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Datasheet for the decision of 9 January 2024

Case Number: T 0688/22 - 3.3.07

Application Number: 07859026.2

Publication Number: 2104490

IPC: A61K9/14, A61K31/4704, A61K31/167, A61P11/06, A61P11/08

Language of the proceedings: EN

Title of invention:
MICRONISED PARTICLES OF LOW-DOSAGE STRENGTH ACTIVE AGENTS FOR POWDER FORMULATIONS FOR INHALATION

Patent Proprietor:
Chiesi Farmaceutici S.p.A.

Opponent:
Maiwald GmbH

Headword:
Powder formulations for inhalation / CHIESI FARMACEUTICI

Relevant legal provisions:
EPC Art. 123(2), 83, 56
RPBA 2020 Art. 12(4)

Keyword:

Amendment to case - amendment admitted (no)
Amendments - added subject-matter (no)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

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Case Number: T 0688/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 9 January 2024

Appellant: (Opponent)	Maiwald GmbH Elisenhof Elisenstr. 3 80335 München (DE)
Representative:	Maiwald GmbH Elisenhof Elisenstraße 3 80335 München (DE)
Respondent: (Patent Proprietor)	Chiesi Farmaceutici S.p.A. Via Palermo, 26/A 43122 Parma (IT)
Representative:	Script IP Limited Suite J, Anchor House School Close Chandlers Ford Eastleigh, Hampshire SO53 4DY (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 January 2022 concerning maintenance of the European Patent No. 2104490 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	S. Ruhwinkel

Summary of Facts and Submissions

I. The appeal was filed by the opponent (appellant) against the interlocutory decision of the opposition division finding that, on the basis of the main request filed on 22 September 2021, the patent met the requirements of the EPC.

II. The claims of the main request were identical to those of the patent as granted. Claim 1 of the main request related to:

"A powder formulation to be administered using a medium- or a high-resistance multidose dry powder inhaler device, said formulation comprising an interactive ordered mixture prepared by blending micronized crystalline particles consisting of formoterol fumarate dihydrate as active ingredient, having a nominal dose delivered after each actuation of said inhaler equal to or lower than 4 µg, with particles of a physiologically acceptable excipient having a mass median diameter (MMD) higher than 90 micron, the particles of said active ingredient fulfilling the following conditions:

i) no more than 10% of the particles have a volume diameter [d(v,0.1)] lower than 0.8 micron;
ii) no more than 50% of the particles have a volume diameter [d(v,0.5)] lower than 1.7 micron; and
iii) at least 90% of the particles have a volume diameter [d(v,0.9)] lower than 10 micron, and
iv) the ratio [d(v,0.9) - d(v,0.5)]/ d(v,0.5) is higher than 1.4 and lower than 2.0 micron,

whereby said volume diameter being measured by laser diffraction; and wherein after the blending, the content uniformity of the active ingredient, expressed

as relative standard deviation (RSD), is equal to or less than 2.5%".

III. The following documents cited in the opposition division's decision are relevant:

D3: WO 2005/089717 A1
D7: US 2003/0180227 A1
D12: Declaration of Francesca Buttini

IV. The opposition division decided the following:

(a) The combination, in claim 1 of the main request, of the features pertaining to the ratio [d(v,0.9) - d(v,0.5)]/d(v,0.5), the content uniformity of the active ingredient expressed as relative standard deviation (RSD), and the active agent being crystalline formoterol fumarate dihydrate, did not constitute added subject-matter.

(b) Neither the lack, in the patent, of any examples of a powder formulation according to the claims, nor the alleged formation of agglomerates in some claimed formulations, led to a finding of insufficiency of disclosure.

(c) As to inventive step, starting from D7 as the closest prior art, the pertinent differentiating features were the particle size parameters features i), ii) and iv), in addition to the use of crystalline formoterol fumarate dihydrate and the nominal dose delivered after each actuation of the inhaler. The objective technical problem was the provision of alternative powder formulations with a particle size distribution appropriate for low dose formoterol fumarate and having good aerosol

performance. The claimed solution involved an inventive step.

V. During the appeal proceedings, the appellant filed document D18 with their statement setting out the grounds of appeal, and documents D19 and D20 with their letter dated 13 April 2023:

D18: WO 03/024396
D19: X. Zeng et al., Particulate Interactions in Dry Powder Formulations for inhalation, 2003, section 5.5.7, pages 165-167.
D20: K. Jarring et al., Thermodynamic Stability and Crystal Structures for polymorphs and solvates of formoterol fumarate, J. Pharm. Sci. 95 (2006), 1144-1161

VI. In reply, the patent proprietor defended their case on the basis of the main request as upheld by the opposition division and, subsidiarily, on the basis of auxiliary requests 1-6 filed in the first instance proceedings.

VII. The appellant's arguments may be summarised as follows:

(a) D18 was to be admitted, because it had been filed in reaction to a significant turn of reasoning of the opposition division regarding D3, and was *prima facie* highly relevant.

(b) The combination, in claim 1 of the main request, of the features relating to the ratio [d(v,0.9)-d(v, 0.5)]/d(v,0.5) (feature iv)) and to the RSD range infringed Article 123(2) EPC.

(c) The main request did not meet the requirements of sufficiency of disclosure. Firstly, claim 1 encompassed formulations wherein the particles would not be capable of reaching the therapeutically relevant bronchiolar and alveolar sites. Secondly, in the absence of a clear definition of the dry powder inhaler to be used, the skilled person could not repeatedly and reliably determine the nominal dose delivered after each actuation.

(d) Regarding inventive step, the closest prior art D7 disclosed each of the parameters i) to iv) of claim 1 of the main request (as supported by D19 and D20). The only differentiating features of claim 1 were:
- the crystalline formoterol fumarate dihydrate form, and
- the nominal dose *per* actuation of the inhaler of 4 µg or less.
No effect on aerosol performance or dose uniformity was shown by D12 or the patent considering that the final formulations tested therein did not comply with parameter iv). The problem was the provision of alternative powder formulations comprising formoterol fumarate as an active ingredient for dry powder inhalers having an arbitrary particle size distribution. The allegedly differing d(v,0.1) and d(v,0.5) values were at least obvious in light of D7 alone or in combination with D18.

VIII. The respondent's arguments may be summarised as follows:

(a) The appellant's new objection, that particles in the size range between 7 to 10 µm cannot reach therapeutically relevant sites in the lungs, represented an amendment to their case which the appellant had neither identified nor justified, and was neither relevant for sufficiency of disclosure nor correct.

(b) The late filing of D18 was not justified by any turn in the opposition division's reasoning. D18 was not *prima facie* relevant and was not to be admitted into the proceedings.

(c) In the first instance proceedings, the appellant had explicitly admitted that features i), ii) and iv) were not disclosed in D7. The appellant's new objection in appeal that these features were disclosed in D7, and the evidence D19 and D20 filed in support thereof, were not to be admitted into the proceedings.

(d) Regarding Article 123(2) EPC, claim 1 of the main request combined the broadest span range [d(v,0.9) - d(v,0.5)]/ d(v,0.5) with an RSD given in the description and did not result from selections from multiple lists.

(e) As to inventive step, the closest prior art D7 did not disclose features i), ii) and iv) of claim 1 of the main request. It was plausible that the effect demonstrated in examples 2 and 5 of the patent and in D12 also occurred throughout the scope of the claims of the main request. The problem was to provide an improved powder formulation for a DPI device containing a low dose of formoterol fumarate as active ingredient, having improved FPF but still

maintaining content uniformity, avoiding agglomeration and dose variability. The claimed solution involved an inventive step.

IX. The appellant requests that the decision under appeal be set aside and that the patent be revoked in its entirety.

X. The respondent requests that the appeal be dismissed, and that the patent be maintained in the form upheld by the opposition division. In the event that the Board considers refusing the main request, the respondent requests that the case be remitted to the opposition division for consideration of the auxiliary requests on file. Alternatively, the respondent requests that the patent be maintained on the basis of one of the auxiliary requests 1-6 filed in the first instance proceedings.

The respondent additionally requests that D18, the objections of insufficiency of disclosure addressed in the Board's preliminary opinion under points 1.1 and 2.3, the amendments to the appellant’s appeal case filed with letters dated 13 April 2023 and 8 December 2023, as well as documents D19 and D20, be not admitted into the proceedings.

Reasons for the Decision

1. Procedural matters

1.1 Admittance of the new objection of insufficiency of disclosure

According to the appellant, claim 1 encompasses formulations in which nearly all of the active

ingredient particles have sizes in a range between 7 to 10 µm, in which case the particles would not be capable of reaching the therapeutically relevant bronchiolar and alveolar sites, as is apparent from D7.

This objection was presented for the first time in the appellant's statement setting out the grounds of appeal, and does not form part of the objections and arguments on which the appealed decision was based. As such, this new objection is to be regarded as an amendment to the appellant's case, to be admitted only at the discretion of the Board (Article 12(2) and (4) RPBA).

The appellant did not identify this new objection as an amendment to their case. The Board considers that this new objection is not in reaction to the appealed decision, but instead amounts to an attempt to bring a fresh case in appeal. In addition, the objection appears *prima facie* not convincing, considering that the ability of the particles to reach the bronchiolar and alveolar sites is not a feature of the claims, and that the embodiment used in the appellant's reasoning, having d(v,0.5) = 9 µm and d(v,0.9) = 9.5 µm, does not have a particle size spread ratio as specified in claim 1, feature iv).

Accordingly, the Board did not admit this new objection.

1.2 Admittance of the appellant's new arguments, facts and evidence regarding the disclosure of features i), ii) and iv) in D7

In their grounds of appeal, the appellant for the first time asserted that D7 discloses the particle diameter

features i), ii) and iv) of claim 1. The appellant further filed the new documents D19 and D20 with their letter dated 13 April 2023 to support their argument.

In the proceedings before the opposition division, the appellant had never contested that features i), ii) and iv) represented differentiating features over D7.

These new arguments, facts and evidence are thus to be regarded as an amendment to the appellant's case in the sense of Article 12 (2) and (4) RPBA, to be admitted only at the discretion of the Board. The admittance of D19 and D20 is additionally subject to the provisions of Article 13(1) RPBA.

The appellant neither identified the above amendments to their case, nor provided any reasons for submitting them in the appeal proceedings. Their admittance would lead to further discussions, which would be contrary to procedural economy. In addition, the Board shares the respondent's view that these new objections are *prima facie* not convincing:

With respect to feature i), namely that no more than 10% of the particles have a volume diameter lower than 0.8 µm, the appellant relies on paragraph [0018] of D7. However, this passage of D7 is a general statement made in the prior art section, and not in the context of the dry powder formulations of the invention used as starting point in D7. Additionally, it pertains to the mass median aerodynamic diameter (MMAD, i.e. the aerodynamic diameter of 50 wt% of the particles) for respirable particles, but says nothing about the particle size volume distribution parameter d(v,0.1) used in the powder formulation. The Board is not convinced by the appellant's theoretical calculations,

based on D19 and D20, for converting the MMAD of D7 into geometric diameters, for the reasons set out by the respondent (see letter of 24 July 2023, page 7). And in any case, the general mention in D7 that respirable particles are considered to be those with diameters from 0.5 to 6 µm does not amount to a clear and unambiguous disclosure that no more than 10% of the particles used in the formulation have a diameter lower than 0.8 µm. For this reason alone, the d(v,0.1) feature i) cannot be derived from D7.

The Board is not convinced either by the appellant's argument regarding the disclosure of features ii) and iv) in D7, at least because their reasoning is based on the assumption that D7 discloses d(v,0.1) ≥ 0.5 µm.

Accordingly, the Board did not admit the above amendments to the appellant's case, nor the evidence D19 and D20 submitted in support therefor.

1.3 Admittance of D18

With their grounds of appeal, the appellant further filed the new document D18 as part of their objection of lack of inventive step starting from the closest prior art D7, and as evidence that it was obvious to provide active ingredient particles having a d(v,0.1) ≥ 2 µm in order to provide pharmaceutical compositions having increased stability and aerosolibility. The respondent objects to the admittance of D18.

D18 represents an amendment to the appellant's case and its admittance is subject to the provisions of Article 12(4) and (6) RPBA. The Board agrees with the respondent that the filing of D18 is to be seen as an attempt to introduce a new objection in appeal, and not

as a reaction to the appealed decision, considering the opposition division's already positive preliminary opinion as to inventive step. Therefore, document D18 could and should have been already submitted in the opposition proceedings in response to the preliminary opinion of the opposition division (see Article 12(6), second sentence RPBA). D18 is not related either to a change in the opposition's reasoning as regards D3, since D18 neither mentions formoterol nor teaches to restrict d(v,0.1) to above 0.8 µm for the active ingredient - the passages cited by the appellant only relate to aerodynamic parameters (see page 2, lines 3-14, and claims 6 and 53). In this sense the Board considers that D18 also is not *prima facie* relevant.

Accordingly, the Board did not admit D18.

2. Main request

2.1 Added subject-matter

2.1.1 Claim 1 of the main request mandates that:
- the active ingredient particles used in the preparation of the claimed formulation are characterised by a ratio [d(v,0.9)-d(v,0.5)]/d(v,0.5) higher than 1.4 and lower than 2.0 micron (feature iv)), and
- the content uniformity of the active ingredient after blending, expressed as relative standard deviation (RSD), is equal to or less than 2.5%.

According to the appealed decision, feature iv) is based on page 7, lines 20-22 of the application as filed, which indicates that, advantageously, the particle size spread is "higher than 1.4 micron and lower than 2 micron, preferably higher than 1.5 micron

and lower than 1.8 micron". The feature of claim 1 pertaining to RSD is based on page 12, lines 4-7, according to which the RSD is "less than 5%, preferably equal/less than 2.5%, more preferably equal or less than 1.5%".

2.1.2 The appellant objects to the combination of these features, and emphasizes that neither the claims as filed nor the examples point to this combination.

The Boards shares the opposition division's view that the range "higher than 1.4 micron and lower than 2 micron" is the broadest range for the spread ratio according to the application as filed and does not require a selection. The appellant's argument based on a combination of selections is accordingly not convincing. The fact that all of the batches 1-3 in the examples of the patent pertaining to micronised formoterol fumarate dihydrate (example 2) and formulations thereof (example 5) have spread ratios iv) well below 1.4 does not change this conclusion, because the combination finds basis in the description without the need for the examples as a pointer.

Accordingly, the appellant's objection under Article 123(2) EPC is not convincing.

2.2 Sufficiency of disclosure

The appellant maintains that, since different dry powder inhalers (DPI) deliver considerably different nominal doses after each actuation, and since claim 1 does not clearly define the DPI, the skilled person cannot repeatedly and reliably determine the nominal dose parameter, contrary to Article 83 EPC (see the

grounds of appeal, §73, referring to the submission dated 23 September 2021).

In the Board's view, the alleged uncertainty as to the nominal dose feature of the formulation imposed by reference to this undefined DPI is not shown to prevent the skilled person from reproducing the claimed invention. The appellant acknowledges that a conventional medium-resistance or high-resistance DPI could be selected by the skilled person without exercising inventive skills. The objection of insufficiency of disclosure is thus unconvincing.

2.3 Inventive step

2.3.1 The opposition division's choice of D7 as closest prior art is not contested by the parties.

D7 relates to powder formulations for inhalation comprising, in one alternative, formoterol fumarate as active agent (see paragraph [31]). D7 further generally discloses that, advantageously, at least 90% of the particles of the drug have a particle size less than 10 µm, preferably less than 6 µm (see paragraph [0082]). Thus, feature iii) of claim 1 of the main request is shown in D7.

2.3.2 The claimed powder formulation differs from the teaching of D7 in that the particles of the formoterol fumarate active ingredient used in the preparation of the interactive ordered mixture fulfill the following conditions (see also 1.2 above):
i) no more than 10% of the particles have a volume diameter lower than 0.8 micron, or in other words $d(v,0.1) \geq 0.8$ µm;

ii) no more than 50% of the particles have a volume diameter lower than 1.7 micron, i.e. d(v,0.5) ≥ 1.7 µm; and
iv) 1.4 < [d(v,0.9)-d(v,0.5)]/d(v,0.5) < 2.0 "micron".

Additionally, D7 does not disclose the features of claim 1 pertaining to formoterol fumarate being crystalline formoterol fumarate dihydrate, and to the nominal dose delivered per actuation of the inhaler of 4 µg or less.

2.3.3 Technical effect and technical problem

For the following reasons, the Board accepts that the claimed feature i) relating to active ingredient particles having a d(v,0.1) ≥ 0.8 µm is associated with a reduced tendency to agglomerate during the blending step in the claimed formulations.

Example 2 of the patent shows the preparation of several batches of micronised formoterol fumarate dihydrate (see table 2):

(a) In batches 1-3, the particles have d(v,0.1), d(v, 0.5) and d(v,0.9) parameters as required by features i), ii) and iii) of claim 1; however, a calculation of the ratio [d(v,0.9)-d(v,0.5)]/d(v, 0.5) gives values (0.73-0.78) below the lower limit 1.4 of feature iv) of claim 1;

(b) In batches 4 and 5, the particles have d(v,0.5) and d(v,0.9) parameters in the claimed range but d(v, 0.1) values (0.60-0.61) below the lower limit of 0.8 µm mandated by feature i) of claim 1; for batch 4, the calculated ratio [d(v,0.9)-d(v,0.5)]/d(v,

0.5) of 1.52 falls within the claimed range of 1.4-2.0 of feature iv).

Examples 2 shows that batches 1-3 can be uniformly dispersed into the carrier without formation of agglomerates. By comparison, batches 4 and 5 lead to agglomerates (see paragraphs [0078] and [0079]).

2.3.4 As pointed out by the appellant and explained above, the formulations of batches 1-3 in examples 2 do not fulfill feature iv) of claim 1. However, this alone does not mean that the evidence based on these formulations must be disregarded. Rather, the question is whether the evidence makes it credible that the alleged effects over the closest prior art arise with the claimed formulations as a result of the differentiating features.

In the Board's opinion, the effect on agglomeration has credibly been linked mainly to the claimed d(v,0.1) range, even though batches 1-3 and 4-5 respectively differ not only by their d(v,0.1) values but also by their ratios of feature iv). Paragraphs [0078]-[0079], [0034]-[0035] and [0009] explicitly establish and explain the link between finer active agent particles or d(v,0.1) (and to a lesser extent d(v,0.5)) values and agglomeration during the blending step. In contrast, it is neither stated nor shown that the ratio [d(v,0.9) - d(v,0.5)]/ d(v,0.5) defined in feature iv) of claim 1, which in effect can be achieved simply by a further limitation of parameter d(v,0.9) within the limits already set by feature iii), has any notable influence on agglomeration. The view that changes in respect of d(v,0.9) or ratio iv) would not be expected to affect agglomeration tendency, uniformity of distribution and aerosol performances is supported by

paragraph 31 of D12. There is furthermore no indication that formulations with a ratio iv) as claimed would fail to exhibit this effect. In particular, in view of the above, the fact that batch 4 of example 2 of the patent leads to agglomeration is to be explained by the fact that its d(v,0.1) value is outside the claimed range, and not by the fact that its ratio iv) is inside the claimed range.

The appellant further argued that batches 1-3 additionally differ from batches 4 and 5 by their specific surface area (SSA) (see table 2 of the patent). However, the Board shares the respondent's opinion that the SSA is not an independent variable, but is related to the other parameters of the particle size distribution (defined in claim 1 by the d(v,0.1), d(v,0.5) and d(v,0.9) parameters), since larger particles have a lower relative surface area per unit mass. Accordingly, the SSA does not represent a further (independent) difference between batches 1-3 and 4-5, but is merely another way to express the difference already defined by the particle size distribution parameters.

Thus an effect on agglomeration has been shown for formulations meeting feature i) of claim 1 in comparison with formulations lacking this feature. Considering that D7 is silent as to the d(v,0.1) of the active ingredient particles used in the formulation, this effect can be taken into account for the formulation of the technical problem.

2.3.5 The appellant further contested that a lower tendency to agglomeration would translate in any improved aerosol properties in the final formulation, and relied on a comparison of example 5 of the patent with example

8 of D7 as evidence that the properties of the formulations are at least as good in D7 as in the patent.

Example 8 of D7 describes powder formulations prepared by mixing micronised formoterol fumarate with different blends of excipient particles, leading to content uniformities (RSD) as low as 1.5% and fine particle fractions (FPF) as high as 64.3%. In example 5 of the patent, the formulation is reported to show "an excellent good uniformity of distribution of the active ingredient (RSD lower than 1.5%) and the aerosol performances are very good with more than 50% of FPF". Similarly, D12 reports an RSD of 2.5% and an FPF of 61.3% (see paragraphs 18-27). However, D7 is entirely silent as to the particle size distribution and d(v, 0.1), d(v,0.5) and d(v,0.9) values of the micronised formoterol fumarate used therein. Accordingly, no meaningful comparison can be made between example 8 of D7 and example 5 of the patent in this regard, i.e. no conclusion can be drawn from this comparison as to the effect, or lack thereof, of the differentiating features relating to the active ingredient particle size distribution. There is no doubt that the reduced tendency to agglomeration during the blending step directly results in improved content uniformity in the claimed formulations, as explained in paragraph [0011] of the patent.

2.3.6 As pointed out by the appellant, the particle size features i), ii) and iv) of claim 1 characterise the active ingredient used (i.e as starting material) in the preparation of the interactive ordered mixture. The appellant argued during the oral proceedings that these features thus amounted to a definition of the claimed formulation in terms of the process for its

preparation, such that any technical effect of these features was not linked to features of the formulation but to feature of the process for its preparation. However, product-by-process claims had to be interpreted in an absolute sense, i.e. independently of the process, and their subject-matter did not involve an inventive step merely because the process for their preparation did so.

The Board does not accept the appellant's argument. The powder formulation is defined in claim 1 as comprising an interactive ordered mixture prepared by blending the active ingredient particles with the excipient particles. There is no evidence that, as a result of this mere step of blending, the particle size distribution features i), ii) and iv) would not characterise anymore the active ingredient particles in the final powder formulation. In fact, the appellant's argument contradicts the position that features i), ii) and iv) represent differentiating features of the claimed subject-matter, i.e. the claimed formulations, over D7, which the appellant no longer contested during the oral proceedings.

2.3.7 The Board concludes that the technical problem is to provide an improved powder formulation for a DPI device containing a low dose of formoterol fumarate as active ingredient, having reduced tendency to agglomeration.

2.3.8 Obviousness

While D7 also addresses the problem of improving the aerosol performance of the powder formulation, the solution proposed in D7 focuses first and foremost on the particle size distribution of the excipient, and not of the active ingredient (see paragraphs [0036],

[0037]). Paragraph [0018] mentions a particle size range of 0.5-6 µm for particles to be considered respirable, but does not mention agglomeration or content uniformity. As to paragraph [0024], it mentions the issue of uniformity in the particular case of low strength active ingredients, without relating this issue to the active ingredient particle size distribution.

Only in paragraph [0019] does D7 mention the influence of the active ingredient particles on agglomeration. This passage states the problem, namely that, although "micronisation of the active drug is essential for deposition into the lower lungs during inhalation, it is also known that the finer are the particles, the stronger are the cohesion forces. Strong cohesion forces [...] reduce the flowability of the particles while favouring the agglomeration and/or adhesion thereof to the walls. In multidose DPI's, said phenomena impair the loading of the powder from the reservoir to the aerosolization chamber, so giving rise to handling and metering accuracy problems". There is however in this passage no hint to the claimed solution, i.e. the selection of a particle size distribution wherein no more than 10% of the particles have a volume diameter lower than 0.8 micron. Contrary to the appellant's view, the fact that example 8 of D7 achieves good aerosol properties cannot be seen as such a hint either, because there is no teaching in D7 that these good properties can be achieved through a selection of the d(v,0.1) value of the active ingredient.

Accordingly, it must be concluded that the prior art does not render the claimed invention obvious.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated