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Datasheet for the decision of 5 August 2019

Case Number: T 0229/17 - 3.3.01

Application Number: 07735602.0

Publication Number: 2046289

IPC: A61K31/137, A61P11/02

Language of the proceedings: EN

Title of invention:
COMPOSITIONS AND KITS OF PHENYLEPHRINE

Patent Proprietor:
The Procter & Gamble Company

Opponent:
Reckitt Benckiser (Brands) Limited

Headword:
Stable Phenylephrine compositions

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
Novelty - (yes) - implicit disclosure (no)
Inventive step - (no) - obvious alternative - improvement not credible

Decisions cited:
T 1523/07, T 2522/10, T 0297/11

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 0229/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 5 August 2019

Appellant: (Patent Proprietor)	The Procter & Gamble Company One Procter & Gamble Plaza Cincinnati, OH 45202 (US)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Opponent)	Reckitt Benckiser (Brands) Limited 103-105 Bath Road Slough, Berks, SL1 3UH (GB)
Representative:	O'Brien, Niall James Reckitt Benckiser Corporate Services Limited Legal Department - Patents Group Dansom Lane Hull HU8 7DS (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 14 November 2016 revoking European patent No. 2046289 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	G. Seufert
	P. de Heij

Summary of Facts and Submissions

I. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division revoking European patent No. 2 046 289.

II. The present decision refers to the following documents:

D8 Summary of Product Characteristics for phenylephrine comprising compositions, Marketing Authorisation Number PL 16028/0006, Revision of the text, April 2005

D9 Advertisements for Covonia Cold & Flu Formula, 2004, three pages

D11 Statement of Cristina Bassi, Head of Regulatory Healthcare, North Europe, Reckitt Benckiser, dated 5 May 2016, one page

D14 H. A. M El-Shibini *et al.*, Arzneimittelforschung, 19. Jahrgang, Heft 4, 1969, pages 676 to 678

D15 WO 2007/125501

D17 Calbiochem®, Buffers, A guide for the preparation and use of buffers in biological systems, 2003, pages i to iv and 1 to 32

D18 J. March, Advanced Organic Chemistry, Fourth Edition, John Wiley & Sons, New York (US), 1992, pages 896 to 898

D19 L. Chafetz, R. Turdiu, Pharmaceutical Research, 1987, Vol. 4, No. 2, pages 158 to 161

D24 Experimental report on aldehyde levels in compositions based on example 5 of EP 2 046 289, provided by the appellant with the statement of grounds of appeal

D25 Statement of Missoune Fériale Bakouche, Senior Regulatory and Medical Affairs Consultant, dated 18 July 2017, one page

D25a Supplementary statement of Missoune Fériale Bakouche dated 4 July 2019, one page

III. Notice of opposition was filed by the respondent requesting revocation of the patent in suit in its entirety based on the grounds of lack of novelty and lack of inventive step.

IV. The decision under appeal is based on the patent as granted (main request), a set of claims according to a first auxiliary request filed on 6 July 2016 at the oral proceedings before the opposition division and a set of claims according to a second auxiliary request filed as the first auxiliary request on 6 May 2016.

V. The opposition division decided that the subject-matter of the main request was novel, but lacked an inventive step starting from, *inter alia*, document D8. The opposition division held that, in the absence of any evidence of an unexpected technical effect, the subject-matter of the main request was an obvious solution to the objective technical problem of providing a packed phenylephrine composition suitable for pharmaceutical use. The same applied to the subject-matter of the first and second auxiliary requests.

VI. With the statement of grounds of appeal, the appellant filed document D24 and an amended set of claims as main request and amended sets of claims as first and second auxiliary requests.

Claim 1 of the main request reads as follows:

"A device: comprising a composition contained in said device; wherein said composition comprises a

pharmaceutical active selected from the group consisting of phenylephrine, phenylephrine hydrochloride, phenylephrine hydrobromide and mixtures thereof; and wherein said composition has a pH of from 2 to 5 and wherein said composition comprises less than 0.01 % of total aldehydes by weight of the composition and wherein said device is colorless or colored and permits a user to see the composition through the device and wherein said device comprises a material and wherein said material is Polyethylene Terephthalate (PET)."

Claim 1 of the first auxiliary request differs from claim 1 of the main request in that the following features of granted claims 3 and 6 have been added:

"and wherein said composition further comprises a sweetener; wherein said sweetener comprises an artificial sweetener; wherein said artificial sweetener is selected from the group consisting of: sodium saccharin, acesulfame potassium, sucralose, aspartame, monoammonium glycyrrhizinate, neohesperidin dihydrochalcone, thaumatin, neotame, cyclamates, and mixtures thereof; and wherein said composition comprising from 0.0001 % to 1% of said artificial sweetener, by weight of said composition, and wherein said composition further comprises an additional ingredient selected from the group consisting of a solvent, a reducing agent, a non-aldehydic flavor and/or aroma, a chloride salt, a coolant, a colorant, a preservative, a fragrance, and combinations thereof."

The second auxiliary request differs from the main request in that claim 1 has been transformed into a method claim, which reads as follows:

"A method for providing a device: comprising a composition contained in said device comprising the step of placing said composition in said device; wherein said composition comprises a pharmaceutical active selected from the group consisting of phenylephrine, phenylephrine hydrochloride, phenylephrine hydrobromide and mixtures thereof; and wherein said composition has a pH of from 2 to 5 and wherein said composition comprises less than 0.01 % of total aldehydes by weight of the composition and wherein said device is colorless or colored and permits a user to see the composition through the device and wherein said device comprises a material and wherein said material is Polyethylene Terephthalate (PET)."

VII. In its reply to the statement of grounds of appeal, the respondent maintained its objections of lack of novelty and lack of inventive step. Additional documents were filed, including D25. Document D25 was supplemented with document D25a, filed by letter dated 5 July 2019.

VIII. The arguments of the appellant, as far as they concern the decisive issues of the present decision, can be summarised as follows:

- Public availability of document D8

D8 had not been available to the public at the relevant date of the patent in suit. Document D11 was a mere assertion by the respondent's CEO. Documents D25 and D25a were not backed up by any evidence, in particular with respect to the date of D8's possible availability. Furthermore, not all documents held by a public authority were available to the public.

- Novelty

Document D8 did not disclose a pH or a pH range. The presence of a citrate buffer in a composition did not necessarily mean that the pH was as presently claimed. The pH range in D17 was for a defined amount of citrate and citric acid in 100 ml of deionised water. It did not mean that compositions comprising citric acid and citrate as well as many other components necessarily had such a pH.

The aldehyde content was not disclosed in D8 either. Various excipients used in D8, such as eucalyptus oil, patent blue V, glycerol, propylene glycol, maltitol or sorbitol, could contain aldehydes as impurities. It was necessary to make a conscious effort to remove these aldehydes. No evidence had been provided by the respondent that the components used in D8 were free of aldehydes or that they contained less than 0.01% aldehydes by weight of the composition. The use of pharmaceutical-grade components was not enough. It was the appellant that had found that aldehydes led to instability over time and compromised shelf life. This key piece of information was not present in D8. There was no implicit disclosure of the claimed aldehyde content in D8 either. A composition with a limited amount of aldehyde, albeit higher than the claimed amount, would not be wholly unstable. However, it would not be as stable as a composition with the presently claimed aldehyde content, which consequently would have a longer shelf life.

- Inventive step

Starting from document D8, the technical problem to be solved was the provision of a device including a

composition comprising phenylephrine, phenylephrine hydrochloride or phenylephrine hydrobromide and mixtures thereof with improved stability and consequently improved shelf life in a PET bottle. This problem was solved by restricting the aldehyde content in the composition (see also paragraphs [0005] and [0022] and the examples of the patent in suit).

The invention was the result of a development of the appellant's Vicks Respiratory Cough/Cold products which required the removal of pseudoephedrine. Phenylephrine was considered a potential alternative, but since it was more reactive than pseudoephedrine, degradation problems occurred. Phenylephrine had multiple functional groups and the range of excipients suitable for pharmaceutical use also had many different functional groups. In numerous experiments and trial formulations with various excipients the appellant had found that the phenylephrine-aldehyde reaction was the key degradation pathway for phenylephrine. Since the initial testing was multi-factorial and went beyond the present invention, the appellant did not want to make the full details of said testing available to the public.

Document D24 repeated some of that work done by the appellant. It served as proof of concept and plausibly demonstrated that improved stability and consequently improved shelf life were achieved in compositions comprising the claimed amount of aldehydes. D24 showed that 100% phenylephrine remained if no formaldehyde was added to a preparation according to example 5 of the patent in suit in which the aldehyde content had been minimised. The most improved stability was therefore achieved when the formulator intentionally avoided the addition of aldehydes by careful selection of the

components. If very low amounts of formaldehyde were added, the stability, although not as improved as removing all aldehyde from the composition, was still improved compared to a composition where the aldehyde content was not restricted to below the claimed threshold. Such very low amounts of aldehyde would only be achieved if the formulator was told to restrict the amount of aldehydes. It was not enough to simply use a set of known excipients.

A direct comparison with D8 was not possible, as the aldehyde content was not disclosed therein.

Documents D18 and D19 did not render the claimed subject-matter obvious. D18 was an organic chemistry textbook describing in general the reaction of amines with aldehydes. It provided no guidance as to whether such a reaction was relevant to pharmaceutical product stability. Document D19 had been selected in hindsight. The skilled person had no reason to turn to this document. Even if the skilled person had considered D19, its disclosure would not have motivated them to limit the aldehyde content to the presently claimed low level, which was required to achieve improved stability and shelf life. D19 described an artificial environment (i.e. worst-case scenario; see page 158, left-hand column, second paragraph, lines 4 to 7), identified the degradation mechanism only for a large excess (see paragraph bridging pages 158 and 159) and left the role of this reaction in the stability of pharmaceutical compositions undetermined (see page 160, final sentence). The appellant had gone beyond the disclosure of D19, as it had found that aldehydes affected the stability of phenylephrine even at low levels and that it was therefore necessary to restrict the aldehyde levels to the very low levels as presently claimed to

improve stability and shelf life. D19 was completely silent in this respect.

The use of a PET bottle provided an additional complication, because the phthalate functionality interacted with the phenylephrine and encouraged reactive precipitation. The formulator had to compensate for this with additional solvents (often polyethylene glycol). This increased the likelihood of aldehydes being introduced, which in turn resulted in the decreased stability of a composition comprising phenylephrine.

As regards the pH value, it was accepted that an acidic pH was favourable for phenylephrine compositions, but other factors were also relevant, as was apparent for example from D15, which disclosed a pH of 6.5 to 7.5 when phenylephrine was formulated with acetophenone.

If improvements in stability and shelf life were not accepted, the problem to be solved would be the provision of an alternative formulation setting a low level of aldehydes. The claimed subject-matter was inventive because impurities were usually present in excipients and there was no pointer in the prior art to restrict the amount of aldehydes, which were merely one of many possible impurities, to such an unusually low level as presently claimed.

Claim 1 of auxiliary request 1 contained additional ingredients, which needed to be specifically selected to achieve a low aldehyde content. It better reflected the compositions that were used in the experiment reported in D24. Neither D19 nor any other document on file contemplated the removal of aldehydes from all these additional ingredients. It was not disputed that

the distinguishing features compared to D8 were the same.

Claim 1 of auxiliary request 2 had been limited to a method claim which further distinguished the claimed invention from the prior art. None of the prior-art documents provided any motivation to control the aldehyde content at the point of manufacture to the extent claimed, which compensated for the potential formation of some amount of aldehyde during storage (see paragraph [0020] of the patent in suit).

IX. The arguments of the respondent, as far as they concern the decisive issues of the present decision, can be summarised as follows:

- Public availability of document D8

D8 was a Summary of Product Characteristics for products approved by the UK Medicines and Healthcare products Regulatory Agency. It had been available in April 2005. Document D11, which was a statement from a regulatory professional with many years of experience, confirmed that documents such as D8 would have been provided by the Regulatory Agency to any third party on request without any duty of confidentiality. The statements in D11 had been confirmed by an independent expert (see documents D25/D25a). The marketing authorisation number was in the public domain (see D9) and requests concerning the respective products could have been made to the Regulatory Agency.

- Novelty

The claimed product was not novel over the disclosure of document D8. Said document disclosed phenylephrine-

comprising compositions in a PET bottle. The claimed pH range and the claimed aldehyde content were implicitly disclosed in D8. As regards the pH range, the composition of D8 comprised a citrate buffer, which made the composition acidic. From document D17 it was apparent that citrate buffers had pH values between 3 and 6.2, which clearly overlapped with the claimed pH range. Furthermore, it was common general knowledge that the use of an acidic pH was essential for the stability of phenylephrine compositions.

As regards the claimed aldehyde content, none of the components disclosed in D8 were aldehydes *per se*. All components were of pharmaceutical grade and therefore contained no aldehyde impurities. The appellant had not shown that components such as sorbitol, mannitol or glycerol contained aldehydes, or the levels of these aldehydes. Even if aldehyde impurities were present, they overlapped with those of the examples of the patent in suit. Example 1 of the patent in suit, for example, used propylene glycol, sorbitol and sweetener. The same components were present in D8. The stability of the products disclosed in D8 was further proof that the aldehyde content was less than 0.01%.

- Inventive step

It was known in the art that an acidic pH value was essential for the stability of a phenylephrine solution (see D14, page 678, left-hand column, lines 7 to 10). According to D14, a pH range of 2 to 6.7 was suitable for this purpose. No particular technical effect was linked to the claimed range of 2 to 5.

The patent did not contain any data demonstrating an improvement in stability as a result of the low

aldehyde content. The appellant could therefore not rely solely on post-published document D24.

The respondent agreed with the opposition division's assessment of inventive step. There was no evidence on file that stability problems existed for phenylephrine in PET bottles or of how they were solved. D24 was silent in this respect. Moreover, the alleged precipitation was compensated for by additional solvent. This was not reflected in claim 1.

Starting from document D8, the problem to be solved was the provision of a stable composition in PET bottles. No improvements had been demonstrated.

If stability problems occurred as a result of using excipients contaminated with aldehydes, D19 provided the skilled person with sufficient motivation to minimise the aldehyde content. Document D24 merely showed a general trend that increasing amounts of formaldehyde in a sample containing phenylephrine resulted in an increasing amount of phenylephrine degradation. This was what the skilled person would have expected based on their common general knowledge (see D18) and the disclosure in D19. As in document D19, the use of excess amounts of formaldehyde in examples 1 and 2 of D24 resulted in the almost complete degradation of phenylephrine. If the amount of formaldehyde was sufficiently limited (see examples 4 and 5), a limited reaction or no reaction would occur. In addition, no data had been provided to indicate that flavours containing aldehydes, such as benzaldehydes or p-tolyl aldehyde (see paragraph [0021] of the patent in suit), caused the degradation of phenylephrine. None of the numerous data and trial formulations on which the appellant relied, and which allegedly showed that the

degradation of phenylephrine was due to aldehydes having been introduced via the raw materials, had been provided in support of the appellant's arguments. The only data available was concerned with the reaction of phenylephrine with formaldehyde and appeared to have been generated retrospectively.

There was nothing inventive in the use of a sweetener or other additional ingredients, such as solvents. Document D8 already disclosed such components. The distinguishing features of claim 1 of auxiliary request 1 compared to D8 were the same as for claim 1 of the main request and the same reasoning applied. The same was true for claim 1 of auxiliary request 2. No technical benefit had been shown for the claimed method.

X. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the set of claims of the main request, or alternatively on the basis of the set of claims of the first or second auxiliary requests, all filed with the statement of grounds of appeal.

XI. The respondent requested that the appeal be dismissed.

XII. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. Public availability of document D8

2.1 Document D8 is a Summary of Product Characteristics (SmPC) for an approved product with market authorisation number "PL 16028/0006" and a market authorisation date of 7 April 2003. The text was revised in April 2005.

2.2 The appellant challenged the opposition division's finding that, in view of document D11 and in the absence of any evidence to the contrary, the information in document D8 had been available to the public before the relevant date of the patent in suit.

2.3 D11 is a signed statement of a professional working in the field of regulatory affairs, who confirmed that all Patient Information Leaflets and SmPC documents for approved product licences were available to the public on request via the Medicines and Healthcare products Regulatory Agency of the United Kingdom (MHRA). This statement is supported by the statement of an independent regulatory and medical affairs consultant (see D25/D25a), who confirmed that D8 was a recorded document held by a public authority (i.e. MHRA) and was covered under the Freedom of Information Act 2000, which provides public access to information. A copy of D8 would be provided to any third party on request without any duty of confidentiality. In addition, D25 stated that the information contained in an SmPC was also included in the Patient Information Leaflet accompanying the product supplied to customers, which was further evidence that this information would not be considered confidential.

2.4 In the absence of any evidence to the contrary, the board has no reason to doubt the veracity of these statements by two professionals working in the UK in the area of regulatory and medical affairs. The appellant provided neither a counter-statement by its own expert nor any other document that could call into question the statements made in D11 and D25/D25a. The appellant's concern with respect to D11 (see point VIII above) was addressed by the filing of documents D25/ D25a. The appellant's assertion that not all documents held by a public authority were available to the public may be true, but no evidence has been provided that this applies to the SmPC of an approved product, to which D11 and D25/D25a refer.

For the sake of completeness, the board notes that the marketing authorisation number was in the public domain (see D9, page 1, Product Information Presentation on the left-hand side of the page). Requests for information concerning this product could therefore have been made to the Regulatory Agency before the relevant date of the patent in suit.

2.5 In view of the above, the board has no reason to deviate from the opposition division's finding that the content of document D8 was available to the public before the relevant date of the patent in suit.

3. Novelty (Article 54 EPC)

3.1 The subject-matter of claim 1 of the main request is directed to a device containing a composition which comprises phenylephrine, phenylephrine hydrochloride, phenylephrine hydrobromide and mixtures thereof. The composition has a pH of 2 to 5 and comprises less

than 0.01% total aldehydes by weight of the composition. The device is colourless or coloured and permits a user to see the composition through the device. The material of the device comprises polyethylene terephthalate (PET) (see point VI above).

3.2 According to the respondent, the subject-matter of claim 1 of the main request was anticipated by the disclosure of document D8.

3.3 This document discloses liquid compositions comprising phenylephrine hydrochloride with a shelf life of 2 years. The composition is supplied in a clear glass or PET bottle (see page 1, points 2 and 3, page 6, point 6.5). The pH and the aldehyde content of the compositions are not explicitly disclosed.

3.4 The question to be answered is therefore whether or not these features are implicitly disclosed, as argued by the respondent. The board notes that, in the context of novelty, implicit disclosure means disclosure which any person skilled in the art would objectively consider to be necessarily implied in the explicit content (e.g. in view of a general scientific law). It means no more than the clear and unambiguous consequence of what is explicitly disclosed (see *inter alia* T 297/11, point 3 of the Reasons; T 1523/07, point 2.4 of the Reasons; and T 2522/10 of 16 April 2015, point 4 of the Reasons).

3.5 The board agrees with the respondent that the skilled person was aware of the importance of acidic conditions for the stability of phenylephrine (see D14, particularly page 678, left-hand column, lines 7 to 10). In view of the stability of the composition disclosed in D8 (see page 5, point 6.3), it is a

reasonable assumption for the person skilled in the art that the pH of the compositions is acidic (i.e. pH <7), which would be in accordance with the presence of citric acid and citrate in the compositions of D8 (see page 5, point 6.1, "List of Excipients"). However, the presence of citric acid and citrate does not necessarily and automatically result in a pH that lies within the claimed range of 2 to 5. As is apparent from document D17, on which the respondent relied in this context and which discloses the preparation of commonly used buffer solutions, including citrate buffers, the pH depends on the amount of citric acid and citrate and can readily lie outside the claimed range (see D17, page 19, point 3, in particular the last three columns in the table with a pH of 5.4, 5.8 and 6.2). Furthermore, the board concurs with the appellant that no conclusion can be drawn from D17 as to the pH of a mixture comprising a number of other ingredients in addition to citrate and acid acid. A pH within the claimed range or the claimed range *per se* are therefore not directly and unambiguously derivable from document D8.

The respondent's argument as to an overlapping area between the pH of commonly used citric acid/citrate buffer solutions and D8 is not accepted, because D8 does not disclose a pH range.

3.6 For similar reasons, the board does not share the respondent's position that the claimed aldehyde content of 0.01% by weight of the composition is implicitly disclosed in document D8. It is true that none of the excipients listed in point 6.1 of D8 is *per se* an aldehyde. However, this does not mean that the composition according to D8 is necessarily and automatically free of aldehydes or has an aldehyde

content of less than 0.01% by weight of the composition. Various excipients used in D8, such as eucalyptus oil, glycerol, Patent Blue, maltitol or sorbitol, could contain aldehydes or aldehyde impurities (e.g. cuminal in eucalyptus oil, 3-hydroxybenzaldehyde in Patent Blue or reducing sugars in maltitol or sorbitol).

The respondent asserted that all excipients in D8 are of pharmaceutical grade and therefore essentially free of aldehyde impurities. However, in the absence of any evidence to back up its assertion, in particular evidence that could demonstrate that the use of pharmaceutical-grade excipients is sufficient to necessarily result in a composition with an aldehyde content below the claimed threshold, the board does not accept the respondent's argument. In this context, the board would like to point out that it is convinced that the product disclosed in D8, being an approved pharmaceutical product, does not contain significant amounts of impurities, including aldehyde impurities. Moreover, in view of the stability of the product according to D8, it is fair to say that the presence of aldehydes which could easily react with phenylephrine is low. However, this does not mean that the aldehyde content in the product according to D8 is necessarily below the claimed threshold.

The respondent also pointed out that the composition according to example 1 of the patent in suit and the composition disclosed in D8 partly used the same excipients, such as propylene glycol, glycerol and sorbitol. However, no conclusion regarding the aldehyde content of the product disclosed in D8 can be drawn from this observation, and certainly not that the aldehyde content is below the presently claimed

threshold (< 0.01% by weight of the composition). In this context, the board notes that example 1, which illustrates the invention according to the patent in suit, does not mention the aldehyde content of the composition and that the patent in suit also encompasses compositions with less than 0.1% of total aldehydes by weight of the composition (see paragraph [0020] and claim 1). The respondent's argument as to an overlapping area between the aldehyde content according to claim 1 of the main request and the aldehyde content of document D8 is not convincing either in the absence of any disclosure concerning the aldehyde content in D8.

3.7 For the aforementioned reasons, the board concludes that the claimed pH range and the claimed aldehyde content are not directly and unambiguously derivable from document D8, either explicitly or implicitly. Hence, the claimed subject-matter is novel over the disclosure of document D8.

4. Inventive step claim 1 (Article 56 EPC)

4.1 In the decision under appeal, the opposition division considered document D8 a suitable starting point for the assessment of inventive step. The board has no reason to deviate from the opposition division's choice. The appellant's initial argument that D8 was not available to the public before the relevant date of the patent in suit was not accepted by the board (see point 2 above).

4.2 The appellant formulated the problem to be solved as the provision of a device including a composition containing phenylephrine, phenylephrine hydrochloride or phenylephrine hydrobromide and mixtures thereof

having improved stability and, consequently, improved shelf life in a PET bottle.

The proposed solution was to keep the pH in the range of 2 to 5 and the aldehyde content below the threshold of 0.01% by weight of the total composition.

4.3 The appellant and the respondent were divided as to whether the experimental evidence on which the appellant relied in this context (see document D24) showed that the technical problem as defined in point 4.2 above has been successfully solved.

4.4 Document D24 is an experimental report on aldehyde levels in compositions based on example 5 of the patent in suit. It describes the preparation of a composition according to said example in which the ingredients were selected to minimise the aldehyde content (see D24, note 1 below the table on page 1). Formaldehyde was added to four samples of said composition (i.e. Samples 1 to 4 on page 2, third paragraph). In Sample 0 no formaldehyde was added. The samples were stirred at room temperature for three hours (see page 2, fourth paragraph). Subsequently, the remaining phenylephrine was determined. The following results were obtained.

Sample	Formaldehyde Added (ppm)	Remaining Phenylephrine (as % of control)
0	0	100
1	527	0
2	308	3.8
3	10.9	89.7
4	5.1	94.1

On page 4 it is stated that the results show a marked degradation of phenylephrine even at surprisingly low aldehyde levels.

4.5 In the board's view, document D24 does not constitute evidence of improvements in the stability of phenylephrine and consequently an improved shelf life of phenylephrine-comprising compositions, as presently claimed, over the composition disclosed in D8, for want of a comparison with a composition reasonably reflecting the closest prior art.

Document D8 discloses a product with a shelf life of two years. It can therefore safely be said that no significant degradation of phenylephrine occurs. The board concurs with the opposition division that a pharmaceutical product that has received market authorisation must fulfil strict stability criteria. A significant loss of phenylephrine - an active ingredient - would not have been acceptable. It is also fair to conclude that the product of D8 is essentially free of formaldehyde, which readily reacts with phenylephrine, even in the absence of any information regarding the aldehyde content in D8. As shown in D24, the addition of even very small amounts of formaldehyde (10.9 or 5.1 ppm) results in a loss of phenylephrine within no more than 3 hours at room temperature (see table above). Hence, none of Samples 1 to 4 of D24 can be said to reasonably reflect a product according to the closest prior art. Moreover, document D24 is silent as to the shelf life of the composition according to the invention, i.e. Sample 0. At best, D24 shows that the addition of increasing amounts of formaldehyde - the most reactive aldehyde - to a stable composition according to the invention with minimised aldehyde content results in increasing loss of phenylephrine. This is not an unexpected result for the skilled person, as it was known that formaldehyde readily reacts with 3-hydroxyphenylethylamines, such as phenylephrine (see D19). Document D24 merely confirms

the findings of D19. No further conclusion can be drawn from D24. In particular, D24 cannot be used as evidence that the claimed product, due to the specifically claimed aldehyde content, is more stable than the product of D8, which, in the board's view, is stable, essentially free of formaldehyde and, as explained in point 3.6 above, low in impurities, including aldehydes.

4.6 The appellant also argued that the use of PET bottles was problematic, because it allegedly encouraged the reactive precipitation of phenylephrine, which had to be compensated for by additional solvents, thereby increasing the likelihood of aldehydes being introduced. However, D8 discloses compositions provided in a PET bottle with a shelf-life of 2 years. No precipitation occurs. As correctly stated by the opposition division the precipitation of an active ingredient would not have been tolerated and no market authorisation would have been received. Hence, the board concurs with the opposition division and the respondent that the appellant has not shown that a problem with precipitation exists for the prior-art product, or that it has been solved by using a composition with an aldehyde content below the claimed threshold. Document D24 is not concerned with this issue as it does not examine the relationship between the use of PET bottles and the aldehyde content. Moreover, the alleged precipitation of phenylephrine is apparently prevented by the selection of appropriate amounts of solvents, a feature which does not form part of claim 1 of the main request.

4.7 Concerning the claimed pH range, the board notes the following.

As explained above (see point 3.5 above), it was known in the art that an acidic medium is an essential condition for the stability of a phenylephrine solution. In alkaline conditions (pH > 7) phenylephrine degrades (see D14, point 3.3). In view of the stability of the product in D8, it is therefore fair to say that the pH of the product is in the acidic range, or at least not far into the alkaline range. There is no evidence on file that the specific pH range of 2 to 5, as presently claimed, is causally linked to any improvements in the stability and shelf life of the claimed product over the product disclosed in D8. D24, which focuses on experiments concerning the aldehyde content, is not pertinent in this context.

4.8 It follows from the above that the alleged advantages of the claimed invention over the prior art (i.e. improvement in stability of phenylephrine and, as a consequence, improvement of the shelf life of the product) are not adequately supported by the experimental evidence on which the appellant relied.

4.9 According to the established case law of the boards of appeal, alleged, but unsupported advantages cannot be taken into account in the determination of the technical problem to be solved. As a consequence, the problem as formulated in point 4.2 above has to be reformulated. In the light of document D8, it can be seen as the provision of an alternative, i.e. stable, packaged phenylephrine composition suitable for pharmaceutical use.

The board considers that this problem has been plausibly solved.

The appellant's formulation of the technical problem for the event that no improvement could be acknowledged, namely the provision of an alternative formulation setting a low level of aldehyde, contains a pointer to the solution and is therefore not accepted.

4.10 It remains to be decided whether the proposed solution, i.e. a product comprising a composition with the claimed specific pH range and the claimed specific aldehyde content, was obvious for the skilled person in view of the prior art.

4.10.1 As indicated above, the skilled person was aware that an acidic pH is essential for the stability of phenylephrine. The choice of the specific range 2 to 5 has not been shown to result in any technical benefit over the prior art. This choice is therefore neither critical nor purposive for solving the objective problem, but is merely an arbitrary restriction of no technical significance.

4.10.2 Similarly, the skilled person faced with the technical problem of providing a further stable phenylephrine-comprising product would, as a matter of routine, avoid the use of any ingredient which could potentially react and therefore destabilise phenylephrine. They would be aware that aldehydes are prone to react with amines, such as phenylephrine (see D18 and D19), and that such a reaction had been implicated in drug decomposition (see D19, abstract, last three lines, and page 158, left-hand column, second paragraph, first three lines). Accordingly, they would be strongly motivated to keep the aldehyde level low and to use excipients which are not aldehydes or are substantially free of aldehyde impurities when attempting to provide a stable alternative to the product disclosed in D8. In the

absence of any technical benefit resulting from the specifically claimed aldehyde level, this level is, in the board's judgement, merely an arbitrary restriction which requires no inventive skill.

4.10.3 According to the appellant, the skilled person would have no reason to monitor the aldehyde content and to work at the very low level as presently claimed without being told to do so. A conscious effort to remove aldehydes was needed.

4.10.4 The board does not find the appellant's arguments persuasive for the reasons set out in point 4.10.2 above. The skilled person had every reason to monitor the aldehyde content when faced with the technical problem as defined in point 4.9 above. A surprising and unexpected technical effect which could potentially support an inventive stephas not been shown to be associated with the specifically claimed range.

4.10.5 The appellant also argued that the results in document D19 were achieved in an artificial environment in which a large excess of formaldehyde had been used. Therefore, D19 could not have motivated the skilled person to limit the aldehyde content to the extent claimed, which was required to achieve improved stability and shelf life for the claimed product. There was no reasonable expectation that the removal of aldehydes to such low levels as presently claimed would improve stability and shelf life.

4.10.6 However, since the alleged improvement has not been shown and therefore does not form part of the objective technical problem, the appellant's arguments are not considered to be relevant. As set out above, D19 provides sufficient motivation for the person skilled

in the art to keep the aldehyde content low in a phenylephrine-comprising composition. It also encourages the skilled person to determine the significance of its findings for pharmaceutical compositions, as correctly observed by the opposition division (see D19, page 160, right-hand column, last paragraph). It is uncontested that D19 uses an excess of aldehyde, as its purpose was the examination of the reaction of formaldehyde with 3-hydroxyphenylalkanol-amines including phenylephrine. However, lowering the amount of aldehyde to minimise the reaction would not be an unexpected measure for the skilled person. No unexpected effect has been shown to be associated with the particularly low aldehyde content presently claimed. The appellant's argument that the invention as presently claimed goes beyond the teaching of D19 is therefore not accepted.

4.10.7 The explanations as regards the background to the invention provided by the appellant in the statement of grounds of appeal (see page 10, paragraphs [0051] and [0052]) cannot change the assessment of inventive step as set out above. According to the appellant, the change of an active ingredient (replacement of methamphetamine with phenylephrine) in a specific product (Vicks Respiratory Cough/Cold) led to stability problems of said product, which were found to be linked to the aldehyde content. These explanations are not contested and the improvement in stability of the appellant's specific product, after the active ingredient has been changed, may well have been the problem the appellant set out to solve. However, the starting point for the assessment of inventive step is an approved stable pharmaceutical phenylephrine-containing product with a shelf life of 2 years, not the appellant's specific product, and the objective

technical problem is the provision of an alternative stable product. The appellant's explanations are therefore not relevant.

4.11 In view of the above, the board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step as required by Article 56 EPC.

Auxiliary request 1

5. Inventive step claim 1 (Article 56 EPC)

5.1 Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the composition contained in the PET bottle further comprises an artificial sweetener selected from the group consisting of sodium saccharin, acesulfame potassium, sucralose, aspartame, monoammonium glycyrrhizinate, neohesperidin dihydrochalcone, thaumatin, neotame, cyclamates and mixtures thereof, in a particular amount, and a further ingredient selected from the group consisting of a solvent, a reducing agent, a non-aldehydic flavour and/or aroma, a chloride salt, a coolant, a colorant, a preservative, a fragrance and combinations thereof.

5.2 The amendments made in auxiliary request 1 do not alter the above assessment of inventive step. As is apparent from page 5, point 6.1, of document D8, the use of artificial sweeteners from the claimed group such as sodium saccharin and ingredients such as solvents or a colorant is already taught in D8, and the particular amount of sweetener (0.0001% to 1%) has not been shown to be associated with any particular technical effect. In fact during the oral proceedings the appellant

acknowledged that the objective technical problem to be solved would be the same as for the main request.

5.3 The appellant referred again to document D24 and re-emphasised that the additional components needed to be specifically selected to achieve the claimed low aldehyde content and that D19 did not contemplate the removal of aldehydes from all these components.

5.4 However, as this selection does not distinguish the claimed subject-matter from the prior art, the effect of the selection is irrelevant for the assessment of inventive step. It is also not apparent that artificial sweeteners, such as sodium saccharin, or solvents, such as water, or specifically selected non-aldehydic flavours or aromas would contain aldehyde impurities above the claimed threshold which needed to be specifically removed.

5.5 Therefore, the board concludes that auxiliary request 1 does not meet the requirements of Article 56 EPC.

Auxiliary request 2

6. Inventive step (Article 56 EPC)

6.1 Claim 1 differs from claim 1 of the main request in that it has been transformed into a claim for a method for providing a device - a PET bottle - comprising a composition contained in said device comprising the step of placing the composition in said device (see point VI above). The composition is defined as in claim 1 of the main request.

6.2 The same step of placing the composition into the PET bottle is required in the manufacture of the product of

document D8. Such a step cannot support an inventive step. Concerning the composition with the specific pH range and aldehyde content comprised in the PET bottle, the board notes that the same argument against inventive step provided in point 4 above applies.

6.3 Hence, the board comes to the conclusion that the subject-matter of claim 1 of auxiliary request 2 does not meet the requirement of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated