polysaccharides. *See* Patent, Col.5:41-47; 6:1-4; 10:5-16.

The '648 patent makes three method claims and the specification includes three examples by way of illustration. The '648 patent claims the following:

1. *A method of identification and* detection of nucleic acids *in a multi-nucleic acid mixture* employing detectably different fluorescent labels to detect at least two nucleic acids of interest, wherein said labels are characterized by: (1) having a donor-acceptor fluorescent pair where said donor and said acceptor are each covalently bonded to a *backbone chain at specific locations thereon* with energy transfer from said donor to said acceptor; and (2) each of the labels absorbs at substantially the same wavelength and emits at a different wavelength;

said method comprising:

covalently bonding different labels to different nucleic acids of said multi-nucleic mixture of [sic] form labeled nucleic acids;

detecting each of said labeled nucleic acids by irradiating at the absorption wavelength of said donor and detecting the fluorescence of each of said labels.

2. A method according to claim 1, wherein said donor absorbs light in the wavelength range of 350-800 nm and said acceptor emits light in the wavelength range of 450-1000 nm.

3. A method according to claim 2, wherein said donor-acceptor pair are 9-phenylxanthenes.

The parties dispute the meaning of four claim terms:

1. "A method of identification and detection of nucleic acids in a multi-nucleic acid mixture";

2. "covalently bonding different labels to different nucleic acids of said multi-nucleic mixture to form labeled nucleic acids";

3. "a backbone chain"; and

4. "at specific locations thereon."

The Court will analyze each of the disputed terms, infra, at Sections IV-A through IV-D.

C. DNA Sequencing Technology

The deoxyribonucleic acid ("DNA") molecule is the main carrier of genetic information in all living organisms. FN6 DNA molecules make up chromosomes, which are divided into thousands of different functional units called genes. Structurally, DNA is a very long polymer made up of four different nucleotide monomers: guanine, adenine, thymine, and cytosine (abbreviated G, A, T, C). In most DNA molecules, two strands of nucleotides join together through a sugar/phosphate backbone to form the well-known double-helix of DNA, resembling a twisted ladder. The two strands are linked together by a large number of weak (hydrogen) bonds formed between complementary base pairs of nucleotides (C pairs with G, and A pairs with T) attached to a sugar/phosphate backbone, thereby forming the ladder's "rungs." The specific order or sequence of the nucleotides along the DNA strand is the crucial information which ultimately determines the structure and function of an organism. Even the smallest variation or alteration in the nucleotide sequence may have profound consequences in an organism. FN7

FN6. See Exs. 201, 202; 5 *McGraw-Hill Encyclopedia of Science & Technology* (7th Ed.1992) at 112-13; Id. Vol. 7 at 690.

FN7. For example, cystic fibrosis is the result of a single nucleotide substitution.

DNA sequencing is the process of determining the order of nucleotides along a particular strand (or chain) of DNA. In the process known as chain terminator or dideoxy sequencing (or the Sanger method, after its inventor), the sequencing is accomplished using a short DNA primer that is complementary to, and can bind, the DNA of interest. An enzyme called DNA polymerase creates a complementary DNA strand by adding nucleotides to the primer DNA using the original DNA strand as a template. This primer is extended until a labeled chain terminator (dideoxynucleotriphosphate) is incorporated into the nascent DNA strand. The rate of this termination is limited so that eventually a complete set of nucleic acids is produced representing termination events 1, 2, 3, 4 ... 500 etc., nucleotides away from the primer. This process is known as a primer extension reaction, or nucleic acid extension, and the result of this extension process is a multitude of nucleic acid strands.

The nucleic acid strands of different lengths may then be separated by a process known as electrophoresis, exploiting the mobility differences that exist between nucleic acid molecules of different lengths to separate smaller nucleic acid molecules from larger nucleic acid molecules. In gel electrophoresis, for example, these nucleic acids are ordered from smallest to largest by forcing them through a gel medium in which the smaller fragments migrate more quickly. Because nucleic acids of the same length and the same sequence share equal mobility, this process separates molecules into fractions that contain nucleic acids of equal length. Identifying the terminal nucleotide on each of these nucleic acid fragments, from smallest to largest, reveals the sequence of the complementary DNA produced during primer extension. If labeled primer is used, the sequence may be known by the length at which the terminator is incorporated on the chains. Where labeled terminator nucleotides are used, the presence of a color (green, red, yellow or blue) will identify the nucleotide ending the extension chain. From the precise length of the fragments or the characteristic colors, the base sequence of the original template DNA strand can be deduced. FN8

FN8. *See* Exs. 73, 201-203, 208-210; TR 11:7-20; 13:12-25, 14:1-25, 15:1-22; 24:4-25; 26:24-27:16; 177:20-178:1. *See also* 7 *McGraw-Hill Encyclopedia of Science & Technology,* at 687-88; id., Vol. 12, at 214-15. Amersham's expert, Dr. Michael Chamberlin, is a professor of biochemistry and molecular biology in the Department of Molecular and Cell Biology at the University of California, Berkeley. Although the

Court did not rely on Dr. Chamberlin's opinions in interpreting the claim language, his expert report and exhibits (Ex. 63), supplemental expert report (Ex. 153), and testimony at the hearing assisted the Court in understanding DNA sequencing methods generally, certain exhibits, and aspects of the '648 patent specification.

The invention uses a different fluorescent, energy transfer coupled label for each of the four (A, C, T, G) nucleotides. Patent, Col.5:29-32. The label is initially attached (i.e., covalently bonded) either to the terminator nucleotide or to the primer DNA. The nucleic acid that results from primer extension contains this covalently attached fluorescent label. Successive nucleotides are covalently bonded to the primer by the DNA polymerase until the last "terminal" nucleotide is covalently added. The nucleic acid fragments resulting from the primer extension reaction are then separated in a single lane by electrophoresis or in a single capillary by electrophoresis. Id., Col.5:62-67. Following separation of the nucleic acid strands by size through electrophoresis, the labeled fragments are identified by detecting the energy emitted from the attached fluorescent labels after they have been activated by a laser. Id. Because electrophoresis does not separate the labeled nucleic acids from their unlabeled counterparts of the same length, when a labeled nucleic acid is detected, also present but undetected, are the unlabeled nucleic acids of the same size or length. Ex.153 at para. 2:13-14; TR 25:1-14.

In practice, the result of sequencing DNA using energy transfer fluorescent labels is a color graph that identifies the labeled nucleotide(s) on each of the fragments produced by primer extension, thereby revealing the sequence of the bases in the template DNA. FN9 Standard automated DNA sequencing machines can produce a graphic and textual "output" of the sequencing process. Each "peak" in this output represents the detection of a labeled nucleic acid, the base type of which is also indicated textually by its representative letter as well as by color. Also present but undetected in each peak are the unlabeled nucleic acids of the same size or length. The overlap of the "shoulders" of these peaks indicates that labeled nucleic acids of similar, but not identical lengths, are not completely separated out by electrophoresis and nucleic acids of different lengths can be found in the same fraction. Similarly, unlabeled nucleic acids of similar, but not identical lengths, are not completely separated and can also be found in the same separated fraction. A sequencing machine using the flourescently labeled fragments produces a colored "wave" picture depicting a multi-nucleic acid mixture containing labeled and unlabeled nucleic acids of very similar, but not identical lengths, along a continuum of nucleic acid molecules of different lengths. *See* TR 23:14-26:21.

FN9. *See* Exs. 77, 211, and 213 (examples of the standard output from an automated DNA sequencing machine); Ex. 153 at para.para. 3-4; TR 15:23-17:3; 24:13-25 (Dr. Chamberlin's explanation of Ex. 77). Perkin-Elmer asserts that, in deposition, Dr. Chamberlin was uncertain of the scientific accuracy of his supplemental expert report describing the sequencing output. The Court reviewed the entire excerpt and does not agree. *See* Declaration of Maureen K. Toohey In Support of Perkin-Elmer's Post-Hearing Claim Construction Brief ("Toohey Decl."), Ex. E (Chamberlin Dep.II, pp. 260-280). *See also* TR 12:12-13:11.

The '648 patent method purports to be an improvement over the methods for automated DNA sequencing using a single dye label, allowing for multiplexing of samples, so that a plurality of components can be determined in the same system and in a single run. Patent, Col.1:25-63; 5:65-67; 10:5-17. The specification teaches that, "for the successful application of donor-acceptor fluorophore labeled primers to DNA sequencing, it is essential that the primers produce the same mobility shifts of the DNA fragments and display distinct fluorescence signals ... the mobility of the primers depends on the distance between the

donor and acceptor." Id., Col.8:15-38.

D. Prosecution History of the '648 Patent

The prosecution history of a patent is of secondary importance to the claims themselves and the patent specification in determining the claim construction, but the Court may consider it, if in evidence. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996). Because both parties rely on the somewhat complicated prosecution history of the '648 and related patents, a description follows. FN10

FN10. While the Court reviewed the patent file wrappers in evidence, the testimony of Amersham's expert, Mr. Bjorge, who is an expert in PTO practice of wide experience and was himself a patent examiner, proved helpful to the Court in understanding the history of the '648 and related patents. *See* TR at pp. 76-101. The Court did not rely on Mr. Bjorge's opinions to interpret specific '648 claim terms.

The parent application, application no.189,924 (the '924 application), which eventually lead to the '648, '419 and '804 patents, was filed on February 1, 1994. The '924 application eventually issued as the '419 patent. FN11 On December 19, 1995, the University of California filed patent application Serial No. 574,890 (the '890 application) as a divisional of the '924 application. FN12 The '890 application had claims directed to methods of identifying and detecting nucleic acids, i.e. sequencing and the like. The '890 application eventually issued as the '648 patent, entitled "Probes Labelled With Energy Transfer Coupled Dyes ." Finally, application Serial No. 410,808 (the '808 application), which eventually issued as the '804 patent, Ex. 141, was filed on March 27, 1995, as a continuation-in-part of the '924 application. FN13 The '924 application is known as the parent application of the applications which led to the '648 and '804 patents. Each of these separate applications was prosecuted before the same Examiner.

FN11. The '419 patent is Exhibit 225; its prosecution history ('924 application) is Exhibit 60.

FN12. The prosecution history of the '648 patent is Exhibit 61.

FN13. The '804 patent is Exhibit 141; its prosecution history is Exhibit 62.

The Examiner issued a restriction requirement during the initial states of the prosecution of the '924 application, which contained 21 claims when filed. Ex. 60 at 59-61. The Examiner separated the filed claims into four separate groups: (1) claims 1-6 drawn to methods of identifying "cells"; (2) claims 7-10 drawn to "separating components of a mixture"; (3) claims 11-16 drawn to "sequencing methods; and (4) claims 17-21 identified as generic to any of the above and directed to kits of labels. Id. at 59. The applicants made a provisional election with a traversal to prosecute the invention described in claims 7-10 and 17-21 of the '924 application. Id. at 59. In response to the Examiner's rejection of those pending claims, in February 1995, the applicants amended the claims, added additional claims and amended the title. Id. at 71-75. In this response, the applicants stated, "[w]hile not agreeing with the Examiner's position that there is no support for other than nucleic acids, in order to expedite the prosecution of this application to allowance, *particularly in view of the fact that it is the Examiner's position that a demonstration of the subject invention with other backbones would be patently distinct, Applicants have limited the claims to nucleic acid backbones*." Id. at

74. Following further rejections and amendments, eventually, a notice of allowability issued, wherein the Examiner commented, "the invention is directed to kits and methods of use thereof wherein nucleic acid components are separated out of a multi-component mixture into different fractions." Id. at 88-93. The '419 patent issued on August 5, 1997, and included claims directed to a method for "separating nucleic acid components of a nucleic acid multi-component mixture." Ex. 225, Col.10:62-63.

The '890 application, which ultimately became the '648 patent, was filed in December 1995. As a divisional of the '924 application, it had the identical specification but only claims 1-6 were pending in the '890 application. Ex.61, at 3-37. The identical information disclosure statement was also filed, which identified references directed to DNA sequencing. Id. at 52-55. In an Office Action dated June 24, 1996, the Examiner rejected claims 1-6. Id. at 45-50. The first rejection was made pursuant to 35 U.S.C. s. 112 (the specification contents) and was addressed to whether the claims should be limited to nucleic acid backbone chains. Id. at 46. The Examiner made another rejection pursuant to 35 U.S.C. s. 101, identified as a provisional "double-patenting rejection" over claims 1-6, then pending in the '808 application which eventually issued as the '804 patent. Id. at 47. The Examiner also made a double-patenting rejection of claim 1, based upon another co-pending application, the '573 application, and pursuant to 35 U.S.C. s. 103, based upon several references directed to methods for nucleic acid sequencing. Id. at 47-49.

In response, the applicants filed an amendment on December 19, 1996. Ex. 61, at 65-76. The amendment responded to the 35 U.S.C. s. 112 rejections, including the Examiner's view that the claims should be limited to nucleic acid backbone chains. That response included an identification of various references, which supported the applicants' arguments concerning the scope of the claim term "backbone chain." Id. at 69-70. With regard to the double-patenting rejection, the applicants advised the Examiner that they had canceled claims 4-6. Id. at 70. With regard to claims 1-3 of the '890 application, the applicants' advised the Examiner that the relevant claims of the pending '808 application were restricted to an "oligonucleotide chain." FN14 Id. at 67, 70. The applicants also submitted a terminal disclaimer. Id. at 77-78. With regard to the 35 U.S.C. s. 103 rejections, the applicants pointed out the differences between the art cited by the Examiner and the applicants' invention, as claimed in the '890 application. Id. at 70-74.

FN14. DNA fragments containing up to 50 nucleotides are generally termed oligonucleotides, and longer fragments are called polynucleotides. 12 *McGraw-Hill Encyclopedia of Science & Technology* at 348.

On February 19, 1997, in response to the applicants' amendment, the Examiner allowed claims 1-3 of the '890 application. Ex. 61 at 81-82. In her "reasons for allowance," the Examiner stated, "[c]laims are directed to methods of use of novel labels, wherein the labels are characterized by having a donor-acceptor fluorescent pair bonded to a backbone chain and wherein each of the labels absorbs at substantially the same wavelength and emits at a different wavelength." Id. at 81. The Examiner did not require recitation of a particular type of backbone chain, even though the Examiner had earlier made this the basis of a 35 U.S.C. s. 112 lack of enablement rejection. Id. The Notice of Allowance further stated, "[t]he labels are used in methods of detecting at least two different nucleic acids in a mixture of nucleic acids." Id. On November 18, 1997, the '648 patentin suit-issued.

On January 13, 1998, the '804 patent issued, based upon an application which was a continuation-in-part of the '924 application. Exs. 62, 141. The '804 patent included method claims for the "identification and detection of components in a multi component mixture employing different fluorescent labels to detect at least two components of interest" (claims 1-3) and method claims for "separating components of a multi

component mixture, wherein each of the different components of interest are labeled with different labels" (claims 4-7). Ex. 141, Col. 13:10-57, 14:10-12. The '804 patent further included method claims for "sequencing a nucleic acid ..." (claims 8-13). Id., Col.14:12-54. Claims 1-7 of the '804 patent include language indicating that the donor-acceptor fluorescent pairs are bonded to an "oligonucleotide chain." Id., Col.13:14-16; 13:35-37. Claims 8-13 of the '804 patent include language indicating that the donor-acceptor fluorescent pairs are bonded to a "nucleic acid chain." Id., Col.14:32-42.

III. LEGAL STANDARD

Claim interpretation is a question of law to be decided by the Court. Markman v. Westview Instruments, Inc., 517 U.S. 370, 371-73 (1996). Courts first look to the claims themselves, both asserted and non-asserted, to define the scope of the patented invention. Vitronics, 90 F.3d 1576, 1582; Molecular Dynamics, Inc. v. Leica, Inc., 1999 WL 111789, (N.D.Cal. February 23, 1999). Words in a claim are given their ordinary or customary meaning unless the specification or file history clearly contains a special definition. *Id*. A technical term in a patent is interpreted as a person experienced in the particular art would understand it unless the patent and the prosecution history indicate that the patentee intended a different meaning. *Hoechst Celanese Corp. v. BP Chemicals Ltd.,* 78 F.3d 1573, 1578 (Fed.Cir.1996). A review of the specification is required to determine whether the patentee used any terms in the claims in a manner inconsistent with their ordinary meaning. Vitronics, 90 F.3d at 1582. Where the patent employs terms that are inconsistent with their ordinary meaning, the specification acts as a dictionary "when it expressly defines terms used in the claims or when it defines terms by implication." *Id*.

The Court may also consider the prosecution history of the patent, if in evidence. Vitronics, 90 F.3d at 1582. "The prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution ." CVI/Beta Ventures, Inc. v. Tura LP, 112 F.3d 1146, 1155 (Fed.Cir.1997); Southwall Technologies, Inc. v. Cardinal IG Co., 54 F .3d 1570, 1576 (Fed.Cir.1995).

The Court should turn to extrinsic evidence- *e.g.,* technical treatises, prior art references, expert testimony, inventor testimony, etc.-only if "some genuine ambiguity" remains after consideration of all intrinsic evidence. Vitronics, 90 F.3d at 1584. Extrinsic evidence, including prior art references, may be used to assist the court in properly understanding the claims, but may not be used to vary or contradict the claim language. *Id*. "[U]nder *Vitronics,* it is entirely appropriate, perhaps even preferable, for a court to consult trustworthy extrinsic evidence to ensure that the claim construction it is tending to from the patent file is not inconsistent with clearly expressed, plainly apposite, and widely held understandings in the pertinent technical filed." Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1307 (Fed.Cir.1999). "This is especially the case with respect to technical terms...." Id. at 1307.

IV. DISCUSSION OF DISPUTED TERMS

A. Identification and Detection of Nucleic Acids In A Multi-Nucleic Acid Mixture

The parties argue at length over the meaning of the disputed language of the preamble to Claim 1, "a method of identification and detection of nucleic acids in a multi-nucleic acid mixture." The central dispute is whether this language means that the '648 patent claims encompass DNA sequencing.

Perkin-Elmer argues that the disputed language must be construed to mean, "a process in which detectably different labels are used to identify and detect nucleic acids while in a mixture of different, pre-existing nucleic acids. This method does not cover DNA sequencing." Perkin-Elmer advances several lines of

analysis to support this position. The first is that the detection step in DNA sequencing does not occur in a mixture but, rather, after the nucleic acid fragments in the mixture are separated into individual components through the step of electrophoresis. Therefore, Perkin-Elmer argues, Amersham's interpretation ignores the language "in a multi-nucleic acid mixture." Perkin-Elmer draws upon the restriction requirement issued in the parent '924 application for support that the Examiner excluded DNA sequencing from the scope of the '648 patent claims. Perkin-Elmer then argues that the claim language actually refers only to probing techniques, which allow nucleic acid to be detected while in a mixture.

Perkin-Elmer next contends that DNA sequencing normally involves the sequencing of one nucleic acid of interest, the template DNA, and does not involve the use of "a multi-nucleic acid mixture" at all. Perkin-Elmer presents its expert, Dr. Roberts, who testifies that one of skill in the art would not understand "multi-nucleic acid mixture" to refer to primer extension products, as these nucleic acids are composed of varying lengths of the same sequence and are therefore not a "mixture." Perkin-Elmer also argues that no "multi-nucleic acid mixture" exists when the fluorescent labels are covalently bonded to the nucleic acids to be detected, again offering Dr. Roberts' testimony.FN15

FN15. The Court will address this particular argument in analyzing the "covalently bonding" claim term, infra, at Section IV-B.

Amersham contends that a "multi-nucleic acid mixture" means "a mixture of nucleic acids that contain two or more non-identical nucleic acids." The disputed language as a whole means, "the different nucleic acids in a multi-nucleic acid mixture that are labeled with different fluorescent labels can be distinguished by irradiating the labels and measuring the fluorescence they emit." Amersham's position is that the claim preamble does not require that the "detection" step take place "in the multi-nucleic acid mixture," but rather only that detection occurs by means of irradiating *followed by* detection, as the "comprising" language allows for any necessary additional method steps. Perkin-Elmer's construction would exclude the preferred embodiment, DNA sequencing, disclosed in the specification. Perkin-Elmer's contention that no "multi-nucleic acid mixture" is involved in DNA sequencing ignores the science. The imperfect separation achieved during DNA sequencing results in a "multi-nucleic mixture" composed of both unlabeled and labeled fragments. As for the prosecution history, Perkin-Elmer's reliance on the restriction requirement in the '924 application is unavailing to limit the scope of the '648 claims. Moreover, it is inconsistent with the Examiner's actions with respect to the '648 patent which supports the construction that DNA sequencing is allowed by the claims.

1. The Importance of the Preamble Language

While generally the preamble does not limit the scope of a claim, the preamble may be read to shed light on the meaning of the claim and to define the invention. In re Paulsen, 30 F.3d 1475, 1479 (Fed.Cir.1994); DeGeorge v. Bernier, 768 F.2d 1318, 1322, n. 3 (Fed.Cir.1985). "[A] claim preamble has the import that the claim as a whole suggests for it." Bell Communications Research, Inc. v. Vitalink Communications Corp., 55 F.3d 615, 620 (Fed.Cir.1995). "No litmus test can be given with respect to when the introductory words of a claim, the preamble, constitute a statement of purpose for a device or are, in themselves, additional structural limitations of a claim ....the effect preamble language should be given can be resolved only on review of the entirety of the patent to gain an understanding of what the inventors actually invented and intended to encompass by the claim." Corning Glass Works v. Sumitomo Elec. USA Inc., 868 F.2d 1251, 1257 (Fed.Cir.1989). If the claim preamble, when read in the context of the entire claim, recites limitations

of the claim, or, if the claim preamble is necessary to give life, meaning, and vitality to the claim, then the claim preamble should be construed as if in the balance of the claim. Pitney Bowes, 182 F.3d 1298, 1305.

Perkin-Elmer argues that the preamble is necessary to give meaning to the claims and properly define the invention. Perkin-Elmer contends that the phrase "identification and detection of nucleic acids *in* a multi-nucleic acid mixture" mandates detection while multiple acids are in a mixture and is, therefore, a limitation that should be read into the claims. From there, Perkin-Elmer argues that the claim excludes the use of the subject energy transfer coupled dyes in DNA sequencing processes, because DNA sequencing requires separation of the nucleic acids from a mixture prior to "identification and detection."

Amersham first contends that the preamble is not required in order to construe the claims and may be ignored by the Court. That being said, Amersham then argues that "a method of identification and detection of nucleic acids *in* a multi-nucleic acid mixture" must be read so that "in" modifies "nucleic acids," not "identification and detection." The claim language means that the method (of identification and detection) is applied to the nucleic acids found in a (multi-nucleic acid) mixture. Amersham insists the language is not restricted so that an "identification and detection step" must take place *while* nucleic acids are in a multi-nucleic acid mixture. In addition, Perkin-Elmer's interpretation would ignore the preferred embodiments and substitute a method not disclosed in either the specification or prosecution history.

In this case, the preamble, properly construed, gives meaning to the claims and helps to properly define the invention. Pitney Bowes, 182 F.3d at 1305. However, the preamble language itself is not without certain ambiguity. "In" is among the most ubiquitous words in the English language, freely used as a preposition, adverb, adjective or noun. *See* Webster's Ninth New Collegiate Dictionary (1984) at 607. The Court cannot say which of the proposed constructions is the correct one without reference to the specification.

2. The Patent Specification Indicates DNA Sequencing Is a Preferred Embodiment of the '648 Claims

Claim 1 requires "detecting each of said labeled nucleic acids by irradiating ... and detecting the fluorescence of each of said labels." It does not require that the detection take place in the multi-nucleic acid mixture. The use of the term "comprising." allows additional method steps to occur within the process contemplated by the claim.FN16 Thus, this claim does not exclude a separation step prior to the detection step, as occurs in DNA sequencing when the nucleic acid extensions are subjected to electrophoresis before any attempt is made to "detect" them. Nor does the claim require that the labeled nucleic acids continue to be part of a multi-nucleic acid mixture throughout the subsequent detecting process.

FN16. "A comprising type claim by definition does not exclude the presence of other steps, elements or materials. Reese v. Hurst, 661 F.2d 1222, 1229 (C.C.P.A.1981). "Comprising" does not exclude additional unrecited elements, or steps [in the case of a method claim]." Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 1271 (Fed.Cir.1986).

"Methods of identification and detection" includes DNA sequencing, which requires the identification and detection of nucleic acid strands of a specific length to determine the DNA sequence. Both the '648 patent specification and prosecution history clearly describe DNA sequencing. In the specification the inventors directly addressed DNA sequencing (Patent, Col.1:15-63; 2:14-19; 4:37-39; 5:23-32; 5:48-67; 39-50; 8:16-42; 9:36-62; 10:1-4; TR 18:13-25; 19:1-25; 20:1-6), clearly assuming that the detection may take place following separation, as the use of electrophoresis makes clear. *See* Patent, Col.5:62-67; Figures 2, 4-7. At

Example III (figure 7), entitled "Preparation of DNA Sequencing Fragments with FAM-3-ROX and FAM-10-FAM" (Patent, Col.9:36-55; 10:1-4), the inventors describe the separation of DNA sequencing fragments and their subsequent detection using laser irradiation, looking at two bases, adenine and thymine. TR 20:1-6 (Dr Chamberlin). In contrast, the inventors do not discuss applications where the labeled fragments are detected without undergoing a separation step in the specification.

The inventors were interested in improving existing automated DNA sequencing processes through the use of their labels, as they state at the beginning of the '648 patent specification. Patent, Col.1:14-63. The specification is quite clear that application of the energy transfer coupled dye labels in DNA sequencing is the preferred embodiment of the invention. *See* id., Col.2:14-19 ("*The subject invention finds particular application in sequencing,* where the fluorophores may be attached to universal or other primers in different fluorophore combinations used for different dideoxynucleosides.") (emphasis added). Because Perkin-Elmer's construction would exclude the best mode of the invention described in the patent, that construction is erroneous.FN17

FN17. Burke, Inc. v. Bruno Independent Living Aids, Inc., 183 F.3d 1334, 1341 (Fed.Cir.1999)(reversing claim interpretation that would exclude the preferred embodiment described in the specification); Enercon GmbH v. International Trade Commission, 151 F.3d 1376, 1384 (Fed.Cir.1998)((claims are not limited to the preferred embodiments); Vitronics, 90 F.3d 1576, 1584 (court's reliance on extrinsic evidence to contradict the specification is reversible error); Howes v. Medical Components, Inc., 814 F.2d 638, 643-44 (Fed.Cir.1987)(claim interpretation which is inconsistent with the specification is erroneous).

The parties expend much effort debating how one or more multi-nucleic acid mixtures figure in DNA sequencing. The premise of all DNA sequencing is that an investigator can "detect and identify" the sequence of bases within a nucleic acid "mixture" (DNA or other genetic fragment) by labeling certain base nucleotides. As previously described, a primer catalyst is used to precipitate a reaction with the subject nucleic acid-the primer extension reaction-to generate the DNA fragments which make sequencing possible. Ex. 210; TR 24:13-25. Sequencing practices may be distinguished by such features as the manner of labeling or marking nucleotides for purposes of detection and identification, by primers used, by whether the primer or the terminator nucleotides are labeled, or by how the DNA strands created by primer extension are separated. FN18 Sequencing processes, where a label is covalently bonded to the nucleic acid, are distinguishable from a probing assay, where a labeled probe is non-covalently attached or "hybridized" to DNA. Ex. 63, at 2:19-21; 184:1-185:13.

FN18. *See, e. g.,* Patent, Col.1:25-39; Ex. 63, at 2:5-18; TR 13:12-25; 14:1-25; 15:1-22; 171:3-13; 182:7-183:8. For example, radioactive end-labeling of one or both DNA strands may be employed, followed by either cleavage or extension of labeled strands to produce end-labeled fragments. 12 *McGraw-Hill Encyclopedia of Science & Technology,* at 214.

Perkin-Elmer argues that nucleic acids formed by primer extension are not a mixture because they are merely different length extension products complementary to the template DNA. To "mix" is to "bring into close association," and "mixture" by definition includes "a portion of matter consisting of two or more components in varying proportions that retain their own properties" or "a combination of several different kinds." *Webster's Ninth New Collegiate Dictionary* (1984) at 761. Whatever their genesis, the extension fragments meet this common usage criteria.

Perkin-Elmer would interpret the claim language so as to exclude DNA sequencing from the invention's scope, by artificially forcing the invention into one stage (the subject mixture) and ignoring the progression of stages (primer extension reaction, attaching labels, electrophoresis, laser activation of the labels) needed to ascertain the sequence of the bases. Available extrinsic evidence shows that one skilled in the art understands that sequencing is accomplished in stages and would read the specification and claims with this understanding. Dr. Chamberlin testified credibly that one of skill in the art would understand that the examples of multi-nucleic mixtures described in the specification would include the nucleic acid mixture produced during DNA sequencing. *See, e. g.,* Ex. 63, at 3:16-23; 9:11-27; TR 23:17-24:3. The Court also finds Professor Glazer's testimony to the same effect credible and internally consistent. TR 117:12-122:5. Dr. Roberts' testimony is not to the contrary. TR 168:16-169:3; 182:24-183:8; Roberts Dep. (10/11/99) 61:12-17. *See* Pitney Bowes, 182 F.3d 1298, 1309 ("[E]xtrinsic evidence is particularly appropriate to ensure that [the trial court's] understanding of the technical aspects of the patent is not entirely at variance with the understanding of one skilled in the art.").

3. The '648 Patent **Prosecution History Shows that the Patent Claims Encompass DNA Sequencing**

The Examiner considered DNA sequencing art in deciding whether to issue the '648 claims. The applicants submitted seventeen scientific references and patents that the inventors believed were relevant to the prosecution of these claims during the prosecution of the '890 application. Ex. 205. Nine references are to publications about DNA sequencing and specifically describe methods for DNA sequencing. Id.; Ex. 63, at 5:6-28. Eight articles explicitly refer to DNA sequencing in their titles. The nine art references concerning DNA sequencing were included in the '648 specification. *See* TR 20:11-24.

Two references discussing the use of labeled primers to identify and detect nucleic acids were cited by the Examiner as a basis for rejecting the pending claims. TR 21:1-22:7; Ex. 61, at 48-49. The article by McKeown et al. in 17 *BioTechniques,* pp. 901-907, entitled "Generation of Mini-Satellite Variant Repeat Codes on an Automated DNA Sequencer Using Fluorescent Dye-Labeled Primers," discloses the use of the polymerase chain reaction in which a fluorescently labeled primer is covalently bonded to the nucleic acid which is then detected. Ex. 74. Dr. Chamberlin testified that this reference is part of the DNA sequencing art because it uses the same primer extension process used in DNA sequencing. Ex. 63, at 6:7-14; TR 21:20-22:7. The Examiner's statements in the Office Action of June 24, 1996, indicate that she considered the McKeown reference to be part of DNA sequencing art. Ex. 61, at 49. She cited the reference because it related to the use of primers which were fluorescently labeled with a single fluorescent dye, like the primers used in DNA sequencing: "McKeown et.al. disclosed methods for identification and detection of target nucleic acids in a mixture of nucleic acids using fluorescently labeled oligonucleotides as primers [sic] amplification by PCR." Id. The use of labeled primers is at the heart of DNA sequencing.

The Examiner also considered an article by Fregeau and Fourney, entitled "DNA Typing with Fluorescently Tagged Short Tandem Repeats: A Sensitive and Accurate Approach to Human Identification," 15 *BioTechniques,* at pp. 100-119 (1993), which discloses the use of fluorescently labeled primers which may be used in DNA sequencing. Ex. 75; TR 21:9-14; 183:9-15. The Examiner wrote that, "Fregeau and Fourney disclosed methods for identification and detection of target nucleic acids in a mixture of nucleic acids using fluorescently labeled oligonucleotides as primers for hybridization and amplification by PCR and detecting labeled components by irradiating with light of appropriate wavelength." Ex. 61, at 40. The prosecution history of the '648 patent and the related '804 patent demonstrate that the Examiner treated the '648 claims as encompassing DNA sequencing. The Examiner's use of the McKeown et al and Fregeau and

Fourney publications, which discuss "methods for identification and detection of target nucleic acids in mixture of nucleic acids" (id. at 40), to reject the '648 claims indicate that the Examiner understood that claims directed to "methods of identification and detection of nucleic acids in a multi-nucleic acid mixture" include sequencing. *See* TR 21:1-22:7; 97:8-99:4.

During the prosecution of the related '804 patent claims, the same Examiner reviewed the patentability of other claims directed to methods of identification and detection. Original claim 4 of the '804 patent parallels claim 1 of the '648 Patent as a "method of identification and detection":

"*A method of identification and detection* of components in a multi-component mixture employing different fluorescent labels to detect at least two components of interest, wherein said labels are characterized by...."

Ex. 62, at 24 (emphasis added). The Examiner repeatedly referred to polynucleotide (*i. e.,* DNA) sequencing when discussing these claims, for example when discussing why this claim was patentable over the prior art:

"The advantage of such labels is that the same excitation wavelength can be used to excite all the labels simultaneously to produce different signals, such as is needed for *polynucleotide sequencing*...."

Id. at 102-103 (emphasis added). And in the Examiner's Notice of Allowance:

"The labels are used in methods of detecting at least two different components in a multicomponent mixture, wherein the multicomponent mixture is *not limited to nucleic acid mixtures*. The labels are also employed as *sequencing primers* and exhibit the advantage that different sequencing reaction can be detected using the same excitation wavelength."

Id. at 112 (emphasis added).

Perkin-Elmer contends that, because these comments were made in the context of the '808 patent application, concerning the claims 11-16 that contain a limitation to DNA sequencing, they have no relevance to understanding the broader claims of the '648 patent which are not so limited. This assumption is unwarranted. The '890 and '804 applications were prosecuted before the same Examiner, and it is reasonable to consider the Examiner's view of that portion of the claim language that the two patents have in common.

Perkin-Elmer also suggests that the '804 patent claims, which include an express limitation to DNA sequencing, should preclude the '648 claims from also covering methods for DNA sequencing. The '804 claims are not the subject of this proceeding and the Court will not draw inferences as to the meaning of the '804 patent claims to construe the '648 claims against the claim language, the preferred embodiment in the specification, and the prosecution history as discussed above.

Extrinsic evidence is helpful in understanding how the prosecution history defeats Perkin-Elmer's contention. Mr. Bjorge testified that it is very common that a patent, such as the '648 patent, may have claims which are broader than those of a related patent, such as the '804 patent. Ex. 1008, para. 37. Mr. Bjorge explained how the double patenting rejections in the '890 and '808 applications operated. *See* Ex. 1008, para.para. 2-4; TR 84:20-89:5; Ex. 61, at 45-47, 65, 70, 77; Ex. 62, at 74, 93, 104-107. During the prosecution of the '808 application, the Examiner made a provisional double patenting rejection of claims 1-

6 as directed to the same inventions as claims 1-6 of the '890 application. Ex. 62, at 74, 100. In response, the applicants canceled claims 1-3 of the '808 application and filed a terminal disclaimer limiting the term of any patent granted on the '890 application. Id. at 93. The Examiner's record for February 5, 1997, stated that the terminal disclaimer "will be reconsidered in light of amendments to claims submitted in 08/574, 890 that may obviate statutory double patenting ." Id. at 105. The applicants argued that the only type of double patenting remaining after the amendment was obviousness-type double patenting, which was overcome by the terminal disclaimer (id. at 104-107), and the Examiner then allowed the claims. Ex. 62A.

In the '890 application, the Examiner issued a provisional double patenting rejection of claims 1-6, as being directed to the same inventions as claims 1-6 of the '808 application. TR: 86:19-89:5; Ex. 61, at 45-46. The Examiner also objected to claims 4-6 "as being substantial duplicates of claims 1-3." Id. at 47. The applicants then cancelled claims 4-6, thereby eliminating same invention-type double patenting. Id at 65, 70, 77. They eliminated obviousness-type double patenting by means of a terminal disclaimer. Id. The Examiner then issued the Notice of Allowance. Ex. 61, at 81-82; Ex.1008, para. 3.

Mr. Bjorge testified that interpretation of claims 1-3 of the '804 patent as being directed to DNA sequencing, as Perkin-Elmer urges, is consistent with the restriction requirement in the prosecution of the '924 application leading to the '419 patent. Ex. 1008, para. 4; TR 82:23-86:18; 88:6-89:5. The Examiner's Amendment in the '808 application indicates that the '804 patent claims, including claims 1-3, are directed to sequencing. The '804 patent addressed the use of the labels as a sequencing primer. Ex. 62-A, at 3; TR 85:13-86:18. Claims 1-3 of the '648 patent are directed to a variation of the same invention as issued claims 1-3 of the '804 patent. *See* Ex. 1008, para. 4; TR 86:19-89:5. This aspect of the prosecution history indicates that the '648 patent claims encompass DNA sequencing.

4. The Restriction Requirement Is Irrelevant To The Claim Construction

Perkin-Elmer argued that the restriction requirement imposed by the Examiner during the initial stages of the prosecution of the parent '924 application should be used to exclude DNA sequencing from the scope of the '648 patent. A restriction requirement is not a rejection and it cannot be used to controvert the plain language of the claim. R2 Medical Systems, Inc. v. Katecho, Inc., 931 F.Supp. 1397, 1438 (N.D.Ill.1996). Here, the restriction requirement is far too ambiguous to subvert the claim language as approved by the Patent Office, when taken with the unambiguous statements in the specification about sequencing and also taken with the prosecution history of the divisional '890 application.

The Examiner separated the original 21 claims of the '924 application into four different categories: (1) methods of identification detection, (2) methods of separating components, (3) sequencing methods, and (4) kit claims. Ex. 206 at 57. Dr. Chamberlin opined that this restriction requirement would not cause one skilled in the art to understand that the claims directed to methods of identification and detection would not cover DNA sequencing. Ex. 63, 8:13-18. The restriction requirement in itself does not compel the conclusion that the '648 patent claims, which are broader than claims limited specifically to DNA sequencing methods, do not also cover DNA sequencing processes.

Few decisions have examined the importance of a restriction requirement in interpreting claims. In *R.* Medical Systems, 931 F .Supp. 1397, 1438, cited by Amersham, the court refused to use an Examiner's restriction requirement to limit the scope of a patent claim. Because a restriction requirement is administrative and does not constitute a "rejection" by the patent examiner, it should not be used to limit the scope of a claim for the purpose of determining infringement. Id. at 1438-39. The court wrote, "[T]here is

some question whether an applicant's response to a restriction has the same preclusive effect as a response to a rejection. In fact, the court has not identified any precedent using prosecution history of the election of a species in order to restrict or otherwise interpret the scope of a patent claim." *Id*. The district court reviewed the claim, the patent specification and the restriction requirement and ultimately refused to limit the scope of the claims because the claims and the patent specification were not limited. *Id*. Signtech U.S.A., Ltd. v. Vutek, Inc., 174 F.3d 1352, 1357-58 (Fed.Cir.1999), cited by Perkin-Elmer, is inapposite. In *Signtech,* the patentee attempted to use a restriction requirement in the prosecution history to "redeem its choice of claim language." 174 F.3d at 1357. The petitioner was unsucessful because the court would not use the prosecution history to contravene the language choices in the claims and specification, and was compelled by statute, 35 U.S.C. s. 112, para. 6, to limit the scope of the means-plus-function claims to the embodiments disclosed in the specification. 174 F.3d 1358. The Federal Circuit's recent decision in Merck & Co., Inc. v. Mylan Pharmaceuticals, Inc., 1999 WL 689731 (Fed.Cir. September 3, 1999), also cited by Amersham, is consistent with *R. Medical*. In *Merck,* the applicant was faced with both a restriction requirement and an obviousness rejection. The court restricted the claim to the elected species because the applicant made the amendment principally to avoid the obviousness rejection.

Here, in contrast, the election was purely administrative and offers little insight into construction of the '648 claims. For the purpose of case management and to control filing and search fees, a patent examiner may require the applicant "to divide his or her claims among distinct, though related, patent applications." *R. Medical,* at 1438. Mr. Bjorge testified that, as a matter of patent office practice during 1994, when the restriction issued, this administrative tool would likely be employed early in the prosecution, at the discretion of the Examiner, to control the Examiner's time (TR 78:1-23), and prior to determining the scope or boundaries of any the claims. Ex. 1007, at 10:25-26.

In Pitney Bowes, 182 F.3d 1298, the Federal Circuit held that complying with an administrative requirement, such as amending the patent title, should not be regarded as having the same or similar effect as an amendment of the claims by the applicant. "[I]f we do not read limitations into the claims from the specification that are not found in the claims themselves, then we certainly will not read limitations into the claims from the patent title." Id. at 1312. In this case, the applicants' compliance with an administrative requirement (*i.e.,* the restriction requirement), over their objection by a traversal, in the *parent* application, is entitled to little weight as against the applicants' claims as amended, and the Examiner's allowance of those claims, in the issued '648 patent. As a matter of practice, as Mr. Borge explained, in working with a restriction requirement, the applicant and the examiner are not disputing what subject matter is included in the invention versus the public domain, or whether the application uses language that is sufficient to satisfy the requirements of 35 U.S.C. s. 112. Ex.1007, at 11:2-5. In the case of the '924 application restriction, the Examiner and the applicants *ignored* the restriction in the subsequent prosecution of both the '648 and '804 patents. Ex. 1008, para. 1; TR 82:14-84:4.FN19 The first Examiner's attempt to organize the '924 application's 21 claims into a more manageable format by means of the restriction requirement, while understandable, is not particularly illuminating for purposes of this proceeding.

FN19. In Mr. Borge's experience, an examiner may have a minimal understanding of the claims and the invention at an early stage of the proceedings. TR 89:25-90:5; Ex. 1007, at 10:33-27. Here, for example, the Examiner's decision to issue a restriction requirement in the '924 application among claims classified in the same class and subclass was highly unusual (TR 80:3-14), and the applicants objected by filing a traversal. TR 81:6-15; 93:14-22. Claims 1-6 of the '924 application were directed to "methods of identification and detection." The Examiner issued the restriction requirement for "Claims 1-6, drawn to methods of identifying cells, classified in Class 435, subclass 6 ...," although none of these claims referred to "cells."

Ex. 206, at 57. The reference to cells is confusing and renders the restriction ambiguous. TR 22:12-23:7 (testimony of Dr. Chamberlin); TR 80:15-81:5 (Borge testimony).

Having considered the claim language, the specification, the prosecution history, and the extrinsic evidence, the Court finds that the language "a multi-nucleic acid mixture" refers to a mixture of nucleic acids that contain two or more non-identical nucleic acids, such as the mixture of acids produced during DNA sequencing. "Method of identification and detection of nucleic acids in a multi-nucleic in acid mixture" means that different nucleic acids in a multi-nucleic acid mixture that are labeled with different fluorescent labels can be distinguished by irradiating the labels and measuring the fluorescence they emit.

B. COVALENTLY BONDING

The parties dispute the construction of the method step of "covalently bonding different labels to different nucleic acids of said multi-nucleic mixture to form labeled nucleic acids." "Covalently bonding" commonly means joining together two chemical entities by a covalent bond. This term construction largely turns on whether DNA sequencing produces a labeled nucleic acid in a mixture of nucleic acids.

Amersham argues that the claim describes how different labels become covalently bonded to different nucleic acids in the "covalently bonding" step-a process whereby a label is covalently bonded with one or more nucleotides or nucleic acids to form at least two different labeled nucleic acids. In sequencing, this occurs during the primer extension reaction whether the labels are attached initially to the primer or to the terminator nucleotides. Exs. 201, 210; TR 26:24-27:16 (Chamberlin testimony); TR 174:6-178:1 (Roberts testimony).

Perkin-Elmer argues that no covalent bonding of a label *to a nucleic acid* takes place in DNA sequencing because, in DNA sequencing, the label is attached to a single nucleotide, not a nucleic acid. *See, e.g.,* Perkin-Elmer Illust. Exh. # 35. By employing the gerund in claim 1's phrase, "covalently bonding different labels to different nucleic acids," the claim requires that a nucleic acid (apparently, at least two nucleotides covalently bonded together) must exist before a label may be covalently bonded to it. Therefore, Perkin-Elmer argues, claim 1 must exclude DNA sequencing because a nucleic acid extension, as opposed to a single nucleotide, is not produced until the primer extension process takes place.

Perkin-Elmer's insistence that, in DNA sequencing, the labels are bonded only to single nucleotide, and not a nucleic acid, ignores the claim as a whole, the specification, and how one skilled in the art understands the DNA sequencing process to occur. The claim language as a whole specifies "covalently bonding different labels to different nucleic acids of said multi-nucleic acid mixture *to form labeled nucleic acids*." *See* Hockerson-Halberstadt, Inc. v. Converse, Inc., 183 F.3d 1369, 1374 (Fed.Cir.1999) ("Proper claim construction ... demands interpretation of the entire claim in context, not a single element in isolation."). This language is commonly understood to describe a process resulting in labeled nucleic acids which need not necessarily occur in a single event, at one fixed moment in time. In addition, the specification discusses the formation of labeled nucleic acids by primer extension. Patent, Col.5:23-32; 9:35-10:5; Fig. 7.

Perkin-Elmer's construction ignores the process by which DNA sequencing works. Both Dr. Chamberlin (Ex.63 at 8:23-9:5; Ex. 73; TR 11:12-12:24; 26:24-27:16; 34:14-23), and Professor Glazer (TR 122:12-123:18), explained how the labeled nucleic acid chains are created in a reaction that rapidly adds nucleotides to a growing extention of nucleotides (*i.e.,* nucleic acid). By primer extension (or nucleic extension)

reaction, the subject DNA is replicated as individual nucleotides are sequentionally (covalently) added to the primer to produce a growing nucleic acid chain. The chain's growth is stopped when a terminator nucleotide, covalently bonded with an energy transfer dye, is incorporated into that chain. Ex. 63, at 9:21-25; Exs. 208, 209; TR 26:24-27:1. Alternatively, a primer containing energy transfer dyes, rather than a terminator, may be used. Labeled primer is covalently bonded to the series of nucleotides and the terminator to form a labeled nucleic acid, as required by the claim. Exs. 73, 203. Dr. Roberts also agreed that labeled nucleic acids are formed by covalent bonding during DNA sequencing. TR 129:13-18; 174:6-178:1. The claim's requirement that labeled nucleic acids be formed by covalently bonding the labels to the nucleic acids is entirely consistent with the primer extension process.

The covalent bonding language is a meaningful limitation in the claim. While the '648 patent method could encompass DNA sequencing processes which rely on covalent bonding of the labels, the method would not cover, for example, probing assays which use non-covalent hybridization. In most such probing assays, the labeled probe is hybridized, and not covalently bonded, to a target sequence. Ex. 63, at 4:18-27; 9:1-2 (Chamberlin); TR 183:21-185:3 (Roberts). This "covalently bonding" requirement may also exclude other methods of detection and identification of nucleic material from the scope of the '648 patent claims as well, though the parties failed to explore other contexts for the Court.

Having reviewed the claims and the specification, and considered the extrinsic evidence, the Court finds that "covalently bonding different labels to different nucleic acids of said multi-nucleic acid mixture to form labeled nucleic acids" means that the labels become covalently bonded to different nucleic acids of the multi-nucleic acid mixture, during nucleic acid extention.

C. Backbone Chain

The parties dispute the meaning of the claim 1 language, "said labels are characterized by: (1) having a donor-acceptor fluorescent pair where said donor and said acceptor are each covalently bonded to a *backbone chain at specific locations thereon* with energy transfer from said donor to said acceptor." The dispute over "a backbone chain" turns on whether, as Perkin-Elmer contends, the backbone chain is limited to polymers in general and, in the particular context of nucleic acid analyses, to a nucleic acid backbone. In addition, Perkin-Elmer argues that the "backbone chain" term excludes any linker arms used to connect the fluorophore dyes.

Amersham would define "backbone chain" to mean, "different types of molecules that are made up of atoms that separate the donor and acceptor dyes." This "backbone chain" is the chain of atoms between the point where the donor dye is covalently bonded and the point where the acceptor dye is covalently bonded. It is described in claim 1 as the entity to which the acceptor and donor dye are covalently bonded at "specific locations." Covalent bonds occur between atoms and so the backbone chain is the *entire* chain of atoms between the donor and acceptor, including any linker arms.

If a claim term is given a particular meaning in the specification, that meaning should control. The specification never defines "backbone chain" expressly but confirms that the terms "backbone" and "chain" describe the chain of atoms between the donor and acceptor: "the distance between the two fluorophores *as determined by the number of atoms in the chain separating the two fluorophores* can be varied in accordance with the nature of the chain." Patent, Col.3:43-46. Also, "*[s]eparation of the donor and acceptor based on number of atoms in the chain will vary* depending on the nature of the backbone, whether rigid or flexible, involving ring structures or non-cyclic structures or the like. Patent, Col.4:65-5:8. Thus, Amersham

argues, those skilled in the art will understand "backbone chain" to mean any chain of atoms which are specifically and covalently bonded to the two separate dyes to form an energy transfer dye unit.

Perkin-Elmer argues that "backbone" is an adjective modifying "chain" and so the phrase "backbone chain" and the terms "backbone" and "chain" cannot be used interchangeably. The applicant is entitled to be his own lexicographer. "Backbone chain," which appears in the '648 patent only in claim 1, is a unique term. Amersham contends that the applicants combined the words "backbone" and "chain," both of which are used freely in the specification to describe the joining of the donor and acceptor fluorophores (*e.g.,* Patent, Col.2:1-4; 3:35-4:2; 4:67-5:12; 5:24-25; 6:11-20; 6:25-39), to lend the claim a distinct clarity and emphasis, analogous to "oring." TR 47:3-8; 60:2-4; 72:5-22. The analogy is an apt one, particularly as the word "chain" also figures in the specification's discussion of nucleic acid extensions, nucleic acid chains as primers in sequencing and also polymerase chain reaction [PCR]. *See* Patent, Col.5:23-32.

The specification describes the labels to "usually" or "particularly" employ a "nucleic acid backbone" (Patent, Col.2:1-4; 6:25-28), or "nucleic acid chain" (id., Col.3:46-53; 5:23-29), or "polymeric chain." Id., Col.3:35-37. The specification also provides a non-exhaustive list of potential chains and backbones, including molecules that are polymeric (nucleic acids, polypeptides and polysaccharides) and non-polymeric (various groups which may be added stepwise, such as di-functional groups, e.g., haloamines or the like). Id., Col.3:46-53. *See also* id., Col.6:31-38; and structures 1-3. The specification uses the terms backbone, chain, oligomer and "linking arm" in describing different ways the labels may be structured, using chains of atoms that may be either part of a polymer or not.

Perkin-Elmer relies on two sentences to argue that "backbone chain" must be limited to a chain of polymers. One states that "fluorophores are bound to a backbone, *particularly* a nucleic acid backbone." Patent, Col.2:1-2 (emphasis added). The other states that "the two fluorophores will be joined by a backbone or chain, *usually* a polymeric chain." Id., Col.3:35-36 (emphasis added). These statements merely confirm that polymeric backbones or chains are contemplated as embodiments, not as a claim limitation. Burke, Inc., 183 F.3d at 1341 ("References to a preferred embodiment, such as those often present in a specification, are not claim limitations."); Intervet Am., Inc. v.. Kee-Vet Labs, Inc., 887 F.2d 1050, 1053 (Fed.Cir.1989)("[I]nterpreting what is meant by a word in a claim is not to be confused with adding an extraneous limitation appearing in the specification, which is improper."). Indeed, Dr. Roberts agreed that a "polymeric chain" was not required by the specification. TR: 178:10-179:9; Roberts Dep. (10/11/99) at 86:6-18.

Perkin-Elmer argues that the specification statement, "the labels will be separated along the backbone" (Patent, Col.6:12-13), does not make sense if the backbone chain is defined as the chain of atoms between the two fluorophores. However, "backbone" as used in the specification refers alternatively to the chain of atoms between the two fluorophores and to a nucleic acid backbone, and in this instance Perkin-Elmer singles out a reference to a nucleic acid backbone. But, as shown at Patent, Col.9:15-20, "nucleic acid backbone" is not coextensive with "backbone chain," as the latter may include a linker arm. The expert testimony supports this construction and the Court rejects Perkin-Elmer's contention in its post-hearing brief (at pp. 17-20) that the specification draws a distinction between "backbone chains" and linking arms or linkers.FN20

FN20. Having reviewed the specification, Dr. Rebek testified that, if the donor and acceptor are covalently bonded through linker arms to some other molecule, *those linker arms are part of the backbone chain* because the attachment of the donor and acceptor defines the ends of the backbone chain. TR 42:7-10;

46:24-48:20. Professor Glazer's testimony is entirely consistent: "I think that the definition of what lies between the donor and the acceptor is explicit in the embodiment. It simply says that there is a number of atoms which represent the shortest covalent path between the donor and acceptor, and that's the backbone chain. It doesn't leave much room for confusion." TR 126:4-25. *See also* Glazer Dep.I at 190:11-15 ("[The linking arm] cannot be the *entire* backbone chain."), Toohey Decl., Ex. E. Dr. Roberts also conceded that, for the amino acid structures disclosed in the specification, the linker arms are included in the "backbone chain." TR 180:23-182:1.

Similarly, Perkin-Elmer insists that the statement, "the fluorophores may be bound internal to the chain" (Patent, Col.3:67-4:1), means that "backbone chain" cannot refer to any chain of atoms connecting the donor and acceptor. They also contend that Professor Glazer admitted that "backbone chain" must refer exclusively to a nucleic acid chain. Glazer Dep.I, at 180:8-13, Toohey Decl., Ex. B; TR 124:22-125:5; 127:8-23. However, this statement, and Professor Glazer's testimony, refer to one aspect of the invention, described at Patent, Col.3:28-34 and Col.5:9-22, in which more than two fluorophores are used in a single label. These additional fluorophores must necessarily be bound internal to the chain of atoms between the two most widely separated fluorophores. This particular example described in the specification should be read as a claim limitation to polymers or to a nucleic acid. FN21

FN21. *E.g.,* Burke, Inc., 183 F.3d 1334, 1340 ("Consistent with the principle that the patented invention is defined by the claims ... limitations cannot be read into the claims from the specification or the prosecution history"); Electro Med. Sys. S.A. v. Cooper Life Sciences, Inc., 34 F.3d 1048, 1054 (Fed.Cir.1994) ("[C]laims are not to be interpreted by adding limitations appearing only in the specification .... although the specifications may well indicate that certain embodiments are preferred, particular embodiments appearing in a specification will not be read into the claims when the claim language is broader than such embodiments.") (citations omitted).

During prosecution of the '890 patent application, the applicants overcame the very same argument that Perkin-Elmer now raises, that the backbone chain must be a polymer. Initially, the Examiner wrote that the chain joining the donor and acceptor had to be a polymer and rejected claims which were not limited to a polymeric backbone chain: "the disclosure is enabling only for claims limited to nucleic acid backbone chains.... The specification does not disclose or exemplify backbone chains other than nucleic acids." Ex.61, at 46; exhibit at Tab 3 to Amersham's post-hearing brief, at 2. This rejection was withdrawn when the applicants demonstrated that "backbone chains" could include flexible (such as $-(CH_2)_n-$ or oligopeptides) or rigid (such as steroids or bi-steroid structures) non-nucleic acid and non-polymeric molecules. Ex.61, at 67-68. The applicants provided the Examiner, both textually and graphically, with examples of fluorescent pairs "linked by flexible (primarily $-CH_2)_n-$) chains" and "bridged by a polypeptide" or "rigid (or partially rigid) spacers" such as "a rigid steroid structure." *Id*. at 67-76; TR 45:23-25; 46:1-20.

The applicants also indicated that no particular chemical composition or structure placed a limitation on this part of claim 1: "*[t]he scope and utility of this invention is not limited to the specific nature of the backbone,* nor is the usefulness of any particular backbone structure relative to any other point of novelty in this invention." Ex.61, at 69 (emphasis added). This same point is implicit throughout the specification.FN22 Instead, what the applicants emphasized to the Examiner, in distinguishing their labels from prior art while responding the Examiner's rejection (*see* Ex.61, at 70-74), was their use of "highly specific covalent structures ....with precise and nonheterogeneous spectroscopic properties ... critical to Applicants' multiplex

applications." *Id*. at 72. In distinguishing their claims from Benson *et al*., for example, the applicants emphasized that they specifically, not randomly, positioned the flurophores and covalently joined the label to the subject component:

FN22. *C.f.,* Pitney Bowes, 182 F.3d 1298, 1311 ("In circumstances ... where the language of the written description is sufficient to put a reader on notice of the different uses of a term, and where those uses are further apparent from publicly-available documents referenced in the patent file, it is appropriate to depart from the normal rule of construing identical terms in the same manner. This entirely accords with the public notice function of claims.").

In Applicant's invention, the labels are formed by covalently linking the donor and acceptor fluorophores to specific positions on the backbone and then covalently and specifically linking the label to the components to be detected. This provides a stable structure that does not change its spectroscopic properties as a function of time and conditions. These are critical advantages in the design and performance of multiplex detection."
Ex. 61, at 73.
The extrinsic evidence supports reading the term "backbone chain" to allow both polymeric and non-polymeric structures. Consistent with the specification (Patent, Col.4:66-5:8), Dr. Rebek testified that the structure of the atoms can be "rigid, flexible, cyclical or linear" (TR 43:2-5), and that one skilled in the relevant art (as to this term, chemistry) would read the specification and understand that "backbone chain" includes polymers.FN23 TR 42:23-44:10. Dr. Roberts agreed that the specification's description of the structures includes non-polymeric chains. TR 179:10-180:1. Dr. Roberts' testimony, and the other extrinsic evidence Perkin-Elmer introduces from technical dictionaries, concerning useage of the term "backbone" in molecular biology as referring to polymers, is not inconsistent with the specification or the testimony of Drs. Chamberlin, Rebek and Glazer concerning nomenclature. This extrinsic information is merely incomplete insofar as the specification explicitly does not limit the scope of the claims to a single backbone structure or require a polymer.

FN23. Perkin-Elmer would have the Court completely discount the testimony of Dr. Rebek, director of the Skaggs Institute for Chemical Biology and a professor of Chemistry at the Scripps Ranch Institute, with extensive experience in organic, synthetic and combinatorial chemistry, simply because he is not a molecular biologist. But Dr. Rebek testifies that one of skill in the relevant art is skilled in chemistry (TR 71:2-11), as is one of the inventors, Dr. Glazer, who was called to testify by Perkin-Elmer in part because he is skilled in the art. Perkin-Elmer's other expert, Dr. Roberts, currently an assistant professor in the Department of Chemistry at the California Institute of Technology (TR 131:15-24), agrees that one skilled in the relevant art must have a "substantial" background in chemistry and the use of fluorescent dyes. TR 133:8-16; 133:25-135:4; Ex. 1012, at 3:24-4:6.

Together, the language of claim 1, the specification, and the prosecution history demonstrate that "backbone chain" refers to the fewest number of atoms between the donor and the acceptor dyes, whether those atoms are in a polymeric or non-polymeric molecule. While extrinsic evidence is not needed to construe this disputed claim term, this evidence supports the Court's construction.

The Court finds that "backbone chain" means the entire chain of atoms that separate the donor and acceptor dyes.

D. At Specific Locations Thereon

The parties dispute the meaning of "at specific locations thereon" in the claim 1 language, "where said donor and said acceptor are each covalently bonded to a *backbone chain at specific locations thereon*." The parties agree that the patent avoids random attachment of the labels, and that the spacing between the donor and acceptor flurophores along the backbone chain may be varied to ensure efficient energy transfer and to adjust the mobility of the labels. The dispute now turns on whether the term "at specific locations thereon" means controlling to which of the three or more potential potential attachment sites on the backbone chain the donor and acceptor are covalently bonded, as Perkin-Elmer urges.

Amersham urges a construction where "at specific locations thereon" means that there is one atom of the backbone chain to which the backbone acceptor dye will always covalently bond and another atom to which the donor dye will always covalently bond. As explained in the specification, the specific locations ensure that the proper spacing between the donor and the acceptor dyes will always be established. Patent, Col. 3:35-59. This is possible because the covalent bonds between the backbone chain and the donor and the acceptor dyes are predetermined and proper orientation of the backbone chain is controlled by the method of synthesis, rather than occurring in a random fashion. *Id.,* Col.5:33-40. *See* TR 38:12-44:22; 47:9-16. The specification discloses the need to ensure that appropriate spacing is maintained between the donor and acceptor fluorophores to promote efficient energy transfer (Patent, Col.2:62-67; 3:1-60), and to control mobility. *Id.,* Col.4:17-31; 6:10-20; 7:56-67; 8:1-38; 10:5-16. *See also* TR 42:11-19; 44:11-22.

Amersham points to the prosecution history to support this construction. The applicants amended their claim to distinguish their "chemically pure labels" from the mixture of labels produced by the random synthesis disclosed in certain prior art, U.S. Patent No. 4,996,143 (the " '143 Heller patent").FN24 A single Heller label is a mixture of chemical species-it is a mixture of labels with their component dyes in alternative orientations. To distinguish the labels claimed in the '890 application from those disclosed in in the Heller patent, the applicants added the claim limitation "at specific locations thereon." This term indicates that the method of synthesis controls the location of the donor dye and the location of the acceptor dye, such that the reaction of each dye with the backbone chain produces a chemically pure label.

FN24. *See* the '143 Heller patent, Col.8:51-9:52, submitted at Tab 2 to Amersham's post-hearing brief; Ex.61 at 66, 71-72; exhibit at Tab 5 to Amersham's post-hearing brief; TR 48:21-49:6 (Rebek testimony).

The applicants argued during prosecution that,

"[i]n [the Heller patent], the method of synthesis is not specific and does not permit control of the location of the donor and acceptor fluorophores ... Heller et al. specifically acknowledge that their probes are a mixture of chemical species.... If one attempted to make families of donor-acceptor labels following the non-specific synthetic methods of Heller et al., the spectroscopic properties would necessarily vary due to unavoidable variations in the synthetic method.... Through the use of specific and covalent linkages as claimed by Applicants, these problems are obviated, producing labels with the desirable pure spectroscopic properties expected for chemically pure labels.

Ex.61, at 71-72. Consequently, the phrase "at specific locations thereon" limits the type of fluorescent labels that can be used in the claimed method to exclude mixtures of labels such as those described in the Heller

patent, because "each donor and acceptor fluorophore is covalently bonded in a unique and specific position to the backbone to form the label." Id. at 63. Thus, Armersham argues, this limitation simply refers to the fact that the covalent bonds between the backbone chain and the donor and the acceptor dyes are predetermined and controlled by the method of their synthesis rather than occurring in a random fashion. Patent, Col.3:41-59; 5:33-40.

Perkin-Elmer argues that, "at specific locations thereon" means controlling to which of three or more potential attachment sites on the backbone chain the donor and acceptor are covalently bonded. It argues that three or more potential attachment sites are required because the specification discloses that the spacing between the donor and acceptor can be varied.FN25 Because two sites are needed to attach the donor and acceptor dyes, a third site is required to provide an alternative attachment point and thus to vary the distance between the donor and acceptor dyes.

FN25. *E.g.,* Patent, Col.3:35-59; 3:67-4:2; 4:17-39; 4:66-5:8; 8:18-38.

While the specification plainly discloses that the distance between the donor and the acceptor fluorophore may be varied to adjust the desired attributes of the label, the specification does not support Perkin-Elmer's construction. The spacing between the donor and acceptor may be varied by using a different backbone chain to bridge these two fluorophores, and by varying the number of intervening atoms: "the distance between the two fluorophores *as determined by the number of atoms in the chain separating the two fluorophores can be varied with the nature of the chain,*" (Patent, Col.3:38-3:46) and, "*[s]eparation of the donor and acceptor based on number of atoms in the chain will vary* depending on the nature of the backbone, whether rigid or flexible, involving ring structures or non-cyclic structures or the like." Id., Col .4:65-5:8. By altering the type of backbone chain used to bridge the donor and acceptor, the number of atoms in the chain is varied, which varies the spacing.

For example, varying the backbone chain to alter the distance between the donor and acceptor dyes is disclosed in the specification in an example using three monosubstituted nucleic acids, each with a different number of nucleotides between the dye attached at the 5' end, and the second site of attachment-the modified based containing a linker arm. Patent, Col.8:42-67. Each of these monosubstituted nucleic acids has a single potential attachment site for a second dye. The second dye is subsequently attached to the linker arm. Id., Col.9:1-35. At no time are three sites of attachment available, yet the spacing between the two dyes is still varied.

The intrinsic evidence does not support Perkin-Elmer's argument that the phrase "at specific locations thereon" requires that the backbone chain contain three or more attachment sites. Having reviewed the claims, the specification and the prosecution history, the Court finds that, "at specific locations thereon" means that the covalent bonds between the backbone chain and donor and acceptor dyes are predetermined and controlled by the method of synthesis rather than occuring in a random fashion.

V. CONCLUSION

The disputed claim terms of the '648 patent are construed as follows:

1. "Method of identification and detection of nucleic acids in a multi-nucleic acid mixture" means that different nucleic acids in a multi-nucleic acid mixture that are labeled with different fluorescent labels can

be distinguished by irradiating the labels and measuring the fluorescence they emit. A "multi-nucleic acid mixture" refers to a mixture of nucleic acids that contain two or more non-identical nucleic acids, such as the mixture of acids produced during DNA sequencing.

2. "Covalently bonding different labels to different nucleic acids of said multi-nucleic acid mixture" means that the labels become covalently bonded to different nucleic acids of the multi-nucleic acid mixture, during nucleic acid extention.

3. "Backbone chain" means the entire chain of atoms that separate the donor and acceptor dyes.

4. "At specific locations thereon" means that the covalent bonds between the backbone chain and donor and acceptor dyes are predetermined and controlled by the method of synthesis rather than occuring in a random fashion.

IT IS SO RECOMMENDED.FN26

FN26. Inasmuch as claims construction is a question of law and may be case dispositive, this ruling is made pursuant to Rule 72(b), Fed . R.Civ.P.

N.D.Cal.,2000.
Amersham Pharmacia Biotech, Inc. v. Perkin-Elmer Corp.