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Datasheet for the decision of 29 May 2024

Case Number: T 0089/22 - 3.3.07

Application Number: 08162152.6

Publication Number: 2036546

IPC: A61K9/20

Language of the proceedings: EN

Title of invention:
Psychostimulant containing pharmaceutical composition

Patent Proprietor:
PEJO Iserlohn Heilmittel-und Diät-GmbH & Co.KG

Opponent:
Kraus & Lederer PartGmbB

Headword:
Psychostimulant containing pharmaceutical composition / PEJO

Relevant legal provisions:
EPC Art. 100(a), 56
RPBA 2020 Art. 13(2)

Keyword:
Inventive step - (no)
Amendment to case - amendment admitted (no)

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Case Number: T 0089/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 29 May 2024

Appellant: (Patent Proprietor)	PEJO Iserlohn Heilmittel-und Diät-GmbH & Co.KG Kuhloweg 37-39 58638 Iserlohn (DE)
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Appellant: (Opponent)	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 12 November 2021 concerning maintenance of the European Patent No. 2036546 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	A. Jimenez

Summary of Facts and Submissions

I. The appeals were filed by the patent proprietor (appellant - proprietor) and the opponent (appellant - opponent) against the interlocutory decision of the opposition division finding that, on the basis of auxiliary request 3, the patent met the requirements of the EPC.

II. The decision was based on the patent as granted as the main request, auxiliary request 1 filed on 4 December 2019, and auxiliary requests 2 and 3 filed on 17 August 2020.

The main request pertained to:
- claim 1:
"Pharmaceutical composition containing an initial dosage of psychostimulant and a second dosage of said psychostimulant, wherein the release of said second dosage is modified, characterized in that the release of said second dosage is modified by an enteric coating comprising (co-)polymers of (meth)acrylic acid and/or (meth)acrylate containing carboxyl groups wherein 2-10, preferably 3-8, most preferably 6% of said carboxyl groups are neutralized, thereby causing a sustained release of said second dosage of the psychostimulant in vivo."
- claim 11:
"A pharmaceutical composition obtainable by the method comprising the steps of:
a) manufacturing the first component by:
- providing spheres,
- preparing a liquid containing a psychostimulant,
- coating the spheres with said liquid, and

- drying the coated spheres;

b) manufacturing the second component by:

- providing spheres manufactured in accordance with step a),
- preparing a liquid suitable for providing an enteric coating on said spheres, the liquid containing (co-)polymers of (meth)acrylic acid and/or (meth)acrylate having carboxyl groups and an alkaline agent,
- coating the spheres with said liquid, and
- drying the coated spheres,

wherein steps a) and/or b) preferably further comprise the step of mixing the spheres with a mixture of micronised talc and colloidal anhydrous silica and/or sieving the spheres obtained, and
wherein the alkaline agent is added to the liquid in an amount sufficient to achieve a neutralisation of 2-10, preferably 3-8, most preferably 6% of said carboxyl groups."

The claims of auxiliary request 1 additionally specified that "the psychostimulant is selected from methylphenidate or a pharmaceutically acceptable salt thereof, an enantiomer or mixtures thereof".

Claim 1 of auxiliary request 2 additionally mandated that "the composition comprises two distinct components, the first component containing the initial dosage, the second component containing the dosage showing a modified release", and that "the first and the second component is present in spherical form, preferably in pellet form".

Claim 1 of auxiliary request 3 corresponded to claim 11 of auxiliary request 1.

III. The following documents were cited in the appealed decision:

D1: WO 00/35450 A1
D5: McGinity J.W., "Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms", Second Edition, 1997, Marcel Dekker, Inc. New York
D6: Lehmann K., Drug. Dev. Ind. Pharm. 1986, 12(3), 265-287

IV. The opposition division decided that:

(a) The main request, as well as auxiliary requests 1 and 2, infringed Articles 76(1) and 123(2) EPC.

(b) Regarding auxiliary request 3, example 6B of D1 was a suitable starting point for the assessment of inventive step. The objective technical problem was the provision of an alternative formulation comprising an immediate release component and an enteric coated sustained release component, both components comprising a psychostimulant. The claimed solution involved an inventive step.

V. With their statement setting out the grounds of appeal, the appellant - proprietor upheld the same claim requests as underlying the appealed decision (see II. above).

VI. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.

VII. Oral proceedings were held before the Board.

VIII. The appellant - proprietor requested that the decision under appeal be set aside and that the patent be

maintained as granted, or, subsidiarily, that the patent be maintained according to one of auxiliary requests 1-3.

IX. The appellant - opponent requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

X. The appellant - proprietor's arguments regarding inventive step for all requests may be summarised as follows:

The closest prior art D1 (see example 6B) disclosed oral methylphenidate formulations comprising a combination of immediate release methylphenidate beads (IR) and enteric coated controlled release (EC·CR) methylphenidate beads coated with Eudragit L 30D-55.

D1 did not disclose the feature of claim 1 that the carboxyl groups of the enteric coating are neutralized to 2-10%. In addition, in auxiliary request 3 and possibly also in the main request, the subject-matter of claim 1 further differed in that the enteric coated controlled release (EC.CR) methylphenidate beads used in example 6B of D1 bore a dual coating which was not covered by claim 1.

The objective technical problem was to provide a pharmaceutical composition showing essentially only one single main plasma concentration, wherein in the further course, the plasma concentration is maintained on a higher level and for a longer time. The data in D1 (formulation 2 of example 6B and figure 8) and in the patent (figure 7) allowed a meaningful comparison and showed that the problem was solved.

The claimed solution involved an inventive step. D5 disclosed the addition of alkaline agents to Eudragit® based coatings thus leading to a partial neutralisation of carboxyl groups. However, the skilled person would have neither added an alkaline agent to the liquid suspension L 30D-55, nor replaced L 30D-55 with redispersed L 100-55. Furthermore, D5 did not disclose a partial neutralisation of the carboxyl groups in the polymer in a range 2-10%.

Thus the requirements of inventive step were met.

XI. The appellant - opponent's arguments regarding inventive step for all requests may be summarised as follows:

Example 6B of D1 showed a formulation prepared by mixing in a 35:65 ratio immediate release beads with enteric-coated controlled release beads. The differentiating feature was the neutralisation of carboxyl groups of the copolymer to 2-10, preferably 3-8, most preferably to 6%. The appellant - proprietor's allegation, at the oral proceedings before the Board, of a further difference pertaining to the dual coating in D1, was late and not to be admitted.

No comparison had been provided between the claimed subject matter and D1. The release profile of example 6B and figure 8 of D1 could not meaningfully be compared with that of figure 7 of the contested patent. In addition, no improvement could credibly arise over the whole scope of the claim, i.e. for all the types and amounts of (co)polymer coatings covered by claim 1. The technical problem was the provision of an alternative formulation comprising methylphenidate.

The claimed solution was obvious taking into consideration common general knowledge (see the handbook D5). The ready-to-use dispersion Eudragit L 30D-55 was equivalent to the corresponding spray dried L 100-55 after redispersion in water with the addition a small amounts of alkali as defined in claim 1. Moreover, the addition of the same amounts of base was also recommended for the ready-to-use dispersion Eudragit L 30D-55. Hence, the skilled person would have added an amount of alkali of 3-5 mol% to the L 30D-55 dispersion of D1, or replaced it with the L 100-55 powder and added the recommended amount of base when redispersing it. Contrary to the appellant - proprietor's view, the percentages of neutralisation reported in D5 (3-5 mol%) referred to the moles of carboxylic groups in the acrylic polymer, and not to the moles of the acrylic polymer itself.

The criteria of inventive step were thus not met.

Reasons for the Decision

1. Inventive step, main request

1.1 Closest prior art

The patent pertains to pharmaceutical compositions containing a psychostimulant such as methylphenidate, comprising an enteric coating and showing a sustained release of said psychostimulant *in vivo*. The compositions are useful in particular in the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

D1 also relates to controlled or modified release oral methylphenidate formulations intended to combine both a rapid onset and sustained plasma concentrations throughout the day (see the bottom of page 4). In one embodiment, the formulations of D1 are composed of a mixture of immediate release particles (e.g., beads) and enteric coated controlled release particles (e.g., beads), blended together and filled into hard gelatin capsules (see page 8, line 6-10).

Both parties take example 6B (formulation 2) of D1 as starting point for the assessment of inventive step (see page 41).

Example 6B describes a formulation comprising a 65:35 mixture of enteric coated controlled release (EC.CR) beads and immediate release beads. The immediate release beads are prepared according to example 1 by coating sugar spheres with a solution of methylphenidate hydrochloride followed by drying. The enteric-coated controlled release beads were prepared according to example 5 and are coated with the same (meth)acrylic acid copolymer component as in all examples of the patent, namely Eudragit L 30D-55. The methylphenidate plasma concentration following administration of the above formulation in fasted and fed subjects is shown in Figures 5, 7 and 8 of D1.

1.2 Differentiating feature; admittance of amended case

1.2.1 The sole differentiating feature over example 6B of D1 identified in the appealed decision (see §22.6) and in the parties's written submissions in appeal (see especially the appellant - proprietor's reply dated 29 July 2022, bottom of page 2) is that 2-10, preferably 3-8, most preferably 6% of the carboxyl

groups of the (meth)acrylic (co)polymer are neutralized. The Board agrees that the feature of claim 1 of the main request regarding a neutralization of 2-10% of the carboxyl groups is not disclosed in D1.

1.2.2 During the oral proceedings before the Board, the appellant - proprietor further submitted that, in auxiliary request 3 and possibly also in the main request, the subject-matter of claim 1 additionally differed in that the enteric coated controlled release (EC.CR) methylphenidate beads used in example 6B of D1 bore a dual coating which was not covered by claim 1.

This submission, made well after notification of the communication under Article 15 RPBA, departs from the appellant - proprietor's appeal case established by their earlier written submissions, i.e. it is not directed to the requests, facts, objections, arguments and evidence relied on by the appellant - proprietor in their statement of grounds of appeal and reply under Article 12(3) RPBA. It cannot be regarded as a mere refinement of the arguments presented earlier, since the appellant - proprietor's written submissions never hinted at any difference other than the 2-10% neutralisation. The allegation of a further difference related to the dual coating does not simply amount to pointing out an obvious fact in example 5 of D1 either, but entails an assessment of, firstly, whether claim 1 excludes such dual coatings (despite its open wording in the main request, or the mention in claim 1 of auxiliary request 3 that manufacturing steps a) and/or b) may optionally comprise further steps), and, secondly, if this number of coatings does represent an additional difference over D1, whether this further difference would involve any inventive step. In other

words, the appellant - proprietor's new submission would essentially change the inventive step reasoning.

Accordingly, this submission constitutes an amendment to the appellant - proprietor's case which is subject to the provisions of Article 13(2) RPBA. The submission shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

No exceptional circumstances were alleged by the appellant - proprietor nor are apparent in the present case. The Board's communication under Article 15(1) RPBA did not extend beyond the framework of the objections and arguments presented by the appellant - opponent in their grounds of appeal. The mere fact that the Board's preliminary opinion expressed in this communication was unfavourable to the appellant - proprietor does not represent an exceptional circumstance in the sense of Article 13(2) RPBA.

Consequently, the Board did not admit this amendment to the appellant - proprietor's case.

1.2.3 Thus the sole differentiating feature over example 6B of D1 considered here is that 2-10% of the carboxyl groups are neutralized.

1.3 According to the appellant - proprietor, the technical problem is the provision of a pharmaceutical composition having a modified *in vivo* release pattern of methylphenidate, and leading to a first and highest blood plasma concentration soon after intake of the pharmaceutical composition and a second, slightly lower peak is generated in a time range of about 6 hours

following intake of the pharmaceutical composition, i.e. within a short term following breakfast.

In support for the alleged effect, the appellant - proprietor relies on a comparison between the data in the patent (see figure 7) and the data in D1 (see figures 7 and 8). In the patent, figure 7 reports the plasma concentration over time under defined testing/ feeding conditions for retard capsules according to batches PL 3780 and PL 3781 (cf. tests 2-4, see page 20 of the patent). As to D1, figures 7 and 8 report the plasma concentrations under fasting or fed conditions for Formulation 2 of example 6B.

The Board does not consider that any meaningful conclusion can be drawn from this comparison, for the following reasons.

1.3.1 While D1 contains no disclosure of a neutralisation degree in formulation 2, the patent does not disclose either the degree of carboxyl group neutralisation in batches PL 3780 and PL 3781. It cannot be assumed that these batches necessarily meet the condition of a 2-10% neutralisation, because this feature was optional in the application as filed. According to the appellant - proprietor, all batches were manufactured according to the formulation indicated in Table 2 of the patent. Table 2 mentions the use of undisclosed amounts of Eudragit L 30 D-55 and sodium hydroxide 15%, but does not give the resulting degree of carboxyl group neutralisation. The appellant - proprietor further stated that batches PL 3780 and PL 3781 were identical to those described in paragraphs [0036]-[0037] of the patent. Paragraphs [0036]-[0037] describe an experimental setting with an expected neutralisation of about 6% of the carboxyl groups in the polymer. This

later statement however contradicts the earlier reference to table 2 since different conditions are indicated in paragraph [0036] (namely 10 vol% of 1N sodium hydroxide vs sodium hydroxide 15%). There is thus no clear information as to the degree of carboxyl group neutralisation in figure 7 of the patent, and no possibility to unambiguously assign any properties of the formulations tested in Figure 7 to the claimed range of 2-10% neutralisation.

1.3.2 Furthermore, the compositions of D1 and of the patent differ in many respects other than the percentage of neutralized carboxyl groups. This is apparent from a comparison of the ingredients and amounts given in examples 6B, 1 and 5 of D1 with the ingredients listed in Table 2 of the patent, and additionally from the fact, uncontested by the appellant - proprietor, that different ratios of immediate release components to enteric coated delayed release components were used (i.e. 35:65 in Formulation 2 of D1 according to example 6B, vs 50:50 in figure 7 of the patent according to paragraph [0028]). As explained by the appellant - opponent, the methylphenidate plasma profile depends on numerous variables, including not only the relative amounts of immediate release and sustained release components, but also the type and amount of acrylic copolymer used, or the presence of further excipients. It is not established that the above formulations are comparable in respect of these further parameters.

1.3.3 Accordingly, the comparison of figure 7 of the patent with figures 7 and 8 of D1 does not convincingly show that the alleged effect on *in vivo* release pattern has its origin in the distinguishing feature over D1, namely that 2-10% of the carboxyl groups are neutralized.

1.3.4 According to the appellant - proprietor, the partial neutralization of the enteric coating leads to the formation of small channels therein, resulting in a leakage of the enteric coating so that already at a pH of lower than 5.5, the psychostimulant will be released (see also paragraph [0030] of the patent). However, the evidence cited in support for this allegation, namely Figures 2, 4 and 5 of the patent, does not contain any direct comparison showing an effect of the degree of neutralisation either.

1.3.5 In addition, the Board shares the appellant - opponent's view that any effect on *in vivo* release pattern, even if it were accepted in the case of the examples, could not be extrapolated to the whole scope of the claims, and in particular to any types of (meth)acrylic acid / (meth)acrylate copolymers. All examples in the patent use the particular enteric coating L 30D-55, whereas claim 1 allows more generally for enteric coatings comprising (co-)polymers of (meth)acrylic acid and/or (meth)acrylate containing carboxyl groups, and without limitation as to their amount. As shown in D1 (see page 18, second paragraph; see page 35, bottom), D5 (page 127, figure 7) or D6 (see figure 9), the claimed class of (co-)polymers covers various types and amounts of materials leading to different swelling, pH-dependent dissolution and release properties. There is no reason to expect the same effect of a 2-10% neutralisation, if any, across all claimed types and amounts of coating.

1.4 Consequently, the problem is formulated as the provision of an alternative formulation comprising an immediate release component and an enteric coated

sustained release component, both components comprising a psychostimulant.

1.5 Obviousness

It is generally known (see the handbook D5, page 125, second and third paragraphs) that:
- Eudragit L 30D-55 is a ready-for-use dispersion known for use as enteric coating;
- Eudragit L 100-55 is a powder prepared by spray drying Eudragit L 30D-55 which can easily be redispersed in water by adding small amounts of alkali, e.g. 3-5 or 3-8 mol% (see table 4 of D5).
- Eudragit L 30D-55 and the redispersed Eudragit L 100-55 have the same gastroresistence and dissolution properties.

Contrary to the appellant - proprietor's view, the molar percentages given in D5 cannot be understood as based on moles of Eudragit polymers, but on acrylic acid monomers, considering the corresponding amounts given as examples in table 4 and at the bottom of page 125 of D5.

In view of this common general knowledge, the skilled person would consider replacing the Eudragit L 30D-55 of D1 with the equivalent L 100-55 redispersed with 3-8% base, thus arriving at a pharmaceutical composition within the scope of the claims. The Board does not concur with the appellant - proprietor that the skilled person would adopt a conservative approach and would avoid modifying the formulation of D1. On the contrary, the skilled person is assumed to seek a solution to the technical problem, which, in the present case, is merely to provide an alternative, and thus would take into account the well-known alternative

shown in D5, namely L 100-55 redispersed with an alkali.

Furthermore, according to D5, it is also recommended to add the same amounts of base to the original Eudragit L 30D-55 latex composition (see page 129, third paragraph). Accordingly, the skilled person would equally consider adding 3-5 mol% alkali to the enteric coating not only in the context of a powder (L 100-55) but also when using a ready-to-use suspension (L 30D-55) as in example 6B of D1. In this respect, the skilled person would not be deterred by the word of caution against raising the pH to 5.5 or above at the end of the third paragraph on page 129 of D5, and would simply ensure that the pH be raised to about 5 as recommanded in D5.

Accordingly, the subject-matter of the main request does not involve an inventive step.

2. Auxiliary requests

None of the auxiliary requests 1-3 overcome the issue of lack of inventive step.

The feature of claim 1 of auxiliary request 1 that the psychostimulant is methylphenidate, and the feature of claim 1 of auxiliary request 2 that the composition comprises two distinct components, both in spherical form, are both shown in example 6B of D1. The definition of the formulation in terms of the process for its preparation according to claim 1 of auxiliary request 3 does not represent an additional differentiating feature either.

Accordingly, none of the auxiliary requests 1-3 meets the requirement of inventive step.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar: The Chairman:

L. Malécot-Grob A. Usuelli

Decision electronically authenticated