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**Datasheet for the decision  
of 10 February 2011**

**Case Number:** T 0058/08 - 3.3.02

**Application Number:** 01974368.1

**Publication Number:** 1322301

**IPC:** A61K 9/72

**Language of the proceedings:** EN

**Title of invention:**

Combination particles for the treatment of asthma

**Patentee:**

Orion Corporation

**Opponent:**

Glaxo Group Ltd.

**Headword:**

Combination particles/ORION CORP.

**Relevant legal provisions:**

EPC Art. 56, 111(1)

RPBA Art. 12, 13

**Keyword:**

"Main request and auxiliary requests 1 to 4; Inventive step  
(no): The claimed particles lack an inventive step"

"Auxiliary request 5: not admissible"

"Auxiliary request 6: admitted into proceedings"

"Remittal"

**Decisions cited:**

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**Catchword:**

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Case Number: T 0058/08 - 3.3.02

**DECISION**  
of the Technical Board of Appeal 3.3.02  
of 10 February 2011

**Appellant:** Glaxo Group Ltd.  
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**Representative:** Florence, Julia Anne  
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**Appellant:** Orion Corporation  
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**Representative:** Sexton, Jane Helen  
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**Decision under appeal:** Interlocutory decision of the Opposition  
Division of the European Patent Office posted  
16 November 2007 concerning maintenance of  
European patent No. 1322301 in amended form.

**Composition of the Board:**

**Chairman:** U. Oswald  
**Members:** M. C. Ortega Plaza  
L. Bühler

## Summary of Facts and Submissions

I. European patent No. 1 322 301, which was filed as application number 01974368.1, based on international application WO 02/28378, was granted on the basis of twenty-two claims.

Claim 1 as granted reads as follows:

- 1.** Inhalation particles incorporating, in an unagglomerated individual particle, a combination of a  $\beta_2$ -agonist and a glucocorticosteroid in a predetermined and constant ratio.

Independent claim 11 as granted reads as follows:

- 11.** Inhalation composition comprising particles incorporating, in an unagglomerated individual particle, a combination of a  $\beta_2$ -agonist and a glucocorticosteroid and in a predetermined and constant ratio.

Independent claim 16 as granted reads as follows:

- 16.** A method for preparing particles incorporating a combination of a  $\beta_2$ -agonist and a glucocorticosteroid, comprising the steps of:

providing liquid feed stock comprising a  $\beta_2$ -agonist and a glucocorticosteroid in a predetermined ratio:

atomising said liquid feed stock to create droplets;  
suspending said droplets in a carrier gas;  
passing said carrier gas and droplets suspended therein through a heated tube flow reactor under predetermined residence time and temperature history; and  
collecting the particles produced.

II. The following documents and exhibits cited during the proceedings are relevant for the present decision:

(1) US 6 051 257

- (2) US 4 590 206
- (3) US 6 030 604
- (5) WO 00/48587
- (6) EP-B1-0 416 950
- (7) EP-B1-0 416 951
- (8) WO 93/11773
- (9) D. Bouros, *Eur Respir J*, 1999, 14:627-632
- (12) WO 99/16419
- (13) WO 01/000312
- (D15a) Note for Guidance on Dry Powder Inhalers, EMEA CPMP, December 1998
- (D15b) Note for Guidance on Development Pharmaceuticals, EMEA CPMP, July 1998
- (16) Declaration of Dr M. van Oort dated October 2007
- (18) Extract from ABPI Data Sheet Compendium 1983-84
- (21) W. Tarsin, *Journal of Aerosol Medicine*, Vol. 17(1), 25-32, 2004
- (22) K. H. Assi, *Journal of Pharmaceutical and Biomedical Analysis* 41, 325-328, 2006
- (23) Declaration of Dr B. van Veen dated 31 December 2010 (together with Exhibits 1 and 2).

III. Opposition was filed and revocation of the patent in its entirety was requested pursuant to Articles 100(b) EPC (lack of sufficiency of disclosure) and 100(a) EPC (lack of novelty and lack of inventive step).

IV. The appeal lies from an interlocutory decision of the opposition division maintaining the patent in amended form on the basis of the second auxiliary request filed with letter of 18 September 2007 (Articles 102(3) and 106(3) EPC 1973).

The opposition division's decision contains an obvious error in the reproduction of claim 1 of the second auxiliary request made in point 5.1. This claim's wording is not a verbatim reproduction of claim 1 of the second auxiliary request, which is annexed to the opposition division's decision. Claim 1 of the second auxiliary request filed with letter of 18 September 2007 differs from claim 1 as granted in that the following has been added at the end of the claim:

", and in which at least 90% of the total weight of the particles is in crystalline form and in which the active ingredients constitute at least 90% of the total weight of the particles".

The opposition division admitted documents (12) to (15b) into the proceedings, but did not admit the test report filed by the opponent after the Rule 71(a) EPC 1973 period (document (16)).

The opposition division considered that the subject-matter in claim 1 of the main request was novel in view of the fact that the prior art did not disclose particles containing simultaneously the two active ingredients. However, in the opposition division's opinion the subject-matter in claim 1 of the main request lacked an inventive step in view of the fact that the combination of the teaching in documents (2) and (12) "cover(ed) each individual feature of claim 1".

As regards the first auxiliary request, the opposition division considered that the amendments met the requirements of Article 123(2) EPC.

The opposition division was of the opinion that the subject-matter claimed in the first auxiliary request lacked an inventive step in the light of documents (1), (2) and (12).

As regards the second auxiliary request, the opposition division's decision stated that no objections were raised by the opponent within the meaning of Article 123 EPC.

Additionally, the opposition division considered that the particles and, thus, the subject-matter claimed in the second auxiliary request involved an inventive step.

The opposition division considered that the requirements of sufficiency of disclosure were also met (Article 83 EPC).

- V. Both the patent proprietor and the opponent filed appeals to said decision.
- VI. The appellant-opponent filed with the grounds of appeal the declaration of Dr Van Oort dated 10 October 2007 (16).
- VII. The appellant-patent proprietor filed with the grounds of appeal a main request (set of claims as granted), and four auxiliary requests. The second auxiliary request filed with the grounds of appeal corresponds to the second auxiliary request before the opposition division.
- VIII. Both appellants filed counterarguments to the other party's appeal.

- IX. The appellant-patent proprietor filed as an additional document the "operating manual of a Büchi Mini Spray Dryer B-191".
- X. A board's communication expressing the board's preliminary opinion was sent to the parties as an annex to the summons to oral proceedings.
- XI. The appellant-patent proprietor filed with its letter of 7 January 2011 a main request and four auxiliary requests in order to replace the requests previously on file. It also filed two post-published documents (documents (21) and (22)) and a declaration by Dr Bert van Veen (23) together with Exhibits 1 and 2.

Claim 1 of the main request reads as follows:

1. **Inhalation particles incorporating, in an unagglomerated individual particle, a combination of a  $\beta_2$ -agonist and a glucocorticosteroid in a predetermined and constant ratio, and in which at least 90 % of the total weight of the particles is in crystalline form and in which the active ingredients constitute at least 90 % of the total weight of the particles.**

Claim 1 of the first auxiliary request reads as follows:

1. **Inhalation particles incorporating, in an unagglomerated individual particle, a combination of a  $\beta_2$ -agonist and a glucocorticosteroid in a predetermined and constant ratio, and in which at least 90 % of the total weight of the particles is in crystalline form and in which the relative crystallinity of an active ingredient is 90 % or higher and in which the active ingredients constitute at least 90 % of the total weight of the particles.**

Claim 1 of the second auxiliary request reads as follows:

1. Inhalation particles incorporating, in an unagglomerated individual particle, a combination of a  $\beta_2$ -agonist and a glucocorticosteroid in a predetermined and constant ratio, and in which at least 90 % of the total weight of the particles is in crystalline form and in which the molar ratio of the  $\beta_2$ -agonist to the glucocorticosteroid is from 1:1 to 1:1000, which particles are free from material other than the active ingredients.

Claim 1 of the third auxiliary request reads as follows:

1. Inhalation particles incorporating, in an unagglomerated individual particle, a combination of a  $\beta_2$ -agonist and a glucocorticosteroid in a predetermined and constant ratio, and in which at least 90 % of the total weight of the particles is in crystalline form and in which the molar ratio of the  $\beta_2$ -agonist to the glucocorticosteroid is from 1:5 to 1:1000, which particles are free from material other than the active ingredients.

Claim 1 of the fourth auxiliary request reads as follows:

1. Inhalation particles incorporating, in an unagglomerated individual particle, a combination of a  $\beta_2$ -agonist and a glucocorticosteroid in a predetermined and constant ratio, and in which at least 90 % of the total weight of the particles is in crystalline form and in which the molar ratio of the  $\beta_2$ -agonist to the glucocorticosteroid is from 1:10 to 1:1000, which particles are free from material other than the active ingredients.

XII. Oral proceedings took place on 10 February 2011.

During the oral proceedings the appellant-patentee filed two further set of claims as fifth and sixth auxiliary requests.

The set of claims of the sixth auxiliary request contains only method claims.

Claim 1 of the sixth auxiliary request reads as follows:



"1. A method for preparing particles incorporating, in an unagglomerated individual particle, a combination of a  $\beta_2$ -agonist and a glucocorticosteroid in a predetermined and constant ratio, and in which at least 90% of the total weight of the particles is in crystalline form and in which the active ingredients constitute at least 90% of the total weight of the particles, said method comprising the steps of: providing liquid feed stock comprising a  $\beta_2$ -agonist and a glucocorticosteroid in a predetermined ratio; atomising said liquid feed stock to create droplets; suspending said droplets in a carrier gas; passing said carrier gas and droplets suspended therein through a heated tube flow reactor **which is in a** vertical configuration under predetermined residence time and temperature history; and collecting the particles produced".

XIII. The appellant-opponent's submissions as far as relevant for the present decision may be summarised as follows:

The appellant-opponent did not object to the admissibility of the main request and auxiliary requests filed with the letter of 7 January 2011. However, it referred to Article 12 RPBA and objected to the admissibility of the declaration, document (23), and of the post-published documents (21) and (22). It submitted that the late-filing of the two post-published documents (21) and (22) was not justified since the issues they intended to respond to were already the subject of dispute during the opposition proceedings (objections were already raised with the grounds of appeal). Moreover, with regards to document (23) even though the appellant-patentee had

submitted that it could not have been filed earlier, this was not a guarantee for its admissibility to such a late stage. The appellant-opponent alleged that the spray dryer model required for the use of acetone as solvent had been available since 2003.

The appellant-opponent contested the admissibility of the auxiliary requests filed at the oral proceedings before the board (i.e. auxiliary requests 5 and 6). It contended that these sets of claims should have been submitted earlier and that they did not represent a response to any of the discussions prior to their filing during the oral proceedings. Moreover, they opened new issues for discussion at such a late stage.

At the beginning of the oral proceedings the board expressed the preliminary opinion that the subject-matter in claim 1 of the main request appeared to meet the requirements of novelty. Thereafter the appellant-opponent stated that it had no further submissions, and referred to its written submissions in relation to its position against novelty.

As regards the issue of inventive step in relation to claim 1 of the main request the appellant-opponent submitted the following. Document (2) which disclosed inhalation particles for penetration to the lung and treatment of allergic airway diseases by inhalation, represented the closest prior art. The following criteria were to be considered for the determination of the closest prior art: same technical field, same purpose or same objective, and most relevant technical features in common, i.e. requiring the minimum of structural modifications (Case Law of the Boards of

Appeal, 6th edition 2010, I.D.3, point 3.1). In this context, the appellant-opponent cited paragraph [0001] of the patent in suit; and column 2, lines 15-18 and column 4, lines 42-49 of document (2).

The appellant-opponent further submitted the following. Document (2) generically disclosed the mixture of inter alia a steroid and a  $\beta_2$ -agonist, and specifically disclosed unagglomerated individual particles incorporating a mixture of two active ingredients in a predetermined constant ratio, in which the active ingredients constitute at least 90% of the total weight of the particles. Document (2) had been acknowledged in paragraph [0007] of the patent in suit. Run 8 in table 1 of document (2) related to particles incorporating a combination of sodium cromoglycate and isoprenaline sulphate which corresponded to a commercial mixture of two active agents in individual particles, as shown by document (18); and run 7 in table 1 disclosed particles incorporating the combination of cromoglycate and salbutamol sulphate (i.e. a  $\beta_2$ -agonist). The active ingredients constituted 100% of the particles prepared in run 7 (this was also the case of runs 6 and 8). Document (2) did not specify the particles as being 90% crystalline but there was a secondary indication to crystallinity at the top of column 6 where it was stated that the spray-drying technique employed for the preparation of the particles removed the need for recrystallization. The problem to be solved was to provide further combination particles for inhalation containing a  $\beta_2$ -agonist. The problem to be solved could not be to provide an improvement since no improvement had been shown over document (2) or anything else. The solution was to use a corticosteroid

together with the  $\beta_2$ -agonist and that 90% of the total weight of the particles was in crystalline form. The mere allegation by the patentee of an improvement or advantage had not been supported by any evidence.

Asked by the board as to whether it made a distinction between providing "further" particles and providing "alternative" particles, the appellant-opponent answered that what it had meant was that the problem was simply to provide for an alternative to the known particles and that the solution was obvious. At the effective filing date of the patent in suit it was well known from the prior art (e.g. documents (3) to (9)) to employ a combination of corticosteroid and a  $\beta_2$ -agonist for inhalation. Documents (6) to (8) were acknowledged in the application as filed. Additionally, particles in crystalline form were known in documents (5) and (1). Thus, to provide particles in crystalline form was an obvious solution.

The appellant-opponent further stated that the patent proprietor had chosen during the written proceedings (in particular it cited the patentee's grounds of appeal) a different starting point rather than choosing document (3) as closest prior art. Document (3) addressed the problem of preparing accurate doses when active ingredients were formulated in association with carriers such as lactose, since the small size particles separate from lactose carrier particles in the reservoir. Document (3) disclosed to preserve separation of lactose particles from active ingredient particles and to ensure content uniformity (active substance and carrier substance being substantially uniformly distributed).

The appellant-opponent also submitted that the issue of having a uniform ratio and dose was not an unknown problem on the effective filing date of the patent in suit. The formulator took it into account when preparing the formulations in order to comply with the regulatory requirements for dose uniformity in medicinal products as shown in documents (15a) and (15b) for dry powder inhaler systems. Thus, the problem of dose uniformity had been recognised and dealt with by the skilled person in the art.

Document (2) disclosed in an unagglomerated individual particle a combination of two active ingredients, and thus provided for a constant and predetermined ratio of the active ingredients. The appellant-patentee's arguments in relation to the crystallinity issue concerned the process of preparation, and did not support the inventiveness of the particles, since crystallinity was a known feature of inhalation particles in the prior art. Document (3) concerned the prevention of dissociation of drug particles and lactose particles; the claimed particles did not solve that problem. It was necessary to distinguish between differences in dose and differences in ratio. The problem defined by the patentee encompassed in fact several partial problems and claim 1 related to a mere aggregation of features (Case Law of the Boards of Appeal, 6th edition 2010, I.D.8, point 8.2.2). The problem of providing two active ingredients in unagglomerated individual particles in a constant ratio was solved in document (2), crystallinity having no bearing in that problem. As regards the alleged improvement in the stability of the particles, it had

not been proven that that problem had actually been solved. The problem of morphology of the particles was a different problem from dose consistency. Dose consistency and reproducibility was a recognised problem, regulated by the authorities. As regards the appellant-patentee's argumentation that those in the field were going for mixtures of the active ingredients and not for a combination incorporated in the individual particles, the time factor alone was not a yardstick for inventive step (T 109/82, OJ EPO 1984, 473). The compositions containing the mixture of components met the regulatory requirements and, thus, the skilled person did not face a long felt need in this respect.

The appellant-opponent further contested the allegation that the claimed invention related to an improvement in relation to either dose consistency or stability. The statement in paragraph [0018] of the patent in suit was not backed up by any evidence. Moreover, the skilled person in the field knew that crystallinity played a role in stability. As a matter of fact, many compounds have polymorphs. A certain polymorph crystal may be more stable than another or vice versa. The state of the art made it clear that to have particles with a partial amorphous and partial crystalline character led to undesirable transformations affecting stability. This problem was dealt with in document (3) by removing amorphous areas for attaining stability (*inter alia* column 2, line 62). Additionally, claim 1 of the main request did not require both active ingredients to be in crystalline form, nor did it express any ratio for the active ingredients incorporated in the particles. Thus, the claim gave no indication as to which was the

component in crystalline form. Additionally, the 90% requirement in the claim did not even imply that a particular component had to be crystalline. The example in the patent in suit showed that only one of the active ingredients was in crystalline form. Thus, the claim's feature related to an arbitrary level of crystallinity and there was a lack of evidence making it plausible that the problem as defined by the patent proprietor had been solved. The problem to be solved had to be defined using objective criteria. The technical problem was not always what the patentee thinks it is. Document (2) provided for a constant ratio of the two active ingredients. It was not important whether this problem had been expressly mentioned therein, what mattered was whether the skilled person objectively recognised it as the problem when comparing the closest prior art with the invention (Case Law of the Boards of Appeal, 6th edition 2010, I.D.4, point 4.3 and T 910/90, date of decision 14 April 1993).

As regards claim 1 of the first auxiliary request, the appellant-opponent submitted the following. Claim 1 contained all features of claim 1 of the main request with the addition of the specification that "the relative crystallinity of an active ingredient is 90% or higher". Apart from the fact that the description in the application as filed mentioned "the relative **degree** of crystallinity of an active ingredient", said feature did not add anything to inventive step nor did contribute functionally to the solution of the technical problem. The active ingredient for which a relative degree of crystallinity was specified may be the one in the smaller proportion and only amount to a

few percent in relation to the total weight of the particles. It had not been shown that the particles had improved stability in the light of said feature. Thus, the arguments submitted for the main request applied *mutatis mutandis* for the first auxiliary request.

As regards the alleged stability of the particles, the appellant-opponent pointed to paragraph [0060] in the patent in suit which mentioned that Figure 5 showed that the powder was stable when exposed to different humidity levels, "with a maximum weight increase of 0.02% when exposed to 80% relative humidity level for 24h". The appellant-opponent stated that it was self-evident when looking at Figure 5 that the total exposure time was 15.3 hours and not 24 hours, and that the exposure to 80% relative humidity took place for one hour only. Figure 5 merely showed that the material "got wetter" when exposed to a higher relative humidity degree and when this level of relative humidity descended, then the material was less wet. Therefore, these experimental data were no proof of stability. Moreover, Figure 5 only reflected one single example according to the patent in suit, without comparison with any prior art products.

Additionally, DVS (dynamic vapour sorption) measurement was a technique of its own which required a particular software. The experimental results shown in the DVS figures in document (23) could not be directly compared with the results in Figure 5 since the time scale was different (minutes instead of hours). The experiments in document (23) were different in their nature from the experiments in example 1 since document (23) did not test particles containing a combination of two active ingredients. In the experiments shown in



Figure 5 in the patent in suit water sorption under a certain relative humidity was observed, and then one went to the next relative humidity level for further observation. It was a known phenomenon that amorphous material adsorbs more water. Moreover, the experimental results shown in document (23) came very close to those shown in the patent in suit.

As regards claim 1 of the second auxiliary request, the introduced feature concerning the specification of a broad range for molar ratios of the active ingredients did not add anything to the inventive step of the particles since it was merely an arbitrary selection of range values. Additionally, it was not credible that the alleged effects considered by the patentee for the definition of the problem were attained within the whole range. One of the active ingredients could be in a very small proportion in the particles. Moreover the ratios for such active ingredients were already known from document (5), page 5. Additionally, in document (2) the particles incorporating the two active ingredients in table 1 were free from other ingredients.

As regards claim 1 of the third auxiliary request, the appellant-opponent submitted that the arguments for the previous requests applied *mutatis mutandis*.

As regards claim 1 of the fourth auxiliary request, the appellant-opponent submitted that the same arguments as for the previous requests also applied, namely that the range of ratios did not change anything with regard to the inventive step issue since they were very similar to those specifically disclosed in document (5). No effect

had been shown, thus the stated ratios were arbitrary limitations of the scope claimed.

In relation to claim 1 of the sixth auxiliary request, the appellant-opponent submitted that the skilled person needed to know which of the components was in crystalline form in order to assess which means would be needed. In view of a lack of specification in claim 1 regarding which component was in crystalline form, the claimed subject-matter lacked clarity within the meaning of Article 84 EPC. Moreover, there was no recognizable feature in the process parameters listed in claim 1 for attaining a particular level of crystallinity.

Asked by the board, the appellant-opponent answered that it did not have any further objections within the meaning of Articles 84 or 123 EPC against the set of claims of the sixth auxiliary request.

As regards the question of remittal, the appellant-opponent stated that remittal to the department of first instance should only be envisaged when substantial amendments were introduced. It cited in this context decision T 063/86 (date of decision 10 August 1987). The appellant-opponent stated that the subject-matter of claim 1 of the sixth auxiliary request had already had "its own fate" before the opposition division.

XIV. The appellant-patentee's submissions as far as relevant for the present decision may be summarised as follows:

The board's communication sent as annex to the summons to oral proceedings mentioned that it may be necessary to redefine the technical problem. Documents (21) and (22) were filed to illustrate the fact that even after the filing date of the application underlying the patent in suit the problem of dose consistency existed. The declaration, document (23), had been late-filed because the equipment used in the experiments of document (16) was prohibited for being used with acetone as solvent. The patentee could reproduce the experiments in document (16) only when it was able to obtain the appropriate equipment. Thus, the experiments in document (23) addressed the same parameters as the experiments in document (16) and the same product and showed X-ray diffraction patterns of an amorphous product.

As regards the arguments in favour of the admissibility of auxiliary requests 5 and 6 the appellant-patentee submitted that they were filed in the light of the discussions during the oral proceedings. The board had stated in the introduction at the beginning of the oral proceedings that the subject-matter of claims 1, 11 and 16 would be considered independently. In the granted patent the corresponding claims were drafted as independent claims. Thus, the opponent could not have been taken by surprise if some of these claims were deleted. Claim 1 of the fifth auxiliary request corresponded to claim 11 of the main request in which some minor amendments had been introduced on the basis of page 5 of the description. Auxiliary request 6 was based on the main request and contained only the method claims.

As regards the inventive step issue for the subject-matter in claim 1 of the main request the appellant-patentee submitted the following. Document (3), and not document (2), represented the closest prior art. For the determination of the closest prior art a realistic approach should be made in which the formulation of the initial problem and the purpose to be achieved should be given enough weight, avoiding ex-post-facto considerations (decision T 686/91, date of decision 30 June 1994) and inappropriate hindsight (decision T 835/00, date of decision 7 November 2002). The patent in suit clearly set out the problem addressed in paragraph [0008] as being to provide a composition that is better adapted than products of the prior art, for delivery to the lungs. The preceding paragraphs, in particular [0006], mentioned the problem of dose inconsistency as a problem to be addressed. Dry powder compositions for administration by inhalation underwent over time segregation in the reservoir as a direct consequence of containing particles of different size and identity. The purpose of the "invention" in the patent in suit was to improve consistency of dosage. Thus, document (3) represented the closest prior art since it addressed this problem (column 3, line 16) and because it specifically disclosed the combination of budesonide and formoterol (column 2, lines 11-12). The selection of document (2), published in 1986, had been made with hindsight, since said document did not address the problem of uniform dosage. Document (2) disclosed a spray-drying method for providing doughnut-like particles for inhalation. There was no disclosure in document (2) about crystalline particles. Documents (3) to (8), all addressing the administration of a combination of the two active ingredients were

published within a ten-year period. The teaching from these documents was to crystallize first the individual ingredients and then mix and mill, with the result of defects in crystallinity. All these documents were facing the problem of trying to obtain a uniform mixture of particles that have a uniform dose.

Document (2) did not teach to select the runs 6 to 8 as preferred, or that they were useful to address that particular problem. In fact, document (2) also disclosed as an option the possibility to have a mixture of two or more different particles mixed (top of column 8). Thus, document (2) did not teach how to solve that problem. During the written proceedings there had been an exhaustive discussion about the crystallinity. The passage mentioned by the appellant-opponent in column 6 should be read within the context of the preceding sentence. Thus, it was only meant that preparing the particles by spray-drying did not require the steps of recrystallization and micronization to be to be performed first. However, spray-drying or flash-drying the active ingredients meant that drying was very rapidly and, thus, crystalline materials were not obtained. Document (3) reflected what has been done for ten years to achieve dose uniformity in terms of a consistent dose and a consistent ratio for administration of a combination of active ingredients, and none of the documents 3 to 8 gave any indication to put two active ingredients in a particle for solving that problem.

The appellant-patentee defined the problem to be solved as providing a composition that ensures a consistent dose and ratio when administering a combination of active ingredients. It further submitted that the

solution was a combination of active ingredients incorporated in the unagglomerated individual particle, and that crystallinity provided stability. The particles in claim 1 of the main request may contain up to 10% of excipient, but the example in the patent in suit made it credible that crystallinity played a role in stability.

The appellant-patentee also stated that the behaviour of particles containing a combination of two active ingredients was different from that of a mixture of particles having separate ingredients since one of the ingredients may be more adhered to the carrier than the other. This could lead to inconsistent ratio and dose. There was no incitement for the skilled person to look into document (2) at the first place. Moreover, even if document (2) was put under the eyes of the skilled person, said document did not teach to solve the problem of an inconsistent ratio. There was nothing in document (2) to suggest the benefits of particles simultaneously containing both ingredients in relation to consistency of dose and constant ratio. It was not inevitable to arrive at the claimed solution.

The appellant-patentee further submitted that the definition of the technical problem should not contain any pointer to the solution proposed in the patent.

As regards claim 1 of the first auxiliary request the appellant-patentee stated that as submitted in writing, the major component in the particles of example 1, constituting 97% of their total weight, was found to be in crystalline state and that these particles were found stable when exposed to different humidity levels

as shown in Figure 5. Even if the exposure at 80% relative humidity only lasted for a couple of hours, the experiments in example 1 showed that the powder according to the "invention" adsorbed a very low percentage of water. The experimental data about vapour sorption and crystallisation in the DVS figures in document (23) showed that when there was a certain amorphous content the particles adsorbed more water and undesirable vapour-induced crystallisation was observed. The particles according to the "invention" were not amorphous but crystalline and, thus, there was less water adsorption.

The appellant-patentee stressed that one could not extrapolate from the XRD (X-ray diffraction) in Figure 4 in the patent in suit that the second active ingredient was in amorphous form (it might be partly amorphous). The relevant feature in the claim was that the particles were at least 90% in crystalline form and free from other ingredients. This excluded the possibility of the excipient being the crystalline material. Thus, the stability derived from the crystallinity of the active ingredient(s).

As regards claim 1 of the third and fourth auxiliary requests the appellant-patentee submitted that as the ranges were defined more narrowly it was more credible that the intended effects were achieved. The opponent had not provided any evidence to disprove it.

In relation to claim 1 of the sixth auxiliary request, the appellant-patentee submitted that it was perfectly clear that it was the unagglomerated individual particles which were in crystalline form (at least 90%

of the total weight of the particles was crystalline). This feature did not determine the relative crystallinity of each component in the particles. Moreover, the skilled person was able to adjust the process parameters within the teaching of the patent in order to attain the features in claim 1.

The appellant-patentee did not express any comments against the remittal to the department of first instance.

- XV. The appellant (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or, in the alternative, one of the auxiliary requests 1 to 4, all filed with the letter of 7 January 2011, or on the basis of auxiliary request 6 submitted during the oral proceedings.

The appellant (opponent) requested that the decision under appeal be set aside and that European patent No 1322301 be revoked.

## **Reasons for the Decision**

### 1. *Admissibility*

1.1 The appeals are admissible.

### 1.2 *Admissibility of the requests*

Article 12(2) RPBA set outs the general principle that the statement of the grounds of appeal and (in the case



of *inter partes* proceedings) the reply to the other party's submissions must contain a party's complete case.

However, according to Article 12(4) RPBA everything presented by the parties in accordance with Article 12(1) RPBA shall be taken into account by the board if and to the extent it relates to the case under appeal and meets the requirements of Article 12(2) RPBA. This is without prejudice to the power of the board to hold inadmissible facts, evidence or requests which could have been presented or were not admitted in the first instance proceedings.

The main request filed with the letter of 7 January 2011 corresponds to a typographical version of the second auxiliary request before the opposition division (this request was never abandoned, it was filed as second auxiliary request with the grounds of appeal). Thus, the main request is admissible.

Additionally, the auxiliary requests filed with the letter of 7 January 2011 relate to a fair attempt to reply to the board's communication sent as an annex to the summons to oral proceedings. The appellant-opponent has not contested their admissibility. Therefore, auxiliary requests 1 to 4 are also admissible.

The sixth auxiliary request was filed at the oral proceedings before the board after the discussion about the inventive step of product claim 1 in the main request and auxiliary requests 1 to 4 had taken place. The set of claims of the sixth auxiliary request differs from the set of claims of the main request in

that all the product claims have been deleted and it only contains the method claims. As pointed out in the board's communication sent as an annex to the summons to oral proceedings, the set of claims as granted contained several independent claims. Independent claim 16 as granted was directed to a method. Thus, the filing as an auxiliary request of an amended set of claims in which all product claims are deleted (claims 1 to 15 in the main request) is an admissible procedural step which cannot be considered to take the appellant-opponent by surprise. Moreover, in view of the remittal to the department of first instance the appellant-opponent's right to be heard is fully preserved. Therefore, auxiliary request six is admissible.

The fifth auxiliary request was filed at the oral proceedings before the board at the same time as the sixth auxiliary request. The amendments introduced in the set of claims of the fifth auxiliary request were not confined to the mere deletion of claims. The product claims directed to particles (claims 1 to 10 in the main request) were in fact deleted, but at the same time some amendments were undertaken to the claim directed to an inhalation composition (claim 11 in the main request). These amendments corresponded to the introduction of several specifications from the description which were not present in any of the sets of claims previously on file. Therefore, the set of claims of the fifth auxiliary request opened at such a late stage in the proceedings new issues for discussion in the product claims. Thus, the fifth auxiliary request is not admissible.

The appellant-patentee argued that the fifth auxiliary request should be found admissible since it represented a direct response to the discussion at the oral proceedings prior to its filing. However, the discussion about inventive step of the particles in claim 1 of the requests on file did not contain any elements not directly derivable from the arguments and evidence in the written file. Thus, the late filing of an amended claim directed to compositions containing particles as those defined in claim 1, in which some other features were introduced from the description, was not justified. A patent proprietor may submit amended claims during the proceedings. However, in *inter partes* appeal proceedings the principles of fairness and equity in relation to all parties must apply. Therefore, the fifth auxiliary request is not admissible.

### 1.3 *Admissibility of further evidence and documents*

The filing of the declaration of Dr van Oort containing an experimental report (document (16)) with the appellant-opponent's grounds of appeal (Article 12(1) RPBA) served as direct support for the grounds of appeal of the appellant-opponent. This is a normally acceptable procedural step and, thus, document (16) is admissible.

During the written appeal proceedings the appellant-opponent had contested the admissibility of document (16) in view of the safety implications in connection with the use of the Büchi mini Spray Dryer B-191 and an organic solvent such as acetone (it was in fact prohibited, as stated in the safety instructions

and recommendations of the manufacturer in the operating manual). Thus, the late-filing of the declaration of Dr van Veen containing an experimental report (document (23)) was justified since the experiments in document (16) could not have been reproduced earlier. The filing of document (23) took place after the appellant-patentee had acquired a new spray dryer model, Büchi B-290, which could be used with acetone, allowing a reproduction of the experiments in document (16). There is no evidence on file to support the appellant-opponent's assertion that the spray dryer model required for the use of acetone as solvent had been available since 2003.

Additionally, the appellant-opponent did not request a postponement of the oral proceedings in order to be able to deal with the content of document (23).

Article 13 RPBA makes it clear that the assessment of the admissibility of late-filed submissions lies within the board's discretionary power, after the circumstances of the case have been examined. Thus, in the light of the circumstances depicted above, the board has decided to exercise its discretionary power to admit document (23).

As regards the admissibility of the two late-filed post-published documents (21) and (22), the board sees no objective reasons for justifying their late-filing. The appellant-patentee's argumentation in favour of their admissibility is based on the content of said documents as indirect proof that dose consistency was a technical problem existing at the time of the "invention". However, the discussion about dose

consistency was a major point of disagreement throughout the opposition and appeal proceedings and thus it was not an issue raised for the first time by the board with the communication sent as an annex to the summons to oral proceedings. Thus, documents (21) and (22) are not admitted into the proceedings.

2. *Main request*

2.1 *Novelty*

Having regard for the fact that the main request manifestly fails for other reasons, the board sees no need to give a full assessment of the novelty of the subject-matter claimed.

2.2 *Inventive step*

2.2.1 Document (3) discloses pharmaceutical compositions suitable for administration by inhalation, in particular dry powder compositions comprising one or more potent pharmaceutically active substances and a carrier substance, all of which are in finely divided form (column 1, lines 26 to 30, column 2, lines 3-4, column 3, lines 20-21).

Document (3) which specifically discloses dry powder compositions containing the combination of budesonide (glucocorticosteroid) and formoterol ( $\beta_2$ -agonist) (column 2, lines 11 to 13) represents the closest prior art.

Document (3) discloses that: "The ingredients of the formulation according to the invention must be in a

finely divided form, i.e. their mass median diameter should generally be less than 10  $\mu\text{m}$ " (column 2, lines 3-4).

Document (3) further discloses that: "The ingredients may be produced in the desired particle size using methods known to those skilled in the art, e.g. milling, micronization or direct precipitation" (column 2, lines 7-10).

Document (3) specifically discloses dry powder compositions containing the combination of budesonide (anti-inflammatory glucocorticosteroid such as those according to the patent in suit) and formoterol (bronchodilator  $\beta_2$ -agonist, such as those in the patent in suit) (column 2, lines 11 to 13).

Document (3) also discloses that when the active substances are formoterol and budesonide the molar ratio of formoterol to budesonide in the composition is preferably from 1:2500 to 12:1 (column 2, lines 14-17).

The compositions are prepared in document (3) by micronizing one or more active substances (or active ingredients) and the carrier substance, optionally followed by conditioning the product and spheronizing (column 2, lines 50-56).

Document (3) further teaches that: "The formulation according to the invention may be made by conventional techniques known per se. Such production processes generally comprise micronizing the ingredients to the required size, **removing the amorphous areas** on the particles obtained", ..., "and then agglomerating,

spheronizing and sieving the powder" obtained (emphasis added) (column 2, lines 59-65).

Document (3) also teaches that: "In solid-solid mixing one of the most important features is to ensure content uniformity. The major problem encountered in the powder mixing of fine powders is the inability of mixers to break down powder agglomerates. It has been found that a remicronization step after the conditioning step of the fine powder with low energy input is advantageous. It should generally be carried out using enough energy to break down powder agglomerates but not with so much energy that the size of the particles themselves is affected. Such a step gives a composition wherein the active substance, and carrier substance are substantially uniformly distributed, having for example a relative standard deviation of less than 3% (preferably less than 1%) and **does not disturb the crystallinity of the fines particles**" (emphasis added) (column 3, lines 6-19).

Example 6 in document (3) illustrates pharmaceutical compositions comprising formoterol fumarate, lactose monohydrate and budenoside, prepared by micronization (using a spiral mill), followed by **removing the amorphous regions**, (mechanical) mixing with the micronized second active ingredient and remicronization.

2.2.2 Therefore, in the light of the closest prior art the problem to be solved lies in the provision of alternative particles suitable for inhalation.

2.2.3 The solution as defined in claim 1 of the main request relates to particles, incorporating in an

unagglomerated individual particle a combination of a  $\beta_2$ -agonist and a glucocorticosteroid, in which the active ingredients constitute at least 90% of the total weight of the particles.

The board is satisfied that the problem has been credibly solved in the light of the description and examples in the patent in suit.

- 2.2.4 As regards the feature that 90% of the total weight of the particles is in crystalline form, this feature does not reflect any teaching going beyond the content of document (3). Document (3) expressly teaches the avoidance of amorphous regions in the crystal structure of the particles and discloses methods which are designed not to "disturb the crystallinity of the fine particles" (column 3, lines 18-19).

Additionally, in the absence of any technical evidence showing an effect linked to the specific choice of the value 90% of the total weight, this value is arbitrary and thus precluded from being considered as part of the solution to the problem defined in the light of the closest prior art. Moreover, it has to be recalled that the particles in claim 1 may contain up to 10% of the total weight of the particles of other ingredients. Thus, the claim does not require that both active ingredients are in crystalline form.

- 2.2.5 It now has to be assessed whether the proposed solution is obvious in the light of the prior art.

The skilled person working in the field of pharmaceutical technology has a comprehensive knowledge



about inhalation formulations and inhalation particles comprising one or more active ingredients and is thus aware of document (2), which discloses a "finely divided inhalation drug comprising a therapeutically effective proportion of **individual particles** capable of penetrating deep into the lung, characterised in that a bulk of the particles which is both **unagglomerated and unmixed with a coarse carrier**, is sufficiently free flowing to be capable of being filled into capsules on an automatic filling machine and to empty from an opened capsule in an inhalation device" (column 2, lines 14-23) (emphasis added).

Document (2) further discloses that the drug incorporated in the particles is to be chosen from among the medicaments used for inhalation treatment of allergic airway diseases and mentions among the list of appropriate drugs bronchodilators such as (inter alia) salbutamol, fenoterol, terbutaline and their salts (i.e.  $\beta_2$ -agonists), and steroids, e.g. beclomethasone dipropionate (i.e. glucocorticosteroid). Document (2) further teaches that a **desired mixture** of medicaments (active substances) may be used (column 4, lines 42-53).

Document (2) discloses two options, a mixture of different particles, incorporating one of the active ingredients (this option is mentioned on top of column 8), and particles simultaneously incorporating in an individual particle both active ingredients (this option is the option exemplified for the combination of two active substances in document (2)). In fact, the preparation of individual particles simultaneously containing two active ingredients is exemplified in example 1 and Table 1. Particles incorporating as

"active compound (A)" simultaneously sodium cromoglycate (an antiallergic drug, but not a steroid) and salbutamol sulphate ( $\beta_2$ -agonist) are exemplified in run number 7 in Table 1.

Therefore, document (2) teaches inhalation particles incorporating two active ingredients as an alternative to inhalation particles that result from a mixture of two different types of particles.

Whether the particles directly obtainable from the spray-drying method disclosed in document (2) contain amorphous regions or have a crystalline content lower than 90% of the total weight of the particles is immaterial for the inventive step assessment of the subject-matter in claim 1, since document (3) explicitly teaches how to attain crystallinity of the particles by further conditioning. In particular, document (3) discloses removal of amorphous regions on the particles using a known method in the art. Furthermore, it has not been shown that the morphology of the particles in claim 1 is only obtainable when using a specific method of preparation, unknown to the skilled person at the effective filing date of the patent in suit. As a matter of fact, the claim's wording does not contain any product-by-process features and is not delimited in any particular way in this respect. Furthermore, paragraph [0026] of the patent in suit states that "(o)ther methods commonly used in the preparation of inhalation particles for pulmonary drug delivery may also be suitable in the preparation of particles of the invention".

Therefore, the skilled person would have arrived at the proposed solution without making use of his/her inventive skills, just by following the teaching in document (2) to incorporate simultaneously the two active ingredients in the individual particles as an alternative to a mixture of different particles.

2.2.6 Therefore, the subject-matter of claim 1 of the main request is obvious in the light of the prior art.

2.2.7 As regards the appellant-patentee's argumentation in favour of a definition of the problem to be solved in which an improvement is considered, the following has to be said. There is no evidence on file relating to a direct comparison between the inhalation composition according to the patent in suit and the inhalation composition according to the closest prior art. Furthermore, there is no proof that the prior art compositions do not attain sufficient dose consistency for the intended uses disclosed. The appellant-patentee's argumentation amounts in fact to an unsupported allegation of non-enabling disclosure for the relevant prior art documents which cannot be followed.

The allegation made by the appellant-patentee that the claimed particles achieve an improvement over the prior art concerns a plausibility argumentation which is disputed by the appellant-opponent.

It has to be recalled that document (3) clearly and unambiguously teaches the skilled person not to disturb the crystallinity of the fine particles, once the amorphous regions are removed. This teaching inevitably

reflects a concern about the stability of the particles and makes the skilled person aware of the need to avoid uncontrolled amorphous-crystalline transformations in the final particles.

The experimental data in document (23) which relate to the undesirable vapour-induced crystallisation of amorphous regions in fluticasone propionate (glucocorticosteroid) particles, prepared by spray-drying from an acetone solution, only confirm this point. Thus, if amorphous particles or particles with amorphous regions are obtained by spray-drying, then the particles have to be further conditioned. However, an additional process requirement does not immediately render inventive the particles claimed.

Additionally, a distinction should be made between a dose consistency of the final composition for inhalation and a constant ratio of the active ingredients. There is no evidence on file that a final composition containing the particles of claim 1 and particles of a carrier such as lactose (see paragraph [0022] of the patent in suit) shows less segregation than the compositions known in example 6 of document (3). Thus, there is no proof that an improvement of dose consistency is achieved by the particles when administered in the final composition. Furthermore, ratio constancy is an elemental characteristic directly resulting from the fact that the individual particles incorporate both active ingredients simultaneously. Ratio constancy, which appears in claim 1 as synonymous for a predetermined and constant ratio of the combination, is an inevitable feature of the combination particles disclosed in document (2), as

shown from the data in the runs in table 1, wherein the bulk of particles containing a combination of the two active ingredients is defined by means of a single, specific value. The technically meaningful reading of claim 1 is that the claim relates to a bulk of unagglomerated particles with a predetermined and constant ratio of the two active ingredients. Nothing else is taught in document (2).

As regards the earlier publication of document (2) (year 1986) in relation to the publication date of document (3) (year 2000), this time factor is not an indirect indication of the existence of an inventive step. The existence during this time period of commercially available medicaments for the combination therapy, which concerned inhalation compositions of the cited prior art documents, raises serious doubts about the validity of the argumentation that there had been a long felt need in respect of a combination therapy.

2.2.8 Consequently, the main request fails since claim 1 does not meet the requirements of Article 56 EPC.

### 3. *First auxiliary request*

#### 3.1 *Inventive step*

3.1.1 Claim 1 of the first auxiliary request differs from claim 1 of the main request merely in that the relative crystallinity of an active ingredient is 90% or higher.

3.1.2 Having regard for the fact that it is the crystallinity of the particles which plays a role in stability (by avoiding undesirable amorphous-crystalline

transformations), the mention of the relative crystallinity of one of the active ingredients (it may even be the one in the smallest proportion) does not add any new function to the other features already present in claim 1. Furthermore, if there is a particular effect in the particles (this has not been proven) attributable to a **particular crystalline form** of one of the active ingredients going beyond those effects directly attributable to the morphology of the particles as such (crystalline *versus* amorphous), said particular effect cannot be generalised as being caused by any crystalline form of any active ingredient encompassed by the claim, in any proportion possible.

The data in Figure 5 show a certain behaviour vis-à-vis humidity for particles containing 97.1% beclomethasone dipropionate and 2.9% formoterol fumarate, in which the major component is in crystalline form, and only the minor component is amorphous or semi-amorphous. The experimental data in document (23) relate to particles containing a single active ingredient (in fact fluticasone propionate), which are amorphous or semi-amorphous. Apart from the fact that the experiments in document (23) do not reproduce either the particles in document (3) or those in document (2), no conclusion can be extracted from the DVS figures other than the teaching already known from document (3), namely to avoid amorphous regions and to aim at crystalline particles.

3.1.3 Therefore, the analysis made above for claim 1 of the main request applies *mutatis mutandis* to claim 1 of the first auxiliary request.

3.1.4 Consequently, claim 1 of the first auxiliary request does not meet the requirements of inventive step either.

3.2 *Second auxiliary request*

3.2.1 *Inventive step*

3.2.2 Claim 1 of the second auxiliary request differs from claim 1 of the main request in that it specifies that the particles are free from material other than the active ingredients and states that the molar ratio of the  $\beta$ 2-agonist to the glucocorticosteroid is from 1:1 to 1:1000.

3.2.3 The unagglomerated individual particles (containing simultaneously two active ingredients) which are exemplified in document (2) are free from other materials. Moreover, the range of molar ratios specified in the claim is known in the field of inhalation for combinations of active ingredients such as those in the claim (see document (5), page 5). Thus, in the absence of any special effect shown for these particular features, their introduction relates to an aggregation of generally known features without any functional contribution to inventive step.

3.2.4 Thus, the analysis made above for the main request applies mutatis mutandis to the second auxiliary request.

3.2.5 Consequently, the second auxiliary request fails for lack of inventive step of claim 1 (Article 56 EPC).

3.3 *Third and fourth auxiliary requests*

3.3.1 *Inventive step*

3.3.2 Claim 1 of the third auxiliary request and claim 1 of the fourth auxiliary request differ from claim 1 of the second auxiliary request in that the range of molar ratio has been defined more narrowly, i.e. as from 1:5 to 1:1000, or as from 1:10 to 1:1000, respectively.

3.3.3 Analogous reasons to those given for the second auxiliary request also apply to claim 1 of the third auxiliary request and claim 1 of the fourth auxiliary request, since these particular molar ratio ranges are known from document (5) (page 5) for formoterol ( $\beta$ 2-agonist)/ fluticasone propionate (glucocorticosteroid). The appellant-patentee has not given any individual reasoning in support of claim 1 of the auxiliary requests 3 and 4, other than that the ranges are more specific than in claim 1 of the second auxiliary request. This, alone, has no bearing on the applicability of the analysis of inventive step made above for the second auxiliary request.

3.3.4 Consequently, the third and fourth auxiliary requests fail for lack of inventive step (Article 56 EPC).

3.4 *Sixth auxiliary request*

3.4.1 *Articles 123 und 84 EPC*

3.4.2 The set of claims of the sixth auxiliary request is based on the second auxiliary request in which all



product category claims have been deleted. Thus, the sixth auxiliary request contains method claims only.

3.4.3 The appellant-opponent has not raised any objection within the meaning of Article 123(2) EPC against this set of claims and the board sees no reason to differ.

3.4.4 Moreover, the board considers that the claim's wording is clear when it requires that at least 90% of the total weight of the particles be in crystalline form. The fact that the claim does not specify which is the component or components in crystalline form only means that it is broad, since the condition set in relation to crystallinity encompasses several possible options. As regards the alleged lack of clarity raised by the appellant-opponent, based on the argument that the skilled person cannot identify which means are needed for attaining the specified product features, the board considers that this is in fact an allegation of lack of sufficiency of disclosure within the meaning of Article 83 EPC. The fact that the claim is broadly defined in relation to the process features does not necessarily imply a lack of clarity.

3.4.5 Therefore, the set of claims of the sixth auxiliary request meets the requirements of Articles 123 and 84 EPC.

#### 4. *Remittal (Article 111(1) EPC)*

4.1.1 The decision under appeal relates to the maintenance of the patent in amended form on the basis of the second auxiliary request.

The opposition division did not make a proper problem-solution approach since it did not state which document it considered to represent the closest prior art. Moreover, the opposition division's decision does not contain a definition of the problem to be solved. A proper problem-solution approach would have also required identification of the solution in each of the independent claims, and an assessment whether the proposed solution plausibly solved the technical problem.

Moreover, the board has concluded that the particles claimed in claim 1 of the main request (identical to claim 1 of the second auxiliary request before the opposition division) lack an inventive step. Thus, the opposition division's decision does not hold.

The set of claims of the sixth auxiliary request filed at the oral proceedings before the board contains method claims only. Thus, the method claimed in claim 1 has to be investigated **on its own merits**.

4.1.2 Consequently, the board uses its discretionary power under Article 111(1) EPC to remit the case to the department of first instance for further prosecution on the basis of a set of claims containing method claims only.

4.1.3 The appellant-opponent was not in favour of a remittal to the department of the first instance since, in its opinion, the subject-matter in the sixth auxiliary request had already had its chance to be examined by the opposition division. The board cannot agree since the opposition division's decision in favour of the

method claims assumed the unconfirmed findings that the claimed particles were inventive *per se*.

**Order**

**For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance for further prosecution.

The Registrar:

The Chairman:

N. Maslin

U. Oswald