

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference see form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below
International application No. PCT/EP2015/073188	International filing date (day/month/year) 07.10.2015	Priority date (day/month/year) 08.10.2014
International Patent Classification (IPC) or both national classification and IPC INV. A61K9/00 A61K9/14 A61K9/16 A61K31/167 A61K31/439 A61K31/58		
Applicant ERATECH S.R.L.		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Giró, Annalisa Telephone No. +49 89 2399-0
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	<u>1-14</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-14</u>
Industrial applicability (IA)	Yes: Claims	<u>1-14</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1 WO 00/33789 A2 (R P SCHERER INC [US]; EMBLETON JONATHAN KENNETH [CH]) 15 June 2000 (2000-06-15)
- D2 WO 02/00197 A1 (VECTURA LTD [GB]; STANIFORTH JOHN NICHOLAS [GB]; MORTON DAVID ALEXANDE) 3 January 2002 (2002-01-03)
- D3 EP 2 682 099 A1 (ARVEN ILAC SANAYI VE TICARET A S [TR]) 8 January 2014 (2014-01-08)
- D4 WO 03/024396 A2 (GLAXO GROUP LTD [GB]; BROWN ANDREW BRUCE [US]; VAN OORT MICHAEL MARY []) 27 March 2003 (2003-03-27)
- D5 WO 2007/045689 A2 (ERATECH S R L [IT]; VENEZIANI CRISTINA [IT]; CAPONETTI GIOVANNI [IT];) 26 April 2007 (2007-04-26)

Unless otherwise indicated, reference is made to the relevant passages emphasized in the International Search Report.

1. Novelty (Article 33(2) PCT).

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of independent claims 1 and 14 is not new over D1 in the sense of Article 33(2) PCT.

1.1 D1 discloses powder formulations comprising coarse lactose (> 80% by mass over 50µm in size), fine lactose (> 90% by mass below 10µm in size), L-leucine and a corticosteroid, all in amounts falling within the ranges and ratios claimed in present claim 1. In this context, it is noted that, although the claimed composition is defined as comprising a first and a second powder, this is merely a conceptual separation of the ingredients, corresponding to the materials used to prepare said composition. In the

final claimed powder, the ingredients are in fact physically mixed with each other. Thus, in view of this and in view of the remarks mentioned under point 1.1, the subject-matter of claim 1 cannot be regarded as novel over the disclosure of D1.

1.2 D1 further discloses that the powder formulations mentioned above are filled into a device for inhalation, thereby resulting in a kit. Therefore, also the subject-matter of independent claim 14 cannot be considered novel over D1.

2. Inventive Step (Article 33(3) PCT).

Even if novelty could be restored over D1, it is noted that the present application might not involve an inventive step in the sense of Article 33(3) PCT in the light of D2 in combination with either D1 or D4, or in the light of D3 in combination with any of D1, D2, D4 or D5

2.1 The idea of formulating powders for inhalation by mixing fine lactose carrier particles (known as respirable fraction) with coarse lactose carrier particles (known as non-respirable fraction) is very well-established practice in the art (see, e.g., D1 to D4).

By way of example, D2 could be regarded as being the prior art closest to the subject-matter of independent claim 1. D2 discloses powder formulations comprising coarse lactose particles (355-600µm in size), fine lactose particles (1-10µm in size), leucine and an active agent. The subject-matter of claim 1 therefore differs from D2 in that the coarse particles have a X50 of 35-75µm.

On the one hand, however, according to the present application, no particular effect appears to be related to the selection of this specific particle size range for the non-respirable fraction.

On the other hand, D1 and D4 suggest the use as non-respirable fraction of particles with diameters falling within the claimed range.

Therefore, even if novelty could be restored, the claimed powder formulations appear to be obvious alternatives to those of the prior art.

2.2 Also D3 could be regarded as being the prior art closest to the subject-matter of independent claim 1. D3 discloses powder formulations comprising coarse lactose particles (X50 of 10-100µm), fine lactose particles (X50 of 1-10µm) and an active agent.

The subject-matter of claim 1 therefore differs from D3 in the presence of leucine.

According to the present application, leucine is added to the formulation as hydrophobic substance in order to reduce the sensitivity to humidity of the whole formulation (see page 11, lines 14-19).

The problem to be solved by the present invention could therefore be regarded as how to reduce the moisture-sensitivity of powder compositions.

Leucine, however, appears to be an excipient of choice in powder formulations for inhalation (see, e.g., D1, D2, D4, D5). D5, in particular, explicitly suggests its utility as hydrophobic substance which is able to reduce sensitivity to humidity.

Thus, even if novelty could be restored, the solution proposed in claim 1 of the present application could not be considered as involving an inventive step.

2.3 The same reasoning applies, *mutatis mutandis*, to the subject-matter of the corresponding independent claim 14, which therefore would also be considered not inventive.

3. Dependent claims.

Dependent claims 2-13 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and inventive step.

Furthermore, it should be noticed that said dependent claims are only allowable in combination with independent claims meeting the requirements of the PCT in regard to novelty and inventive step.

4. Industrial applicability (Article 33(4) PCT).

Claims 1-14 are industrial applicable in the sense of Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

The application does not meet the requirements of Article 6 PCT, because claims 1 and 5 is not clear for the following reasons.

a) As also apparent from the description (see paragraph bridging pages 12 and 13), the features "fine particle fraction" (FPF) and "delivered fraction" (DF) mentioned in claim 1 relate to methods of using the claimed composition (at delivery from inhaler) rather than clearly defining the composition in terms of its technical features. The intended limitations are therefore not clear from this claim and said features are not regarded as technical features further limiting the scope of the claim.

b) The term "derivatives" used in claim 5 renders its scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by this term. Terms like analogues/derivatives include compounds obtained from another compound by a chemical reaction (including compounds which are structurally remote from the starting material), functional derivatives (such as compounds, wherein hetero-atoms are exchanged by alternative atoms), compounds with numerous different types of side groups. Consequently the subject-matter of claim 5 does not fulfil the requirements of clarity of Article 6 PCT.