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Datasheet for the decision of 15 October 2024

Case Number: T 0034/21 - 3.3.08

Application Number: 07777180.6

Publication Number: 2018441

IPC: C12Q1/689

Language of the proceedings: EN

Title of invention:
Tagged microorganisms and methods of tagging

Patent Proprietor:
International N&H Denmark ApS

Opponents:
Dutch Dairy Ingredients B.V.
Chr. Hansen A/S

Headword:
Methods of tagging using CRISPR/INTERNATIONAL N&H DENMARK

Relevant legal provisions:
EPC 1973 Art. 54, 56, 83, 87, 123(2)
RPBA 2020 Art. 12(3)

Keyword:
Main request - requirements of the EPC met - (yes)

This datasheet is not part of the Decision. It can be changed at any time and without notice.

Decisions cited:

T 1278/14, T 1931/14

Catchword:

This datasheet is not part of the Decision
It can be changed at any time and without notice

Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 0034/21 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 15 October 2024

Appellant: (Opponent 2)	Chr. Hansen A/S Boge Allé 10-12 2970 Horsholm (DK)
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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 November 2020 concerning maintenance of the European Patent No. 2018441 in amended form.**

Composition of the Board:

Chair	D. Pilat
Members:	M. Montrone
	D. Rogers

Summary of Facts and Submissions

I. An appeal was lodged by opponent 02 ("appellant") against an interlocutory decision of the opposition division according to which the European patent No. 2 018 441 could be maintained in amended form. This patent is based on European patent application No. 07777180.6 which has been filed as International patent application published as WO 2007/136815 (the "patent application").

Summary of the proceedings

II. A first decision of an opposition division to maintain the patent in amended form was set aside in a first appeal due to a substantial procedural violation (T 1278/14). The case was remitted to the opposition division for further prosecution on the basis of auxiliary request 1 filed on 12 February 2014 for assessing the following issues:

- the sufficiency of disclosure of document D1 (priority document) and the patent in suit in view of document D3; and
- inventive step in the light of the disclosure of document D19 in combination with either documents D6 or D8.

III. During the second opposition proceedings, opponent 01 withdrew their opposition. The patent proprietor ("respondent") submitted 16 auxiliary requests of which three were new (AR2 to AR4) (respondent's submission dated 18 August 2020, Table bridging pages 15 and 16).

IV. In the present decision under appeal, which is the second appeal, the opposition division held that the

main request (being identical to auxiliary request 1 filed on 12 February 2014) complied with the requirements of Articles 56 and 83 EPC and that a patent based on this request could accordingly be maintained.

V. With their statement of grounds of appeal (hereafter "SGA"), the appellant submitted arguments against the subject-matter of the main request under added subject-matter, lack of sufficiency of disclosure, priority, novelty and inventive step *inter alia* by referring in general to submissions made in their SGA of the previous appeal T 1278/14.

VI. In reply, the respondent re-submitted the main request and auxiliary requests 1 to 16 as already filed during the second opposition proceedings and provided counter arguments.

VII. In a communication pursuant to Article 15(1) RPBA, the parties were informed of the board's preliminary opinion.

VIII. Oral proceedings were held in the presence of all parties.

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

D1: US provisional application 60/474,682 (priority document ("P1") of the patent in suit)

D3: WO 2007/025097

D4: US provisional application 60/747,683 (second priority document of document D3)

D5: US provisional application 60/711,396 (first priority document of document D3)

D6: Bolotin A. *et. al.*, (2005), Microbiology, Vol. 151, 2551-2561

D8: Pourcel C. *et. al.*, (2005), Microbiology, Vol. 151, 653-663

D10: Barrangou R. *et. al.*, (2007), Science, Vol. 315, 1709-1712

D16: Haft D. H. *et. al.*, (2005), PLoS, Vol. 1(6), 474-483

D19: Sturino J. M. & Klaenhammer T. R., (2004), Adv. in Appl. Microbiol., Vol. 56, 331-378

D24: WO 2012/054726

D25: Lucchini S. *et. al.*, (2000), Virology, Vol. 275, 267-277

D29: Lévesque C. *et. al.*, (2005), Applied and Environmental Microbiology, Vol. 71(7), 4057-4068

D44: Horvath P. *et. al.*, (2008), J. Bacteriology, Vol. 190(4), 1401-1412

X. Claims 1 and 19 of the main request read:

"1. A method for labelling a bacterium comprising the steps of:

(a) exposing a parent bacterium comprising a CRISPR locus to a bacteriophage to introduce an additional repeat spacer unit into the CRISPR locus to produce a labelled bacterium, wherein the additional repeat-spacer unit provides the label;

(b) selecting a bacteriophage insensitive mutant;

(c) comparing a CRISPR locus or a portion thereof from the parent bacterium and the bacteriophage insensitive mutant;

(d) selecting a labelled bacterium comprising said additional repeat-spacer unit in the CRISPR locus that is not present in the parent bacterium.

19. A method for generating a CRISPR variant comprising the steps of:

(a) exposing a parent bacterium comprising a CRISPR locus to a bacteriophage to introduce an additional repeat spacer unit into the CRISPR locus to produce a labelled bacterium, wherein the additional repeat-spacer unit provides the label;

(b) selecting a bacteriophage resistant bacterium;

(c) comparing the CRISPR locus or a portion thereof from the parent bacterium and the bacteriophage insensitive mutant;

(d) selecting a labelled bacterium comprising an additional repeat spacer unit in the CRISPR locus that is not present in the parent bacterium; and

(e) isolating and/or cloning and/or sequencing the additional repeat spacer unit".

The subject-matter of claims 2 to 18 depends on that of claim 1.

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

Main request

Claim construction - claims 1 and 19

Neither the purpose of claim 1 ("*A method for labelling a bacterium*") nor the feature "*wherein the additional repeat-spacer unit provides the label*" in steps (a) of claims 1 and 19 were limiting for the claimed methods since these features were the inevitable consequence of process steps (a) to (d), or (a) to (e), respectively and hence implicit or inherent in those steps. According to established case law, these features were thus not to be taken into account for assessing novelty and inventive step (T 1931/14).

Added subject-matter

The feature "*a parent bacterium comprising a CRISPR locus*" in claims 1 and 19 as granted had no basis in the application as filed. The application as filed solely disclosed parent bacteria comprising a natural CRISPR locus either as alternative, or in the context of specific parent bacteria/offspring combinations. Claim 1, however, referred to parent bacteria comprising a CRISPR locus irrespective of its origin which was an intermediate generalisation of the patent application's disclosure.

Further the reference to step (d) in claim 12 as granted (being identical to claim 12 of the main request) had no basis in claim 12 as filed. Claim 12 as granted referred back to step (d) of claim 1 which was the sole preceding claim that mentioned a step (d). However, this specific combination of features in claim 12 had no basis in the application as filed.

Sufficiency of disclosure

The subject-matter of step (a) of claims 1 and 19 was not sufficiently disclosed in the patent. In the following the terms bacteriophage and phage are used interchangeably.
The opposition division over-simplified the issue of insufficiency by merely asking whether there existed an undue burden for the skilled person in finding other combinations of phages/bacteria.
It had however to be assessed whether there existed an undue burden in finding other combinations of phages/ bacteria so that upon exposure of the bacterium to the bacteriophage an additional repeat-spacer unit was introduced into the CRISPR locus of the bacterium.
This required that (1) bacteria with a CRISPR locus were identified and selected and that (2) bacteriophages were identified which upon exposure to the selected bacterium were able to introduce an additional repeat-spacer unit into the CRISPR locus of the bacterium. Serious doubts existed, substantiated by verifiable facts, that the skilled person could achieve both requirements by undue burden only.

Firstly, the patent provided no guidance for identifying bacteria with a CRISPR locus.

Most of the bacteria reported in the patent comprising a CRISPR locus were archaea and not bacteria as required by claims 1 and 19. Furthermore, the patent did not disclose a single strain of Streptococcus or Lactobacillus that contained a natural CRISPR locus although these bacteria were indicated as preferred. The post-published document D24 disclosed that solely a single Lactococcus strain existed which had a natural CRISPR locus. This was stated to be an "*extremely surprising finding*" (D24, page 3, last paragraph) and indicated that the finding of the strain many years after the filing date of the patent was based on chance.

Secondly, the patent provided also no guidance for identifying a bacteriophage that introduced a spacer into the CRISPR locus.
The post-published document D44 (page 1407, left column and page 1410, right column), for example, disclosed that different CRISPR loci existed in bacteria which were specific for target sequences ("proto-spacers") in the genome of phages. This specificity was due to the so-called proto-spacer associated motif ("PAM") sequences in the phage genome which were recognised by specific Cas nucleases, these Cas nucleases themselves being associated with different CRISPR loci. In case there was no match between a PAM and a Cas nuclease, spacer sequences were not introduced into the CRISPR locus. The spacer incorporation was thus locus (and Cas) dependent as further corroborated by document D3, Example 12.
A skilled person without knowing that the selected bacterium contained a CRISPR locus and hence a Cas enzyme that recognised a PAM sequence in the phage genome was unable to find a bacterium with incorporated spacer sequences in the CRISPR locus.

Also the patent was silent on the necessity of functional Cas enzymes and PAMs for incorporating spacers and that CRISPR loci were phage-specific. This information did not belong to the common general knowledge of the skilled person at the relevant filing date of the patent. In this situation the skilled person was left with trial and error in reproducing the methods of claims 1 and 19 which amounted in undue burden.

Priority - claims 1 and 19

The methods of claims 1 and 19 were not entitled to claim priority from the US application No 60/747682 (document D1, hereafter "P1").
Firstly, the working examples of P1 did not provide an enabling disclosure because they neither disclosed the genomic sequence of phage D858 mentioned in Example 2, nor was the genomic sequence of this phage publicly available at the filing date of P1 from another source.

Secondly, although document D29 mentioned a phage named "*858*" (see Figure 1), there was no evidence that this phage was identical to D858 mentioned in P1, nor did P1 refer to document D29 as a source for D858. The non-availability of phage D858 had the effect that Example 4 of P1, which disclosed that the new spacer in the CRISPR cluster was present in D858, could not be re-worked by the skilled person as well. P1 thus provided not a single reproducible starting point for carrying out the claimed inventions, i.e. P1 did not provide an enabling disclosure.

Thirdly, the use of the indicated additional repeat-spacer unit as label in step (a) of claims 1 and 19 was not directly and unambiguously disclosed in P1.

Instead, P1 disclosed exclusively the bacteriophage-derived sequence (i.e. the spacer) for tagging/labelling purposes (page 36, lines 13 to 15, page 37, lines 18 to 28 and page 38, line 1). This excluded the bacterial repeat sequences as part of the label.

Consequently, the methods of claims 1 and 19 were entitled to the filing date of the patent only, which meant that documents D3 and D10 were prior art under Article 54(2) EPC for the methods claimed.

Novelty - claims 1 and 19

The disclosure of documents D3 and D10 anticipated the methods of claims 1 and 19.

Example 11 and Figure 6 of document D3 disclosed the methods of claims 1 and 19.

Inventive step - claims 1 and 19

Documents D19 or D25 represented the closest prior art for the methods of claims 1 and 19.

Document D19 belonged to the common general knowledge of the skilled person and taught the relationship between lactic acid bacteria ("LAB") and their phages. This document disclosed that at the relevant filing date of the patent it was common practice that bacteriophage-insensitive mutants ("BIMs") of LABs were generated by exposing LABs to phages followed by a subsequent selection of BIMs (i.e. steps (a) and (b) of claims 1 and 19). Further, document D19 disclosed several strategies for generating BIMs, including "*by spontaneous mutation or chemical mutagenesis*", wherein "*The random introduction of one or more specific*

mutation(s) may confer partial or complete insensitivity to phages which enables the straightforward selection of BIMs" (paragraph bridging pages 342 and 343). Since the methods of claims 1 and 19 were likewise directed to the generation of BIMs, document D19 was a realistic starting point for the claimed subject-matter.
Document D19 was silent on the use of a parent bacterium comprising a CRISPR locus and the labelling of bacteria. However since labelling was not a technical feature of claims 1 and 19, the claimed methods differed from the mutation-based generated BIMs in document D19 only in the use of a CRISPR locus for screening and selecting naturally occurring BIMs. Even if labelling as a technical feature had to be taken into account, the mutations randomly introduced into the bacterial genome by the method of document D19 allowed likewise a labelling of BIMs. There was no evidence available that the use of a CRISPR locus for generating and labelling BIMs was associated with an advantageous technical effect over other mutation-based approaches, in particular, since labelling and generating BIMS by CRISPR was also a random process. Nor was the introduction of a spacer at a known locus, i.e. within CRISPR, associated with advantageous technical effects either, in particular not for its use as label.

The objective technical problem was thus the provision of an alternative method for generating BIMs.

The solution to this problem, i.e. the use of a CRISPR system was obvious for the skilled person based on the teaching of document D19 alone, or when combined with the teaching of either document D6 or D8.

Document D19 alone provided already a pointer for using CRISPR. This was so because document D19 focused on *Streptococcus thermophilus* (*S. thermophilus*) and its phages (page 333, last three lines, page 351, second paragraph), i.e. the bacterium and phages likewise used in the patent. In addition document D19 suggested the use of genomic data and their analysis for improving the understanding of bacteria/phage relationships so that BIMs with enhanced phage resistance properties could be generated (page 352, second paragraph and page 369, last paragraph). Although the passage on page 352 of document D19 mentioned conserved gene targets within phage genomes, document D19 envisioned also the use of other phage targets. Document D19 thus suggested the use of sequence data in general.
The skilled person would have also turned to document D6, which was concerned with *S. thermophilus* and its phages for studying a bacterial phage defence system based on CRISPR.
Document D6 concerned a sequence analysis study wherein CRISPR structures of different Streptococci showed a homology to spacers of various phages. Moreover, document D6 mentioned that the phage sensitivity of *S. thermophilus* was correlated with the number of spacers in the CRISPR locus (abstract). This finding in document D6 was based on the data disclosed in Table 2 on page 2556 and Figure 6. Thus a clear link existed between the presence of spacers and *S. thermophilus*'s phage resistance. The spacers disclosed were also sequenced (page 2552, left column, second and third paragraph). Document D6 suggested further explicitly that the spacers reflected past phage infections (page 2558, right column, first paragraph). This provided an indication for the skilled person to select those mutants which had additional spacers in their CRISPR locus and rendered the spacer's use as label obvious.

Although document D6 stated that the phage resistance based on spacers in the CRISPR locus was a hypothesis, this was irrelevant for inventive step since no absolute proof was required in this respect. Accordingly, by following this route the skilled person would have arrived at the methods of claims 1 and 19 without employing an inventive effort.

Alternatively, the methods of claims 1 and 19 lacked an inventive step by combining the teaching of documents D19 and D8.
Document D8 taught a comparison of genomes of different bacterial strains from the species *Yersinia pestis* and provided thus an analysis of genomic data as suggested by document D19. Document D8 reported that the CRISPR locus acquired phage DNA (page 661, right column, second paragraph, first sentence) as part of a defence mechanism (page 661, right column, second paragraph). Thus the skilled person faced with the technical problem of providing an alternative method of screening and selecting spontaneous naturally occurring BIMs was motivated to conduct a sequence comparison of the CRISPR locus of these BIMs and their respective parent bacteria. By doing so, the skilled person would have arrived at the claimed method without an inventive effort as well.

Document D25 as an alternative springboard was already mentioned in document D19 (page 342, second paragraph) in the context of generating BIMs by introducing a spontaneous mutation. In fact, document D25 disclosed a plasmid-based method for generating randomly generated bacterial mutants which were selectable upon phage exposure. This included a method for labelling a bacterium which comprised the following steps:
bacterial phage exposure (page 268, left column, last

paragraph); BIM selection (page 268, left column, last paragraph, page 276, left column, second paragraph); a genomic DNA comparison of BIMs (page 268, right column, second paragraph); a selection of labelled bacteria (page 268, right column, second paragraph); and a sequencing of added sequences in BIMs (page 268, right column, last paragraph, page 269, right column, last paragraph, page 275, paragraph bridging left and right column).
The claimed methods differed therefrom by the introduction of an additional repeat-spacer unit into the CRISPR locus of the parent bacterium.
Since there was no advantageous technical effect associated with this distinguishing feature, the technical problem resided in the provision of an alternative method of obtaining offspring bacteria with traceable mutations in the genome.
The solution to this problem, i.e. the methods of claims 1 and 19, was obvious.
The skilled person faced with the disadvantage of introducing a heterologous plasmid into the genomes of bacteria (i.e. the generation of a genetically modified organism ("GMO")), and the desire to obtain food-grade bacteria (document D25, page 268, right column, second paragraph), would have looked for alternative means in the related art for replacing the plasmid. Document D6 was concerned with the integration of foreign DNA sequences into the genome of *S. thermophilus* resulting in phage resistance (title and abstract). Furthermore, document D6 taught the skilled person that phages left an imprint in the bacterial genome and that a modified *S. thermophilus* was more phage-resistant. The skilled person would have understood from this that phages were not only usable for selecting mutated strains but also for introducing a mutation within the bacterial genomes

that was selectable by phage exposure. This replaced the plasmid used in document D25 as a label.

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

Main request

Claim construction - claims 1 and 19

Claim 1 was limited by its purpose. Also the feature "*wherein the additional repeat spacer unit provides the label*" in step (a) of claims 1 and 19 was a technical feature that limited the claimed methods. The repeat-spacer unit defined in step (a) of claims 1 and 19 provided a unique means for identifying BIMs. Contrary to the situation underlying T 1931/14, claim 1 did not only mention a purpose but comprised several steps that used the label for selecting BIMs that comprised the additional repeat-spacer unit (step (d) of claims 1 and 19). The method of claim 19 even generated an isolated label, which is an additional repeat-spacer unit (step (e)).
Contrary to the appellant's argument, the label or the use of the additional repeat-spacer unit as label was not the inevitable result of a bacterium being merely exposed to a phage. Instead this label had to be actively selected and as regards claim 19 in addition to be isolated.

Added subject-matter - claims 1 and 19

Claims 1 and 19 are in essence based on claims 1 and 26 as filed. The feature "*a parent bacterium comprising a CRISPR locus*" in step (a) of claims 1 and 19 was implicitly disclosed in step (c) of claim 1 as filed,

and had a basis in claims 2, 7, 9 and 10 as filed too. Page 2, fourth paragraph, lines 3 and 4 and page 9, last paragraph of the application as filed disclosed this feature as well.
Step (a) of claims 1 and 19 therefore comprised no intermediate generalisation from specific Streptococcus strains or from naturally occurring CRISPR loci.

Claim 12 as filed was identical to claim 12 except that it lacked the reference to "*in step (d)*". In the claims to which dependent claim 12 as filed referred to by back reference, solely claim 1 as filed mentioned a step (d) wherein moreover the selected labelled bacterium comprised an additional repeat-spacer unit. Thus claim 12 as filed directly and unambiguously related to step (d) of claim 1 as filed.

Sufficiency of disclosure - claims 1 and 19

The patent provided sufficient guidance to the skilled person for (1) identifying bacteria with CRISPR loci and (2) identifying bacteriophages that introduced a spacer into the CRISPR locus. Methods for identifying bacteria comprising natural CRISPR loci were disclosed in paragraphs [0034] and [0035] of the patent while examples of these bacteria were mentioned in paragraph [0102] of the patent. The patent also disclosed that parent bacteria with a heterologous CRISPR locus could be used. Moreover the Examples of the patent provided evidence that the concept of labelling bacteria with additional repeat-spacer units in the CRISPR locus was generally applicable.
Post-published documents, for example, D44 disclosed that different CRISPR loci recognised a specific PAM. Due to the short length of PAMs, these motifs were present in high numbers within any given phage genome.

Thus any phage genome contained target sequences (proto-spacers) that were recognised by a specific Cas nuclease and incorporated into a respective CRISPR locus. It was also commonly known that CRISPR loci were associated with cas genes (documents D6 and D16, abstracts). The specificity of a given CRISPR locus for its target sequence did not confer phage-specificity but rather determined the target sequence to be incorporated into the locus. Accordingly the skilled person for carrying out the claimed method merely required access to phage/bacteria pairs, i.e. means known since the early 20th century (document D19, paragraph bridging pages 331 and 332).

Priority - claims 1 and 19

P1 (document D1) as a whole contained an enabling disclosure for the methods of claims 1 and 19. It was irrelevant whether or not the working examples of P1 contained an enabling disclosure of the sole phage mentioned, since this was not required for sufficiency of disclosure. The claimed methods comprised any parent bacterium with a CRISPR locus and any phage being virulent thereto and were not limited to phage D858. Also phages other than D858 were publicly available to the skilled person.

Furthermore page 28, lines 17 to 22, page 31 following the heading "*Tagging Sequence*" to page 33, first paragraph and claims 13 to 15 of P1 directly and unambiguously disclosed the additional repeat-spacer unit as label mentioned in step (a) of claims 1 and 19.

Consequently the methods of claims 1 and 19 were entitled to claim priority from P1. Document D10 was

therefore not prior art and document D3 was prior art under Article 54(3) EPC only.

Novelty - claims 1 and 19

The methods of claims 1 and 19 were novel over document D3. It was not contested that Example 11 and Figure 6 of document D3 were entitled to claim priority from document D5 (filing date: 19 May 2006) only. Since document D5 had the same filing date as P1, the disclosure of Example 11 and Figure 6 in document D3 did not anticipate the subject-matter of claims 1 and 19.

Inventive step - claims 1 and 19

The method of claims 1 and 19 involved an inventive step over the teaching of document D19 either alone or in combination with documents D6 or D8.

Document D19 did not disclose CRISPR or a method for labelling bacteria. Nor was document D19 directed to the problem of labelling bacteria. Since bacteria could be labelled by other means, the use of the CRISPR locus for labelling was a separate distinguishing feature. Since document D19 was not directed to the claimed purpose, the skilled person would not have used this document as a starting point. If document D19 was nevertheless selected, the claimed subject-matter was distinguished therefrom by two features: tagging/ labelling a bacterium and the CRISPR locus. This had the effect that the selected labelled bacterium was not a GMO unlike the bacteria obtained by the other methods disclosed in the prior art. Moreover, the introduction of the additional repeat-spacer unit was unique in each bacterial strain and occurred at a known genomic site

only, i.e. the CRISPR locus. Document D19 provided various avenues for the skilled person to explore ways of solving the problem of generating BIMs, and none of them involved the CRISPR system. Also the passages in document D19 which suggested the use of genome data for understanding bacterial defence systems for developing and exploiting these systems further did not provide any motivation for the skilled person to turn to documents D6 or D8 which both mentioned CRISPR. CRISPR was unknown for defence purposes. The skilled person would have turned to these documents only by an impermissible hindsight knowledge of the claimed invention.

Further the claimed methods were inventive in light of document D25's teaching combined with document D8 too.

Document D25 was silent on CRISPR, including its use in the generation of BIMs or for labelling bacteria. Instead this document explored the possibility of obtaining BIMs by a plasmid-based insertional mutagenesis. This approach targeted the bacterial genome at random sites followed by the selection of BIMs. Nor was a unique element integrated into the genome by this approach since two resistant strains had the same plasmid albeit integrated at different sites. Document D25 did also not suggest any amendments to the method disclosed therein. Nor did document D25 provide any motivation for combining its teaching with that of another document, let alone D8.
Document D8 taught that CRISPR loci were found in *Yersinia pestis* and compared the structure of different CRISPR loci, motif arrangements within the loci and assessed possible origins of some of these motifs. Document D8 suggested the use of these motifs for evolutionary studies, while a method of labelling a

bacterium was neither disclosed nor suggested. Document D8 was also silent on any element of the CRISPR locus which was unique and hence suitable as a label or suggested additional repeat-spacer units as label.

XIII. The relevant requests of the parties for this decision are (for the complete set of requests, see the minutes of the oral proceedings):

(a) The appellant requests that:

- the decision under appeal be set aside and that the patent be revoked.

(b) The respondent requests that:

- that the appeal be dismissed and the patent be maintained according to the main request.

Reasons for the Decision

Admittance/consideration of all arguments, facts and objections in relation to T 1278/14

1. The appellant submitted in their SGA (page 3, third paragraph) the following general statement: "*We also maintain all objections raised in our attached Grounds of Appeal in T1278/14, i.e. against the first decision of the OD. The facts and arguments presented in the Grounds of Appeal in T1278/14 are incorporated herein in their entirety*".

2. This sweeping reference to maintain in their entirety all objections, facts and arguments raised in the appellant's previous SGA in case T 1278/14 in these appeal proceedings contravenes Article 12(3) RPBA which sets out that the SGA shall contain a party’s complete appeal case and should "*specify expressly all the*

requests, facts, objections, arguments and evidence relied on". It is not for the board nor for the other party to construct the details of a party's case.

3. The unspecified objections, facts and arguments of the appellant with reference to T 1278/14 are therefore disregarded in the present appeal (Article 12(3) RPBA).

Main request

Claim construction - claims 1 and 19

4. Claim 1 is directed to "*A method for labelling a bacterium*" which comprises steps (a) to (d).

5. Claim 19 is directed to "*A method for generating a CRISPR variant*" which comprises steps (a) to (e).

6. Since steps (a) to (d) are identical between claims 1 and 19, both claims differ from each other by their indicated purpose and in that claim 19 has step (e) in addition.

7. The construction of step (a) of claims 1 and 19 was contentious between the parties.

8. The appellant in essence argued that the method of claim 1 did not relate to a method of labelling but to a method for generating BIMs since the labelling of the bacteria was implicit in the other process steps. Similar arguments applied for claim 19 which solely related to a method for generating a CRISPR variant. In particular, the appellant argued that the feature in the second half sentence of step (a) of claims 1 and 19 ("*wherein the additional repeat spacer unit provides the label*") was the inevitable consequence of the first

half sentence of step (a) ("*exposing a parent bacterium comprising a CRISPR locus to a bacteriophage to introduce an additional repeat spacer unit into the CRISPR locus to produce a labelled bacterium*"). Consequently the information that a label was provided in step (a) was held to be implicit or inherent by the mere introduction of an additional repeat-spacer unit into the CRISPR locus and hence devoid of a limiting technical effect. In support of their case the appellant referred to decision T 1931/14.

9. The board does not agree.

9.1 Step (a) of claims 1 and 19 does not necessarily generate parent bacteria that comprise an additional repeat-spacer unit in their CRISPR locus. This was uncontested because it is common general knowledge that bacteria have several phage defence systems at their disposal including, for example, CRISPR. This does not change in the presence of a CRISPR cluster as required in step (a). Thus bacteria comprising a CRISPR locus may become insensitive to phages for several reasons. The integration of an additional repeat-spacer unit in the CRISPR locus is only one of several possibilities.

9.2 The skilled person reading step (a) thus immediately understands that the feature "*exposing a parent bacterium comprising a CRISPR locus to a bacteriophage*" defines the activity, while the remaining features in step (a) define the result to be achieved by this activity, i.e. "*to produce a labelled bacterium, wherein the additional repeat spacer unit provides the label*".

9.3 In order to achieve this aim, claims 1 and 19 provide further process steps:

9.4 Step (b) requires "*selecting a bacteriophage insensitive mutant*" ("BIM"); i.e. all phage resistant bacteria must be selected irrespective of the underlying ground for their resistance.

9.5 Step (c) requires "*comparing a CRISPR locus or a portion thereof from the parent bacterium and the bacteriophage insensitive mutant*"; this serves the purpose of identifying specifically those BIMs in which the additional repeat-spacer unit in the CRISPR locus caused the phage resistance. The finding of an additional repeat-spacer unit (by comparing the parental CRISPR locus with that of the BIM) identifies (labels) a specific sub-group within the BIMs generated and selected in steps (a) and (b).

9.6 Step (d) then requires "*selecting a labelled bacterium comprising said additional repeat-spacer unit in the CRISPR locus that is not present in the parent bacterium*"; i.e. the labelled BIM sub-group is then selected.

9.7 The additional step (e) in claim 19 requires "*isolating and/or cloning and/or sequencing the additional repeat-spacer unit*", i.e. the label which uniquely identifies the generated "*CRISPR variant*".

9.8 Owing to the considerations above, the "*additional repeat-spacer unit*" indicated in steps (a), (d) and (e) of claims 1 and/or 19 has two functions. Firstly the generation of a BIM/CRISPR variant and secondly, the introduction of a molecular label which uniquely identifies the BIM/CRISPR variant.

9.9 The method steps in claims 1 and 19 thus explicitly define what the label is (step (a)) and its use in identifying (step (c)) and selecting BIMs (step (d)), and moreover generates an isolated label (step (e) of claim 19 only). Consequently the purpose "*for labelling*" in claim 1 consists in assigning an identifying element to the bacteria, which describes and qualifies them and plays a role in their selection and the proper determination of their fate, i.e. whether or not they are to be used. This resembles the situation dealt with in T 1931/14 (Reasons, 2.2.4) wherein the indicated purpose in a claim defines the use of the method, and not an effect that merely arises from the method steps and being implicit therein. The purpose of claim 1 is thus a limiting functional feature. The same applies for the contentious feature of step (a) of claims 1 and 19.

10. The "*repeat-spacer unit*" in steps (a), (d) and (e) of claims 1 and 19 refers to a pair of bacterial-derived ("*repeat*") and bacteriophage-derived ("*spacer*") genomic nucleic acid sequences. The "*repeat*" elements in the CRISPR locus concern identical short bacterial sequences that are regularly interspersed by unique intervening bacteriophage-derived "*spacer*" sequences forming a cluster (patent, paragraph [0033]).

10.1 Thus while the repeat element of the repeat-spacer unit is present in several copies within a CRISPR locus, each spacer element is unique. Consequently each unit consisting of a repeat and a spacer element is unique within a CRISPR locus too and hence suitable as molecular label for a specific bacterium (patent, paragraphs [0020], [0024], [0126] and [0127]).

10.2 Furthermore, this additional repeat-spacer unit renders the bacterium resistant against a bacteriophage infection, i.e. it generates BIMs. The dual suitability of the additional repeat-spacer unit as label and for generating BIMs is uncontested between the parties.

11. The term "*parent bacterium comprising a CRISPR locus*" in step (a) of claim 1 neither defines the type of bacterium nor the origin of the CRISPR locus. Thus according to ordinary claim construction wherein each feature in a claim must be given its broadest technical sensible meaning, step (a) comprises any bacterial species which contains a CRISPR locus irrespective of its origin (e.g. being natural or of heterologous origin and being recombinantly introduced).

Added subject-matter - claims 1 and 19

12. Reference in the following to the application as filed/ claims as filed is to the patent application (WO 2007/136815). The decision of the opposition division dated 28 March 2014 in T 1278/14 is referred to in the following as the "first" decision.

13. The appellant raised an objection under added subject-matter against the feature "*a parent bacterium comprising a CRISPR locus*" in step (a) of claims 1 and 19 as granted representing an unallowable intermediate generalisation. A further objection was raised against the reference "*wherein in step (d)*" in claim 12 as granted.

14. The two contentious features in claims 1, 12 and 19 as granted indicated above are likewise present in claims 1, 12 and 19 of the main request. Accordingly, the appellant's objections are relevant for this set of

claims too. The opposition division held that the feature "*a parent bacterium comprising a CRISPR locus*" in claims 1 and 19 as granted was inherently derivable from claims 2, 5, 9 and 10 as filed and that claim 12 as granted had a basis in claim 12 as filed (first decision under appeal, Reasons 3.1.1 to 3.1.3). The respondent indicated as further basis for the contentious feature in claims 1 and 19 *inter alia* step (c) of claim 1 as filed.

15. The methods of claims 1 and 19 are in essence based on claims 1 and 26 as filed. As regards the feature "*a parent bacterium comprising a CRISPR locus*" in step (a) of claims 1 and 19, step (a) of claims 1 and 26 as filed reads instead "*a parent bacterium*", i.e. the feature "*comprising a CRISPR* locus" is missing.

15.1 This missing feature in step (a) of claims 1 and 26 as filed is implicit in step (c) of these claims which reads "*comparing a CRISPR locus or a portion thereof from the parent bacterium and the bacteriophage insensitive mutant*" (emphasis added), i.e. this step mentions "*a CRISPR locus ... from the parent bacterium*". Since the identifiers (a) to (d) in claims 1 and 26 as filed define an order, the skilled person immediately understands that step (c) is carried out subsequent to step (a). Moreover since step (c) mentions the term "*parent bacterium*" which is only mentioned in step (a), the back reference of step (c) to step (a) is immediately derivable and evident. Therefore the feature "*comprising a CRISPR locus*" is necessarily implied in step (a) of claims 1 and 26 as filed too.

15.2 In these circumstances the issue whether the application as filed discloses specific parent

bacteria/offspring with a (natural) CRISPR locus only is irrelevant for added subject-matter since parent bacteria comprising a CRISPR locus in general are directly and unambiguously disclosed.

16. As regards the contentious feature "*wherein in step (d) a labelled bacterium comprising two or three or more additional repeat-spacer units is selected*" in claim 12, the board agrees with the opposition division that this feature does not comprise added subject-matter (first decision under appeal, Reasons 3.1.2). Claim 12 is identical to claim 12 as filed, except that the latter lacks the reference to "*step (d)*". Claim 12 as filed refers to "*any of the preceding claims*". Since claim 1 as filed is moreover the sole preceding claim mentioning a step (d) which, also refers to a selection of a labelled bacterium that comprises *"an additional repeat-spacer unit*" (i.e. the subject-matter of claim 12 as filed), the incorporation of "*step (d)*" into claim 12 does not add subject-matter either.

17. In view of the considerations above, the main request complies with Article 123(2) EPC.

Sufficiency of disclosure- claims 1 and 19

18. The appellant raised objections under sufficiency of disclosure against the subject-matter of step (a) of claims 1 and 19, in essence for two reasons. Firstly, because the patent application did not provide a sufficient teaching for the skilled person identifying bacteria with CRISPR loci and secondly, the patent application lacked any guidance for identifying bacteriophages that were capable of introducing spacers into the CRISPR locus.

19. Since for the present (amended) main request the requirements of Article 83 EPC are relevant, the document to be taken into account is not the patent in suit as referred to by the opposition division and the parties but the application as filed.

20. The board agrees with the opposition division's finding in the first decision under appeal (page 23, fifth to seventh paragraph) and this decision under appeal (Reasons 1.1) that the application as filed taking the skilled person's common general knowledge into account sufficiently discloses the methods of claims 1 and 19 (Article 83 EPC).

20.1 As regards the appellant's first line of argument, the application as filed discloses that, at its relevant filing date, more than 40 prokaryotes with natural CRISPR loci were known from the prior art. The appellant's argument that most of these prokaryotes were archaea is irrelevant for the issue of sufficiency since bacteria are mentioned as well. As an alternative source, the application as filed (page 29, second and third paragraph) mentions bacteria with heterologous CRISPR loci (i.e. CRISPR loci that have been introduced by recombinant means). In addition, the application as filed (page 14, second and third paragraph) teaches the use of computer-based methods for searching bacterial genomic sequences in gene databases for identifying bacteria comprising a CRISPR locus.

20.2 The appellant further argued that based on the post-published document D24 the identification of substantially all parent bacteria falling within the scope of step (a) of claim 1 was an undue burden because within the genera Lactococcus solely a single strain with a natural CRISPR locus existed. This is

likewise not persuasive, since as set out above under claim construction (point 11), the term "*parent bacterium comprising a CRISPR locus*" in claims 1 and 19 encompasses bacteria with natural and recombinant CRISPR loci (also point 20.1 above).

21. The appellant's second line of argument in essence was that different CRISPR loci were specific for bacteriophage-derived sequences due to the specificity of the Cas nucleases and the presence of specific recognition motifs ("PAMs") within the phage genomes. Since neither the application as filed nor the available prior art reported on the need for functional cas genes encoding those nucleases and PAMs for incorporating spacers into the CRISPR locus, the finding of other suitable bacteria/bacteriophage pairs than those disclosed in the application as filed constituted an undue burden.

21.1 The board does not agree. The use of parent bacteria comprising a CRISPR locus as indicated in step (a) of claims 1 and 19 normally implies that said locus has associated therewith functional cas genes encoding the nucleases since otherwise a CRISPR locus would not exist (e.g. application as filed, page 24, fifth paragraph to page 25, fifth paragraph, documents D6 and D16, abstracts respectively). The presence of a CRISPR locus implies further that bacteriophages containing PAMs must exist as well because otherwise a CRISPR locus cannot contain "*spacer*" elements, i.e. the locus would not naturally exist either (document D6, abstract). Independent thereof post-published documents, for example, D44 (Figure 7) disclose that PAMs are normally short sequence motifs and occur statistically at sufficient high frequencies within any bacteriophage genome, so that all phages contain

sequences suitable for being (specifically) incorporated into a bacterial CRISPR locus. Therefore in agreement with the respondent, the specificity of an integrated phage sequence in a CRISPR locus is determined by the PAM and the Cas nuclease associated with that locus and not by the individual phage. Since bacteria with a CRISPR locus normally contain functional Cas nucleases and phage genomes contain different PAMs, the existence of some CRISPR loci having inactivated cas genes (either spontaneously or mutationally induced, e.g. document D3, Example 12) is irrelevant in terms of sufficiency of disclosure.

21.2 Owing to these considerations, the board agrees with the opposition division (this decision under appeal, page 3, third paragraph) that there is no need for the skilled person at the relevant filing date of the application as filed to know which mechanism generates a CRISPR locus in a bacterium. Rather all that is needed for carrying out the method of claims 1 and 19 is that the skilled person is able to identify suitable pairs of phages/bacteria for carrying out the claimed methods. Such pairs are commonly known since the early 20th century (document D19, paragraph bridging pages 331 and 332, pages 333 and 336, second paragraphs respectively).

22. The main request complies with Article 83 EPC.

Priority

23. The appellant submitted that the methods of claims 1 and 19 were not entitled to claim priority from the US application No 60/747682 (document D1, hereafter "P1"), essentially because firstly the working examples of P1 were not reproducible and secondly because the

additional repeat-spacer unit mentioned in steps (a), (d) and (e) of claims 1 and 19 was not directly and unambiguously disclosed in P1.

24. The board does not agree.

25. As regards the appellant's first line of argument. The requirement that the subject-matter claimed must be reproducible with the information available at the earliest filing date (here the filing date of P1 (19 May 2006)) does not require that the priority application contains a single working example, let alone that the working examples disclosed therein must be reproducible. All that is required is that the claimed invention can be carried out over substantially the whole breadth claimed in view of the teaching of the priority application as a whole taking the skilled person's common general knowledge into account. While the appellant argued that phage D858 was not disclosed in an enabling manner in P1 or available from other sources, the appellant did not argue that bacteriophages in general were not available at the filing date of P1 (see also point 21.2 above). Thus even if D858 was not available, other phages for carrying out the claimed method were available to the skilled person. Already for this reason the appellant's first line of argument is not convincing. Therefore the question whether phage D858 mentioned in P1 was available taking into account either document D29 or other sources, does not need to be addressed.

26. As regards the appellant's second line of argument the following is relevant: P1 discloses in the paragraph bridging pages 3 and 4 in essence the method of claim 1. Instead of mentioning "*an additional repeat-spacer unit*" (see claim 1, steps (a) and (d)), the method in

P1 mentions the term "*an additional DNA fragment*". Further page 4, last paragraph of P1 discloses in essence the method of claim 19. Again the term "*an additional DNA fragment*" is used in P1 instead of "*an additional repeat spacer unit*" mentioned in steps (a), (d) and (e) of claim 19. The same disclosure is found in claims 1 and 26 of P1.

26.1 P1 discloses further on page 7, lines 22 to 27 that "*Preferably, the additional DNA fragment comprises a first nucleotide sequence that has at least 95% identity, preferably, 100% identity to a CRISPR repeat in the CRISPR locus of the parent bacterium and a second nucleotide sequence that has at least one nucleotide sequence that has at least 95% identity, preferably, 100% identity to a nucleotide sequence in the genome of the bacteriophage used for the selection of the labelled bacterium*". A similar disclosure is found in claims 13 to 15 of P1. The bacterial-derived repeat sequence of the CRISPR locus in P1 is also termed "*duplicated sequence*" (page 32, lines 18 and 19), while the phage-derived genomic sequence is termed "*tagging sequence*" (page 31, lines 1 to 3).

26.2 Although the term "*repeat-spacer unit*" indicated in claims 1 and 19 is not literally disclosed in P1, this term means in fact one pair of sequences comprising a duplicated bacterial sequence: i.e. a "*repeat*" and a phage-derived genomic sequence: i.e. a "*spacer*". Such pairs are mentioned in P1 on page 33, lines 1 to 3 and page 36, lines 16 and 17 too. Thus the repeat-spacer units of claims 1 and 19 are directly and unambiguously derivable from P1.

27. In view of these considerations, the board concludes that the methods of claims 1 and 19 are entitled to

claim priority from P1 (19 May 2006). Consequently document D3 is an Article 54(3) EPC document, while document D10 is not prior art.

Novelty

28. The appellant submitted that the methods of claims 1 and 19 lacked novelty over the disclosure of documents D3 and D10.

28.1 As indicated above (point 27), document D10 is not prior art.

28.2 As regards document D3, the appellant based their objection under lack of novelty on the disclosure of Example 11 and Figure 6 of document D3. It is uncontested that neither Example 11 nor Figure 6 of document D3 is disclosed in D3's first priority application (US 60/711396 (D5), filing date: 26 August 2005). Since D3's second priority application (US 60/747683 (D4)) has been filed on 19 May 2006, i.e. the same day as P1 (point 27 above), Example 11 and Figure 6 of document D3 cannot anticipate the methods of claims 1 and 19.

29. Thus the methods of claims 1 and 19 are novel and the main request complies with Article 54 EPC.

Inventive step

30. The appellant submitted that either document D19 or document D25 represented the closest prior art for the methods of claims 1 and 19. The methods of claims 1 and 19 were considered obvious in the light of the teaching of document D19 alone or combined with either documents D6 or D8. Alternatively the methods of claims 1 and 19

lacked an inventive step in the light of the teaching of document D25 combined with D6.

31. The board is not persuaded by the appellant's submissions.

Document D19 as closest prior art

32. It was undisputed that document D19 did not mention methods for labelling bacteria, the CRISPR locus and methods for generating a CRISPR variant. Document D19 is a textbook chapter that summarises the skilled person's knowledge in the dairy industry about defence systems in lactic acid bacteria confronted with repeated phage infections (e.g. title and page 333, second paragraph). Various approaches for generating BIMs are reported which include the selection of spontaneous or chemically induced mutants (page 342, second paragraph to page 343, second paragraph).

33. According to the appellant since document D19 reported on the generation of BIMs, it was directed at the same aim and hence represented a realistic starting point for the claimed methods. Furthermore, the methods of claims 1 and 19 differed from the selection of spontaneous BIM mutants disclosed in D19 solely by the type of mutation and the type of sequence introduced. Since these differences did not result in advantageous effects, the technical problem to be solved was the provision of an alternative method for the generation of BIMs.

34. As set out above under claim construction (point 9.8), the methods of claims 1 and 19 are directed at the generation of labelled and phage-resistant bacteria, i.e. labelled BIMs or a CRISPR variant. A further

difference between the claimed methods and document D19 resides in the insertion of the spacer (the element which renders the bacteria phage-resistant and labelled) at a specific locus: CRISPR. Thus, the mutation happens not randomly at unknown genomic site(s), but targeted to a known site.

35. In the board's view the issue can be left aside whether or not these differences are associated with an advantageous technical effect. The claimed methods are non-obvious over the teaching of document D19 either alone or combined with documents D6 or D8 even starting from the appellant's less ambitious technical problem (point 33 above) for the reasons set out below.

36. The board has no doubts that the methods of claims 1 and 19 solve the problem defined above. This was also not disputed by the appellant.

Obviousness

37. In a first line of argument the appellant submitted that the claimed methods were obvious in the light of document D19's teaching alone. Firstly this document focussed on *S. thermophilus*, i.e. the strain likewise used in the patent and, secondly suggested the use of *in silico* methods as tool for improving the knowledge on bacteria-phage interplays.

38. This is not persuasive. As set out above, document D19 is silent on CRISPR, CRISPR's involvement in phage resistance, or the use of phage- and bacterial-derived sequences as molecular labels for identifying and generating BIMs. Document D19 thus provides no pointer for the skilled person to look at CRISPR. Since CRISPR was also not mentioned in any other available source of

common general knowledge in the field of bacterial phage resistance, the skilled person was even unaware of the use of CRISPR as an alternative (standard) tool for generating BIMs, let alone for labelling bacteria.

39. In these circumstances, the skilled person had no expectations of solving the problem defined above using a CRISPR-based approach for generating labelled BIMs or a CRISPR variant. This conclusion is not put into doubt by the generic suggestion in document D19 (page 369, second paragraph) for using *in silico* approaches in analysing bacteria-phage relationships. Document D19 lacks any pointer for the skilled person as regards the sequence data to be analysed or the targets to be looked at. Also the mere mentioning of *S. thermophilus* in document D19 is at best accidental. In this situation any potential arrival at the methods of claims 1 and 19 starting from document D19 alone must be the result of an *a posteriori* analysis based on hindsight knowledge of the claimed invention.

40. In a second line of argument, the appellant submitted that the methods of claims 1 and 19 were obvious in the light of the combined teaching of documents D19 and D6 or of D19 and D8.

40.1 As set out above, document D19 is silent on CRISPR and its use for generating BIMs and labelling. Moreover, this document provides no pointer for the skilled person in using a CRISPR-based system for these purposes.

40.2 In assessing the question of obviousness in the context of solving an alternative technical problem (here the provision of an alternative BIM generating method) it is established case law that a motivation is not always

necessary for amending a prior art method since the skilled person would take all common alternative solutions applied in the field into account. This, however, presupposes that these "alternatives" are indeed commonly used for the purpose at hand. As set out above (point 38), this is not the case for CRISPR.

40.3 The appellant asserted that starting from document D19, the skilled person would have turned to document D6 because the results disclosed therein were obtained from an *in silico* analysis of genomic data in *S. thermophilus*, i.e. using the same method and the same organisms as those proposed in document D19. Furthermore, document D6 (abstract) speculated that CRISPR might be involved in phage resistance since the amount of spacers in the cluster correlated with the observed phage resistance of *S. thermophilus* (Table 2 and Figure 6).

40.4 Irrespective of whether document D19 provides pointers for document D6, or whether a speculation in D6 about an effect (spacers might provide immunity against a phage infection) would suffice to provide an expectation of success, the appellant's arguments are not persuasive. Document D6 is silent about using CRISPR in generating BIMs and labelling, in particular, in using an "*additional repeat-spacer unit*" as a label, or in generating a CRISPR variant. Thus even if the skilled person would have combined documents D19 and D6, having regard to the technical problem referred to in point 35 above, the skilled person would not have arrived at the methods of claims 1 and 19. And even less so because the obvious "alternatives" must be commonly known as alternative solutions to the technical problem to be solved, which is not the case here.

41. Similar considerations apply for the combination of documents D19 and D8. Document D8 speculates as well about the uptake of spacers in the CRISPR locus "*as part of a defence mechanism*" (page 661, right column, second paragraph). Document D8 is also silent on BIM generation. Nor does document D8 disclose or suggest the use of a repeat-spacer unit as molecular label. Instead, document D8 proposes the use of CRISPR "*loci*" (i.e. the locus as a whole) as "*phylogenetic tools*" (page 662, left column, second paragraph). The mentioning of "*a new and robust identification tool*" in the abstract of document D8 has to be seen in this context. A phylogenetic tool is used for evolutionary studies but is neither a label, nor used for labelling. Nor is the use of a whole CRISPR locus the same as the "*additional repeat-spacer unit*" (i.e. a single element of the locus) mentioned in claims 1 and 19. Thus also in combining the teaching of document D19 with that of document D8, the skilled person would not have arrived at the methods of claims 1 and 19.

Document D25 as closest prior art

42. Document D25 discloses a plasmid-based random mutagenesis approach for isolating phage resistant lactic acid bacteria (abstract). The targeted genes are sequenced to study the molecular and biochemical basis of the found bacterial phage resistance (page 271, left column, first paragraph, page 272, left column, second paragraph and page 273, right column, first paragraph).

43. It is undisputed that document D25 is silent on CRISPR, CRISPR's involvement in phage resistance, or the use of phage-derived sequences as natural molecular labels for identifying and generating BIMs or CRISPR variants.

44. The appellant asserted that the claimed methods differed from document D25 in that an additional repeat-spacer unit was introduced into the CRISPR locus of the parent bacterium. The appellant's arguments as regards obviousness and in defining the technical problem are inconsistent. In the context of obviousness, the appellant stated that the method of D25 had "*inherent disadvantages*" because "*a heterologous plasmid*" was integrated into the bacterial genome when compared to the claimed phage-derived spacers. Despite this disadvantage the objective technical problem to be solved resided in the mere provision of an alternative method of obtaining offspring bacteria with traceable mutations in the genome. In the appellant's opinion, the distinguishing feature did not result in any advantageous technical effect. The opposition division considered that the technical problem resided in the provision of alternative tagging methods (first decision under appeal, page 20, seventh paragraph).

45. The board agrees with the appellant insofar only as the use of a natural means for labelling a BIM is advantageous over a heterologous label since the so labelled BIM is not affected by potential regulatory restrictions concerning genetically modified organisms. Moreover, since the additional repeat-spacer unit indicated in claims 1 and 19 has a dual function (point 10.2 above), the board considers that the technical problem to be solved resides in the provision of improved tagging methods.

46. In view of the patent's teaching (e.g. paragraph [0024]), the board is convinced that the methods of claims 1 and 19 solve this technical problem.

Obviousness

47. The appellant in essence submitted that starting from document D25 the skilled person due to the inherent disadvantages of using a heterologous plasmid for generating labelled BIMs was motivated to look for other suitable labelling means. Since document D6 was likewise concerned with insertional mutagenesis and relied on *S. thermophilus* as model organism, its teaching belonged to the related art which would be looked at by the skilled person. Moreover document D6 taught that phage exposures left an imprint in the bacterial genome and that these strains were more phage resistant. In view of this teaching in document D6 the skilled person would have recognised that the plasmid used in document D25 was dispensable.

48. The board does not agree. As set out above (point 40.4), document D6 is silent on any labelling, let alone suggests or points at the use of an additional repeat-spacer unit as a label. The appellant's assertion that the skilled person would have nevertheless and despite this factual situation recognised that the introduced spacer in the CRISPR locus in document D6 made the plasmid in document D25 superfluous is not based on facts and hence speculative. Irrespective thereof, since document D6 is silent on the use of an additional repeat-spacer unit as a label, the skilled person combining the teaching of documents D25 and D6 would not have arrived at the methods of claims 1 and 19. Although document D6 shows that phage exposures leave an imprint in the bacterial genome, it only speculates that CRISPR spacers might reflect past phage and plasmid infections (page 2558, right hand column first full sentence) and that they

might protect bacteria not only against phage infection, but also against an invasion of other extrachromosomal elements thus inhibiting expression of the genes they carry (page 2560, right hand column). Consequently, the skilled person would not be motivated either, on the basis of this speculative information, to combine the teachings of documents D25 and D6 to arrive at the claimed solution.

49. The subject-matter of claims 1 and 19 is thus inventive over the cited prior art documents. The main request complies with the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

C. Rodríguez Rodríguez D. Pilat

Decision electronically authenticated