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Datasheet for the decision of 28 November 2019

Case Number: T 2717/17 - 3.3.07

Application Number: 11784951.3

Publication Number: 2640389

IPC: A61K47/12, A61K47/14, A61K31/485, A61K9/70

Language of the proceedings: EN

Title of invention:
TRANSDERMAL THERAPEUTIC SYSTEM COMPRISING BUPRENORPHINE

Patent Proprietor:
Hexal AG

Opponents:
LTS LOHMANN Therapie-Systeme AG
Generics [U.K.] Limited
Graf von Stosch, Andreas

Headword:
Buprenorphine/ HEXAL

Relevant legal provisions:
RPBA Art. 13(1), 13(3)
EPC Art. 100(b), 100(a), 54, 56

Keyword:

Late-filed document - admitted (no)
Late-filed attack on inventive step - admitted (no)
Grounds for opposition - insufficiency of disclosure (no)
Novelty - (yes)
Inventive step - (yes)

Decisions cited:

G 0003/97

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Beschwerdekammern

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Case Number: T 2717/17 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 28 November 2019

Appellant: (Opponent 1)	LTS LOHMANN Therapie-Systeme AG Lohmannstrasse 2 56626 Andernach (DE)
Representative:	Plate, Jürgen Plate Schweitzer Zounek Patentanwälte Rheingaustrasse 196 65203 Wiesbaden (DE)
Appellant: (Opponent 2)	Generics [U.K.] Limited Station Close Potters Bar Herfordshire EN6 1TL (GB)
Representative:	FRKelly 27 Clyde Road Dublin D04 F838 (IE)
Appellant: (Opponent 3)	Graf von Stosch, Andreas Prinzregentenstrasse 22 80538 München (DE)
Representative:	Maiwald Patent- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstraße 3 80335 München (DE)
Respondent: (Patent Proprietor)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 9 October 2017 rejecting the opposition filed against European patent No. 2640389 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman J. Riolo
Members: A. Usuelli
C. Schmidt

Summary of Facts and Submissions

I. European patent No. 2 640 389 was granted on the basis of 15 claims.

Independent claims 1 and 13 read as follows:

"1. A transdermal therapeutic system comprising
1) a backing layer,
2) at least one drug containing adhesive layer containing a transdermal drug delivery composition comprising
i. 1 to 20 % by weight of buprenorphine, based on the total weight of the composition,
ii. an adhesive component, which preferably forms an amorphous mass, comprising a crosslinked acrylic polymer and a non-crosslinked acrylic polymer in a ratio of 10 to 90 parts by weight to 90 to 10 parts by weight,
iii. and 1 to 50 % by weight of a penetration enhancer, based on the total weight of the composition, comprising a keto acid, and
3) optionally at least one further adhesive layer, and
4) further optionally, a release liner."

"13. A method of producing a transdermal therapeutic system comprising a backing layer, at least one adhesive layer and a release liner, comprising the steps of
1) preparing a solution comprising
a. buprenorphine,
b. a crosslinkable acrylic polymer,
c. a non-crosslinkable acrylic polymer, and

d. a penetration enhancer comprising a keto acid, and
e. optionally one or more of a solubilizer or tackifier,
2) coating the solution on the backing layer or on the release liner,
3) drying the coating to form the at least one adhesive layer, and
4) coating the at least one adhesive layer with the release liner or the backing layer."

II. Three oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step and was not sufficiently disclosed. The documents cited during the opposition proceedings included the following:

E2: EP 430019
E3: US 6,231,886
E4: US 6,344,211
E5: US 5,240,711
E8: US 6,264,980
E9: EP 819 438
E21: Excerpt from AU Register dated 7 August 2017 concerning opposition against Australian patent 2011331511

III. By decision posted on 9 October 2017, the opposition division rejected the oppositions.

In its decision, the opposition division came to the conclusion that the patent met the requirement of sufficiency of disclosure. Specifically, with regard to the ratio of crosslinked to non-crosslinked polymer, it held that the skilled person would have known how to prepare compositions with the desired ratio taking into account the information disclosed in [0028] of the

patent. The claims of the patent were considered novel. As to inventive step, the opposition division considered that E3 was the closest prior art. The transdermal therapeutic system (TTS) defined in claim 1 of the patent differed from those disclosed in E3 in the presence of a non-crosslinked acrylic polymer in the adhesive. Having regard to the experimental data disclosed in the patent and to those contained in the patent-proprietor's letter of 22 June 2017, the technical problem was the provision of a TTS providing a higher blood plasma level of buprenorphine and thus an increased analgesic effect. There was nothing in the prior art documents that would have prompted the skilled person to add a non-crosslinked acrylic polymer to solve this problem. Hence, the patent met the requirements of Article 56 EPC.

IV. Opponents 1 and 3 ("appellant-opponent 1" and "appellant-opponent 3") filed an appeal against that decision. An appeal was also filed by opponent 2, but it was subsequently withdrawn.

In their statements setting out the grounds of appeal, the appellants focused on the issue of sufficiency of disclosure in relation to the ratio of crosslinked to non-crosslinked acrylic polymer and the requirement of inventive step starting from E3 as the closest prior art.

V. In its reply to the appeals filed on 3 July 2018, the patent-proprietor ("respondent") requested the dismissal of the appeal or, in the alternative, that the patent be maintained on the basis of one of the six auxiliary requests filed during the opposition proceedings on 1 August 2017.

VI. In a communication pursuant to Article 15(1) RPBA issued on 12 September 2019, the Board commented on the issues of novelty, sufficiency of disclosure and inventive step. In relation to the requirement of novelty, the Board expressed the view that the patent was novel over E3 and E4. Concerning the sufficiency of disclosure, it observed that paragraph [0028] of the description explained how to calculate the ratio of crosslinked acrylic polymer to non-crosslinked acrylic polymer. As to inventive step, the Board observed that the closest prior art document E3 did not disclose a TTS containing a non-crosslinked acrylic polymer in the adhesive. On the basis of the experimental data disclosed in the patent and those submitted by the respondent during the opposition proceedings, the technical problem appeared to be the provision of a TTS providing a higher blood plasma level of buprenorphine. In the Board's view, the prior art did not indicate that combining crosslinked and non-crosslinked acrylic polymers had a positive impact on the blood plasma level of the active ingredient.

VII. The following documents were submitted by appellant-opponent 1 on 14 November 2019:

E29: Proceedings of Singapore Healthcare, 19(3), 2010, 276-278
E30: British Medical Journal, 292, 1986, 746-750
E31: Engineering Statistic Handbook, Chapter 1.3.6.7.2

In the submissions filed on the same date, appellant-opponent 1 commented on the lack of statistic relevance of the respondent's experimental data by referring to E29 to E31. Additionally, it submitted arguments on inventive step starting from E2 or E5 as the closest prior art.

VIII. Oral proceedings were held on 28 November 2019. They were attended by the appellants and the respondent.

IX. The appellants' arguments can be summarised as follows:

(a) Issues of admittance

Documents E29 to E31 described the general knowledge of the skilled person in the field of statistical analysis. The appellants had already commented in their previous submissions on the lack of statistical significance of the respondent's data. Thus, E29 to E31 and the arguments concerning these documents were clearly admissible.

The new attack on inventive step starting from E2 or E5 as the closest prior art was admissible since it was based on documents already on file.

(b) Sufficiency of disclosure

According to paragraph [0028] of the description, the crosslinkable acrylic polymer was preferably completely crosslinked. This statement implied that some non-crosslinked crosslinkable polymer could be present in the adhesive. It was indeed quite common to keep some amount of non-crosslinked crosslinkable polymer in the adhesive to increase its adhesive strength. In the case of partial crosslinking, the patent did not explain how to calculate the ratio of crosslinked to non-crosslinked polymer. No information was give on how to analyse the final product to calculate this ratio. Thus, this ratio was an ambiguous parameter. The respondent did not provide any evidence that the ratio of crosslinked to non-crosslinked was identical to the

ratio of the corresponding starting materials. Moreover, since claim 1 was not a product-by-process claim, it made no sense to refer to the starting materials to determine a parameter concerning the final product.

The *in vivo* study disclosed in the patent could not be reproduced because some information had been omitted such as the size of the patch used and the number of person involved in the study. There was no guidance on how to achieve the effect of increasing the blood plasma levels of buprenorphine. The subject-matter of claim 1 was not sufficiently disclosed also for this reason. The process of claim 13 did not mention any addition of a crosslinking agent. Thus, claim 13 was not sufficiently disclosed since it did not contain an essential feature for carrying out the process.

(c) Novelty

In view of the term "preferably" in claim 1, the feature concerning the ratio of crosslinked to non-crosslinked polymer could be considered optional. In this case, the subject-matter of claim 1 would lack novelty in view of E3 and E4.

(d) Inventive step

The TTS defined in claim 1 differed from the TTS disclosed in example 1 of E3 in the presence of a non-crosslinked polymer in the adhesive. The experimental data disclosed in the patent as well as those submitted by the respondent on 22 June 2017 were not statistically relevant. There was an extensive overlap of the curves representing the buprenorphine plasma levels obtained by the use of the TTS of claim 1

or the TTS of E3. As explained by Professors Poulton and Roberts in E21, it would have been necessary to determine the 95% confidence interval using a t-test to show a statistically significant improvement. In contrast, the standard error of the mean (SEM) used by the respondent was not sufficient to establish a statistically significant improvement. Furthermore, only 12 patients were treated in the study described in the report of 22 June 2017. Similar considerations applied to the *in vitro* data submitted on 22 June 2017. The experimental data were in any case not sufficient to show that an effect was present over the whole scope of the claim. Hence, the technical problem was the provision of an alternative TTS containing buprenorphine as the active ingredient. Documents E2 and E5 disclosed TTSs containing a mixture of crosslinked and non-crosslinked acrylic polymer in the adhesive. The skilled person would have arrived without any inventive effort at the subject-matter of claim 1 by combining the teachings of E3 with E2 or E5. Furthermore, E9 suggested that the cohesive forces of of an adhesive layer could be improved by using a combination of a crosslinked and non-crosslinked acrylic polymer. Thus, the skilled person would have been encouraged by E9 to test adhesives containing such a combination of acrylic polymers.

The subject-matter of the patent would have also been obvious when starting from E2 or E5 as the closest prior art. In this case, the distinguishing feature of the TTS of claim 1 was the use of a keto acid as penetration enhancer. However, the skilled person would have known from E8 that levulinic acid, a keto acid, was a very effective penetration enhancer. Hence, claim 1 would have been obvious in view of the combinations of the teachings of E2 or E5 with E8.

X. The respondent's arguments can be summarised as follows:

(a) Issues of admittance

Documents E29 and E31 had been filed only two weeks before oral proceedings without any justification. The submissions of 14 November 2019 contained new data and a new attack on inventive step starting from a different closest prior art. This new evidence and new arguments were not admissible.

(b) Sufficiency of disclosure

Paragraph [0028] of the patent explained how the ratio of crosslinked to non-crosslinked acrylic polymer was to be calculated. The appellants were not correct in assuming that the adhesive contained relevant amounts of crosslinkable acrylic polymer that was not crosslinked because the patent taught to carry out a complete process of crosslinking and explained how this was to be done. Thus, as explained in the patent, the ratio recited in claim 1 was equivalent to the ratio of the starting materials.

(c) Novelty

The objections on novelty were based on an incorrect interpretation of claim 1. Contrary to what appellant-opponent 3 affirmed, the term "preferably" only referred to the feature "forms an amorphous mass". Hence, the patent was novel over E3 and E4.

(d) Inventive step

The TTS of the patent differed from the one of E3 in the presence of a non-crosslinked acrylic polymer in the adhesive. This resulted in an increase of the buprenorphine plasma level. This effect was supported by the data of the patent and the data contained in the report submitted on 22 June 2017. There was no obligation to carry out the statistical analysis that was commonly done for scientific publications. Figure 1 of the report of 22 June 2017 showed that there were at least 11 points in which the curve representing the buprenorphine plasma level for the TTS of claim 1 was above the curve representing the buprenorphine plasma level for the TTS of the prior art. This was convincing evidence of an improved effect. This effect was also supported by the *in vitro* studies. The technical problem was therefore the provision of a TTS providing a higher blood plasma level of buprenorphine. None of the prior art documents suggested that this effect could be achieved by combining a crosslinked and a non-crosslinked acrylic polymer in the adhesive. Thus, the patent met the requirements of Article 56 EPC.

XI. Appellant-opponents 1 and 3 requested that the decision under appeal be set aside and that the patent be revoked.

XII. The respondent requested that the appeals be dismissed or that the patent be maintained on the basis of one of auxiliary requests 1 to 6 filed with the letter dated 1 August 2017. It further requested that documents E29 to E31, the arguments related to these documents submitted on 14 November 2019, and the inventive-step attack based on documents E2 and E5 as the closest

prior art, presented for the first time with the letter dated 14 November 2019, not be admitted.

Reasons for the Decision

1. Issues of admittance

1.1 Appellant-opponent 1 submitted documents E29 to E31 on 14 November 2019, i.e. two weeks before the oral proceedings. E29 and E30 are articles discussing the use of the confidence intervals as tools for the statistical analysis of experimental data. E31 is a document disclosing the "Critical values of the Student's *t* distribution".

On the basis of the teaching of these documents, appellant-opponent 1 has reworked the experiments contained in the patent-proprietor's letter of 22 June 2017. The result of this reworking is represented graphically in two figures contained in appellant-opponent 1's letter of 14 November 2019. The purpose of this reworking of the respondent's data is to demonstrate that they are not statistically significant.

1.2 E29 and E30 indicate that the confidence intervals are known tools for statistical analysis. Despite this, the Board considers that statistical analysis is a complex matter and that the respondent would need adequate time to get acquainted with the new submissions of appellant-opponent 1 and to check the validity of the data contained in appellant-opponent 1's letter of 14 November 2019. Given the advanced state of the proceedings and the complexity of the new submissions, the Board, in the exercise of its discretion, decides not to admit into the appeal proceedings documents E29

to E31 and the arguments relating to these documents submitted on 14 November 2019 (Article 13(1),(3) RPBA 2007).

1.3 Appellant-opponent 1's letter of 14 November 2019 also contains a new attack on inventive step based on E2 or E5 as the closest prior art. E2 and E5 belong to the same patent family.

In its statement setting out the grounds of appeal, appellant-opponent 1 argued on inventive step starting from E3 as the closest prior art. The same approach was followed by the opposition division in its decision. E2 and E5 had never been proposed previously as possible starting points for the assessment of inventive step. Document E8, considered by appellant-opponent 1 in combination with E2 or E5, had never been discussed during the appeal proceedings.

1.4 The selection of E2 or E5 as the closest prior art results in a substantial change of appellant-opponent 1's case. Whereas the distinguishing feature over E3 lies in the presence of a non-crosslinked acrylic polymer in the adhesive, the difference over E2 and E5 lies in the presence of a keto acid as a penetration enhancer. It follows that the experimental data submitted by the respondent to show the effects arising from the presence of a non-crosslinked acrylic polymer lose their relevance when E2 or E5 are chosen as the closest prior art. This may possibly result in a different definition of the technical problem.

In the Board's view, the respondent cannot reasonably be expected to deal with the new attack on inventive step in the short time available before the oral proceedings. Thus, the new attack on inventive step

starting from E2 or E5 as the closest prior art is not admitted into the appeal proceedings (Article 13(1),(3) RPBA 2007) .

Main request (patent as granted)

2. Sufficiency of disclosure

2.1 The objections of insufficiency of disclosure of the appellants are primarily focused on the feature of claim 1 concerning the ratio between the crosslinked acrylic polymer and the non-crosslinked acrylic polymer. They essentially argue that the sentence *"it is preferred that the crosslinkable acrylic polymer is crosslinked completely"* (paragraph [0028] of the patent - emphasis added) indicates that the crosslinking reaction may not be complete. In such cases, the ratio of claim 1 would not be equivalent to the ratio of the starting materials (i.e. the cross**linkable** acrylic polymer and the non-cross**linkable** acrylic polymer) as indicated in paragraph [0028]. The skilled person would therefore have had no guidance in the patent on how to determine the ratio of claim 1 in these situations.

2.2 The entire paragraph [0028] reads as follows:

"The adhesive component is formed from an adhesive composition comprising a non crosslinkable and a crosslinkable acrylic polymer, in which the crosslinkable acrylic copolymer is crosslinked by a process as described further below. In the methods for preparing the adhesive layer of the TTS according to the subject invention, it is preferred that the crosslinkable acrylic polymer is crosslinked completely. Consequently, the above mentioned ratio of crosslinked : non-crosslinked acrylic polymer present

in the adhesive component formed upon crosslinking is regarded in the present invention as being equal with the ratio of the crosslinkable : non-crosslinkable acrylic polymer before crosslinking."

The final passage of this paragraph, starting from the word *"Consequently"*, explains how to determine the ratio recited in claim 1, namely, by calculating the ratio of the starting materials, i.e. the ratio of crosslinkable : non-crosslinkable acrylic polymer.

This instruction on how to determine the ratio of claim 1 is independent of the outcome of the crosslinking process, i.e. it applies also in a (hypothetical) case of an incomplete crosslinking reaction. In other words, the sentence *"the above mentioned ratio of crosslinked : non-crosslinked ... is regarded in the present invention as being equal with the ratio of the crosslinkable : non-crosslinkable" (emphasis added)* indicates that "by definition" the ratio of claim 1 is identical to the ratio of the starting materials.

Thus, contrary to the appellants' argument, the description of the patent does provide instruction on how to determine the ratio between the crosslinked acrylic polymer and the non-crosslinked acrylic polymer. This instruction applies also when some amount of crosslinkable acrylic polymer is still present in the adhesive because the crosslinking reaction was not 100% effective.

2.3 It is in any case clear from the whole teaching of the patent that the amount of crosslinkable polymer not crosslinked during the crosslinking process, if any, is negligible. Indeed, the specification of the patent does not make any mention of compositions comprising

non-crosslinked crosslinkable polymers, i.e. compositions in which the crosslinking reaction is incomplete. Quite the opposite, paragraph [0050] explains how the process is to be carried to ensure the completeness of the crosslinking reaction, and paragraph [0097] states that *"[i]n the method of producing a transdermal therapeutic system according to the subject invention, the coating is dried until the solvent is removed completely and therefore the crosslinking reaction is complete, i.e. the crosslinked acrylic polymer forms the crosslinked acrylic polymer"* (emphasis added).

Thus, having regard to the general teaching of the description, the Board considers that the sentence *"it is preferred to have a complete crosslinking"* (paragraph [0028] of the patent) does not imply that an objective of the invention is to provide a TTS in which substantial amounts of non-crosslinked crosslinkable polymers are present, i.e. only a partial crosslinking occurred.

2.4 The appellants also argued that the skilled person would not have been able to reproduce the clinical study disclosed in paragraphs [0116] to [0118] of the patent because some information had been omitted such as the size of the patch used and the number of persons involved in the study. Accordingly, in their opinion, there was no guidance on how to achieve the effect of increasing the blood plasma levels of buprenorphine.

In this regard, the Board notes that independent claims 1 and 13 of the patent relate respectively to a TTS and a method for producing a TTS. The relevant question to answer in assessing the requirement of sufficiency of disclosure is whether the skilled person would have

been able to carry out the invention defined in the claims. The Board sees no reason to doubt that this indeed would have been the case since the description illustrates the preparation of TTSs according to claim 1 (examples 1 to 3) and provides details on how to perform the process of claim 13 (section "Manufacture").

The clinical study disclosed in the patent demonstrates the effectiveness of the TTS of claim 1 in providing an adequate plasma level of buprenorphine. Whether the skilled person would have been able to reproduce this study does not, in this case, affect the assessment of the requirement of sufficiency of disclosure since achieving a certain plasma level of buprenorphine is not a feature of the claims. In other words, the invention defined in the claims, in respect of which the assessment of the requirement of sufficiency of disclosure is to be made, does not require that a minimum plasma level of buprenorphine is obtained.

2.5 As to the objection that claim 13 was not sufficiently disclosed due to the absence of an essential feature (crosslinking agent), the Board agrees with the opposition division (point 3 of the decision) that this issue concerns the assessment of the requirement of support of the description (Article 84 EPC). As discussed in point 2.4 above, the description provides information on how to perform the invention of claim 13.

2.6 Therefore, the Board concludes that the patent meets the requirements of sufficiency of disclosure.

3. Novelty

3.1 In its statement setting out the grounds of appeal, appellant-opponent 3 argued that the term "preferably" in claim 1 (*"..., which preferably forms an amorphous mass,..."*) referred to all the features that followed this term in part 2) ii. of the claim. These features were therefore to be considered optional features of claim 1. On the basis of this reading of the claim, examples 1 of documents E3 and E4 were considered novelty-destroying since they disclosed a TTS comprising a layer containing buprenorphine, a polyacrylate polymer and a keto acid.

3.2 In its communication pursuant to Article 15(1) RPBA, the Board disagreed with the interpretation of claim 1 proposed by appellant-opponent 3 arguing that the presence of the two commas in the sentence *"..., which preferably forms an amorphous mass,..."* indicated that only the "amorphous mass" was an optional feature. It further considered that this interpretation was in line with paragraphs [0017] and [0018] of the description.

3.3 Since during the oral proceedings the appellant-opponents did not make any further submission with regard to the issue of novelty, the Board sees no reason to deviate from the opinion expressed in its communication. Accordingly, the features of part 2) ii. of claim 1 requiring the presence in the adhesive layer of a crosslinked acrylic polymer and a non-crosslinked acrylic polymer in a certain ratio, do limit the scope of the claim. It follows that the attack of lack of novelty in view of E3 and E4 based on the assumption that these features are not limiting features of claim 1 must fail.

4. Inventive step

4.1 The patent addresses the problem of providing a TTS for the administration of buprenorphine that results in high plasma levels of the drug (see [0007]).

4.2 Closest prior art

4.2.1 It is not disputed by the parties that document E3 represents the closest prior art.

Example 1 of E3 discloses a buprenorphine transdermal patch in which the adhesive layer contains a crosslinked acrylic polymer. The TTS defined in claim 1 of the patent in suit differs from this patch in the additional presence of a non-crosslinked acrylic polymer in the adhesive.

4.3 Technical problem

4.3.1 The technical problem is to be formulated on the basis of the technical effects due to the distinguishing feature. In this regard, the most relevant data are those disclosed in example 1 (and Figure 1) of the patent and in the experimental report submitted on 22 June 2017.

Example 1 of the patent describes an *in vivo* study for the evaluation of the buprenorphine blood plasma concentration following the application of a TTS according to claim 1 or the application of comparative TTSs coated with reference compositions 1 or 2. In the experimental report submitted on 22 June 2017, which relates to the same *in vivo* study, it is explained that 12 subject were involved in the trial.

The TTS according to claim 1 differs from the TTS coated with reference compositions 1 only in that the adhesive contains a mixture of crosslinked and non-crosslinked acrylic polymers whilst reference composition 1 only contains a crosslinked acrylic polymer. The TTS coated with reference compositions 2 contains a different adhesive and a different penetration enhancer compared with the TTS of claim 1. Thus, the data concerning this TTS are not relevant in the context of the present decision since it does not reflect the teaching of the closest prior art.

The buprenorphine blood plasma concentrations are plotted in Figure 1 of the patent as a function of the time. The experimental report of 22 June 2017 contains the same Figure 1 as included in the patent with the additional information of the error bars for each measurement.

4.3.2 The figure shows that the TTS of the patent in suit provides a higher plasma concentration than the TTS coated with reference composition 1. In particular, the interval of 50h to 160h comprises 11 measurement points in which the mean buprenorphine plasma concentration provided by the TTS of the invention is always higher than the mean concentration provided by the reference TTS. The difference is more marked in the central region of the graph (from ca. 70h to ca. 130h) where it is present also when the error bars are considered (Figure 1 of the report of 22 June 2017).

4.3.3 The experimental report of 22 June 2017 additionally includes data relating to *in vitro* buprenorphine skin permeation measurements. The results reported in table 2 show for two TTSs according to the patent a flux of 2.25 ± 0.07 µg/(cm^2h) and 2.33 ± 0.05 and µg/(cm^2h)

respectively. A comparative TTS, coated with a composition in which the adhesive does not contain a non-crosslinked acrylic polymer provides a flux of 1.90 ± 0.05 and µg/(cm^2h).

4.3.4 The appellant-opponents dispute the relevance of the experimental evidence filed by the respondent with the argument that the results are not statistically significant. They criticise the fact the that respondent did not perform a valid statistical analysis of the experimental data, for instance, by determining the 95% confidence interval using a t-test. In their view, the standard error of the mean (SEM) used by the respondent was not sufficient to establish a statistically significant improvement.

4.3.5 In relation to this argument of the appellant-opponents, the Board observes that a party filing experimental data is not under the obligation to perform any specific statistical analysis of these data. The appellant-opponents referred to the 95% confidence interval as a standard tool for statistical analysis in the pharmaceutical field. The Board does not dispute that this may be the case in certain contexts. It is not, however, a requirement in procedures before the EPO.

In establishing whether a certain technical effect alleged by a party has been achieved, the EPO has to apply the general principle of free evaluation of evidence.

In *inter partes* proceedings, presenting experimental data in support of a position is an option available to both the patent-proprietor and the opponent(s). Typically, experimental data are filed to demonstrate

(or deny) the existence of a technical effect that may become relevant in the definition of the technical problem. The deciding body of the EPO has to draw its conclusions on the basis of all the evidence available before it in the light of its conviction. The principle of free evaluation would be contradicted by laying down firm rules of evidence defining the extent to which certain types of evidence were, or were not, convincing (G 3/97 OJ EPO 1999, 245, Reasons No. 5).

4.3.6 In the present case, the sole experiments before the Board are those filed by the respondent. The following observations can be made in respect of this experimental evidence.

(a) The experiments comprise comparative data that make it possible to assess the effects arising from the distinguishing feature, namely, the presence of a non-crosslinked acrylic polymer in the adhesive (see points 4.3.1 and 4.3.3 above).

(b) There is no indication of errors of inaccuracies occurring during the experiments. Determining the blood plasma concentration of an active ingredient following the application of a patch to the skin of human subjects is a common test for assessing the effectiveness of a patch. A test of this kind is disclosed for instance in example 1 of E3. Similar considerations apply in respect of the *in vitro* tests carried out using human skin (see [0119]) of the patent. E2 discloses in example I similar *in vitro* tests carried out with mice skin. The Board sees therefore no reason to question the soundness of the experiments.

(c) Concerning the *in vivo* experiments, Figure 2 of the report of 22 June 2017 shows that when the error bars are considered, there is some overlap between the curves representing the buprenorphine plasma concentrations provided by the TTS of claim 1 and by the TTS coated with reference composition 1. However, as explained in paragraph in point 4.3.2 above, in the 11 measurement points of the interval from 50h to 160h, the buprenorphine mean plasma concentration provided by the TTS of the patent is always higher than the mean plasma concentration provided by the reference TTS. Moreover, as discussed above, in the central region of the graph (from ca. 70h to ca. 130h), there is no overlap between the curves also when the error bars are considered.

(d) The *in vitro* experiments (see point 4.3.3 above) show that the TTS of claim 1 provides better results in terms of buprenorphine flux than a comparative TTS.

On the basis of these considerations, the Board concludes that the experiments filed by the respondent are convincing evidence that the TTS of the patent provides a higher buprenorphine plasma level than the TTS disclosed in E3.

4.3.7 The appellant-opponents also considered that the experimental data submitted by the respondent were not sufficient to show that an effect was present over the whole scope of the claim, in particular having regard to the fact that the boundaries of the claim were not clearly defined due to the presence of an ambiguous parameter, namely, the ratio between the crosslinked

acrylic polymer and the non-crosslinked acrylic polymer.

For the reasons set out in points 2.1 to 2.3, the Board does not regard the ratio recited in claim 1 as an ambiguous parameter. Moreover, this ratio does not represent the distinguishing feature of claim 1 over E3. This is rather to be seen in the presence of a non-crosslinked acrylic polymer in the adhesive of the TTS according to the patent. The main purpose of comparative experiments is to illustrate the effects brought about by the distinguishing feature(s). As explained above, the evidence filed by the respondent makes it possible to appreciate that the presence of a non-crosslinked acrylic polymer in the adhesive results in an increase of the buprenorphine plasma level.

4.3.8 Therefore, the objective technical problem is the provision of a TTS providing a higher blood plasma level of buprenorphine.

4.4 Obviousness

4.4.1 Documents E2 and E5 disclose TTSs containing a mixture of crosslinked and non-crosslinked acrylic polymer in the adhesive. However, these documents do not indicate that adding a non-crosslinked acrylic polymer to an adhesive containing a crosslinked acrylic polymer results in an increase of the buprenorphine plasma concentration.

E9 teaches that the adhesive properties can be improved by combining a crosslinked and a non-crosslinked acrylic polymer. However, this document does not disclose that this combination results in an increase of the buprenorphine plasma levels.

4.4.2 It follows from the above considerations that the subject-matter of claim 1 meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeals are dismissed

The Registrar: On behalf of the Chairman (according to the Art. 8(3) RPBA):

B. Atienza Vivancos C. Schmidt

Decision electronically authenticated