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Datasheet for the decision of 6 July 2006

Case Number: T 0313/05 - 3.3.04

Application Number: 98110423.5

Publication Number: 0872562

IPC: A61K 39/395

Language of the proceedings: EN

Title of invention:
Instrument for monitoring nucleic acid amplification reactions

Patent Proprietor:
Applera Corporation

Opponents:
Bio-Rad Laboratories Inc.
THE SECRETARY OF STATE FOR DEFENCE
Bibby Sterilin Ltd
M.J. Research, Inc.
Stratagene Inc.

Headword:
Apparatus for monitoring a polymerase chain reaction/APPLERA

Relevant legal provisions:
EPC Art. 54, 76(1), 84, 111(1), 113(1), 117(1), 123(2)
EPC R. 67, 62

Keyword:

"Compliance with Article 76(1) EPC at the filing date of the divisional application - (yes)"
"Clarity - (yes)"
"Compliance with Article 76(1) EPC of the subject-matter of the claims of the main request - (yes)"
"Scope of the claims of the main request broader than scope of the claims of the divisional application as filed - (yes)"
"Added subject-matter - (no)"
"Priority - (yes)"
"Availability of a document to the public - (no)"
"Public prior use - (not established)"
"Novelty - (yes)"
"Remittal - (yes)"
"Substantial procedural violation - (no)"

Decisions cited:

G 0002/98, T 0381/87, T 0523/89, T 0729/91, T 0472/92, T 0782/92, T 0296/93, T 0097/94, T 0750/94, T 0848/94, T 0091/98, T 0720/02, T 0797/02, T 0039/03, T 0264/03, T 0474/04, T 1040/04, T 1409/05

Catchword:

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Case Number: T 0313/05 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 6 July 2006

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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 7 January 2005 revoking European patent No. 0872562 pursuant to Article 102(1) EPC.

Composition of the Board:

Chair: U. Kinkeldey
Members: G. Alt
G. Weiss
R. Gramaglia
R. Moufang

Summary of Facts and Submissions

I. European patent No. 0 872 562 based on the divisional application 98 110 423.5 and claiming the priority date 2 May 1991 of the parent application No. 92 106 989.4 (filed on 24 April 1992 and published as EP-A-0 512 334) was granted on the basis of 10 claims.

II. Claim 1 of the divisional application as filed read:

"1. An instrument for monitoring a nucleic acid amplification reaction comprising:
a thermal cycler having a support adapted for accomodating [*sic*] one or more nucleic acid amplification reaction volumes; and
an optical system adapted for being optically coupled to the one or more nucleic acid amplification reaction volumes accommodated by the support."

III. Five notices of opposition were filed. Revocation of the patent was requested on the grounds of Article 100(a) EPC, lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), Article 100(b) EPC, and Article 100(c) EPC.

IV. Notice of intervention was filed by M. J. Research, Inc. (opponent 06).

V. Opponent 05 withdrew its opposition.

VI. During oral proceedings, the opposition division decided to take evidence by hearing Prof. Biebricher as a witness regarding the question whether or not the document "Report on Evolution Research" (referred to as

document D30) was made available to the public during the workshop held in Göttingen, Germany, on April 18 to 20, 1991. The opposition division came to the conclusion that document D30 was made available to the public at said workshop.

The opposition division revoked the patent pursuant to Article 102(1) EPC because the subject-matter of claim 1 of all the three claim requests before it was considered to lack novelty (Article 54 EPC).

VII. An appeal was lodged by the patentee against the decision of the opposition division.

VIII. Notice of intervention was filed by Stratagene Inc. (opponent 07).

IX. Opponent 04 withdrew its opposition.

X. With letter of 2 June 2006, the patentee (appellant) filed a new main request and four new auxiliary requests.

The main request contained ten claims with claim 1 directed to an apparatus and claims 2 to 9 dependent on claim 1. Claim 10 was directed to a use of the apparatus according to any one of claims 1 to 9.

Claims 1, 2, 7 and 8 read:

"1. An apparatus for monitoring a polymerase chain reaction (PCR) for nucleic acid amplification over multiple thermal cycles, comprising:

(a) a thermal cycler for carrying out an automated PCR process, said thermal cycler capable of alternately heating and cooling, in a reaction vessel, a PCR amplification reaction mixture comprising a target DNA, reagents for said nucleic acid amplification, and a detectable nucleic acid binding agent; and

(b) an optical system including a detector operable to detect an optical signal related to the amount of amplified nucleic acid in the reaction mixture over a multiple-cycle period, without opening the reaction vessel once the amplification reaction is initiated.

2. The apparatus of claim 1, wherein the thermal cycler is capable of alternately heating and cooling a plurality of reaction vessels, each containing a said amplification reaction mixture.

7. The apparatus of any of the preceding claims, further comprising a reaction vessel adapted to contain a said amplification reaction mixture comprising a target DNA, reagents for said nucleic acid amplification, and a detectable nucleic acid binding agent.

8. The apparatus of claim 7 which comprises a plurality of reaction vessels, each adapted to contain a said amplification reaction mixture."

XI. Oral proceedings before the board took place from 4 to 6 July 2006.

On the first day of these oral proceedings, opponent 02 withdrew its opposition.

XII. As parties to these proceedings, there now remain the patentee (appellant), and opponents 01 and 03, and the interveners/opponents 06 and 07 (respondents).

XIII. The following documents are mentioned in the present decision:

D1: EP 0 512 334 (parent application as filed)

D4: Higuchi et al., Biotechnology 10, 413-417 (1992)

D6: Haff et al., Amplifications 1, 8-10 (1989)

D11: Morrison et al., Analytical Biochemistry 183, 231-244 (1989)

D12: EP-A-0 236 069

D15: Chehab and Kan, P.N.A.S. USA 86, 9178-9182 (1989)

D17: Holland et al., FASEB Journal 5, pA621 (1989)

D19: Cardullo et al., P.N.A.S. USA 85, 8790-8794 (1988)

D22: GB-A-1 486 210

D25: DE 26 51 356

D26: Brochure of Eppendorf AG (undated)

D28: EP-A-0 487 218

D29: FR 2 250 991

D30: Report on Evolution Research; Department of Biochemical Kinetics of the "Max-Planck-Institut für biophysikalische Chemie", Göttingen

D33: Fluorolog-2 Spectrofluorometer, Spex (brochure; undated)

D34: Fluorolog-2 Spectrofluorometer, Spex (brochure; 1996)

D35: English translation of JP 294305/90 (priority of EP-A-0 487 218, document D28)

D36: Letter from Bojan Savic to Prof. Eigen of 30 August 2000

D37: Reply from Prof. Eigen's secretary to Dr Savic of 5 September 2000

D42: Holland et al., P.N.A.S. USA 88, 7276-7280 (1991)

D47: Affidavit of Prof. Eigen of 20 December 2000

D48: Affidavit of Dr Winkler-Oswatitsch of 20 December 2000

D49: Report on the International Workshop Selection - Natural and Unnatural - In Biotechnology (June 1991)

D50: Declaration of Prof. Eigen (undated)

D51: Affidavit of Prof. Biebricher of 22 April 2004

D55: Real Time PCR - An Essential Guide; Eds. Edwards, Laugan and Saunders; 2004; Chapters 1 and 2

D56: Declaration of Prof. Biebricher of 10 June 2004

D57: Mullis and Faloona, Methods Enzymol 115, 335-350 (1987)

D58: Affidavit of Prof. Eigen of 19 September 2004

D60: Declaration of Dr Schober of 7 December 2004

D61: Affidavit of Dr Lindemann of 19 December 2000

D62: Affidavit of Dr Schwienhorst of 18 December 2000

D63: Affidavit of Dr Günther of 20 December 2000

D66: Declaration of Dr Schröder of 24 February 2005

D67: Sworn declaration of Prof. Sydney Brenner of 17 March 2005

D68: Sworn declaration of Steven Dickman of 25 February 2005

D69: Sworn declaration of Prof. Lawrence Gold of 6 May 2005

D70: Declaration of Prof. Joyce of 14 July 2005

D71: Instruction manual of Thermo Haake Bath and Circulator A81 (undated)

D72: Holton et al., Nucleic Acids Research, vol. 29, 4014-4024 (2001)

D73: Affidavit of Dr Daum of 11 September 2005

D74: Affidavit of Mrs Haake of 12 September 2005

D75: Affidavit of Mrs Lechten of 8 September 2005

D76: Affidavit of Dr Rohde of 11 September 2005

D77: Affidavit of Dr Lindemann of 7 September 2005

D78: Affidavit of Dr Günther of 13 October 2005

D79: Affidavit of Dr Rigler of 12 September 2005

D80: Sworn declaration of Prof. von Kiedrowski of 2 December 2005

D82: Declaration of Prof. von Kiedrowski of 5 June 2006

(In the following, affidavits, sworn declarations and declarations will be referred to as "declarations".)

XIV. The submissions made by the respondents in writing and during the oral proceedings as far as they are relevant for the present decision, may be summarized as follows:

Article 76(1) EPC with respect to the divisional application as filed

When the divisional application underlying the patent in suit was filed, it did not comply with Article 76(1) EPC. Page 3, lines 52 to 57 of the published version of the divisional application referred to advantages of an apparatus, which advantages had been presented in the parent application only for the disclosed method. Furthermore, the instrument disclosed in the divisional application in the passage from page 3, line 58 to page 4, line 3 (published version) and in claim 1 extended beyond the content of the parent application which disclosed neither a thermal cycler having a **support** adapted for accommodating one or more nucleic acid amplification reaction volumes, nor an optical system as broadly defined as in the divisional application. Only optical systems for detecting a signal generated by a DNA binding agent were disclosed in the parent application (see page 8, line 7 of the published version).

Main request

Article 84 EPC

In claim 1, the expression "for carrying out an automated PCR process", which was not present in the claims as granted, was unclear since it left the reader in doubt as to what aspect was to be automated. Therefore, claim 1 did not comply with Article 84 EPC.

Article 76(1) EPC with respect to the claims of the main request

The omission from claim 1 of a reference to the optical signal to be detected being generated by a **DNA binding agent**, which feature was presented as an essential feature in the parent application, resulted in added subject-matter.

Furthermore, there was no basis in the parent application for a thermal cycler capable of **alternately** heating and cooling as stated in claim 1, since the term "alternately" required that a heating step was always followed by a cooling step and vice versa, whereas PCR could require two heating steps in sequence.

Also, the feature in claim 1 that a detector was operable to detect an optical signal over a **multiple-cycle period**, which covered the concept that the monitoring could be done over a fraction of the amplification process, for example over as few as two cycles, was not directly and unambiguously derivable from the parent application.

There was also no basis in the parent application for the optical signal to be detected being **related to** the amount of amplified nucleic acid in the reaction mixture, as stated in claim 1.

Moreover, the references to a **plurality** of reaction vessels in claims 2 and 8 extended beyond the content of the parent application, since the term "plurality" was to be interpreted as a range of from two up to infinity, and there was no disclosure of two reaction vessels in the parent application.

Scope of the claims of the main request when compared to the scope of the claims of the divisional application as filed

Since the claims of the main request required neither the optical coupling of the optical system to the reaction volumes, nor the presence of a support adapted for accommodating the reaction volumes, their scope was broader than that of the claims of the divisional application as filed.

Added subject-matter (Article 123(2) EPC)

The subject-matter of the claims of the main request contained added subject-matter, contrary to Article 123(2) EPC. The respondents arguments were the same as those under Article 76(1) EPC. Furthermore, claim 1 did not comply with Article 123(2) EPC since it did not state that the thermal cycler had a **support** adapted for accommodating one or more nucleic acid amplification reaction volumes and that the optical system was adapted for being **optically coupled** to the one or more amplification reaction volumes accommodated by the support, contrary to claim 1 of the divisional application as filed.

Novelty (Article 54 EPC)

Prior art status of documents D4 and D30

"Intermediate" document D4; entitlement to priority of the patent

Document D4 was novelty-destroying because the patent was not entitled to the claimed priority date. The priority document did not disclose the invention now claimed. In particular, claim 1 of the main request did not state that the optical signal to be detected was generated by the DNA binding agent, although this feature was presented in the priority document as an essential feature. Therefore, the nature of the invention was no longer the same.

Document D30

The standard of proof required was that of balance of probabilities and not proof beyond reasonable doubt. The correct test was not whether it was possible to entertain a doubt, even a reasonable doubt, but whether it was sufficiently proven that it was more likely than not that the document was available (see the established case law of the boards of appeal, for example decisions T 381/87 and T 729/91).

The declarations by Prof. Eigen (documents D47, D50 and D58), Prof. Biebricher (testimony and documents D51 and D56), Dr Winkler-Oswatitsch (document D48), Prof. Joyce (document D70) and Prof. von Kiedrowski (document D80) showed the public availability of document D30.

For the details of this evidence see point 36 below.

Public prior use

From a number of declarations (documents D60, D70 and D80) it was apparent that the feasibility of an apparatus capable of performing a nucleic acid amplification reaction and of monitoring the production of amplification products during the course of the reaction by fluorescence was shown and explained to attendees of the laboratory demonstrations held at the workshop in Göttingen in April 1991 referred to in these documents.

During the oral proceedings the respondents no longer maintained the objection based on the public prior use.

Document D11

Claim 1 of the main request lacked novelty over the apparatus disclosed in document D11, pages 234 and 235 under the heading "melting curves", said apparatus having a circulating refrigerated water bath with external temperature-control linked to a spectrophotometer or spectrofluorometer, whereby the temperature-control of the circulating water bath and the data acquisition were automated by use of a computer. The apparatus was used to follow sample adsorption or fluorescence while the sample temperature was linearly increased or decreased. Although the document disclosed the apparatus in the context of the measurement of melting curves, this apparatus could also be used for performing PCR since it was capable of alternately heating and cooling a reaction mixture over multiple cycles. Document D71, page 5, last paragraph, showed that temperatures from -50 to 150°C could be

achieved with the water bath used in document D11. The fact that in document D11, the temperature was increased and decreased relatively slowly did not mean that faster rates were not possible. In any case, PCR could also be carried out slowly. In order to get amplification, it was not necessary to use an optimized PCR machine. Documents D57 and D72 showed that PCR could be performed using a single water bath.

Documents D22, D29, D33, D34, D25, D26, and D19

The patent in suit stated on page 8, lines 20 to 21 that "[i]n a spectrafluorometer capable of heating and cooling a surface, or vessel, an optic fibre is not required", and thus made clear that such apparatuses were covered by the claimed invention. Consequently, the apparatus of claim 1 lacked novelty over the optical devices capable of heating and cooling a vessel as disclosed in documents D22, D29, D33, D34, D25, D26 and D19.

With respect to document D25, it did not matter that this document described the use of a Peltier element only as a thermostat, since said element could equally be used for heating and cooling. From the post-published document D55, pages 18 to 21, it was evident that Peltier elements were used in thermocycling devices.

Document D15

Document D15 described the determination of fluorescence using a commercially available fluorometer following DNA amplification by PCR using different

oligonucleotide primers labelled with different fluorophores (page 9179, heading "Fluorescent Multiplex PCR"). Page 9182, column 1, final paragraph, mentioned the adaptability of the assay to automation and suggested the determination of the colour of the amplified DNA by fluorometry through a fiber optic bundle. Consequently, a thermal cycler and a fluorometer linked together by a fibre optic bundle to form an associated piece of apparatus as required by claim 1 was disclosed in the document. This apparatus did not necessarily require the opening of the reaction vessel in order to detect the amount of amplified DNA, in particular if an oligonucleotide probe of the type disclosed in document D42 was used, which would be degraded into detectable smaller fragments by the 5' → 3' exonuclease activity of the Taq DNA polymerase.

If one were to deny a connection between the thermal cycler and the fluorometer in document D15, as had been done by the opposition division in its decision, then one would also have to deny this connection for the apparatus disclosed in the parent application of the patent in suit, since its Example VIII stated that the fibre optic was glued to the top of the reaction tube, and was thus not linked to the thermal cycler itself.

Document D28

Document D28 disclosed a process for detecting or quantifying nucleic acids using an intercalating fluorescent pigment. The device used for carrying out this process comprised a thermal cycler and a fluorescence detector, and Example 4 stated that the fluorescence intensity could be monitored during the

PCR process under sealed conditions. Consequently, the document was prejudicial to the novelty of the claimed subject-matter.

Document D17

Document D17 disclosed a PCR detection method which generated signal simultaneously with target sequence amplification. By carrying out this method, the skilled person would necessarily produce an apparatus falling under claim 1. The document did not say that an optical signal was generated, but clearly fluorescence was one of the possibilities. Later work showed that fluorescence or radioactivity were used as signals.

Document D6

Figure 1 of document D6 disclosed a PCR method, whereby a series of identical samples containing a PCR reaction mixture were amplified over multiple thermal cycles. Samples were withdrawn after different cycle numbers, the dye Hoechst 33258 was added, and the amount of DNA produced by the amplification process was measured by fluorescence. By opening a first pot of identical samples and adding the dye, one could detect a signal related to the amount of DNA in a second pot, without opening this second pot. Therefore, the instrumentation used in this method, a fluorescence spectrophotometer with an autosampler (page 9, column 1, heading "Instrumentation") was encompassed by claim 1.

XV. The submissions made by the appellant in writing and during the oral proceedings, insofar as they are

relevant to the present decision, may be summarized as follows:

Article 76(1) EPC with respect to the divisional application as filed

The content of the divisional application as filed underlying the patent in suit did not extend beyond that of the parent application as filed. The changes made to the divisional application found basis in particular on pages 16 and 17 of the parent application as filed (document D1). Furthermore, the disclosure of the parent application was not confined to optical signals generated by the DNA binding agent, as was apparent from page 10, lines 1 to 18 of document D1.

Main request

Article 84 EPC

It was clear for a skilled person that an "automated PCR process", as referred to in claim 1, was automated to cycle through the temperatures necessary for PCR.

Article 76(1) EPC with respect to the claims of the main request

The subject-matter of the claims of the main request was clearly and unambiguously derivable from the parent application as filed. The claims did not have to refer to the DNA binding agent in view of page 10, lines 1 to 19 of document D1. Furthermore, those features which the respondents considered to be not supported, notably "alternately heating and cooling", "multiple-cycle

period", "related to" and "plurality", were all clearly based on the disclosure of the parent application.

Scope of the claims of the main request when compared to the scope of the claims of the divisional application as filed

The question whether the scope of the claims under consideration was broader than the scope of the claims of the divisional application as filed was of no relevance for the patent in suit since question (3) of decision T 39/03 referred to the Enlarged Board of Appeal started from the premise of a divisional application which did not comply with Article 76(1) EPC at its actual filing date. In the present case, however, the divisional application underlying the patent in suit did comply with Article 76(1) EPC at its actual filing date. Notwithstanding this, there was no broadening anyway, since a thermal cycler adapted for PCR had to have a support for holding the tubes or vessels, and since optical coupling was an implicit feature of the apparatus according to claim 1.

Added subject-matter (Article 123(2) EPC)

The subject-matter of the claims of the main request did not extend beyond the content of the divisional application as filed because each of the features of the claims was directly and unambiguously derivable from the application documents as filed.

Novelty (Article 54 EPC)

Prior art status of documents D4 and D30

"Intermediate" document D4; entitlement to priority of the patent

The priority document contained support for all passages of the parent application of the patent in suit. Since the subject-matter of the claims of the main request was clearly and unambiguously derivable from the parent application, the priority was validly claimed having regard to decision G 2/98. Therefore, since the patent was entitled to its priority date, document D4 was not novelty-destroying.

Document D30

The availability of document D30 had to be fully and properly proven. The evidential burden was high, and it had to be proved beyond reasonable doubt that the document was available before the priority date (see the established case law of the boards of appeal, for example decisions T 750/94 and T 91/98).

Declarations from external scientists (documents D67, D69 and D79), journalists (documents D66 and D68) and from in-house scientists and staff of the Max-Planck Institute (documents D61 to D63, D73 to D78) showed that document D30 was not publicly available at the workshop which took place in Göttingen in April 1991.

For the details of this evidence see point 37 below.

Public prior use

The evidence provided by the respondents failed to reach the high standard of proof to be applied in case of public prior use.

Document D11

The apparatus disclosed under the heading "Melting curves" on pages 234 and 235 of document D11 was not prejudicial to the novelty of the subject-matter of the claims since said apparatus did not comprise a thermal cycler suitable for carrying out an automated PCR process. In order to successfully perform PCR, it was necessary to rapidly and reliably achieve the temperature jumps required for PCR. This was not possible with the slow rates of temperature increase and decrease described for the apparatus in document D11. Moreover, there was no evidence on file showing that fast enough temperature rates could be achieved with this apparatus and that it had the capability of holding the temperature in the required way.

Contrary to the respondents' assertion, document D57 did not show that PCR was possible using a single water bath, since in the PCR described on page 340, the heating to 100°C was performed in a metal block and not in the water bath used for the cooling to 25°C.

Furthermore, the water bath referred to in document D72 was especially adapted to perform PCR and not comparable to that described in document D11.

Documents D22, D29, D33, D34, D25, D26, and D19

None of the apparatuses disclosed in documents D22, D29, D33, D34, D25, D26, and D19 comprised a thermal cycler suitable for carrying out an automated PCR process, as required by claim 1. The apparatuses disclosed in documents D22, D29, D25 and D26 were designed to maintain a sample at a constant temperature, not to alternately heat and cool it.

Document D15

Document D15 did not disclose an apparatus according to claim 1 since there was no suggestion in this document of combining a thermal cycler and an optical system in a single apparatus. Using the method disclosed in document D15, it was furthermore not possible to detect the optical signal related to the amount of amplified nucleic acid without opening the reaction vessel.

Document D28

Document D28 (prior art according to Article 54(3) EPC) described a thermal cycler and a separate fluorescence detector, but there was no disclosure of combined equipment capable of thermal cycling of the reaction mixture and also detecting an optical signal directly from that sample without the need for additional manipulation. Thus the subject-matter of the claims was novel over document D28.

Document D17

Document D17 did not destroy the novelty of the apparatus of claim 1 since it did not disclose an apparatus comprising an optical system. From this document, the skilled person would not infer the use of fluorescence as the signal. The post-published document D42 described the use of radioactivity as the signal, not fluorescence.

Document D6

Document D6 did not disclose an apparatus as claimed, since claim 1 required that the detector of the optical system could detect an optical signal related to the amount of amplified nucleic acid in **the sample**, not related to something which was left behind. Moreover, the autosampler referred to on page 9 under the heading "Instrumentation" was a device to line up the samples and to take them to the fluorometer; it was not attached to the thermal cycler.

XVI. Requests

The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained in an amended version on the basis of the main request or one of the auxiliary requests I to IV, all filed with a letter dated 2 June 2006; it requested to remit the case to the opposition division for consideration of inventive step and sufficiency. Further it requested the reimbursement of the appeal fee.

The respondents (opponents) requested that the appeal be dismissed. They further requested to stay the appeal proceedings until the Enlarged Board of Appeal has handed down its decision in the cases G 1/05, G 1/06 and G 3/06.

Reasons for the Decision

1. The appeal complies with the provisions of Articles 106 and 108 EPC and of Rule 64 EPC and is, therefore, admissible.

2. The interventions comply with the provisions of Article 105 EPC and are also admissible. This has not been contested by the patentee.

Article 76(1) EPC with respect to the divisional application as filed

3. The respondents argue that the divisional application as filed underlying the patent in suit contains subject-matter not directly and unambiguously derivable from its parent application as filed. The board is aware of the referrals to the Enlarged Board of Appeal pending under G 1/05 (referring decision T 39/03, OJ EPO 2006, 362) and G 3/06 (referring decision T 1040/04, OJ EPO 2006, 597) where the issue at stake is whether a divisional application which does not meet the requirement of Article 76(1) EPC at its actual filing date can be amended later. The question thus arises whether the present case should be stayed until the Enlarged Board of Appeal has handed down its decisions. However, the need to stay proceedings in this case does

not arise if the requirement of Article 76(1) EPC was fulfilled at the filing date. Therefore, the board will examine this as an initial point. In the following, the published version of the parent application is referred to, this version being identical to the parent application as filed.

4. One point raised by the respondents is that the advantages of the method disclosed in the parent application are presented in the divisional application (page 3, lines 52 to 57 of the published version) as advantages of an apparatus, and that this contravenes Article 76(1) EPC. The board considers, however, that page 8, lines 6 to 55 of the parent application (published version) provides a basis for an apparatus suitable for carrying out the disclosed method in general, and that a skilled person would thus conclude that the advantages presented for the disclosed method (page 4, lines 2 to 7 of the published version of the parent application) would also apply to this apparatus. Therefore, the statement on page 3, lines 52 to 57 of the published version of the divisional application does not constitute added subject-matter in relation to the parent application.

5. As concerns the reference to "a thermal cycler having a **support** adapted for accommodating one or more nucleic acid amplification reaction volumes" in the divisional application (claim 1 and page 3, line 58 to page 4, line 1 of the published version), there is indeed no explicit mention in the parent application that the thermal cycler used for amplification may have such a support. Therefore, in accordance with the established case law of the boards of appeal, it has to be assessed

whether there is an implicit disclosure of this feature in the parent application, i.e. whether said feature is directly and unambiguously derivable from what is explicitly mentioned (see "Case Law of the Boards of Appeal of the EPO", 4th edition 2001, III.A.3.3., 218). A skilled person would know from common general knowledge that a thermal cycler to be used for amplification would normally have to have some kind of a support for holding the reaction tubes or vessels and would not reasonably assume that they would be freely floating. The board is thus convinced that a skilled person cannot but conclude from the entire disclosure of the parent application that the thermal cycler used should have a support adapted for accommodating the vessel(s) or tube(s).

6. According to the respondents, the divisional application as filed furthermore extends beyond the parent application as filed since the latter did not disclose any apparatus comprising an optical system capable of detecting an optical signal other than the signal generated by a DNA binding agent, whereas the apparatus as defined in claim 1 and on page 3, line 58 to page 4, line 1 of the divisional application (published version) was not limited to the detection of a signal generated by a DNA binding agent. The board acknowledges that the presence of the DNA binding agent is presented in the parent application as an essential feature of the disclosed **method**, and page 8, line 7 of the parent application also refers to an "apparatus for detecting the signal generated by the binding agent". However, the board fails to see that the origin of the optical signal to be detected, be it from a DNA binding agent or from some other agent, has any influence on

the nature of the optical system comprised in the **apparatus**, and no evidence has been presented by the respondents to this effect. With other words, the board is not convinced that an optical system capable of detecting an optical signal generated by a DNA binding agent would in any way differ from an optical system as defined in claim 1. Therefore, the omission of the reference to the DNA binding agent in the definition of the apparatus given in the divisional application is not considered to add subject-matter in relation to the parent application.

7. The board concludes that when the divisional application underlying the patent in suit was filed, it did comply with the requirements of Article 76(1) EPC. Therefore, there is no need to stay these proceedings for this reason.

Main request

Article 84 EPC

8. Claim 1 has been amended to state that the thermal cycler is "for carrying out an automated PCR process". While there are various possibilities as to what aspect of a PCR process could be automated, a skilled person would recognize that the heating and cooling of the reaction mixture would represent the essential technical aspect of a PCR process which at least has to be automated in order to qualify a process as an "automated PCR process". Therefore, the board is satisfied that by this amendment the claims are not rendered unclear. Thus the requirements of Article 84 EPC are fulfilled.

Article 76(1) EPC with respect to the claims of the main request

9. According to the respondents, the subject-matter of the claims of the main request extends beyond the content of the parent application as filed. One point raised in this context is that claim 1 does not state that the optical signal to be detected is generated by a **DNA binding agent**. The same objection is also raised for the claims of the divisional application as filed, and the reasons set out in point 6 above thus also apply here. Consequently, the omission of the reference to the DNA binding agent in the claims relating to an apparatus does not contravene Article 76(1) EPC.

10. The reference in claim 1(a) to a thermal cycler capable of **alternately** heating and cooling is not considered to extend beyond the content of the parent application as filed in view of the disclosure on page 8, lines 19, 21 to 22 and 39 (published version). In the context of a thermal cycler suitable for carrying out an automated PCR process, it is hardly imaginable that the skilled person could interpret the expression "alternately heating and cooling" in the strictest sense as excluding, for instance, a repeated sequence of two heating steps followed by a cooling step.

11. The board further considers that it is directly and unambiguously derivable from the parent application that the disclosed apparatus includes a detector operable to detect an optical signal over **a multiple-cycle period**, as stated in claim 1(b). On page 6, line 6 of the parent application (published version) it

is explained that "PCR amplification of DNA involves repeated cycles" and on page 8, lines 7 to 8 it is stated that "[a]n apparatus for detecting the signal generated by the binding agent can be used to detect, measure, and quantify the signal before, during, and after amplification". In order to detect the signal during and after PCR amplification involving repeated cycles, the detector must necessarily be capable of detecting the signal over a multiple-cycle period.

12. As concerns the reference in claim 1(b) to the optical signal to be detected being **related to** the amount of amplified nucleic acid in the reaction mixture, the board finds basis for this feature in the parent application, in particular on page 8, lines 11 to 12 (published version) and in Examples II and III, which disclose that the detected increase in fluorescence is due to the amplification of nucleic acid.

13. With respect to the references to a **plurality of reaction vessels** in claims 2 and 8, the board judges that this feature is clearly and unambiguously derivable from the parent application, page 8, lines 30 to 31 (published version), which discloses that there is no limitation with respect to the number of reaction vessels. The respondents argue that the term "plurality" would have to be interpreted as a range of from two up to infinity, and that there is no disclosure in the parent application of two reaction vessels. The board cannot follow this argumentation since in the present context, the interpretation of the term "plurality" matches the disclosure as mentioned above and would not be interpreted by the skilled

person as a disclosure of a definite number of vessels, which rules out the respondents' argument.

Scope of the claims of the main request when compared to the scope of the claims of the divisional application as filed

14. In the referring decision T 39/03 (see above), pending before the Enlarged Board of Appeal under G 1/05, the question is raised whether an amended divisional application can be directed to aspects of the earlier application not encompassed by those to which the divisional as filed had been directed (see question (3) of decision T 39/03). Furthermore, in decision T 1409/05 (OJ EPO, 2007, 113), the question is raised whether the subject-matter of the claims of a divisional application has to be nested within the subject matter of the claims of its divisional predecessors. In view of these two questions and in view of the decisions T 720/02 of 23 September 2004 and T 797/02 of 23 September 2004 the legal issue has arisen as to whether or not the claims of a divisional application can be amended such that their scope is broader than the scope of the divisional application as filed. To decide this legal issue would be inappropriate for the board in view of the pending referrals. However, there is no need to postpone a decision on Article 76(1) EPC if the claims according to the amended main request are not broader in scope than the original claims of the divisional application as filed. Therefore, the board has to consider this issue, i.e. whether the claims of the main request cover subject-matter not covered by the claims of the divisional application as filed.

15. The respondents argue that the scope of claim 1 of the main request is broader than the scope of claim 1 of the divisional application as filed, firstly because the thermal cycler would no longer have to have a **support** adapted for accommodating one or more nucleic acid amplification reaction volumes, and secondly because the optical system would no longer have to be **optically coupled** to the reaction volumes accommodated on the support.

16. As concerns the presence of a **support**, the board considers that on the basis of common general knowledge, a thermal cycler suitable for carrying out a PCR process implicitly has to have some kind of a support adapted for accommodating one or more nucleic acid amplification reaction volumes, see point 5 above.

17. With respect to the feature stated in claim 1 of the divisional application that the optical system is **adapted for being optically coupled** to the one or more nucleic acid amplification reaction volumes, it has to be decided whether or not this feature is also implicit in the apparatus of claim 1 of the main request. In order to detect an optical signal related to the amount of amplified nucleic acid in the reaction mixture over a multiple-cycle period, without opening the reaction vessel once the amplification reaction is initiated, as required by claim 1 of the main request, the optical system must be optically coupled to the reaction vessel during detection, otherwise no optical signal could be detected. Therefore, the optical system in claim 1 of the main request must necessarily be adapted for being optically coupled to the reaction vessel.

18. However, the board considers that claim 1 of the main request does not state any features which imply that the optical system is adapted for being optically coupled to the one or more nucleic acid amplification reaction volumes **accommodated by the support**. In contrast to claim 1 of the divisional application as filed, claim 1 of the main request encompasses the possibility that the optical system is optically coupled to the reaction vessel and the signal is detected while the vessel is **not** accommodated by the support of the thermal cycler, for instance by the action of a robot arm which moves the vessel between the thermal cycler and the optical system after each PCR cycle. In this regard, the board concludes that the scope of claim 1 of the main request is broader in scope than claim 1 of the divisional application as filed.

19. It follows from the above that the claims of the main request would not comply with the requirements of the EPC if the legal issue as set out above in point 14, namely that the scope of the claims of a divisional application cannot be broadened later, is answered in the affirmative by the Enlarged Board of Appeal. As to the consequence of this procedural situation see below point 62.

Added subject-matter (Article 123(2) EPC)

20. The respondents have raised objections with respect to the same features under Article 123(2) EPC against the claims of the main request as under Article 76(1) EPC. Since the divisional application as filed contains the relevant passages of the parent application which

provide a basis for the features in question as set out in points 6 and 9 to 13 above, necessarily these amendments also comply with Article 123(2) EPC.

21. The respondents further argue that the subject-matter of claim 1 contains added subject-matter because, in contrast to claim 1 of the divisional application as filed, the claim does not state, firstly, that the thermal cycler has a support adapted for accommodating one or more nucleic acid amplification reaction volumes and secondly, that the optical system is adapted for being optically coupled to the one or more amplification reaction volumes accommodated by the support.

22. Article 123(2) EPC stipulates that a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. Hence, when amending a claim the appellant is not bound to subject-matter claimed in the originally filed claim. Rather, the basis for amendments is, according to Article 123(2) EPC, the whole application document as filed.

23. By the non-mentioning of the feature "support adapted for accommodating one or more nucleic acid amplification reaction volumes", no change of subject-matter has taken place because for the skilled person the presence of a support is an implicit feature of a thermal cycler suitable for carrying out a PCR process (see points 5 and 16 above).

24. As concerns the feature "optical system adapted for being optically coupled to the one or more

amplification reaction volumes accommodated by the support" it is apparent from points 17 and 18 above that the board constructs claim 1 of the main request such as to relate to two alternatives, i.e. that the optical system is adapted for being optically coupled to the reaction vessel and the signal is detected while the vessel **is or is not** accommodated by the support of the thermal cycler. Basis for the first alternative comes from claim 1 as filed. The second alternative is based on the whole disclosure of the application documents as filed, especially on the teaching on page 7, line 39 to page 8, line 24 (published version) from which the skilled person derives that no particular limitation of design of the apparatus is contemplated in respect of the location of the vessels during detection of the signal.

25. Therefore, the claimed subject-matter does not extend beyond the content of the application as filed and thus fulfils the requirement of Article 123(2) EPC.

Novelty (Article 54 EPC)

Prior art status of documents D4 and D30

"Intermediate" document D4; entitlement to priority of the patent

26. The content of the priority document corresponds to that of the parent application. Since the board considers that the subject-matter of the claims of the main request can be directly and unambiguously derived from the parent application (see points 9 to 13 above),

the priority document must necessarily disclose the same invention as the one now claimed.

One of the respondents (opponent 07) argues that since claim 1 no longer states that the optical signal is generated by the DNA binding agent, it does not relate to the same invention as disclosed in the priority document. However, as the origin of the optical signal to be detected does not have any influence on the nature of the optical system comprised in the **apparatus** (see point 6 above), the omission of said feature from the claims does not change the nature of the invention. Therefore, the priority can validly be claimed.

27. Consequently, document D4, published after the priority date, does not constitute prior art under Article 54(2) EPC.

Document D30

General remarks

28. Document D30 is entitled "Report on Evolution Research" and was prepared by the Department of Biochemical Kinetics of the "Max-Planck-Institut für Biophysikalische Chemie" in Göttingen. It is a collection of articles describing the results of research activities performed by members of said department under the direction of Prof. Eigen and was prepared as a report of the department's work for a council of the Max-Planck-Institute ("Beirat"). One of the articles authored by Andreas Schober relates to a machine suitable for PCR and its on-line monitoring. It contains inter alia the following passages (page 55):

"This technique has already been used successfully in a prototype, constructed to perform fast polymerase chain reactions (see below)."

"The evolution machine, which provides a temperature jump device, can easily be adapted to perform many nucleic acid amplification reactions (PCR) (Mullis et al. 1987) in parallel. In contrast to other PCR machines, the temperature course is guaranteed from one well to the next, and large, rapid temperature jumps can be made: Jumps of over 50°C can be made within several seconds. In addition, the fluorimeter permits the *on line* monitoring of nucleic acid amplification."

29. In the light of the above, the board agrees that prima facie the disclosure of document D30 has to be considered as highly relevant for subject-matter of the claims now before the board. Therefore, the board has to assess whether or not the document was made available to the public before the priority date of the patent in suit.

30. The respondents asserted that document D30 was made available to the public at the international workshop "Selection - Natural and Unnatural - in Biotechnology" held from 18 to 20 April 1991 at the "Max-Planck-Institut für Biophysikalische Chemie" in Göttingen (hereinafter referred to as the "workshop"), thus before the priority date of the patent in suit. This assertion was contested by the appellant.

31. The opposition division decided on the basis of the evidence before them that document D30 was made

available to the public at said workshop and decided that the document was prejudicial to the novelty of the subject-matter of the claims of auxiliary requests I (corresponding to the pending main request) and II before it.

32. According to the established case law of the boards of appeal, when lack of novelty is alleged, the burden of proof lies with the party claiming that the information in question was made available to the public.

33. The case law of the boards of appeal has developed certain principles on the standard of proof necessary to establish the facts on which a decision is to be based.

In some decisions the boards of appeal have applied the standard of "the balance of probabilities", which means that in relation to, for example, the question of when a document was first made available to the public, the board must decide what is more likely than not to have happened (see for example decisions T 381/87, OJ EPO 1990, 213, T 296/93, OJ EPO 1995, 627, and T 729/91 of 21 November 1994).

In other decisions the boards took the view that a fact had to be proved "beyond reasonable doubt" or "up to the hilt" (see for example decisions T 782/92 of 22 June 1994, T 97/94, OJ EPO 1998, 467, T 848/94 of 3 June 1997, T 472/92, OJ EPO 1998, 161 and, in particular, T 750/94, OJ EPO 1998, 32).

34. The board considers the latter approach to be the appropriate one in cases where the revocation of a

granted European patent is at issue. To base a revocation decision on the mere balancing of probabilities of what might have occurred would be difficult to reconcile with the need for reliability in the decision-making procedures of the EPO, which is of utmost importance for users of the patent system as well as the general public. Thus, the public availability of document D30 before the priority date of the patent in suit can only be regarded as established if in view of the evidence the board does not entertain any reasonable doubt in this respect.

35. An impressive quantity of declarations and documents are before the board for evaluating the issue of the public availability of document D30 before the priority date of the patent. Already in the first instance several declarations were filed and a witness was heard. During appeal proceedings numerous further declarations were submitted.

Evidence on the public availability of document D30

36. The respondents relied on the following evidence to prove that document D30 was generally distributed at the workshop without confidentiality restrictions before the priority date of the patent in suit and thus made publicly available in the sense of Article 54(2) EPC:

36.1 Prof. Biebricher has submitted two declarations and was heard as a witness before the opposition division. He stated that the purpose of the workshop was to exchange results and to coordinate efforts of the leading groups in the field of evolutionary biochemistry. Inter-

nationally known scientists from all over the world were invited as speakers. Among the participants were representatives from science and industry as well as journalists.

The most relevant results of the Eigen group were bundled in a brochure (document D30). Said brochure was distributed by two secretaries to all persons indicated on the list of participants at the information desk together with the name tags and the list of participants. The participants were not obliged to keep the brochure confidential.

In his oral testimony Prof. Biebricher could not remember the title of the brochure, but remembered a certain symbol, a hypercube, on the title page.

Prof. Biebricher further stated that in addition to the distribution of document D30 during the workshop, the brochure was sent to people from America who could not participate in the workshop. One of them could have been Prof. Joyce. Moreover, he said that he handed over the brochure and the name tag to Prof. von Kiedrowski personally.

36.2 Prof. Eigen has submitted three declarations (documents D47, D50 and D58). Prof. Eigen declared that document D30 was initially prepared as an internal working document and was treated confidentially. Then, on his instructions, the report was distributed to the participants of the workshop since the reason for the confidentiality - the filing of an own patent application - had ceased to exist.

36.3 Dr Winkler-Oswatitsch declared (document D48) that document D30 was generally made available at the workshop.

36.4 Prof. Joyce understood the workshop as a sort of "showcase" that would help spread the word about what was being done in the field of directed evolution by the scientists of the Max-Planck-Institute.

Prof. Joyce declared that, after having been shown a copy of document D30 by the respondent Bio-Rad, it matched his recollection of a document that he had received at the workshop, except that the original document had a yellow cover. Although he did not remember the specific circumstances in which the document was given to him and did not bring back a copy when he returned to California, he recalled that he read the document at the workshop and that copies of it were available at the workshop. He declared that the document was given to him with no requirement that it be maintained confidential in any way (document D70).

36.5 In a sworn declaration Prof. von Kiedrowski (document D80) declared that he was not a regular member of the Eigen group, but had, due to his own scientific interest, established a close contact with it, especially to Prof. Biebricher. He often went to the "Tee-Seminare" of the Eigen group. Briefly before the workshop, he became interested in Gerhard Zieboll's work. He remembered having received at the workshop from either Prof. Biebricher or Dr Ruthhild Winkler "a document or a copy of a document which contained among other things a brief description of Gerhard Zieboll's work. It also contained an introduction of

Manfred Eigen about the background of the work summary of Zieboll and others." He did not remember about any special confidentiality requirements about this meeting.

37. The counter-evidence relied on by the appellant was the following:

37.1 In a first set of short declarations submitted by Dr Lindemann, Dr Schwienhorst and Mr Günther (documents D61, D62 and D63) they declared that Prof. Eigen had instructed them not to make available document D30 or any information deriving from it to external people. Drs Lindemann and Schwienhorst declared that they were also not aware that the report had actually been made publicly available. This statement has been qualified in the declaration of Mr Günther that he was not aware that the document had been made publicly available before the priority date of the European Patent 0 583 265 (see point 36.2 above). The board notes that these three declarations were originally prepared for opposition proceedings relating to this patent.

37.2 In a later and more detailed declaration Dr Lindemann declared (document D77) that he recalled well the workshop for which he had prepared two posters. The character of the workshop was informal and he could not recall a registration of the participants at an information desk, let alone the distribution of name tags; he did also not believe that this happened. He recalled document D30 very well since he was involved in its preparation and authored one of its articles. He said that, having been sensitised by Prof. Eigen's instructions to keep the document confidential, it would have attracted his attention if copies of the

report with their eye-catching design had been laid out or if a participant had openly shown his possession of one of it. He had a firm recollection that the document was not made available to third parties at the workshop.

37.3 Also Mr Günther, one of the authors of an article contained in document D30, submitted a further, more detailed declaration (document D78). He stated that he was not aware of any change of instructions of Prof. Eigen to keep the document confidential during his time in Prof. Eigen's group and in particular during the workshop. In keeping with these instructions he had no recollection that the document was made available to the participants of the workshop or to any other external person.

37.4 Two scientists of Prof. Eigen's department, Dr Daum and Dr Rhode (documents D73 and D76, respectively), also both authors of articles in document D30, could not recall that it was made available during the workshop. Neither do they have any memory of a registration of the participants at an information desk, let alone of name tags.

37.5 In a declaration Mrs Haake (document D74), chief secretary of Prof. Eigen from 1974 to 1995 declared that she had a recollection of the workshop at which she took care of participants, but that she did, firstly, not believe that a further secretary was present and, secondly, that she had no recollection of any formal registration of the participants, the handing out of workshop material or of name tags at an information desk. She did, thirdly, not believe that such an information desk had been present at all

because, if it had, she would have taken part in its organisation. Finally, she had hardly any recollection of document D30 and she did not remember that it was handed out to the participants.

37.6 Mrs Lechten, secretary in Prof. Eigen's department from 1980 to 1996 and secretary of Prof. Eigen from 1996 to 2001, in her declaration (document D75) stated that she was neither present at the workshop nor had she taken part in its organisation. She stressed that Mrs Haake would have been entrusted with the organisation of the workshop.

37.7 Prof. Rigler, who was closely affiliated to the Eigen group and who was a participant at the workshop, declared in his declaration (document D79) that he did not recall that document D30 had been laid out or distributed to the participants.

37.8 Prof. Brenner, a Nobel laureate, attended the entire workshop and was one of the speakers. He stated in a sworn declaration (document D67) that: "I definitely did not receive a copy of this report at the April 1991 workshop, and to the best of my knowledge it was not distributed at that conference."

37.9 Prof. Gold declared also in a declaration (document D69) that he attended the workshop as a speaker, attended the entire conference and had a strong memory of it. However, he had no memory of the "Report on Evolution Research" (document D30) having been passed out at the workshop.

37.10 Dr Schröder stated to have attended all sessions of the workshop as a journalist. She declared (document D66): "I do not remember receiving a copy of the Report at the time of the workshop or any other time, that is, I neither have a concrete, explicit memory, nor any vague notion of receiving this report." She further stated: "Following the workshop, I wrote an article about the technologies I learned about at the workshop (...). My article clearly reflects many details and references that appear in the "Report on the International Workshop" [*NB by the board: a document published after the workshop; document D49*], but not in the "Report on Evolution Research". This is in line with my lack of any memory of receiving the "Report on Evolution Research"."

37.11 A second journalist, Mr Dickman, employed as a reporter by *Nature*, declared *to* have a strong recollection of the workshop. He stated in his declaration (document D68): "The workshop was attended by several Nobel Prize-winning scientists and concerned several exciting new technologies. It is one of the most memorable scientific meetings that I have attended. (...) I believe that this publication was not made available at the April 1991 workshop. I believe that the Report was not provided to the attendees when they arrived at the workshop, and that it was not distributed at any other time during the workshop. (...) Because I was a reporter, it was my job to collect all documents from meetings I attended. If the Report on Evolution Research was available at the April 1991 workshop, then I certainly would have taken a copy. However, I believe I did not receive a copy. Following the workshop, I wrote two articles about the technologies I learned

about at the workshop. (...) When I wrote about technologies I learned about at a conference, it was my practice to review the materials I had collected at the conference. I did not have a copy of the Report on Evolution Research when I wrote these two articles." Further, Mr Dickman in his declaration commented on the declaration by Prof. Biebricher (document D56) and disagreed with the statements therein that document D30 was distributed to the participants of the workshop and that copies of the document were provided to participants at a conference desk.

37.12 Finally documents D36 and D37 showed that in response to a inquiry made in August 2000 of the appellant to receive a copy of document D30 Mrs Lechten, secretary of Prof. Eigen, answered that this document was an internal work report of the Max-Planck-Institute which had not been published in this form.

Evaluation of evidence relating to the general distribution of document D30 at the workshop

38. When evaluating the whole body of evidence and counter-evidence, the principle of free evaluation of evidence applies. In this context, the board considers that a particularly important piece of evidence is the testimony of Prof. Biebricher made orally before the opposition division.

The oral testimony given in the course of a formal hearing by a witness may be particularly convincing, because of the possibility of gaining a direct impression of the witness and of putting questions to

the witness, while written declarations have to be taken as they are.

The board furthermore notes that the opposition division has based its decision on the availability of document D30 essentially on the testimony of Prof. Biebricher. The board therefore recognizes that coming to a different conclusion in this point needs good reasons. All the more so, since the opposition division, in contrast to the board, had the advantage to gain a direct impression of the witness.

39. The following statements in Prof. Biebricher's testimony are contradicted by evidence now before the board:

39.1 The precise circumstances under which document D30 was distributed at the workshop, according to the recollection of Prof. Biebricher, were an information desk where two secretaries handed out copies of document D30 with name tags and the list of participants. This does not correspond to the recollection of a number of declarants according to which there was no information desk (see for example documents D73, D74, D76, D77), only one secretary (see document D74) and no handing out of name tags (see for example documents D73, D74, D76, D77).

39.2 According to Prof. Biebricher's testimony, document D30 was not to be treated as a confidential document at the time of the workshop. It follows from several declarations (documents D61 to D63, D77 and D78) that there was an instruction of Prof. Eigen that the document should not be handed out to external persons.

While the respondents maintain that this instruction was made in view of an own patent application of Prof. Eigen's group which had been filed on 16 April 1991 and that it was no longer effective when the workshop took place (see document D58), the declarants of documents D77 and D78 stated that they were not aware of any change in the instruction of Prof. Eigen.

39.3 Furthermore, as to the issue as to whether document D30 was generally distributed to the participants at all, the board notes that participating scientists declared either that they had not received (document D67) or that they did not recollect the distribution of document D30 at the workshop (see documents D67 and D69).

In addition, two participating journalists (documents D66 and D68) made corresponding statements in their declarations.

This is further supported by document D74, a declaration of Prof. Eigen's secretary who stated that she had no recollection of the document having been handed out.

39.4 With respect to the issues in points 39.1 to 39.3 above the board is required to assess statements which are contradictory. As set out above, the testimony of Prof. Biebricher was accepted as having a strong weight, but is now contradicted by an impressive number of declarations of persons who were present at the workshop. The respondents whose attention had been drawn to the doubts entertained by the board in its communication of 18 April 2006 did not submit further

evidence and, in particular, did not request the hearing of witnesses. The board must therefore reach its decision on the basis of the evidence on file. Taking the submissions, facts and available evidence in their entirety and in context, the board concludes that they are not sufficient to establish beyond reasonable doubt that document D30 was made available to the attendees at the workshop.

Evaluation of evidence relating to the availability of document D30 to Prof. Joyce and Prof. von Kiedrowski

40. The respondents have argued that in order to prove the availability of document D30, it would be sufficient if one member of the public had been in possession of it before the priority date of the patent in suit, and that this was the case in respect of Prof. Joyce and Prof. von Kiedrowski.

40.1 With respect to Prof. Joyce, Prof. Biebricher's testimony is somewhat vague in that he declared that he believed he had sent a copy of document D30 to Prof. Joyce as one of the persons from America who could not attend the workshop. However Prof. Joyce declared that he participated in the workshop and received a copy of the document there. Thus, there is an apparent discrepancy between these statements.

40.2 The board notes that according to the declaration of Prof. Joyce he does not recall the specific circumstances under which the document was given to him and could not corroborate his evidence for example by producing a copy of the document in his possession. In view of the above conclusion that the general

availability of document D30 to all the participants of the workshop cannot be regarded as proven, and in view of the fact that Prof. Joyce has not alluded that he received the document under different circumstances than the other participants, a serious doubt is cast on the reliability of his declaration. While the theoretical possibility remains that document D30 may have been handed out specifically to Prof. Joyce on a personal basis, the board considers that it would be upon the opponents to substantiate and prove this fact beyond reasonable doubt. However, the declaration of Prof. Joyce does not contain any indication of such a specific treatment.

40.3 With respect to Prof. von Kiedrowski, Prof. Biebricher testified that he personally handed out document D30 and the name tag to Prof. von Kiedrowski. The latter in his declarations (documents D80 and D82) stated that he received a copy of a document containing, among other things, a brief description of Gerhard Zieboll's work and an introduction of Prof. Eigen.

40.4 The board notes that, as argued by the appellant, doubts may be entertained as to whether Prof. von Kiedrowski has indeed received a copy of document D30 at the workshop. In particular, the recollection of Prof. Biebricher as to the handing over of a name tag is inconsistent with the recollection of several other declarants (see above) that the participants did not have name tags at all. Like Prof. Joyce, Prof. von Kiedrowski could not corroborate his evidence, for example, by producing a copy of the document in his possession. In addition, since he specifically recalls the work of Gerhard Zieboll who was an author of only

one of the articles in document D30 and the introduction of Prof. Eigen, the possibility remains that only excerpts of document D30 were made available to Prof. von Kiedrowski.

40.5 Even if it were assumed in favour of the respondents that Prof. von Kiedrowki did receive a copy of document D30 at the workshop, the further question would arise as to whether he qualifies as a member of the public. According to his declarations, he had close contact with the Eigen group and often went to its "Tee-Seminare". It is not uncommon among scientists who share their latest research results with selected colleagues, to expect and respect the non-public nature of such communications. Under these circumstances, the board cannot assume without any further evidence that Prof. von Kiedrowski was a member of the public for the purposes of Article 54(2) EPC.

40.6 Hence, by the evidence on file it cannot be established beyond reasonable doubt that a member of the public was in possession of document D30 before the priority date of the patent in suit.

41. Consequently, the board concludes that document D30 does not qualify as prior art within the meaning of Article 54(2) EPC.

Public prior use

42. During the written proceedings the respondents asserted that a novelty destroying public prior use occurred during the workshop, since participants were guided on a tour through the laboratories of the Max-Planck-

Institute during which they were shown apparatuses with features supposedly falling within the ambit of claim 1. In this context the respondents referred to documents D60, D70 and D80. The appellant has heavily contested the occurrence of such a public prior use and has maintained that the evidence on file did not reach the necessary level of certainty as to what was shown and explained. In a communication the board has expressed doubts as to whether the asserted public prior use could be considered as sufficiently proven and pointed to the high standard of proof to be applied in this situation. When the board invited the parties to argue this issue during oral proceedings the respondents declared that none of them wished to further pursue this matter. Under these circumstances the board maintains the position expressed in its communication and, given that the burden of proving the public prior use rests upon the respondents' shoulders, comes to the conclusion that this use has not been established.

Document D11

43. Claim 1 is directed to "an apparatus for monitoring a polymerase chain reaction (PCR) for nucleic acid amplification over multiple thermal cycles", said apparatus comprising, inter alia, "a thermal cycler for carrying out an automated PCR process, said thermal cycler capable of alternately heating and cooling, in a reaction vessel, a PCR amplification mixture (...)".

44. According to established case law by the boards of appeal of the EPO, the indication in a claim of an intended use is only to be seen as limiting the subject-matter of the claim to the extent that the

article has to be suitable for this use, see for instance decision T 523/89 of 1 August 1990. Therefore, claim 1 has to be interpreted as being directed to an apparatus **suitable** for monitoring a PCR for nucleic acid amplification over multiple thermal cycles, comprising, inter alia, a thermal cycler **suitable** for carrying out an automated PCR process.

45. Document D11 relates to the detection of nucleic acids using interacting fluorescent labels and competitive hybridization. In order to **record DNA melting curves**, either sample absorbance or fluorescence is monitored while the sample temperature is linearly increased or decreased. In the apparatus used for these experiments, "[t]emperature control and data acquisition were **automated** with a Hewlett-Packard Model 9836 computer interfaced to Analog Devices (Norwood, MA) Model AD363 12-bit integrated data acquisition system (multiplexed analog-to-digital converter) and a Model AD3860 12-bit digital-to-analog converter through a Hewlett-Packard Model GPIO 98622A 32-bit parallel interface. The analog-to-digital converter was used to digitize analog voltages from either the Cary 17 **spectrophotometer** or the SLM 4800 **spectrofluorometer**. Sample temperature was maintained with a Haake Model A81 **circulating water bath** with external temperature control through an analog voltage from the computer via the digital-to-analog converter. Actual sample temperatures were measured with a (...) thermistor (Yellow Springs, OH), cemented into the sample cuvette stopper" (see the paragraph bridging pages 234 and 235; emphasis added by the board). Figure 3 shows the results of the experiments, which start near 5°C and are gradually increased to 75°C followed by a gradual return to the

starting temperature. It is disclosed on page 235, column 1, end of first paragraph that "rates of temperature change were generally **10°C/h** except for samples containing DNA concentrations of 10 nM and lower for which the rates were reduced to 2 to **5°C/h**".

46. The respondents submit that the apparatus disclosed in document D11 has all features of the apparatus according to claim 1 and was suitable for monitoring a polymerase chain reaction. In particular it is argued that the temperature-controlled Haake Model A81 circulating water bath, although it is disclosed for a different purpose in document D11, could perform all functions required by the thermal cycler as defined in part a) of claim 1 and is therefore suitable for carrying out an automated PCR process.

The appellant contests that the Haake Model A81 circulating water bath as used in the experimental set-up in document D11 is suitable for carrying out an automated PCR process.

Hence, the suitability or non-suitability for carrying out an automated PCR process of the water bath disclosed in document D11 is material for the decision of whether document D11 is novelty-destroying or not for the subject-matter of claim 1.

47. When carrying out a PCR process, the reaction mixture is first submitted to heat denaturation, typically at 90 to 100°C for 0.5 to 3 minutes. Then, the reaction mixture is allowed to cool to a temperature which promotes hybridization so that the primers can anneal to the target DNA; this step is usually carried out at

temperatures between 35 and 65°C, typically for 1 to 3 minutes. After this, the polymerase step is performed. If the thermostable Taq polymerase is employed, a temperature of 72°C for 1 to 3 minutes is typically used (see for instance document D12, pages 32 to 33).

47.1 During the melting curve experiments disclosed in document D11 rates of temperature change are either 10°C/h or 2 to 5°C/h" (see point 45 above).

47.2 The board notes that none of the many documents on file disclosing a PCR process describes such slow temperature changes which is a prima facie sign that these conditions are unusual.

48. Therefore, in order to convince the board that the temperature-controlled Haake Model A81 circulating water bath as used in document D11 is indeed suited for carrying out an automated PCR process, it would have to be proven that (i) either a polymerase chain reaction can be achieved with the slow temperature change rates disclosed in document D11 or that (ii) the water bath as used in the context of the experiments in document D11 was suitable for carrying out an automated PCR process that can be run at faster temperature change rates.

The burden of proof for establishing these facts rests upon the respondents who relied on document D11.

"Slow" PCR

49. The respondents have not submitted evidence to prove that PCR can be carried out at the slow rates described in document D11.

"Fast" water bath

50. Concerning the speed of temperature adaptation achievable with the Haake Model A81 **circulating water bath** as used in document D11, the respondents rely inter alia on document D71, an instruction manual for the water bath referred to in document D11. It gives inter alia information on the temperature ranges which can be achieved with the water bath, but not on the times required to achieve them and is thus not helpful to establish whether the water bath is suited for faster temperature jumps.

51. Moreover, the respondents, relying on documents D57 and D72, argue that PCR was originally performed using water baths and should therefore also be possible with equipment comprising the water bath of document D11.

51.1 Document D57 is an early scientific publication from 1987 by the inventor of the polymerase chain reaction, K. Mullis. It discloses a PCR method, whereby "[t]he solution is brought to 100°C for 1 min, and is cooled to 25°C for 30 sec in a water bath" (page 340, last two lines). To the board this passage is however not a clear and unambiguous teaching that heating to 100°C is performed in the same device as that used for the cooling to 25°C, i.e. that the adaptation to both temperatures is achieved by a single water bath.

51.2 But even if the respondents' argument that a single water bath was used for the denaturation and annealing steps in document D57 was accepted, this would not lead to the conclusion that the water bath used to heat and

cool the sample cuvette of document D11 would be suitable to perform these steps in the same way. This is because there is no indication that the water baths disclosed in documents D57 and D11 are the same.

51.3 In document D72 it is stated that "PCRs were performed on an Autogene II programmable cycling water bath" (page 4015, column 2, lines 1 to 2). However, the suitability of a water bath specifically adapted to PCR cannot be taken as an indication that the different water bath disclosed in document D11 is also suitable for carrying out an automated PCR process.

52. Hence, the respondents have neither established that a PCR process can be run at the slow temperature change rates disclosed in document D11 nor that the temperature controlled water bath as disclosed in document D11 can perform temperature changes faster than those described in that document.

53. Apart from this evidential situation, an indication that the heating-cooling equipment used for recording melting curves is indeed not suited for carrying out a PCR process may be seen in the fact that the PCR experiments disclosed in document D11 are not performed with the apparatus used for recording of the melting curves, but that temperature-cycling is performed with a Perkin-Elmer Cetus DNA Thermal Cycler (page 235, column 1, paragraph 2).

54. Hence, it has not been proven that the temperature-controlled Haake Model A81 circulating water bath as used in document D11 is suitable for carrying out an automated PCR process. Therefore, the apparatus

disclosed in document D11 for monitoring of melting curves does not have all of the features of the apparatus according to claim 1 and is therefore not prejudicial to the novelty of the subject-matter of claim 1.

Documents D22, D29, D33, D34, D25, D26, and D19

55. In the course of the opposition and appeal procedure, further documents disclosing spectrometers or photometers with temperature-controlled cuvette chambers have been cited by the respondents against the novelty of the claimed subject-matter.

Document D22 and its French language counterpart document D29 disclose a cuvette assembly comprising a plurality of individual cuvettes. Page 4, lines 70 to 73 of document D22 states that the cuvette element stand can be thermo-regulated so that the cuvettes of the assemblies and the liquids in them will have a desired temperature.

Documents D33 and D34 are brochures for the Fluorolog-2 Spectrofluorometer, which is referred to in the Examples of the patent. Figure 14A on page 31 of document D33 indicates a "sample heater/cooler".

Document D25 describes a measurement device for the photometry of liquid samples. The reaction vessel may be temperature controlled, and the holder may comprise a Peltier element as a heat source or heat sink (see page 15, lines 3 to 7; page 25, line 5).

Document D26 is a brochure of Eppendorf AG. Page 10 discloses the so-called measurement station 5086, which includes an analogue photometer and a thermostating device. With its notice of opposition, opponent 04 (who has withdrawn its opposition during opposition proceedings) had filed a test report referred to as "Annex 2", aiming to show that real-time PCR was possible with an apparatus corresponding essentially to that of document D26. However, the apparatus used in this test report differs from that of document D26, inter alia, by the use of two water baths.

Document D19 refers to a "Perkin-Elmer spectrofluorimeter (model MPF-3) equipped with a temperature controlled chamber" (page 8791, column 1, last full paragraph).

56. None of these documents discloses that any of these apparatuses is suitable to carry out PCR, and there is also no other evidence on file showing this. Therefore, the board considers that none of said documents discloses an apparatus comprising a **thermal cycler suitable for carrying out a PCR process**. Moreover, there are no indications in these documents that any of the apparatuses could perform the heating and cooling steps in an **automated** way.

Consequently, none of said documents is prejudicial to the novelty of the subject-matter of claim 1.

Document D15

57. Document D15 describes a DNA detection method based on the simultaneous amplification of two or more DNA

segments with fluorescent oligonucleotide primers labelled with different fluorescent dyes. PCR amplification is carried out in the presence of the labelled primers using a thermal cycler. The unincorporated primers are removed before the fluorescence of each dye is determined on a fluorometer (see page 9179, column 1, paragraphs 2 and 3). At the end of the document, page 9182, column 1, paragraph 3, it is pointed out that an important advantage of the assay is its adaptability to automation. It is stated that "[b]y incorporating an appropriate ligand such as biotin to one PCR primer and a fluorophore tag to the other primer, the amplified DNA segments thus carry at each 5' end a biotin or a fluorophore molecule. The amplified DNA could be separated from the unincorporated fluorescent primers by using streptavidin magnetic beads. The color of the amplified DNA would then be determined by fluorometry through a fiber optic bundle."

However, there is no explicit disclosure to connect the fiber optic bundle with a thermal cycler. Neither is there an implicit disclosure. In the board's judgment, a skilled person reading document D15 would infer that such connection should not be present or would not be desirable. In this context, it is important to note that the method disclosed in this document requires that the unincorporated primers are removed after PCR and before detection. If biotin is incorporated into the primers used for amplification, as suggested, it can serve to take the amplified DNA out of the reaction vessel using streptavidin magnetic beads, but it is not possible to take the unincorporated primers out of the reaction vessel and then proceed directly to the

detection of the amplified DNA. Therefore, a skilled person would not derive from document D15 a fluorometer connected to a thermal cycler via a fiber optic bundle.

As the mere juxtaposition of a thermal cycler and a fluorometer, even if used in one experiment, cannot be considered as **an apparatus** for monitoring PCR for nucleic acid amplification over multiple thermal cycles, as required by claim 1, document D15 is not prejudicial to the novelty of the subject-matter of claim 1.

Documents D28/D35

58. Document D28 is a European patent application which was published on 27 May 1992, thus after the filing date of the patent in suit, and which has the priority date 31 October 1990 which is earlier than the validly claimed priority date of the patent in suit (see point 26 above). Therefore, said document constitutes prior art under Article 54(3)(4) EPC as far a its priority date is validly claimed and for the designated Contracting States DE, FR, GB and IT.

The document describes a PCR method in the presence of a fluorescent pigment, whereby the sealed reaction vessel in which the PCR was conducted is applied to a fluorometer and measured without opening the seal of the vessel. However, there is no disclosure in document D28 of a **single** apparatus suitable for monitoring PCR for nucleic acid amplification over multiple thermal cycles comprising a thermal cycler and an optical system including a detector operable to detect an optical signal. Therefore, the document is not

prejudicial to the novelty of the subject-matter of claim 1.

Document D17

59. Document D17 discloses a PCR detection method which generates a signal simultaneously with target sequence amplification. A labelled oligonucleotide probe designed to hybridize within the target sequence is added to the PCR assay and degraded into smaller fragments by the 5' → 3' exonuclease activity of the Taq DNA polymerase during amplification. These smaller fragments can be differentiated from undegraded probe.

There is no mention in this document of any apparatus for monitoring the polymerase chain reaction. It is not even mentioned that the signal generated in the method should be an optical signal detectable by an optical system. The document thus provides no clear and unambiguous disclosure of an apparatus according to claim 1.

Document D6

60. Document D6 discloses a method of measuring PCR amplification by fluorescence. In this method, the dye Hoechst 33258, which binds to DNA, is added to the sample after amplification by PCR, and fluorescence enhancement is measured. In the experiment shown in Figure 1, a series of identical samples containing target DNA and reagents for PCR amplification including Taq DNA polymerase were submitted to up to 25 cycles of PCR. Samples were withdrawn after different cycle numbers and the amount of DNA produced by the

amplification process was measured by the fluorescence of the added Hoechst 33258 dye.

As instrumentation to be used for the disclosed method, a scanning fluorescence spectrophotomoter is recommended. It is furthermore stated that the assay may also be automated using a fluorescence spectrophotomoter with an autosampler (page 9, column 1, heading "instrumentation"). The board is convinced that the autosampler referred to has to be understood as a device used to automate the spectrophotometric measurement, and cannot be interpreted as a thermal cycler suitable for carrying out a PCR process. Consequently, there is no disclosure in document D6 of a single apparatus comprising both a thermal cycler suitable for carrying out a PCR process and a spectrophotometer. Hence, document D6 cannot deprive the subject-matter of claim 1 of novelty.

61. Consequently, the subject-matter of claim 1, and also of claims 2 to 10 of the main request meet the requirements of Article 54 EPC.

Requests for remittal

62. Both the appellant and the respondents did not wish the board to decide on the issues of sufficiency of disclosure (Article 100(b) EPC) and inventive step (Article 56 EPC). However, having regard to the still open legal issue relating to Article 76(1) EPC (see point 19 above) they took different positions on the further procedural conduct of the case. The appellant requested immediate remittal to the first instance. The respondents asked for a stay of the appeal procedure

until a decision in the consolidated cases pending before the Enlarged Board of Appeal was handed down.

The board agrees with the parties insofar as it should not deal with the issues of Articles 100(b) and 56 EPC in order for them to be considered by two instances in fairness to the parties, as there was no discussion of these issues at the opposition oral proceedings.

With respect to the further issue, namely the alternative between immediate remittal or stay of proceedings, the board has to weigh the interests at stake in the light of procedural efficiency. Without anticipating the decision of the Enlarged Board of Appeal, the possibility exists that the Enlarged Board of Appeal will come to the conclusion that the scope of the claims of a divisional application as filed can be later on broadened. In this case staying the procedure in the board would cause unnecessary delay. Therefore the board considers it appropriate to remit the case.

Substantial procedural violation

63. The appellant requested the reimbursement of the appeal fee pursuant to Rule 67 EPC arguing that a substantial procedural violation occurred during the opposition proceedings and, in particular, due to Prof. Biebricher's appearing as a witness (Article 117(1)(d) EPC) and because of unfairness in the conduct of these proceedings, which did not allow the appellant to present a full and proper defence, all this being contrary to the fundamental right of a party to be heard (Article 113(1) EPC). Further, the appellant's arguments were as follows: it was only in a

communication dated 30 November 2004, shortly before the oral proceedings scheduled for 7 December 2004, that the opposition division indicated that it "might" hear the witness and asked about providing a waiver for costs; this did not suggest that it had made a formal decision to hear the witness. No indication was given in the submissions provided by the respondent/ opponent 01 or in any communication from the opposition division that the witness was available or would attend the hearing. The request filed by the patentee for adjournment of the oral proceedings was justified, since the patentee was given no proper opportunity to present counter-witnesses. The new evidence that was introduced by Prof. Biebricher's testimony took the appellant by surprise. Reference was made to decisions T 264/03 of 12 March 2004 and T 97/94 of 15 July 1997, holding that under Rule 72 EPC and Article 113(1) EPC each party must be able to conduct its defence in a manner as fair as possible.

The board's position is as follows: First, the respondent's request to hear Prof. Biebricher as a witness was filed two months before the oral proceedings, i.e. before expiry of the time limit set according to Rule 71a EPC; thus the appellant had the opportunity to offer counter-witnesses. Second, the two-month notice period provided for in Rule 72(2) EPC is not designed to protect the interests of parties to the proceedings, but those of the witness(es); this is expressed by the wording of Rule 72(2) EPC according to which witnesses *can* agree to a shorter period. Third, the witness heard, Prof. Biebricher, had already supplied declarations (documents D51 and D56) during the proceedings in writing which could have alerted the

appellant to the possibility that he might give evidence as a witness. Although the board considers it regrettable that more than seven weeks elapsed between the offer of the witness on the one hand and the communication by the opposition division that it might hear the offered witness on the other hand, this cannot be regarded as a violation of the right to be heard. Therefore, a substantial procedural violation has not occurred.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution.

3. The request for reimbursement of the appeal fee is refused.

The Registrar: The Chair:

P. Cremona U. Kinkeldey