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Datasheet for the decision of 16 May 2023

Case Number: T 1322/21 - 3.3.07

Application Number: 13704372.5

Publication Number: 2806855

IPC: A61K9/14, A61K31/167, A61K31/57, A61P11/00, A61P11/06

Language of the proceedings: EN

Title of invention:
DRY POWDER FORMULATION COMPRISING A CORTICOSTEROID AND A BETA-ADRENERGIC FOR ADMINISTRATION BY INHALATION

Patent Proprietor:
Chiesi Farmaceutici S.p.A.

Opponent:
ZBM PATENTS, S.L.

Headword:
Dry powder formulation / CHIESI FARMACEUTICI

Relevant legal provisions:
EPC Art. 100(a), 100(b), 100(c), 56

Keyword:
Amendments - added subject-matter (no)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

Decisions cited:
G 0002/10, T 1845/14

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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 1322/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 16 May 2023

Appellant: (Opponent)	ZBM PATENTS, S.L. Rambla Catalunya, 123 08008 Barcelona (ES)
Representative:	ZBM Patents - Zea, Barlocci & Markvardsen Rambla Catalunya, 123 08008 Barcelona (ES)
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:	**Decision of the Opposition Division of the European Patent Office posted on 16 June 2021 rejecting the opposition filed against European patent No. 2806855 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	A. Jimenez

Summary of Facts and Submissions

I. The appeal was filed by the opponent (appellant) against the decision of the opposition division to reject the opposition filed against the patent in suit.

II. Claim 1 of the patent read as follows:

"A dry powder formulation for use in a dry powder inhaler (DPI) comprising:

a) a fraction of fine particles made of a mixture of 90 to 99.5 percent by weight of particles of alpha-lactose monohydrate and 0.5 to 10 percent by weight of magnesium stearate, said mixture having a mass median diameter lower than 20 micron;

b) a fraction of coarse particles constituted of alpha-lactose monohydrate having a mass median diameter equal to or greater than 175 micron, wherein the ratio between the fine particles and the coarse particles is between 2:98 and 20:80 percent by weight; and

c1) formoterol fumarate dihydrate in the form of micronized particles;

c2) beclomethasone dipropionate (BDP) in the form of micronized particles;

wherein i) no more than 10% of said BDP particles (d(v, 0.1)) have a volume diameter lower than 0.6 micron; ii) no more than 50% of said particles (d(v,0.5)) have a volume diameter comprised between 1.5 micron and 2.0 micron; and iii) at least 90% of said particles (d(v, 0.9)) have a volume diameter lower than 4.7 micron, and wherein said BDP particles are further characterized by a particle size span, defined as [d(v,0.9) - d(v,0.1)]/ d(v,0.5), comprised between 1.2 and 2.2 and by a

specific surface area comprised between 5.5 and 7.0 m^2/g."

III. The decision cited the following documents among others:

D4: US 2010/0055192 A2
D5: L. M. Fabbri wt al., "Inhaled beclometasone dipropionate/formoterol extra-fine fixed combination in the treatment of asthma", Expert Opin. Pharmacother 2008, vol. 9, pp. 479-490
D6: C. Leach et al., "Particle size of inhaled corticosteroids: Does it matter?" K Allergy Clin Immunol 2009, vol. 124, pp. S88-93
D12: Malvern Mastersizer 2000 instrument manual (2007)
D14: WO 2011/131663
D15: Experimental report filed by the patent proprietor on 18 March 2021
D17: Experimental report filed by the opponent on 18 March 2021

IV. The opposition division decided the following:

(a) D14, D15 and D17 were admitted into the proceedings.

(b) The introduction of the parameters d(v,0.1), d(v, 0.5) and d(v,0,9) in parentheses into points i)-iii) of claim 1 of the original claims did not add subject-matter.

(c) The criteria of sufficiency of disclosure were met with respect to the methods for the particle size determination.

(d) Regarding inventive step, starting from the closest prior art D14, the differentiating features were the specific surface area, the specific values i), ii) and iii), and the particle size span as defined in claim 1. Taking into account D15, the problem to be solved was the provision of an improved dry powder formulation comprising a mixture of formoterol fumarate (FF) dihydrate and beclomethasone dipropionate (BDP) with which a higher fraction of particles is deposited into the lungs. The claimed solution involved an inventive step. Even if the problem was to provide an alternative powder formulation, it would not be obvious to select the specific particle size distribution, surface area and particle size span. Hence the criteria of inventive step were met.

V. The Board issued summons to oral proceedings, and set out its preliminary opinion in a communication under Article 15(1) RPBA.

VI. In their letter dated 31 March 2023, the appellant indicated that they would not attend the oral proceedings and withdrew their request for oral proceedings.

VII. The Board cancelled the oral proceedings.

VIII. The parties' requests are the following:

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

(b) The respondent requests, as the main request, that the appeal be dismissed and the patent be

maintained as granted. Alternatively, the respondent requests that the case be remitted, or the patent be maintained, on the basis of one of the auxiliary requests 1-11 filed with the reply on 8 March 2022.

The respondent requests further than D14 and D17 be excluded from the appeal proceedings. The respondent also request that, if the Board considers D17 to prejudice the maintenance of the patent, the case be remitted to the opposition division.

IX. The appellant's arguments can be summarised as follows:

(a) In the main request, the parameters d(v,0.1), d(v, 0.5), and d(v,0.9) had been introduced between parentheses into points i)-iii) of claim 1. As a result of this amendment, claim 1 was to be interpreted such that the numerical ranges of each feature i), ii), and iii) applied also to the parameters d(v,0.1), d(v,0.5), and d(v,0.9). This represented added subject-matter

(b) The patent did not specify the experimental conditions for the measurement of the particle sizes. High variability was observed in when using different conditions, in particular when using the dry or the wet method. As a result of that uncertainty, the criteria of sufficiency of disclosure were not met.

(c) D14 represented the closest prior art. The claimed formulation differed from those of D14 by the particle size distribution. Neither examples 5 and 6 of the patent nor the data reported in D15 were

appropriate to support any improved effect. The problem to be solved was to provide an alternative dry powder formulation. The claimed solution, which represented a selection from D14, did not involve an inventive step. The advantages of smaller particles were known from D4-D6. Hence the criteria of inventive step were not met.

X. The respondent's arguments can be summarised as follows:

(a) D14 and D17 should not have been admitted to the first instance proceedings, and should therefore be excluded from the appeal proceedings.

(b) The relevant question under Article 100(c) EPC was whether the scope of claim 1 as granted was any different from claim 1 as filed. The terms introduced in parentheses in claim 1, namely d(v, 0.1), d(v,0.5) and d(v,0.9), were merely illustrative and not limiting, and did not change the interpretation of original claim 1. They simply referred to the points 10%, 50% and 90% in the volume distribution, which were already mentioned in claim 1 as filed. Hence no subject-matter had been added.

(c) A skilled person could easily make a particle size determination for the BDP preparation using common general knowledge. Hence, a single, specific method for accurately determining the particle size distribution did not need to be defined. In any case, D17 did not show that particle size could not be determined accurately. Any variability shown in D17 did not deprive the skilled person of promise

of the invention. Thus, the criteria of sufficiency of disclosure were met.

(d) Starting from D14, the differentiating features of claim 1 were the parameters of parts i), ii) and iii), the specific surface area and the particle size span of the BDP particles. As a result, the claimed formulations showed improved aerosol properties. A further consequence of these improvements in aerosol properties was that the claimed DPI formulations were therapeutically equivalent to a corresponding pMDI formulation. The objective technical problem was to provide a DPI formulation that was therapeutically equivalent to the corresponding pMDI formulation. The claimed solution involved an inventive step.

Reasons for the Decision

1. Admittance of D14 and D17 - Remittal in relation with D17

The Board did not accede to the respondent's request to exclude D14 and D17 from the appeal proceedings, and thus considered these documents to be part of the proceedings. In view of the Board's decision to grant the respondent's main request, namely to dismiss the appeal and maintain the patent as granted (for the reasons given below), a reasoning in this respect is not necessary, nor is it necessary to consider the respondent's conditional request for remittal to the opposition division.

2. Main request (patent as granted), Article 100(c) EPC

2.1 The appellant objects to the introduction, between parentheses, of the parameters d(v,0.1), d(v,0.5), and d(v,0.9) into points i)-iii) of claim 1 (as shown below, amendments as compared with claim 1 as filed emphasized by the Board):

"i) no more than 10% of said BDP particles (d(v,0.1)) have a volume diameter lower than 0.6 micron;
ii) no more than 50% of said particles (d(v,0.5)) have a volume diameter comprised between 1.5 micron and 2.0 micron; and
iii) at least 90% of said particles (d(v,0.9)) have a volume diameter lower than 4.7 micron"

2.2 In accordance with the "gold standard" of G 2/10, amendments can only be made within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the application as filed. After the amendment the skilled person may not be presented with new technical information.

2.3 According to the appellant, the above amendment changes the interpretation of claim 1 of the main request. The skilled person reading claim 1 of the main request would understand that:
- the numerical ranges in each feature i)-iii), namely lower than 0.6 µm, between 1.5 µm and 2.0 µm, and lower than 4.7 µm,
- respectively apply not only to the "no more than 10%", "no more than 50%" and "at least 90%" of the particles,
- but also to d(v,0.1), d(v,0.5) and d(v,0.9).

According to the appellant, the application as filed lacks a basis for applying the above ranges to d(v, 0.1), d(v,0.5) and d(v,0.9).

2.4 According to the established case law, the skilled person should try, with synthetical propensity, i.e. building up rather than tearing down, to arrive at an interpretation of the claim which is technically sensible and takes into account the whole disclosure of the patent. The patent must be construed by a mind willing to understand, not a mind desirous of misunderstanding.

2.5 For the following reasons, the Board does not accept the appellant's interpretation, because it neither stems from the wording of claim 1, nor is it technically sensible.

2.5.1 Firstly, the mere presence, in features i)-iii), of both the parameters d(v,0.1)/d(v,0.5)/d(v,0.9) and the ranges (lower than 0.6 µm / between 1.5 µm and 2.0 µm / lower than 4.7 µm) does not entail that these parameters must be in these ranges.

For a given particle size distribution, the generally accepted definitions of the parameters d(v,0.5), d(v, 0.9) and d(v,0.1) are the following (see e.g. D12, chapter 6, page 6-5; paragraph [0032] of the patent):
- the volume median diameter d(v,0.5) is the volume diameter where 50% of the distribution is above and 50% is below,
- d(v,0.9), where 90% of the volume distribution is below, and
- d(v,0.1), where 10% of the volume distribution is below.

Accordingly, in the expression "no more than 10% of said BDP particles (d(v,0.1)) have a volume diameter lower than 0.6 micron", d(v,0.1) is a volume diameter expressed in microns. This volume diameter cannot itself "have a volume diameter". Thus, in each of the features i)-iii) of claim 1 of the main request, the expression "have a volume diameter" (using the plural "have") refers to the 10/50/90% of particles, and not to the diameter d(v,0.1), d(v,0.5) or d(v,0.9).

In other words, the literal wording of claim 1 does not support the appellant's interpretation for any of the features i)-iii).

2.5.2 Secondly, in the case of feature i), it is technically illogical to consider that the range "lower than 0.6 micron" could apply to "no more than 10% of the particles", and at the same time to d(v,0.1).

This is because, as submitted by the respondent (see page 7 of the reply dated 8 March 2022), "no more than 10% of said BDP particles have a volume diameter lower than 0.6 micron" has exactly the same meaning as "the d(v,0.1) is 0.6 micron or above". This precludes that d(v,0.1) be lower than 0.6 µm.

Accordingly, the skilled person would rule out the appellant's interpretation because it is illogical.

2.6 Nonetheless, the Board does not accept the respondent's interpretation either, according to which the terms d(v,0.1), d(v,0.5) and d(v,0.9) in parentheses only refer to the points, mentioned in claim 1 as filed, of 10%/50%/90% in the particles volume distribution. The parameters d(v,0.1), d(v,0.5) and d(v,0.9) are diameters, not percentages of particles. In addition,

in the case of feature ii), d(v,0.5) expresses that 50% of the particles have a volume diameter in the range 0-d(v,0.5), which is unrelated to saying that no more than 50% of the particles have a volume diameter in the range 1.5-2.0 µm. The Board also emphasizes that, contrary to the respondent's arguments, the question under Article 100(c) EPC is not whether the amendment changes the scope of the claims (see the gold standard, 2.2 above).

2.7 The fact that the parameters d(v,0.1), d(v,0.5) and d(v,0.9) are put between parentheses in features i)-iii) of claim 1 of the main request may raise doubts as to their significance for the definition of the claimed subject-matter. But, more importantly, as explained above, their presence in features i)-iii) of claim 1 *cannot* be given any meaningful interpretation, both for technical reasons and considering the wording of claim 1.

In these circumstances, the Board cannot share the appellant's opinion that the addition of the parameters d(v,0.1), d(v,0.5) and d(v,0.9) renders claim 1 ambiguous. Their addition in parentheses does not present the skilled person with two technically possible interpretations, but would on the contrary be simply disregarded by the skilled reader when interpreting claim 1, because they cannot be ascribed any technically sensible meaning. As a consequence, claim 1 of the main request cannot be considered to present the skilled person with new technical information.

Accordingly, the main request does not contain added subject-matter.

3. Main request (patent as granted), Article 100(b) EPC

3.1 According to the appellant, claim 1 defines a narrow range of small particle sizes, which requires an indication not merely of the apparatus used but also of the measurement conditions. The patent would not specify these experimental conditions. D17 would show that high variability is observed in when using different conditions, in particular when using the dry or the wet method. As a result of that uncertainty, the skilled person would not know when a product according to the alleged invention has been arrived at, or if it has the requirements to fulfill the alleged technical effect, and would be deprived of the alleged invention.

3.2 The Board does not share the appellant's view.

Firstly, even if it were accepted, the lack of accuracy in the determination of the particle sizes, or the appellant's argument that the skilled person does not know when a product according to the alleged invention has been arrived at, are not as such a valid basis for denying sufficiency of disclosure. To the extent that the conditions for measuring the particle sizes are not defined, the features of claim 1 relating to these particle sizes should be given their broadest technical sensible meaning in the context they appear.

The Board furthermore agrees with the findings of T1845/14 (see point 9 of the reasons) that in case of an unclear parameter defined in a claim whose values required in the claim are indicated in the specification to be essential to solving the problem underlying the patent at issue, the ability of the skilled person to solve that problem by reproducing what is claimed is not a suitable criterion for

assessing sufficiency of disclosure when the problem or an effect derivable from it are not explicitly or implicitly part of the definition of the claimed subject-matter (see the Case Law of the Boards of Appeal, 10th edition, 2022, II.C.5.5.1). In the present case, there is no demonstration that, as a result of the lack of precision in claim 1 as to the method for determining the particle sizes, the skilled person is unable to prepare dry powder formulations which meet the features of claim 1.

Accordingly, the criteria of sufficiency of disclosure are met.

4. Main request (patent as granted), inventive step

4.1 Closest prior art

The appellant identifies D14 as the closest prior art.

D14 (see example 6, with reference to examples 5 and 1) discloses dry powder formulations comprising:

a) a fraction of fine particles made of a 98:2 mixture of particles of α-lactose monohydrate and magnesium stearate having a mass median diameter (MMD) of 6 µm, either conditioned (samples #2 or #8) or not;

b) a fraction of coarse α-lactose monohydrate particles with a mass diameter of 212-355 µm, the ratio fraction a) : fraction b) being 90:10,

c1) micronized FF dihydrate particles, and

c2) micronized BDP particles.

D14 merely discloses that the BDP particles in example 6 are micronized, but does not disclose their particle size distribution. Contrary to the appellant's opinion, it cannot be derived from the general disclosure of D14 (see page 13, lines 23-25) that at least 90% of the BDP particles have a particle size lower than 6 µm. This passage ("Advantageously, at least 90% of the particles of the drug (active ingredient) have a particle size less than 10 micron, preferably less than 8 micron, more preferably less than 6 micron") neither refers to example 6 nor specifies which active ingredient is meant, and considers particle sizes of up to 10 µm. Likewise, the passage of D14 on page 6 (lines 23 to 26) generally defines the respirable dose as corresponding to particles ≤ 4.7 µm, but says nothing about the size distribution of the BDP particles present in the formulation of example 6 of D14.

4.2 Differentiating features

The Board concurs with the opposition division that D14 does not disclose that the BDP particles have the following features of claim 1:
- the particle size distribution values i), ii) and iii),
- the particle size span of 1.2-2.2, and
- the specific surface area of 5.5-7.0 m^2/g.

4.3 Technical effect and problem to be solved

4.3.1 According to the respondent, the claimed formulations show improved aerosol properties, in particular a higher fine particle fraction (FPF) of BDP less than 1 micron and a lower mass median aerodynamic diameter (MMAD) compared to D14. As a result of these improvements in aerosol properties, the claimed DPI

formulations would be therapeutically equivalent to a corresponding pMDI formulation (see paragraph [0049] of the patent).

4.3.2 The Board agrees that an improvement in aerosol properties is credibly demonstrated by a comparison of:
- the formulation of example 4 of the patent (see table 2, paragraph [0123]), with
- a comparative formulation according to example 6 of D14 and its evaluation in D15 (part B).
The BDP particles in the comparative formulation of D15, part B, are in particular characterised by a d(v, 0.1)=0.547 and a span of 2.264 (see the respondent's letter dated 31 March 2023, page 3), i.e. the comparative formulation neither fulfills condition i) nor has a span value as defined in claim 1 of the main request.

The comparison shows improvements in particular with regards to:
- higher BDP fine particle fraction (FPF) <1 micron (26.9% or 26.2% in the patent vs. 23.5% in D15), and
- lower BDP mass median aerodynamic diameter (MMAD) (1.23 or 1.25 µm in the patent vs 1.4 µm in D15).

The appellant contends that this comparison is invalid because the sample analysed in D15, part B, has an MMAD of 1.4, which is the worst value reported in D14 for the various samples of example 6 (1.38, 1.4, 1.31). The Board does not share this position. Firstly, the formulations compared credibly show that the above effects are associated with the differentiating features, namely the particle size distribution. And secondly, as reasoned by the opposition division (see point 8.5 of the appealed decision), D15 (part B) evaluates a formulation of D14 and finds it to have an

MMAD of 1.4. This does not mean that a specific sample of example 6 of D14 was taken, or that other samples of D14 would come closer to the claimed invention in terms of particle size distribution. Thus this argument does not call into question the observed effects.

4.3.3 The respondent further relies on part C of D15. Part C evaluates a comparative formulation prepared similarly to example 4 of the patent, except for the particle size distribution, in particular where the d(v, 0.9)=8.799 µm is outside the range of feature iii) of claim 1 ("lower than 4,7 µm"). The Board accepts this comparison as suitable to show an effect over D14, because D14 is silent as to the BDP d(v,0.9) in example 6 (see 4.1 above), and because a d(v,0.9) of 8.799 µm falls within the ambit of the general statement on page 13 of D14 (lines 23-25) which considers that "at least 90% of the particles of the drug (active ingredient) have a particle size less than 10 micron".

The comparison of part C of D15 with example 6 of the patent shows that the claimed particle size distribution is associated with an higher FPF (59.4%-60.1% in example 4 of the patent vs 44.4% in D15 part C) and improved MMAD (1.23-1.25 µm in example 4 of the patent vs 3.66 µm in D15 part C).

4.3.4 The objective technical problem is thus, as concluded by the opposition division, the provision of an improved dry powder formulation comprising a mixture of FF dihydrate and BDP with which a higher fraction of particles is deposited into the lungs.

4.4 Obviousness of the solution

The prior art provides no pointer to select a particle size distribution as claimed for the formulation of example 6 of D14 so as to improve aerosol properties, in particular a higher FPF less than 1 microns, and achieve the deposition of a higher fraction of particles into the lungs.

D14 does not focus on the properties of the active ingredient but rather on a conditioning of the carrier particles so as to reduce electrostatic charges and increase the uniformity of distribution of the drug particles (see page 8, lines 2-6). Neither the passage on page 13 (lines 23-25, regarding a particle size less than 10, 8 or 6 µm for at least 90% of the particles of the active ingredient), nor the passage on page 6 (lines 23-26, mentioning a respirable dose corresponding to particles ≤ 4.7 µm) teach to use the claimed particle size distribution for the BDP particles in the formulation, nor the resulting improvements.

The further documents cited by the appellant do no change this conclusion.

D4 addresses the different problem of preventing agglomeration when delivering low-dosage strength active ingredients (see paragraphs [0015]-[0016]). These low-dosage strength active ingredients are defined by a nominal dose per actuation of less than 20 µg (see paragraph [0030]), which covers FF or carmoterol, but not BDP (see paragraph [0097] of the patent). The appellant's reasoning, relying on a generalisation of the teaching of D4 regarding the low-dosage strength active ingredient FF (see paragraphs

[0040]-[0044] and [0052]; example 2) to the much higher-dosed BDP, is based on hindsight. D4 mentions that BDP may be present as a second active ingredient (see paragraph [0069]), possibly with the same particle size distribution of the low-dosage strength active ingredient (see paragraph [0070]), but there is no indication that this would solve the problem of providing a high respirable fraction of BDP. The general teaching in D4 (see paragraph [0007]), according to which micronized particles considered respirable are generally those with a particle size of 0.5-10 µm, preferably 0.5-5 µm, does not lead the skilled person to the claimed solution either. As argued by the respondent, the question is not whether it is desirable to provide a formulation that penetrates the lungs better, but how to achieve this in a DPI formulation.

D5 and D6 relate to pMDI solution formulations, and their teaching cannot be extrapolated to the present dry powder (DPI) formulations. Thus, the statements in D5 (see section 3, page 480; figure 1; section 10, lines 7-11, lines 25-30) regarding an extra-fine BDP / FF combination are made in the context of pMDI HFA formulations. No particle size distribution as claimed, nor any teaching of how any such characteristics might transpose to DPI formulation, are shown in D5. The brief mention, in D6 (see page S88, right column, "Inhaled drug deposition studies"), of aerosolized droplets in a size range resulting in smaller solid drug particles, would not bring the skilled person, starting from D14, any closer to the claimed invention.

4.5 Accordingly, the main request fulfills the requirements of inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated