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D E C I S I O N
of 19 June 1996

Case Number: T 0148/93 - 3.3.4

Application Number: 84101909.4

Publication Number: 0120301

IPC: A01N 59/12

Language of the proceedings: EN

Title of invention:
Method of producing standardized iodophor preparations and such preparations

Patentee:
Euro-Celtique S.A.

Opponent:
West Design Chemical, Inc.

Headword:
iodophor/EURO-CELTIQUE

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request - Inventive step (yes) - after amendments"

Decisions cited:
-

Catchword:
-

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Case Number: T 0148/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 19 June 1996

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 9 December 1992 revoking European patent No. 0 120 301 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison Brunel
S. C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 120 301 with the title "Method of producing standardized iodophor preparations and such preparations" was granted for eleven Contracting States with fourteen claims.

Claims 1, 5, 6, 10 and 12 read as follows:

"1. A method of producing a pharmaceutical iodophor preparation having a predetermined, constant concentration of free iodine, predictable microbicidal effectiveness and long duration of action, the method comprising the steps of

(a) treating a mixture of an iodophor-iodine component and iodide ions in acidic solution with iodate ions to form an acidic solution containing between 2 and 20 ppm of free iodine and having an available iodine to iodide ratio between 2:1 and 10:1;

(b) increasing the pH of the acidic solution to between 5 and 6, and

(c) adding an amount of additional iodate ions to the thus formed solution, sufficient to maintain the amount of free iodine in the solution at a concentration between 2 and 20 ppm.

5. The method according to any one of claims 1 through 4, wherein the iodophor-iodine component is polyvinylpyrrolidone iodine.

6. A pharmaceutical iodophor preparation producible by the method of anyone of claims 1 through 5, comprising an iodophor-iodine component, iodide ions and iodate ions, the preparation having a ratio of available iodine to iodide between 2:1 and 10:1, and, in solution, a pH between 5 and 6, and a concentration between 2 and 20 ppm of free iodine, the concentration being stable for at least 12 months at 20°C.

10. The preparation according to any one of claims 6 through 9, wherein the amount of available iodine is at least 0.5 weight percent of the preparation.

12. The preparation according to any one of claims 6 through 11, wherein the iodophor-iodine component is polyvinylpyrolidone iodine."

Dependent claims 2 to 4 and 7 to 9, 11, 13 and 14 specified further features of the claimed process and iodophor preparation, respectively.

II. Notices of opposition were filed by two parties requesting the revocation of the patent under Article 100(a) EPC (lack of novelty and lack of inventive step, Opponents I and II) and under Article 100(b) EPC (Opponent I).

III. The documents cited during opposition proceedings which were considered most relevant by the opposition division are the following:

(1): DE-A-2 540 170;

(4): US-A-4 271 149;

(6): The label of the sanitizing teat dip "Quater-Mate™" taken together with a sale invoice dated 23 February 1982 and an affidavit from Prof. M.W. Winicov dated 7 February 1991;

(7): Wyss O. and F.B. Strandskov, Archives of Biochemistry, 1945, vol. 6, 261 to 268;

(8): Schmidt W. and M. Winicov, Soap and Chemical Specialties, 1967, vol. 43, 61 to 64;

(9): Gottardi, W., Hyg. + Med., 1983, vol. 8, 105 to 107.

IV. Before the opposition division, there were put forward a main request for maintenance of the patent with the claims as granted, together with an auxiliary request in which claim 6 was limited to the iodophor-iodine component being polyvinylpyrrolidone-iodine (PVP-iodine), that is the feature of claim 12 as granted.

V. By decision dated 9 December 1992, the opposition division revoked the patent according to Article 102(1) EPC.

Product claim 6 of the main request was found to lack novelty in view of the prior art product "Quater-Mate™", the composition of which on the evidence fell within the range disclosed for the claimed pharmaceutical composition (document (6)).

Process claim 1 of the main and the auxiliary requests was considered novel, the distinction over document (4) being that the method is characterized by a first addition of iodate, then a pH adjustment and then a further iodate addition.

Product claim 6 of the auxiliary request, which was limited to the iodophor-iodine component being PVP-iodine was considered novel since, though documents (1) and (4) also referred to PVP iodophor-iodine preparations, they did not explicitly disclose the amount of free, non-complex bound iodine therein.

Claim 1 and claim 6 of the auxiliary request were however considered to lack inventive step in view of documents (1), (4), (7), (8),(9).

The objection under Article 100(b) EPC was not considered to have been made out.

VI. The appellant (patentee) lodged an appeal against the decision of the opposition division and with the statement of grounds of appeal filed a main request and six auxiliary requests. Submissions were received from all parties, including fourteen new exhibits and one new document. The appellant filed on 29 March 1995 a new main request and four auxiliary requests.

VII. Opponent I withdrew his opposition with letter dated 5 September 1995.

VIII. A communication was sent according to Article 11(2) EPC of the Rules of Procedure of the Boards of Appeal setting out the Board's preliminary position. In reply thereto a further submission was received from the appellant.

IX. The following further document is referred to in the present decision:

(26): Berkelman, R.L. et al., Journal of Clinical Microbiology, 1982, vol. 15, No. 4, 635 to 639.

X. Oral proceedings were held on 19 June 1996. During these proceedings, the appellant filed a new main request together with five subsidiary requests in replacement of all previous requests on file. The new main request (claims 1 to 11) differed from the granted set of claims in that granted claims 5, 10 and 12 were deleted with the consequent necessary renumbering of some claims. Claims 1 and 5 read as follows (the differences in respect of the corresponding granted claims 1 and 6 are emphasized in bold-type, the deleted passages are in square brackets)):

"1. A method of producing a pharmaceutical [iodophor] **polyvinylpyrrolidone (PVP) iodine** preparation having a predetermined, constant concentration of free iodine, predictable microbicidal effectiveness and long duration of action, the method comprising the steps of

(a) treating a mixture of [an iodophor-iodine compound] **PVP-iodine** and iodide ions in acidic solution with iodate ions to form an acidic solution containing between 2 and 20 ppm of free iodine and having an available iodine to iodide ratio between 2:1 and 10:1;

(b) increasing the pH of the acidic solution to between 5 and 6, and

(c) adding an amount of additional iodate ions to the thus formed solution, sufficient to maintain the amount of free iodine in the solution at a concentration between 2 and 20 ppm".

5. A pharmaceutical [iodophor] **polyvinylpyrrolidone (PVP)**-iodine preparation producible by the method of anyone of claims 1 through 4, comprising [an iodophor-iodine component] **polyvinylpyrrolidone-iodine**, iodide

ions and iodate ions, the preparation having a ratio of available iodine to iodide between 2:1 and 10:1, and, in solution, a pH between 5 and 6, and a concentration between 2 and 20 ppm of free iodine, the concentration being stable for at least 12 months at 20°C, **wherein the amount of available iodine is at least 0.5 weight percent of the preparation**".

XI. The submissions in writing and during oral proceedings by the appellant can be summarized as follows:

- The amended claims satisfied the requirements of Articles 123 and 84 EPC. The amendments restricted the scope of the granted independent claims by introducing features of dependent claims. The basis in the application as originally filed for the feature that the available iodine is at least 0.5 weight percent of the preparation is in Example 1, batches 1 to 8 with concentrations of 1% and 0.5%.

- At the priority date, the skilled person had become aware from document (26) that concentrated iodine preparations did not possess as good a microbicidal activity as diluted solutions. The reason therefor was thought to be that diluted solutions contained more free iodine which could be responsible for the microbicidal activity. It was, thus, generally advised to dilute the concentrated iodine preparations at the time of use (documents (26) and (9)).

- The problem dealt with in the patent in suit, which was the provision of a ready-to-use, bactericidally efficient, storage stable iodine preparation had not even been perceived. Accordingly, the proposed solution, an iodophor preparation of defined composition, could not have been obvious.

- Example IIIB in document (4) disclosed an iodophor preparation with a qualitative and quantitative composition which was practically the same as that of the claimed iodophor preparation, PVP being replaced by Pluronic-85. However, in consideration of the facts that:

  - Example IIIB was one of many compositions disclosed in document (4);

  - Document (4) was not concerned with providing an iodophor preparation with a defined constant amount of free iodine but with a defined constant amount of available iodine (free and complexed iodine);

  - the amount of free iodine in a composition varies independently from the amount of available iodine,

  it had to be pure hindsight to argue that this document suggested the invention.

- Finally, the experiments which were conducted by the appellant to reproduce Example IIIB clearly showed that the iodophor preparation contained less than 2 ppm of free iodine.

XII. The respondent (opponent) argued as follows:

- The restriction in claim 5 by the feature that the available iodine is at least 0.5 weight percent of the preparation, was contrary to Article 123(2) EPC. There was no claim with this feature in the application as filed, and while specific available iodine concentrations of 0.5% and above might be disclosed in the examples, the limitation as phrased in the claim could not be derived from this. The amendment was also objectionable under Article 84 EPC.

- The closest state of the art could not be document (26), because this document was not concerned with the stabilization of iodine preparations. Rather the product "Quater-Mate™" (see document (6)) should be considered as closest prior art since the product was shown to contain between 2 and 4 ppm of free iodine and to be stable for three years.

- Thus, at the priority date, a product was already on the market which had exactly the same composition and properties as the claimed product except that pluronic acid was used instead of PVP as a complexing agent.

- The problem to be solved by the patent in suit was, thus, to provide another iodine preparation with a range of free iodine above 2 ppm and a stability of twelve months. PVP was already very much used as a complexing agent. It took no inventive step to exchange the pluronic acid contained in "Quater-Mate™" for PVP.

- The product "Quater-Mate™" was sold prior to the priority date with a reference to document (4) appearing on its label. Document (4) disclosed that an increased stability of available iodine could be achieved in the presence of iodide through the addition of iodate and control of pH within the range of pH 5 to 7. Thus, document (4) provided a means to stabilize the amount of available iodine (free and complexed). As the levels of available and free iodine were known to vary in parallel, document (4) would certainly have suggested to the person skilled in the art the means to arrive at a composition with a constant level of free iodine. Consequently, the claimed method which also involved the addition of iodate and the control of pH to between 5 and 6 had to be considered obvious.

XIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of one of the set of claims submitted as new main request or respectively, first, second, third, fourth or fifth subsidiary request at the oral proceedings on 19 June 1996.

XIV. The respondent requested that no patent be maintained on the basis of the new main request, or the first, second or third subsidiary request submitted at oral proceedings on 19 June 1996.

Reasons for the decision

1. The appeal is admissible.

Main request

2. *Article 123(2)(3) EPC*

2.1 The respondent objected to the introduction into claim 5 of the main request of the feature that the available iodine is at least 0.5 weight percent of the preparation, as being contrary to Article 123(2) EPC in that it added subject-matter extending beyond the content of the application as filed. However, this same feature had been the subject of dependent claim 10 as granted, and in the opposition no objection under Article 100(c) EPC that the subject-matter of the European patent extends beyond the content of the application as filed had been raised. The objectionable subject-matter, if any, has not been introduced by the amendment but was present in the patent as granted. In these circumstances the Board holds that the respondent is not entitled to raise the objection for the first time on appeal.

2.2 The changes to the claims as granted all arise from the incorporation into independent claims 1 and 6 as granted of the features of dependent claim 5 or dependent claims 10 and 12 respectively. For none of the changes does any question of the amendments adding subject-matter contrary to Article 123(2) EPC arise.

2.3 The scope of independent claims 1 and 5 at issue is restricted compared to that of granted claims 1 and 6 from which they derive by amendment. Thus the requirements of Article 123(3) EPC are also fulfilled.

3. *Clarity (Article 84 EPC)*

3.1 The respondent objected to some amendments to the claims also on the basis of Article 84 EPC. Yet, the amendments made, namely the incorporation into independent claims 1 and 5 of features previously appearing in dependent claims as granted, do not introduce any ambiguity or other lack of clarity. No question, thus, arises for consideration under Article 84 EPC.

4. *Novelty (Article 54 EPC)*

4.1 Novelty of the claims of the main request, as finally put forward at the oral proceedings before the Board, was no longer in dispute.

5. *Inventive step (Article 56 EPC)*

5.1 Starting point for problem/solution approach

5.1.1 Two different items of prior art have been suggested by the parties as closest prior art: the respondent suggested the product "Quater-Mate™" together with its label document (6) which states its composition and refers to the product being made in accordance with the US patent (document (4)), and the appellant suggested document (26). The product "Quater-Mate™" was sold in 1982 for the purpose of sterilizing cow teats.

5.1.2 The prior art product "Quater-Mate™" uses pluronic acid-iodine as an iodophor, whereas the claims of the main request are now limited to the iodophor being PVP-iodine. Document (4) does mention the possibility of a composition using a PVP-iodine iodophor in which the desired level of elemental iodine can be maintained through addition of iodate and maintenance of pH in the range of 5 to 7 (column 5, lines 30 to 37), but its

examples relate only to the use of pluronic acid-iodine as an iodophor, and it contains no discussion of any relationship between the concentration of available iodine and germicidal effectiveness. Neither the label of the product "Quater-Mate™" nor document (4) give information on the free iodine content achieved by the product sold, or achievable by following the instructions in document (4) or as to any importance of free iodine content for germicidal effectiveness. The Board can accept, as did the opposition division, that on the evidence if someone had reason to measure the free iodine content of the prior art product "Quater-Mate™" using pluronic acid, he or she would have found it to be within the limits stated in claims 1 and 5 of between 2 to 20 ppm and to be germicidally effective, but neither the product nor document (4) contain any information relating to making such a measurement.

5.1.3 The difference between claim 1 and the teaching of document (4) lies not only in the specific steps required but also in the effect that is intended to be achieved thereby. Thus, step (a) of the claim requires "treating a mixture of a PVP-iodine and iodide ions in acidic solution with iodate ions to form an acidic solution containing between 2 and 20 ppm of free iodine and having an available iodine to iodide ratio between 2:1 and 10:1". Document (4), although referring to a series of iodine complexing agents, including PVP, makes use in the examples of pluronic acid-iodine, which already introduces a distinction over the process of claim 1 which is specifically limited to PVP-iodine. Furthermore, it is stated at column 7, lines 12 to 15 that "Below pH 5, at pH 4.5 for example, it is not practicable to add iodate, since iodine concentration in the teat dip formula has been found to actually increase on standing." According to the patent in suit, however, this initial increase is desired to achieve the free iodine level of between 2 and 20 ppm.

Achieving this effect is a further technical feature which distinguishes the process of claim 1 over the teaching of document (4).

5.1.4 The feature (b) of claim 1, increasing the pH of the acidic solution to between 5 and 6, is taught in document (4), but feature (c), adding an amount of additional iodate ions to the thus formed solution, sufficient to maintain the amount of free iodine in the solution at a concentration between 2 and 20 ppm, is not. For the purpose suggested in document (4) there seems no reason why anyone should adopt all the steps required in claim 1, in place of the more simple steps taught in document (4).

5.1.5 As regards claim 5, this is limited to using PVP, which already produces one distinction over the product "Quater-Mate™". Claim 5 also requires the amount of available iodine to be at least 0.5 weight percent of the preparation. The product "Quater-Mate™" has only 0.1 weight percent. Document (4), on the other hand, does mention PVP as a possibility, and also mentions using another iodophor, namely pluronic acid-iodine at up to 1% iodine. However document (4) also states at column 3, lines 60 to 64 "..the need for this invention will be most apparent for weakly complexed iodine compositions, since these generally show greater iodine losses while standing on the shelf compared to strongly complexed iodine." There is no mention of the importance of free iodine, and document (4) suggests that stabilized compositions with available iodine of 0.1% or less are likely to be most satisfactory.

5.1.6 For the purpose of a problem/solution approach assessment of claims 1 and 5, the Board would thus not consider that either the product "Quater-Mate™" with its label (6), or document (4) are suitable starting points, because they are not concerned with free iodine, and neither provides information on what is required for a germicidally effective solution using PVP-iodine as iodophor.

5.1.7 Document (26) is cited as closest prior art by the appellant. This document is a study published in 1982 of the bactericidal effect of three commercial preparations of 10% povidone-iodine solution at various dilutions, povidone being another name for PVP. The available iodine content of all stock povidone-iodine solutions was stated to be approximately 1%. The authors in discussing the results stated that their investigation demonstrated that low concentrations (i.e. 0.1 to 1%) were more rapidly bactericidal than a full strength (i.e. 10%) solution. This thus means that available iodine concentrations of 0.01 to 0.1% were in this test more effective germicides than the full strength solution with 1% available iodine. The authors also state:

"The chemistry of povidone-iodine is complex and not well understood. Therefore the phenomenon of increased bactericidal activity with dilution is difficult to explain. Certainly this study establishes that the available or thiosulphate titratable iodine, currently the only routine measurement of iodine content in povidone-iodine products, is not directly related to bactericidal activity. One hypothesis is that the concentration of "free" iodine (i.e. the elemental iodine in solution) significantly contributes to the bactericidal activity of povidone-iodine solution."

At the end of the article it is stated:

"In summary, dilutions of povidone-iodine solutions demonstrated more rapid bactericidal action than did full strength povidone-iodine solutions. Although 10% povidone-iodine solutions fulfil a useful role in antiseptic practice today, further chemical and microbiological research is warranted. If dilute preparations of povidone-iodine are found to be safe and efficacious, substantial financial savings as well as improved antiseptic care may be realized. In addition, our results suggest that brief exposure of inanimate objects to undiluted solutions of 10% povidone-iodine may be inadequate for disinfection."

5.1.8 Document (26) appears to the Board as an appropriate starting point for the problem/solution approach, because it is concerned with the germicidal effectiveness of solutions using PVP-iodine as the iodophor.

5.2 Problem to be solved

5.2.1 Starting from document (26) the technical problem to be solved may be seen as the provision of a process for making iodine preparations using PVP-iodine as iodophor, which preparations are germicidally effective when undiluted, and which stably retain this effect for a length of time.

5.2.2 The solution to this problem is the process of claim 1 and the product of claim 5. The Board is satisfied from the examples given in the patent that this problem has been solved. The appellant has emphasized that his process for the first time provides a method of varying the free iodine level independently of the available iodine concentration, a possibility not even contemplated in the prior art. The respondent expressed

doubts as to this, but provided no experimental evidence to show that the claimed method did not allow this to be achieved. The burden of proof here was on the respondent, so that on the evidence the Board accepts the appellant's statements.

5.3 Solutions that prior art suggests

5.3.1 Faced with the problem to be solved, the skilled person can derive from document (26) that a 0.1% available iodine solution (or one with a still lower percentage) with PVP-iodine as iodophor will be germicidally effective. The skilled person would also be expected to be acquainted with document (4), and to conclude that the method of this document could be used to provide the necessary stability. However, this combination of documents (26) and (4) would not lead to the process of claim 1 as there is no teaching in either of them that the more complicated sequence of steps of claim 1 can be used to achieve a desired level of free iodine independently of the available iodine concentration. Nor does the combination lead to the product of claim 5, which has an available iodine concentration of at least 0.5%. On the contrary, document (26) suggests that at full strength such a solution would not be germicidally effective. There would seem no point in using the method of document (4) to stabilize available iodine at a germicidally ineffective level.

5.3.2 The skilled person could also refer to document (9), which is a study of the relative amounts of free and available iodine in watery solution of PVP-iodine. It discloses that, at pH 4, a 20% solution of iodine contains 1ppm of free iodine whereas a 0.1% solution of iodine contains 25.4 ppm of free iodine. This takes the skilled person no further. There is no reason in fact why the disclosed relationship between free and available iodine at pH 4 in water should be indicative

of the relationship to be expected at a higher pH and in the presence of iodide and iodate. Document (9) also suggests that a compromise should be found between having sufficient free iodine to achieve disinfection and sufficient available iodine to remain stable. However, it remains completely silent on how to achieve this compromise.

5.3.3 The Board concludes that neither the method of claim 1 nor the product of claim 5 can be derived in an obvious manner from the state of the art. Inventive step can thus be acknowledged, and the patent be maintained on the basis of the main request. Under these circumstances, there is no need to discuss the further requests on file.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The matter is remitted to the first instance with the order to maintain the patent on the basis of the set of claims submitted as the new main request at the oral proceedings on 19 June 1996.

The Registrar:

A. Townend

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE
CHAMBRES DE RECOURS DE L'OFFICE EUROPÉEN DES BREVETS
BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

The Chairman:

L. Galligani

Beglaubigt/Certified
Certifiée conforme:
München/Munich

Geschäftsstelle
Registry/Greffe:
16. JUNI 1997

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