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Datasheet for the decision of 16 October 2020

Case Number: T 0464/17 - 3.3.07

Application Number: 09176388.8

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Title of invention:
Composition for the Transdermal Delivery of Fentanyl

Applicant:
3M Innovative Properties Company

Headword:
Composition for the Transdermal Delivery of Fentanyl / 3M

Relevant legal provisions:
EPC Art. 56
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Keyword:
Remittal to the department of first instance - (no)
Inventive step - (no)

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Case Number: T 0464/17 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 16 October 2020

Appellant: (Applicant)	3M Innovative Properties Company 3M Center P.O.Box 33427 St. Paul, MN 55133-3427 (US)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 20 July 2016 refusing European patent application No. 09176388.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	P. Schmitz

Summary of Facts and Submissions

I. The appeal was filed by the appellant (applicant) against the decision of the examining division to refuse the European patent application No 09176388.8 ("the application").

II. The decision was based on a main request filed by letter dated 9 October 2015 and auxiliary requests 1-4 filed by letter dated 16 May 2016.

Claim 1 of the main request read as follows:

"A device for the transdermal delivery of fentanyl comprising a backing and a transdermal drug delivery composition, said transdermal drug delivery composition being adhered to one surface of the backing, wherein said transdermal drug delivery composition comprises
(a) a copolymer comprising
(i) one or more A monomers selected from the group consisting of alkyl acrylates containing 4 to 12 carbon atoms in the alkyl group and alkyl methacrylates containing 4 to 12 carbon atoms in the alkyl group; and
(ii) one or more ethylenically unsaturated B monomers copolymerizable with the A monomer; and
(b) 8% to 24% by weight fentanyl based on the total weight of the composition."

Claim 1 of each of the auxiliary requests 1-4 differed from claim 1 of the main request in that the B monomers in (ii) were further defined as followed:

Auxiliary request 1: "and containing a functional group selected from the group consisting of sulfonamide,

urea, carbamate, carboxamide, hydroxy, amino, and cyano"

Auxiliary request 2: "and containing a functional group selected from the group consisting of sulfonamide, urea, carbamate, carboxamide, hydroxy, amino, and cyano, wherein the one or more B monomers are present in an amount of 5 to 55 % by weight based on the total weight of all monomers in the copolymer"

Auxiliary request 3: "and containing a hydroxy functional group"

Auxiliary request 4: "and containing a hydroxy functional group, wherein the one or more B monomers are present in an amount of 5 to 55 % by weight based on the total weight of all monomers in the copolymer"

III. In the present decision, reference is made to the following documents:

D2: Roy S.D. et al: "Controlled Transdermal Delivery of Fentanyl: Characterizations of Pressure-Sensitive Adhesives for Matrix Patch Design", Journal of Pharmaceutical Sciences, (85)1996, nr. 5, pages 491-495
D3: WO 01/26705 A
D5b: copy of a poster that Mr. Hyun Suk Yu presented at the public conference Millennial World Congress of Pharmaceutical Sciences held in San Francisco (Attachment A)
D7: EP 887075 A2
D8: Clin. Tox. 33(5), 439-447, 1995
D9: Declaration by Dr. Majella E. Lane dated August 14, 2017
D10: Citizens' Petition regarding ANDA 76-258 submitted by D. Brookoff, MD, PhD

D11: US 4,588,580

IV. The examining division decided in particular that

(a) The main request lacked novelty over D3, prior art pursuant to Article 54(3) EPC.

(b) D5b represented the closest prior art for the subject matter of claim 1 of auxiliary request 1. The distinguishing feature was the amount of fentanyl required to be 8 to 24 %w/w. The objective technical problem was the provision of a device for the transdermal delivery of fentanyl which worked to some extent. The skilled person would have considered the range of 8 to 24% of fentanyl without exercising an inventive activity. Claim 1 of auxiliary request 1 thus lacked an inventive step in view of D5b.

The subject matter of auxiliary requests 2-4 also lacked an inventive step in view of D5b.

V. With its statement setting out the grounds of appeal, the appellant maintained its main request underlying the appealed decision and filed auxiliary requests 1-9.

Auxiliary requests 2, 4, 6 and 8 were respectively identical to auxiliary requests 1-4 underlying the appealed decision. Auxiliary requests 1, 3, 5, 7 and 9 differed respectively from the main request and auxiliary requests 2, 4, 6 and 8 in that the upper limit for the amount of fentanyl was 12%.

VI. In a communication pursuant to Article 15(1) RPBA, the Board set out its preliminary opinion, cited D7, and expressed its intention to assess inventive step for

all requests starting from D2, rather than D5b as in the appealed decision.

VII. In a letter dated 14 September 2020, the appellant made further submissions concerning inventive step and filed documents D8-D11.

VIII. Oral proceedings were held before the Board.

IX. The appellant's arguments can be summarised as follows:

(a) The examining division had not yet rendered a decision on inventive step for the main request. In order to guarantee a full review of inventive step for the main request by two instances, when its novelty has been accepted, the case should be remitted to the examining division for assessment of obviousness.

(b) The subject-matter of claim 1 of the main request differed from D2 by the concentration of fentanyl.

Since the application related to transdermal drug delivery devices containing the opioid fentanyl, both the safety and the release profile were essential and had to be taken into account for the determination of the objective technical problem. Thus, the objective technical problem could not be just the provision of an alternative transdermal drug delivery device because this would also cover devices which could be unsafe or even lethal to the patients.

The application showed that the claimed transdermal drug delivery devices generally had significantly higher cumulative amounts for the permeation of

fentanyl through cadaver skin in 24 h as compared with D2, and that the delivery continued for up to 7 days even with the lowest performing formulations, and nearly unchanged from the initial rate of delivery.

The assumption that the specific amount of fentanyl recited in claim 1 did not have any effect on the safe administration of fentanyl, or also resulted in a suitable serum concentration of fentanyl, was part of the solution provided by the present invention and should not be confused with the objective technical problem with which the skilled person was faced.

Consequently, the objective technical problem in view of D2 was the provision of a composition with which fentanyl could be safely delivered for an extended period of time.

This problem had been solved by the claimed transdermal drug delivery compositions, as shown by clinical trials with human test subjects (see examples 47 and 48 of the patent).

In view of the potentially life threatening side effects of Fentanyl if overdosed (see D8, page 441, "Abuse and Toxicity"), a skilled person would be very careful in increasing its dosage in a matrix. As explained in D9 (see points 13, 20), it was not easy to predict how the change of one component, such as the concentration of the drug, would affect the properties of the transdermal drug delivery device as a whole, e.g. with respect to administration rate, integrity of the matrix or adhesion. D11 (see col. 1, line 47 to col. 2, line

5) emphasized that the amount of fentanyl in the transdermal delivery device should be kept to a minimum due to the potentially fatal side effects. This prejudice was also evidenced by D10 (see page 8, third paragraph). Thus the prior art contained no motivation for a skilled person to come to an acrylate-based transdermal drug delivery composition comprising 8-24 wt.% fentanyl as required by the main request.

The statement of D2 concerning the effect of an increase in fentanyl loading from 2% to 4% related to data obtained under perfect sink conditions, which conditions were not correlated with the more realistic model of permeation through cadaver skin. Thus a skilled person would not have been able to predict with any degree of certainty how a transdermal drug delivery composition including fentanyl in a much higher concentration, i.e. 8-24 wt.% as required by claim 1, would perform. The results of examples 47 and 48 of the application, showing functioning transdermal drug delivery compositions comprising high amounts of fentanyl, were surprising.

Furthermore, although monolithic transdermal fentanyl delivery devices were known 14 years before the earliest priority date, no prior art disclosed any device including fentanyl in any amounts close to the claimed range of 8-24 wt.%. Thus, an unbiased skilled person not knowing the present invention would not have made this modification of the prior art.

The same arguments applied to the auxiliary requests.

X. The appellant requests that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed on 9 October 2015 during the proceedings before the examining division, or, in the alternative, on the basis of one of auxiliary requests 1-9, filed with the statement setting out the grounds of appeal. The appellant also requests that, when novelty of the main request has been accepted, the case be remitted to the first instance for assessment of obviousness.

Reasons for the Decision

Remittal to the examining division

1. Before assessing inventive step for the main request, the appellant's request that the case be remitted to the first instance must be examined.

Under Article 11 RPBA 2020, the Board shall not remit a case to the department whose decision was appealed for further prosecution, unless special reasons present themselves for doing so.

The Board can identify no such special reasons here. It is acknowledged that, for the main request, the appealed decision is limited to novelty over D3 (prior art under Article 54(3) EPC). However, parties do not have a fundamental right to have their case examined at two levels of jurisdiction. In addition, the examining division examined and decided on the issue of inventive step in respect of the narrower auxiliary requests 1-4. The essential facts and evidence used in the appeal proceedings for the assessment of inventive step,

including document D2, were already part of the first-instance proceedings, so that no fresh case is created.

Thus, the Board carries out an examination of inventive step for the main request pursuant to Article 111(1) EPC.

Main request

2. Inventive step

2.1 The invention relates to a transdermal drug delivery composition containing fentanyl and to methods of providing sustained analgesia to subjects in need thereof.

2.2 D2 represents the closest prior art. This is not contested by the appellant. D2 belongs to the same technical field of transdermal delivery of fentanyl.

D2 discloses transdermal devices comprising 2-4% fentanyl in a single, pressure sensitive adhesive acrylate copolymer matrix (see table 3, "Materials" and Figure 2). The acrylate copolymer (Gelva 737) comprises in particular, as monomers, 67% by weight of ethyl hexyl acrylate (corresponding to monomer A of claim 1(a)(i)) and 5% by weight of hydroxyethylacrylate (corresponding to the monomer B; see D7, table 2 on page 8). This Gelva 737 acrylate matrix is thus a copolymer falling under the definition (a) of claim 1. The devices of D2 provide a sustained delivery of fentanyl, without any apparent burst effect (see Table 3 and Figure 4).

2.3 The subject-matter of claim 1 of the main request differs from the devices disclosed in D2 in that the fentanyl concentration is in the range of 8-24%.

2.4 According to the appellant, the problem to be solved is the provision of a transdermal delivery device which can safely deliver fentanyl over an extended period of time. The appellant refers in particular to examples 47 and 48 to illustrate the advantages of using a high concentration of 8-24% of fentanyl in an acrylate matrix.

2.4.1 However, the application contains no evidence that an increase of the concentration of fentanyl from 2-4% to 8-24% leads to any improvement over D2 in terms of a more sustained release of fentanyl. Nor does the application disclose any data as to the safety of the transdermal device. Examples 47 and 48 of the application show the preparation of transdermal patches comprising 17.2-20.2% fentanyl in specific compositions comprising particular copolymers. These patches are tested for permeation through the skin of human test subjects over 168 hours (see table 13). The application does not provide any comparable results for analogous patches comprising 2-4% fentanyl. Tables 1, 4, 6, 8, 11, 12 and 15 show the human cadaver skin permeation results for transdermal patches comprising varying concentrations of fentanyl in compositions comprising specific copolymers and adjuvants. However, the human cadaver skin permeation data in D2 and in the application cannot be directly compared since they pertain to patches comprising fentanyl in different compositions and were obtained under different conditions. Additionally, the appellant did not demonstrate that the claimed devices overcome any of the safety problems known for the prior art transdermal

fentanyl devices with regard to life-threatening side effects when overdosed. Thus, the presence of any surprising result as regards the safety of the transdermal devices of claim 1 has not been credibly demonstrated.

2.4.2 The appellant argues that, since the application related to transdermal drug delivery devices containing the opioid fentanyl, both the safety and the release profile are essential and have to be taken into account for the determination of the objective technical problem. The objective technical problem could not be just the provision of an alternative transdermal drug delivery device because this would also cover devices which could be unsafe or even lethal to the patients.

The Board does not share this view. In the absence of any evidence as to the safety of the device, the appellant's subjective assessment of the claimed devices as safe cannot be taken into account for the determination of the objective technical problem. Additionally, a formulation of the problem as the provision of an alternative transdermal drug delivery device would anyway not cover devices which would be unsuitable for use as transdermal drug delivery devices.

2.4.3 As to the alleged effect of an increased fentanyl concentration in the range of 8-24% on its delivery for an extended period of time, the Board finds that this effect, even if accepted in the appellant's favor, would not modify its assessment of inventive step, for the following reasons.

2.5 The objective technical problem in view of D2 may be formulated as the provision of a composition with which

fentanyl can be delivered for an extended period of time.

2.6 According to D2 (see Table 1), the solubility of fentanyl in the adhesive Gelva 737 is 21.9 mg/ml, thus around 2.19% by weight. D2 shows that the skin flux obtained with a concentration of 2% by weight of fentanyl in this acrylate adhesive matrix is 0.9 µg/cm^2 /hr (see table 4). D2 also discloses (see Table 3) transdermal devices with a fentanyl concentration in the same acrylate adhesive matrix of 4% by weight, thus beyond the solubility limit of fentanyl in this adhesive. Furthermore, D2 mentions that this increase in fentanyl loading from 2% to 4% in the acrylate adhesive matrix has very little effect or no effect on the release rate constant and the apparent diffusion coefficient of fentanyl (see page 493, last paragraph). This observation is based on drug release measurements in water. As the appellant points out, the release rates measured in water do not correlate well with the skin fluxes measured on cadaver skin for different copolymer matrices (see D2, page 495, left column, lines 6-11). However this does not render less credible the trend observed in D2 for different concentrations of the drug in the same copolymer.

Thus, D2 discloses transdermal devices comprising fentanyl in a copolymer as defined in claim 1, with fentanyl concentrations both below (2%) and above (4%) the solubility limit. The skilled person would not regard the solubility of fentanyl in the acrylate as an upper limit for its concentration in the adhesive matrix. Furthermore, D2 teaches that this increase in fentanyl concentration has no effect on the release rate of fentanyl. It would be obvious to the skilled person that an increased concentration of fentanyl

coupled with a constant release rate lead to prolonged release. Thus, when faced with the problem of delivering fentanyl for an extended period of time, the skilled person would consider increasing the concentration of fentanyl in the adhesive matrix beyond its solubility limit, such as 8% by weight or more.

2.7 According to the appellant, the prior art teaches away from, or shows a prejudice against, considering fentanyl concentrations beyond its solubility limit. The Board is not convinced.

2.7.1 Firstly, according to the appellant, since fentanyl is a highly potent narcotic analgesic which can cause serious side effects and even death if it is overdosed, a skilled person would be very careful in increasing the dosage of this drug in a matrix and would only do so if there is a clear pointer in the art that a functioning transdermal drug delivery composition would result which would not endanger the health and life of the patients. The appellant cites D9 (see points 13 and following, especially point 20) to show the difficulty in predicting how the change of one component will affect the properties of the transdermal drug delivery device as a whole.

In the Board's view, D9 mentions numerous aspects to be taken into account for the formulation of drug-in-adhesive transdermal patch, including the selection of the adhesive matrix and various properties of the drug. However, the only change to be considered here is the increase, in the acrylate matrix of D2, of the fentanyl concentration from 4% to e.g. 8% (as in claim 1). Considering that the value of 4% is already nearly twice the solubility limit indicated in D2 for fentanyl in the acrylate matrix, and in view of the statement

that this increased concentration had essentially no effect on the release rate and diffusion coefficient of the drug, the skilled person had no cause to expect that a further increase to 8% would compromise the properties of the transdermal drug delivery device. Likewise, there were no reasons for the skilled person to anticipate that issues with respect to integrity of the matrix, adhesion or the alleged catastrophic crystallisation would occur in the context of the device and acrylate copolymer of D2 when merely going from 4% to 8% fentanyl.

2.7.2 The appellant also refers to D10 (see page 8, third paragraph), D11 (see column 1, line 47 to column 2, line 5) and D2 (see the conclusions) to show the existence of a prejudice, namely that the amount of drug in the dosage form should be kept to a minimum due to the severe, or potentially fatal side effects.

According to the case law of the boards of appeal, inventiveness can sometimes be established by demonstrating that a known prejudice, i.e. a widely held but incorrect opinion of a technical fact, needs to be overcome (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019, I.D. 10.2).

Here, it is not proven that any prejudice has been overcome. Firstly, it is doubtful that the citizens' petition D10 or the patent specification D11 can represent suitable evidence of a widely or universally opinion held by experts in that field. Secondly, even if the existence of such a widely held opinion were accepted, it is not shown that this opinion is incorrect, i.e. that the invention overcomes any such prejudice. D10 and D11 emphasize the need to keep the

amount of drug or dosage level of fentanyl to a minimum because of the potential for abuse or the risk that excessive amounts of the drug be delivered. There is however no demonstration that, despite the higher concentration of fentanyl in the claimed devices, these safety concerns do not arise (see 2.4.1 above). Additionally, the concerns expressed in D10 and D11 pertain to the dosage or (absolute) amount of fentanyl in the device, which cannot be equated with concentration of fentanyl without taking into account the size of the transdermal delivery device. The dosage or amount of fentanyl in the device is not a feature of claim 1.

2.8 In conclusion, the Board finds that the skilled person, starting from D2, not only could, but would consider higher concentrations of fentanyl such as 8% by weight or more in order to provide a fentanyl delivery for an extended period of time.

The subject-matter of claim 1 of the main request does not involve an inventive step.

3. Since the main request must be rejected for lack of inventive step, an assessment of novelty over D3 is not necessary.

Auxiliary requests

4. None of the auxiliary requests 1-9 comprise any further differentiating feature over D2 with regard to the adhesive copolymer, since the Gelva 737 acrylate matrix comprise 5% of hydroxyl-containing monomer. Furthermore, the reasoning set out above regarding the choice of a fentanyl concentration of 8-24% applies

equally to the range of 8-12% defined in auxiliary requests 1, 3, 5, 7 and 9.

Thus, the subject-matter of auxiliary requests 1-9 also lacks an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated