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Datasheet for the decision of 10 November 2009

Case Number: T 1215/06 - 3.3.02

Application Number: 94926421.2

Publication Number: 0717616

IPC: A61K 9/14

Language of the proceedings: EN

Title of invention:
Process for conditioning substances

Patentee:
AstraZeneca AB

Opponents:
SCHERING-PLOUGH CORPORATION
GENCHEM PHARMA LTD.
IVAX Pharmaceuticals UK Limited

Headword:
Conditioning by water vapour/ASTRAZENECA

Relevant legal provisions:
EPC R. 80

Relevant legal provisions (EPC 1973):
EPC Art. 100(b)(c)

Keyword:
"Main request and first auxiliary request: amendments - added subject-matter (yes) - particular feature not originally disclosed"
"Second auxiliary request: disclosure - sufficiency (no) - functional features not defined"

Decisions cited:
-

Catchword:
-

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Case Number: T 1215/06 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 10 November 2009

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 30 May 2006 concerning maintenance of European Patent No. 0717616 in amended form.**

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
T. Karamanli

Summary of Facts and Submissions

I. European patent No. 0 717 616, based on the international application PCT/SE94/00780 and published as WO 95/05805, was granted with 22 claims.

Independent claims 1 and 14 as granted read as follows:

"1. A process for providing a stable crystalline form of a fine-grained substance or a substance mixture, which can be produced, stored and used while maintaining the aerodynamic properties required for inhalation of such a substance or a substance mixture, characterized in

a) in case of a substance mixture, preparing a homogenous mixture of the substances;

b) micronizing, direct precipitating or diminishing by any conventional method the substance or substance mixture into a particle size required for inhalation, the particle size being less than 10 µm;

c) optionally preparing a homogenous mixture of the desired substances when each substance has been introduced from stage b) as separate fine-grained particles;

d) conditioning said substance or substance mixture by treatment with a water-containing vapour phase at a temperature/relative humidity combination suppressing the glass temperature of the substance or substance mixture below the process temperature;

e) drying; and

f) optionally preparing a homogenous mixture of the desired substances when each substance has been introduced from stage e) as separate fine-grained particles.

14. Formoterol fumarate dihydrate having a particle size less than 10 µm, which when subjected to water-containing vapour gives off heat of less than 0.5 J/g."

II. Opposition was filed against the granted patent under Article 100(a), (b) and (c) EPC 1973. Under Article 100(a) objections regarding novelty and inventive step were introduced.

The following documents were cited *inter alia* during the proceedings before the opposition division and the board of appeal:

(4) Briggner, L.E. et al., "The use of isothermal microcalorimetry in the study of changes in crystallinity induced during the processing of powders"; Int. J. Pharmaceutics, 1994, 105, 125-135

(12) Vidgren, P. et al., "Physical stability and inhalation behaviour of mechanically micronized and spray dried disodium cromoglycate in different humidities"; Acta Pharm. Fennica, 1989, 98, 71-78

III. The opposition division held that, because of the deletion of claims 15 to 22 and the deletion of optional point f) in claim 1, and after having modified claim 11 of the claims as granted, the set of claims of

the single remaining request met the requirements of the Convention.

IV. The appellants I, II and III (opponents 1, 2, and 3) filed appeals against that decision and submitted grounds of appeal.

V. Dated 20 May 2009, a communication was sent out, expressing, in particular, the board's concern with respect to the sets of claims of the requests then on file containing amendments as compared with the claims as maintained by the opposition division, even though the respondent had submitted that the claims of the main request were identical to the claims upheld by the opposition division.

In addition, it was indicated in the communication that the respondent apparently had not explained why these amendments were occasioned by a ground for opposition (Rule 80 EPC).

VI. With a letter of 10 September 2009, the respondent submitted experimental data evidence; in a further letter of 9 October 2009 it filed nine sets of claims replacing all previous requests.

VII. On 10 November 2009, oral proceedings took place before the board.

During the oral proceedings, the respondent filed a main request and first and second auxiliary requests which were admitted into the proceedings. In addition a third auxiliary request was filed.

In accordance with the wording of claims 1 and 14 as maintained by the opposition division, the wording of claims 1 and 14 of the main request read:

"1. A process for providing a stable crystalline form of a fine-grained substance or a substance mixture, which can be produced, stored and used while maintaining the aerodynamic properties required for inhalation of such a substance or a substance mixture, characterized in

a) in case of a substance mixture, preparing a homogenous mixture of the substances;

b) micronizing, direct precipitating or diminishing by any conventional method the substance or substance mixture into a particle size required for inhalation, the particle size being less than 10 µm;

c) optionally preparing a homogenous mixture of the desired substances when each substance has been introduced from stage b) as separate fine-grained particles;

d) conditioning said substance or substance mixture by treatment with a water-containing vapour phase at a temperature/relative humidity combination suppressing the glass temperature of the substance or substance mixture below the process temperature; and

e) drying.

14. Formoterol fumarate dihydrate having a particle size less than 10 µm, which when subjected to water-containing vapour gives off heat of less than 0.5 J/g."

Claim 14 of the main request was discussed with regard to Article 100(c) EPC 1973.

This claim was deleted in the first auxiliary request; in addition, the first auxiliary request contained several amendments in claims 3 to 12.

In claim 1 of the second auxiliary request all features relating to a substance mixture were deleted; it reads:

"1. A process for providing a stable crystalline form of a fine-grained substance, which can be produced, stored and used while maintaining the aerodynamic properties required for inhalation of such a substance, characterized in

a) micronizing, direct precipitating or diminishing by any conventional method the substance into a particle size required for inhalation, the particle size being less than 10 µm;

b) conditioning said substance by treatment with a water-containing vapour phase at a temperature/relative humidity combination suppressing the glass temperature of the substance below the process temperature; and

c) drying."

VIII. The appellants' submissions can be summarised as follows:

In claim 1 as granted, the respondent had tried to substitute point d) of claim 1 as originally filed, namely "conditioning in a controlled fashion" for particular conditions as disclosed in the description. This substitution was a point of concern with respect to Article 100(c) EPC 1973.

Regarding the same article of the EPC, product-claim 14 as granted - being derived from example 3 as originally disclosed, as the respondent had submitted - lacked particular conditions of the experiment and as far as conditions of the experiment were set out in the claim, they were not generalisable.

In addition, no product was disclosed throughout the application as originally filed having a defined particle size, let alone a particle size of less than 10 µm. The feature of particle size in claim 14 as granted was based on the opposition division's assumption that the starting material of example 3 was micronised to this extent, and on the further assumption that the conditioning step did not at all alter this grade of particle size. The first assumption was apparently derived from the micronising or diminishing step specified in claim 1, while it was stated in the description that coarser particles than such as less than 10 µm of particle size could also be conditioned under the teaching of the invention. The second assumption was apparently based on the functional feature of maintenance of "the aerodynamic properties required for inhalation". Both assumptions,

at least in terms of resulting in the definition of exactly measurable parameters, were not supported by the text of the application as filed, and the mere fact that they were no more than assumptions meant that the situation was already far away from providing a clear and unambiguous disclosure.

With respect to claim 1 of the second auxiliary request, there was no disclosure sufficiently clear and complete for the claimed teaching to be carried out by a person skilled in the art.

The examples were devoid of any substantive data on the necessary process parameters, in particular temperature and time. In addition, there was no information about the particular value of the glass transition in the case of the experiments and thus, no information at all could be derived from the examples as to how they could represent the teaching of the claimed process.

Moreover, neither the particle size of the product nor the heat to be set free by one gram of product on isothermal exposure to moisture were *de facto* set out as compulsory features of the product **to be obtained** by the process. In addition, the measurement of the particle size - as claimed state of the substance **before the conditioning** - was not possible in an unambiguous way because even the disclosed instruments for measurement led to totally different results, finding a substance's particle size under or above 10 µm just by choosing the instrument arbitrarily.

Even assuming that a particle size of less than 10 µm and a heat evolution of less than 0.5 J/g were

acknowledged as features of the product to be obtained and that the skilled person could measure them unambiguously, there was a high probability of choosing unsuitable process parameters as was shown in documents (4) and (12); and if the skilled person measured these features and found that no product as claimed had been produced, the whole patent in suit contained no guidance in what direction to change the process parameters in order to get a higher probability of successful conditioning with the next experiment.

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

With respect to claims 1 of the main request and the first auxiliary request, the provisions of Article 100(c) EPC 1973 were fulfilled since point d) of claim 1 as set out in the description as originally filed (see page 5, lines 9 to 11 of WO 95/05805) referred to "the conditioning of said substance or substance mixture", while in the following text, being the source of the amendment of original claim 1 as introduced into claim 1 as granted (see *ibid*., page 5, lines 20 to 27), "the suppressing of the glass temperature of substances involved" did in fact express nothing else.

Regarding the objections under Article 100(b) EPC 1973, the teaching of the patent in suit, at least after restriction to the conditioning of substances and not mixtures (second auxiliary request), could be carried out by the skilled person without undue burden. He could take plenty of information from the description to be guided in the direction of successful experiments; for instance, particular information with regard to

suitable ranges of relative humidity and temperature, the time required, and the necessary equipment for the conditioning step and the measurement of particle size. All this information was disclosed in the text of the description including examples 1 to 6.

Finally, the tests as disclosed by the teaching of the patent in suit were applicable to the product produced by the claimed process as an inevitable consequence of the patent's teaching as a whole. These tests were measuring particle size, which should be unchanged during the conditioning step and evolution of less than 0.5 J/g in the isothermal exposure to humidity after the conditioning step. They supplied a sufficient basis to find the conditions leading to products successfully presenting the functional features of claim 1, in particular maintenance of the aerodynamic properties required for inhalation.

The appellants' arguments with respect to literature presenting unsuccessful experiments, or as far as experimental evidence was submitted by themselves, could not challenge the teaching of the patent in suit, because the jurisprudence of the boards made it clear that it was necessary to submit evidence that the examples set out in the patent would not work. Such evidence was not filed. The teaching of the documents as cited by the appellants was too far away from the teaching of the patent in suit, and when looking at the patent it was easy for the person skilled in the art to turn failure into success.

X. The appellants I, II and III (opponents 1, 2, and 3) requested that the decision under appeal be set aside and that the patent be revoked.

XI. The respondent (patentee) requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims according to the main request, auxiliary request I or auxiliary request II, all filed during oral proceedings, or in the alternative, that the case be remitted to the first instance if the particle size was a crucial part of the decision (auxiliary request III).

Reasons for the Decision

1. The appeals are admissible.

2. *Admissibility of first and second auxiliary request*

The amendments in these requests are occasioned by the board's opinion set out in the communication as well as the appellants' and the board's arguments during the oral proceedings.

In addition, the amendments only contain deletions from or simple returns to the text of the claims as granted. They are clear-cut and *bona fide* attempts to answer the arguments brought forward during the oral proceedings.

Accordingly, the requests fulfil the requirements of Rule 80 EPC and they are admitted into the procedure.

3. *Article 100(c) EPC 1973*

3.1 Main request

According to claim 14 of this request, the particle size of formoterol fumarate dihydrate is less than 10 µm.

The only original disclosure of formoterol fumarate dihydrate as the subject-matter of a product claim is example 3 of the application as originally filed (WO 95/05805).

In the description as originally filed it is stated under "Experimental procedure" on page 11 that "the mixture" is to be micronised. Although the substance formoterol fumarate dihydrate cannot be regarded as a mixture, the micronising step can be generalised within the understanding of the application as filed, because it is disclosed under "EXAMPLES" which includes example 3. The particle size to be attained by this micronising step, however, is not defined specifically within the description given in the examples.

According to the description as a whole, after the micronising step, the conditioning in example 3 may start either

- with a particle size according to the micronising step of claim 1 as originally disclosed, being less than 10 µm

or, as is disclosed on bottom of page 6 of the description as originally filed,

– with "coarser particles having a size above 10 µm", which "may also be conditioned using the process according to the present invention".

Thus, there is no clear teaching that the product in example 3 is based on the micronising step as disclosed in claim 1 resulting in a particle size of less than 10 µm. Accordingly, such a particle size is not clearly and unambiguously disclosed in the application as filed as regards micronised formoterol fumarate dihydrate.

Consequently, claim 14 of the main request contains an unallowable extension beyond the content of the application as originally filed (Article 100(c) EPC 1973).

3.2 *First auxiliary request*

Point d) in claim 1 of the first auxiliary request refers to a "glass temperature of the substance or substance mixture". This term, defining details of the conditioning step, was introduced during the examination proceedings on the basis of page 5, lines 20 to 23 of the description as originally filed: "The conditioning step is carried out at a temperature/relative humidity combination, which suppresses the glass temperature of substances involved below the process temperature".

In the case of the conditioning of a mixture, therefore, reference was originally made to the (normally different) glass temperatures of the single substances ("substances involved") and not to a single glass temperature of the mixture.

An ideal mixture, however, has a single glass temperature which is different from the glass temperatures of the mixed substances and depends on the relative content of these substances.

Thus, suppressing "the glass temperature of the substance mixture" below the process temperature, as claimed in claim 1 of the first auxiliary request, was not originally disclosed and this request is not allowable because of Article 100(c) EPC 1973.

4. *Article 100(b) EPC 1973; second auxiliary request*

4.1 Claim 1 of the second auxiliary request concerns a process for the preparation of a "stable crystalline form" of a substance that *inter alia* can be used "while maintaining the aerodynamic properties required for inhalation of such a substance".

4.2 When carrying out the teaching of this claim, the functional features as quoted have to be fulfilled by the product. Therefore it is necessary to know how this can be secured and controlled.

While maintenance of the aerodynamic properties could be controlled by measuring the particle size after the preparation of the product, which "should be identical before and after the conditioning step" (see page 4, lines 36 to 37 in the patent in suit), the feature of a "stable crystalline form" is to be assessed in another way.

It is emphasised in the patent in suit that successful conditioning of a substance means the disappearance of amorphous regions produced by micronising or diminishing processes (see page 2, lines 34 to 41 in combination with page 5, lines 2 and 3 of the patent in suit), but there is no direct and indicative statement to what extent amorphous regions should disappear in order to have a "stable crystalline form" as the result and how this could be measured.

According to claim 1 as granted, successful conditioning relates to process step d), where the glass temperature of the substance is to be suppressed below the process temperature.

This, however, is only a necessary condition for disappearing amorphous regions, when "the mobility of an amorphous material undergoes changes from an immobile glassy state to mobile rubbery state (phase transition)" as is set out in the description on page 2, lines 34 to 35 of the patent in suit. The knowledge of the glass temperature of the substance in relation to the process temperature alone is of no use because the real step from amorphous material in the rubbery state to the crystalline state still has to be done and this transition and its extent has to be controlled.

With respect to this control, various methods are indicated on page 5, lines 2 to 6 of the patent in suit with "BET gas adsorption and isothermal microcalorimetry being the best methods for distinguishing the different forms of the tested compounds". Again, no specific method including specific conditions for measuring is derivable.

The only specifically defined method that allows conditioned single substances to be distinguished from their unconditioned form is the one to measure an evolution of heat of less than 0.5 J/g when subjected to water-containing vapour (page 4, lines 48 to 50 of the patent in suit) under the conditions of isothermal microcalorimetry. In exactly the same cited lines, however, this method, is introduced into the patent in suit as "yet **another** object of the present invention", namely to provide particular pharmaceutical preparations, which means in connection with product claims only and not in connection with process claim 1 (see page 4 of the patent in suit, the lines 48 to 50 in relation to lines 41 and 44 on the same page).

In addition, this method is to be seen as a check for **any** amorphous content (ibid. page 6, line 42), the meaning of which is clarified as follows:

With regard to Figure 1, relating to the example of "micronised lactose before (I) and after (II) conditioning", it is stated that "thus, a **complete** crystallinity has been obtained during the conditioning according to the invention" (page 6, lines 41 to 43 of the patent in suit).

As a consequence, the evolution of heat of less than 0.5 J/g when subjected to water-containing vapour as evidence on the one hand refers to obtaining "complete crystallinity" and not to the degree of crystallinity being necessary to define a "stable crystalline form" and on the other hand constitutes "yet another object

of the present invention" which is different from the subject-matter of claim 1 as granted.

Thus, with respect to the teaching of the process according to claim 1 of the patent as granted, the value of "0.5 J/g evolution of heat" cannot be seen as the measurable feature enabling the skilled person to assess whether or not a "stable crystalline form" of a fine-grained substance was obtained.

Therefore, the skilled person trying to carry out the teaching of claim 1 of the second auxiliary request in context with the patent in suit has no means of assessing, whether the functional feature "stable crystalline form" is fulfilled by the result of his experimental work. Consequently, he is not in a position to test whether or not his experimental results comply with the claimed teaching: he cannot carry it out.

4.3 In addition to this, there are still further problems with respect to Article 100(b) EPC 1973 concerning the teaching of the second auxiliary request:

As may be seen from document (4), normal conditions which are within the ranges set out in the patent in suit, und thus representative of normal working conditions, lead to a product that cannot be seen as "stable crystalline" or "maintaining the aerodynamic properties required for inhalation of such a substance" as claimed in the patent in suit:

With the patent in suit offering as working conditions

- "generally at a temperature between 0 and 100°C, preferably between 10 and 50°C" and
- "of practical reasons the conditioning is often performed at ambient temperature" and
- "the relative humidity (RH) at which the conditioning is carried out is chosen so that the phase transition occurs, mainly above 35% RH, preferably above 50% RH, and most preferably above 75% RH"

(see page 3, lines 36 to 39 of the patent in suit), the conditioning in document (4) is performed at ambient temperature (25°C) and at 85% RH (see document (4), figure 2 on page 128).

The result, however, appears in the form of one lump of material (see document (4), page 128, left-hand column, lines 8 to 13), far away from "the aerodynamic properties required for inhalation" as claimed in the patent in suit.

Trying now for instance to turn to the most preferable use of a relative humidity above 75% as proposed on page 3, line 39 of the patent in suit, the skilled person finds that this is already realised, because 85% is applied in document (4). Then looking for help in the examples supplied in the patent in suit, he finds them to be of no use, because essential data are missing, for instance the temperature correlating with the relative humidity applied there.

Consequently, the teaching of claim 1 as amended in context with the patent in suit provides no guidance at all in what direction to amend the parameters to succeed when performing follow-up experiments.

Such a situation of plain trial and error being necessary to find embodiments of the claimed teaching, represents lack of sufficiency of disclosure under Article 100(b) EPC 1973.

5. Under these circumstances of the case, the further arguments of the respondent cannot succeed either.

5.1 The respondent argued that when objections with regard to Article 100(b) EPC 1973 were raised, there was jurisprudence of the boards of appeal requiring evidence that the examples of the attacked teaching would not work.

In the case of the patent in suit, however, the examples themselves lack essential data (for instance, as already set out above, the temperature of the experiment correlated to the relative humidity as indicated). Therefore, the examples cannot be carried out per se and the requirement cited from the jurisprudence even if of general importance, cannot be fulfilled.

5.2 According to the arguments of the respondent, the teaching of document (4) was too far away from the teaching of the patent in suit to be able to show its failure.

The aim of document (4) was to probe the potential for application of microcalorimetry in the study of changes in crystallinity which have been induced by processing substances (see last paragraph of point 1.2. in the right-hand column of page 126), in particular the

surface of crystals becoming amorphous during processing, which influences interactions, including cohesiveness and adhesion between the powder and other phases (see first paragraph in the right-hand column of page 126). Thus, samples of lactose monohydrate were prepared by either micronisation in an air jet mill or by spray drying.

Having this in mind, the very same problems turn out to be under investigation in the patent in suit: first, that diminishing procedures are the source of amorphous regions in the processed powders that lead to problems of cohesiveness of the particles involved, and, second, that processes of recrystallisation are to be investigated.

In addition, the result of the conditioning of spray dried lactose monohydrate at 25°C and 85% relative humidity is only an example indicating that the teaching according to claim 1 of the second auxiliary request may lead to failure; the fact that no guidance is provided by the teaching of the patent in suit to amend parameters in the direction of successful experiments is independent of that statement.

Therefore, this argument of the respondent cannot succeed either.

6. Thus, the main request and the first auxiliary request are not allowable because of the ground for opposition under Article 100(c) EPC 1973, and the second auxiliary request is not allowable because of the ground for opposition under Article 100(b) EPC 1973.

Remittal to the first instance (third auxiliary request) did not have to be taken into account, because this decision is not based on the question whether or not the particle size can be measured unambiguously.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

N. Maslin U. Oswald