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D E C I S I O N
of 18 May 1994

Case Number: T 0566/91 - 3.3.2

Application Number: 83303845.8

Publication Number: 0100157

IPC: A61K 9/20

Language of the proceedings: EN

Title of invention:
Nystatin pastille formulation

Patentee:
E.R. Squibb & Sons, Inc.

Opponent:
Dr. R. Pfleger Chemische Fabrik GmbH

Headword:
Nystatin/SQUIBB

Relevant legal norms:
EPC Art. 56, 113(1), 114(2)
EPC R. 67, 68(2)

Keyword:
"New document used by Opposition Division - more complete version of a cited document - no procedural violation"
"Late-filed documents - refused except one relevant"
"Disregard of auxiliary requests by Opposition Division - substantial procedural violation (yes) - refund of appeal fees precluded"
"Inventive step - obvious solution"

Decisions cited:
T 0024/81, T 0219/83, T 0013/84,

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0566/91 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 18 May 1994

Appellant: (Proprietor of the patent)
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Respondent: (Opponent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office dated 30 April 1991, posted on 7 June 1991 revoking European patent No. 0 100 157 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: A. J. Nuss
S. C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 100 157 was granted on 4 May 1988 with seven claims in response to the European patent application No. 83 303 845.8.

II. Notice of opposition was filed against the European patent by the Respondents (Opponents). Revocation of the patent was requested on the grounds of Articles 100(a) and 56 EPC.

During the procedure before the Opposition Division the following documents, *inter alia* were cited:

(1): DD-A-132 404
(9): Hagers Handbuch der pharmazeutischen Praxis, 1971, pages 527/528, 682 and 685
(12): HUSA's Pharmaceutical Dispensing, Fifth Edition, 1959, page 80
(14): Journal of Oral Therapeutics and Pharmacology, 1968, Vol. 4, pages 464-466.

III. The Opposition Division revoked the patent by a decision delivered orally on 30 April 1991, with written reasons posted on 7 June 1991. The ground for the revocation was lack of inventive step.

In its decision, the Opposition Division first stated that no concrete improvement had been demonstrated vis-à-vis the prior art formulation described in document (1). It then took the view that the claimed soft nystatin gelatin pastille could not be regarded as meeting the requirement of inventive step in view of the

teachings provided in document (1) and (14). The former showed that many of the criteria mentioned in the patent in suit were satisfied by the known formulation, namely:

(a) providing a constant level of nystatin to the infected area of the buccal cavity,
(b) using as carrier an "indifferent" vehicle such as gelatin in a concentration of 0.5 to 50% by weight,
(c) assuring that the contact with the lesion is prolonged,
(d) providing a formulation of elliptical form suggesting a lozenge,
(e) providing a formulation further containing flavours and colouring agents,

whereas (14) mentioned the development of a "long-lasting lozenge" which might serve as a carrier for oral lozenges to be used over prolonged periods of time; in the case of nystatin (mycostatin) the lozenge contained 100,000 units, corresponding practically to the claimed 5000 units per mg of nystatin. The use of sugar as sweetener was also considered.

Consequently, documents (1) and (14) were sufficient to lead a skilled person to the claimed invention.

IV. The Appellants (Proprietors of the patent) lodged an appeal against this decision.

At the oral proceedings on 18 May 1994 the Appellants submitted a main request and two auxiliary requests in which Claim 1 as granted had been amended by the inclusion of at least one additional feature (see point VII below).

In their written submissions and at the oral proceedings before the Board, the Appellants argued in essence that (1) concerned a drug delivery system for general use very different from the one claimed in that there, not only the film-like excipient or strip absorbed water and swelled, but it also formed an adhering contact with dental ware or a specific section of the mucous membrane. Moreover, (1) mentioned distribution of the active substance by body fluids as being a problem. In the mid-seventies a new grade of nystatin in crystalline form became available which soon replaced the previously used amorphous form in ready-made up suspensions as the new crystalline product was more convenient in use. In order to be optimally effective when treating oral thrush, the nystatin had to be applied to the infected areas and maintained, at a constant effective saliva level, over a sustained period of time. However, although both forms showed equal potency, the crystalline product was easily washed away. Consequently, the treatment was not as effective as it could have been. Moreover, because of the unpleasant taste of nystatin the conventional forms of formulation led to patient complaints and non-observance of the medical instructions. In particular children tended to swallow or spit out the nystatin preparation before it became effective. In view of the severity of infections caused by oral thrush, aged patients required efficient medication because otherwise they might be prevented from eating properly which in combination with other serious diseases from which they were suffering could be fatal. In document (1) the problem of poor patient compliance had not been recognised.

Although gelatin-containing pastilles were generally known, it was not obvious to incorporate nystatin into a soft gelatin pastille to be sucked in order to overcome the said problem of poor patient compliance. The

statement in (1) that the formulation could be of elliptical form had been taken out of context and did not,in fact, suggest a lozenge form. Thus, contrary to the adherent strip described in (1), the inherent non-adherency of the claimed sugar-containing nystatin pastille to the oral mucosa not only ensured a maximised continuous distribution of the nystatin but it also aided tolerance of the pastille by an infected patient, thereby providing a persistent level of medication. The presence of gelatin provided the persistent effect over a sufficient period of time whereas the presence of sugar, apart from masking the unpleasant taste of nystatin, ensured a concentrated application of the active substance to the infected areas of the mouth. Nothing in the prior art suggested that a solid delivery system could be effective for solving the problem of poor patient compliance if it had the specific properties of the one claimed, namely softness and sweetness. The formulation as such could only be regarded as obvious with hindsight, namely only once the problem of poor patient compliance had been recognised first.

V. The Respondents disagreed with these submissions and expressed the view that (1) did relate to the problem of oral candidiasis (oral thrush) and the prerequisites for a successful treatment of this ailment. Contrary to the Appellant's allegations, the film-like excipient mentioned there was only cited as an example since in the description reference was made to any other suitable form of drug carrier, the choice of the carrier depending on the mucous membrane to be brought into contact with the drug carrier. The actual teaching provided by (1) was to provide a gelatin and nystatin-containing drug formulation of practically any form and dimension, including those of the type now claimed. This document further mentioned the inclusion of additional

ingredients such as bulking agents, flavouring and colouring agents. Moreover, document (9) showed that it was known to use extremely high amounts of saccharose in comparison with the gum base when preparing pastilles. In the present case a possible risk of caries would be a quite secondary consideration which could be disregarded if the obvious measure of masking the unpleasant taste of nystatin by sweetening the formulation with sugar ensured patient compliance. Other supposedly beneficial effects due to the addition of sugar were not supported by any evidence. Document (15) submitted in the appeal procedure showed that gelatinous materials other than gelatin could also be used in combination with high amounts of sugar.

VI. The Appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or on the basis of auxiliary request I or auxiliary request II submitted during the oral proceedings on 18 May 1994.

The Respondents requested that the appeal be dismissed.

VII. The three requests read as follows:

(i) Main request: Claim 1

"A soft nystatin pastille formulation for treatment of candidiasis in the oral cavity and oesophagus, comprising nystatin and a soft pastille carrier therefor in the form of a soft gelatinous sweetened base, wherein the nystatin is present in the nystatin pastille in an amount of from 0.1 to 6% by weight of the total formulation, based on a potency of 5,000 units

per mg of nystatin, and wherein the nystatin pastille contains from 2 to 20% by weight of one or more gelatinous materials and from 75%-95% by weight sugars."

(ii) Auxiliary request I: Claim 1

This claim differs from Claim 1 of the main request essentially in that at the end the phrase "and wherein the gelatinous material comprises gelatin, glycerinated gelatin, pectin or a mixture thereof" has been added.

(iii) Auxiliary request II: Claim 1

"A soft nystatin pastille formulation for treatment of candidiasis in the oral cavity and oesophagus, comprising nystatin and a soft pastille carrier therefore in the form of a soft gelatinous sweetened base, wherein the nystatin is present in the nystatin pastille in an amount of from 15 to 25 mg/pastille, based on a potency of 5,000 units per mg of nystatin, and wherein the nystatin pastille contains from 108 to 180 mg/pastille of gelatin, 500 to 750 mg/pastille of granular sucrose, 750 to 1,000 mg/pastille of liquid glucose, 150 to 200 mg/pastille sugar syrup; 100 to 200 mg/pastille of dextrose, and 5 to 40 mg/pastille of flavor oils."

Reasons for the Decision

1. The appeal is admissible.

2. *Procedural matters*

2.1 Document (1) as basis for the revocation of the patent by the first instance.

During discussion of (1) at the oral proceedings before the Board, it rapidly emerged that the text of (1), cited in the decision under appeal as DD-A-132 404, and a copy of which was present in the opposition file, contained substantially more than the text of (1) which both parties present at the oral proceedings had in their possession, and which had been cited by the Respondents as DD-C-132 404 when filing the opposition. The latter was in fact a reissue of the DDR Patent in an amended form, with claims limited to a film-like pharmaceutical carrier and a particular embodiment of the invention using Nystatin no longer appearing in the amended text. That different texts were being used appears to be the result of the fact that document (1) was not provided to the Opposition Division which ordered a copy for itself which turned out to be a different text. The differences might have been apparent on extremely careful examination from the fact that the line numbers cited by the Respondents for various passages did not correspond exactly with the position of those passages in the text used by the Opposition Division. But these dicrepancies did not spring to the eye, as the cited passages did appear close to the lines actually cited and the lines of the pages were not numbered. The version of (1) relied on by the Opposition Division, is the most relevant one. The decison of the first instance was thus based, albeit inadvertently, on

evidence (the fuller version of document (1)) on which the parties concerned had not had the opportunity to comment, contrary to the requirements of Article 113 EPC.

To remedy this unfortunate situation, the Board offered a half hour suspension of the proceedings for the parties to consider the fuller version of (1) with the interpreters, present to translate the Respondents submissions from German to English, kindly agreeing to help the Appellants to understand the German language full version of (1). The Appellants and Respondents both accepted this offer. At the end of this suspension both parties were prepared to continue with the proceedings and deal with the full version of (1), so that in the proceedings before the Board Article 113 EPC was complied with. The Appellants withdrew their original main request that the patent be maintained as granted, proceeding only with the requests as stated in VII above.

2.2 Late-filed documents

At the oral proceedings the Board had to decide whether the Respondents' late-filed citation (15), the Appellants' expert opinion of Dr. M.V. Martin based on experimental work as well as the statement in response of Dr. Ulrich Schwantes subsequently submitted by the Respondents, a letter from Dr. Martin commenting briefly on Dr. Schwantes' statement, and the data submitted as evidence in support of a commercial success of the claimed invention, should be admitted for consideration.

(15) had been cited by the Respondents directly in response to the Statement of Grounds of appeal wherein the Appellants for the first time submitted a restricted main claim differing from the granted claims in that it

related to a specific formulation reflecting the preferred soft nystatin formulation defined on page 3, lines 14 ff. of the patent in suit. As the technical content of this document could not be considered to be irrelevant for assessing inventive step of the said formulation, the Board made use of its discretion under Article 114(2) EPC to admit (15) into the appeal proceedings.

By contrast, the Board decided on the basis of the same provision not to admit for consideration the other documents submitted by the parties in the course of the appeal proceedings.

3. *Allowability of amendments in the main and the auxiliary requests I and II*

There are no formal objections on the basis of Articles 123(2) and (3) EPC to the three sets of claims (see point VII above) since these claims are adequately supported by the original description and do not extend the protection conferred when compared to the claims as granted. This was not contested by the Respondents.

4. *Novelty*

None of the documents considered in the present proceedings discloses a soft nystatin pastille formulation presenting all the features indicated in the claims in accordance with the main or the two auxiliary requests. This was not contested by the Respondents. The said claims must thus be regarded as novel.

5. *Inventive step*

5.1 In relation to the invention as claimed in all the requests, document (1) is regarded as constituting the closest prior art. It relates to a process for preparing a pharmaceutical carrier designed to provide a continuous release of an active pharmaceutical substance over a sustained period of time and in a much higher concentration than the usual carriers, thereby obviating the known deficiencies and drawbacks of the latter in terms of continuity and duration of the release to accessible mucous membranes, for example those of the buccal cavity of subjects suffering from mucosal lesions due to *Candida albicans*. This goal is achieved by incorporating an active substance into an organic, physiologically indifferent and swellable carrier mass under addition of a polar solvent or suspension agent (preferably water) and a softening agent (preferably glycerol) in an amount of 0% to 40%, whereby gelatin is considered to be a suitable carrier material. It can be used in an amount of 1,5% to 50%. Among the many groups of potential active substances to be used figure antifungal agents, in particular those active against *Candida albicans* such as nystatin. Although the amount of active substance in the carrier mass is not limited, in practice it ranges between 0.05 mg and 5.0 grams per carrier unit. The pharmaceutical carrier may actually have any shape depending on the body cavity and the mucosal membranes to be treated (mouth, ear, nose etc.), including an elliptical form or the shape as represented in figure 1, i.e. a film-like shape or strip if oral application to the mucosal membrane of the palate is envisaged. A single carrier unit may have a thickness from 0.5 mm to 4.0 mm and a surface ranging between 1 mm^2 and 100 cm^2, whereby the weight per unit is between 0.1 g and 20 g. If necessary, the formulation may contain additional ingredients such as flavouring and

colouring agents (see claims; page 1, last paragraph to page 3, line 13; page 3, lines 19 ff.; page 4, lines 10 to 36; page 5, lines 10 to 13 and figure 1).

As can be seen from the example on page 6 of (1), a suitable pharmaceutical carrier formulation may have the following composition:

1.	nystatin	10^6 units	(active substance)
2.	citric acid	0.04g	(stabilising agent/ solubility promoter)
3.	gelatin	0.8g	(carrier)
4.	glycerol	1.5g	(softening agent)
5.	water	3.0g	(solvent)
6.	citronella oil	0.001g	(flavouring improver)
7.	ester of p-benzoic acid	0.0075g	(preservative)

The resulting mixture is poured into a mould having a shape adapted to the anatomical site to which it is intended to be applied and divided after cooling. The above working example merely serves as an illustration and is not to be construed as a limitation (see page 6, last two paragraphs).

5.2 The Board does not agree with the submission by the Appellants that the technical problem underlying the patent in suit consisted in the unrecognised problem of poor patient compliance.

In the Board's view, this approach is not realistic because the mere posing of a problem, even if it were new, does not represent a contribution to the inventive merits of a solution to that problem if it could have been posed by the average person skilled in the art. Such is the case where, as here a problem necessarily comes to light when an object or product is used. Consequently, a problem which amounts to no more than

noticing an obvious non-compliance with an obvious *desiderata* in a given situation, namely poor patient compliance using nystatin formulations as a result of the unpleasant taste of the active substance, cannot be retained as the actual problem to be solved, all the more since in accordance with the "problem-and-solution" approach" developed in the jurisprudence of the Boards of Appeal, the problem underlying a patent or patent application must be **objectively** defined vis-à-vis the closest prior art (see for example T 24/81, OJ EPO 1983, 133, in particular points 4 and 14 of the Reasons and T 13/84, OJ EPO 1986, in particular points 10 and 11 of the Reasons).

Thus, in the light of (1) the Board can only see the technical problem to be solved in the present case as being finding another suitable nystatin containing pharmaceutical formulation of the known type.

The Board is satisfied that the above-stated problem has been solved by the pastille with the features required in accordance with Claim 1 of any of the Appellants' requests.

5.3 As can be seen from point 5.1 above, the teaching of document (1) covers the preparation of a large number of pharmaceutical bodies of different shape and size depending on the body cavity and the mucosal membranes to be treated including those containing sufficient nystatin for the treatment, over a sustained period of time, of the buccal cavity of subjects suffering from mucosal lesions due to *Candida albicans* and which contain 1.5 to 50% of gelatin as a carrier. These formulations may also contain a softening agent (preferably glycerol) and, if necessary, additional

ingredients such as flavouring and colouring agents. The known formulations are thus **soft** formulations designed to provide a persistent level of medication.

Moreover, from the general statement in (1) that flavouring and colouring agents could be added if necessary, and the working example, the man skilled in the art would certainly have understood that such additives might be required to make a formulation more appealing to the user and that especially in the case of nystatin (known for its unpleasant taste) such a measure indeed makes sense. When trying to find out which flavouring agents would be suitable apart from the expressly mentioned citronella oil, he would inevitably have come across document (9) reflecting a common practice in galenics to use for the preparation of pastilles, i.e. a **soft** variety of lozenge (cf. page 80 of (12)), an extremely large excess of saccharose in comparison with the gum base. As a matter of fact, for preparing 100 pastilles the following composition can be used: saccharose (finely powdered) 100 g, arabic gum (finely powdered) 7 g, water q.s. Since according to (9) pastilles are moreover known to be small bodies of a pharmaceutical formulation of variable size and shape which deploy their activity in the mouth or throat region by dissolving slowly in the mouth, the skilled man would have readily realised that the closely related formulation described in (1) could not only be very strongly sweetened by incorporating large amounts of sugar, i.e. one of the most famous allround flavouring agents, but also readily presented in the form of a pastille without risk of impairing the softness and sustained release properties characteristic of the formulations described in (1). Furthermore, (9) illustrates well that when using medication by pastilles, the concern of the skilled man to provide efficient medication obviously prevails over a possible

risk of caries due to the presence of a high amount of saccharose. This would particularly apply in the case of treatment of a severe disease like candidiasis, as emphasised by the Appellants.

5.4 The Appellants unsupported argument that, apart from masking the unpleasant taste of nystatin, sugar ensured a concentrated application of the active substance to the infected areas of the mouth tends to suggest an unexpected advantage or effect due to the high sugar content of the claimed formulation. As this was contested by the Respondents, the Board is faced with a situation which it is unable to resolve on the strength of its own knowledge. It is however jurisprudence of the Boards of Appeal of the EPO that in such a situation it is the party whose argument rests on the alleged facts who fails in the absence of supporting evidence (see T 219/83 , OJ EPO 1986, 211).

5.5 As can be seen from (15), the use of different sugars in solid and/or syrup form in accordance with Claim 1 of auxiliary request II is an obvious measure when preparing heavily saccharinated soft gum articles containing gelatinous materials such as gelatin and/or pectin. As explained in the patent in suit such mixtures prevent sugar crystallisation.

5.6 In view of the preceding and the fact that the Appellants presented in support of their auxiliary requests I and II the same arguments as those for the main request, the Board has come to the conclusion that Claim 1 of all three requests does not involve an inventive step in the sense of Article 56 EPC.

The dependent claims in each of the three requests must fall with the main claim, since each request can only be considered as a whole.

6. *Additional requests at the stage of opposition*

As correctly pointed out by the Appellants in their Statement of Grounds of appeal, the Opposition Division did not deal in its decision with Appellants' two auxiliary requests, corresponding to the present main and first auxiliary request. Since the patent was revoked in its entirety solely on the basis of the claims of the main request submitted at that time without mentioning reasons for the non-allowability of the two additional auxiliary requests, the decision of the Opposition Division did not in this respect meet the requirements of Rule 68(2) EPC. This omission constituted a substantial procedural violation which would have justified a reimbursement of the appeal fees if the Board had decided that the appeal were allowable (Rule 67 EPC). However, in view of the conclusion reached in point 5.6 above, the appeal must be dismissed so that the Board has no power to refund the appeal fees.

Order

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Martorana P. A. M. Lançon