EPA/EPO/OEB
D-80298 München
+49 89 2399-0
TX 523 656 epmu d
FAX +49 89 2399-4465

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VOSSIUS & PARTNER
Postfach 86 07 67
81634 München
ALLEMAGNE

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Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
ENZO BIOCHEM, INC.

The appeal filed with your letter of 07.04.00 & 07.06.00 against the decision of the Examining Division of the European Patent Office of 28.01.00 has been referred to the Technical Board of Appeal 334

The reference number of the appeal file is T0749/00-334
You are asked to quote that reference in any further communication submitted on this appeal and to address such communication to Directorate General 3 (Appeals) of the European Patent Office in Munich.

Registry
Tel.(089)2399-

VOSSIUS & PARTNER
Patentanwälte

Vossius & Partner POB 86 07 67 81634 München Germany

To the
European Patent Office
Munich

PATENTANWÄLTE
EUROPEAN PATENT ATTORNEYS
EUROPEAN TRADEMARK ATTORNEYS
Dr. VOLKER VOSSIUS, Dipl.-Chem.
(bis 1992; danach in anderer Kanzlei)
Dr. PAUL TAUCHNER, Dipl.-Chem.
Dr. DIETER HEUNEMANN, Dipl.-Phys.
Dr. PETER A. RAUH, Dipl.-Chem.
Dr. GERHARD HERMANN, Dipl.-Phys.
JOSEF SCHMIDT, Dipl.-Ing.
Dr. HANS-RAINER JAENICHEN, Dipl.-Biol.
Dr. ALEXA VON UEXKÜLL, M.Sc.
Dr. RUDOLF WEINBERGER, Dipl.-Chem.
Dr. WOLFGANG BUBLAK, Dipl.-Chem.
AXEL STELLBRINK, Dipl.-Ing.
Dr. JOACHIM WACHENFELD, (Biol.)
Dr. FRIEDERIKE STOLZENBURG, Dipl.-Biol.
RAINER VIKTOR, Dipl.-Ing.
EUROPEAN PATENT ATTORNEYS
Dr. RENATE BARTH, Dipl.-Chem.
Dr. URSULA ENGLBRECHT, Dipl.-Chem.
RECHTSANWÄLTE
HELGA TREMMEL
BARBARA GUGGENMOS, Dipl.-Chem.
DR. THURE SCHUBERT

SIEBERTSTRASSE 4
81675 MÜNCHEN
GERMANY
TEL.: +49-89-41 30 40
FAX: +49-89-41 30 41 11 (G3/G4)
+49-89-41 30 44 00 (G3)
(Marken - Trademarks)
E-MAIL: info@vossiusandpartner.com
HOMEPAGE: www.vossiusandpartner.com

EP 92 11 4727.8-2116
ENZO BIOCHEM, INC.
Our Ref.: S 808 EP/I

June 7, 2000
Ba/ne

In the following the Grounds of the Appeal dated April 7, 2000, are set out:

In their Decision dated January 28, 2000, the Examining Division stated that the Auxiliary Request did not meet the requirements of the EPC due to lack of inventive step.

Applicant disagrees for the following reasons:

1. KNOWLEDGE OF THE PERSON SKILLED IN THE ART AT THE PRIORITY DATE

The present invention has been filed some time ago, i.e. its priority date is in the year 1983. It concerns a field wherein the knowledge has increased immensely in the meantime. In such a case it is especially important to differentiate

between what was really known at that time and what may be interpreted into the teaching of the prior art by hindsight on the basis of the present knowledge.

2. CASE LAW

When asserting inventive step certain standards have to be applied based on decisions of the Technical Boards of Appeal. According to T2/83 ("Simethicone Tablet/RIDER") the question is not whether the skilled could have done something, i.e. could have applied a known teaching, but whether he would have applied the teaching in expectation of some improvement or advantage. It is further stated that a patentable subject matter may exist in spite of the fact that the claimed solution is retrospectively trivial and in itself obvious. A similar statement is made in T60/89 ("Fusion Proteins/HARVARD") where the key question raised is whether it was obvious for a skilled person to try the idea outlined with a reasonable expectation of success.

3. PROBLEM AND SOLUTION OF THE PRESENT INVENTION

3.1 If one takes document D1 as the closest prior art, the **problem** to be solved is the provision of a method for detecting a polynucleotide sequence which allows the quantitative determination (page 21, lines 18 to 21) and which consequently permits easy automation and instrumentation of the detection of a signal associated with the presence and/or quantity of the target polynucleotide sequence.

The **solution** provided by the invention is a method for detecting a polynucleotide sequence by performing the steps as described whereby a quantifiable signal is generated upon hybridization of the probe with the

sequence. The signal provides means to quantify the target polynucleotide by the techniques indicated in claim 1, especially photometric techniques.

Specific embodiments are contained in the dependent claims.

The further independent claims are based on the same principle.

3.2 The method claimed is not made obvious by the prior document D1 because the combination of fixing a polynucleotide sequence, which is non-radioactively labelled, to a substrate with a quantifiable detection system, e.g. an ELISA, is not suggested.

3.2.1 At the priority date of the present application quantitative detection methods using quantifiable signals, such as enzyme-linked immunosorbent assays (ELISA) were well known and had been around for years. But these detection methods involved a labelling of an antibody, enzyme or other protein and were typically only used for the detection of antigens and/or antibodies.

3.2.2 With respect to the field of nucleic acid detection, quantitative detection techniques involving signals such as ELISA were not available in the early 1980s. Nucleic acids were detected primarily by means of Southern and Northern blotting and other in situ hybridization (see e.g. the disclosure in D1) or immunoprecipitation techniques. The present patent application taught the industry for the first time how to use quantitative detection techniques typically used in the antigen/antibody detection field for nucleic acid detection. The characteristics of nucleic acids would have discouraged and even would have predicted away from the application of colorimetic assays for the detection of nucleic acids in the claimed method. In ELISA detection based systems for antigen/antibody one merely had to deal with ligand-receptor specificity and the non-specific binding of the protein to the support. On the other hand, if

colorimetic determination of nucleic acids were to be used, several problems may occur, i.e.

- it would require a higher capacity of the matrix for the nucleic acid which is a linear molecule (ligands and proteins are three-dimensional);

- it would require immobilization in a single-stranded form, thus necessitating nucleic acid melting and re-hybridization; and

- besides the desired specific binding, there can be more non-specific interactions, e.g. between protein and nucleic acid, protein and matrix, nucleic acid and matrix and ligand and nucleic acid.

At the time the present invention was made, one could not have conceived that these interactions could be effectively dealt with and that the claimed method would provide the desired result.

3.2.3 With regard to the feature "quantifiable", it was argued by the Examining Division that according to D1 the probe can be enzymatically or fluorescently labelled whereby both kinds of labels give rise to a quantifiable signal and that the signal is quantifiable, independent of whether it is actually quantified or not. Although this may be theoretically the case, it is a fact that in D1 the signal has not been used for quantification.

The focus of D1 is on insoluble coloured precipitates and direct light microscopic visualization which elements are opposed to and actually teach away from the present invention and the notion of a quantifiable signal.

D1 is limited to in situ hybridization which can only be practised in the context of well-defined morphology against which a localized signal must be produced and interpreted. When performing in situ hybridization, the technician or researcher is looking under the microscope and observing form or morphology as well as signalling events within the context of any such form or morphology.

Such a person only observes and amasses information within the context of clearly defined boundaries and visible shapes. The cells or the contents of cells under examination must have such boundaries and shapes in order to carry out the detection in in situ hybridization. Separation and analytical techniques are largely based on precipitates and defined boundaries.

With soluble signals, however, the approach is entirely antithetical to the purposes of and the information being sought with through light microscopic examination. With a quantifiable soluble signal there are no clearly defined boundaries, shapes and morphology with which a technician or researcher must contend. In fact, the quantifiable signal, which is a material element in the claims of the present application, is in no way localized nor is morphology either required, maintained or viewed. Rather, with the generation of a quantifiable signal, a dispersed or scattered signal in solution is obtained without any regard to any limitation or requirement for morphologic integrity.

With in situ hybridization, in order that the morphological integrity is maintained, the samples, i.e. tissue sections or cultured cells, have to be treated in a certain way, e.g. by a fixation with formaldehyde or glutardehyde or by treatment with a protease.

3.2.4 Thus, the problem to be solved in D1 is completely different from that in the present invention where the DNA sequence has on the one hand to bind to the support but on the other hand has still to be able to hybridize with the probe to allow the quantitative determination. In fact, the method is concerned with the total amount of the target nucleic acid analyte in the sample or specimen – and not with its location or distribution in the cells or tissues.

The focus of D1 is on insoluble coloured precipitates and direct light microscopic visualization which elements are diametrically opposed to and actually teach away from the present invention and the notion of a quantifiable signal.

4. CONCLUSION

In view of the different problems to be solved in D1 and in the present invention, there is no suggestion in D1 for the solution provided in the present application.

It was not foreseeable that the DNA sequence would bind sufficiently to the support to make the quantitative test possible.

The fact that in D1 only a precipitate is used as a signal which cannot provide an exact quantitative measurement, can only mean that it was not clear at that time that a quantifying signal can be generated for the desired purpose. Only in the present invention it was recognized that the signal can be used for quantitative measurement and it has been used therefor for the first time in the present invention.

Therefore, the present invention involves an inventive step.

5. COMMERCIAL DEVELOPMENT

In addition to the technical and scientific reasons why the present invention is patentable and represents an inventive step over D1, Applicant respectfully points out that two decades of ongoing commercial development described in the following is also clear testament to the inventive step of the present invention.

Since 1981 Applicant has been the exclusive licensee of the technology covered by the cited document D1 [EP-A-0 063 879]. See the accompanying **Exhibit 1** consisting of the Applicant's December 15, 1987 news release announcing the issuance of U.S. Patent No. 4,711,955 (top copy of patent also included). D1 and U.S. 4,711,955 share the same priority document, U.S.

Application Serial No. 255,223, filed on April 17, 1981. See also Applicant's March 19, 1990 news release provided in **Exhibit 2** also announcing that "Enzo has exclusively licensed from Yale University European Patent 0063879 and German Patent P 32 80 032.0-08 which issued late last year [1989] and protect this technology in Austria, Belgium, France, Germany, Italy, Lichtenstein, Luxembourg, Netherlands, Sweden, Switzerland, and the United Kingdom."

Thus, it was with full knowledge and awareness of D1's disclosure that Applicant conceived, invented and developed the present invention. The course of the present invention has spanned almost two decades, resulting not only in the issuance of several patents, but also in the development of key commercial products sold and distributed worldwide. In addition to the aforementioned U.S. Patent No. 4,994,373, other significant patents have been issued in Canada and Japan. See Canadian Patent No. 1,309,672 and Japanese Patent No. 2,825,090, copies of top sheets provided in **Exhibits 3 and 4**, respectively. See also Applicant's January 12, 1999 news release (**Exhibit 5**) announcing the issuance of Japanese Patent No. 2,825,090 and its use for quantitative determination of nucleic acids present in a sample and for forming an array of nucleic acids attached to a matrix or microchip.

Applicant has expended considerable time, effort and expense in developing commercially useful products based upon the present invention. In the same year following the issuance of U.S. 4,994,373 (see Applicant's February 25, 1991 news release provided in **Exhibit 6**), Applicant launched one of its premier products for HIV detection using a microplate hybridization assay. See Applicant's December 4, 1991 news release provided in **Exhibit 7**. As stated in the December 4, 1991 news release (**Exhibit 7**):

This product also can measure virus concentrations, making it easier for researchers to determine HIV levels in patients and look for relationships between these levels and other disease indicators such as antibody production or appearance of symptoms.

This product, called "HIV Microplate Hybridization Assay", employs the company's proprietary nucleic acid test method which produces a soluble signal in solution. Using this method, many samples can be processed simultaneously and the results can be automatically determined by microplate readers, instruments commonly used in laboratories.

A copy of Applicant's product brochure for its Microplate Assay for HIV DNA is provided in **Exhibit 8**. Also provided are copies of reprints of two scientific publications based upon this product and technology. The first is titled "Nonradioactive, Color-imetric Microplate Hybridization Assay for Detecting Amplified Human Immuno-deficiency Virus DNA" [Rapier et al., Clinical Chemistry, Vol. 39, No. 2, Pages 244-247 (1993)] and is provided in **Exhibit 9**. See also Applicant's March 24, 1993 news release announcing the Clinical Chemistry report on its HIV Microplate Hybridization Assay, copy provided in **Exhibit 10**. The second publication is titled "Anti-body-Enhanced Microplate Hybridization Assay" [Christine L. Brakel, BioTechniques, Vol. 22, No. 2, Pages 346-348 (1997)] and is provided in **Exhibit 11**.

Since the introduction of its HIV Microplate Hybridization Assay, Applicant has been successfully selling and distributing other microplate assays directed to other pathogens, including *Mycobacterium tuberculosis*, Hepatitis B Virus, the latter including core antigen sequences, surface antigen sequences and direct detection in serum. See copy of pages 21 and 22 from Applicant's 1992

Product Catalog provided in **Exhibit 12**. See also copy of pages 99-114 from Applicant's 1995 Research Product Catalog provided in **Exhibit 13**.

In addition to the foregoing developments, Applicant also wishes to point out that products and reagents covered by the present invention are gaining increased acceptance and use in the highly acclaimed DNA (micro)chip and array field. As indicated above, Applicant has obtained array claims in Japan for a related and corresponding Japanese patent. Furthermore, Applicant is the sole supplier of labeling and detection products for one of the world's leading DNA microchip manufacturers, Affymetrix, Inc. See Applicant's May 27, 1998 news release provided in **Exhibit 14** announcing its agreement with Affymetrix to be the sole supplier of reagents for the latter's GeneChip® arrays. See also Applicant's March 23, 1999 news release provided in **Exhibit 15** announcing its agreement with Gene Logic, Inc. under which it will be the exclusive supplier of reagent products for labeling and detecting gene sequences with Gene Logic's Flow-thru Chip™ probe arrays. Applicant has also obtained a similar arrangement with another leading chip manufacturer, Gene Logic, Inc. See Applicant's February 24, 2000 news release provided in **Exhibit 16** announcing its expanded product line, Enzo's BioArray Labeling Systems, for gene chip and other microarray methods. In Applicant's current 2000 product catalog is a listing of products for its BioArray™ Labeling Systems. See copy of pages 21-24 provided in **Exhibit 17**.

The above described commercial success being reflected in the agreements with and uses by other manufacturers is a clear indication of the inventive step involved in the present invention. Moreover, it defies logic and common sense to hold that D1 renders the present invention obvious. The patent record in other significant patent examining authorities and the worldwide commercial success of Applicant's products based upon the present invention clearly confirm otherwise that the inventive step of the present invention is indeed not negated in any way by D1, or for that matter, any other document cited of record in this case.

5. REQUESTS

Based on the above submitted argumentation it is requested that the Decision to refuse the patent application be set aside and the patent be granted on the basis of the Auxiliary Request.

Renate Barth

Dr. Renate Barth
European Patent Attorney

Encl.
Exhibits 1 to 17

DOAP 3.

10.06.00 OR

→ Application fill