

**Internal distribution code:**

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

**Datasheet for the decision  
of 19 March 2019**

**Case Number:** T 0476/16 - 3.3.07

**Application Number:** 02712031.0

**Publication Number:** 1359902

**IPC:** A61K9/14, A61K9/72, A61K31/565,  
A61K31/167

**Language of the proceedings:** EN

**Title of invention:**  
BIMODAL DRY POWDER FORMULATION FOR INHALATION

**Patent Proprietor:**  
Innovata Biomed Limited

**Opponent:**  
NORTON HEALTHCARE LIMITED

**Headword:**  
Bimodal dry powder/ INNOVATA

**Relevant legal provisions:**  
EPC Art. 56

**Keyword:**  
Inventive step - (no)



**Beschwerdekammern**  
**Boards of Appeal**  
**Chambres de recours**

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

Case Number: T 0476/16 - 3.3.07

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.07**  
**of 19 March 2019**

**Appellant:** NORTON HEALTHCARE LIMITED  
(Opponent) Regent House  
5-7 Broadhurst Gardens  
Swiss Cottage  
London NW6 3RZ (GB)

**Representative:** Elkington & Fife LLP  
Prospect House  
8 Pembroke Road  
Sevenoaks, Kent TN13 1XR (GB)

**Respondent:** Innovata Biomed Limited  
(Patent Proprietor) 37 Queen Street  
Edinburgh EH2 1JX (GB)

**Representative:** Adamson Jones  
BioCity Nottingham  
Pennyfoot Street  
Nottingham NG1 1GF (GB)

**Decision under appeal:** **Interlocutory decision of the Opposition  
Division of the European Patent Office posted on  
15 December 2015 concerning maintenance of the  
European Patent No. 1359902 in amended form.**

**Composition of the Board:**

**Chairman** J. Riolo  
**Members:** A. Usuelli  
Y. Podbielski

## Summary of Facts and Submissions

- I. European Patent 1 359 902 was opposed on the grounds that its subject-matter lacked novelty and inventive step, was not sufficiently disclosed and extended beyond the content of the application as filed. By decision issued on 11 June 2010 the opposition division revoked the patent since it considered that the requests on file did not comply with the requirements of Article 123(2) EPC (main request and auxiliary requests 2, 3 and 5) or 123(3) EPC (auxiliary requests 1 and 4).

The decision of the opposition division was appealed by the patent proprietor (case T 1664/10). The competent board decided that the set of claims according to the first auxiliary request filed with the statement setting out the grounds of appeal met the requirements of Article 123(2) and (3) EPC and remitted the case to the opposition division for further prosecution.

- II. The present appeal of the opponent (appellant) lies from the 2nd decision of the opposition division according to which the claims of the main request met the requirements of the Convention. The decision announced during the oral proceedings held on 10 November 2015 was based on the main request filed on 7 October 2015.

Claim 1 of this request read as follows:

"1. A bimodal pharmaceutical composition comprising effective amounts of (i) a particulate coarse active ingredient and (ii) a particulate fine active ingredient, characterised in that the coarse ingredient possesses a greater mass median aerodynamic diameter

(MMAD) than the fine ingredient, wherein the aerodynamic particle size of at least 50% w/w of the particles of the coarse active ingredient is from 4 to 12  $\mu\text{m}$  and the aerodynamic particle size of at least 50% w/w of the particles of the fine active ingredient is from 1 to 4  $\mu\text{m}$ , and wherein the coarse ingredient comprises an agent which is active in the central/upper airways of a patient."

III. The following documents were among those cited during the first-instance proceedings:

D5: Pharmaceutical inhalation aerosol technology, pages 61-82 "Targeting by Deposition", 1992

D7: WO 96/19968

D8: US 5,192,528

D13: American Journal of Respiratory and Critical Care Medicine, 172, 2005, 656-657

The opposition division held that the main request was sufficiently disclosed and met the requirement of novelty. As to inventive step, document D7 was regarded as the closest prior art. The subject-matter of claim 1 differed from the disclosure of D7 in that the coarse ingredient possessed a mass median aerodynamic diameter greater than the fine ingredient and in the features defining the aerodynamic particle size of the ingredients. The technical problem was the provision of an alternative formulation for inhalation. The skilled person would not have arrived at the subject-matter of claim 1 by combining the teachings of D7 and of the documents considered by the opponent. Hence, the main request met the requirements of Article 56 EPC.

IV. With the statement setting out the grounds of appeal filed on 25 April 2016 the appellant requested that the

decision under appeal be set aside and the patent be revoked. It furthermore submitted the following documents:

D17: Journal of Aerosol Medicine 1999, 12(4), 275-284

D18: Respiratory Care, 2000, 45(6), 597-608

- V. The patent-proprietor (hereinafter: the respondent) replied to the appeal of the opponent by letter of 6 September 2016. It requested to dismiss the appeal or alternatively to maintain the patent on the basis of auxiliary request 1 submitted during the opposition proceedings on 7 October 2015.

Claim 1 of auxiliary request 1 read as follows:

"1. A bimodal pharmaceutical composition suitable for the treatment of respiratory disorders and comprising effective amounts of (i) a particulate coarse active ingredient that comprises a bronchodilator and (ii) a particulate fine active ingredient that comprises a corticosteroid, characterised in that the coarse ingredient possesses a greater mass median aerodynamic diameter (MMAD) than the fine ingredient, wherein the aerodynamic particle size of at least 50% w/w of the particles of the coarse active ingredient is from 4 to 12  $\mu\text{m}$  and the aerodynamic particle size of at least 50% w/w of the particles of the fine active ingredient is from 1 to 4  $\mu\text{m}$ , and wherein the coarse ingredient comprises an agent which is active in the central/upper airways of a patient."

The following document was submitted by the respondent with the reply to the appeal:

D20: Summary of published MMAD data

- VI. In a communication pursuant to Article 15(1) RPBA issued on 17 December 2018 the Board expressed the opinion that neither the main request nor auxiliary request 1 met the requirements of Article 56 EPC starting from D7 as the closest prior art and considering the teaching derivable from D5, D8 and D17.
- VII. Oral proceedings took place as scheduled on 19 March 2019.
- VIII. The appellant's arguments on inventive step can be summarised as follows:

The compositions defined in claim 1 of the main request differed from those disclosed in D7 in that the two medicaments had different particle size, with those sizes being defined as 4 to 12  $\mu\text{m}$  for the coarse particles and 1 to 4  $\mu\text{m}$  for the fine ones. The data disclosed in D13 could not be used to establish an improvement since there was no comparison with the compositions of D7. Moreover, D13 referred only to monodisperse aerosol compositions whereas claim 1 covered polydisperse formulations as well. The technical problem was the provision of an alternative composition. D7 did not indicate that the two active ingredients had to have the same particle size. Several prior art documents, such as D5, D8, D17 and D18 showed that it was known to target different areas of the lung by changing the particle size of the active ingredient. It was therefore obvious to the skilled person to choose different particle sizes for different classes of active ingredients. The fact of including in the compositions coarse particles of large size did not justify the presence of an inventive activity as argued by the respondent. Indeed, there was no prejudice in the art against using active ingredients with a

particle size in the range of 4 to 12  $\mu\text{m}$ . Hence, claim 1 of the main request did not comply with the requirements of Article 56 EPC. The same considerations applied to auxiliary request 1.

IX. The respondent's arguments on inventive step can be summarised as follows:

The compositions claimed in the main request and in auxiliary request 1 differed from those disclosed in D7 in that the two active ingredients had a different particle size. The particle size of the coarse ingredient, namely 4 to 12  $\mu\text{m}$ , was not suggested in any of the prior art documents. Thus, the subject-matter of claim 1 was inventive already for the reason of containing particles of that size. The post-published document D13 showed that albuterol of large particle size provided better results in terms of bronchodilation than albuterol of small particle size. Although this document referred to a study in which only monodisperse compositions were tested, it could be assumed that the results could be extrapolated also to polydisperse compositions. The objective technical problem was therefore the provision of an improved formulation for inhalation. The documents considered by the appellant in combination with D7 described the correlation between particle size and site of particle deposition in the lung. However, all these documents suggested using active ingredients of very small particle size. D20 showed that several products on the market contained an active ingredient of small particle size. The conventional wisdom at the relevant time was that it was necessary to produce particles of a small size to achieve the desired effect. Hence, the skilled person would not have considered to prepare a composition containing an active ingredient having a

particle size in the range of 4 to 12  $\mu\text{m}$ . Therefore, the requests on file met the requirement of inventive step.

- X. The appellant requested that the decision under appeal be set aside and the patent be revoked.
- XI. The respondent requested that the appeal be dismissed (main request) or, as an auxiliary measure, that the patent be maintained on the basis of the auxiliary request filed on 7 October 2015.

## **Reasons for the Decision**

### Main request

- 1. Inventive step
  - 1.1 Closest prior art
    - 1.1.1 The Board agrees with the parties and with the opposition division that document D7 is the closest prior art.

D7 indicates on page 3 (lines 24 to 32) that the formulations disclosed therein may contain two active ingredients. Said formulations are useful for instance in the treatment of respiratory disorders such as asthma. Particularly preferred are combinations containing a bronchodilator and a corticosteroid such as fluticasone propionate (page 4, lines 2 to 6). Concerning the particle size of the medicaments, D7 reports on page 2 (lines 11 to 16) that this should be less than 15  $\mu\text{m}$ , preferably in the range of 1 to 10  $\mu\text{m}$ .



1.1.2 The compositions defined in claim 1 of the main request differ from those disclosed in D7 in that the two medicaments have different particle size, those sizes being 4 to 12  $\mu\text{m}$  for the coarse particles and 1 to 4  $\mu\text{m}$  for the fine particles.

1.2 Technical problem

1.2.1 The respondent did not claim any advantage or surprising effect deriving from the fact that the two active ingredients have different particle size.

However, by referring to the post-published document D13, it argued that the use of a coarse active ingredient having an aerodynamic particle size of at least 50% w/w of the particles in the range 4 to 12  $\mu\text{m}$  resulted in an improvement of the bronchodilation. This was unexpected since according to the common general knowledge of the person skilled in the art it was preferable to formulate the active ingredient in the form of particles having a size in the range 1 to 4  $\mu\text{m}$ .

1.2.2 Document D13 briefly reports the results of a study which explores the relationship between particle size and bronchodilator response in an albuterol monodisperse aerosol formulation. It comes to the conclusion that uniform 6  $\mu\text{m}$  albuterol particles give greater bronchodilation than small particles of 1.5 or 3  $\mu\text{m}$  (page 656, right-hand column, lines 8 to 11).

1.2.3 As observed by the appellant, D13 relates to monodisperse compositions containing only albuterol as active ingredient whereas claim 1 of the main request covers mono- and polydisperse compositions containing two undefined active ingredients.

Monodisperse aerosols are described in D5 as "systems with a well-characterized size that does not change between the point of generation and deposition" (page 67, first sentence of chapter "Studies with stable monodisperse aerosols"). Therapeutic aerosols are polydisperse, and their size usually changes after generation (D5, page 69, lines 5-6). According to D5, "[S]everal theoretical calculations indicate that there should be very significant differences in the regional deposition of aerosols with the degree of polydispersity found in therapeutic aerosols compared to the deposition of monodisperse aerosols" (page 69, lines 10-13). This document reports a reduction of 30% in alveolar deposition for a polydisperse aerosol having a degree of polydispersity characterised by the geometric standard deviation of 3.5 compared to a monodisperse aerosol having the same mass median aerodynamic diameter (page 69, lines 13 to 18). Document D17 (page 281, left-hand column, lines 27-33) suggests that the possibility of deriving the deposition behaviour of polydisperse compositions from the behaviour of monodisperse particle depends on the geometric standard deviation of the polydispersed aerosol. The Board notes that claim 1 covers polydispersed aerosol compositions without any restriction in terms of geometric standard deviation.

Thus, in the Board's view, the results disclosed in D13 cannot be extrapolated to the whole group of pharmaceutical compositions covered by claim 1 already for the fact that the study of D13 only concerns a monodisperse composition.

- 1.2.4 Furthermore, as mentioned above, the formulation tested in the study described in D13 contains only one active ingredient, namely albuterol. It is not clear whether

the results in terms of bronchodilation reported in D13 would be maintained in a formulation containing a second active ingredient in addition to albuterol as required by claim 1 of the main request. D13 itself does not appear to provide any indication in this regard. It is however the burden of the respondent, who claims the presence of an improved effect, to provide convincing evidence in this regard.

1.2.5 Furthermore, the particle size of the albuterol formulation studied in D13 is of 6  $\mu\text{m}$ , whereas the coarse particles of the formulation of claim 1 have a size of 4 to 12  $\mu\text{m}$ . As discussed below (see in particular point 1.3.1), the particle size of the active ingredient determines its site of delivery and therefore its therapeutic action. Thus, the conclusions made by the authors of D13 as to the bronchodilator response provided by a monodisperse albuterol formulation containing particles of 6  $\mu\text{m}$  cannot be extended to formulations containing a drug of different particle size.

1.2.6 In the light of the above considerations, the Board comes to the conclusion that D13 is no evidence of an improved effect for the formulations of claim 1 over the formulations of the closest prior art. Hence, the technical problem underlying the invention is the provision of an alternative composition for inhalation comprising two active ingredients.

1.3 Obviousness

1.3.1 Document D5 underlines the importance for the therapeutic efficacy of a medicament the fact that the active agent is delivered directly to the site of action in the respiratory tract (paragraph linking

pages 61 and 62). It furthermore indicates that the extent to which selectivity of spatial targeting within the respiratory tract is required depends *inter alia* on the sites of the desired drug receptors (see final paragraph of the "Introduction").

Similar concepts are disclosed in D8 (column 1, lines 41 to 43 and column 6, lines 38 to 60) and D17 (see abstract). These documents further indicate that in order to be delivered in specific regions of the lung an active ingredient needs to have a suitable particle size (D8 Figure 1, and column 6, lines 38-54; D17 sentence linking the two columns of page 281). For instance, the particle size of a drug that must be delivered in the terminal or primary bronchi may be greater than the particle size of a drug which needs to be delivered in the alveoli (Figure 1 of D8).

- 1.3.2 Document D7 does not specify whether the particle size of different drugs contained in the same formulation should be the same or not. In the Board's view, having regard to the knowledge derivable from D5, D8 and D17 (see above) the skilled person would consider to provide in the same formulation two active ingredients with different particle sizes, especially if these ingredients are active in different sites of the respiratory tract. Hence, the requirement that the two active ingredients have a different mass median aerodynamic diameter does not justify the presence of an inventive step.
- 1.3.3 As to the respondent's argument that the composition of claim 1 would be inventive already for the fact of containing a coarse active ingredient with aerodynamic particle size of 4 to 12  $\mu\text{m}$ , the Board notes that this range overlaps with those reported in D7, namely "less

than 15 micrometres, preferably in the range of 1 to 10 micrometres, for example 1 to 5 micrometres" (page 2, lines 14 to 16). Moreover, D18 suggests using particles between 2 and 6  $\mu\text{m}$  when the target are the central airways (page 601, left hand-column, lines 7 to 11). Similarly to D18, also D17 indicates that large particles should be inhaled when the conducting airways are the target (page 281, right-hand column, lines 5 to 9). Large particles are for instance particles of 5  $\mu\text{m}$  (page 280, paragraph linking the two columns).

Hence, active ingredients with particle size within the range defined in claim 1 are disclosed in several prior art documents. This conclusion is not altered by the respondent's argument that the customary mass median aerodynamic diameter for dry powder and metered dose inhaler formulations is 2-3  $\mu\text{m}$ .

- 1.3.4 Hence, since active ingredients with a particle size within the range 4 to 12  $\mu\text{m}$  are suggested in the prior art, and the respondent did not demonstrate any particular effect associated with this range, the Board considers that the feature defining the particle size of the coarse active ingredient does not render the subject-matter of claim 1 inventive.

Thus, claim 1 of the main request does not comply with the requirements of Article 56 EPC.

#### Auxiliary request 1

2. Claim 1 of this request specifies that the pharmaceutical composition is suitable for the treatment of respiratory disorders and that the active ingredients are a bronchodilator and a corticosteroid.

2.1 The amendments introduced in auxiliary request 1 do not add any further distinguishing feature over the closest prior art (see point 1.1.1 above). Indeed, the respondent did not submit any argument on inventive step specific to the subject-matter of this request.

It follows that auxiliary request 1 does not meet the requirements of Article 56 EPC for the same reasons as the main request.

## Order

### For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



B. Atienza Vivancos

J. Riolo

Decision electronically authenticated