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**Datasheet for the decision  
of 23 April 2012**

**Case Number:** T 2124/09 - 3.3.02

**Application Number:** 01977934.7

**Publication Number:** 1328251

**IPC:** A61K 9/00, A61K 31/4458,  
A61K 9/50

**Language of the proceedings:** EN

**Title of invention:**  
Methylphenidate modified release formulations

**Applicant:**  
Shire Pharmaceuticals Ireland Limited

**Headword:**  
Methylphenidate modified release formulations/SHIRE  
PHARMACEUTICALS IRELAND LTD.

**Relevant legal provisions:**  
EPC Art. 123(2), 56

**Keyword:**  
"Main request - allowability of amendments (no): unallowable  
generalisation"  
"Auxiliary request I - inventive step (no): obvious  
modification"

**Decisions cited:**  
T 0201/83, T 0714/00

**Catchword:**  
-



Case Number: T 2124/09 - 3.3.02

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.02  
of 23 April 2012

**Appellant:** Shire Pharmaceuticals Ireland Limited  
(Applicant) Riverwalk  
City West Business Campus  
Dublin 24 (IE)

**Representative:** Atkinson, Jonathan David Mark  
Harrison Goddard Foote  
Belgrave Hall  
Belgrave Street  
Leeds LS2 8DD (GB)

**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 24 July 2009  
refusing European patent application  
No. 01977934.7 pursuant to Article 97(2) EPC.

**Composition of the Board:**

**Chairman:** U. Oswald  
**Members:** A. Lindner  
L. Bühler

## Summary of Facts and Submissions

- I. European patent application No. 01 977 934.7 was refused by a decision of the examining division, pronounced on 6 July 2009 and dispatched on 24 July 2009 on the basis of Article 97(2) EPC, on the ground that the subject-matter claimed in the main request and in auxiliary request I did not involve an inventive step.
- II. The documents cited during the opposition and appeal proceedings included the following:
- (1) WO 00/35426
  - (8) S.C. Porter and C.H. Bruno: "Coating of pharmaceutical solid dosage forms", page 96, in "Pharmaceutical dosage forms: tablets", Lieberman, Lachman and Schwartz (eds.), 1990, Marcel Dekker, New York
- III. The examining division argued that the term "seal coat" was unclear and thus not suitable as a distinguishing feature over the prior art. Regarding inventive step, the examining division defined the problem to be solved vis-à-vis document (1), which constituted the closest prior art, as the provision of a delivery system with an alternative percentage of seal coat as compared to document (1). As the skilled person would regard the solution thereof in the form of a decrease in the amount of seal coat from 9.9% according to document (1) to 4% as claimed in the main request as an obvious modification, the requirements of Article 56 EPC had not been met. The examining division emphasised that formulation II of document (1) was characterised by a

bimodal release profile. Moreover, the examining division concluded that the fact that said formulation II, in contrast to the compositions according to the present invention, additionally contained a final pH-dependent Eudragit coating was of no consequence. Reference was made to figure 2 of the present application in this context, which depicted a square wave release profile. The examining division further concluded that even if the applicant's argument that the Eudragit coating of example 6B of document (1) was not considered to constitute a seal coat was accepted, the claimed subject-matter would still lack inventive step, as addition of a further seal coat comprising HPMC was already suggested in document (1) as an optional step.

The subject-matter of auxiliary request I also lacked inventive step, as the change concerning the IR/ER ratio from 33/65 according to document (1) to 30/70 as claimed in auxiliary request I also constituted an obvious modification for the skilled person.

- IV. The applicant (appellant) lodged an appeal against this decision.
  
- V. In the annex to the summons to oral proceedings issued by the board pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), the board in its preliminary opinion raised objections under Article 123(2) EPC in connection with the binder concentration of 0.5 to 5 wt.% introduced into claim 1 of the main request and of auxiliary request I.
  
- VI. At the oral proceedings, which were held on 23 April 2012, the appellant submitted a main request and an

auxiliary request I. The independent claim 1 of each request reads as follows:

*(i) Main request*

"1. Modified release methylphenidate 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 core particle layered with a water soluble film-forming composition containing methylphenidate and a binder at a concentration of 0.5 to 5 weight %, said layered IR particle further being coated with a seal coat in an amount up to 4% w/w to form an IR bead, 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."

*(ii) Auxiliary request I*

"1. Modified release methylphenidate 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 a water soluble film-forming composition containing methylphenidate and a binder at a concentration of 0.5 to 5 weight %, said layered IR particle further being

coated with a seal coat in an amount up to 4% w/w to form an IR bead, 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."

VII. The appellant essentially argued as follows:

Regarding the introduction of the binder concentration into claim 1 of the main request, reference was made to page 5 of the original application. Even if the concentration range of 0.5 to 5 weight % was disclosed in connection with sugar spheres, the skilled person knew that a wide variety of cores could be coated with such a binder concentration.

Document (1) was not pertinent for inventive step, as the ER beads disclosed therein did not comprise a seal coat. The term "seal coat" excluded functional coatings such as the ones used in document (1). Moreover, the release profiles of document (1), i.e. the "square waves" were completely different from the bimodal release profile of the formulations according to the present invention.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request, or alternatively, of the auxiliary request I, submitted during oral proceedings on 23 April 2012.

## Reasons for the decision

1. Admission of the main request and auxiliary request I

These requests were not filed until the oral proceedings before the board. Their admissibility is therefore at the board's discretion and depends upon the overall circumstances of the case under consideration (see Article 13 RPBA). The board notes that the amendments were made to overcome objections concerning Article 123(2) EPC. They were of a simple nature and did not complicate the proceedings. As a consequence, the board decided to admit these requests into the proceedings.

2. Main request - Article 123(2) EPC

As compared to claim 1 as originally filed, the modified release methylphenidate capsule drug delivery system according to claim 1 of the present main request comprises, among others, the additional feature that the IR bead is an inert core particle layered with a water soluble film-forming composition containing methylphenidate and a binder at a concentration of 0.5 to 5% by weight. The basis for this concentration range can be found in the penultimate paragraph on page 5 of the original application. However, the third sentence of said paragraph, in which said binder concentration is disclosed, cannot be read in isolation. When read in the whole context and in particular in conjunction with the preceding sentence, it turns out that the binder concentration of 0.5 to 5% by weight is linked to the presence of inert sugar spheres.

The appellant cited decisions T 0201/83 (OJ EPO 1984, 481) and T 0714/00 of 6 August 2002 in this context and argued that according to these decisions, an amendment of a concentration range in a claim for a mixture was allowable on the basis of a particular value described in a specific example, provided the skilled person could readily recognise this value as not so closely associated with the other features of the example as to determine the effect of that embodiment of the invention as a whole in a unique manner and to a significant degree. The board, however, notes that the core material has a significant influence on the amount of binder necessary for fastening the layer containing the methylphenidate onto the core particles. Extension of the binder concentration range, originally disclosed in conjunction with inert sugar beads, to any inert core particle is therefore not allowable. As a consequence, the requirements of Article 123(2) EPC are not met.

### 3. Auxiliary request I

#### 3.1 Amendments - Article 123(2) EPC

As compared to claim 1 of the main request, the core particles in claim 1 of auxiliary request I are now limited to inert sugar core particles. As a consequence, the objections raised in point 2 above in connection with claim 1 of the main request no longer apply. The requirements of Article 123(2) EPC are met.

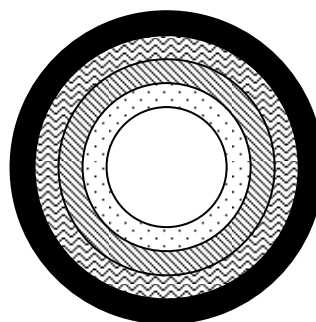
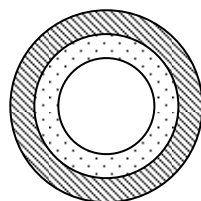
#### 3.2 Inventive step - Article 56 EPC



3.2.1 The present invention concerns the provision of multi-particulate methylphenidate containing dosage forms comprising both immediate release IR beads and extended release ER beads. Said dosage forms are supposed to guarantee a rapid onset of action provided by the IR beads, while the ER beads release the remainder of the total dose over an extended period of time, which eliminates the need to treat children with attention deficit disorder (ADD) or attention deficit disorder in conjunction with hyperactivity (ADHD) during school hours (see the second complete paragraph on page 2 of the original application). Figure 1 depicts the structure of the beads according to claim 1 of auxiliary request I:

IR bead

ER bead








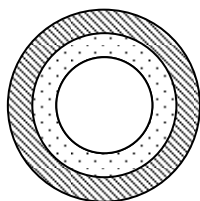
-  = inert sugar core particle,
-  = methylphenidate HCl (5-20% w/w)+ binder such as HPMC (0.5-5% w/w)
-  = seal coat (up to 4% w/w)
-  = dissolution rate controlling polymeric coating
-  = seal coat (up to 4% w/w).

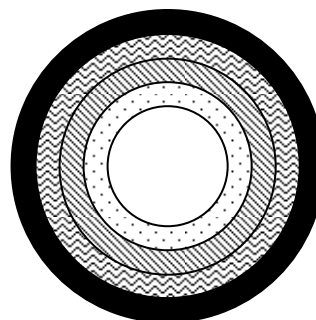
figure 1: IR and ER beads according to claim 1

3.2.2 Document (1), which constitutes the closest prior art, also concerns dosage forms comprising methylphenidate for treatment of ADHD (see page 4, 4th complete paragraph). The formulations according to document (1) allow a once-per-day administration, thus also eliminating the need to treat children during school hours (see page 4, paragraphs 1 to 3 from the bottom and page 5, 4th paragraph). Example 6B discloses capsules comprising the ER beads of example 5 and the IR beads of example 1 with a ratio of IR beads to ER beads of 35:65. The IR beads according to example 1 comprise sugar beads 14/18 (inert sugar core particle) coated with a layer comprising 15.0% of methylphenidate hydrochloride plus the binder Opadry clear (HPMC = hydroxypropylmethylcellulose), which in turn is coated with a further layer of Opadry clear. The ER beads (named EC-CR beads in example 5) as per document (1) consist of IR beads further coated with a layer comprising Eudragit® RS 30 D, triethylcitrate and talc and a further layer comprising Eudragit® L 30 D 55, triethylcitrate and talc (see figure 2 below).

IR bead



ER bead








-  = sugar bead 14/18
-  = methylphenindate HCl (15%)+  
Opadry clear YS-1-7006 (between 1 and 5%)
-  = Opadry clear (ca. 1%)
-  = Eudragit® RS 30 D + triethylcitrate + talc
-  = Eudragit® L 30 D 55 + triethylcitrate + talc  
(ca. 9%)

figure 2: IR and ER beads as per example 6B of  
document (1)

In view of the fact that Opadry clear is a preferred seal coat of the present invention (see page 3, lines 6-9 of the original application), the IR beads as per example 6B are identical to the IR beads of claim 1 of auxiliary request I. This fact was confirmed by the appellant.

Regarding the ER beads, it is noted that in both cases the IR beads are coated with two additional layers (see figures 1 and 2). The Eudragit® RS 30 D selected in document (1) is a copolymer of acrylic and methacrylic acid ester having quaternary ammonium groups and therefore constitutes a specific embodiment of the dissolution rate-controlling polymeric coating used in the corresponding layer of the invention defined in claim 1 of auxiliary request I. It is noted that example 5 of document (1) does not specifically disclose the concentration of the Eudragit® RS 30 D but only mentions "Methylphenidate CR beads" (see Table 7). However, said "Methylphenidate CR beads", which are described in examples 2 to 4, comprise 8.63% (example 2), 5.8% (example 3) and 3.9% (example 4),

respectively, and therefore overlap with the concentration range as claimed (5 to 25%).

In connection with the last layer, it has to be evaluated whether the Eudragit® L 30 D 55, which is an anionic polymer with methacrylic acid as a functional group and therefore belongs to the functional coatings, is encompassed by the functional term "seal coat", which defines the last layer of the ER beads according to claim 1 of auxiliary request I. According to the appellant, seal coatings have the function to improve appearance and flowability of the beads, to preserve the texture of the underlying particles and to prevent sticking without changing the release rate, thus excluding functional coatings. However, the board concurs with the examining division that "seal coat" does not have a clearly defined meaning in the art. The appellant cited document (8) in this context. Document (8) (see paragraph "Types of film coatings used") essentially says that there are functional and non-functional coatings and that non-functional coatings are typically reserved for situations in which it is necessary to improve product appearance, ease of swallowing, product stability and taste-masking and that functional coatings are used when drug release characteristics need to be modified. However, this passage does not mention seal coats at all and is therefore irrelevant. In the statement of the grounds of appeal (see second complete paragraph on page 3), the appellant also made reference to Dr. Tenjarla's submissions at the oral proceedings before the examining division, according to which the expert in formulation chemistry knows exactly what "seal coat" implies. However, if said term is as well defined as

asserted by the appellant, there must be documentary evidence in the prior art in support of this assertion. In the absence of such evidence, the board concludes that the term "seal coat" simply defines the outermost layer of the drug vehicle, which may be of the functional or nonfunctional type. As a consequence, the Eudragit<sup>®</sup> L 30 D 55 coating of example 6B of document (1) (see figure 2 above) is encompassed by the functional term "seal coat".

This means that the concentration of the outermost layer of the ER beads (ca. 9% in document (1) vs. up to 4% w/w in present claim 1) constitutes the only distinguishing feature of present claim 1 over example 6B of document (1).

3.2.3 In the light of these findings, the problem to be solved can only be defined as the provision of a further composition for a once-per-day administration of methylphenidate to children suffering from ADD or AHDD.

The solution proposed by the invention defined in claim 1 of auxiliary request I consists of the reduction of the concentration of the outermost layer of the ER beads from about 9% to up to 4% w/w. In view of the examples in the original application, the board is convinced that this problem has been plausibly solved.

As for whether reduction of the concentration of the outermost layer of the ER beads is an obvious step for the skilled person, the board wishes to emphasise that the teaching of document (1) is not confined to a

specific concentration of about 9%. Reference is made to page 21 (see third and second sentence from the bottom of the first paragraph), which indicates that an enteric coating comprising Eudragit® L 30 D 55, triethyl citrate and talc is applied onto the CR beads to convert the same into enteric coated CR (ECCR) beads. This instruction is not accompanied by any provisions regarding the amounts to be used. The board concludes therefrom that the skilled person is not limited to the concentration of about 9% as per example 6B, but could vary these amounts. As there is no evidence that the selection of up to 4% w/w for the concentration of the outermost layer of the ER beads is accompanied by any particular effects, the subject-matter of claim 1 of auxiliary request I does not involve an inventive step. The requirements of Article 56 EPC are therefore not met.

#### 3.2.4 Additional arguments of the appellant

3.2.4.1 Making reference to the fourth paragraph on page 5 of document (1), which mentions the so called "square wave" profile, which is characterised by a rapid onset and a rapid offset of effect, the appellant argued that such release profiles were quite distinct from the bimodal release profiles of the present invention.

This argument cannot succeed, as document (1) also discloses bimodal release rates as a preferred embodiment. Reference is made to the third paragraph on page 3 and to figure 5 (see in particular formulation 2 (fed)), where a bimodal release rate is obtained with a composition corresponding to example 6B. On the other hand, the present invention includes formulations with

a non-bimodal release profile, as is shown in figure 2 of the present application (see in particular the release profile of MR 40:60 20 mg, which is characterised by a rapid onset followed by a small plateau and a slow offset). As a consequence, the board concludes that the release profiles of the present invention are not distinguished from those of document (1).

3.2.4.2 An amount of seal coating exceeding 4% will lead to a mottled and uneven coating resulting in poor appearance, tackiness and incomplete protection against the ingress of moisture.

In the absence of any evidence, this argument is not convincing. It is quite possible that higher amounts of coating material require an adjustment of the conditions applied during the coating process. However, this adjustment is known to the skilled person and does therefore not require inventive skill. As a consequence, this argument does not stand up to scrutiny either.

**Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairman

N. Maslin

U. Oswald