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Datasheet for the decision of 3 September 2020

Case Number: T 0214/18 - 3.3.01

Application Number: 07836046.8

Publication Number: 2040672

IPC: A61K31/137

Language of the proceedings: EN

Title of invention:
Enhanced stability phenylephrine liquid compositions

Patent Proprietor:
PF Consumer Healthcare 1 LLC

Opponent:
Reckitt Benckiser (Brands) Limited

Headword:
Phenylephrine composition with PEG/PFIZER

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)

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Case Number: T 0214/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 3 September 2020

Appellant: (Opponent)	Reckitt Benckiser (Brands) Limited 103-105 Bath Road Slough Berkshire SL1 3UH (GB)
Representative:	O'Brien, Niall James Reckitt Benckiser Corporate Services Limited Legal Department - Patents Group Dansom Lane Hull HU8 7DS (GB)
Respondent: (Patent Proprietor)	PF Consumer Healthcare 1 LLC Corporation Trust Center 1209 Orange Street Wilmington, DE 19801 (US)
Representative:	Gundel, Isabelle GlaxoSmithKline Global Patents CN925.1 980 Great West Road Brentford, Middlesex, TW8 9GS (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 13 November 2017 rejecting the opposition filed against European patent No. 2040672 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	M. Pregetter
	R. Romandini

Summary of Facts and Submissions

I. European patent No. 2 040 672 is based on European patent application No. 07836046.8, filed as an international application published as WO2008/008364.

II. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(2) J. March, "Advanced Organic Chemistry", 4th edition, John Wiley & Sons, Inc., 1992, 896 to 898

(3) Chafetz et al., Pharm. Res., 1987, 4(2), 158 to 161

(4) Internet publication: "Croda presents new high purity excipients", In-PharmaTechnologist, 2005, 1 page

(8) WO03/011306

(13) Affidavit of Dr William Bubnis, 3 August 2016, 4 pages

(13a) Exhibit WB1 accompanying the affidavit of Dr Bubnis (document (13)), 11 pages

III. The European patent was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.

Claim 1 of the patent in suit reads as follows:

"1. An oral liquid pharmaceutical composition comprising:

(a) phenylephrine or a pharmaceutically acceptable salt thereof; and
(b) substantially aldehyde-free polyethylene glycol, wherein the substantially aldehyde-free polyethylene glycol has less than 10 ppm total aldehyde content and maintains said level of aldehyde content for at least six months; wherein the composition is buffered to maintain the pH below 5.4."

IV. The opposition division rejected the opposition. The opponent (appellant) appealed this decision. The appellant's sole objection was lack of inventive step.

V. With the agreement of all parties, oral proceedings by video conference were held on 3 September 2020.

VI. The appellant's arguments, in so far as they are relevant to the present decision, may be summarised as follows.

Document (8) exemplified a composition comprising pseudoephedrine and polyethylene glycol. According to claim 7 of this document, the pseudoephedrine could be replaced by phenylephrine. Having made the change from pseudoephedrine to phenylephrine, the skilled person would have assessed the stability of the composition in a systematic way using standard analytical techniques. Such techniques included the generation of spectroscopic data. The skilled person, routinely performing a methodical series of experiments, would have seen from the spectroscopic data that the phenylephrine degradants were products of a reaction with aldehydes. It was common general knowledge that

aldehydes, including formaldehyde and aldehydes with more carbon atoms, reacted with amines (see document (2)). Furthermore, such a reaction was even disclosed for phenylephrine in document (3). Document (4) provided the general teaching that purer grade polyethylene glycols could improve the stability of pharmaceutically active ingredients and that such polyethylene glycols would have lower levels of aldehydes. The skilled person was thus in a normal "try and see" situation and faced no technically challenging hurdles when carrying out their routine approach. Consequently, they would have identified the grade of polyethylene glycol, especially the content of aldehydes, as a potential problem for phenylephrine stability.

In sum, the steps taken by the patent proprietor in developing the claimed formulation represented nothing more than obvious/non-inventive steps which would have been readily contemplated by the person skilled in the art, as was apparent from document (13a).

Furthermore, the problem of providing a stable and thus commercially acceptable composition had not been solved by the claims under consideration. Document (13a) established that high fructose corn syrup had a much higher impact on the stability of phenylephrine than the grade of polyethylene glycol. However, the claims allowed for the presence of high fructose corn syrup.

VII. The respondent's (patent proprietor's) arguments, in so far as they are relevant to the present decision, may be summarised as follows.

Starting from document (8) there were two differences: the active agent and the use of a polyethylene glycol

with a low aldehyde content. The replacement of pseudoephedrine by phenylephrine was pushed for by regulatory requirements. Example 5 and Figure 1 of the patent in suit showed that the use of a polyethylene glycol having a very low aldehyde content improved the stability of phenylephrine. The technical problem was thus as described in paragraph [0004] of the patent in suit. The mere mention in the patent in suit that pharmaceutical formulations needed to be commercially acceptable did not lead to an obligation to formulate the problem in such a broad way. Stability effects caused by high fructose corn syrup were not linked to effects due to the use of low aldehyde content polyethylene glycol.

It was common general knowledge that aldehydes reacted with amines. However, both compounds disclosed in document (8), phenylephrine and pseudoephedrine, had almost identical side chains, both of which contained an amine group. The skilled person would thus not have expected that aldehydes were the main source of the different stabilities.

Document (3) related to very specific reactions. In particular, the high amounts of formaldehyde used in the reactions would have prevented the skilled person from considering this document when trying to identify potentially problematic impurities.

Document (4) was general and did not mention phenylephrine. Furthermore, it had been shown in document (13a) that Croda's Super Refined PEG, as disclosed in document (4), was inadequate.

Document (8) was silent on stability issues when changing the active agent. It was unclear which agent

or ingredient caused the instability of the phenylephrine and where the cause of the instability came from. The skilled person was thus not prompted to consider total aldehydes. Phenylephrine could undergo many different reactions that would not necessarily be identified, for instance from spectroscopic data, as stemming from a reaction with aldehydes.

Since neither the impurity causing the degradation of phenylephrine nor the source of this impurity was known to the skilled person, they would not have arrived in an obvious way at the claimed subject-matter. An inventive step was thus present.

VIII. The final requests were as follows.

The appellant (opponent) requested that the decision under appeal be set aside and that European patent No. 2 040 672 be revoked.

The respondent (patent proprietor) requested that the appeal be dismissed, or, alternatively, that the patent be maintained on the basis of any of auxiliary requests 1 to 4 submitted with the reply to the grounds of appeal.

Reasons for the Decision

1. The appeal is admissible.

2. Inventive step

2.1 The patent in suit relates to oral liquid pharmaceutical compositions comprising phenylephrine. A palatable liquid dosage form comprising phenylephrine

with reduced propensity for degradation of phenylephrine is to be provided (paragraphs [0001] and [0004]). To this end, a composition comprising phenylephrine and substantially aldehyde-free polyethylene glycol is taught (paragraph [0005]). The patent puts forward that phenylephrine degradation is facilitated by the presence of aldehydes and reducing sugars (paragraph [0011]).

2.2 The decision under appeal relies on document (8) as the closest prior art. This has not been contested by the appellant.

Document (8) discloses several compositions having the required pH and comprising pseudoephedrine hydrochloride and Polyethylene Glycol 1450 (Examples 1-3 and 5). It furthermore defines compositions having a pH of 2.0 to 5.0 and comprising sucralose and at least one active (claim 1). Phenylephrine may be selected as the active (claim 7).

2.3 When starting from one of Examples 1-3 and 5 of document (8), the difference between claim 1 of the patent in suit and the closest prior art is the active agent and the use of polyethylene glycol having a low aldehyde content as excipient.

It was common ground that the replacement of pseudoephedrine hydrochloride by phenylephrine (or a salt thereof) was prompted by regulatory changes and did not involve an inventive step.

The focus of the present decision is thus on the difference in excipients, in particular in the selection of a polyethylene glycol having less than 10 ppm total aldehyde content.

The effect linked to this difference is an increased stability of phenylephrine (see Figure 1 of the patent in suit).

The appellant has argued that excipients other than polyethylene glycol have a much higher impact on the stability of the composition, and has referred explicitly to high fructose corn syrup.

However, the influence of high fructose corn syrup on the degradation of phenylephrine has not been shown to influence the effects of low aldehyde content polyethylene glycol on the degradation of phenylephrine. The effects of low aldehyde content and presence of high fructose corn syrup thus have to be considered independently. Consequently, the effect of the low aldehyde content of the polyethylene glycol excipient is to be taken into account over the whole scope of claim 1 of the patent as granted.

2.4 The problem to be solved may therefore be formulated as the provision of a palatable liquid dosage form comprising phenylephrine with reduced propensity for degradation of phenylephrine, as is disclosed in the patent in suit, paragraph [0004].

As can be seen from the discussion above, the problem has been solved.

2.5 It remains to determine whether it would have been obvious to the skilled person to use polyethylene glycols having very low total aldehyde contents as excipients for phenylephrine.

Document (8) does not discuss the influence of the

excipients used in its examples on the stability of the pharmaceutical actives. Thus, document (8) itself does not provide any guidance to the skilled person on stability issues when changing the active agent from pseudoephedrine to phenylephrine.

It is common ground that a skilled person, faced with a composition in which the pharmaceutically active ingredient shows degradation, would have undertaken steps towards a stable composition. These steps include analytical research, which would probably generate spectroscopic data. However, in the present case, no spectra of any kind have been submitted by the appellant. The respondent has argued that it might not be easily derivable from spectroscopic data that the degradation products resulted from a reaction of phenylephrine with an aldehyde. In the absence of any such data, the board is in no position to come to a finding on whether the skilled person would have realised that the degradation products resulted from a reaction with aldehydes. Thus, it has not been established that the skilled person would have been led directly to consider aldehydes and would have looked for an aldehyde source. Consequently, the present case does not represent a "try and see" situation.

When starting from document (8), and in particular when starting from one of the examples comprising pseudoephedrine as pharmaceutically active agent, the skilled person would have based their consideration on the differences and similarities to the compounds present in these examples. The respondent has pointed to the chemical structures of pseudoephedrine and phenylephrine (see structures depicted in the reply to the grounds of appeal, page 5). In these structures the amine group, which can possibly react with an aldehyde,

is present in the side chain. The respondent has stressed that the side chains of the two compounds merely differed in the presence of a methyl group. The appellant has not commented on a possible change in reactivity of the amine group due to the vicinity of this methyl substituent. It is thus unclear whether the skilled person would have expected the amine group of phenylephrine to be more reactive, or put differently, more prone to degradation reactions, than the amine group of pseudoephedrine. Therefore, the skilled person is not led to consider impurities capable of reacting with an amine group such as aldehydes.

The appellant has further pointed to document (3), which teaches that phenylephrine reacts with formaldehyde. However, the reaction conditions in document (3) do not resemble the conditions in a pharmaceutical composition where the active agent is present in considerable excess over any impurities and where any impurities, whether their presence is known or unknown (as in the present case where it has not been established that the skilled person would have known that aldehydes were responsible for the degradation of phenylephrine), are usually present in very low concentrations. Thus, when starting from document (8) as the closest prior art, and especially starting from an example having a structurally related, pharmaceutically active agent, the skilled person would not have considered this document to be pertinent. The same applies to document (2), which represents the common general knowledge on reactions of amines with aldehydes.

Document (4) cannot lead the skilled person to the subject-matter of claim 1 of the patent in suit either. Document (4) relates to super refined PEG and super

refined oleic acid as excipients "claimed to enhance active pharmaceutical ingredient (API) and formulation stability" (page 1, paragraph 1). It discloses the removal of several polar impurities, including aldehydes. It is thus a document that would have been considered by the skilled person faced with a formulation in which the pharmaceutically active ingredient shows degradation. However, as can be seen from document (13a) (see page 6, paragraph 2 of section 5.14.8), the removal of polar impurities, including aldehydes, according to document (4) does not result in a total aldehyde content of less than 10 ppm. In fact, total aldehyde contents ranging from 38 to 490 ppm were found for the ""super refined" Croda 400 PEGs". The skilled person, not being focused on aldehydes, would not have considered lowering the aldehyde content further, in general or in particular, in the polyethylene glycol disclosed in document (4).

In sum, when starting from document (8), the skilled person would not have automatically identified aldehydes as the cause of the degradation of phenylephrine and, consequently, would not have sought to use polyethylene glycol having a very low content of total aldehydes as excipient.

2.6 The subject-matter of the claims of the patent as granted involves an inventive step (Article 56 EPC).

2.7 In the statement setting out the grounds of appeal, the appellant has not specifically contested any other points of the decision under appeal. Nor has it raised any further specific objections in the course of these appeal proceedings. For this reason the board is not required to review the other findings of the appealed

decision and the appeal is dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

M. Schalow T. Sommerfeld

Decision electronically authenticated