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JUDGMENT

Court of District The Hague
Sector civil law

Case number / Docket number: 287721 / KG ZA 07-586

Judgment in preliminary injunction proceedings of July 13, 2007

In the case of:

The company under foreign law,
APPLERA CORPORATION,
established in Foster City, Verenigde Staten,
plaintiff,
procurator: mr. W.E. Pors
attorney: mr. W.E. Pors, the Hague

against

1. The company under foreign law
STRATAGENE CORPORATION,
established in La Jolla, California, USA
2. The company under foreign law
BIOCREST CORPORATION,
established in La Jolla, California, USA
3. The company under foreign law
BIOCREST MANUFACTURING L.P.,
established in Cedar Creek, Texas, USA

4. The private company with limited liability
BIO CREST BV,
also acting under the name STRATAGENE EUROPE
established in Amsterdam South east,
5. The private company with limited liability
BIO-CONNECT BV
established in Huissen,
defendants,
procurator: mr. W. Heemskerk
attorneys: mr. P.J.M. Steinhauser and mr. A.E. Heezius

Hereinafter parties will be referred to as Applera and Stratagene c.s.

1. Course of the proceedings

1.1 By writ of May 23, 2007 Applera summoned Statagene c.s. to appear before the preliminary judge of the District court The Hague on July 4, 2007. Prior to the hearing Applera has submitted 19 exhibits, a file with respect to the seizures which are executed, as well as an estimate of the procedural costs. Stratagene c.s. has submitted 23 exhibits and a costs estimate.

1.2 The attorney of Applera, assisted by the patent attorney dr. ir. H.W. Prins, has explained the claims on the basis of pleading notes and exhibits. On the basis of pleading notes and exhibits, the attorneys of Stratagene c.s. have put up defence and concluded to reject the claims of Applera.

1.3 Then parties have asked to rule a judgment, on submission of all documents, including the pleading notes and the costs estimates.

2. The facts

2.1 Applera is the proprietor of European patent EP 0 872 562 B1, hereafter referred to as EP562. The allowance of EP562 is published on September 11, 2002, with a priority date of May 2, 1991 and the patent is i.e. in force in the

Netherlands.

2.2 The claims of the B1 publication of EP562 are:

1. An apparatus for monitoring a nucleic acid amplification reaction over multiple thermal cycles, comprising:
    a. a thermal cycler capable of alternately heating and cooling, in a reaction vessel, an amplification reaction mixture comprising a target nucleic acid, reagents for 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 an amplification mixture.

3. The apparatus of claim 1 or claim 2, wherein the detector, in detecting the optical signal, is operable to sample optical signal values over multiple thermal cycles.

4. The apparatus of any one of the preceding claims wherein the detector is operable to detect a fluorescence optical signal.

5. The apparatus of claim 4 wherein the detector is operable to detect a fluorescence optical signal at a wavelength at or about 570 nm.

6. The apparatus of any one of the preceding claims, wherein the optical system includes a fiber optic cable.

7. The apparatus of any one of the preceding claims, further comprising a

reaction vessel adapted to contain an amplification reaction mixture comprising a target nucleic acid, reagents for 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 an amplification reaction mixture.

9. The apparatus of claim 7 or claim 8, wherein the reaction vessel(s) include a clear or translucent cap optically coupled to the detector.

10. Use of an apparatus according to any one of the preceding claims for monitoring a nucleic acid amplification reaction over multiple thermal cycles.

2.3. The Dutch translation of the claims:

1. Inrichting voor het volgen van een nucleïnezuuramplificatiereactie over meerdere temperatuurcycli, omvattende:

(a) een thermocycler die in staat is tot het in een reactievat afwisselend verwarmen en afkoelen van een amplificatiereactiemengsel omvattende een doelwitnucleïnezuur, reagentia voor nucleïnezuuramplificatie en een detecteerbaar nucleïnezuurbindend middel; en

(b) een optisch systeem omvattende een detector die in staat is een optisch signaal te detecteren dat gerelateerd is aan de hoeveelheid geamplificeerd nucleïnezuur in het reactiemengsel over een periode van meerdere cycli, zonder het reactievat te openen nadat de amplificatiereactie eenmaal is gestart.

2. Inrichting volgens conclusie 1, waarbij de thermocycler in staat is tot het afwisselend verwarmen en afkoelen van meerdere reactievaten die elk een amplificatiereactiemengsel bevatten.

3. Inrichting volgens conclusie 1 of 2, waarbij de detector bij het detecteren van het optische signaal optische signaalwaarden over meerdere temperatuurcycli kan bemonsteren.

4. Inrichting volgens één der voorgaande conclusies, waarbij de detector in staat is een optisch fluorescentiesignaal te detecteren.

5. Inrichting volgens conclusie 4, waarbij de detector in staat is een optisch fluorescentiesignaal te detecteren bij een golflengte van 570 of ongeveer 570 nm.

6. Inrichting volgens één der voorgaande conclusies, waarbij het optische systeem een vezeloptische kabel omvat.

7. Inrichting volgens één der voorgaande conclusies, verder omvattende een reactievat dat zo is uitgevoerd dat het een amplificatiereactiemengsel kan bevatten omvattende een doelwitnucleïnezuur, reagentia voor nucleïnezuuramplificatie en een detecteerbaar nucleïnezuurbindend middel.

8. Inrichting volgens conclusie 7, die meerdere reactievaten omvat die elk geschikt zijn om een amplificatiereactiemengsel te bevatten.

9. Inrichting volgens conclusie 7 of 8, waarbij de één of meer reactievaten een heldere of doorzichtige dop bevatten die optisch gekoppeld is aan de detector.

10. Gebruik van een inrichting volgens één der voorgaande conclusies voor het volgen van een nucleïnezuuramplificatiereactie over meerdere temperatuurcycli.

2.4 A number of parties have initiated opposition proceedings against EP 562 amongst which Stratagene Corporation. Following the oral proceedings on December 8, 2004, the Opposition Division decided to revoke EP562 which decision was appealed by Applera. During the oral proceedings on July 6, 2006, the Board of Appeal of the EPO reversed the decision of the Opposition Division and upheld the patent in slightly amended form. The amendments as proposed by Applera concern the main claim. The amendments are shown by underlining in the representation below.

2.5 The new main claim, after opposition, reads:

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.

The Dutch translation reads:

1. Inrichting voor het volgen van een polymerasekettingreactie (PCR) voor nucleïnezuuramplificatie over meerdere thermale cycli, omvattende:
   (a) een thermocycler voor het uitvoeren van een geautomatiseerde PCR-werkwijze waarbij de genoemde thermocycler in staat is tot het in een reactievat afwisselend verwarmen en afkoelen van een PCR-amplificatiereactiemengsel omvattende een target DNA, reagentia voor de genoemde nucleïnezuuramplificatie en een detecteerbaar nucleïnezuurbindend middel; en
   (b) een optisch systeem omvattende een detector die in staat is een optisch signaal te detecteren dat gerelateerd is aan de hoeveelheid geamplificeerd nucleïnezuur in het reactiemengsel over een periode van meerdere cycli, zonder het reactievat te openen nadat de amplificatiereactie eenmaal is gestart.

2.6 For examination of the grounds of opposition of inventive step and sufficiency of disclosure the case has been remitted to the Opposition Division.

2.7 On April 12, 2007 Applera partly waived to the matter of EP 562 and registered an act of abdication with the amended claims in the Dutch patent register.

2.8 Stratagene Corporation (defendant under 1) is the parent company of e.g. Biocrest Corporation (defendant under 2), Biocrest Manufacturing L.P. (defendant under 3) and Bio Crest B.V. (defendant under 4). The manufacture of the litigious apparatus is performed in the USA by the subsidiary Biocrest Manufacturing L.P. These apparatus are sold by Biocrest Corporation. Bio Crest B.V. is responsible for the sale and distribution of the apparatus in The

Netherlands and the West European countries. This company also acts under the trade name Stratagene Europe. Bio Connect B.V. is specialized in the sale of apparatus and products in the biotechnology. This company is agent for more manufacturers. Since the beginning of 2007 this company is agent for Bio Crest B.V. with respect to the sale of Stratagene products in the Benelux.

2.9 “Stratagene” offers through the website (http:/www.stratagene.com) the Mx3000P, Mx3005P and Mx4000 quantitative PCR amplifications.

2.10 By leave of the preliminary judge in Amsterdam, Applera has prepared an inventory of the infringing products and executed an evidential seizure on in each time one copy of the thermal cyclers of the systems Mx3000P, Mx3005P and Mx4000. Additionally by leave of the preliminary judge in Arnhem, Applera executed an evidential seizure at Bio-Connect.

2.11 In its judgment of June 14, 2007 the Landgericht Dusseldorf imposed an injunction, which includes in short that Stratagene Corporation is prohibited to infringe the amended main claim of EP 562.

3. The dispute

3.1 Applera claims immediately enforceable and on all days and hours, the following:

1. Order defendant sub 1 through 3, Stratagene Corporation, Biocrest Corporation and Biocrest Manufacturing L.P., to immediately after service of the judgment to be issued in these proceedings, stop any direct or indirect infringement on the patent EP 0 872 562 in The Netherlands, especially by the sale or further commercialisation of real-time thermal cyclers and more specifically by the sale and further commercialisation of the combinations of reagents for nucleic acid amplification and detectable nucleic acid binding agents and thermal cycler Mx3000P® System and/or Mx3005P® System and/or Mx4000P® System, or the separate components of those systems;

2. Order defendant sub 4, Bio Crest BV, to immediately after service of the judgment to be issued in these proceedings, stop any direct or indirect infringement on the patent EP 0 872 562 in The Netherlands, as well as in Belgium, Denmark, France, Italy, Lichtenstein, Austria, Spain, Sweden and Switzerland, especially by the sale or further commercialisation of real-time thermal cyclers and more specifically by the sale and further commercialisation of the combinations of reagents for nucleic acid amplification and detectable nucleic acid binding agents and thermal cycler Mx3000P® System and/or Mx3005P® System and/or Mx4000P® System, or the separate components of those systems;

3. Order defendant sub 5, Bio-Connect BV, to immediately after service of the judgment to be issued in these proceedings, stop any direct or indirect infringement on the patent EP 0 872 562 in The Netherlands and in Belgium, especially by the sale or further commercialisation of real-time thermal cyclers and more specifically by the sale and further commercialisation of the combinations of reagents for nucleic acid amplification and detectable nucleic acid binding agents and thermal cycler Mx3000P® System and/or Mx3005P® System and/or Mx4000P® System, or the separate components of those systems;

4. Order each of defendants to provide Applera's counsel within 14 days after service of the judgment to be issued in these proceedings with a correct and complete written statement of:
   a. The number of thermal cyclers and the amount of reagents for nucleic acid amplification and detectable nucleic acid binding agent that said defendant, through a direct or indirect infringement on EP 0 872 562, has produced in or for his company, has used, marketed, sold, delivered of otherwise traded in, imported of kept in stock, with regard to the countries mentioned in claims 1 and 2;
   b. All purchase and sales prices of said infringing products;

c. Names and addresses of all applicable suppliers of each defendant who have supplied said infringing products, together with the individual dates of delivery and the individual amounts ordered and delivered;

d. Names and addresses of all applicable customers of each defendant who have purchased said infringing products, together with the individual dates of delivery and the individual amounts ordered and delivered,

Accompanied by a declaration by an independent registered accountant, which inter alia states that his investigation of the accounts and the financial administration of such defendant shows that the statement is correct as well as accompanied by copies of all relevant order, purchase, sale, transport and customs documents;

5. Order each of defendants to provide Applera's counsel within 14 days after service of the judgment to be issued in these proceedings with a correct and complete written statement of the gross profit obtained by said defendant as a consequence of the infringement, accompanied by a declaration by an independent registered accountant, which inter alia states that his investigation of the accounts and the financial administration of such defendant shows that the statement of this gross profit is correct;

6. Order each of defendants to provide Applera's counsel within 7 days after service of the judgment to be issued in these proceedings to inform in writing (and in English where this relates to foreign parties) each party who has ordered or purchased infringing products from said defendant, regardless whether these have actually been delivered, using the usual letterhead of said defendant and in a usual and well legible font, without any additions of deletions:

"*Dear customer,*

In its judgment of [insert date of judgment], the preliminary injunction

judge (“ Voorzieningenrechter”) of the District Court in The Hague has ruled that our thermal cycler systems Mx3000P® System and/or Mx3005P® System and/or Mx4000P® System and their components infringe on patent EP 0 872 562 owned by Applera Corporation, Foster City, CA, USA. As a consequence of this judgment we are no longer allowed to produce, offer for sale or sell these products.

In case we have already delivered one of these products to you, we request you to return it within one week. Of course we will reimburse you and we will pay for the costs of the return shipment. Any outstanding orders of the aforementioned products are hereby cancelled.

Yours sincerely,

[Insert name of defendant].”;

7. Order each of defendants to provide Applera’s counsel within 10 days after service of the judgment to be issued in these proceedings with copies of all the aforementioned letters including names and addresses of the addressees to enable him to check whether the order sub 5 has been complied with;

8. Order that each of defendants will forfeit a penalty of € 100.000,-- that is collectible immediately for each violation of the aforementioned orders or each day that the defendant is not in compliance with complete and immediate fulfilment of the aforementioned orders, at the discretion of plaintiff;

9. Order defendants to pay the costs of these proceedings.

3.2 Stratagene c.s. put forward a defence. In so far as necessary the preliminary judge hereinafter will go into the assertions of the parties further.

4. The technical field of the invention

4.1 The following technical introduction is based on the part bearing the same name in the writ of summons, drafted by dr. ir. H.W. Prins en dr. A. Van Kooij, Applera's patent attorneys.

General Introduction

4.2 The polymerase chain reaction is an important Biochemical and Molecular Biology technique. In the Art, the polymerase chain reaction is often referred to as PCR derived from the English term for the polymerase chain reaction: Polymerase Chain Reaction. Since its discovery by Kary Mullis (receiving for this the Nobel price in 1993) in 1983, the technique has evolved into one of the basic techniques of medical and biological research and analysis laboratories. The PCR-technique is used for a large number of purposes such as detection of hereditary diseases, identification based on genetic finger printing, diagnosis of many infectious diseases, the use of hereditary material for the development of medicaments, parenthood determinations, etc.

The PCR Technique

4.3 The polymerase chain reaction or PCR is a method for multiplying or amplifying nucleic acids (the hereditary or genomic material). In fact, the PCR-technique is based on in vitro mimicking in vivo copying of hereditary or genomic material during the cellular division.

4.4 The enzyme (catalytic protein) responsible for in vivo copying hereditary or genomic material is the polymerase enzyme. As is already indicated by the name polymerase chain reaction, this enzyme is also used for amplifying nucleic acids in the PCR-technique.

4.5 Besides the polymerase enzyme, the PCR-technique also uses two short synthetic fragments of nucleic acid, designated as primers. These primers provide annealing on specific positions on the nucleic acid (hereafter referred to as target DNA) to be copied. The annealing of these two primers to the target DNA allows the formation of two anchor and starting positions for the

polymerase enzyme. Using these anchor and start positions the polymerase enzyme is able to copy the target DNA located between the primers.

4.6 The first preparatory step of the PCR-technique is combining in a reaction vessel the polymerase enzyme, the target DNA, the two primers and further reagents necessary for the amplification. Subsequently, the polymerase chain reaction (PCR) can be initiated.

4.7 The polymerase chain reaction (PCR) is based on many times cyclic repeating copying of the target DNA by the polymerase enzyme. A chain reaction is developing because the amplified product of an earlier cycle, along with the target DNA, is copied again in the subsequent cycle. In other words, the amount of DNA present in the reaction vessel is doubled every cycle. As a consequence, after 20 cycles, the original amount of target DNA in the reaction vessel is multiplied with a factor of 2^{20} (1 million).

The PCR-cycle

4.8 A PCR amplification cycle as at issue in these proceedings comprises three separate steps commonly designated as the denaturation step, the annealing step and the elongation step.

In the denaturation step, the target DNA is prepared for annealing of the primers. This is achieved by heating the PCR-mixture in the reaction vessel to more than 90°C during, for example, 10 seconds. The target DNA, consisting of two nucleic acid strands entwined and connected to each other in a helix structure, is “disentwined” thereby liberating the two nucleic acid strand and making them available for primer annealing.

In the annealing step, allowing the primers to anneal forms the anchor and starting positions on the target DNA. Quickly lowering the temperature of the PCR-mixture of the denaturation step to, for example, 54 °C and maintaining this temperature during approximately 30 seconds provides this.

The actual copying by the polymerase enzyme takes place in the third step of the cycle, the elongation step. After the anchor and starting positions on the target DNA are formed during the annealing step, the temperature of the PCR-mixture is quickly raised to, for example, 72 °C and this temperature is maintained during approximately 2 minutes. The polymerase enzyme forms, based on each nucleic acid strand, again a double strand identical to the target

DNA (consisting of two strands).

After this step, the PCR-cycle is completed and the target DNA, originally present in the reaction vessel, is doubled. Subsequently, a new cycle can be initiated with a new denaturation step by reheating the PCR-mixture to more than 90 °C.

4.9 Summarizing, the PCR-technique involves combining the necessary ingredients in a reaction vessel and subsequently subjecting this reaction vessel to cyclic rapidly heating and cooling in a specific sequence. Usually, this rapid heating and cooling of the reaction vessel is accomplished by using an automated and for PCR specifically developed apparatus, the thermal cycler.

4.10 A thermal cycler comprises a holder for usually a large number of reaction vessels, an element for heating, an element for cooling and control elements. In practice, a user programs the temperature and duration of the denaturation step, the annealing step and the elongation step. Subsequently, the user places the reaction vessels in the holder and starts the thermal cycler.

After approximately one or two hours, this results in the accumulation of a particularly large amount of identical copies of the target DNA between the primers in the reaction vessels.

Application of the PCR-technique

4.11 It is particularly desirable, or even necessary, to be able to multiply or amplify (parts of) nucleic acids at a large scale with respect to many clinical or scientific applications such as detection of hereditary diseases, identification based on genetic finger printing, diagnosis of many infectious diseases, the use of hereditary material for the development of medicaments, parenthood determinations, etc.

4.12 The usual source of a nucleic acid is a cell of an organism such as a human or a unicellular organism like a bacterium. Particularly with respect to clinical applications, these sources often provide not enough nucleic acid molecules for a useful analysis or diagnosis.

The fact that the PCR-technique is able to amplify these small amounts of nucleic acids (target DNA), possibly comprising life-saving diagnostic information, into analyzable amounts has certainly contributed to the general

use of this technique.

Additionally, the PCR-technique has contributed to the development of a new generation of (future) medicaments based on biotechnology such as medicaments for curing cancer, diabetes, rheumatism, muscle diseases, etc.

Limitations of the PCR-technique

4.13 The advantage of the PCR-technique to be able to exactly copy large amounts of target DNA has been simultaneously a major disadvantage of this technique.

A contamination of, for example, a diagnostic sample with a very limited amount of already amplified DNA from an earlier PCR amplification can very easily result in that a diagnosis based on this sample is no longer possible. This because, due to the presence of the contamination, amplification will always occur even if the target DNA to be analyzed is absent in the sample.

An important source of contamination is opening of the reaction vessel containing the PCR amplified product. The escape of a very limited amount of the reaction fluid there from (1/billion of a liter) to the surroundings is often sufficient to make further diagnostic analysis impossible in the laboratory concerned.

Opening of the vessel is often necessary in order to, for example, determine the status of the PCR reaction. This can result in a (temporal) interruption of the PCR reaction. Opening of the vessel results in a risk of sample contamination with as a consequence a wrong PCR result.

Additionally, it could be necessary to analyze diagnostic information present in the amplified nucleic acids. If the final result of the PCR is not sufficient then the PCR can be repeated using adapted reaction parameters. This adaptation occurs without using information with respect to the PCR run and its end-point.

Extreme, time consuming and mostly expensive measures are thus necessary to control the problem of PCR contamination. Thus, it is important to decrease the steps of sample preparation, sample handling and sample analysis particularly once the amplification has been completed.

Analyzing (amplified) nucleic acids.

4.14 A large number of techniques are known for analyzing (amplified) nucleic acids. The majority of these techniques concern the addition of an agent capable of binding nucleic acids. Subsequently, the presence or absence of (amplified) nucleic acids is determined by detecting the presence or absence of the agent. The amount of binding is indicative for the amount of amplified nucleic acid present.

This detection is often based upon the detection of an optically detectable signal such as a fluorescent signal derived from the agent (dye) bound to the (amplified) nucleic acids.

The use of agents capable of binding to target DNA and amplified DNA also involves a potential risk for the developing amplification process. As is already indicated in their name, these agents bind target DNA and the amplified DNA however both are also used in the subsequent cycle of the PCR for making copies.

It is known in vivo that many of the genomic or hereditary material (DNA) binding agents, such as ethidium bromide, are carcinogenic (cancer is often the result of copying errors).

There is a risk that, due to the binding of the same agents during the PCR-amplification, exact copies of the target DNA can longer be made. This would be disastrous for the PCR-amplification.

This is because every copying error is carried into the next cycle in which new copying errors occur which are again carried into the next cycle, etc. The accumulation of errors can ultimately result in a totally unusable end product.

The scenario outlined above, based on in vivo observations, could be one of the reasons why one conducted an in vitro technique such as the PCR technique separately from a detection step using nucleic acid binding agents around 1991.

"Real-Time" PCR

4.15 However, it is advantageous to be able to determine the development of the PCR-reaction already during the PCR-reaction, i.e., to be able to follow the amplification of target DNA. In the English language, the usual term for this is "Real-Time" (RT)

4.16 Using Real-Time-PCR, it becomes possible to optimalize the course of PCR, thus not by using an analysis of the end result after completion of the cycles, but instead during the cycles themselves. This because the duration and temperature of the denaturation step, the annealing step and the elongation step are important parameters for a successful PCR-reaction. Additionally, these parameters often differ for each combination of target DNA and primers. Because these parameters are programmed by the user before the PCR-reaction, testing of new parameters requires a new PCR. Using Real-Time-PCR, this optimalization can be remarkably reduced. Needless to say that combining amplification and detection is also faster compared to separately conducting these steps after one another.

5. The Assessment

Revocation of EP 562.

5.1 Stratagene's cs defence is concentrated on the argument that there is a realistic (serious), change which is not negligible that EP 562 will be revoked. Statagene cs do not contest the fact that the systems Mx3000P, Mx3005P and Mx4000 contain the characteristics of EP 562's claims 1 up to and including 5.

5.2 Statagene cs bring forward three arguments based on which, according to Stratagene cs, the claims of EP 562 will as yet be dismissed in the opposition procedure. They argue that (A) there is a violation of article 76 (1) EPC; (B) there is lack of novelty, in the light of the subsequently to be described thesis by Otten en (C) lack of an inventive step, also in the light of the before mentioned thesis.

Additionally, (D) Stratagene cs challenge the conclusions drawn by the Technical Board of Appeal, relating to the document 'Report on Evolution Research' (referred to in the opposition as D30). The judge in preliminary injunctions understands that Statagene means to say that that the judge in proceedings on the merits will destroy the Dutch part of EP 562 when reassessing of EP 562's validity, because it is not new in view of D 30.

A. Article 76 (1) EPC

5.3 In its decision of July 6, 2006, the Technical Board of appeal considered:

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.

5.4 This point of law has now, on 28 June 2007, been answered negatively by the Enlarged Board of Appeal in the case G 1/05 (B9 4306). Summarizing the Enlarged Board of Appeal deems that divisionals can be amended during the procedure, and they can be restricted to the original subject matter from the mother application. The divisional applications have then been legally applied for, even if they extend the subject matter compared to the scope of the preceding application.

5.5 In view of decision G 1/05 it is not definitely likely that the continued opposition EP 562 will be nullified for violation of article 76 paragraph 1 European Patent Regulation.

B. Not new in view of Otten

5.6 In the opposition procedure H. Otten's doctoral dissertation: *Ein betrag zur Durchführung von kontrollierten Evolutions-experimenten mit biologischen Makromolekulen, Fakultät Maschinenbau und Elektrotechnik der technischen*

Universität Carola- Wilhelmina zu Braunsweig, 1988 has not come up for discussion. Stratagene has submitted this publication as exhibit 16.

5.7 The judge in preliminary relief remarks that in this document the concept of PCR is not discussed. Discussed is the automation of an augmentation process of parts of the RNA molecule. With this not the enzyme Polymerase is used but the so-called Qβ virus. The multiplication of RNA requires not three, but only two temperature ranges namely approximately 0 C, by which temperature no reaction follows and approximately 37 C, by which temperature the multiplication occurs. The reaction time is longer, which entails that the temperature jump does not necessarily need to go as rapidly as with the PCR-technique. The doctoral dissertation mentions on p. 24 a cooling-off period of 90 to 120 seconds and a warm-up period of approximately 30 seconds.

5.8 What Otten describes is a cooling/heating process which makes use of a liquid bath. This is in the essence the technology which is also used and discussed in the publication *Solution-Phase detection of Polynucleotides Using Interacting Fluoriscent labels and Competitive Hybridization* from 1989. This publication is discussed in the opposition procedure as D11. The Technical Board of Appeal judged that the technique revealed in D11, which pertains to the detection of DNA after amplification, can not be deemed to harm novelty as it has not been demonstrated that with the water bath-technique a heating respectively a cooling-off rapidity can be achieved which is sufficient for an automated PCR process.

5.9 Provisionally the preliminary judge is of the opinion that Stratagene has demonstrated insufficiently that the system revealed in Otten's doctoral dissertation is suitable for an automated PCR process, even less in this document an automated PCR revealed in its entirety. Therefore the document does not harm novelty.

C. Inventive steps

5.10 The preliminary judge understands that Stratagene cs regards the above mentioned doctoral dissertation in connection with the question to inventive steps as the *Closest Prior Art.*

5.11 As described above Otten does not reveal an apparatus which is suitable for an automated PCR process. It reveals even less the problem EP 562 solves.

5.12 From conclusion 1 of EP 562 it appears that the invention pertains to an amplified PCR system and detection system whereby the detector is operable to detect an optical signal over a multiple-cycle period related to the amount of amplified nucleic acid in the reaction mixture, without opening the reaction vessel once the amplification reaction is initiated (underlines added by the judge in preliminary proceedings.)

5.13 The fact that the reaction vessel does not need to be opened during the process is fundamental for the invention described in EP 562. The PCR technique implies a great number of repetitions of the reaction cycle. Manipulations like opening the reaction vessels, for example to add detection fluid, should be avoided to prevent contamination. To exclude these contaminations, the detection fluid should already be added to the reaction fluid at the beginning of the process. In addition, the continuous presence of the detection fluid is a condition to be able to follow the Real Time course of the PCR process. The problem is that usual detection fluids will intervene with the material to be multiplied. This is inherent to the carcinogenic characteristics of the used detection fluids such as the Ethidiumbromide (EtBr) which is used in the system as described by Otten as well as in the system according to the invention. This intervention leads to the evolution of the material so that there is no longer an amplification of the original basic material.

5.14 In the Qβ technique, for example Otten, it was known that the detection fluid could be added at the beginning of the reaction. This is logical for the RNA Qβ amplification since the process in principle proceeds in a batch and not in cycles. The interference of the detection fluid with the basic material is with Otten however not a problem but more a purpose. Otten's apparatus is namely designated for Evolutionsexperimenten. For this it is not the intention to get a bigger quantity of the same basic material, but a mutation of the basic material into the desired result. Together this implies that system as described by Otten does not suggest a solution of the problem solved with the invention at all.

Otten can therefore by no means be regarded as Closest Prior Art. It does not provide a basis for disputing the inventive steps of EP 562.

D Not new in view of the Report on Evolution Theory

5.15 In the procedure before the Technical Board of Appeal the question as to whether the document D30 was publicly available was extensively discussed. D30 is a document with the title Report on Evolution Research, published by the Max-Planck-Institut für biophysikalische Chemie at Göttingen in 1990, in connection with an International Workshop Selection – Natural and Unnatural – in Biotechnology which was held from 18 to 20 April 1990 in the abovementioned institution.

5.16 In a contribution to this report from Andreas Schober (p. 53-55) an "evolution machine" is described which more or less resembles the apparatus as described in Otten's doctoral dissertation. Schober proceeds nevertheless with the following:

"The evolution machine, which provides a temperature jump device, can easily be adapted to perform many nucleic acid amplifications 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. Preliminary experiments, performed by Lindemann and Günther, showed that the nucleic acid concentrations van be measured during the PCR using a fluorescence indicator, which does not interfere with the amplification reaction. The multichannel fluorimeter will significantly reduce the effort required to detect the presence of or measure the concentration of specific nucleic acids by PCR. Patent applications for various technical devices involved have been filed (Eigen 1990)."

5.17 In view hereof, the Technical Board of appeal qualified D30 in principle as detrimental to the novelty – just like previously the Opposition department. Applera acknowledges this, but contests that D30 was handed out without reservation on the workshop of 18 up and to 20 April 1991.

5.18 The Opposition department considered that D30 had been accessible to the public by distribution during the workshop. In appeal the Technical Board of Appeal regarded this again, and it established that there was insufficient evidence to prove D30 was publicly available. As necessary ‘standard of proof’, the Technical Board of Appeal applied the principle of ‘beyond reasonable doubt’ or ‘up the hilt’. The principle ‘the balance of probabilities’ was deemed unsuitable by the Chamber in the given case where the revocation of a patent was under discussion. The Chamber took into consideration a great amount of affidavits by persons involved in its assessment.

5.19 Stratagene cs submitted an amount of additional affidavits. As they remark themselves, these contain a repetition of the affidavits which were previously made relating to the public availability of D30. Stratagene cs do not dispute the principle of ‘beyond a reasonable doubt’ as applied by the Technical Board of Appeal. The principle is considered to be correct, but it would not have been applied correctly by the Technical Board of Appeal.

5.20 Jointly, this means that Stratagene cs ask the judge in preliminary proceedings in fact to assess the same material again, while applying the same principle.

5.21 When providing evidence is concerned, the preliminary injunction procedure is not the most accurate procedure. The procedure has its limitations when assessing the available evidence as well. This assessment, and also the discussion during the hearing, gives rise to new questions, which call for producing evidence. In this case, the question rose whether there was no witness who could show the document from first hand, for instance out of his own bookcase, and could attach to it an affidavit that the document was handed out to him and to others during the Workshop. Furthermore, the question rose whether it has not been shown that D30 was included in a publicly available technical or academic library. Taking this into account, the question remains what the status of D30 is. It seems that D30 was “officially” published as appendix to the final report of the Workshop. This report titled ‘Report on the internal Workshop, Selection – Natural and Unnatural – in Biotechnology, held from April 18 to 20 1991 at the Max Planck-Institut für

biophysikalische Chemie in Göttingen - Germany' is submitted by Stratagene cs as exhibit 9. The judge in preliminary proceedings did not find a contribution relating to the technique described in D30 in the final report. The only reference is the appendix 'List of posters, referring to laboratorium demonstrations' which mentions a 'Temparaturegradient PCR-Machine'. The final report does not contain references to any attachments like the document D30.

5.22 Under these circumstances, the provisional opinion of the judge in preliminary proceedings cannot diverge from the judgment of the Technical Board of appeal. It should be assumed in the interim that this document was not available to the public.

5.23 This leads to the conclusion that Stratagene cs infringe Applera's patent. Applera has right to an injunction on further infringement. The injunction can however not be given in respect to the entire scope and effect as claimed by Applera.

5.24 Stratagene cs deny amongst others that the infringement can be attributed to all defendants.

5.25 The judge in preliminary proceedings considers that it is an established act that the Mx3000P, Mx3005P and Mx4000 quantitative PCR systems are offered for sale via the website www.stratagene.com worldwide, hence also in the Netherlands. Stratagene cs did not dispute that this website is operated by Stratagene Corporation. Now that the relationship between the companies can be assumed to be as described in 2.8. Of this judgment, the infringement should be attributed to all defendants.

5.26 Applera claims a cross-border injunction. However, Applera did not clarify that EP 562 is validated in all the countries the injunction should be extended to, and she clarified even less to which scope the patent applies in all those countries. In the interim, the judge in preliminary proceedings assumes that an

act of abdication was only registered in the Netherlands. The injunction will therefore only be adjudged in the Netherlands.

5.27 The injunction on direct infringement relates primarily to the delivery of reagents for nucleic acid amplification and detectable nucleic acid binding agents. Set against the challenge by Stratagene cs, Applera insufficiently demonstrated that the ancillary materials delivered by Stratagene are suitable and destined to apply EP 562. The injunction will therefore be limited to the sale and other trade of the infringing systems.

5.28 As the parties which have mainly been found in the wrong, Stratagene cs will be ordered to pay the costs of the proceedings. Stratagene cs have challenged of the justification of the costs as far as they have been made for the attachments.

5.29 The attachments have been made to protect the evidence of infringement. They have nevertheless also given Applera the opportunity to –in accordance with her intention- do research to establish the infringement. In hindsight the attachments have not proved to be of great importance since Stratagene cs have not contradicted the infringement. This does not however take away the justification of the attachments. At the time of the attachments there was reason for Applera to reckon with a fundamental infringement defence such as the Stratagene Corporation also held in the German procedure. This entails that also the costs of the attachments, to which moreover a large part of the costs of the patent attorney are to be accounted, have to be refunded by Stratagene cs. The costs as given up by Applera amount to € 133,553.32 (one-hundred-thirty-three-thousand-five-hundred-fifty-three-point-thirty-two) and are otherwise not contested. Stratagene will be ordered to pay the abovementioned amount.

6. The decision

The judge in preliminary relief:

forbids Stratagene cs with immediate effect after service of this judgment every infringement on EP 562 in the Netherlands, particularly by sale or other trade of real-time thermocyclers and particularly by sale or other trade of the thermocycler Mx3000P System and/or Mx3005P System and/or Mx4000P System;

orders Stratagene cs each individually within six weeks (days) after service of the hereto given judgment to hand over to the attorney of Applera a correct and complete written specification of:

a. The number thermocyclers that the concerning defendant, by infringement of EP 562, in or for his business has manufactured, used, put into the market, sold, delivered or otherwise has traded or for this purpose has offered, introduced or holds in stock, all this regarding the Netherlands;
b. Names and addresses of all buyers in the Netherlands of the concerning defendant that have taken delivery of the infringing systems, accompanied with the purchase information and the numbers of systems that have been ordered and purchased; which is accompanied by a statement of a registered accountant, which states that he by means of auditing the books and financial administration of the concerning defendant has determined that the written specification is correct;

orders Stratagene cs each individually within six weeks after service of the hereto given judgment to hand over to the attorney of Applera a correct and complete written specification of the gross profit which the concerning defendant has made as a consequence of the above determined infringement of EP 562 , which is accompanied by a statement of a registered accountant, which states that he by means of auditing the books and financial administration of the concerning defendant has determined that the written specification of the gross profit is correct;

decides that Stratagene cs each individually will forfeit and owe to Applera a immediately payable penalty of € 100,000 (one-hundred-thousand) for every time or - and such exclusively up to Applera – for every day that concerning defendant is in default of the timely and complete compliance of the above mentioned prohibitions or orders;

orders Stratagene to pay Applera the costs of the proceedings to this day estimated at € 133,553.32 (one-hundred-thirty-three-thousand-five-hundred-fifty-three-point-thirty-two);

declares this judgment to have immediate effect;

dismisses all claims that exceed or are different from judgment;

determines the term as meant in article 1019i of the Dutch Civil Procedures Code to be six months.

This judgment has been passed by mr. Chr A.J.F.M. Hensen and has been publicly pronounced on the 13th of July 2007 in the presence of the clerk of the court.