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Datasheet for the decision of 28 April 2011

Case Number: T 0241/08 - 3.3.02

Application Number: 01908465.6

Publication Number: 1257260

IPC: A61K 9/72

Language of the proceedings: EN

Title of invention:
Powder formulation for inhalation

Patentee:
Rijksuniversiteit te Groningen

Opponent:
BOEHRINGER INGELHEIM Pharma GmbH & Co KG

Headword:
Powder formulation for inhalation/RIJKSUNIVERSITEIT

Relevant legal provisions:
EPC Art. 83
RPBA Art 15

Relevant legal provisions (EPC 1973):
-

Keyword:
"Decision taken in the absence of the duly invited parties (yes)"
Non-medical use claims: sufficiency of disclosure (no)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0241/08 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 28 April 2011

Appellant: (Opponent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 31 October 2007 concerning maintenance of European patent No. 1257260 in amended form.

Composition of the Board:

Chairman: U. Oswald
Members: M. C. Ortega Plaza
C.-P. Brandt

Summary of Facts and Submissions

I. European patent No. 1 257 260, based on international application No. WO 01/60341, was granted on the basis of twelve claims.

Claim 1 as granted reads as follows:

> **1.** Powder formulation for administration by inhalation comprising an active substance and a pharmaceutically acceptable excipient, which composition has the form of a physical mixture and comprises from 5 to 25 wt.% of the excipient, and wherein the active substance has a particle size distribution of from 0.5 to 10 μm, and wherein the excipient has a particle size distribution of from 15 to 500 μm, the particle size distribution being defined as to indicate that at least 50 wt.% of the specific component has a size within the specified range.

Independent claims 10, 11 and 12 as granted read as follows:

> **10.** Dry powder inhaler having a cyclone chamber operatively connected to a dosage compartment containing a powder formulation according to any of the preceding claims.
>
> **11.** Dosage cartridge for use in a dry powder inhaler according to claim 10, containing one or more dosage units of a powder formulation according to any of the claims 1-9.
>
> **12.** Use of a pharmaceutically acceptable excipient having a particle size distribution of from 15 to 500 μm in a powder formulation for administration by inhalation for preventing accumulation of active substance in the cyclone chamber of a dry powder inhaler according to claim 10.

II. Opposition was filed and revocation of the patent in its entirety was requested pursuant to Article 100(a) EPC for lack of novelty and lack of inventive step and Article 100(b) EPC for lack of sufficiency of disclosure.

III. The present appeal lies from a decision of the opposition division maintaining the patent in amended form (Articles 102(3) and 106(3) EPC 1973) on the basis of the set of claims (sole request) filed at the oral proceedings before the opposition division.

IV. The following documents cited during the proceedings are relevant for the present decision:

E1 WO-A-0016745
E2 WO-A-9703649
E10 US-A-5301666
E11 WO-A-9826827

V. The opposition division considered that the main and sole request met the requirements of Article 123(2) and (3) EPC.

The opposition division was of the opinion that the subject-matter of claim 1 was novel vis-à-vis document E1 in view of the fact that document E1 did not disclose "the use of [a] dry powder inhaler comprising a cyclone chamber connected to a dosage compartment". Moreover, none of the cited prior-art documents disclosed the combination of the particular powder formulation in the particular dry powder inhaler claimed. Thus, the subject-matter of independent claims 1 and 10 was novel.

Additionally, in the opposition division's view the subject-matter claimed involved an inventive step (Article 56 EPC). The opposition division considered document E2 to represent the closest prior art and defined the problem to be solved as the provision of powders with reduced adhesion for use in dry powder inhalers. The opposition division justified the presence of an inventive step for the subject-matter in independent claims 1 and 10 on the grounds that there was no incentive in the prior art to incorporate the

aerosol compositions disclosed in document (E2) in the aerosol devices of documents (E10) or (E11).

Furthermore, the opposition division was of the opinion that the requirements of Article 83 EPC were met since the example provided the skilled person with sufficient technical information to reproduce the invention over the whole breadth of the claims.

VI. Claim 1 of the main request maintained by the opposition division reads as follows:

1. Dry powder inhaler having a cyclone chamber operatively connected to a dosage compartment containing a powder formulation for administration by inhalation comprising an active substance and a pharmaceutically acceptable excipient, which composition has the form of a physical mixture and comprises from 5 to 25 wt.% of the excipient, and wherein the active substance has a particle size distribution of from 0.5 to 10 µm, and wherein the excipient has a particle size distribution of from 15 to 500 µm, the particle size distribution being defined as to indicate that at least 50 wt.% of the specific component has a size within the specified range.

Independent claim 10 of the main request maintained by the opposition division reads as follows:

"10. Use of a pharmaceutically acceptable excipient having a particle size distribution of from 15 to 500 µm in a powder formulation for preventing accumulation of active substance in the cyclone chamber of a dry powder inhaler according to any of the previous claims".

VII. The opponent (appellant) filed an appeal against said decision and requested that the first-instance decision be set aside and the patent be revoked in its entirety. The appellant contested the maintenance of the patent

and raised objections on the grounds of lack of novelty, lack of inventive step and insufficiency of disclosure. It also filed further documents.

VIII. The respondent (patent proprietor) filed with its response dated 10 July 2008 counter-arguments to the grounds of appeal. It also filed three auxiliary requests.

Claim 1 of the first auxiliary request reads as follows:

1. Dry powder inhaler having a cyclone chamber operatively connected to a dosage compartment containing a powder formulation for administration by inhalation comprising an active substance and a pharmaceutically acceptable excipient, which composition has the form of a physical mixture and comprises from 5 to 25 wt.% of the excipient, and wherein the active substance has a particle size distribution of from 0.5 to 10 μm, and wherein the excipient has a particle size distribution of from 15 to 500 μm, the particle size distribution being defined as to indicate that at least 75 wt.% of the specific component has a size within the specified range.

Independent claim 10 of the first auxiliary request reads as follows:

10. Use of a pharmaceutically acceptable excipient having a particle size distribution of from 15 to 500 μm in a powder formulation for preventing accumulation of active substance in the cyclone chamber of a dry powder inhaler according to any of the previous claims.

Claim 1 of the second auxiliary request reads as follows:

1. Dry powder inhaler having a cyclone chamber operatively connected to a dosage compartment containing a powder formulation for administration by inhalation comprising colistin and a pharmaceutically acceptable excipient, which composition has the form of a physical mixture and comprises from 5 to 25 wt.% of the excipient, and wherein the active substance has a particle size distribution of from 0.5 to 10 µm, and wherein the excipient has a particle size distribution of from 15 to 500 µm, the particle size distribution being defined as to indicate that at least 50 wt.% of the specific component has a size within the specified range.

Independent claim 8 of the second auxiliary request reads as follows:

"8. Use of a pharmaceutically acceptable excipient having a particle size distribution of from 15 to 500 µm in a powder formulation for preventing accumulation of colistin in the cyclone chamber of a dry powder inhaler according to any of the previous claims".

Claim 1 of the third auxiliary request reads as follows:

1. Use of a pharmaceutically acceptable excipient having a particle size distribution of from 15 to 500 µm in a powder formulation for administration by inhalation for preventing accumulation of active substance in the cyclone chamber of a dry powder inhaler, wherein

- the powder formulation comprises an active substance and the pharmaceutically acceptable excipient and has the form of a physical mixture, and comprises from 5 to 25 wt.% of the excipient, and wherein the active substance has a particle size distribution of from 0.5 to 10 µm;
- the dry powder inhaler has a cyclone chamber operatively connected to a dosage compartment containing a powder formulation for administration by inhalation; and
- the particle size distribution is defined as to indicate that at least 50 wt.% of the specific component has a size within the specified range.

IX. A communication from the board pursuant to Article 15(1) RPBA was sent to the parties as an annex to the summons to oral proceedings. In said communication the board drew the parties' attention *inter alia* to the fact that the subject-matter of the independent claims required a separate analysis in relation to novelty and inventive step. Moreover, in said communication the board expressed the preliminary opinion that an inspection of the priority document of the patent in suit had shown that the priority date was only partially valid for the subject-matter claimed. Therefore, document (E1) was part of the state of the art within the meaning of Article 54(2) EPC for those parts which were not entitled to the priority date as the effective filing date (Article 89 EPC 1973). Document (E1) was part of the state of the art within the meaning of Article 54(3) EPC for those parts entitled to the priority date and for all contracting states except Turkey.

Furthermore, the board stressed the relevance of a separate assessment in relation to the requirements of Article 83 EPC for the subject-matter claimed in the use claims and expressed serious doubts in respect of the use in the breadth claimed.

X. With a letter dated 23 February 2011 the respondent announced that it would not attend the oral proceedings scheduled for 28 April 2011. However, the respondent did not file any substantive comments in reply to the board's communication sent as an annex to the summons.

XI. With a letter dated 13 April 2011 the appellant announced that it "will not be able to participate in the oral proceedings scheduled for April 28, 2011".

XII. The board sent a communication on 19 April 2011 informing the parties that the oral proceedings scheduled for 28 April 2011 were maintained.

XIII. Oral proceedings took place on 28 April 2011 in the absence of both parties.

XIV. In the course of the appeal proceedings the appellant only filed substantive arguments together with its grounds of appeal. The appellant's arguments, as far as they are relevant for the present decision, may be summarised as follows:

The patent should be revoked in its entirety since the subject-matter claimed lacked novelty and inventive step. Moreover, the claimed "invention" was not disclosed in a sufficient and complete manner.

As regards the lack of disclosure, the appellant pointed to the following. The powder formulation for inhalation as defined in the claims comprised an active substance and a pharmaceutically acceptable ingredient with particle sizes defined as particle size distribution ranges, and with a content of excipient in the formulation of 5 to 25 wt%. Said powder formulation was contained in a dry powder inhaler merely characterised by the fact that it had a cyclone chamber operatively connected to a dosage compartment. The powder formulation was further defined in the claims as being in the form of a "physical mixture". Thus, there was a lack of disclosure in the patent in suit for determining when a mixture was to be considered as a "physical mixture". Moreover, if this expression was to

be taken as an antonym of an "adhesive mixture", then the patent in suit did not disclose how to differentiate between a "physical mixture" and an "adhesive mixture". It inevitably followed from the laws of nature that any powder mixture made out of an active ingredient and an excipient was subject to adhesive forces. The patent in suit gave no guidance as how to measure the intensity of the adhesive forces.

The patent in suit disclosed one single specific example which concerned the active substance colistin and the excipient lactose. This specific example did not provide the skilled person with sufficient technical information for reproducing the "invention" over the whole breadth of the claims.

Moreover, the dry powder inhaler was characterised by the fact that it had a "cyclone chamber" which was not further specified in the claims. Thus, the "cyclone chamber" could be understood as any chamber in which an air flow could be generated which was rotating, turbulent and had a tangent displacement.

XV. In the course of the appeal proceedings the respondent only filed substantive arguments together with its reply to the grounds of appeal. The respondent's arguments, as far as they are relevant for the present decision, may be summarised as follows.

As regards the objection of lack of sufficiency of disclosure, the respondent argued that the objections raised by the appellant were a clarity issue and that clarity was not a ground for opposition. Moreover, the difference between physical and adhesive mixtures was

not obscure but well-known in the field. The objection regarding the breadth of the definition of the expression "cyclone chamber" was also a clarity issue. Moreover, it was established case law that an invention was to be considered as sufficiently disclosed if at least one way of performing the invention was clearly indicated, enabling the person skilled in the art to carry out the invention (e.g. T 292/85, OJ EPO 1989, 275 and T 81/87, OJ EPO 1990, 250). Thus, the patent fulfilled said condition by providing a detailed example of how the person skilled in the art could carry out the invention. In the example it was specifically stated the a physical mixture was obtained. Moreover, the example referred to the "cyclone disintegration principle test inhaler", which was shown in Figure 1 and explained in paragraphs [0048] and [0049] of the patent in suit.

It was also established case law that the disclosure of one way of performing the invention was only sufficient if it allowed the invention to be performed over the whole range claimed (T 484/92 of 30 December 1993 and T 923/92, OJ EPO 1996, 564). However, this condition was also fulfilled since in order to obtain a physical mixture it was essential to have a relatively low amount of 5-20 wt% of excipient. The presence of a relatively large amount of active substance resulted in less interactions between the active substance and the excipient, such that an adhesive mixture was not formed. The example further taught how to use low intensity mixing conditions (tumbling mixer, relatively short mixing time of 10 min, 90 rpm). Furthermore, the general teaching about the cyclone chamber in paragraphs [0048] and [0049] of the patent in suit

provided the skilled person with sufficient information to prepare suitable variants of the test inhaler depicted in Figure 1. The skilled person would be able to carry out the invention over the whole breadth of the claims through the patent specification and on the basis of common general knowledge. As long as there were no concrete grounds for believing that the invention could not be carried out over the whole range claimed, there was no reason for not allowing the claims (T 242/92 and T 484/92). It was also to be noted that the appellant bore the burden of providing that the invention could not be carried out over the whole range claimed (T 417/91 of 23 August 1994, T 456/91 of 3 November 1993 and T 548/91 of 7 February 1994).

XVI. The appellant (opponent) requested that the decision under appeal be set aside and the patent be revoked in its entirety.

The respondent (patent proprietor) requested that the appeal be dismissed or, in the alternative, that the patent be maintained in amended form on the basis of one of the auxiliary requests 1 to 3 filed with the letter of 10 July 2008.

Reasons for the Decision

1. *Formal matters*

1.1 The appeal is admissible.

1.2 Both parties had requested in writing that oral proceedings be held under Article 116 EPC. The board

summoned the parties to oral proceedings with the intention of arriving at a final decision.

Moreover, as becomes evident from point IX of the Facts and Submissions, the board sent, as an annex to the summons, a detailed communication pointing to essential aspects for discussion. In particular, the board pointed to some of the weaknesses of the broadly defined principle underlying the use claim.

The respondent chose not to file any comments in reply to the board's communication, although it was evident from its tenor that, as the facts on file stood, the board was disinclined to maintain the patent on the basis of the requests on file.

The duly summoned parties chose not to attend oral proceedings and announced their intention not to attend the oral proceedings in writing. Moreover, they did not further react to the board's communication in which they were informed that the oral proceedings were maintained.

Thus, the board was in a position to decide at the conclusion of the oral proceedings, since the case was ready for decision (Article 15(5) and (6) RPBA) and the voluntary absence of the parties was not a reason for delaying the decision (Article 15(3) RPBA).

2. *Main request*

2.1 *Sufficiency of disclosure*

Article 100(b) EPC is a ground of opposition within the framework of the present appeal. The ground pursuant to Article 100(b) EPC precludes maintenance of a patent when it does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

It has to be recalled that the content of the whole patent, including the description and the examples, has to be investigated by the skilled person in the light of the general common knowledge of the technical field involved and that it is the claimed "invention" which has to be assessed in respect of sufficiency of disclosure. The general legal principle is that the claims define the matter for which protection is sought and the examples illustrate specific ways of performing the invention.

As for the amount of technical detail needed for a sufficient disclosure, this is a matter which depends on an assessment of the facts of each particular case, such as the character of the technical field and the actual technical detail disclosed.

The sets of claims of the main request and of the first and second auxiliary requests contain two different kinds of independent claims: a product claim directed to a dry powder inhaler and a use claim directed to a "non-medical use". The third auxiliary request only contains claims directed to a use.

The "invention" claimed in use claim 10 of the main request is based on an alleged new and inventive non-medical use, namely to **prevent accumulation of active substance in the cyclone chamber of a dry powder inhaler** by using a pharmaceutically acceptable excipient having a particle size distribution of from 15 to 500 µm.

Neither the nature of the active substance nor the nature of the excipient are defined in the use claim of the main request. As regards the dry powder inhaler, claim 10 of the main request contains a reference to "any of the previous claims". Claim 1 relates to a dry powder inhaler, but the only definition of the dry powder inhaler in claim 1 is that it has a "cyclone chamber operatively connected to a dosage compartment containing a powder formulation for administration by inhalation".

The dimensions of the cyclone chamber are not specified in the claims, nor is there any mention of the air flow rate.

Thus, the "invention" claimed in claim 10 of the main request relates to the general principle that any pharmaceutically acceptable excipient suitable for being used in a powder formulation for inhalation which is to be administered by means of any dry powder inhaler having a cyclone chamber (the only condition being that the cyclone chamber is operatively connected to a dosage compartment) is capable of preventing accumulation (in the cyclone chamber) of any active substance suitable for being administered by inhalation

owing to the fact that it has **a particle size distribution of from 15 to 500 µm**.

Paragraph [0037] of the patent in suit makes it clear that "the excipient has a particle size distribution chosen such that **the particles are larger** than the effective cut-off diameter of the cyclone, which depends primarily on the flow rate and the dimensions of the cyclone chamber, and secondly on the **aerodynamic particle properties** (**shape and density**)" (emphasis added). The use of the excipient claimed in claim 10 is, however, much broader, since there is no mention of any particular shape or density constraint for the particles of excipient for which the use is claimed and the dimension of the cyclone chamber and the flow rate are also open-ended in the claims.

Paragraph [0037] of the patent in suit further states: "Typically, it is preferred that the excipient's particle size distribution has a lower limit of at least 15 µm, more preferably at least 25 µm. The upper limit of the particle size distribution of the excipient will mostly **be determined by the dimensions of the dose compartment in the DPI**. **Compared to those dimensions the particles should be relatively small**. Further, the particles **should not be so large that segregation of the physical mixture** and **disturbance of the flow pattern inside the cyclone chamber may occur**. It is further to be noted that variations in weighed powder quantities, e.g. in the dose compartments, will increase with increasing excipient particle size. Accordingly, the excipient has a particle size distribution below 500 µm" (emphasis added).

However, there is no guidance in paragraph [0037] on how to achieve the technical effect underlying the use, i.e. how to avoid accumulation of the active substance in a cyclone chamber of a dry powder inhaler by using any pharmaceutically acceptable excipient with a particle size distribution of from **15** to 500 µm, for an active substance with a particle size distribution of from 0.5 to **10 µm** (see claim 1). The general knowledge of the skilled person does not suffice to fill the gap in technical information, and there is no indication in the patent in suit of the aerodynamic behaviour required by the excipient particles (expressed in terms of aerodynamic diameter or in terms of shape and density) in comparison to that of the active substance particles.

Even though claim 1 mentions that, for each of the two stated components in the dry powder formulation, at least 50 wt% of the specific component has a size within the specified range, this definition does not serve to delimit the small size fraction of the excipient in the absence of any shape and density requirements. In fact, the definitions for the excipient to be used according to the claims do not exclude the possibility of a dual size distribution curve over the broad particle size range of the excipient.

Moreover, the dry powder inhaler shown in the figures does not serve to delimit the claims which are broad but technically meaningful. Paragraphs [0042] to [0053] merely explain the drawings. Additionally, paragraph [0049] states: "As discussed above, the **cyclone action of the cyclone chamber** 11 **and the cyclone chamber exit**

6 **provide for a separation of the particles of the physical powder mixture**, such that the **small active substance particles exit** the channel 14 in a powder flow P', **while the large excipient particles remain**, at least for a substantial portion in the cyclone chamber 11 or the cyclone chamber outlet 6 during inhalation" (emphasis added).

Thus, paragraph [0049] makes it clear that the size difference between the active substance particles and the excipient particles is essential for the active substance particles leaving the powder inhaler (i.e. for not being left behind in the cyclone chamber together with the excipient, accumulated or not). However, there is no guidance in the patent in suit as regards how much difference in particle size is required to achieve the intended effect (e.g. in terms of specific small size fraction requirements for the excipient particle size distribution range).

Even if assuming in the respondent's favour that the only example in the patent in suit contains detailed information allowing the skilled person to reproduce the particular dry powder formulation containing colistin as an active substance and a particular lactose as an excipient, as well as the administration of this particular dry powder formulation by means of a dry powder inhaler having a cyclone chamber, a close inspection of the example shows the following. The excipient used in the dry powder formulation is a **lactose size fraction of 106-105 µm**. This fraction was prepared by **subsequent vibratory sieving** (20 minutes) and **air jet sieving** (10 minutes) of small quantities of a certain commercially available lactose excipient. In

other words, the steps undertaken in the specific example confirm that great care has to be given to avoid a certain (unknown) content of small size fractions for the excipient, and that there must be a significant difference between the particle size of excipient and that of the active substance in order that the effect claimed can be achieved.

Thus, there is a gap between the specific teaching in the specific example and the general principle claimed in the use claim, reflecting an essential lack of technical information, which cannot be filled by the skilled person making use of the general knowledge but without showing inventive skills.

Although the appellant was aware that the board had serious doubts about the sufficiency of disclosure of the use claimed, it chose not to provide any arguments in this respect. Again, there is an essential difference between the assessment of sufficiency of disclosure for the dry powder inhaler claimed in the product claims (such powder inhalers are generally known) and the "non-medical" use claimed in the use claim, which itself requires sufficient disclosure to enable the technical effect to be attained over the whole range claimed.

Summarising, after due consideration of the contents of the patent in suit and in the absence of any arguments in favour of the sufficiency of disclosure for the use claimed, the board concludes that the main request fails for lack of sufficiency of disclosure (Article 83 EPC).

3. *First auxiliary request*

3.1 The analysis mentioned above for use claim 10 of the main request applies *mutatis mutandis* to the use claimed in claim 10 of the first auxiliary request. The only difference is that the dry powder referred to, which is contained in the dry powder inhaler according to claim 1, has a particle size distribution of "at least 75 wt%" instead of "at least 50 wt%". However, in view of the lack of any definition in relation to the content in small size particle fractions for the excipient, and to the shape and density of the particles of the excipient, this delimitation alone does not change the validity of the assessment to be made which is analogous to that of the main request.

Therefore, the first auxiliary request also fails for lack of sufficiency of disclosure.

4. Second auxiliary request

4.1 The assessment made for claim 10 of the main request applies *mutatis mutandis* to claim 8 of the second auxiliary request. The only difference is that the active substance has been specified to be colistin, which is the active substance in the example. However, in the absence of any further specification in the claim as to the requirements to be fulfilled by the excipient, the analysis made in the main request applies in an analogous manner.

Therefore, the second auxiliary request also fails for lack of sufficiency of disclosure.

4.2 *Third auxiliary request*

Claim 1 of the third auxiliary request essentially relates to the use in claim 10 of the main request in which the definition for the dry powder inhaler appearing in claim 1 of the main request has been incorporated. Thus, the analysis made above in the main request directly applies.

Therefore, the third auxiliary request also fails for lack of sufficiency of disclosure.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The European patent No. 1257260 is revoked.

The Registrar: The Chairman:

N. Maslin U. Oswald