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**Datasheet for the decision  
of 11 July 2011**

**Case Number:** T 1955/08 - 3.3.02  
**Application Number:** 99919947.4  
**Publication Number:** 1073466  
**IPC:** A61K 47/00, A61K 31/465  
**Language of the proceedings:** EN

**Title of invention:**  
Solution containing nicotine

**Applicant:**  
Duke University  
United States Government as represented by the Department of  
Veterans Affairs

**Headword:**  
Solution containing nicotine/DUKE UNIVERSITY

**Relevant legal provisions:**  
EPC Art. 56

**Relevant legal provisions (EPC 1973):**

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**Keyword:**  
"All requests - inventive step (no): obvious alternative"

**Decisions cited:**

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**Catchword:**

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Case Number: T 1955/08 - 3.3.02

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.02  
of 11 July 2011

**Appellants:**  
(Applicants)

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**Decision under appeal:**

**Decision of the Examining Division of the  
European Patent Office posted 16 April 2008  
refusing European patent application  
No. 99919947.4 pursuant to Article 97(2) EPC.**

**Composition of the Board:**

**Chairman:** U. Oswald  
**Members:** A. Lindner  
L. Bühler

## Summary of Facts and Submissions

- I. European patent application No. 99 919 947.4 was refused by a decision of the examining division pronounced on 18 January 2008 on the basis of Article 97(2) EPC on the grounds that the subject-matter claimed in the main and sole request lacked inventive step.
- II. The documents cited during the examination and appeal proceedings included the following:
- (3) B.J. Zins, et al., J. Clin. Pharmacol., vol. 37, 426-436 (1997)
  - (4) S. Tomar, et al., Tobacco Control, vol. 6, 219-225 (1997)
  - (7) US-A-5 549 906
  - (11) E.C. Westman, et al., Nicotine & Tobacco Research, 3, 391-396 (2001).
- III. The examining division essentially argued that starting from document (7) as closest prior art the problem to be solved could be seen in providing alternative smoking cessation means with an acceptable pharmacokinetic profile. This problem was allegedly solved by a nicotine solution as defined in claim 1 of the main request. The examining division had, however, serious doubts that the technical problem had indeed been solved over the whole scope of the claims, as the application under appeal did not contain any data demonstrating that the desired pharmacokinetic profile was indeed obtained. Even if it was assumed in favour of the applicant that the problem was plausibly solved, there was still lack of inventive step in the light of

the teachings of document (7) combined with document (3), as in that case the claimed invention merely constituted a modification of the closest prior art with the foreseeable disadvantage of a low oral bioavailability which the skilled person could clearly predict and assess.

- IV. The appellants (applicants) lodged an appeal against this decision.
- V. With the statement of the grounds of appeal dated 15 August 2008, the appellants filed a new main request and auxiliary requests 1 to 3. The sole independent claims of each request read as follows:

*(i) Main request:*

"1. The use of nicotine in the preparation of a solution to be swallowed through the mouth by drinking, for treating addiction to smoking tobacco, characterised in that:  
the solution is not for buccal or sublingual administration;  
the solution contains from 1 to 42mg of nicotine per 300 ml of solution;  
the solution has been made palatable by adjustment of its pH to be acidic, wherein an acid is employed as a pH control agent for the pH adjustment;  
and dosing is repeated with at least one dose of the solution per day."

*(ii) Auxiliary request 1:*

"1. The use of nicotine in the preparation of a solution to be swallowed through the mouth by drinking, for treating addiction to smoking tobacco, characterised in that:  
the solution is not for buccal or sublingual administration;  
the solution contains from 1 to 42mg of nicotine per 300 ml of solution;  
the solution has been made palatable by adjustment of its pH to be acidic, wherein an acid is employed as a pH control agent for the pH adjustment;  
dosing is repeated with at least one dose of the solution per day; and in that dosing is repeated with at least one dose of the solution per day;  
and the solution is provided as a bottled or canned beverage or is a beverage prepared by dissolving in aqueous solution a powder composition comprising nicotine and said pH control agent."

*(iii) Auxiliary request 2:*

"1. The use of nicotine in the preparation of a solution to be swallowed through the mouth by drinking, for treating addiction to smoking tobacco, characterised in that:  
the solution is not for buccal or sublingual administration; the solution contains from 1 to 42mg of nicotine per 300 ml of solution;  
the solution has been made palatable by adjustment of its pH to be less than 5.5, wherein an acid is employed as a pH control agent for the pH adjustment;

dosing is repeated with at least one dose of the solution per day; and the solution is provided as a bottled or canned beverage or is a beverage prepared by dissolving in aqueous solution a powder composition comprising nicotine and said pH control agent."

*(iv) Auxiliary request 3:*

"1. The use of nicotine in the preparation of a solution to be swallowed through the mouth by drinking, for treating addiction to smoking tobacco, characterised in that:

the solution is not for buccal or sublingual administration;

the solution contains from 1 to 42mg of nicotine per 300 ml of solution;

the solution has been made palatable by adjustment of its pH to be less than 5.5, wherein an acid selected from carbonic acid, citric acid, acetic acid, maleic acid, ascorbic acid, adipic acid and combinations thereof, is employed as a pH control agent for the pH adjustment;

to further enhance the palatability of the solution it contains a flavoring;

dosing is repeated with at least one dose of the solution per day;

and the solution is provided as a bottled or canned beverage or is a beverage prepared by dissolving in aqueous solution a powder composition comprising nicotine and said pH control agent."

VI. In the annex to the summons to oral proceedings issued by the board pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), the board in

its preliminary opinion raised, among others, objections under Article 56 EPC with regard to all requests on file.

- VII. In their letter dated 7 July 2011, the appellants informed the board that he would not be attending the oral proceedings.
- VIII. Oral proceedings were held on 11 July 2011, in the absence of the duly summoned appellants, in accordance with Rule 115 EPC and Article 15(3) RPBA.
- IX. The appellants' submissions in connection with inventive step can essentially be summarised as follows:

Starting from document (7) as closest prior art, the provision of an alternative user-acceptable smoking cessation means with an acceptable pharmacokinetic profile could be defined as the problem underlying the present invention. Making reference to post-published document (11), the appellant concluded that said problem was solved by the claimed subject-matter. Document (7) described a method for smoking cessation involving a nicotine lozenge that was designed such that the nicotine was released into the buccal cavity, which meant that the lozenge had to be held in the mouth for as long as possible so that the nicotine could be absorbed through the buccal mucosa. The lozenge should be administered in the absence of food or beverages and a basic environment should be maintained in the mouth. Moreover, document (7) mentioned the acrid, burning taste of nicotine. Contrary to the reasoning in the decision under appeal, document (3) did not suggest the use of acidification

for improving the palatability of nicotine but rather referred to the use of an acid addition salt or metal salt of nicotine, which was different from acidification. Documents (7) and (3) related to very different teachings; therefore the skilled person would not combine these documents in order to solve the technical problem defined above. The same applied to the combination of the teachings of documents (7) and (4). A key point in the solution of the technical problem was that palatability was linked to the acidity of the solution. In contrast, documents (4) and (7) taught the use of higher pH values for obtaining an acceptable bioavailability. As a consequence, the claimed subject-matter involved an inventive step.

- X. The appellants requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of the main request or, alternatively, on the basis of one of auxiliary requests 1 to 3, all filed with the statement of the grounds of appeal dated 15 August 2008.

### **Reasons for the decision**

1. The appeal is admissible.
2. Inventive step - Article 56 EPC
  - 2.1 Main request
    - 2.1.1 The present invention relates to a method of alleviating the craving for tobacco smoking (see page 9, lines 2-5).



Document (7), which constitutes the closest prior art, concerns a method for reducing nicotine craving comprising buccally administering a lozenge comprising nicotine and a non-nutritive sweetener (see claim 1). The nicotine can be used in free base form or as an acid addition salt (see column 5, line 66 to column 6, line 3) and the pH of the lozenge is preferably in the range from 6-11 (see column 8, lines 17-19). The lozenges are used by the patient *ad libidum* to alleviate cravings for nicotine as they arise (see column 10, lines 40-42).

In the light of this prior art, the problem to be solved can be defined as the provision of a further method for alleviating the craving for tobacco smoking.

As a solution to this problem, the present application proposes a use as defined in claim 1, in which an acidic solution which is not buccally or sublingually administered is swallowed through the mouth by drinking. In the light of the results obtained in example 2, the board is satisfied that the problem defined above was plausibly solved. In view of this finding, an evaluation of document (11), which had been submitted by the appellants in order to demonstrate that the technical problem had indeed been solved (see point IX above) is not necessary. It therefore has to be evaluated whether the skilled person would replace the buccal or sublingual application of lozenges according to document (7) by peroral administration of nicotine solutions as claimed in the present main request. The skilled person is aware of document (3), which concerns a study with the purpose to determine the bioavailability and pharmacokinetic parameters of

various administration routes of nicotine tartrate in connection with ulcerative colitis (see abstract). This study includes the administration of an oral solution of 133.3 µg nicotine tartrate in 100 ml of sterile water to a group of participants (see the penultimate paragraphs of the left-hand column on page 428 and of the right-hand column of page 429). Although mean AUC and  $C_{\max}$  values were considerably lower than those obtained with intravenous application (see paragraph bridging the right- and left-hand columns on page 431), serum concentrations of nicotine could be detected 30 minutes after administration (see paragraph bridging pages 430 and 431). In this context, it is emphasised that it is not unusual for intravenous administration to yield a higher bioavailability than other routes of administration. This result was therefore not surprising for the skilled person. From the presence of nicotine in the serum, the skilled person would conclude that the oral nicotine solutions according to document (3) are suitable for nicotine replacement. As a consequence, the subject-matter claimed in claim 1 of the main request does not involve an inventive step.

#### 2.1.2 Further arguments of the appellant

Making reference to the paragraph bridging pages 3 and 4 of the original application, the appellants reasoned that the skilled person would be kept from using oral solutions for treating addiction to smoking tobacco because of the problems encountered with such an administration, which included a pronounced first-pass effect of nicotine absorbed by the small intestine and an aversive, bitter, burning taste. These arguments cannot succeed for the following reasons:

The board is aware of the fact that nicotine, if swallowed, is subject to a pronounced first-pass effect. Reference is made to document (7) (see column 2, lines 59-64), which confirms this teaching. However, as was explained above, document (3) shows that the administration of an oral solution of nicotine tartrate yields detectable nicotine serum concentrations despite the first-pass effect (see point 2.1.1 above). The first-pass effect may make the skilled person use higher amounts of active agent in order to compensate for the inactivation caused by it, but it won't keep him from using oral nicotine solutions for treating nicotine addiction.

As regards the aversive, bitter, burning taste of nicotine if present in the form of its base (see also column 5, lines 59-63 of document (7)), the board would point out that the nicotine solutions of document (3) are acidic. Reference is made to the last paragraph of the left-hand column on page 428, where it is stated that the oral solution was prepared by dissolving 133.3 µg of nicotine tartrate from Sigma in 100 ml of sterile water. It is noted that nicotine tartrate is an acidic salt so that its aqueous solution has a pH <7, which means that the nicotine is present in the much less unpalatable salt form (see also column 5, lines 63-65 of document (7)). The argument of the appellants that a distinction has to be made between acidified nicotine on the one hand and nicotine addition salts or metal salts on the other hand (see point IX above) cannot be followed. The important point in connection with palatability is whether the nicotine is present in free base or in salt form, which depends

on the pH of the solution but is completely independent of whether the salt form is obtained by adding an acidic metal salt to the solvent (as in document (3)) or whether the free base is ionised by subsequent acid addition.

## 2.2 Auxiliary request 1

Compared to claim 1 of the main request, claim 1 of auxiliary request 1 additionally comprises the feature that the beverage is provided as a bottled or canned beverage or is prepared by dissolving a suitable powder composition. According to the appellants (see point 12 of the statement of the grounds of appeal), these features emphasise that the invention was an "ordinary, palatable, everyday" drink of a type one could drink again and again, but which contained a dose of nicotine for treating smoking addiction.

The board cannot see how these additional features could distinguish the composition defined in claim 1 of auxiliary request 1 from the oral solution according to document (3). A beverage includes any drinkable solution and therefore encompasses the oral solutions of document (3). Moreover, beverages including oral solutions are usually bottled or otherwise stored. As regards the feature "the beverage ... is prepared by dissolving a suitable powder composition", reference is made to page 428, last full paragraph of the left-hand column of document (3), which indicates that the oral solution was prepared in exactly the same way, namely by dissolving 133.3 µg nicotine salt/kg in 100 ml of sterile water.

As a consequence, the reasoning of paragraph 2.1 in connection with inventive step of claim 1 of the main request applies *mutatis mutandis* to claim 1 of auxiliary request 1. The requirements of Article 56 EPC are therefore not met.

### 2.3 Auxiliary request 2:

Claim 1 of auxiliary request 2 differs from claim 1 of auxiliary request 1 by defining the pH of the solution as being less than 5.5. Document (3) implicitly discloses an acidic pH by the selection of an acidic nicotine salt (see last paragraph of point 2.1.2 above). A pH of less than 5.5 is not specifically mentioned in document (3). However, there is no evidence that a further decrease of an already acidic pH to a level below 5.5 has a beneficial influence on the palatability of nicotine containing beverages.

The paragraph bridging pages 10 and 11 of the original application stresses the importance of an acidic pH in connection with palatability. The pH should be adjusted to less than about 6.9, more preferably to less than about 5.5 and most preferably to a range from about 2.0 to about 4.0 (see page 10, lines 19-21). However, the table on pages 14 and 15 shows that there is no correlation between pH and palatability. Thus, spring water with a pH of 6.2 (day 23) has the same scratch rate, namely 3.5, as spring water acidified to a pH of 3.0 with citric acid (day 9), which shows that the allegedly preferred pH range of less than 5.5 is not accompanied by improved palatability.

As a consequence, the reasoning of paragraphs 2.1 and 2.2 applies *mutatis mutandis* to claim 1 of auxiliary request 2. The requirements of Article 56 EPC are therefore not met.

#### 2.4 Auxiliary request 3

As compared to claim 1 of auxiliary request 2, claim 1 of auxiliary request 3 comprises the additional features that (a) the acid is selected from carbonic acid, citric acid, acetic acid, maleic acid, ascorbic acid, adipic acid and combinations thereof, and (b) the palatability of the solution is further enhanced by a flavouring agent.

Regarding (a), it is noted that the replacement of nicotine tartrate according to document (3) by another nicotine salt formed by addition of an acid figuring in claim 1 of auxiliary request 3, all of which are common ingredients in food compositions, is a common measure for the skilled person that does not require inventive skill. It is once again emphasised that the improved palatability of nicotine salts as compared to the free base is known to the skilled person (see last sentence of point 2.1.2 above). As a consequence, said replacement cannot establish an inventive step over the teaching of document (7) in combination with document (3) either (see point 2.3 above). Neither can the presence of a flavouring agent establish an inventive step. If the skilled person is faced with the problem of aversive taste of an oral composition, he would add a flavouring agent to improve its palatability. That is what flavouring agents are for. It is additionally noted that flavouring agents have

even been used to improve the palatability of nicotine-containing oral compositions. Reference is made to the lozenges according to examples 1 and 3 of document (7), which comprise mint flavour as a flavouring agent. As a consequence, the subject-matter of claim 1 of auxiliary request 3 does not meet the requirements of Article 56 EPC either.

## **Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairman

N. Maslin

U. Oswald