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Datasheet for the decision of 14 June 2023

Case Number: T 1402/19 - 3.3.08

Application Number: 11193696.9

Publication Number: 2465947

IPC: C12Q1/68

Language of the proceedings: EN

Title of invention:
Generic matrix for control nucleic acids

Patent Proprietors:
F. Hoffmann-La Roche AG
Roche Diagnostics GmbH

Opponent:
Pajaro Limited

Headword:
Matrix for control nucleic acids/HOFFMANN LA ROCHE

Relevant legal provisions:
EPC Art. 56, 84, 100(a), 123(2)
RPBA 2020 Art. 13(1)

Keyword:
Inventive step (no) - obvious alternative
Claims - clarity after amendment (no)
Amendments - added subject-matter (yes)
Amendment to appeal case - exercise of discretion

Decisions cited:
T 0967/97, T 1379/11

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Case Number: T 1402/19 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 14 June 2023

Appellant: (Opponent)	Pajaro Limited 12 New Fetter Lane London EC4A 1JP (GB)
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Representative:	Bösl, Raphael Konrad Patentanwälte Isenbruck Bösl Hörschler PartG mbB Eastsite One Seckenheimer Landstraße 4 68163 Mannheim (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 11 March 2019 rejecting the opposition filed against European patent No. 2465947 pursuant to Article 101(2) EPC**

Composition of the Board:

Chair	T. Sommerfeld
Members:	A. Schmitt
	R. Winkelhofer

Summary of Facts and Submissions

I. The opponent's (appellant's) appeal lies from the opposition division's decision to reject the opposition filed against European patent No. 2 465 947 entitled "*Generic matrix for control nucleic acids*" (hereinafter "the patent"). The patent was granted based on European patent application No. 11 193 696.9 (hereinafter "the application").

Claim 1 of the patent as granted reads as follows:

"1. A process for isolating, amplifying and detecting at least one target nucleic acid that may be present in at least one fluid sample, wherein said fluid sample is a body liquid, said process comprising the automated steps of:
a. adding an internal control nucleic acid to said fluid sample
b. combining together a solid support material and said fluid sample in a vessel for a period of time and under conditions sufficient to permit nucleic acids comprising the target nucleic acid and the internal control nucleic acid to be immobilized on the solid support material
c. isolating the solid support material from the other material present in the fluid sample in a separation station
d. purifying the nucleic acids in said separation station and washing the solid support material one or more times with a wash buffer
e. contacting the purified target nucleic acid and the purified internal control nucleic acid in at least a first vessel and at least one external control nucleic

acid in an aqueous buffer in at least a second vessel with one or more amplification reagents
f. incubating in said reaction vessels said purified target nucleic acid, said purified internal control nucleic acid and said at least one external control nucleic acid in an aqueous buffer with said one or more amplification reagents for a period of time and under conditions sufficient for an amplification reaction indicative of the presence or absence of said target nucleic acid and said control nucleic acids to occur

wherein the conditions for amplification in steps e. to f. are identical for said purified target nucleic acid, said internal control nucleic acid and said at least one external control nucleic acid in an aqueous buffer, and wherein said at least one external control nucleic acid in an aqueous buffer is subjected to the steps following step a."

II. The opposition proceedings were based on the grounds for opposition in Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and in Article 100(b) EPC.

III. With their reply to the appeal the patent proprietors (respondents) submitted sets of claims of auxiliary requests 1 to 3, which were identical to the sets of claims of auxiliary requests 2 to 4 filed in the opposition proceedings.

Claim 1 of auxiliary request 1 differs from claim 1 as granted (see section I.) in that it comprises the additional feature "wherein the process comprises more than one external control nucleic acid, wherein at least one external control nucleic acid in an aqueous buffer is subjected to the steps following step a., and

at least one other external control nucleic acid in an aqueous buffer is only subjected to the steps following step d.".

Claim 1 of auxiliary request 2 differs from claim 1 as granted (see section I.) in that it comprises the additional feature "wherein in step a.: adding said internal control nucleic acid to at least one external control nucleic acid in an aqueous buffer".

Claim 1 of auxiliary request 3 differs from claim 1 as granted (see section I.) in that it comprises the additional feature "wherein after step d.: adding said internal control nucleic acid to at least one external control nucleic acid in an aqueous buffer".

IV. On 23 March 2020, the respondents submitted, *inter alia*, a set of claims of auxiliary request 4.

Claim 1 of auxiliary request 4 differs from claim 1 as granted in that it comprises the additional feature "wherein after step d.: also adding said internal control nucleic acid to said at least one external control nucleic acid in an aqueous buffer".

V. The oral proceedings were held as scheduled.

VI. The following documents are mentioned in this decision:

D6 M. Beld et al., J. Clin. Microbiol. 42(7), 2004, 3059-3064

D7 Roche Molecular Systems, cobas® TaqScreen MPX Test for use on the cobas s 201 system, 2009, 1-60

D21 Argene product catalogue "Diagnostic d'agents infectieux", 2009, 1-48

D28 U.S. Department of Health and Human Services et al., "Guidance for Industry and FDA Staff - Assayed and Unassayed Quality Control Material", 2007, 2-13

D29 Chapter 4 "Standards and Controls: Concepts for Preparation and Use in Real-time PCR Applications" in: "Real-Time PCR in Microbiology - From Diagnosis to Characterization", Ian M. Mackay, Caister Academic Press Norfolk, UK, 2007, pages 101-131

VII. The appellant's arguments relevant to this decision are summarised as follows.

Main request (patent as granted)
Inventive step (Article 100(a) EPC and Article 56 EPC)
Claim 1

Document D6 represented the closest prior art. The claimed method differed from that of document D6 only in the automation of all method steps, but this was the general way forward for the skilled person and was therefore obvious.

If an aqueous buffer as the matrix for processing the external control nucleic acid was considered a further distinguishing feature having regard to document D6, this would nevertheless simply amount to an obvious alternative. No technical effect was associated with this feature compared to the teaching in document D6. Specifically, the alleged technical effects of an increased flexibility when dealing with samples of a different nature and a reduced variability associated with different inhibitors possibly present in human-plasma matrices was not associated with this feature compared to the disclosure in document D6. The reason

for this was that document D6 did not describe the use of human plasma or other biological specimens as the matrix for processing the external control nucleic acid. The disclosure in document D6 that control nucleic acids were spiked into clinical specimens as internal controls and into virus-negative specimens for determining the lower detection limit of the virus was irrelevant. The skilled person would not have turned to document D28 as this only concerned non-binding recommendations on quality control specimens (page 4, first sentence of section I).

In any case, the teaching in document D28 was superseded by that of document D21. The latter had been published later than document D28 and disclosed that water was a suitable matrix for processing the external control nucleic acid. The purpose of the assays in document D21 was to follow up particular viral infections (e.g. last sentence on page 4), and the external control served as a positive assay control. There was no difference in the assay steps, and nor was there any difference in the nature of the external control RNA used in document D21 compared to that used in the examples of the patent. Document D21 taught the skilled person that it was not necessary to use body fluids as the matrix for processing the external control nucleic acid in an assay of this type.

Aqueous buffers were commonly used in methods dealing with nucleic acids, including nucleic acid extraction, PCR and PCR control reactions. An aqueous buffer was thus - also for this reason - the most obvious matrix for processing the external control nucleic acid in such types of assay. The use of an aqueous buffer as the matrix for processing the external control nucleic

acids in the method of document D6 was hence obvious to the skilled person and not inventive.

Auxiliary request 1
Inventive step (Article 56 EPC) - claim 1

The addition of a second external control nucleic acid that was subjected only to the amplification step did not provide for a more reliable method, contrary to what had been argued by the respondents. It only allowed the pinpointing of the method step in which a possible problem detected by the first control nucleic acid occurred, i.e. it provided more information as to the correctness of, in particular, the amplification step. There was no synergistic effect of the two external controls. Each just assessed a different step of the claimed two-step method. A skilled person faced with the problem of pinpointing where in the procedure a possible problem lay would include a second external control in the second method step. Solving the technical problem in this manner was so obvious that neither this feature nor a specific incentive to include this feature had to be explicitly mentioned in any of the cited prior-art documents. Document D29 confirmed that external control reactions comprising control nucleic acids (positive controls) were routinely used to assess amplification efficiency.

Auxiliary request 2
Clarity (Article 84 EPC) - claim 1

The amendment to claim 1 led to an inconsistency in the claim. It was indicated in claim 1 as granted that "said at least one external control nucleic acid in an aqueous buffer" was "subjected to the steps following step a.", i.e. the external control nucleic acid

entered the process only after step a.. However, claim 1 of auxiliary request 2 required that "said" internal control nucleic acid be added to at least one external control nucleic acid in an aqueous buffer in step a.. This feature was inconsistent with the other features of the claim, in particular step e., and it was not clear which external control nucleic acid was used in all steps.

Auxiliary request 3
Amendments (Article 123(2) EPC) - claim 1

Lines 5 to 6 on page 11 of the application disclosed that the internal control nucleic acid was "also" added to "said" at least one external control nucleic acid after step d.. This sentence hence disclosed that the internal control nucleic acid was added not only to the fluid sample in step a., but also to the external control nucleic acid referred to in the other method steps after step d.. This disclosure was different from what was claimed, since the claim stipulated that said internal control nucleic acid should be added to at least one external control nucleic acid in an aqueous buffer, i.e. any external control nucleic acid.

Auxiliary request 4
Admittance (Article 13(1) RPBA 2020)

The respective objections raised under Article 84 EPC and Article 123(2) EPC against former auxiliary requests 3 and 4 filed in the opposition proceedings had already been submitted in the statement of grounds of appeal (points 131 to 141 on pages 23 to 25 of the statement of grounds of appeal). In reply to the appeal, the respondents maintained former auxiliary requests 3 and 4 as auxiliary requests 2 and 3, and

they did not respond to the objections by filing corresponding amendments. Current auxiliary request 4 was not filed until 23 March 2020 and was therefore not filed at the earliest opportunity. It should hence not be considered in appeal, pursuant to Article 13(1) RPBA 2020.

VIII. The respondents' arguments relevant to this decision are summarised as follows.

Main request (patent as granted)
Inventive step (Article 100(a) EPC and Article 56 EPC) - claim 1

The opposition division was right in that document D7 constituted the "closest prior art". If starting from document D6 as the closest prior art, the differences to the claimed methods were that the method of document D6 was not fully automated and that it did not use an aqueous buffer as the matrix for processing the external control nucleic acid.

The use of an aqueous buffer as the matrix for processing the external control nucleic acid was not obvious since the general teaching in the art was that control samples should be as close as possible to the analytical sample (see, e.g., last paragraph on page 9 of document D28).

This was also evident from document D6, in which the lower detection limit of the disclosed method was determined by spiking control RNA into virus-negative cerebrospinal fluid, i.e the same sample-type as one of the analytical samples (see last paragraph of right-hand column on page 3061). The provision of the "armoured" control RNA, i.e. an RNA protected from

degradation, as taught in document D6, made sense only if the control RNA was spiked into clinical specimens, as indeed disclosed in the last sentence before the "Material and Methods" section on page 3060 of document D6. Any modification of this process would jeopardise the results of the assay, as clearly follows from document D28.

The core idea of the invention of the patent was that an aqueous buffer was equivalent to plasma as the matrix for processing the external control nucleic acid (see Examples 1, 2 and 4 and Figure 2 of the patent), which provided the advantage of a more flexible test system. Document D6 lacked an incentive to change the disclosed assay, as the latter was already highly sensitive (see the title of document D6). The skilled person would not have turned to document D21, as the purpose of the control reaction described in the figure on page 3 of document D21 was to assess whether the sample contained an inhibitor (see "Interprétation" in the bottom right corner of the figure) and not to control the integrity of the reaction components. For this purpose, water had to be used because the ingredients of a buffer could also influence the test system.

The method of document D21 used a single type of nucleic acid ("IC" in the figure on page 3) as the internal and external control nucleic acid. This was different from the claimed method, in which two different control nucleic acids were used, namely a target-specific external control and a generic internal control (see pages 4 and 28 of the patent for a definition of the different controls). There was no incentive in document D6 to turn to document D21 at all or to use only the part of the method of document D21

that concerned water as the matrix for processing the external control nucleic acid and then choose an aqueous buffer instead of water.

Auxiliary request 1
Inventive step (Article 56 EPC) - claim 1

Adding an additional external control nucleic acid that was subjected only to the method steps following step d. allowed an assessment of the amplification and detection steps separately and therefore allowed the pinpointing of the step of the claimed method in which a possible problem was located. This resulted in a more reliable method. This second external control nucleic acid acted synergistically with the first external control nucleic acid since it allowed a cross-check between the two external controls. This feature was not disclosed in any of the cited prior-art documents and, therefore, none of the cited documents provided an incentive to include it in the method. Without any incentive, this feature involved an inventive step.

Auxiliary request 2
Clarity (Article 84 EPC) - claim 1

It was a clear and implicit feature that a part of the internal control nucleic acid was "also" added to the external control nucleic acid. The addition of the internal control nucleic acid also to the external control nucleic acid that was then processed in the subsequent method steps was hence clear.

Auxiliary request 3
Amendments (Article 123(2) EPC) - claim 1

Support for the additional feature of claim 1 was provided in lines 5 to 6 on page 11 of the application.

Auxiliary request 4
Admittance (Article 13(1) RPBA 2020)

Auxiliary request 4 was filed in response to the formalistic objections raised by the appellant in the grounds of appeal and in the appellant's submission dated 4 February 2020. The respondents merely did what the appellant requested and, therefore, auxiliary request 4 did not raise any new issues. It was not possible for every minor issue that had been criticised in the opposition proceedings to be picked up in a separate auxiliary request, as that would result in too many auxiliary requests from the beginning of the proceedings.

IX. The parties' requests relevant to the decision were as follows.

The appellant requested that the decision under appeal be set aside and the patent be revoked, and that auxiliary request 4 not be admitted.

The respondents requested that the appeal be dismissed, i.e. the patent be maintained as granted, or, in the alternative, that the patent be maintained on the basis of one of the sets of claims of auxiliary requests 1 to 3, all submitted with the statement of grounds of appeal, or on the basis of the set of claims of auxiliary request 4 submitted on 23 March 2020.

Reasons for the Decision

Main request (patent as granted)
Inventive step (Article 100(a) and Article 56 EPC) - claim 1

Closest prior art

1. The parties were in dispute as to whether document D6 or document D7 constituted the "closest prior art" for the claimed method. Both documents relate to methods for isolating, amplifying and detecting target nucleic acid molecule(s) in a fluid sample and the use of internal and external control nucleic acids in these methods. Documents D6 and D7 are therefore from the same technical field and directed to the same purpose as the claimed method. According to established case law (see, e.g., third paragraph of point 4.1.2 of T 1379/11 and the decisions cited therein), documents D6 and D7 are hence both suitable starting points for the assessment of inventive step by the problem-solution approach, and an inventive step can only be acknowledged if the claimed subject-matter is not obvious having regard to any prior art. On the other hand, if an inventive step is to be denied, it is sufficient to show that the claimed subject-matter is obvious starting from at least one piece of prior art, and in this scenario, the choice of starting point needs no specific justification (see, e.g., Catchword I of T 967/97).

2. It follows from the above that it is in fact irrelevant whether the technical teaching in one of these documents could be seen as being "closer" to the claimed subject-matter than the teaching in the other document (see, e.g., Catchword II and point 3.2 of the

Reasons of T 967/97). In particular, even if the method of document D6 had fewer features in common with the claimed method than the method of document D7, as argued by the respondents, this would not be a sufficient reason to disregard document D6 as the starting point in the assessment of inventive step. If the opponent (in this case, the appellant) relies, for the closest prior art, on a document which the patent proprietor (in this case, the respondents) considers more remote from the claimed subject-matter than another document, then this can be detrimental only to the opponent and not to the patent proprietor. Since the opponent considered that document D6 was the closest prior art, inventive step will be assessed starting from the disclosure of document D6.

Document D6 as closest prior art

3. Document D6 discloses an assay for detecting enterovirus (EV) in clinical specimens, including, *inter alia*, liquid samples, such as cerebrospinal fluid (CSF) and pleural fluid samples (see section "Clinical specimens" in left-hand column on page 3060), by reverse-transcription polymerase chain reaction (RT-PCR) in the presence of so-called "armoured" internal control (IC) RNAs, i.e. IC RNAs packaged into an MS2 phage core particle (see section "Construction of armored IC RNA control" in right-hand column on page 3060). The RNA isolation and purification steps are described in the last paragraph on page 3060 and comprise combining the clinical specimen with a mixture of silica particles and lysis buffer. Unlike the nucleic acid amplification and detection steps, which are performed in an Applied Biosystems 9600 thermocycler (see the sentence bridging left-hand and

right-hand column on page 3061), these steps are not directly and unambiguously described as automated.

4. Therefore, a distinguishing feature between the claimed method and the process disclosed in document D6 is that in the method as claimed the nucleic acid isolation and purification steps are also automated.

5. The claim also states that an "*external control nucleic acid in an aqueous buffer is subjected to the steps following step a.*" (see section I.). The method of document D6 included an external control reaction containing 500 armoured IC RNA copies that "*served as a control for the entire procedure*" (see section "Criteria for diagnostic RT-PCR" in right-hand column of page 3061) and was hence processed in the reaction mixture containing a lysis buffer and a silica particle suspension as described in the last paragraph of the right-hand column on page 3060 and then subjected to nucleic acid amplification and detection. Document D6 also discloses that the armoured IC RNA stock solutions were diluted in a Tris-based aqueous buffer to obtain a final IC RNA solution containing 100 control RNA copies per µl (see section "Dilution buffer for armoured RNA controls" in the right-hand column on page 3060 of document D6). Hence, for 500 control RNA copies, as contained in the external control reaction, 5 µl of the final IC RNA solution must be used (hereinafter "control RNA").

6. However, document D6 does not contain any information on whether or how these 5 µl of control RNA were further diluted for processing in the external control reaction mixture. In particular, document D6 discloses neither that the control RNA was only diluted in an aqueous buffer, as argued by the appellant, nor that a

control body fluid was used as the "matrix" for processing the external control RNA, as argued by the respondents. The last sentence of the first paragraph in the left-hand column of page 3060 of document D6 cited by the respondents in support of their argument refers to the addition of the control RNA to clinical specimens to monitor the nucleic acid extraction and amplification process "*for each specimen*". This sentence hence only refers to the internal control RNA added to the clinical samples and thus does not allow any conclusions to be drawn on the matrix used for processing the external control RNA.

7. The respondents also referred to the last paragraph of the right-hand column on page 3061 of document D6. This passage describes an experiment to determine the lower detection limit of the EV RT-PCR assay. It is only for this specific purpose that decreasing amounts of armoured control RNAs diluted in TSM buffer were spiked into 200 µl of EV-negative CSF. This experiment is thus different to, and independent from, the external control reactions described in the second full paragraph of the right-hand column of page 3061 and therefore neither explicitly nor implicitly discloses that a control CSF specimen was used as the matrix for processing the external control RNA.

8. Therefore, the type of matrix in which the external control RNA was processed is not known from the disclosure in document D6. The claimed method differs from that disclosed in document D6 in two features: in the automation of all steps of the method (see point 4. above), and in that the external control nucleic acids are processed "in an aqueous buffer". Neither the opposition division nor either of the parties

considered that these differences had a synergistic effect. They are therefore assessed separately.

Automation of all process steps

9. The mere automation of functions previously performed by human operators is in line with the general trend in technology and thus cannot be considered inventive (see the decisions summarised in Case Law of the Boards of Appeal of the European Patent Office, 10th edition, 2022 ("CLBA"), I.D.9.21.6). Indeed, the automation of each step in a process for isolating, amplifying and detecting target nucleic acids is commonly known in the art (see, e.g., the chapter "PRINCIPLES OF THE PROCEDURE" on pages 6 to 8 of document D7; see fourth paragraph on page 7 of document D21). The automation of the entire method of document D6 hence only requires routine modifications by the skilled person and thus does not involve an inventive step.

10. The respondents conceded that automation of any of steps of the method was commonly known to the skilled person, but argued that document D6 did not suggest a process in which all steps were automated. However, a suggestion in the closest prior art to automate all disclosed process steps is not required since - as outlined above (see point 9.) - automation is a general aim of the skilled person. The respondents did not even argue that the automation of the nucleic acid isolation and purification steps posed any problems to the skilled person. In actual fact, automated nucleic acid isolation and purification methods were already known (see, e.g., document D7, *supra*). No inventive step can therefore be acknowledged based on the automation of all method steps.

Aqueous buffer as the matrix for the external control reaction

11. To put the method of document D6 into practice, the skilled person has to select a matrix in which the external control RNA is processed, since document D6 is silent on this matter (see point 8. above). In view of this, the respondents' argument that document D6 lacked a motivation to change the disclosed "highly sensitive" assay is beside the point. The skilled person did not actually have to change the assay, but, instead, had to supplement the incomplete disclosure of document D6. While document D6 contains no information on the matrix, various options concerning how to process the external control RNA were theoretically possible, and the use of an aqueous buffer was one of these options.

12. It would be in line with common practice to carry out external control reactions in the same volume as the test reactions, especially in an automated method. The skilled person would therefore have considered adding the 500 control RNA copies present in 5 µl of the final control RNA solution (see point 6. above) to a liquid (a "matrix") to obtain the same volume as the clinical specimens. Since the control RNAs were diluted in an aqueous buffer to produce the final control RNA solution (see point 5. above; see the last part of the fourth paragraph in the right-hand column of page 3060), the use of this same buffer to further dilute the control RNA to obtain the appropriate assay volume constituted an obvious solution for the skilled person. Indeed, the appellant is right in that aqueous buffers are commonly used in methods dealing with nucleic acids. An aqueous buffer was hence, also for this reason, an obvious matrix for processing the external control RNA. Moreover, using the buffered control RNA solution directly or diluting it in water

instead of a buffer would also result in an "external control nucleic acid in an aqueous buffer". Therefore, based on the teaching in document D6 alone, the skilled person would have provided the external control RNA in an aqueous buffer for further processing in the external control reaction.

13. The respondents' argument that the skilled person would have necessarily used the biological specimen that was analysed for the nucleic acid of interest as the matrix in the external control reaction is not persuasive. Document D6 does not point towards this option in any way. The respondents referred to documents D7 and D28 in support of their argument. Document D7 proposes using virus-negative human plasma as the matrix in the external control reaction (see "TS(-)C" in the MPX Control Kit described on page 9 and in section B on page 14). Although this makes sense in the context of document D7, which is directed to detecting viral nucleic acids in human plasma (and human plasma only), using human plasma as the matrix for the external control reaction would not have made any technical sense in the method of document D6. Human plasma is not a clinical specimen analysed in document D6, and the control specimen should be as close as possible to the clinical specimen (see document D28 discussed in point 14. below). The choice of matrix for the external control reaction in document D7 is therefore not relevant for the method of document D6.

14. Document D28 recites the non-binding recommendations of the U.S. Food and Drug Administration (FDA) on the preparation and labelling of quality control material and explains that quality control material should simulate the composition of patient samples as closely as possible, in order to minimise matrix effects. It

refers to both animal and synthetic matrices (see the last paragraph on page 9). However, document D6 analysed many different types of specimens, including CSF, throat-swap samples, vesicle fluid samples, pleural fluid samples, broncheoalveolar lavage fluid samples, amniotic fluid samples and urine samples. To follow the recommendations in document D28, the skilled person would have needed to use an external control for each of the different types of specimen analysed in document D6. Document D6, however, teaches the use of a single external control reaction comprising control RNA. The skilled person would not therefore have considered the non-binding recommendations in document D28 when putting the teaching in document D6 into practice.

15. It is, moreover, also untrue that the prior art only taught the use of control clinical specimens as matrices in the external assay control reaction. This is evident, for example, from document D21, which discloses a process for isolating, amplifying and detecting a target nucleic acid in a body fluid (human blood), where an external control RNA is processed in water (see the figure on page 3 of document D21). Document D21 therefore teaches that the external control nucleic acid does not necessarily need to be processed in the same type of sample as the clinical specimens.

16. It is irrelevant to this teaching in document D21 that it is shown in a drawing of a product catalogue or that the same type of control RNA ("IC") is added to the external assay control reaction as the external control nucleic acid and to the sample as the internal control nucleic acid. The latter feature is, in any case, not excluded in the claimed method. It it also not relevant

that document D21 teaches how to assess whether the clinical sample contained an inhibitor by comparing the amplification results of internal and external control nucleic acids, since the external control reaction also serves as a control for the entire process, namely when it had a negative result. Thus, at the priority date of the patent, commercial products for the isolation, amplification and detection of nucleic acids were available that taught that external control nucleic acids did not need to be processed in a control clinical specimen.

17. Consequently, none of the respondents' arguments as to why the skilled person would necessarily have used a control clinical specimen in the method of document D6 when putting the teaching in document D6 into practice are persuasive. The claimed subject-matter does not involve an inventive step (Article 100(a) EPC in conjunction with Article 56 EPC).

Auxiliary request 1
Inventive step (Article 56 EPC) - claim 1

18. Claim 1 of auxiliary request 1 differs from claim 1 as granted in that the process comprises a further external control nucleic acid in an aqueous buffer that is only subjected to the steps following step d., i.e. the amplification steps. This feature is not disclosed in document D6 and therefore constitutes a further difference from the method of document D6.

19. The technical effect of this difference is that it allows an assessment of whether a possible problem in the method detected by the first external control nucleic acid has occurred in the nucleic acid amplification steps or in the preceding nucleic acid

isolation and purification steps. In conjunction with the first external control nucleic acid, it is hence possible to pinpoint in which of these two steps of the claimed method a problem might have occurred. However, this does not result in a more reliable method, as argued by the respondents, but more detailed error diagnostics. The objective technical problem may thus be formulated - as suggested by the appellant - as the provision of a method that allows the pinpointing of the step of the process in which an inhibition may have occurred.

20. The solution to this objective technical problem is the method as claimed. Since the method of document D6 already comprises an external control nucleic acid for the entire process, it would have been obvious to the skilled person that the inclusion of a second external control nucleic acid only for the amplification steps of the method would solve this technical problem.

21. The respondents argued that since none of the cited documents disclosed the use of a second external control nucleic acid, there was no motivation for the skilled person to include it in the method of document D6. This argument is, however, not convincing as the use of an external control nucleic acid in amplification reactions is part of the common general knowledge of the skilled person, who therefore does not require a specific motivation in document D6 or in any other document in order to solve the technical problem in this manner. The fact that external control nucleic acids were routinely used in the art for assessing the performance of an amplification process is, for example, evident from document D29 (see, in particular, page 113). The claimed method hence does not involve an inventive step (Article 56 EPC).

Auxiliary request 2
Clarity (Article 84 EPC) - claim 1

22. Claim 1 of auxiliary request 2 differs from claim 1 as granted in that it comprises an additional feature taken from the description, namely "wherein in step a.: adding said internal control nucleic acid to at least one external control nucleic acid in an aqueous buffer".

23. This feature is not clear (Article 84 EPC), since step a. only concerns the addition of an internal control nucleic acid to the body fluid sample suspected of containing a target nucleic acid. An external control nucleic acid is not subject to step a., as is also evident from the feature expressed in the claim that "said at least one external control nucleic acid in an aqueous buffer is subjected to the steps following step a.". Step a. of the claimed method is therefore now unclear.

24. Moreover, as the new feature refers to "at least one external control nucleic acid" and not to "said" external control nucleic acid, it is also not clear to which external control nucleic acid the new feature refers. The respondents' argument that it was clear from the wording of the claim that the feature meant that the internal control nucleic acid was "also" added to "said" external control nucleic acid, i.e. the same as is then subjected to the steps following step a., is not persuasive.

25. Consequently, auxiliary request 2 is not allowable for lack of clarity (Article 84 EPC).

Auxiliary request 3
Amendments (Article 123(2) EPC) - claim 1

26. Claim 1 of auxiliary request 3 differs from claim 1 as granted in that it comprises the additional feature "wherein after step d.: adding said internal control nucleic acid to at least one external control nucleic acid in an aqueous buffer".

27. According to the respondents, the basis for this feature is in lines 5 to 6 on page 11 of the application. However, this passage of the application discloses an embodiment wherein "*said internal control nucleic acid is also added to said at least one external control nucleic acid in an aqueous buffer in step a or after step d*". This passage therefore requires that the internal control nucleic acid "also" be added to "said" external control nucleic acid, i.e. the same external control nucleic acid referred to in the other steps of the claimed method.

28. These requirements are, however, not reflected in the wording of the claim, which uses neither the term "also" [added] nor the term "said" [external control nucleic acid]. It therefore allows for the addition of the internal control nucleic acid to an external control nucleic acid after step d., which is not the same external control nucleic acid that is subjected to steps e. and f., as recited in the claim (see also point 24. above). The application as filed, however, does not disclose this option. Claim 1 of auxiliary request 3 therefore contains subject-matter that extends beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

Auxiliary request 4
Admittance and consideration (Article 13(1) RPBA 2020)

29. Auxiliary request 4 was submitted on 23 March 2020, i.e. after the respondents had filed their reply to the appeal. Pursuant to Article 13(1) RPBA 2020, applicable pursuant to Article 24 and Article 25(1) RPBA 2020, submission of this auxiliary request therefore constituted an amendment of the respondents' case which was subject to the respondents' justification and the admittance of which was at the discretion of the board.

30. The respondents argued that auxiliary request 4 was filed in response to "*the additional (formalistic) objection*" raised against auxiliary request 3 in the appellant's submission and could not therefore have been filed earlier (see the sentence bridging pages 6 and 7 of the respondents' submission dated 23 March 2020).

31. However, in points 139 and 140 of the statement of grounds of appeal, the appellant had already raised objections under Article 123(2) EPC and Article 84 EPC with respect to the former auxiliary request 4 as submitted in the opposition proceedings. Auxiliary request 3 submitted in appeal is identical to this former auxiliary request 4. The appellant's objections under Article 84 EPC and Article 123(2) EPC were therefore not newly raised, but, instead, they had already been raised in the statement of grounds of appeal. Therefore, auxiliary request 4 dealing with these objections could and should have been submitted with the reply to the appeal.

32. The further argument of the respondents, namely that not every issue that was criticised in opposition

proceedings could be addressed in a separate auxiliary request since this would inflate the number of auxiliary requests presented in opposition proceedings, did not excuse the advanced stage of the appeal proceedings at which the request was submitted. The appellant had specifically maintained the objections raised under Article 84 EPC and Article 123(2) EPC against former auxiliary request 3 in their statement of grounds of appeal. The respondents could therefore have been expected to address these objections in their reply to the appeal, even if they considered them to be "formalistic".

33. The respondents hence did not submit any convincing argument that there had been exceptional circumstances, justified by cogent reasons, for filing auxiliary request 4 at such a late stage of the appeal proceedings. Auxiliary request 4 could thus not be admitted into the appeal proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated