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Datasheet for the decision of 19 November 2015

Case Number: T 0528/11 - 3.3.08

Application Number: 02780211.5

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IPC: C12N1/20, A61K35/74

Language of the proceedings: EN

Title of invention:
LACTIC ACID PRODUCING BACTERIA FOR USE AS PROBIOTIC ORGANISMS IN THE HUMAN VAGINA

Patent Proprietor:
Ellen Aktiebolag

Opponent:
SCA Hygiene Products AB

Headword:
Selection Lactobacillus menstrual discharge administration/ ELLEN

Relevant legal provisions:
EPC Art. 123(2), 123(3), 83, 56
RPBA Art. 12(4), 13(1)

Keyword:
Admissibility of new evidence (no)
Admissibility of the Main Request (yes)
Main Request
added subject matter (no); sufficiency of disclosure (yes); inventive step (yes)

Decisions cited:
G 0001/03, T 0994/95, T 0157/03, T 1262/04

Catchword:

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Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0528/11 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 19 November 2015

Appellant: (Opponent)	SCA Hygiene Products AB 405 03 Göteborg (SE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Patent Proprietor)	Ellen Aktiebolag Svärdvägen 27 182 33 Danderyd (SE)
Representative:	Ström & Gulliksson AB Järnvägsgatan 3 252 24 Helsingborg (SE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 27 December 2010 rejecting the opposition filed against European patent No. 1427808 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. Wieser
Members:	P. Julià
	D. Rogers

Summary of Facts and Submissions

I. European patent No. 1 427 808, based on European patent application No. 02 780 211.5 (published as WO 2003/038068, hereinafter "*the application as filed*"), was opposed on the grounds as set forth in Articles 100(a) and (b) EPC. The opposition division considered these grounds of opposition not to prejudice the maintenance of the patent and, accordingly, rejected the opposition (Article 101(2) EPC).

II. An appeal was lodged by the opponent (appellant). In the statement setting out the Grounds of Appeal, the appellant filed new evidence (documents D14, D14a - D14f) and, with a further submission, documents D15 - D17.

III. In reply thereto, the patentee (respondent) filed Auxiliary Requests 1 - 6 and, in a further submission, requested the board not to admit appellant's newly filed evidence into the appeal proceedings.

IV. The appellant repeated its request to admit the new evidence into the proceedings.

V. The parties were summoned to oral proceedings. In a communication pursuant to Article 15(1) RPBA annexed to the summons, the board informed the parties of its preliminary, non-binding opinion on issues of the case.

VI. In reply thereto, the respondent filed Auxiliary Requests 1 - 12 and further substantive arguments.

VII. In a letter dated 19 October 2015, the appellant, without making any substantive submission, informed the board that it would not attend the oral proceedings.

VIII. Oral proceedings were held on 19 November 2015 in the absence of the appellant. At these oral proceedings, the respondent made its former Auxiliary Request 6 the Main Request.

IX. Claims 1 and 2 of the **Main Request** read as follows:

"1. An isolated bacterial strain of the genus Lactobacillus characterized by that it is selected from the group consisting of the strain of Lactobacillus casei subsp rhamnosus, LN 113, deposited under number LMG P-20562, and the strain of Lactobacillus fermentum, LN 99, deposited under number LMG P-20561, and having the ability to colonise and become established in a human vagina, displaying a disturbed vaginal flora of microorganisms, upon vaginal administration, even during menstrual discharge, wherein said bacterial strain or strains is/are considered established if the bacterial strain or strains is/are still present in the vagina after at least two menstrual cycles from the time of administration, said strains were deposited at Belgian Coordinated Collections of Microorganisms on 14 June 2001.

"2. A method for isolation of a bacterial strain of the genus Lactobacillus or Pediococcus having the ability to colonise and become established in a human vagina, even during menstrual discharge, comprising the following steps:

a) a bacterial sample is collected from the vaginal tract of a woman with a normal, healthy vaginal flora of microorganisms,

b) lactic acid producing bacteria are selected from the vaginal sample of step a),

c) the lactic acid producing bacteria of step b) are pure cultured in vitro in a suitable nutrient medium providing at least one isolated bacterial strain,

d) at least one pure cultured bacterial strain of step c) and/or a combination of at least two bacterial strains of step c) is evaluated as to its ability to colonise and become established in the vagina upon vaginal administration of the bacterial strain to a woman during her menstrual discharge, said woman displaying a disturbed vaginal flora of microorganisms, wherein said bacterial strain or strains is/are considered established if the bacterial strain or strains is/are still present in the vagina after at least two menstrual cycles from the time of administration, and

e) at least one bacterial strain of step d) that display said ability to colonise and become established in the vagina is selected."

Claims 3-5 were directed to specific embodiments of claim 2. Claim 6-7 and 8-9 were directed, respectively, to a composition and to a sanitary article for treatment of infections of the urogenital tract, comprising at least one of the bacterial strains according to claim 1. Claims 10-11 were directed to the use of at least one of the bacterial strains according to claim 1 for the production of a composition or a sanitary article for treatment of infections of the urogenital tract.

X. The following documents are cited in this decision:

D2: US-B1-6,180,100 (publication date: 30 January 2001);

D3: WO-A1-92/13577 (publication date: 20 August 1992);

D5: WO-A2-00/71138 (publication date: 30 November 2000);

D9: WO-A1-99/45099 (publication date: 10 September 1999);

D13: "*Colonisation potential of LN bacteria in women using the Ellen® tampons during ONE menstruation period*" filed by the patentee/respondent on 24 September 2010.

XI. Appellant's submissions, insofar as they are relevant to the present decision, may be summarised as follows:

Admissibility of new evidence

The set-up and completion of the studies disclosed in documents D15 - D17 rendered it technically impossible to submit the results of these studies with the Grounds of Appeal. The data of these studies were *prima facie* highly relevant, not complex and served only to support previously submitted arguments.

Main Request

No submissions were filed specifically relating to the Main Request (not even with regard to its admissibility). However, as claim 1 related to subject-matter comprised in granted claim 1 and claim 2 was identical to granted claim 2, some of the objections

raised in the written procedure against granted claims 1 and 2 could have also been raised against claims 1 and 2 of the Main Request.

Article 123(2),(3) EPC

No objections were raised under these articles against the claims as granted or any of the Auxiliary Requests filed in the appeal procedure.

Article 100(b) EPC (Article 83 EPC)
Product-claim 1

Although the deposit of strains LN 99 and LN 113 ensured their availability, this did not guarantee that they fulfilled the functional feature required by claim 1. None of the examples of the patent showed that the deposited strains indeed had this feature, which was necessary in order to meet the requirements of Article 83 EPC. The *in vivo* assay, required to reliably determine whether the strains had the alleged feature, was not described in the prior art. Post-published document D13 could not be used to prove sufficiency of disclosure. The functional feature that strains LN 99 and LN 113 were required to exhibit was not reproducible. Thus, according to decision G 1/03 (OJ EPO 2004, page 413), there was a lack of sufficiency of disclosure.

Method-claim 2

Steps (a), (b), (c) and (e) involved standard procedures only. Step (d), the only technically relevant step, required an assay for determination of the functional feature. However, an *in vivo* assay was subject to stochastic phenomena and many variables

influenced its outcome, such as amount of administered strains, administration mode and frequency, culture conditions, conditions in the human vagina (hormonal, nutritional, acidity, pre-existing flora), etc. In essence, a standard woman had to be defined, or, alternatively, specific instructions had to be given in terms of test panel size, choice of test candidates, statistical evaluation of results, etc. so as to enable a skilled person to compensate for the variability of the *in vivo* assay. None of the strains disclosed in the patent were selected by using the method of claim 2. Rather all of these strains were isolated using standard approaches and had, as was shown in retrospect, the ability described in step (d) of claim 2. The patent did not provide sufficient guidance with regard to the conditions to be employed in an assay to test the functional feature required in step (d) of claim 2.

Article 100(a) EPC (Article 56 EC)
Product-claim 1

Starting from the closest prior art document D2, the objective technical problem was the provision of lactic acid producing bacterial strains with an improved ability to colonize and become established in a human vagina displaying a disturbed vaginal flora of microorganisms. In order to solve this problem, strains LN 99 and LN 113 had to individually exhibit the functional feature required in claim 1. Examples 1 and 2 of the patent were not suitable to prove that these strains had this feature. According to document D13, these strains were detected in vaginal samples taken after two menstrual cycles, but only few positive results were determined (30% for LN 99 and 20% for LN

113). Thus, these strains did not convincingly solve the problem.

Even if the problem was solved, the solution was obvious. Given the fact that the patent did not provide a reliable assay for determining whether a strain had the functional feature required in claim 1 and that many variables influenced the results of an *in vivo* assay, any strain could be tested positive in an assay for which no conditions were defined. Since the *Lactobacillus* strains known from document D2 were able to become established in a disturbed human vagina (for 5 weeks), it would have been obvious for a skilled person to look for and to identify strains with an improved ability to colonise and become established in a human vagina, wherein the improvement was merely a longer persistence in the vagina. The same applied to document D9 which disclosed *Lactobacillus plantarum* strain LB931, a strain shown to adhere to vaginal epithelial cells.

Method-claim 2

Starting from the closest prior art document D5, the objective technical problem was the provision of a method for selecting bacterial strains with an improved ability to colonize and become established in the human vagina. Steps (a), (b), (c) and (e) involved only standard procedures. The only feature contributing to the solution of the problem was step (d). The feature, requiring that the bacterial strain(s) was/were detectable in the vagina after at least two menstrual cycles after the administration, was arbitrary and did not involve an inventive step. Document D2 disclosed that the most challenging conditions prevailed during menstrual discharge. It was thus obvious for a skilled

person to administer a strain to be tested for its ability to colonise and become established in a human vagina during menstrual discharge. Document D3 disclosed the addition of isolated lactic acid producing bacteria to tampons (method suitable for administration of the bacteria during menstrual discharge) and their use for restoring the microorganism flora in the urogenital region. The method of claim 2 was thus obvious in view of document D5 in combination with either document D2 or D3.

XII. Respondent's submissions, insofar as they are relevant to the present decision, may be summarised as follows:

Admissibility of new evidence

Documents D14, D14a - D14f were late filed, related to objections previously raised in opposition and could have been submitted earlier at the first instance proceedings. The same applied to documents D15 - D17, which in addition were *prima facie* not relevant.

Admissibility of the Main Request

The Main Request was based on requests filed in reply to the Grounds of Appeal. It did not raise any new issue and was filed in direct reply to the comments made by the board in its communication.

Main Request
Article 123(2),(3) EPC

Claim 1 has been limited to two strains and to a human vagina displaying a disturbed vaginal flora of microorganisms. Basis for this limitation was found in

original claim 4, page 8, lines 3 - 20 and page 13, line 28 to page 15, line 6 of the application as filed.

Article 100(b) EPC (Article 83 EPC)
Product-claim 1

Strains LN 99 and LN 113 had been deposited and were shown to have the feature defined in claim 1 (document D13). Example 1 of the patent disclosed an assay performed under conditions indicated in claim 1 and the results, even though measured after one menstrual cycle and not two, supported the claimed subject-matter.

Method-claim 2

Examples 1 and 2 of the patent described one way of performing step (d). A skilled person had no difficulty to evaluate if a strain was established as required. The claimed method could not produce false positives because the strains selected in step (e) inherently had the ability described in step (d). The fact, that it was possible that some strains were wrongly dismissed, did not imply that a skilled person could not carry out the claimed method, which was not a method for identifying strains lacking this ability or a method of grading strains in terms of their ability to colonise and become established in a human vagina.

Article 100(a) EPC (Article 56 EC)
Product-claim 1

The closest prior art document D2 disclosed *Lactobacillus* strains isolated from the vagina of a healthy woman, which differed from strains LN 99 and LN 113 by their identity (deposition number) and their functional properties (ability to colonise the vagina

during menstrual discharge, establishment in the vagina for at least two menstrual cycles). The objective technical problem was the provision of bacterial strains having improved colonizing ability. The results disclosed in Example 1 of the patent, even though not measured after two menstrual cycles, and document D13 showed that the claimed subject-matter solved this problem.

Document D2 did not provide any incentive for a skilled person to further improve the *Lactobacillus* strains disclosed therein, let alone to improve them with the ability exhibited by strains LN 99 and LN 113. Moreover, there was no evidence on file showing that, when trying to achieve such improvement, the skilled person would have arrived at the specific strains LN 99 and LN 113 in an obvious manner.

Method-claim 2

The closest prior art document D5 disclosed methods and compositions for oral administration of *Lactobacillus* for establishing and maintaining a healthy urogenital flora. The selection criterion for vagina colonisation was an *in vitro* adherence criterion limited only to oral administration (ability to pass through the stomach, reach the small and large intestine, grow and persist in gastrointestinal and urogenital tracts). Document D5 did not disclose step (a), since it disclosed that the bacteria originated from the women to be treated. With regard to step (d), the strains were not administered during menstruation and the evaluation was not performed *in vivo* in the vagina and was not measured after two menstrual cycles.

The objective technical problem was the provision of a method for isolating bacterial strains with improved properties for treating infections of the urogenital tract. The method of claim 2 solved this problem.

Document D3 did not disclose a method for isolating bacteria with improved properties for treating infections of the urogenital tract. The skilled person lacked any incentive for turning to this document which only disclosed that lactic acid bacteria suitable for treating urogenital infections could be isolated from women with a healthy vaginal flora. The document provided no guidance whatsoever with respect to step (d) of claim 2.

Document D2 did not provide an incentive for an *in vivo* evaluation. On the contrary, according to document D2, there was a correlation between *in vivo* and *in vitro* adhesion assays of lactic acid producing bacteria. Thus, a skilled person had no reason to consider a time consuming and complex *in vivo* assay as an alternative to an *in vitro* evaluation. Moreover, from the reference in document D2 to the presence of a maximum adherence prior to ovulation and menstruation, no conclusions could have been derived regarding the minimal adherence found during the menstrual cycle. It was only the present patent which contained a discussion relating to the minimum adherence.

XIII. The appellant (opponent), in writing, requested that the decision under appeal be set aside and the patent be revoked. In addition, it requested that documents D14, D14a - D14f and D15 - D17 were admitted into the proceedings.

XIV. The respondent (patentee) requested that the decision under appeal be set aside and that the patent be maintained upon the basis of claims 1 - 11 of the Main Request filed at the oral proceedings before the board on 19 November 2015. In addition, the respondent requested that documents D14, D14a - D14f and D15 - D17 were not admitted into the proceedings.

Reasons for the Decision

Admissibility of new evidence

1. Documents D14, D14a - D14f were filed by the appellant with the statement of Grounds of Appeal in support of its arguments relating to the reproducibility of the method of claim 2 (Article 83 EPC).

   The reproducibility of this method was addressed in opponent/appellant's Notice of opposition and in a communication of the opposition division annexed to the Summons to oral proceedings. Documents D12 and D13 were filed by the patentee/respondent in order to address this issue. In the communication pursuant to Article 15(1) RPBA, the board noted that the appellant had not provided reasons to explain the filing of these documents at that late stage of the proceedings and why they could not have been filed at first instance. The appellant did not respond and thus no reasons were provided.

2. Three months after filing its Grounds of Appeal, the appellant submitted documents D15 - D17. It was stated, that these documents were filed in reply to the comments of the opposition division made in the decision under appeal, concerning the presence of the

functional feature of claim 1 in lactic acid producing bacteria known from the prior art (cf. page 9, point 5.4.8 of the decision under appeal) (Article 56 EPC).

In the Notice of opposition, the opponent/appellant relied on the lactic acid producing bacteria of document D2 as the closest prior art and formulated the objective technical problem as the provision of alternative lactic acid producing strains (cf. *inter alia*, pages 19-20, points 3.2.1 and 3.2.2 of Notice of opposition). This line of argumentation was addressed at first instance by the patentee/appellant and by the opposition division in a communication annexed to the Summons to the oral proceedings. The comments made by the opposition division in the decision under appeal do not differ from the comments already made in said communication and cannot therefore be used as an explanation for the late filing of new evidence. Documents D15 - D17 could and should have been filed at an earlier stage of the proceedings.

3. Therefore, the board, exercising its discretion, decides not to admit documents D14, D14a - D14f and D15 - D17 into the appeal proceedings (Articles 12(4) and 13(1) RPBA, respectively).

Admissibility of the Main Request

4. The Main Request, filed at oral proceedings before the board, is identical to former Auxiliary Request 6 filed in reply to the board's communication. This Auxiliary Request was identical to Auxiliary Request 4 filed in reply to the Grounds of Appeal, except for the introduction of the feature "*displaying a disturbed vaginal flora of microorganisms*" to qualify the "*human vagina*" in claim 1, and for the deletion of all

references to "*prophylaxis*", thus limiting the Main Request to "*treatment of infections of the urogenital tract*".

5. These amendments, with regard to former Auxiliary Request 4, have been made in reply to the board's comments made in the communication pursuant to Article 15(1) RPBA. The amendments reduce the complexity of the case, do not raise new issues and do not negatively affect procedural economy. The appellant has not contested the admissibility of this request (or any other of the respondent's claim requests filed in appeal proceedings; cf. point VII *supra*). Therefore, the Main Request is admitted into the appeal proceedings.

Scope of the appeal

6. Whilst claims 1 and 2 have been extensively discussed under Articles 83 and 56 EPC in the decision under appeal, all other claims were referred to only in a general manner (cf. page 10, point 5.4.12, page 12, point 5.9.3 and page 22, point 6.14.6 of the decision under appeal). In the statement of Grounds of Appeal, the appellant maintained the objections raised under Articles 83 and 56 EPC against claims 1 and 2 as upheld by the opposition division (claims as granted). No other claims were attacked in the Grounds of Appeal. Thus, the scope of the appeal is limited to claims 1 and 2.

Main Request
Article 123(2),(3) EPC

7. The amendments introduced into the Main Request restrict the scope of the granted claims (cf. point 4

supra). Basis for the feature introduced into claim 1 is found on page 14, line 27 to page 15, line 2, page 15, lines 21 - 33, and Example 1, page 16, line 3 to page 18, line 6 of the application as filed. Article 100(c) EPC was not a ground for opposition. Thus, the Main Request fulfils the requirements of Articles 123(2) and (3) EPC.

Article 100(b) EPC (Article 83 EPC)
Product-claim 1

8. The deposited bacterial strains LN 99 and LN 113 are described in claim 1 as having a specific functional property, namely "*the ability to colonise and become established in a human vagina, displaying a disturbed vaginal flora of microorganisms, upon vaginal administration, even during menstrual discharge, wherein said bacterial strain or strains is/are considered established if the bacterial strain or strains is/are still present in the vagina after at least two menstrual cycles from the time of administration*" (cf. point IX *supra*).

9. According to decision G 1/03 (*supra*), "(i)*f an effect is expressed in a claim* [and is not achieved by the claimed subject-matter; added by the board]*, there is lack of sufficient disclosure. Otherwise, i.e. if the effect is not expressed in a claim but is part of the problem to be solved, there is a problem of inventive ste*p" (cf. G 1/03, *supra*, point 2.5.2 of the Reasons). In line therewith, the claimed strains LN 99 and LN 113 must have the functional feature cited in claim 1. Otherwise, there is lack of sufficient disclosure.

10. The isolation and evaluation of the *Lactobacillus* strains is described in paragraph [0064] of the patent.

It is stated that strains LN 99 and LN 113 are, among others, the best strains, "*i.e. the strains having best potential to colonise a disturbed vaginal flora of microorganisms*". Further evaluation by means of clinical studies showed these strains to colonise and become "*established in the vagina ... after at least two menstrual cycles from the time of administration (the administration of bacteria started during the first menstrual discharge)*" (cf. page 7, lines 1 - 7 of the patent). However, the data and results from these clinical studies are not disclosed in the patent.

11. Example 1 discloses the "*Colonisation and establishment of lactic acid producing bacteria upon vaginal administration*". 15 women diagnosed with bacterial vaginosis (displaying disturbed vaginal microorganism flora) were treated with antibiotic and afterwards, "*6 patients used tampons comprising approximately 10^3 cfu lyophilised bacteria of the strains LN 01, LN 23, LN 99, LN 113, and LN 40 during the first menstrual period ... During the second menstrual period, all 15 patients used conventional tampons without lactic acid producing bacteria, and a vaginal sample was taken a few days after this menstruation*".

While all patients using tampons with the bacterial strains showed no Gram strains after the second menstrual period, almost all patients using conventional tampons without lactic acid producing bacteria showed Gram strains (see Table 2). Although the presence of strains LN 99 and LN 113 was not explicitly tested as required in claim 1 ("*present in the vagina after at least two menstrual cycles from the time of administration*"), these results do not cast any doubts on the assertion made in paragraph [0064] of the patent.

12. Example 2, which refers to the use of "*tampons comprising approximately 10^3 cfu lyophilised bacteria of the strains LN 01, LN 23, LN 99, LN 113, and LN 40 during their monthly menstrual discharge during a period of 12 - 18 months*", is not relevant for the assessment of claim 1, since it concerns only "*healthy women with no vaginal complaints*" (cf. page 8, paragraph [0071] of the patent).

13. According to the case law, post-published documents may be used as evidence whether the invention is indeed reproducible without undue burden at the relevant filing date (cf. *inter alia*, T 994/95 of 18 February 1999, point 8 of the Reasons; T 157/03 of 4 January 2005, point 9 of the Reasons, T 1262/04 of 7 March 2007, points 2 - 5 of the Reasons).

The studies reported in post-published document D13, in particular the results shown in Table 1, confirm that strains LN 99 and LN 113 have the functional feature cited in claim 1. Although not present in all women diagnosed with bacterial vaginosis and treated as in Example 1 of the patent, the presence of these strains is identified in one (LN 113) respectively two (LN 99) patients (out of 9 patients) measured under the conditions referred to in claim 1. Although the positive results, carried out according to the conditions in Examples 1 and 2, are low, it has to be considered that the amount of bacteria administered is also extremely low compared to the amount reported in the prior art for this type of studies (10^3 *vs* 10^9; cf. point 18 *infra*). In any case, the results obtained do not cast any doubts on the assertion made in paragraph [0064] of the patent.

14. Thus, in the light of the evidence on file, the invention according to claim 1 is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

Method-claim 2

15. It is not contested that steps (a), (b), (c) and (e) of claim 2 are straightforward and well-known in the prior art. It is, however, objected that the patent does not provide sufficient information to carry out step (d) without undue burden (cf. point XI *supra*).

16. Step (d) requires to evaluate a lactic acid producing bacteria isolated in step (c) "*as to its ability to colonise and become established in the vagina upon vaginal administration of the bacterial strain to a woman during her menstrual discharge, said woman displaying a disturbed vaginal flora of microorganisms*". The criteria for a strain to be "*considered established*" are defined as being present "*in the vagina after at least two menstrual cycles from the time of administration*" (cf. point IX *supra*).

17. Steps (a) - (c) are referred to on page 6, lines 38 - 43 of the patent, steps (d) - (e) are described on page 6, line 44 to page 7, line 7, although in general terms and with additional selection steps (generation time <30 minutes, ability to inhibit uropathogens growth *in vitro*). Strains LN 99 and LN 113, among others, were selected according to step (d) in a later evaluation (cf. page 7, lines 5 - 7).

In Example 1, the bacterial strains were administered to patients with bacterial vaginosis using "*tampons comprising approximately 10^3 cfu lyophilised*

bacteria ... during the first menstrual period after the antibiotic treatment" (cf. page 7, paragraph [0065] of the patent). The results obtained "*show that the lactic acid producing bacteria were still present in the vagina after the second menstrual cycle*" and that "*a relatively small number of administered bacteria ... are enough for a complete vaginal colonization and establishment during menstrual discharge*" (cf. page 8, paragraphs [0068] and [0069]). In Example 2, the bacterial strains were administered to healthy women in the same manner as in Example 1 and the presence of the bacterial strains was evaluated and measured during a period of 12 - 18 months.

18. The conditions described in the patent also match with the disclosure in the prior art evidence on file.

Example 16 of document D2 refers to "*intravaginal ... instillation of lactobacilli into human female patients*", wherein "*each of the patients instilled 1 mL of this viable bacterial solution* [with a concentration of 10^{11} organisms/mL] *deeply into the vagina ... After instillation, in the adult patients a tampon was inserted into the vagina to prevent leakage overnight, with a view to maximizing colonization with lactobacilli*" (cf. column 17, lines 40 - 57). At least one patient "*was protected by lactobacilli therapy for 4 months, and has remained colonized by lactobacilli and infection free for an additional 5 months*" (cf. column 20, lines 49 - 54).

Document D3 refers to a "*bacterial powder ... used to be added to a tampon* [containing] *about 100 mg powder, corresponding to >10 billion viable lactic acid producing bacteria*", and further indicates how to apply the bacterial powder to said tampon (cf. page 6, lines

15 - 25). According to this document, the tampon "*can be used with a good result to rapidly restore the natural flora of micro-organisms of the urogenital region after an antibiotic treatment*" (cf. page 5, lines 15 - 19). Claim 9 of this document is directed to a "*tampon ... characterized in that the amount of* [lactic acid producing] *bacteria added is at least* 10^4 *and at most 50 x* 10^9 *per unit*".

Although mainly concerned with oral administration, document D5 also refers to a medical device (tampon) which "*is contacted or coated with lactobacillus at a concentration of about* 10^9 *organisms/ml prior to introduction into a patient in need of such device*" (cf. page 19, lines 21 - 30).

19. In the light of the patent itself and the evidence on file concerning methods of vaginal administration, relevance of growth media for adherence properties, amount, dosage and frequency of administration (cf. *inter alia*, documents D2, D3, D5 above), the board does not consider that undue burden is required from a skilled person to carry out step (d). None of these factors is essential for a successful performance of the claimed method. They might all be adjusted so as to achieve better or optimal results but this optimization lies within the normal capabilities of a skilled person.

20. Claim 2 fulfils the requirements of Article 83 EPC.

Article 100(a) EPC (Article 56 EPC)
Product-claim 1

21. Document D2, representing the closest state of the art, discloses several *Lactobacilli* strains isolated, *inter*

alia, from the vagina of healthy women (cf. column 7, lines 48 - 50 and column 8, Table 2). The strains are selected by using an *in vitro* adherence assay using "*uroepithelial cells ... harvested from women on the tenth day of their menstrual cycle, to optimise subsequent attachment of lactobacilli*" (cf. column 7, Example 4). One of these strains (*L. casei* ssp. *rhamnosus* GR-1) is intravaginally instilled into patients with disturbed vaginal microorganism flora and used for therapeutical purpose, namely to colonise and become established in the vagina and to thereby inhibit the growth of pathogenic bacteria (cf. Example 16, columns 17 - 20). At least one patient "*was protected by lactobacilli therapy for 4 months, and has remained colonized by lactobacilli and infection free for an additional 5 months*" (cf. column 20, lines 49 - 52).

22. The objective technical problem has been formulated as "*the provision of lactic acid-producing bacterial strains with an improved ability to colonize and become established in the human vagina*" (cf. point 5.1, paragraph bridging pages 28-29 of appellant's Grounds of Appeal and page 10, penultimate paragraph of respondent's reply thereto).

However, according to the case law of the Boards of Appeal, when inventive step is based on an improved effect over a claimed area, comparative tests with the closest prior art must convincingly show that the effect has its origin in the distinguishing feature of the invention (cf. "Case Law of the Boards of Appeal of the EPO", 7th edition 2013, I.D.4.2 and I.D.10.9, pages 175 and 231, respectively). In the present case, there are no tests on file in which strains LN 99 and LN 113 are compared with any of the bacterial strains disclosed in document D2, in particular with the strain

L. casei ssp. *rhamnosus* GR-1 used in the therapeutic treatments disclosed in Example 16 of document D2. In absence of these comparative tests, the objective technical problem is defined by the board as the provision of alternative *Lactobacillus* strains for the therapeutic treatment of human vagina displaying a disturbed vaginal flora of microorganisms.

23. In the light of the decision taken with regard to the requirements of Article 83 EPC in points 10 - 13 *supra*, the claimed subject-matter solves this problem.

24. Moreover, none of the prior art documents on file would have led a skilled person to the specific strains LN 99 and LN 113 in an obvious manner. Contrary to appellant's contention, none of these strains is obviously derivable from document D2 alone or in combination with document D9.

There is no evidence on file to show that *Lactobacilli* strains LN 99 and LN 113 could have been isolated by using the *in vitro* adherence assay referred to in Example 4 of document D2 (cf. point 28 *infra*). The identification and selection of these specific strains from all other possible *Lactobacilli* strains is not obvious. Moreover, there is no reference in document D2 to an administration of *Lactobacilli* strains to a patient during menstrual discharge. These deficiencies are not remedied by reference to the adherence test disclosed in Example 7 of document D9. This test is used only to study the properties of *Lactobacillus plantarum* strain LB931, a strain isolated from the urogenital tract of a healthy woman by a screening based on the ability to inhibit the growth of enterobacteria (cf. page 7, Example 1 of document D9).

25. Claim 1 fulfils the requirements of Article 56 EPC.

Method-claim 2

26. Document D5, representing the closest prior art, discloses a method for selecting *Lactobacilli* useful for establishing, maintaining and/or improving a healthy gastrointestinal and urogenital flora in women. Among several criteria provided for characterizing the selected *Lactobacilli*, there are the ability to adhere to vaginal and uroepithelial cells and the ability to grow and persist in the gastrointestinal and urogenital tracts (cf. page 5, lines 8 - 17, page 10, line 30 to page 11, line 10, page 18, lines 20 - 28). Besides the general reference to the adherence criterion, the document does not indicate how to measure or test said adherence.

27. Starting from document D5, the objective technical problem is the provision of a method for selecting *Lactobacilli* strains with an improved ability to colonize and become established in a human vagina (cf. page 21, point 6.14 of the decision under appeal; page 35, point 5.2, first paragraph of the Grounds of Appeal; page 17, last paragraph of respondent's reply). The finding of the opposition division, that claim 2 is a credible solution to this technical problem, has not been contested (cf. page 21, point 6.14.1 of the decision under appeal).

28. Document D2 is the sole document on file disclosing an adherence test. In Example 4, reference is made to an *in vitro* assay for testing the adherence of *Lactobacilli* strains isolated, *inter alia*, from vagina of healthy women. In Example 3, it is stated that "(t)*here is a correlation between the receptivity of*

uroepithelial cells for bacteria/bacterial adherence to the cells in the in vivo and in vitro environment ... Accordingly, the in vitro results ... are considered a reliable indication of the corresponding in vivo situation" (cf. column 7, lines 34 - 43). In view of these clear statements the skilled person, facing the aforementioned technical problem, had no reason to contemplate a much more complex, cumbersome and demanding *in vivo* assay for replacing the *in vitro* assay referred to in document D2.

Moreover, document D2 further discloses that "(t)*he menstrual cycle affects this* [host cell] *receptivity*" and, according thereto, "(t)*he uroepithelial cells used in the* [in vitro] *experiments ... were harvested from women on the tenth day of their menstrual cycle, to optimise subsequent attachment of lactobacilii*" (cf. column 7, lines 57 - 65; inserts added by the board). However, these conditions are far removed from those of step (d) of claim 2, where "*vaginal administration of the bacterial strain to a women during her menstrual discharge*" is required.

Finally, all references in Example 16 of document D2 to the ability of the disclosed *Lactobacilli* strains to colonize and to remain established in the vagina of treated patients are made only in the context of evaluating the properties of these strains and not for screening, identifying and/or isolating them. To change this context would have required hindsight knowledge of the present patent.

29. Document D3 refers to the administration of "*a tampon or sanitary napkin ... impregnated with viable cultures of lactic acid producing bacteria*" for restoring "*the natural flora of micro-organisms of the urogenital*

region after an antibiotic treatment", wherein the bacteria "*suitably used for this purpose are isolated from the genital region of healthy women*" (cf. page 3, lines 5 - 8 and page 5, lines 15 - 19, 28 - 30). These *Lactobacilli* bacteria are selected according to several criteria, such as antagonist properties against uropathogens, stability at cultivation, genetic stability, viability, etc. (cf. *inter alia*, page 3, lines 9 - 17, 30 - 36 and page 5, line 36 to page 6, line 9). There is no disclosure at all of any specific assay for any of these criteria, let alone a suggestion that could have led a skilled person to an *in vivo* assay under the specific conditions of step (d) of claim 2.

30. Since step (d) of claim 2 is not derivable in an obvious way from the documents on file, there is no reason to consider in detail other arguments put forward by the appellant concerning other steps of the method of claim 2.

31. Claim 2 fulfils the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent with the following claims and a description to be adapted:

   Claims No. 1 - 11 of the Main Request received during the oral proceedings of 19 November 2015.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated