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**Datasheet for the decision
of 30 June 2017**

Case Number: T 1133/13 - 3.3.04

Application Number: 07815021.6

Publication Number: 2073836

IPC: A61K38/54

Language of the proceedings: EN

Title of invention:

Methods and Compositions for the Treatment of Vaginal Diseases
Employing Peroxide-Producing Enzymes and Peroxidases

Applicant:

Laclede, Inc.

Headword:

Peroxidase system for the treatment of vaginal diseases/
LACLEDE

Relevant legal provisions:

EPC Art. 56

Keyword:

Inventive step - (no)

Decisions cited:

Catchword:



Beschwerdekammern
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Case Number: T 1133/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 30 June 2017

Appellant:
(Applicant)

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Decision under appeal:

**Decision of the Examining Division of the
European Patent Office posted on 17 December
2012 refusing European patent application No.
07815021.6 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman G. Alt
Members: A. Chakravarty
M. Blasi

Summary of Facts and Submissions

- I. Appeal was filed by the applicant (appellant) against the decision of the examining division to refuse European patent application 07 815 021.6. The application was filed as an international application and published as WO 2008/045696 (the application as filed). The title of the application is "*Methods and Compositions for the Treatment of Vaginal Diseases Employing Peroxide-Producing Enzymes and Peroxidases*".
- II. The examining division considered a main and four auxiliary requests. It held that the subject-matter of the claims of the main and auxiliary requests 1 and 4 lacked an inventive step. Auxiliary requests 2, 3 and 4 contravened the requirements of Article 123(2) EPC and Article 84 EPC.
- III. The appellant filed a statement of grounds of appeal in which the grant of a patent was requested, as main request, on the basis of the claims filed before the examining division on 24 May 2012 or on the basis of one of the five sets of claims filed with the statement of grounds of appeal as auxiliary requests 1 to 5.
- IV. The board appointed oral proceedings and subsequently issued a communication pursuant to Article 15(1) RPBA.
- V. Oral proceedings before the board were held on 30 June 2017. The appellant's final requests at the oral proceedings were that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request (filed as auxiliary request 2 together with the statement of grounds of appeal) or alternatively on the basis of the claims of auxiliary requests 1 or 2 (filed as auxiliary requests

4 and 5 together with the statement of grounds of appeal). At the end of the oral proceedings, the chairman announced the decision of the board.

VI. Claim 1 of the main request reads:

"1. Composition for use in the treatment of vaginal infections, wherein the composition consists of:
(a) a peroxidase enzyme that catalyzes a reaction between hydrogen peroxide and a salt that acts as an oxygen acceptor and is capable of reacting with hydrogen peroxide to form a biocide, the peroxidase enzyme being present in a sufficient quantity such that the biocide is produced in a therapeutically effective concentration;
(b) a salt that acts as an oxygen acceptor and is capable of reacting with hydrogen peroxide to form a biocide in a quantity sufficient to form a therapeutically effective concentration of the biocide;
(c) at least one of an ingredient selected from the group consisting of lysozyme, lactoferrin, and/or a steroid; and
(d) an aqueous medium in which the peroxidase enzyme and the salt that acts as an oxygen acceptor are stable, such that the composition is suitable for vaginal administration".

VII. Claim 1 of auxiliary request 1 is identical to claim 1 of the main request up to feature (d) but in addition includes features (e) and (f) as follows:

"(e) the composition further comprises an effective amount of an inhibitor that is specific for catalase, which is a salt of ascorbic acid; and wherein
(f) the composition further comprises an iron salt".

VIII. Claim 1 of auxiliary request 2 differs from claim 1 of auxiliary request 1 only in the first sentence of the claim, where the word "comprises" replaces the phrase "consists of".

IX. The following documents are mentioned in this decision:

D4: US 4,576,817

D5: WO 92/01466

D7: US 5,389,369

D8: US 5,503,853

D9: US 2005/0197495

X. The appellant's arguments relevant to the decision, made in writing and at oral proceedings, are summarised as follows:

Main request - claim 1

Claim construction

The claim was for "*a composition for use in the treatment of vaginal infections*". The skilled person, reading the claim in the light of the description, especially, the "*Summary of the Invention*" on page 10, would understand that the term "*vaginal infections*" as used in claim 1 included "*vaginal infections caused by pathogenic bacteria and yeasts*" but did not extend to viral infections.

Inventive step - Article 56 EPC

The examining division had not correctly applied the "*problem-and-solution approach*" in reaching its decision on inventive step. In particular, the wrong document had been chosen to represent the closest prior

art. The examining division held that the closest prior art for the subject-matter of claim 1 was any of documents D5, D7 or D8. However, the technical field of the present invention was the treatment of vaginal infections and none of documents D5, D7 and D8 disclosed compositions for this purpose.

Document D5, an international patent application, concerned the prophylactic and therapeutic application of compositions comprising peroxidases for the prevention and treatment of enveloped virus infections, in particular herpes simplex virus (HSV) and human immunodeficiency virus (HIV) infections. It was disclosed that these compositions could also contain lactic acid bacteria (cf. page 16, second paragraph). Document D8 represented the U.S. patent equivalent of document D5, so that the arguments submitted in relation to document D5 applied equally.

Document D7 concerned a composition containing a haloperoxidase and at least one α -amino acid for killing yeast and sporular microorganisms. It did not explicitly mention that vaginal infections could be treated.

Instead of the documents selected by the examining division, document D9 was the closest prior art for the claimed invention. It disclosed therapeutic formulations containing an "*ultra-cleansed lactoferrin preparation*" and was the only document that clearly mentioned the vagina as a target organ for treatment (see paragraph [0052]). It also disclosed the preparation of vaginal healthcare formulations (see Example 11, especially paragraph [0190]).

Starting from this closest prior art, the objective technical problem was the provision of simplified alternative compositions, in particular those free of living bacteria and not requiring ultra-purified lactoferrin, turmeric root extract, or vitamin C, for use in vaginal healthcare and the treatment of vaginal infections.

Alternatively, should the board hold document D8 to represent the closest prior art, the claimed subject-matter differed from the compositions disclosed therein in that they lacked both live bacteria and the ingredients listed under item (c) of the claim. The effect of this difference was the avoidance of the risk to the patient associated with the administration of live microorganisms and also of regulatory problems, e.g. FDA approval, associated with them. In view of the above differences and the effect thereof, the objective technical problem was the provision of a safer composition for the treatment of vaginal infections.

The solution was the cell-free composition as defined in claim 1.

Such a simplified composition was not obvious in the light of either document D8 or document D9 alone or in combination with any of the other documents on file. Only with an inadmissible hindsight view, having in mind the appellant's invention, could the examining division have arrived at a different opinion.

Auxiliary requests 1 and 2 - claim 1

The subject-matter of claim 1 of both requests differed from claim 1 of the main request in that the composition further included the features referred to

in items (e) and (f), i.e. an effective amount of an inhibitor specific for catalase, being a salt of ascorbic acid and an iron salt.

Contrary to the view expressed by the examining division in the decision under appeal (see point 13 of the decision), there was nothing in the cited prior art that would have provided any motivation for the skilled person to combine the peroxidase system of claim 1 (a) and (b) with a catalase inhibitor and an iron salt. In the absence of any such motivation, teaching or pointer in the art, the claimed subject-matter had to be considered as involving an inventive step.

Reasons for the Decision

The invention

1. The application concerns a composition containing a peroxidase enzyme and a salt (together referred to as a peroxidase system) for use in the treatment of vaginal infections. The peroxidase enzyme catalyses a reaction between hydrogen peroxide and the salt which results in the production of a biocide (see paragraph [0046]). The hydrogen peroxide may be naturally present in the vagina (claim 1; see paragraph [0029]) or be supplied by an oxidoreductase enzyme (claim 2; see paragraph [0029]).

Main request - claim 1

Claim construction

2. The claim is for "*a composition for use in the treatment of vaginal infections*". In the board's view, the "*treatment of vaginal infections*" includes the treatment of any type of infection i.e. where the pathogen is a bacteria and a yeast, but also may be a virus.
3. The appellant argued that the skilled person, reading the claim in the light of the description, especially, the "*Summary of the Invention*" on page 10, would consider that the term "*vaginal infections*" as used in claim 1 meant "*vaginal infections caused by pathogenic bacteria and yeasts*".
4. The board can find nothing in the description of the application to support this limited reading. The application as filed contains no worked examples of the invention, but paragraph [0028] of the description reads "*there is a need for improved methods and compositions to treat vaginal diseases and conditions, **particularly** vaginal diseases and conditions that are bacterial or fungal in origin*" (emphasis added by the board). From this, the skilled person would understand that "*vaginal diseases and conditions that are bacterial or fungal in origin*" are the preferred diseases to be treated, but not the only ones.

Inventive step - Article 56 EPC

5. To assess whether or not a claimed invention meets the requirements of Article 56 EPC, the board applies the "*problem and solution*" approach, long established in

the case law of the boards of appeal (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition, 2016, I.D.2). The first step is the determination of the closest prior art.

Closest prior art

6. The closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (*Id.*, I.D.3.1).
7. The claimed compositions contain the peroxidase system defined in (a) and (b) of claim 1 in an aqueous medium, item (d). They also contain one or more of lysozyme, lactoferrin and a steroid, as referred to in item (c) of claim 1. The purpose of the compositions is the treatment of vaginal infections.
8. Document D9 relates to "*treatments for contaminant reduction in lactoferrin preparations and lactoferrin containing compositions*" (see title) and discloses methods for preparing an ultra-cleansed lactoferrin preparation (termed "LF-TCR") suitable for pre-biotic applications, i.e. for promoting growth of beneficial microorganisms (see paragraph [0002]). Table 6 on page 21 shows the composition of an LF-TCR base formulation for different human *in vivo* applications which consists of ultra-cleansed lactoferrin, turmeric root extract, sodium bicarbonate and vitamin C.
9. Example 11 of document D9 discloses vaginal healthcare formulations, including vaginal suppositories, for the treatment of vaginal infections of bacterial, fungal or

parasitic origin (see paragraph [0189]). These compositions comprise the LF-TCR base formulation, a hydrogen peroxide-producing *Lactobacillus crispatus*, and an active lactoperoxidase system composed of either "Mixture (A)" containing lactoperoxidase, urate oxidase, urate and potassium thiocyanate, or "Mixture (B)" containing lactoperoxidase, sodium thiocyanate, benzylalkonium chloride and DMSO (see paragraph [0190]).

10. Document D8 is a US patent that relates to prophylactic and therapeutic applications of peroxidases for the prevention and treatment of enveloped virus infections by administration of a peroxidase system i.e. a system comprising a peroxidase and an oxygen acceptor salt, equivalent to the features in items (a) and (b) of present claim 1 (see document D8, column 6, lines 6 to 46). The antiviral activity of these compositions is due to the peroxidase-catalysed oxidation of a substrate - a halogen or pseudo-halogen - by an oxygen donor - a peroxide, for example hydrogen peroxide - to form negatively-charged, monovalent oxidising compounds (*Id.*, column 5, lines 1 to 6).
11. The peroxide is preferably supplied by an enzymatic system including a substrate, an enzyme specific to such substrate or, alternatively, by microorganisms, such as the *Streptococci* and *Lactobacilli* that are commonly referred to as lactic acid bacteria. It is further stated that the "Use of such microorganisms (microbes) is especially preferred in the medicaments formulated for use as a vaginal cream for topical application" (see column 8, lines 17 to 29).
12. Thus, both documents D8 and D9 disclose compositions for the treatment of vaginal infections. However, the

compositions disclosed in document D9 contain lactoferrin as the main ingredient and do not necessarily contain a peroxidase system, mandatory in the presently claimed compositions. The compositions disclosed in document D8 all contain such a peroxidase system. These latter compositions therefore have the most relevant technical features in common with the compositions of claim 1 and represent the closest prior art for the subject-matter of claim 1.

The technical problem to be solved

13. The claimed compositions differ from those representing the closest prior art in that they do not contain lactic acid bacteria and additionally contain one or more of lysozyme, lactoferrin and a steroid. The technical effect of the absence of lactic acid bacteria is that the peroxide substrate for the peroxidase has to be additionally supplied, for example by microorganisms naturally present in the vagina or by an additionally administered oxidoreductase system (see paragraph [0029] of the description). The absence of live bacteria also removes any safety risks associated therewith. The increased ease of regulatory approval, mentioned by the appellant, is not considered by the board to constitute a technical effect and is therefore disregarded in the formulation of the technical problem. The lysozyme, lactoferrin and the steroid exert their known activities. Lysozyme and lactoferrin being known to have antimicrobial activity and steroids to have anti-inflammatory activity.

14. In view of the above differences and the technical effects thereof, the board considers that the technical problem to be solved by the composition of claim 1 may

be formulated as the provision of safer, alternative compositions for treating vaginal infections.

Obviousness

15. The question to be answered by the board is whether or not the skilled person, faced with the above formulated technical problem and starting from the compositions disclosed in document D8, representing the closest prior art, would have considered it obvious to provide the claimed, lactic acid bacteria-free, compositions as a solution to the problem.
16. As set out above in points 10 and 11, document D8 discloses compositions containing a peroxidase system, i.e. a system comprising a peroxidase and an oxygen acceptor salt, for use in the prophylaxis and treatment of enveloped virus infections, which in the case of suppositories for the treatment of vaginal infections, include lactic acid bacteria, these bacteria being included to generate the hydrogen peroxide substrate needed for the peroxidase to act on.
17. In seeking to provide safer, alternative compositions for treating vaginal infections, and in particular addressing safety concerns associated with the administration of live bacteria, the skilled person would logically have had to consider whether the inclusion of live lactic acid bacteria was an essential requirement for the supply of peroxide, i.e. for the functioning of the peroxidase system and thus ultimately for treating infections via the generation of negatively charged, monovalent oxidising compounds (cf. document D8, column 6, lines 10 to 14).

18. As noted above, document D8 discloses that the "[u]se of *[lactic acid bacteria]* is especially preferred in the medicaments formulated for use as a vaginal cream for topical application" (*supra*). However, the document discloses also that "[p]referably, the oxygen donor is an enzymatic system including a substrate, an enzyme specific to such substrate and other necessary reactants, such as water and/or oxygen and/or hydrogen." (see column 8, lines 17 to 20). Thus, the skilled person knew that lactic acid bacteria as a source of peroxide could be replaced by an alternative source, such as an enzymatic system.
19. The board therefore concludes that adapting the compositions disclosed in document D8 to omit lactic acid bacteria would have been obvious to the skilled person as a solution to the problem formulated above.
20. A second difference between the claimed compositions and those disclosed in document D8 is that the former include at least one of lysozyme, lactoferrin and/or a steroid.
21. There is no disclosure in the application as filed that these ingredients exert anything other than their commonly known activities nor has the appellant put forward any arguments to this effect. Lysozyme and lactoferrin were known to have antimicrobial activity and steroids to have anti-inflammatory activity. The board is of the view that, since the skilled person knew that each of these activities was useful in the context of treating infections, they would have considered it obvious to include one or more of the three compounds in a composition intended for the treatment of vaginal infections.

22. Hence the subject-matter of claim 1 lacks an inventive step.

Auxiliary requests 1 and 2 - claim 1

23. The subject-matter of claim 1 of these requests differs from that of the main request in that the claimed composition further includes ascorbic acid and an iron salt. The former acts as an inhibitor specific for catalase (see claim 1) and the latter acts as a potentiator for ascorbic acid salt in its role as catalase inhibitor (see paragraph [0055] of the application as filed).
24. Document D4 is a US patent that relates to enzymatic absorbent materials such as bandages and pads that produce a bacteriostatic effect upon contact with body fluids such as serum. In one embodiment, the absorbent material incorporates an oxidoreductase enzyme which produces hydrogen peroxide, as well as a peroxidase that catalyses a reaction between hydrogen peroxide and an oxygen-accepting anion in serum to produce an oxidised anionic bacterial inhibitor (see column 3, lines 55 to 60).
25. Document D4 further discloses, as part of a discussion of the common general knowledge of the skilled person, that *"the operable integrity of the enzymatic system can be affected by catalase which is present in commercial glucose oxidase as well as mucous membrane tissue, blood and blood serum"* and *"to reduce loss of hydrogen peroxide through the presence of catalase, an effective amount of an enzymatic inhibitor specific to catalase can be [...] incorporated into the enzymatic absorbent material"*. Examples of catalase inhibitors are given as *"sodium ascorbate, potassium ascorbate,*

ascorbyl palmitate". It is also discloses that "*iron salts such as ferrous sulfate can be incorporated into the enzymatic absorbent material as a potentiator for ascorbate salt in its role as catalase inhibitor*" (see column 4, lines 27 to 44).

26. The presence of catalase in mucus membranes and hence in vaginal tissue and the problems associated therewith, as well as the use of ascorbic acid salts and iron salts to obviate this problem, was therefore common general knowledge in the art.
27. Consequently, the additional features of claim 1 of auxiliary requests 1 and 2 vis-à-vis claim 1 of the main request do not alter the conclusion reached by the board for claim 1 of the main request.
28. Hence, auxiliary requests 1 and 2 do not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated