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Datasheet for the decision of 8 November 2016

Case Number: T 2164/14 - 3.3.07

Application Number: 04768542.5

Publication Number: 1663155

IPC: A61K9/14

Language of the proceedings: EN

Title of invention:
DRY POWDER COMPOSITION COMPRISING CO-JET MILLED PARTICLES FOR PULMONARY INHALATION

Patent Proprietor:
Vectura Limited

Opponent:
Teva UK Limited

Headword:
DRY POWDER COMPOSITION COMPRISING CO-JET MILLED PARTICLES FOR PULMONARY INHALATION/Teva UK Limited

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - All requests (no)

Decisions cited:

Catchword:

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Case Number: T 2164/14 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 8 November 2016

Appellant: (Patent Proprietor)	Vectura Limited 1 Prospect West Chippenham, Wiltshire SN14 6FH (GB)
Representative:	Clarke, Christopher John Vectura Limited Intellectual Property Department One Prospect West Chippenham Wiltshire SN14 6FH (GB)
Appellant: (Opponent)	Teva UK Limited Ridings Point Whistler Drive Castleford WF10 5HX (GB)
Representative:	Gillard, Richard Edward Elkington and Fife LLP Thavies Inn House 3-4 Holborn Circus London EC1N 2HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 26 August 2014 concerning maintenance of the European Patent No. 1663155 in amended form.**

Composition of the Board:

Chairman	J. Riolo
Members:	D. Boulois
	I. Beckedorf

Summary of Facts and Submissions

I. European patent No. 1 663 155 (based on application No. 04 768 542.5) was granted on the basis of a set of 24 claims.

Independent claims 1 and 12 read as follows:
"1. A method for making composite active particles for use in a pharmaceutical composition for pulmonary inhalation, the method comprising jet milling active particles in the presence of particles of additive material so that the additive material coats the active particles, wherein the additive material comprises an amino acid, a metal stearate, or a phospholipid."

"12. Composite active particles for use in a pharmaceutical composition made using a method as claimed in any one of the preceding claims."

II. An opposition was filed against the patent under Article 100 (a), (b) and (c) EPC 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.

III. The appeal by the opponent and by the patent proprietor lies from the decision of the opposition division to maintain the patent as amended. The decision was based on 3 sets of claims, namely a new main request filed during oral proceedings, a main request corresponding to the claims as granted, and auxiliary request 1 filed with letter of 09 May 2014.

IV. The documents cited during the opposition proceedings included the following:
D6: WO2004/089374

D7: WO2004/093848
D8: WO00/61108
D9: WO 97/03649
D21: WO02/43701

V. According to the decision under appeal, the new main request filed during oral proceedings could not be admitted into the proceedings, since the introduction of a passage from the description into the claims at such late stage represented an unfair advantage.

Claim 1 of the main request was not novel over D21, since by selecting the additive materials and the jet mill process, the coating of additive particles onto the active particles was inevitable and inherent.

In claim 1 of auxiliary request 1, the process was restricted by the specification of the inlet pressure, namely: "wherein the jet milling is carried out at an inlet pressure of between 0.1 and 3 bar, or at an inlet pressure of between 3 and 12 bar".

Auxiliary request 1 fulfilled the requirements of Article 123(2) EPC and was sufficiently disclosed. Since D21 did not disclose the pressure range, this document was not novelty destroying. Since the spay-drying process of D8 led to melting of surfactants onto the whole surface of the active particles which are then subjected to jet milling which could lead to a final coating. The resulting particles were also clearly distinguishable from the composite particles of claim 11 of auxiliary request 1.

As regards inventive step of auxiliary request 1, D21 which was seen as closest prior art, did not define the specific inlet pressure and proposed numerous milling

processes. The unexpected effect was the improvement of the bioavailability as shown by the examples of the patent. The technical problem was to provide an improved aerosol. The skilled person would not have selected co-jet milling in view of D8 or D21 and the claimed invention was inventive.

D9 was also considered as closest prior art, and this document was silent on the possible coating of the particles. This document di not envisage jet-milling as process, and the claimed invention was also inventive over D9.

VI. The patent proprietor (hereafter called appellant-proprietor) and the opponent (hereafter called appellant-opponent) filed an appeal against said decision.

VII. With its statement setting out the grounds of appeal dated 23 December 2014, the appellant-proprietor submitted a main request and auxiliary requests 1-4, whereby auxiliary request 4 was identical to the request maintained by the opposition division.

VIII. With a letter dated 19 May 2015, the appellant-opponent submitted arguments and contested the admission of the main request and auxiliary requests 1-3 into the proceedings.

IX. A communication from the Board was sent to the parties. In this it was stated in particular that the main request was not admissible under Rule 80 EPC, and lacked novelty over D6, D7, in view of the invalid priority, D8 and D21.

X. With a letter dated 21 October 2016, the appellant-proprietor withdrew the main request and auxiliary requests 1-3, and auxiliary request 4 became the new main request. It also submitted a new auxiliary request.

The subject-matter of the independent claims 1 and 11 of the main request read as follows:

"1. A method for making composite active particles for use in a pharmaceutical composition for pulmonary inhalation, the method comprising jet milling active particles in the presence of particles of additive material so that the additive material coats the active particles, wherein the additive material comprises an amino acid, a metal stearate, or a phospholipid, **wherein the jet milling is carried out at an inlet pressure of between 0.1 and 3 bar, or at an inlet pressure of between 3 and 12 bar.**"

"11. Composite active particles for use in a pharmaceutical composition made using a method as claimed in any one of the preceding claims."

The auxiliary request 1 was restricted to the process claims 1-10.

XI. Oral proceedings took place on 27 October 2016.

XII. The arguments of the appellant-proprietor may be summarised as follows:

Both D9 or D21 could be considered as closest prior art for the assessment of inventive step.

At the priority date, the state of the art process for producing coated particles was mechano-fusion, whereas jet-milling was not thought to be suitable (see paragraphs [0043]-[0047] of the patent). This was confirmed by D21 itself which proposes 12 different milling methods (see page 6, line 28 to page 7, line 21) and which stated that preferably, the milling was not jet milling (page 12, line 21-22). Several techniques (mechano-fusion, ball milling and high pressure homogenisation) were exemplified in D21, but jet milling was not one of them. Page 13, lines 7-10 also taught away from less controlled methods than mechano-fusion; ball milling was named, but such "less controlled" methods also included jet milling. The teaching of D21 was therefore that other techniques were eminently more suitable than jet milling.

Thus the skilled person, reading D21 and seeking to produce coated active particles, would have selected a preferred method, such as mechano-fusion (page 7, lines 22-23) or one of the other methods that was actually exemplified in D21, such as high pressure homogenisation and ball milling in Examples 1 and 2. Since jet-milling was not only thought to be unsuitable for producing coated particles but also explicitly not preferred in D21, it would certainly not have been the most promising starting point for the skilled person. The opponent's selection of co jet-milling could only be arrived using ex post facto analysis.

Compared to the mechano-fusion embodiment of D21, the distinguishing feature of claim 1 was that the coated active particles were produced by co-jet-milling the active and additive at an inlet pressure of between 0.1 and 12 bar.

Tables 1, 2 and 3 of the patent demonstrated the technical effect of producing the composite active particles by co jet-milling the active and additive particles, namely improved aerosol performance as evidenced by significantly higher fractions of particles in the optimum size range for deposition in the lungs, and reduced throat deposition (see also paragraphs [0138] and [0157]).

Surprisingly, the results were better than for particles produced by the best prior art process mechano-fusion (see for example paragraphs [0138], [0157], [0162], [0174] and [0175]). Video observations showed that this was due to different distributions of the particles within the plume. Mechano-fused formulations showed a highly concentrated, fast moving bolus at the front of the air jet, whereas co-jet milled formulations showed a greater spread of the plume and a less concentrated front, because the powder was emitted for considerably longer (paragraph [0162]). This appeared to result from the fact that the co-jet milled formulations were less free-flowing than the mechano-fused powders. A degree of powder hold-up within the device or blister allows a less dense and more extended plume to form, in which the particles moved at slower speeds on leaving the device (paragraphs [0174 - 0175]).

As to the results of Table 7, 8 and 9, the subject-matter of claim 1 was implicitly limited to a process providing a sufficient coating and adjusted to the type of inhaler device. The skilled person was able to tailor the process.

Therefore the objective technical problem starting from D21 was to provide composite active particles for use

in pharmaceutical compositions for inhalation which have better aerosol performance than those produced by mechanofusion and which resulted in a greater proportion of the active ingredient being deposited in the lung.

There was nothing in D21 that gave any suggestion to the skilled person that co-jet milling the active and additive in order to produce coated particles would have solved this problem and provide better aerosol performance than mechano-fusion, in terms of exceptional fine particle fractions and reduced throat deposition.

The skilled person, starting from D21 and seeking to improve the aerosolization properties of powders would not have started from a method (jet milling) that was believed to be worse than the best available process (mechano-fusion) for producing coated particles. There was nothing in any of the secondary documents that suggested that jet milling would have resulted in better powder aerosolization properties than mechanofusion. Therefore co-jet milling could only be arrived at with hindsight knowledge of the invention.

Notably, there was nothing in any of the prior art documents that provided any hint that increasing (rather than decreasing) the cohesiveness of the powder would lead to improved aerosolization properties due to the beneficial effect of a degree of powder hold up within the device.

Therefore claim 1 involved an inventive step in view of D21 alone, or in combination with any other cited document.

XIII. The arguments of the appellant-opponent may be summarised as follows:

Both D9 or D21 could be considered as closest prior art for the assessment of inventive step.

D21 related to a process for preparing composite active particles (page 1, first paragraph) where the active particles were milled in the presence of the additive material (page 4, lines 3-4). One of the techniques stated to be suitable was jet milling (page 7, line 19). The purpose was to enhance the dispersion of the active particles on actuation of the inhaler and dispersion of the powder (page 3, lines 20-31). D21 therefore related to the same purpose/effect. It also had a number of technical features in common with the present invention. It therefore represented a suitable candidate for the closest prior art. Possible starting points for the problem-solution approach could have been the jet-milling process disclosed in D21 or the mechano-fusion process disclosed therein.

(a) When starting from the jet-milling process, the distinguishing feature of the present invention over D21 was that D21 does not explicitly disclose the inlet pressure for the jet milling.

As stated in the decision of the opposition division, the patentee has not shown any advantage associated with the claimed inlet pressure. Accordingly, the specific pressures cannot provide any improvement to the definition of the objective technical problem and was obvious over D21.

(a) When starting form the mechano-fusion process, the distinguishing feature was the jet-milling process and its inlet pressure.
It was clear from the disclosure of the patent that he problem could not be solved over the the whole claimed subject-matter as shown in Table 2 for the fine particle fraction (FPF) under 1 µm. Table 7 also showed a result which was worse for the particles of the present invention in comparison to particle obtained by a mechano-fusion process when using certain types of inhalers.

Accordingly, the objective technical problem was the provision of an alternative approach for preparing composite active/additives particles for inhalation.

The teaching of D21 was that jet milling was one of a number of suitable techniques for preparing the claimed active/additive composite particles (see page 7, line 19). It was not a preferred process, but it is stated as being suitable. D21 rendered jet milling an obvious alternative technique to use for preparing the claimed active/additive composite particles. There were also numerous references on file which support the position that the skilled person would have used jet milling at the priority date without the benefit of hindsight and with a reasonable expectation of achieving the goal of coating the active particles as set out in the contested patent.

XIV. Requests

Appellant-proprietor requested that the appeal of the opponent be dismissed (*i.e.* that the patent be maintained in amended form found by the opposition division in the decision under appeal to meet the

requirements of the EPC, identical to auxiliary request 4 filed with letter of 23 December 2014, main request), or, that in setting aside the decision under appeal the patent be maintained in amended form on the basis of set of claims filed as auxiliary request 1 with letter of 21 October 2016.

Appellant-opponent requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

1 Main request - Inventive step

1.2 The invention relates to methods of making particles for pulmonary administration comprising a pharmaceutically active material and an additive material by a co-jet milling process. The invention aims to provide a method of producing dry powder compositions which have physical and chemical properties which lead to an enhanced FPF (fine particle fraction) and FPD (fine particle dose). This will lead to greater dosing efficiency, with a greater proportion of the active agent being dispensed and reaching the desired part of the lung for achieving the required therapeutic effect.

1.3 Both D9 and D21 have been considered as potential closest prior art in the decision of the opposition division, as well by appellants I and II in the statement of grounds of appeal; both documents relate to the same purpose than the claimed invention.

D9 discloses the preparation of powder particles for inhalation of a drug and an additive material such as lecithin or leucine which forms a coating (see page 7,

lines 17-21). Example 1 shows a ball milling process. This document does not relate to a jet-milling process.

D21 discloses the preparation of coated active particles coated with an additive (see *inter alia*, page 5, lines 11-16). It suggests the use of the jet milling process for coating the active, but does not give any indication as to the inlet pressure used (see page 7, line 19). It is clear from the teaching of D21 that jet milling is not the preferred method of preparation, and that the preference goes to a mechanofusion method (page 19,, lines 20-34) or a ball milling method. Example 1 of D21 discloses a ball milling process, while example 4 relates to a mechanofusion process resulting in the production of an aerosol powder comprising salbutamol and magnesium stearate having a FPF of 66%.

The technical teaching of document D21 shows undeniably the largest number of similarities with the claimed subject-matter; this document thus represents the closest state of the art.

As stated by the appellants, D21 presents several starting points for assessing inventive step, namely the disclosed ball milling process, the disclosed mechanofusion process and the suggested jet milling process. Since the appellant-proprietor considers the mechanofusion process of D21 to be the closest prior art for the main request, it appears necessary to examine first the validity of the decision in relation to this part of disclosure of D21.

1.4 According to the appellant-proprietor, the problem to be solved is to provide a process for preparing composite active particles for use in pharmaceutical

compositions for inhalation which have better aerosol performance than those produced by mechanofusion and which result in a greater proportion of the active ingredient being deposited in the lung.

1.5 As a solution to this alleged problem, claim 1 of the main request proposes a jet-milling process wherein the jet milling is carried out at an inlet pressure of between 0.1 and 3 bar, or at an inlet pressure of between 3 and 12 bar.

1.6 It has to be investigated whether there is sufficient evidence supporting the alleged effect.

1.6.1 According to the contested patent, an improvement in the aerosol performance translates into an enhanced and consistent fine particle fraction (FPF) (see *inter alia* par. [0015], [0023] [0029]). The fine particle fraction (FPF) is defined as the fine particle dose (FPD) divided by the emitting dose (ED) and expressed as a percentage.

1.6.2 The patent in suit provides numerous examples of aerosol powders obtained by jet-milling processes and comparisons with aerosol powders produced by mechano-fusion processes:

- Tables 1, 2 and 3 show a comparison between powders obtained by a jet-milling process involving an inlet pressure of 7 bar and a grinding pressure of 5 bar and powders obtained by a mechanofusion process. Table 2 gives in particular a comparison based on the FPF of all powders.
- Tables 4, 5 and 6 show a comparison between powders obtained by a jet-milling process involving an inlet pressure of 7 bar, a grinding pressure of 5 bar and a feed rate of 5 ml/mn with powders obtained by a

mechanofusion process. Table 5 gives a comparison based on the FPF of all powders.
- Table 7 compares the FPF of powders obtained by a jet-milling process with the FPF of a mechanofused powder according to the type of inhaling device used, namely a passive or an active inhaler.
- Tables 8 and 9 show a comparison between jet-milled powders obtained with an inlet pressure of 7 or 8 bar, a grinding pressure comprised between 1.5 bar and 5 bar, and a a feed rate comprised between 1 g/mn and 10 g/mn, and a mechanofused powder.

1.6.3 Said examples and Tables show undeniably that, under chosen specific operating parameters, the jet-milling process is superior to the mechanofusion process. It is however also clear from the examples and Tables that this superiority is not systematic, and above all does not depend exclusively on the claimed inlet pressure, but depends also on operating parameters which are not specified in claim 1 of the main request. In other words, the inlet pressure range of claim 1 does not systematically provide an aerosol powder with improved properties, *i.e* an improved FPF, over a mechanofused powder. Some examples show indeed explicitly that a jet-milling process with the claimed inlet pressure was not able to provide aerosol powders having the expected high FPF or at least a higher FPF than a corresponding powder prepared by mechanofusion:
- Table 9 and its examples 19 and 20 show in particular that, at a grinding pressure of 1 bar, when the feed rate is set high, namely at 10 g/mn instead of 1 g/mn the FPF drops from 84% to 64%, thus less than many mechanofused powders disclosed in the Tables of the contested patent or than the powders in D21.
- Table 7 discloses a mechanofused powder with a FPF of 69%, higher than its corresponding jet-milled powder

processed at 2 or 7 bar, having a respective FPF of 68% and 52%, without any explanation.
- Table 7 shows further jet-milled powders processed at 2 and 7 bar with a FPF of respectively 53% and 39% when used in passive inhaling devices, lower to the FPF of 57% of the corresponding mechanofused powders used in the same passive inhaling device.

1.6.4 It follows that the examples of the contested patent are not representative of the claimed subject-matter since important operating parameters, such as the feed rate, the grinding pressure and the type of inhaling device to be used, are absent from claim 1 of the main request. The unique operating parameter present in claim 1, namely the inlet pressure, does not guaranty an improvement in the FPF of jet-milled powders over mechanofused powders.

The improved effect observed with the process and compositions of the examples of the contested patent is therefore intimately linked to specific operating parameters absent from the subject-matter of claim 1 of the main request and this effect cannot be extrapolated to the whole subject-matter of claim 1.

Consequently, it is not possible to establish the existence of an improvement over the prior art.

1.6.5 The argument of the appellant-proprietor relating to the tailoring ability of the skilled person to adapt the claimed process in order to achieve an improvement could not be followed.

The subject-matter of claim 1 relates very generally to a process "for pulmonary inhalation" without any more specific functional restriction, and is further limited

by all technical features indeed present in said claim 1 and the technical effects linked therewith.
If it is shown that a part of the claimed subject-matter is not able to achieve the desired technical effect and to solve the posed problem, it is not possible to base the reality of such effect only on a specific part of the claimed subject-matter which is not claimed as such. Inventive step has to be assessed over the claimed subject-matter as a whole, and there is no possibility to tailor the claimed subject-matter to select a part of the claimed subject-matter able to achieve said effect or improvement in order to show the existence of an inventive step.

1.6.6 Consequently, in the absence of any experimental evidence or arguments establishing a minimum plausibility, the presence of an improvement of the claimed jet-milling process over the mechanofusion process of D21 has not been credibly demonstrated and the technical problem must be reformulated as the provision of an alternative process for the preparation of aerosol powders for pulmonary administration. In view of the information found in the examples of the contested patent, the Board is convinced that the problem has been plausibly solved.

1.7 It remains to be determined whether the solution was obvious to the person skilled in the art.

1.7.1 The skilled person, starting from the teaching of D21 would see the jet-milling process as a plausible alternative to the mechanofusion or ball-milling process. The choice of the claimed inlet pressure appears to be also conventional in the field of aerosol powders as shown by D8 (see examples and page 10, lins 6-21). The skilled person would thus arrive at the

subject-matter of claim 1 of the main request in an obvious manner in order to solve the problem posed.

1.7.2 The Board could not follow the argument of the appellant-proprietor that D21 taught away the solution of jet-milling.

The mechanofusion process is undeniably the preferred option taught by document D21, and the jet-milling process is also undeniably the less preferred process taught in D21, in view of the losses of ultrafine particles or vapour occurring in jet milling (see D21 page 12, lines 17-22). It remains that, independently from the mention of the powder problem, the jet-milling process was explicitly mentioned in D21 as a possible alternative miling process for providing a composition comprising coated particles for pulmonary administration.
Moreover, the obviousness of a solution must be assessed on the basis of the problem posed to the skilled person, here namely the provision of a process for the preparation of an aerosol powder for pulmonary administration, and not the problem of losses of ultrafine particles or vapour which is here irrelevant.
In view of the properties conferred to an aerosol powder by the jet-milling process of claim 1 with the inlet pressure as only claimed operating parameter, the skilled person would have considered any alternative process described or mentioned in D21 as a valuable alternative.

1.7.3 Consequently, the main request does not meet the requirements of Article 56 EPC.

2. Auxiliary request 1 -Inventive step

This request differs from the main request in the suppression of the product claims 11-23.

Since claim 1 of auxiliary request 1 is identical to claim 1 of the main request, the points raised for the main request apply *mutatis-mutandis* for this request, which does also not meet the requirements of Article 56 EPC.

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:

S. Fabiani J. Riolo

Decision electronically authenticated