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Datasheet for the decision of 20 November 2020

Case Number: T 1904/16 - 3.3.08

Application Number: 10713524.6

Publication Number: 2419527

IPC: C12Q1/68

Language of the proceedings: EN

Title of invention:
Method for the detection and characterization of a toxinogenic Clostridium difficile strain

Patent Proprietor:
Koninklijke Philips N.V.

Opponents:
Leeming, John Gerard
Nederlandsch Octrooibureau N.V.

Headword:
Assay for toxinogenic C. difficile strains/KONINKLIJKE PHILIPS

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

Keyword:
Admission of new evidence and a new line of argument submitted at oral proceedings due to a change of representative – (no)
Auxiliary request 2 - requirements of the EPC met - (no)

Decisions cited:
T 1585/05

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1904/16 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 20 November 2020

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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 1 June 2016 concerning maintenance of the European Patent No. 2419527 in amended form.**

Composition of the Board:

Chairman	B. Stolz
Members:	M. Montrone
	A. Bacchin

Summary of Facts and Submissions

I. The appeal lies against the decision of an opposition division to maintain European patent No. 2 419 527 in amended form. The patent was filed under the PCT and published as international patent application WO 2010/116290 (hereinafter the "patent application").

II. The opposition division held that the subject matter of claims 1 of the main request and of auxiliary request 1 lacked novelty and an inventive step, respectively, while auxiliary request 2 was found to comply with the requirements of the EPC.

III. With its statement of grounds of appeal, opponent 01 (hereinafter the "appellant") submitted that claim 1 of auxiliary request 2 as considered allowable comprised added subject-matter and lacked an inventive step starting from either one of documents D3 or D16 as closest prior art.

IV. In reply, the patent proprietor (hereinafter the "respondent") submitted counter-arguments on these issues.

V. In a communication pursuant to Article 15(1) RPBA, the parties were informed of the board's provisional, non-binding opinion.

VI. In reply, the appellant and opponent 02 announced that they would not be attending the oral proceedings.

VII. Oral proceedings before the board were held on 20 November 2020, in the absence of the appellant and of

opponent 02, as announced in their letters of 13 October and 13 November 2020, respectively.

VIII. Claim 1 of auxiliary request 2 reads:

"1. A method for the detection and characterization of a toxinogenic *Clostridium difficile* strain in a sample, wherein the following steps are performed,
a. a sample is provided for;
b. in a multiplex PCR assay,

i the sample is analyzed with respect to the presence or absence of the cytotoxin tcdB gene;

ii the sample is analyzed with respect to the presence or absence of the following deletions in the tcdC gene,

a) an 18 bp deletion in SEQ ID NO. 1 from nucleotide 330 to nucleotide 347;
b) a 39 bp deletion in SEQ ID NO. 1 from nucleotide 341 to nucleotide 370;
c) a single nucleotide deletion at position 117 of SEQ ID NO. 1, wherein the multiplex PCR amplification is quantitative real-time PCR, wherein

the sample is additionally analyzed with respect to the presence or absence of the enterotoxin tcdA gene 1.8 kb deletion, wherein the sample is additionally analyzed with respect to the presence or absence of the binary toxin cdtA and/or cdtB, wherein

a. if the tcdB gene sequence is present, the tcdA deletion is absent, neither the single nucleotide deletion at position 117 of SEQ ID NO. 1 is present, nor the 18 bp deletion is present, nor the 39 bp

deletion is present, then the sample is scored as toxinogenic *Clostridium difficile*,

b. if the tcdB gene sequence is present, the tcdA deletion is absent, the single nucleotide deletion at position 117 of SEQ ID NO. 1 is present, the 18 bp deletion is present, and the cdtA/B binary toxin gene is present, then the sample is scored as a ribotype 027 *Clostridium difficile* strain,

c. if the tcdB gene sequence is present, the tcdA deletion is present, neither the single nucleotide deletion at position 117 of SEQ ID NO. 1 is present, nor the 18 bp deletion is present, nor the 39 bp deletion in SEQ ID NO. 1 from nucleotide 341 to nucleotide 370 is present, and the cdtA/B binary toxin gene is absent, then the sample is scored as a ribotype 017 *Clostridium difficile* strain and

d. if the tcdB gene sequence is present, the tcdA deletion is absent, the 39 bp deletion in SEQ ID NO. 1 from nucleotide 341 to nucleotide 370 is present, and the cdtA/B binary toxin gene is present, then the sample is scored as a ribotype 078 *Clostridium difficile* strain,

wherein the multiplex amplification reaction is done in a closed system in the presence of fluorescent indicators in the reaction mixture(s), the fluorescent indicators being capable of generating an optical signal related to a presence and/or quantity of each amplicon in the amplification reaction and monitoring the optical signal of the fluorescent indicators in the amplification reaction, wherein the closed system gives an optical output for the user, indicating the scoring assignment".

IX. The following documents are referred to in this decision:

D2: Martin H., *et al.*, Journal of Clinical Microbiology, 2008, Vol. 46(9), 2999-3004;

D3: Persson S., *et al.*, Clinical Microbiology and Infection, 2008, Vol. 14, 1057-1064;

D15: A press release dated 9 November 2008 detailing the release of the Xpert™ *C. difficile* assay;

D16: Product brochure for the diagnostic medical device Xpert™ *C. difficile*, dated December 2008;

D25: van den Berg R.J., *et al.*, Journal of Clinical Microbiology, 2004, Vol. 42, 1035-1041;

D32: Huang H., *et al.*, Journal of Clinical Microbiology, 2009, Vol. 47(11):3729.

X. The appellant's submissions, insofar as relevant to the present decision, may be summarised as follows:

Auxiliary request 2 (set of claims considered allowable by the opposition division)

Added subject-matter - claim 1

The method of claim 1 comprised added subject-matter.

Claim 1 specified that a *Clostridium difficile* (*C. difficile*) sample was analysed by a multiplex quantitative real-time PCR (hereinafter "multiplex qPCR") for the presence or absence of:

the cytotoxin tcdB gene,
the deletions of 18 base pairs (bp), 39 bp, or a single nucleotide at position 117 in the tcdC gene,
and additionally, by any other suitable method for the presence or absence of:
the enterotoxin tcdA 1.8kb deletion, and
the binary toxin cdtA and/or cdtB.

Claim 4 as originally filed was cited as basis for the amendment in claim 1. This claim specified that in the context of *inter alia* analysing the presence/absence of all three deletions in the tcdC gene (deletions of 18 bp, 39 bp, and of a single nucleotide at position 117), the presence/absence of both binary toxin genes cdtA and cdtB must be analysed too (see part (f)).

The method of claim 1 selected for the analysis all three tcdC gene deletions from claim 4 as originally filed. However claim 1 was not limited to the detection of both binary toxin genes (cdtA and cdtB) too, but allowed one of the toxins to be determined only.

Since claim 4 as originally filed required the concomitant assessment of *inter alia* all three tcdC gene deletions and both binary toxin genes (cdtA and cdtB), but not only one of them, claim 1 comprised added subject-matter.

Inventive step - claim 1

Documents D3 and D16 represented the closest prior art since both documents were directed at the detection and characterisation of toxinogenic *C. difficile* strains, i.e. the purpose underlying the claimed method.

Document D3 described the use of a multiplex PCR assay for the characterisation of *C. difficile* strains, including the evaluation of their pathogenic profile. A 5-plex PCR assay was disclosed for detecting the toxin genes tcdA, tcdB, cdtA, cdtB, and as a control 16s rDNA. This assay offered a one-step, rapid and specific screening of toxin genes in *C. difficile* (see abstract, page 1058, column 2, fourth paragraph). Document D3 reported that various deletions in the tcdA and tcdC genes were additionally investigated because their contribution to *C. difficile*'s pathogenicity was known. Several tcdC deletion mutants were disclosed on page 1061, right column, second paragraph, including a 18 bp, a 39 bp and a single nucleotide deletion at position 117. Various tcdA gene deletions were mentioned on page 1062, left column, first paragraph of document D3, including a deletion of 1.8 kb. Thus, the document mentioned all of the genes including the deletion mutants cited in claim 1. Document D3 was silent on using a multiplex qPCR assay, and its use for detecting at least the three specific tcdC gene deletions and the tcdB gene mentioned in claim 1.

The claimed method differed from the method of document D3 in the selection of the marker genes to be analysed, and in the way in which they were analysed.

Since in the claimed method no interrelationship existed between the specific markers and the format for their analysis, the claimed method provided separate solutions to these two partial problems.

The claimed method was an obvious solution to these problems. Document D3 mentioned all of the markers to be analysed for completely typing pathogenic *C. difficile* strains.

Furthermore, document D16 disclosed a multiplex qPCR assay to detect in *C. difficile* samples genes encoding tcdB, the binary toxins cdtA, cdtB, and a single nucleotide deletion at position 117 in tcdC. The assay was used for the identification of the so called "*027 ribotype*" strain. The incorporation of the two further tcdC deletions cited in claim 1 into a multiplex assay was a matter of routine for the skilled person.

The claimed method differed from that in document D16 in testing for additional deletions in the tcdC and the tcdA genes, which were known to be associated with pathogenic *C. difficile* strains (see documents D2 or D3). The problem to be solved was the provision of a modified assay to expand the range of *C. difficile* types to be determined. The solution to this problem was obvious, i.e. the inclusion in the assay of the determination of the presence/absence of two further tcdC gene deletions and one tcdA gene deletion. The skilled person in light of the rationale of the assay in document D16 was prompted to consider other genes allowing the full characterisation of pathogenic *C. difficile* strains. The relevance of analysing the tcdC and tcdA deletions mentioned in claim 1 to achieve this purpose was known from the prior art (see documents D2 and D3), and their incorporation in the assay a matter of routine.

XI. The respondent's submissions, insofar as relevant to the present decision, may be summarised as follows:

Auxiliary request 2 (set of claims considered allowable by the opposition division)

Added subject-matter - claim 1

The method of claim 1 had a basis in claims 1 to 3 and 5 as originally filed. Furthermore, the claimed method is disclosed on page 17, lines 7 to 20 in conjunction with the disclosure on page 17, line 21 to page 18, line 11 of the patent application.

Admission of new evidence and a new line of argument concerning the public availability of document D16

Document D16 was no prior art document under Article 52(4) EPC. Although the document mentioned a date for the revised version C ("*Rev. C, December 2008*") of a product brochure for the "*Xpert™ C. difficile Assay*", this date was not equivalent to a publication date of the assay, nor indicated, by applying a balance of probability, that the assay itself was made available to the public on that date. A date for the public availability of the assay in document D16 was also not derivable from documents D15 and D32. To substantiate the argument, the submission of documents retrieved by the "*Wayback machine*" from the Internet was offered.

Inventive step - claim 1

Document D3 disclosed a multiplex PCR for detecting the tcdA, tcdB, cdtA, cdtB genes in toxinogenic *C. difficile* strains. The document further disclosed the sequencing of various tcdC deletions in *C. difficile*

strains. However, document D3 was silent on the use of multiplex qPCR for characterising pathogenic *C. difficile*. Likewise the knowledge that different *C. difficile* ribotypes possessed different toxin genes and deletion mutants thereof did not teach the skilled person how to determine by multiplex qPCR the tcdB gene and the three tcdC deletions referred to in claim 1.

Document D16 disclosed a multiplex qPCR cartridge-based system for identifying the *C. difficile* ribotype 027 in a sample by determining the presence/absence of the tcdB, cdtA and cdtB genes, and a point mutation at position 117 in the tcdC gene. The claimed method differed therefrom by using multiplex qPCR at least for the determination of two further tcdC gene deletions, and in that a 1.8 kb tcdA gene deletion was determined. This allowed the identification of more *C. difficile* strains. The technical problem to be solved was the provision of an improved method for detecting and characterising toxinogenic *C. difficile* strains.

The characterisation of toxinogenic *C. difficile* ribotypes by the toxin genes tcdA, tcdB, cdtA and/or cdtB, including various deletions within the tcdC and tcdA genes was known in the art. Moreover, the sequences encoding these genes or deletion mutants were known in the art, including methods for designing appropriate primers for their amplification.

However, the skilled person starting from the cartridge system of document D16, in view of the technical problem identified above, was confronted with several technical hurdles. The document did not disclose any information about the primer sequences used for amplifying the marker genes. These sequences could only be obtained by opening the cartridge followed by

reverse engineering. While this was not impossible, the skilled person knew that the multiplex system of document D16 was sensitive and validated with the primer set provided in the cartridge. Thus the skilled person would have refrained from modifying the assay described in document D16, since it warned explicitly that modifications "*may alter the performance of the test*" (see page 8, first paragraph under the heading "*Limitations*").

Even if the skilled person would have tried to modify the assay of document D16, there was no teaching available how he/she could determine three deletions within the tcdC gene by multiplex qPCR without interfering with the sets of primers used for the other marker genes. The prior art relied on sequencing methods for analysing the presence/absence of multiple deletions within the tcdC gene. Since this was a different method, the use of multiplex qPCR was not obvious. Lastly, the skilled person would have arrived at subject-matter falling within the claimed method only by combining three documents. The 18 and 39 bp deletions of the tcdC gene were disclosed in documents D2 and D3, while the 1.8 kb deletion of the tcdA gene was disclosed in document D25. Thus, starting from the closest prior art method the skilled person would have arrived at the combination of features set out in claim 1 either with undue burden in view of the technical hurdles mentioned above, or with hindsight only.

XII. The appellant requested that the decision under appeal be set aside and the patent be revoked.

XIII. The respondent requested that the appeal be dismissed.

Reasons for the Decision

Auxiliary request 2 (set of claims considered allowable by the opposition division)

Added subject-matter - claim 1

1. Claim 1 is directed to a method for the detection and characterisation of a toxinogenic *Clostridium difficile* (*C. difficile*) strain in a sample. The claim requires that the sample is analysed by a multiplex quantitative real-time PCR ("multiplex qPCR") assay for the absence or presence of:

(i) the cytotoxin tcdB gene,

(ii) specific deletions in the tcdC gene, of
(a) 18 bp in a first defined region in SEQ ID NO. 1,
(b) 39 bp in a second defined region in SEQ ID NO. 1, and
(c) a single deletion at position 117 of SEQ ID NO. 1,

and in that the sample is additionally analysed for the absence or presence of:

(iii) a 1.8 kb deletion in the enterotoxin tcdA gene,

(iv) the binary toxin cdtA **and/or** cdtB (emphasis added).

Depending on the absence/presence of the marker genes and/or their specific deletions indicated above, the *C. difficile* strain is scored as toxinogenic (i.e. as toxin-producing), or as belonging to one of the specific ribotypes 027, 017 or 078. The multiplex

amplification reaction is performed in a closed system in the presence of fluorescent labels generating optical signals. The optical output of the system indicates to the user the scoring assignment.

2. The appellant submitted that the patent application provided a basis for the claimed method wherein the sample was analysed *inter alia* for the presence or absence of **both** binary toxins cdtA and cdtB (i.e. the "**and**" alternative, see point (iv) above), but not for one of the two toxins only (i.e. the "**or**" alternative).

3. Accordingly, the sole question to be answered under added subject-matter is whether the analysis of either cdtA or cdtB in the claimed method is directly and unambiguously derivable from the patent application.

4. The method of claim 3 as originally filed is dependent on claims 1 and 2 as originally filed. Its subject-matter concerns the additional analysis of the presence or absence of the binary toxin "*cdtA and**/or** cdtB*" (emphasis added). In other words, it discloses the contested "or" alternative set out above. Claim 3 as originally filed in conjunction with the methods of claims 1, 2 and 5 as originally filed is identical to the presently claimed method, except for an additional reference to the specific "*36 bp deletion*" and "*54 bp deletion*" within the tcdC gene (see claim 1 step b.ii as originally filed).

5. The relevant issue is thus whether or not the omission of the "*36 bp*" and the "*54 bp*" deletions of the tcdC gene in present claim 1 from the list of five tcdC deletions in original claim 1 results in added subject-matter by generating a combination of genetic markers

that is not directly and unambiguously derivable from the patent application.

5.1 Claim 1, step b.ii as originally filed states with regard to the five cited tcdC gene deletions that the "*presence or absence of one or more*" of these deletions is analysed. In the board's view, the term "*one or more*" in this context implies to the skilled person that all five deletions are equally preferred and suitable as markers in the claimed method. In other words, the properties of the individual tcdC gene deletions do not differ from the properties of the group of five deletions.

5.2 In present claim 1, the three cited tcdC gene deletions result from the omission of two further tcdC gene deletions from a single list of five. The properties of the remaining three deletions in present claim 1 do not differ from those of the five deletions in claim 1 as originally filed.

5.3 Furthermore, claim 4 as originally filed specifically limited the group of deletions to be assayed in the tcdC gene to the three deletions referred to in items a) to c) of step b.ii in present claim 1 (i.e. an 18 bp, 39 bp, and a single deletion at position 117 of SEQ ID NO. 1). This also points the skilled person to the method of present claim 1.

6. The appellant submitted that the method of claim 4 as originally filed provided the sole basis in the patent application for selecting the three tcdC gene deletions referred to in present claim 1. Claim 4 as originally filed required however that both genes of the binary toxin (cdtA and cdtB) be analysed too, not only one of them.

7. The board is not convinced by these arguments. As set out above, claims 1 to 5 as originally filed provide a direct and unambiguous disclosure of the subject matter of claim 1. Therefore claim 1, and hence auxiliary request 2, complies with Article 123(2) EPC.

Claim interpretation - claim 1

8. As mentioned above, the method of claim 1 is directed to the detection and characterisation of a toxin-producing *C. difficile* strain by using a multiplex qPCR assay at least for the determination of the tcdB gene (coding for a cytotoxin), and three specific deletions within the tcdC gene (a presumed negative regulator of the tcdA and tcdB toxin genes; see document D3, column 1, last paragraph).

8.1 Multiplex in this context means that the qPCR assay determines in parallel the different marker genes in a single sample.

8.2 Claim 1 further requires that the strain be assessed for additional marker genes, i.e. a 1.8 kb tcdA gene deletion (encoding an enterotoxin), and the cdtA and/or cdtB genes (encoding a binary toxin). Claim 1 does not define the type of assay to be used, which means that any suitable detection assay is encompassed, for example, multiplex qPCR, partial sequencing, etc.

8.3 Thus, the method of claim 1 requires that the presence or absence in a *C. difficile* sample of at least the tcdB gene and three specific tcdC gene deletions be assayed by multiplex qPCR, while the other markers (a tcdA gene deletion, cdtA and/or cdtB genes) may either be assayed by multiplex qPCR too or by any other

suitable method. The claimed method does not require that the truncated tcdA gene and the cdtA/B genes are necessarily analysed in separate/different assays. The claim encompasses their analysis in the same assay as used for the tcdB and tcdC genes. On this point, the board disagrees with the opposition division's interpretation of the claim (see point 17.2.3 of the decision under appeal).

8.4 The multiplex qPCR reactions of claim 1 are carried out in a "*closed system*" in the presence of fluorescent dyes. Since this system is undefined, any closed system falls within claim 1, for example, a cartridge-based system (see page 1, seventh paragraph of document D16). Based on the optical outputs, i.e. signals, the strains are scored as toxin-producing (pathogenic) in general, or as belonging to a specific pathogenic *C. difficile* ribotype (i.e. subtype).

Admission of new evidence and a new line of argument concerning the public availability of document D16

9. During the oral proceedings and for the first time in appeal proceedings, the appellant objected to the public availability of document D16 before the priority date of the patent in suit (7 April 2009).

10. Document D16, a product brochure of the company Cepheid AB, dated December 2008 ("*71001617 Rev. C, December 2008*", see e.g. last line on front page) and concerning the Xpert™ *C. difficile* assay, was filed by the appellant (then opponent 01) with the notice of opposition.

11. In opposition proceedings the respondent (then patent proprietor) contested, albeit without providing

counter-evidence, that document D16 constituted prior art under Article 54(2) EPC as it was not clear whether the document was available to the public before the priority date of the patent. The printed date, December 2008, apparently referred to a revised version ("*Rev. C*").

12. According to the minutes of the oral proceedings (see point 2.3.3) this issue was discussed before the opposition division and decided (see point 6 of the decision) in the sense that document D16 was published before the priority date of the opposed patent. The opposition division considered that the press statement published on 9 November 2008 (see document D15, page 1, line 3 and first paragraph) was a confirmation that on that date the release of the Xpert™ *C. difficile* assay into the European market took place. This conclusion was further corroborated by a report on the experimental use of the Xpert™ *C. difficile* assay (see document D32, abstract), published in September 2009 but submitted for publication on 30 June 2009, so that the relevant study must have been performed before the date of priority.

13. At the oral proceedings, the respondent raised doubts as to the public availability of document D16. It held that the experimental use of the product Xpert™ *C. difficile* was first mentioned in document D32, published in September 2009, and thus after the priority date. The press release published on 9 November 2008 (see document D15) was no proof of the product's actual availability. Based on a search using the Wayback Machine, which was carried out in preparation of the oral proceedings in appeal, it seemed that a text on the Xpert™ *C. difficile* assay was first made available in the web in March 2010. The

respondent was prepared to submit new evidence, namely three screenshots allegedly confirming this statement. It thus followed that the appellant had not discharged its burden of proof, since it did not establish to the applicable standard, in the present case the balance of probabilities, that it was more likely than not that document D16 was made available before the priority date.

14. This issue could not be addressed by the appellant, as it was not represented at the oral proceedings.

15. The board regards the respondent's submissions at the oral proceedings as an amendment to the party's appeal case made after notification of the summons to oral proceedings. In principle such an amendment is not to be taken into account by the board unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned (Article 13(2) RPBA 2020). It is recalled that under Article 12(2) RPBA 2007, which substantially corresponds to Article 12(3) RPBA 2020, the statement of grounds of appeal and the reply shall contain a party's complete case. Together with the appealed decision the statement of grounds of appeal and the reply to it determine the subject-matter of an appeal (Article 12(1) RPBA 2020). The purpose of this provision, under both rules of procedure, is to ensure fair proceedings for all concerned and to enable the board to start working on the case on the basis of the parties' complete submissions. Thus, a submission made in opposition proceedings which is not further pursued in appeal is in principle not within the scope of the appeal proceedings, unless the board exercises its discretion to admit it. The discretion is exercised in view of *inter alia* the complexity of the new subject-matter

submitted, the reason for the amendment, the current state of the proceedings and the need for procedural economy.

16. In the board's view, the following facts are of relevance for the present case:

16.1 When the respondent filed its reply to the statement of grounds of appeal at the outset of the appeal proceedings, it made its "complete appeal case" within the meaning of Article 12(2) RPBA 2007. Despite having the opportunity at that stage, it did not object to the date of public availability of document D16. It rather chose to present arguments on the merit of this document, in order to rebut the lack of inventive step attack without prior contesting its status as prior art document.

16.2 It can therefore be assumed that the respondent's appeal case was made on the implicit acceptance of document D16 as state of the art pursuant to Article 54(2) EPC.

16.3 The board does not see any cogent reasons why the new facts and evidence could be filed at the latest possible stage of the appeal proceedings only, i.e. at the oral proceedings. Document D16 was a relevant document since the outset of the appeal proceedings. Neither the board nor the appellant have in the meantime raised a new factual or legal situation, which could justify the late filing of an objection to its date of availability, nor can this objection be regarded as a normal procedural development. This issue should have been brought up immediately in reply to the statement of grounds of appeal (back in 2017), or at the latest in advance of the oral proceedings after the

board issued its provisional opinion. It would have also been possible for the respondent to file an appeal against these findings of the opposition division, since he was clearly negatively affected by them. To admit these submissions into the proceedings would be against the principle of fair proceedings, since the respondent's conduct led the appellant to believe that this objection was no longer matter of discussion. Furthermore, it would be contrary to procedural economy, since its admission would require additional discussions, which could not be done without adjournment of the proceedings, especially if considering the absence of the appellant.

16.4 Contrary to the respondent’s argument, the belated submissions are also not justified by the change of representative shortly before the oral proceedings, namely on 16 September 2020. In this respect the board finds that under normal circumstances a change of representative is a fact which belongs to the sphere of the party affected and, being extraneous to the proceedings, it cannot influence the decision whether a procedural action is timely made. On the contrary, a new representative is bound by the procedural actions performed by his predecessor and continues the proceedings from the point they had reached when he takes over (see also T 1585/05, point 5. of the reasons). Thus, a change of representative is as such not a sufficient justification for late filings (cf. Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019 (hereinafter "Case Law"), V.A.4.8.2) and - under the present circumstances where the issue to be overcome was raised at the outset - it is certainly not a cogent reason in the sense of Article 13(2) RPBA 2020.

17. On account of these considerations, the board exercised its discretion not to take into account the amendment of the respondent's appeal case concerning the public availability of document D16 at such a late stage of the appeal proceedings. Document D16 was regarded as state of the art for the patent at stake.

Inventive step - claim 1

Closest prior art

18. The appellant considered that documents D3 or D16 represented the closest prior art. This was not contested by the respondent.

19. It is established case law that the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common (see Case Law, I.D.3.1.).

20. Document D3 concerns a study of *C. difficile* strains derived from clinical isolates. A multiplex PCR assay in combination with partial sequencing and standard PCR is used to analyse the strains for the absence/presence of various toxin marker genes.

20.1 In a first assay, samples are analysed by a multiplex PCR method for the potential presence of the four toxin genes tcdA, tcdB, cdtA and cdtB, and that of a control DNA (i.e. "*5-plex PCR*"). Primers amplify the genes and their known variants. The obtained amplicon sizes are distinguishable on agarose gels (see page 1059, Table 1 and column 1, last paragraph to column 2, first paragraph). The 5-plex PCR assay determines the

presence/absence of the marker genes at the end of the reaction, not in real-time, i.e. during the reaction.

20.2 In a second assay, the tcdC gene (a presumed negative regulator of the major toxins TcdA and TcdB, see page 1061, column 1, third paragraph) is amplified by PCR and then partially sequenced to find "*previously identified inactivation features*", for example, C-terminal deletions, including a 18 bp and 39 bp deletion and a single nucleotide deletion at position 117, characteristic for the "*Canadian 027 strain*" (see page 1061, column 2, second paragraph).

20.3 In a third assay, a PCR detects the presence/absence of tcdA gene deletions (see page 1058, column 2, fourth and fifth paragraph, Table 1, page 1059). Document D3 states that: "*Only one type of tcd A deletion of 700 bp (estimated after agarose gel electrophoresis) was observed, by use of the primer system originally developed by Kato et al. (1999). This primer system amplifies a stretch of 2535 bp if no deletion is present, and, in their study, truncated genes were reduced by 1821 bp, due to two different 3'-end deletions. This primer system has also been used by van der Berg et al. (2004), who observed deletions of 1.8, 1.7 and 0.8 kb*" (page 1062, column 1, first paragraph, emphasis added). In other words, the primer system detects the presence of several tcdA gene deletions, including the 1.8 kb deletion referred to in claim 1.

20.4 All strains that are positive for the binary toxin cdtA/cdtB are then ribotyped by PCR (see page 1060, column 2, second paragraph, and Table 2).

20.5 Document D3 further states that the "*5-plex PCR method offers a one-step, rapid and specific screening method*

for C. difficile toxin genes", and that "*toxin gene profiling, together with deletion studies in tcdA and tcdC, may allow an evaluation of the pathogenic potential of C. difficile*" (see abstract).

20.6 Consequently, document D3 reports a set of assays that determine the pathogenicity and the ribotype of *C. difficile* samples based on the presence/absence of the marker genes referred to in claim 1, but is silent on the use multiplex qPCR for this purpose.

21. Document D16 describes the "*Xpert™ C. difficile Assay*" for detecting toxin-producing *C. difficile* strains, in particular a presumed "*027-NAP1-BI*" strain (see page 3, third to eight paragraph, page 7, second and third paragraph), i.e. the 027 ribotype cited in claim 1. The assay is cartridge-based (i.e. is "*closed*"), and uses a multiplex qPCR for determining the tcdB gene, the binary toxin genes cdtA/cdtB, and a nucleotide deletion at position 117 of the tcdC gene (see page 3, last paragraph, page 7, lines 7 and 8).

21.1 Accordingly, the document discloses a multiplex qPCR assay for the detection of various toxin marker genes, in the diagnosis of pathogenic *C. difficile* strains, including a specific ribotype.

21.2 Although document D16 mentions that the tcdA gene is one of "*C. difficile's primary virulence factors*" and that "*deletions in the regulatory gene tcdC*" are associated with various "*hypervirulent*" ribotypes (see page 3, second full paragraph), the "*Xpert™ C. difficile Assay*" does not include primers for detecting tcdA, a 1.8 kb deletion mutant thereof, or for tcdC gene deletions, except for the deletion at position 117.

22. Thus the methods in documents D3 and D16 are both directed to the detection and characterisation of toxinogenic *C. difficile* strains, i.e. the purpose of the claimed method.

23. As regards the distinguishing features between the methods, the following is relevant.

23.1 The claimed method differs from document D3 in using a multiplex qPCR in a "*closed system*", at least for the analysis of the tcdB gene, and the specific deletions within the tcdC gene. In essence a single method, i.e. multiplex qPCR, may be sufficient for the analysis of *C. difficile* strains. Document D3 is silent on using qPCR, let alone closed systems. This results in a faster detection of toxinogenic *C. difficile* strains.

23.2 The claimed method differs from the assay of document D16 in assessing the presence/absence of three more gene markers, at least two of them (the 18 bp and 39 bp deletions in the tcdC gene) by multiplex qPCR, and the third one (a 1.8 kb tcdA gene deletion) by the same or a different assay. Thereby more than one toxinogenic *C. difficile* ribotype can be detected and characterised.

24. In light of these differences, the board considers, in line with the case law, that document D16 represents the closest prior art for the claimed method since it shares more of the relevant technical features with the claimed method, in particular a multiplex qPCR assay.

25. The technical problem to be solved by the claimed method is defined as the provision of an improved method for the detection and characterisation of toxinogenic *C. difficile* strains in a sample.

26. It is uncontested that the claimed method provides a solution to this problem.

Obviousness

27. It remains to be assessed whether or not the skilled person starting from the closest prior art method and faced with the problem defined above would have modified the multiplex qPCR assay to arrive at the claimed method in an obvious manner.

28. Document D16 discloses that *C. difficile* outbreaks are accompanied in human patients by diarrhoea and severe life-threatening pseudomembranous colitis. It further mentions that *C. difficile*'s primary virulence factors are the enterotoxin A and cytotoxin B (encoded by the tcdA and tcdB genes), and that some strains produce in addition a binary toxin (encoded by the cdtA and cdtB genes). Moreover, some hypervirulent strains of various ribotypes are associated with deletions in the regulatory gene tcdC (see page 3, second full paragraph, headed "*Summary and Explanation*"). Lastly, document D16 states that the multiplex qPCR assay allows a "*rapid identification and differentiation of Toxin B, and Binary Toxin from appropriate stool specimens*", and identifies toxin-producing *C. difficile* strains, including a "*presumptive*" ribotype 027 (see page 3, first and fifth full paragraph).

29. In the board's view, the skilled person would derive from these paragraphs in document D16 that various pathogenic *C. difficile* ribotypes cause severe infections and that combinations of different virulence factors are associated with these strains. The method disclosed in document D16 allows the detection of one

specific pathogenic strain only. In view of this apparent limitation of the method and the need to understand the full cause of the infection, the skilled person would derive the motivation from the teaching of document D16 to modify the method so that more than one pathogenic *C. difficile* strain can be characterised.

30. Since the motivation to modify the closest prior art method is derivable from document D16, the question arises whether or not the skilled person had a reasonable expectation of success in arriving at subject-matter falling within the scope of claim 1.

31. It is uncontested that the sequences of the tcdB, cdtA/cdtB genes, and the respective deletions in the tcdA and tcdC genes were well known to the skilled person before the priority date of the patent in suit. This included their use as genetic markers for characterising pathogenic *C. difficile* strains, including the 027, 017 and 078 ribotypes (see e.g. document D2, abstract and Table 1; document D3, abstract and page 1061, column 2, first paragraph; document D25, abstract and Tables 3 and 4). Likewise it is uncontested that the design of primers for the amplification of these markers, and the use of a multiplex qPCR assay for detection purposes was a matter of routine at the relevant date. It is also not contested that the skilled person by opening the cartridge disclosed in document D16 and performing a reverse engineering would have received the sequence information about the primer sets used therein.

32. The respondent submitted that the skilled person would have refrained from modifying the assay in document D16 in view of the warning that modifications to the "*procedures may alter the performance of the test*" (see

page 10, first paragraph), and the technical problems to be encountered.

32.1 While the board agrees with the respondent that the skilled person would have refrained from modifying the cartridge of document D16 *per se* and the reagents contained in it, this holds not true for modifying a multiplex qPCR assay as such to expand its potential detection range. Document D16 demonstrates that this type of assay is successfully used in rapidly detecting toxin-producing *C. difficile* strains, including a presumptive 027 ribotype.

32.2 Arguments why the modification of a multiplex qPCR assay in general might have imposed technical problems for the skilled person have not been submitted by the respondent. The respondent submitted, however, that there was no teaching available how the skilled person could have implemented the detection of the three tcdC gene deletions referred to in claim 1 into a multiplex qPCR assay without disturbing the detection of the other markers disclosed in document D16. This would have resulted in undue burden.

32.3 As set out above, it is undisputed that the sequence of the tcdC gene including its deletions were known at the priority date of the patent in suit, as were tools to design amplification primers. Thus, the skilled person by applying routine skills would have designed appropriate primers for each tcdC gene deletion so that it is amplified by multiplex qPCR.

32.4 Moreover, indications are lacking from the prior art that these tcdC gene deletion primers might interfere either with their own amplifications or the amplifications of the various toxin genes cited in

document D16. Nor are indications derivable from the patent in suit that point to technical problems associated with the selection and use of appropriate primers. Notably, the patent neither discloses specific primers nor any experimental data. This implies that the inventors did not expect and have not encountered any problems in finding appropriate primers to be used in a multiplex qPCR assay for the marker genes cited in claim 1. It is established case law that any party raising an issue carries the burden of proof. In the absence of such evidence, the board is not convinced by the respondent's arguments that the skilled person could only with undue burden find primers for a single multiplex qPCR that also detects the three tcdC gene deletions cited in claim 1.

33. In a further line of argument, the respondent submitted that the selection of the specific marker genes as referred to in claim 1 and their detection by multiplex qPCR was based on hindsight, since it required the combination of more than two prior art documents.

33.1 The board is not convinced by this argument either. Firstly, as set out above, all of the marker genes referred to in claim 1 were known from the teaching of document D3. This includes their association with specific pathogenic *C. difficile* strains (see documents D3 and D16, above).

33.2 Secondly, the combination of the analysis by multiplex qPCR of the marker genes mentioned in document D16 with the analysis of the marker genes mentioned in document D3 leads directly to the analysis of the marker genes according to claim 1 (see above). As set out above, technical reasons preventing the skilled person from incorporating into a multiplex qPCR assay primers

detecting these marker genes are neither apparent from the prior art nor from the patent in suit. Thus by combining the teachings of both documents, D3 and D16, the skilled person would have arrived at subject-matter falling within claim 1 in an obvious manner. The combination of the teachings of the two documents with that of a third document is not required, nor is hindsight knowledge of the method of claim 1.

33.3 Consequently, auxiliary request 2 lacks an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated