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Datasheet for the decision of 2 October 2020

Case Number: T 1490/19 - 3.3.01

Application Number: 09164379.1

Publication Number: 2103307

IPC: A61K31/4458, A61K9/50

Language of the proceedings: EN

Title of invention:
Methylphenidate modified release formulations

Patent Proprietor:
Shire Pharmaceuticals Ireland Limited

Opponent:
isarpatent - Patent- und Rechtsanwälte Behnisch Barth Charles Hassa Peckmann und Partner mbB

Relevant legal provisions:
EPC Art. 123(2), 76(1)

Keyword:
Amendments - allowable (no)

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Case Number: T 1490/19 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 2 October 2020

Appellant: (Patent Proprietor)	Shire Pharmaceuticals Ireland Limited 5 Riverwalk Citywest Business Campus Dublin 24 (IE)
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Respondent: (Opponent)	isarpatent - Patent- und Rechtsanwälte Behnisch Barth Charles Hassa Peckmann und Partner mbB Friedrichstrasse 31 80801 München (DE)
Representative:	Isarpatent Patent- und Rechtsanwälte Behnisch Barth Charles Hassa Peckmann & Partner mbB Friedrichstrasse 31 80801 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 22 March 2019 revoking European patent No. 2103307 pursuant to Article 101(2) and 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	R. Romandini

Summary of Facts and Submissions

I. European patent No. 2 103 307 (the patent in suit) derived from application No. 09 164 379.1, which is a divisional of European patent application No. 01 977 934.7 (the parent application, published as international application No. WO 02/34234).

II. **Claim 1** of the divisional application No. 09 164 379.1 **as filed** is identical to claim 1 of the parent application as filed and reads as follows:

> *"1. Modified Release Methylphenidate Hydrochloride Capsule drug delivery system comprising a multitude of IR (immediate release) and ER (extended release) Beads filled into capsules at a ratio of 10 IR/90 ER to 50 IR/50 ER Beads each of said IR and ER beads containing about 5 to 20% methylphenidate hydrochloride."*

The parent and divisional applications were filed with identical descriptions.

III. The patent in suit was granted with a set of 14 claims. **Claim 1 as granted** reads as follows:

> *"1. Modified release methylphenidate hydrochloride capsule drug delivery system comprising a multitude of IR (immediate release) and ER (extended release) beads filled into capsules at a ratio of 10 IR/90 ER to 50 IR/50 ER beads each of said IR and ER beads containing about 5 to 20% w/w methylphenidate hydrochloride,*

wherein the IR bead is an inert sugar core particle layered with methylphenidate containing a binder at a concentration of 0.5 to 5 weight %, said layered particle further being coated with a seal coat in an amount up to 4% w/w,

and wherein the ER bead comprises an IR bead coated with a dissolution rate controlling polymeric coating in an amount from 5 to 25% by weight based on the total weight of the coated particle, the ER bead being seal coated in an amount up to 4% w/w, wherein the sealcoat is hydroxypropylmethyl-cellulose (HPMC)."

IV. The patent in suit was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter

- did not involve an inventive step;
- was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art;
- and extended beyond the content of the application and parent application as filed.

V. The patent proprietor requested that the opposition be rejected (main request) and in the course of the opposition proceedings filed three auxiliary requests.

Claim 1 of auxiliary request I (filed with a letter dated 18 December 2018) is identical to claim 1 as granted, except that it additionally specifies the following:

"and wherein said capsule comprises 10 to 40 mg methylphenidate as a hydro chloride salt consisting of ER and IR beads at a ratio of 20/80 to 40/60."

Claim 1 of auxiliary request II (also filed with the letter dated 18 December 2018) is identical to claim 1 as granted, except that the definition of the ratio:

"at a ratio of 10 IR/90 ER to 50 IR/50 ER beads"

was replaced by:

"at a ratio of 30 IR/70 ER beads".

VI. The decision under appeal is the opposition division's decision revoking the patent, announced on 19 February 2019 and posted on 22 March 2019.

VII. According to the decision under appeal:

(a) there was no basis in the parent and divisional applications as filed for the technical feature relating to the concentration of binder of 0.5% to 5% by weight in the drug-containing layer of the IR bead, as defined in claim 1 as granted (Articles 100(c), 76(1) and 123(2) EPC);

(b) the same objection applied to claim 1 of each of auxiliary requests I and II;

(c) claim 1 of auxiliary request III was not allowable pursuant to Article 123(3) EPC.

VIII. The patent proprietor (appellant) filed an appeal against this decision and requested that the decision under appeal be set aside in respect of Articles 123(2) and 76(1) EPC and that the case be remitted to the opposition division.

IX. Oral proceedings before the board of appeal were held on 2 October 2020.

X. This decision is based on the following claim requests pursued by the appellant:

- the claims as granted (main request);
- auxiliary request I (filed by letter of 18 December 2018);
- auxiliary request II (filed by letter of 18 December 2018).

XI. The appellant's arguments may be summarised as follows:

The technical feature recited in claim 1 of all requests

"wherein the IR bead is an inert sugar core particle layered with methylphenidate containing a binder at a concentration of 0.5 to 5 weight %"

referred to the concentration of the binder in the drug-containing layer of the IR bead.

It was supported by the sentence on page 4, lines 23 to 26 of the description as filed, which reads:

"Binders (...) may be used at concentrations of 0.5 to 5 weight %".

This concentration likewise referred to the concentration of the binder in the drug-containing layer of the IR bead rather than to its concentration in the initial (liquid) coating formulation.

The working examples set out in the description corroborated the appellant's position since all the synthetic examples (examples 1, 3, 5 and 6) described formulations in which the binder formed between 0.5% and 5% by weight of the drug-containing layer deposited on the surface of the inert sugar core.

There were further indications supporting the view that the range of 0.5 to 5% by weight of binder mentioned on

page 4, paragraph 3 of the description was based on the drug-containing layer of the IR beads:

Firstly, it was clear from the description as filed that the invention centred on the timing of the drug release and was put into practice by combining IR beads, for an early onset of action, with ER beads, for attaining an extended release period and thereby maintaining high plasma concentrations of the drug over some time. The person skilled in the art was aware that the release properties of both types of beads were determined by the choice of excipients and their relative amounts. Thus, the excipient concentrations of interest to the person skilled in the art were those present in the final coated beads, indicated as weight percentages. Accordingly, any proportions disclosed as weight percentages throughout the description were indicated based on the coated particles rather than the initial liquid coating formulation (see page 3, paragraphs 1 and 3; page 5, paragraphs 1 and 2). The skilled person reading the description would thus infer that page 4, paragraph 3, referring to "concentrations of 0.5 to 5 weight %" of binder, likewise meant the percentage of binder in the drug-containing coating layer. Contrary to the respondent's argument, the term "concentration" in itself was not restricted to concentrations in a liquid.

Secondly, the assumption that the binder concentration of 0.5 to 5% by weight was based on the drug-containing coating layer resulted in a more reasonable scope for the ratio of drug to binder when considering the upper and lower limits given for the concentrations of drug and binder:

- According to the description on page 4, paragraph 3, the concentration of the drug in the coating formulation could be up to 55% by weight.

Assuming that the lower limit was at least 1% methylphenidate in the coating formulation, and further assuming (as argued by the respondent) that the concentration of binder of 0.5 to 5% was also based on the coating formulation, the ratio of drug to binder could vary within extremely wide limits, namely between 1:5 and 110:1. However, it did not make technical sense to include up to five times as much binder as drug since this would affect the release time of the IR beads and prevent the desired early onset of drug action. Hence, the respondent's interpretation appeared unreasonable.

- On the other hand, assuming that the binder concentration of 0.5 to 5% by weight was based on the drug-containing coating layer, the drug concentration in that layer must conversely be between 99.5% and 95% by weight. The ratio of drug to binder would thus vary between 19:1 to 199:1. This was a more realistic range since it did not include options having more binder than drug. It was also consistent with the ratio of about 20:1 which had actually been used in the working examples.

XII. The respondent's (opponent's) arguments may be summarised as follows:

The text of the parent and divisional applications as filed did not support the concentration range of 0.5 to 5% by weight of binder in the drug-containing layer of the IR beads defined in claim 1 as granted since the passage on page 4, paragraph 3 (relied on by the appellant) referred to a concentration of 0.5 to 5% of binder in the coating liquid used, rather than in the final dried coating layer. This was made clear by

the context of the complete passage on page 4, lines 7 to 28.

The ratios of drug and binder used according to the working examples were consistent with either interpretation and, therefore, did not corroborate the appellant's view.

According to the passage relating to the binders (page 4, paragraph 3), any binder could be used. These could be chemically different substances with varying properties. The concentration range of 0.5 to 5% was merely a general proposal which was not mandatory and was not linked in the text to any specific technical effect.

Furthermore, the person skilled in the art reading the description as filed would not carry out a detailed analysis of all the concentration ranges mentioned, or carry out calculations combining the extremes of ranges in the manner set out by the appellant. The appellant's analysis of the description in that respect amounted to over-interpretation and arrived at conclusions which were not actually implied in the text.

XIII. The appellant requested that the decision under appeal be set aside in respect of Articles 123(2) and 76(1) EPC and that the case be remitted to the opposition division.

XIV. The respondent requested that the appeal be dismissed or, in the alternative, that the case be remitted to the opposition division.

Reasons for the Decision

1. The appeal is admissible.

2. Amendments (Articles 76(1) and 123(2) EPC)

2.1 Since the text of the descriptions of the parent and divisional applications as filed is identical (see point II. above), reference will be made in the following to "the description as filed".

2.2 The feature at issue is the following feature present in claim 1 as granted:

> *"wherein the IR bead is an inert sugar core particle layered with methylphenidate containing a binder at a concentration of 0.5 to 5 weight %".*

2.3 It was common ground that, within the meaning of claim 1 as granted, the binder concentration of 0.5 to 5% by weight was based on the total weight of the coating layer which contains the drug and the binder.

2.4 For the purposes of Articles 76(1) and 123(2) EPC it must be established whether this feature is supported by the parent and divisional applications as filed or constitutes added subject-matter going beyond the original disclosure.

2.5 In support of this feature, the appellant relied on the sentence on page 4, lines 23 to 26 of the description as filed, which reads: *"Binders (...) may be used at concentrations of 0.5 to 5 weight %".*

2.6 The board does not consider this to be a direct and unambiguous disclosure of a binder concentration of 0.5% to 5% by weight in the dried drug-containing coating layer. On the contrary, the context in which

this sentence is used in the description as filed strongly suggests that the indicated concentration is based on a liquid coating formulation.

2.6.1 The preceding second paragraph on page 4 (see lines 7 to 19) relates to the method for manufacturing the methylphenidate dosage forms according to the invention. The paragraph sets out three manufacturing steps:

> *"1. coating an inert particle such as a non-pareil seed with methylphenidate and a polymeric binder to form IR Beads, which may be present in the unit dosage form to act as a bolus dose;*
>
> *2. coating said particle with a plasticized solution or suspension of a water insoluble polymer or a mixture of water soluble and water insoluble polymers and curing at high temperatures (e.g. , 50°-70°C) for 4 to 12 hours, to form extended release (ER) Beads; and*
>
> *3. filling into hard gelatin capsules beads of (1) and/or (2) at a ratio of 20IR/80SR to 40IR/60SR Beads, each capsule containing 10 to 40 mg methylphenidate hydrochloride."*

2.6.2 Paragraph 3 on page 4 (see lines 20 to 28) consists of four sentences and continues as follows:

> *"An aqueous or a pharmaceutically acceptable solvent medium may be used for preparing drug containing core particles.*
>
> *The type of film forming binder that is used to bind the water soluble drug to the inert sugar sphere is not critical but usually water soluble, alcohol soluble or acetone/water soluble binders are used.*

Binders such as polyvinylpyrrolidone (PVP), polyethylene oxide, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), polysaccharides such as dextran, corn starch may be used at concentrations of 0.5 to 5 weight %.

The drug substance may be present in this coating formulation up to 55 weight %, preferably up to about 40% weight % [sic]*, and most preferably up to about 20% weight, depending on the viscosity of the coating formulation."*

2.6.3 It is immediately apparent to a reader that paragraph 3 describes further details of step 1, namely that the drug is to be deposited on the surface of the inert core particles with the help of a binder to form IR beads. The following paragraph (starting on page 4, line 29) then goes on to discuss dissolution rate-controlling polymers needed in step 2 for producing ER beads.

2.6.4 The first sentence of paragraph 3 states that an aqueous or other solvent medium may be used to prepare drug-containing particles. The second sentence specifies that a film-forming binder is used to bind the drug to the particle surface. The third sentence indicates a general concentration range for the binder. The fourth sentence gives an upper limit for the concentration of the drug in the coating formulation, which may be adjusted depending on the viscosity of the coating formulation.

It is thus evident that all four sentences in paragraph 3 relate to the same coating process for depositing the drug on the particle surface and cannot be regarded in isolation. Rather, the reader understands that this passage specifies the components of the coating formulation and, in the case of the drug

and the binder, their concentrations. The reader would infer from the mention of a solvent medium and the parameter "viscosity" that the concentration of the drug (*"up to 55 weight%"*) is based on the liquid coating formulation, which includes the solvent medium, and that the concentration of the binder - mentioned in close proximity and in the very same context - also refers to the liquid coating formulation.

2.7 The appellant argued that, by analysing the description as filed, the person skilled in the art would nevertheless understand that the range of 0.5 to 5% by weight of binder indicated on page 4 must be based on the dried drug-containing coating layer (see point XI. above):

(a) it was not mandatory to use a liquid medium in step 1 to coat the drug on the particles;

(b) other instances in the description of component proportions indicated as weight percentages were based on the drug particles and not a liquid coating formulation;

(c) taking into account the upper and lower limits of the drug and binder concentration ranges, the assumption that the binder concentration was based on the weight of the coating liquid led to technically unreasonable options for the ratio of drug to binder;

(d) the amounts of drug and binder used in the working examples (examples 1, 3, 5 and 6) were consistent with the interpretation that the concentration of 0.5 to 5% binder was based on the weight of the dried drug-containing layer of the particles.

2.8 The board does not reach the same conclusion, for the following reasons.

2.8.1 Concerning point (a)

While step 1 as described in paragraph 2 on page 4 does not mention a liquid coating formulation, a liquid formulation is the conventional means of applying a coating containing a film-former to a surface. While expressly referring to a solvent medium and a film-forming binder in paragraph 3 on page 4 (a passage which elaborates on step 1), the parent and divisional applications as filed do not describe or suggest any other method for depositing the drug-containing layer on the particles. The reader, therefore, has no reason to assume that a different, more unusual method is envisaged for coating the drug on the core particles.

2.8.2 Concerning point (b)

The passages in the description cited by the appellant as disclosing component proportions as weight percentages are the following:

(i) Page 3, paragraph 1 states that the percentage of sealcoat on the drug-layered beads is up to 4% by weight. This is, presumably, the percentage of sealcoat film-former based on the total weight of the coated bead particle.

(ii) Page 3, paragraph 3 states that the dissolution rate-controlling polymeric coatings (which are required for the ER beads) vary from 5 to 25% by weight based on the total weight of the coated particle.

(iii) Page 5, paragraph 1 states that dissolution rate-controlling polymers are usually plasticised and that the plasticiser "may comprise" 3 to 30%

by weight based on the polymer, which presumably means that the plasticiser is present in an amount of 3 to 30% of the weight of the rate-controlling polymer.

(iv) Page 5, paragraph 2 states that the release characteristics of the IR beads may be modified by coating them with a mixture of a water-insoluble polymer and a water-soluble polymer *"at a thickness of from 1 weight% up to 5 weight %"*.

Paragraph 3 on page 4 (see point 2.6.2 above) describes how the core particles are to be coated with the drug, with the help of a binder. In this technical context it is neither unusual nor technically nonsensical to indicate the concentration of the binder in the coating liquid. Nothing in the above-cited passages on pages 3 and 5 changes this assessment, for the following reasons.

It is not pertinent to the issue in hand that passages (i), (ii) and (iv) indicate the quantity of each coating material based on the total weight of the coated particle.

- Firstly, none of these passages is concerned with the preparation of the drug-containing layer and none of the coating materials referred to is the binder of the drug-containing layer.
- Secondly, indicating the proportion of a coating material (in this case a polymer or polymer mixture) based on the total weight of the coated particle is not the same as indicating the proportion of a component based on the total weight of the coating layer in which it is present (as in current claim 1).

- Thus, on the basis of these unrelated passages, no conclusion can be drawn to the effect that the binder concentration of 0.5 to 5% by weight is based on the drug-containing layer.

Passage (iii) (i.e. page 5, paragraph 1) indicates the proportion of plasticiser as a weight percentage based on the weight of the rate-controlling polymer, which is yet another way of indicating the proportion of a coating component. It also makes technical sense in that case since the plasticiser is supposed to modify the properties of the rate-controlling polymer, but this has no relevance to the issue of the binder concentration.

2.8.3 Concerning point (c)

As explained in paragraph 3 on page 4, the binder is required in order to bind the drug to the inert core particles. Any suitable binder may be used, and the board agrees with the respondent's view that the concentration range of 0.5 to 5% by weight of binder mentioned in that context is simply a general indication or estimate, giving the skilled person a framework in which to operate.

On the basis of common general knowledge, the person skilled in the art would moreover be aware that:

- firstly, the higher the amount of drug, the more binder needed;
- secondly, the ratio of binder to drug should not be so high as to impair the immediate-release properties of the IR beads;
- thirdly, the coating formulation should not contain excessive amounts of liquid since removing the

liquid solvent medium requires energy (which is relevant for cost reasons).

The person skilled in the art would read the description in the light of this general knowledge.

- In view of the first two aspects, it is not realistic to combine the lower limit of the concentration range given for the binder with the maximum concentration of the drug (or vice versa), as suggested by the appellant. Rather, the person skilled in the art would combine a low drug concentration in the coating liquid with a low binder concentration, and match a high drug concentration with a high binder concentration.

- The appellant's calculation based on the assumption that the drug concentration could be as low as 1% by weight in the liquid coating formulation while the binder would be present at a concentration of 5% also appears unrealistic. In fact, the parent and divisional applications as filed do not specify a lower limit for the drug concentration in the liquid coating formulation. Since it can be "most preferably up to about 20% weight" (see page 4, line 28), it can be inferred that the drug concentration may be lower than 20%, but nothing in the vicinity of 1% is mentioned. The examples use drug concentrations in the coating formulation of at least 13% by weight (see examples 1, 3 and 6).

- In view of the second and third aspects mentioned above, the board is convinced that the person skilled in the art would choose a drug concentration considerably higher than 1% and would simply adapt and optimise the binder concentration to fulfil its function of binding the drug to the

particle surface without affecting the desired immediate-release properties.

For these reasons, the board disagrees with the appellant's argument that a binder concentration of 0.5 to 5 weight % in the liquid coating formulation in combination with a drug concentration of "up to 55 weight %" would not make technical sense.

2.8.4 Concerning point (d)

The concentration of binder used according to the examples was between 0.5 and 5% by weight in both the liquid coating formulation and the drug-containing coating layer, which is consistent with either interpretation.

Example 1
Drug: 200 g, binder: 10 g, liquid: 56.7 g
Percentage of binder
- in the coating formulation: 3.7% by weight
- in the drug-containing layer: 4.8% by weight

Example 3
Drug: 1 168.4 g, binder: 58.4 g, liquid: 7 536 g
Percentage of binder
- in the coating formulation: 0.7% by weight
- in the drug-containing layer: 4.8% by weight

Example 5
Drug: 11 700 g, binder: 500 g, liquid: unknown
Percentage of binder
- in the coating formulation: unknown
- in the drug-containing layer: 4.1% by weight

Example 6

Drug: 2 336.8 g, binder: 116.8 g, liquid: 14 072 g

Percentage of binder

- in the coating formulation: 0.7% by weight
- in the drug-containing layer: 4.8% by weight

2.9 For the reasons set out in points 2.2 to 2.8 above, claim 1 as granted does not meet the requirements of Articles 76(1) and 123(2) EPC.

2.10 The same reasoning and conclusion apply to claim 1 of each of auxiliary requests I and II.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated