Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 20 September 2021

Case Number: T 1535/16 - 3.3.07

Application Number: 04701381.8

Publication Number: 1635783

IPC: A61K9/00, A61K31/4468, A61P25/04

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITIONS COMPRISING FENTANYL FOR INTRANASAL DELIVERY

Patent Proprietor:
Kyowa Kirin Services Ltd

Opponent:
Generics [UK] Limited

Headword:
Compositions comprising fentanyl / KYOWA KIRIN

Relevant legal provisions:
EPC Art. 100(c), 100(a), 56

Keyword:
Amendments - allowable (yes)
Inventive step - (yes)

This datasheet is not part of the Decision
It can be changed at any time and without notice

Decisions cited:
T 0985/06

This datasheet is not part of the Decisior
It can be changed at any time and without notic

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1535/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 20 September 2021

Appellant: (Patent Proprietor)	Kyowa Kirin Services Ltd 1st Floor, Sackville House 143-149 Fenchurch Street London, EC3M 6BN (GB)
Representative:	Potter Clarkson The Belgrave Centre Talbot Street Nottingham NG1 5GG (GB)
Appellant: (Opponent)	Generics [UK] Limited (trading as Mylan) Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
Representative:	Isarpatent Patent- und Rechtsanwälte Barth Charles Hassa Peckmann & Partner mbB Friedrichstrasse 31 80801 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 2 May 2016 concerning maintenance of the European Patent No. 1635783 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	F. Bostedt

Summary of Facts and Submissions

I. European patent 1 635 783 (hereinafter "the patent") was granted on the basis of 23 claims. The independent claims of the patent as granted read as follows:

"1. A composition for the intranasal delivery of fentanyl or a pharmaceutically acceptable salt thereof, which comprises an aqueous solution of

(i) fentanyl or a pharmaceutically acceptable salt thereof;
(ii) a pectin having a degree of esterification (DE value) of less than 30%;
(iii) a non-metal ion osmolality adjusting agent selected from polyhydric alcohols and sugars

provided that the composition is substantially free of divalent metal ions; and the composition has an osmolality of from 0.1 to 1.0 osmol/kg."

"17. A composition according to any one of the preceding claims for use in the treatment or prevention of acute or chronic pain."

"18. The use of a pectin having a degree of esterification (DE value) of less than 30% and a non-metal ion osmolality adjusting agent selected from polyhydric alcohols and sugars in the manufacture of a medicament for the intranasal delivery of fentanyl or a pharmaceutically acceptable salt thereof to a patient in need thereof, which medicament is substantially free of divalent metal ions and has an osmolality of from 0.1 to 1.0 osmol/kg."

"23. A process for preparing a composition according to any one of claims 1 to 17, which process comprises mixing fentanyl or a pharmaceutically acceptable salt thereof with the pectin and the non-metal ion osmolality adjusting agent in water."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as originally filed.

III. The opposition division took the interlocutory decision that, on the basis of auxiliary request 3, the patent and the invention to which it relates met the requirements of the EPC. Auxiliary request 3 was filed during the oral proceedings held on 17 November 2015 and contained 21 claims.

IV. The decision of the opposition division, posted on 2 May 2016, cited *inter alia* the following documents:

D2: US 6,432,440
D3: WO 02/00195
D8: Gennaro, Alfonso R, "Remington's Pharmaceutical Sciences" Mack Publishing Company, 1985, Ed 17th
D10: Christrup et al, "Pharmacokinetics, Efficacy, and Tolerability of Fentanyl Following Intranasal Versus Intravenous Administration in Adults Undergoing Third-Molar Extraction; A Randomised, Double-Blind, Double-Dummy, TwoWay, Crossover Study", Clinical Therapeutics, Vol. 30, No. 3, 2008, P469-481
D11: Fisher et al, "Pharmacokinetic comparisons of three nasal fentanyl formulations; pectin, chitosan and chitosan-poloxamer 188", International Journal of

Clinical Pharmacology and Therapeutics, Vol. 48, No. 2/2010, pages 138-143
D12: Annex 2, filed by the Proprietor with letter dated 11.01.2010
D13: Annex 3, filed by the Proprietor with letter dated 11.01.2010
D14: Annex A, filed by the Proprietor with letter dated 05.09.2012
D15: Annex B, filed by the Proprietor with letter dated 05.09.2012
D16: An Introduction to Pectins: Structure and Properties; James N. BeMifler, pp. 2-12; in: Chemistry and Function of Pectins; Editor(s): Marshall L. Fishman, Joseph J. Jen, Volume 310, Publication Date (Print): June 05, 1986, American Chemical Society
D17: WO 93/21903

V. The opposition division decided in particular as follows:

(a) The wording used for the amended feature defining the degree of esterification of the pectin, namely "less than 30%", implied that the specific value of 30% was excluded. This exclusion did not have a basis in the original application. Claim 1 of the patent as granted did consequently not meet the requirements of Article 123(2) EPC.

(b) The examples of the patent in suit did provide sufficient information to carry out the invention. In the absence of evidence to the contrary, the first auxiliary request thus met the requirements of Article 83 EPC.

(c) Several selections would have to be performed within the disclosure of D2 to arrive at the

claimed subject-matter. Furthermore, the claimed osmolality was not explicitly disclosed in D2. The first auxiliary request thus met the requirements of Article 54 EPC.

(d) Starting from D2 as the closest prior art the solution offered by auxiliary request 1 to the problem of providing an alternative intranasal fentanyl composition was not obvious. The skilled person would not have found in D2 alone or in combination with D17, D16 or D3 any incentive to the specific combination of features of the first auxiliary request. The first auxiliary request thus met the requirements of Article 56 EPC.

(e) However, claim 14 of auxiliary requests 1 and 2 did not meet the requirements of Article 123(2) EPC.

(f) The third auxiliary request met the requirements of the EPC.

VI. Both the patent proprietor (appellant - patent proprietor) and the opponent (appellant - opponent) lodged an appeal against the decision of the opposition division.

VII. With its statement setting out the grounds of appeal the appellant - patent proprietor defended its case on the basis of the patent as granted as the main request, and on the basis of auxiliary requests 1, 2, 2A and 3 filed therewith.

VIII. On 13 April 2021, a communication pursuant to Article 15(1) RPBA 2020 was issued by the Board. In said communication the Board provided *inter alia* its preliminary opinion that:

(a) the amendments performed in the patent in suit, in particular the modification of the degree of esterification (DE) as being "less than 30%", met the requirements of Article 123(2) EPC, and

(b) regarding inventive step, the selection of a DE of less than 30% for the pectin in order to achieve advantageous release profile of fentanyl did not appear to be suggested in any of the cited prior art documents.

IX. By letter dated 30 July 2021, the appellant - opponent announced that it would not be attending the oral proceedings scheduled to take place before the Board of Appeal on 5 October 2021.

X. By letter dated 10 August 2021, the appellant - patent proprietor announced the conditional withdrawal of its request for oral proceedings, should the Board maintain the patent as granted (main request).

XI. The oral proceedings were cancelled.

XII. The appellant - patent proprietor requested that the decision under appeal be set aside and the patent be maintained as granted (main request), or that the patent be maintained on the basis of one of the auxiliary requests 1, 2, 2A and 3 submitted with the statement setting out the grounds of appeal, wherein auxiliary requests 1, 2 and 3 corresponded to auxiliary requests 1, 2 and 3 filed during the first instance oral proceedings held on 17 November 2015.

XIII. The appellant - opponent requested that the decision under appeal be set aside and that the patent be revoked.

XIV. The arguments of the appellant - patent proprietor, as far as relevant for the present decision, can be summarised as follows:

(a) The subject-matter of the claims of the main request did not extend beyond the content of the original application. In particular, in line with T 1170/02, the feature "less than 30%" was directly and unambiguously derivable from the original application, especially from original page 6 lines 9-12 and lines 21-24. The remaining amendments also found a basis in the original application (see in particular original page 3 lines 18-27, original page 12 lines 10-16 and original page 11 line 21).

(b) The closest prior art was D2. D2 did not disclose a composition being aqueous, having an osmolality of 0.1 to 1.0 osmol/kg and containing each of the following elements:
(i) fentanyl,
(ii) a pectin with a degree of esterification (DE) of from 5 to 25%, and
(iii) a non-metal ion osmolality agent selected from polyhydric alcohols and sugars.
The problem to be solved resided in the provision of a composition for the intranasal administration of fentanyl in a practical dose volume that provided rapid absorption in combination with a lower peak plasma concentration than that provided using a simple aqueous solution. As substantiated by D12-D13, the use of a pectin having a DE below 30% led to a modification of the release profile,

which would allow reducing the risk of dangerous side-effects while still achieving a rapid pain relief. This effect was neither suggested in D2 nor in the further documents cited by the appellant - opponent. The main request thus met the requirements of Article 56 EPC.

XV. The arguments of the appellant - opponent, as far as relevant for the present decision, can be summarised as follows:

(a) Claims 1 and 18 of the main request infringed Article 123(2) EPC, for the following reasons:

- The feature regarding the peak plasma concentration represented an essential feature of the described composition for intranasal delivery of fentanyl (see original abstract, original claim 1, original page 5 first paragraph, original page 14 second and third paragraph and paragraph bridging pages 3-4). Its deletion thus extended the claimed subject-matter beyond the originally disclosed content.

- Furthermore, the presently claimed combination of features (specific DE, limitation of the additive to pectin, specific non-metal ion osmolality adjusting agent and specific osmolality) was not originally disclosed. The respective specific features were selected and combined in an arbitrary manner.

- Finally, the feature "a pectin having a degree of esterification (DE value) of less than 30%" was not originally disclosed because the upper value of said range was not individually disclosed. The

present situation was similar to the one underlying T 985/06. The originally disclosed ranges ("less than 35%" and "7 to 30%"), despite encompassing any value therein, did indeed not disclose any such value individually.

(b) The closest prior art was D2. The opposed patent aimed at providing an alternative nasal spray containing fentanyl without any unexpected effects. The features allegedly constituting distinguishing features versus D2 were generally disclosed in D2, as follows:
(i) Fentanyl was mentioned in column 7 line 25,
(ii) a pectin with a DE falling under the presently claimed range was described (see reference to Slendid which has a DE of 10%),
(iii) polyhydric alcohols and sugars, generally known as non-metal ion osmolality agents, were suggested (see reference to sucrose or non-ionic polysaccharides in column 8 third paragraph and reference to a composition free of divalent metal ions in column 5 lines 11-13 and 31-39 together with D16-D17, which provided further indications towards the osmolality adjusting properties of such components) and
(iv) an aqueous solution was described (see column 5, second paragraph and column 6, 2nd paragraph).
Furthermore the provision of an isotonic composition, *i.e.* a composition having an osmolality within the presently claimed range, constituted a standard approach in the field as revealed by D8. The subject-matter of claim 1 of the main request was thus not inventive in the light of D2 together with the general knowledge in the field as evidenced by D8, D16 and D17. Moreover the subject-matter of claim 1 was also rendered

obvious when combining the teachings of D2 and D3. The latter indeed described the treatment of pain of the mucous nasal membrane (page 6 lines 21-22) using muco-adhesive pectin (page 7 line 9) and iso-osmotic agents such as dextrose (see page 14 lines 24-27). Hence, the main request did not meet the requirements of Article 56 EPC.

Reasons for the Decision

Main request - Patent as granted

2. Amendments

2.1 Claim 1 of the main request is based on original claim 1 wherein *inter alia*:

(a) a specific degree of esterification (DE) has been indicated for the pectin, namely "less than 30%",
(b) the subject-matter has been limited to the alternative relating to the presence of a pectin,
(c) the presence of a non-metal ion osmolality adjusting agent selected from polyhydric alcohols and sugars has been added,
(d) the osmolality of the composition has been specified, namely as being from 0.1 to 1.0 osmol/kg, and
(e) the functional feature relating to the peak plasma concentration has been deleted.

2.2 As underlined by the appellant - patent proprietor, compositions not limited by the functional feature mentioned above under (e) are generally described as representing the subject-matter of the invention on original page 3 lines 18-27. Furthermore, the Board observes that the paragraph following this passage

(paragraph bridging pages 3 and 4, as cited by the appellant - opponent) actually indicates that the described compositions do fulfill said functional feature. Contrary to the opinion of the appellant - opponent, the Board accordingly considers that the skilled person would not have understood said paragraphs in such a way that only parts of the structurally defined compositions fulfill said functional feature. The skilled person would rather have understood that all the disclosed compositions, *i.e.* including those defined by the structural features of amended claim 1, achieve the originally claimed peak plasma concentration, thus rendering said functional definition non-essential.

2.3 The features (c) and (d) find support on original page 12 lines 10-16 and original page 11 line 21, respectively. These passages describe the corresponding features in a general way. As argued by the appellant - patent proprietor, the skilled person would have understood that these features apply to all the disclosed compositions. Furthermore, the Board observes that the alternative relating to pectins (see feature (b)) is supported by original claim 1 and even individualised in original claim 5. The argument of the appellant - opponent that the combination of features of claim 1 of the main request would not be disclosed as such in the original application is therefore not convincing.

2.4 Regarding feature (a), the ranges "less than 35%" and preferably (*inter alia*) "7 to 30%" are disclosed on original page 6 lines 9-12. The appellant - opponent argued that the new upper limit of the range, namely "less than 30%", cannot be directly and unambiguously derived from the application as filed because the

disclosed ranges ("less than 35%" or "7 to 30%"), despite encompassing any value therein, do not disclose any such value individually. The Board finds that, in the present case, such an approach appears overly literal. Said percentage refers to the degree of esterification (DE) of a heterogenous polymeric material (see original description page 5 lines 10-14), which according to common general knowledge, actually corresponds to an average value determined for a sample of said heterogenous material by intrinsically uncertain analytical chemistry methods. The Board therefore considers that no technical difference can be made between a sample having a DE very close to 30% and a sample having a DE at 30%. This is confirmed by the use in the original application of exact values or "about" values to refer to the same ranges (see *e.g.* original description page 6 lines 9-12 and line 24). Accordingly, the new upper limit ("less than 30%") does not introduce any new technical information compared to the originally explicitly disclosed ranges and values, including the value of 30%. The Board consequently considers that the above-mentioned feature (a) is directly and unambiguously derivable from the original application taken as a whole. This opinion was already provided in the preliminary opinion of the Board issued on 13 April 2021 and the appellant - opponent did not provide any further argument in reply thereto. The Board therefore confirms its opinion. Regarding T 985/06 cited by the appellant - opponent in its reply to the statement of grounds of appeal, the Board notes that in the case underlying said decision the range concerned a molar ratio (*i.e.* a different physico-chemical value). In said earlier case, it was considered that the upper-end value of the newly claimed range could actually be distinguished from the one originally claimed. For the reasons developed

above, the Board is of the opinion that this is not possible in the technical circumstances of the present case. The conclusion reached in T 985/06 cannot therefore be "directly applied to the present case" as argued by the appellant - opponent in its reply.

2.5 The same conclusion applies to claim 18 of the main request, in so far as it contains the same features as claim 1. The appellant - opponent did not object to the remaining claims of the main request. Claims 2-17 and 19-23 of the main request are further based on the original claims and description.

2.6 Accordingly the ground of opposition under Article 100(c) EPC does not prejudice the maintenance of the granted patent (main request).

3. Sufficiency of disclosure and novelty

The appellant - opponent did not pursue at the appeal stage its objections under Article 100(b) EPC and Article 100(a) EPC in combination with Article 54 EPC. In line with the conclusions of the opposition division regarding auxiliary request 1, which apply *mutatis mutandis* to the main request, the Board considers that the grounds of opposition under Article 100(b) EPC and Article 100(a) EPC in combination with Article 54 EPC do not prejudice the maintenance of the granted patent (main request).

4. Inventive step

4.1 Closest prior art

4.1.1 The patent in suit relates to an aqueous intranasal fentanyl composition comprising a pectin with a

specific low degree of esterification (namely less than 30%), which is useful in the treatment of pain. The composition further contains a non-metal ion osmolality adjusting agent selected from polyhydric alcohols and sugars and has an osmolality of 0.1 to 1.0 osmol/kg. The purpose of the invention is to provide a liquid composition which forms a gel once administered through the nasal route and provides rapid absorption in combination with a lower peak plasma concentration and optionally an extended plasma-concentration time profile (see B1 paragraph [0019]). The composition is defined as being substantially free of divalent metal ions in order to avoid gelation during storage (*i.e.* prior to administration).

4.1.2 In accordance with both parties' submissions, D2 is considered to represent the closest prior art. D2 discloses liquid pharmaceutical compositions for administration to the mucosal surface, in particular the nasal mucous. Said compositions comprise an aqueous carrier, a therapeutic agent and a pectin having a degree of esterification of less than 50% (see for example claim 1). As identified by the appellant - opponent, D2 further discloses several features of the present claims:

- fentanyl is listed as possible therapeutic agent on column 7 line 25,
- Slendid Type 100, a pectin having a DE of the order of 10%, is mentioned among other useful pectins on column 6 lines 5-12, and
- the addition of sugars or non-ionic polysaccharides as gelation aid is disclosed on column 8 lines 15-18.

The purpose of the teaching in D2 is to provide a liquid pharmaceutical composition which gels at the site of application (see column 4 lines 43-48) and

allows the retention of the therapeutic agent for a longer period (see column 6 lines 49-55).

4.2 Distinguishing feature

D2 very generally describes all the components of the present compositions. However, D2 does not disclose any preferred embodiment or specific example of a composition comprising the present combination of features (specific therapeutic agent, specific DE for the pectin and specific osmolality-adjusting agent). In particular, D2 does not describe any specific example of a fentanyl composition, letting alone a fentanyl composition containing pectin having a DE value of less than 30%. Furthermore, D2 does not provide osmolality values for the disclosed compositions.

4.3 Technical effect and objective technical problem

4.3.1 The data reported in D12-D13 relate to a comparison between compositions with fentanyl and pectins having a DE below 30% and compositions differing therefrom only in that the pectins have a DE above 30%. Such a comparison is therefore suitable to substantiate an effect linked to the specific choice of the DE according to the present claim 1 in combination with fentanyl, which constitutes a distinguishing feature *versus* the closest prior art D2. These data reveal that compositions containing a pectin with a DE below 30% show a higher gel strength (see table on page 2 of D13) as well as a lower immediate release followed by a slow controlled release (see figure 2 of D12 and the figure of D13). It appears further credible, as mentioned by the appellant - patent proprietor, that this release profile may reduce undesirable side-effects linked to high initial absorption rates.

4.3.2 In this context, the appellant - opponent disputed the presence of any particular effect by merely referring to the first instance decision, in which it was assumed that no technical effect was present without discussing the data provided in D12-D13. In the absence of specific arguments with respect to data provided in D12-D13, the presence of the effect as detailed under point 4.3.1, *i.e.* an advantageous release profile of fentanyl, is considered as credibly substantiated.

4.3.3 For the sake of completeness, the Board notes that the documents D10-D11, D14 and D15 further cited by the appellant - patent proprietor in this context are not suitable to substantiate a technical effect directly linked to a distinguishing feature *versus* the closest prior art D2. D14 provides indeed a comparison with a composition containing a different therapeutic agent than fentanyl and D10, D11 and D15 relate to features which do not constitute a distinguishing feature towards D2.

4.3.4 The Board consequently considers that the objective technical problem to be solved, starting from D2, consists in the provision of further intranasal compositions comprising fentanyl and pectin and having an advantageous release profile.

4.4 Obviousness of the solution

The Board observes that a pectin according to the present claims is generally disclosed and used in the examples of D2 together with therapeutic agents different from fentanyl (see Slendid 100 having a DE of around 10%). According to example 4 and figure 2 of D2, adding said pectin to an intranasal formulation of

fexofenadine drastically modifies the drug release profile thereof (no immediate release any more when using pectin). As brought forward by the appellant - patent proprietor, the drug release profile obtained in the case of fexofenadine in D2 is however different from the one desired in the case of fentanyl (still some immediate release needed to ensure fast pain relief). Furthermore, there does not appear to be an indication in D2 that the value of 30% for the DE of pectin would have a particular influence on the release profile of fentanyl. The present release profile of fentanyl when using a pectin having a DE of less than 30% would not have been expected in view of D2. Contrary to the opinion of the appellant - opponent, there is consequently no suggestion in D2 to use Slendid in combination with fentanyl so as to achieve the present release profile. None of the further documents cited by the appellant - opponent (namely D3, D8, D16 and D17) provides a hint to the selection of this particular value of DE for the pectin so as to achieve a lower Cmax and a subsequent plateauing release of fentanyl. D3 generally mentions fentanyl as suitable therapeutic agent and pectin as useful muco-adhesive. D3 does however not disclose a composition comprising both fentanyl and a pectin having the present DE, let alone the effect of said pectin on the release profile of fentanyl. D8 relates neither to fentanyl nor to a pectin according to the present claims. D16, which is a review on pectins, teaches that mono- or multivalent cations have an influence on the viscosity of pectins depending on the DE value of the pectin. However D16 does not disclose any specific value of DE. Finally D17 concerns ophthalmic compositions which contain neither fentanyl nor a pectin. The Board concludes therefore that the selection of a DE of less than 30% for the pectin in

order to achieve an advantageous release profile of fentanyl (*i.e.* providing some immediate pain relief while reducing the risk of undesirable side effects) is not suggested in any of the cited prior art documents.

4.5 Accordingly, the ground of opposition under Article 100(a) EPC in combination with Article 56 EPC does not prejudice the maintenance of the granted patent (main request).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained as granted.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated