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Case Number: T 0025/14 - 3.3.07

Application Number: 07808579.2

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Language of the proceedings: EN

Title of invention:
GRANULATE CONTAINING A PHARMACEUTICALLY ACTIVE SUBSTANCE AND AN EMULSIFIER AND METHOD FOR ITS MANUFACTURE

Patent Proprietor:
Echo Pharmaceuticals B.V.

Opponent:
GW Pharma Limited

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

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Case Number: T 0025/14 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 7 November 2017

Appellant: (Patent Proprietor)	Echo Pharmaceuticals B.V. Rijnkade 16a 1382GS Weesp (NL)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Appellant: (Opponent)	GW Pharma Limited Porton Down Science Park Salisbury, Wiltshire SP4 OJQ (GB)
Representative:	Wells, Andrew HGF Limited 4th Floor, Merchant Exchange 17-19 Whitworth Street West Manchester M1 5WG (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 October 2013 concerning maintenance of the European Patent No. 2061427 in amended form.**

Composition of the Board:

Chairman J. Riolo
Members: R. Hauss
Y. Podbielski

Summary of Facts and Submissions

I. European patent No. 2 061 427 was granted with fourteen claims.

Independent claim 10 reads as follows:

"10. A process for the preparation of a granulate containing a pharmaceutically active substance, which process employs:

- *a pumpable emulsion comprising*

  (i) a continuous phase containing at least 30 wt.% of a polar solvent and

  (ii) a dispersed phase containing at least 10 wt.% of an emulsifier and at least 0.1 wt.% of a pharmaceutically active substance;

- *an extractant comprising at least 60 wt.% of a supercritical, subcritical or liquefied gas;*

said solvent being substantially more soluble in the extractant than said emulsifier;

the process comprising the successive steps of:

a. combining the pumpable emulsion with the extractant under mixing conditions;

b. allowing the formation of granules containing the emulsifier and the pharmaceutically active substance;

c. collecting the granules and separating them from the extractant."

II. An opposition was filed against the patent, on the grounds that the claimed subject-matter lacked novelty and inventive step and was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(a) and (b) EPC).

III. The documents submitted in the course of the opposition and appeal proceedings included the following:

D16: Journal of Pharmaceutical Sciences, 91(9), 1948-1957 (2002)

D18: WO 2004/004862 A1

IV. The decision under appeal is the interlocutory decision of the opposition division, announced on 19 September 2013 and posted on 21 October 2013,

- rejecting the patent proprietor's main request for rejection of the opposition and

- finding that the patent as amended in the form of auxiliary request I, filed during oral proceedings before the opposition division, met the requirements of the EPC.

Claim 9 of auxiliary request I was identical to claim 10 as granted.

In the decision under appeal, the opposition division held that the subject-matter claimed in the patent as granted (main request) and in auxiliary request I was novel and was also disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. However, the subject-matter of claim 1 as granted did not involve an inventive step.

Starting from the technical teaching of document D16, which was regarded as the closest prior art by both the opponent and the patent proprietor, the subject-matter of independent claim 9 of auxiliary request I involved an inventive step. The opposition division observed that the opponent had not relied on late-filed document D18 as a starting point for attacking inventive step, or placed any particular emphasis on that document; moreover, the process of claim 9

differed in certain relevant technical features from the disclosure of D18.

The subject-matter defined in the remaining claims of auxiliary request I was also held to be inventive.

V. The patent proprietor and the opponent each lodged an appeal against that decision.

VI. In its statement setting out the grounds of appeal, the appellant - opponent submitted, with respect to claim 9 of auxiliary request I (identical to claim 10 as granted), that document D18 rather than D16 was the most appropriate starting point for the assessment of inventive step.

VII. With its statement setting out the grounds of appeal, the appellant - patent proprietor submitted two sets of claims entitled "main request" and "auxiliary request I", each containing an independent process claim identical to claim 10 of the patent as granted.

VIII. In a communication issued in preparation for oral proceedings and advising the parties of its preliminary opinion, the board *inter alia* drew attention to a process embodiment disclosed in document D18 (paragraph [0047]) as a possible starting point for the assessment of inventive step for the independent process claim (see point 3.3.3 of the board's communication dated 31 August 2017).

IX. In reply to that communication, the appellant - opponent indicated that it would not be attending the oral proceedings and asked that a decision be taken on the merits of the case. It did not present any further substantive arguments in support of its case.

X. With letter dated 6 October 2017, the appellant - patent proprietor filed a new main request and new auxiliary requests I to III. Each request includes an independent process claim identical to claim 10 of the patent as granted (viz. claim 9 in the main request and auxiliary requests I and III, and claim 1 in auxiliary request II).

XI. Oral proceedings were held on 7 November 2017 in the absence of the appellant - opponent, in accordance with Article 15(3) RPBA and Rule 115(2) EPC.

XII. The appellant - opponent's inventive-step arguments relating to the independent process claim may be summarised as follows:

It was known from document D18 that particles could be precipitated from emulsions using supercritical fluids as anti-solvents, whereas the process taught in document D16 used a solution and not an emulsion. Hence document D18 was a more appropriate starting point for the assessment of inventive step than document D16.

The process as claimed differed from the process disclosed in D18 primarily in the higher concentration of emulsifier employed. That technical feature had not however been linked to any specific technical effect.

In view of document D16 teaching that the emulsifier could advantageously also act as a carrier material with solubilising properties, the person skilled in the art would contemplate employing more than 10 wt.% of emulsifier in a process according to D18.

XIII. The arguments presented by the appellant - patent proprietor may be summarised as follows:

The process of claim 9 of the main request differed from the process disclosed in document D18 in the use of high emulsifier levels of at least 10 wt.%, in that the solvent was extracted from the continuous phase and not from the dispersed phase of the emulsion, and most notably in the end product obtained, which was a powder granulate rather than a suspension of particles in a liquid.

The claimed process yielded fine granules comprising emulsifier and a pharmaceutically active substance. The granules were formed *in situ* in one single step and could easily be collected and separated from the extractant, as illustrated in example 3 of the patent in suit. In contrast, a suspension of particles in the liquid continuous phase was invariably formed with the process according to D18.

In comparison with the process of D18, the simplified process according to the patent in suit thus avoided the need for further laborious and time-consuming process steps in which the dispersed particles had to be separated from the suspending liquid by filtration or centrifugation, and then dried to obtain a dry powder (D18: paragraphs [0032], [0046]).

Since the particles were produced in a controlled manner, the process of the patent in suit offered the further advantage of enabling the preparation of a granulate with a very homogeneous particle size.

The objective technical problem was thus the provision of an improved, simplified process for the manufacture of a granulate containing a pharmaceutically active substance.

The solution to that problem as defined in the current process claim would not have been obvious to the person skilled in the art, for the following reasons:

- The process according to D18, which relied on solvent removal from the emulsion droplets (dispersed phase) to cause particle precipitation of a solute present in the droplets, was designed to produce a suspension of particles in the continuous phase. D18 did not teach or suggest a process modification in which the continuous phase was replaced by the extractant and granulate particles were then formed in the extractant.

- In the process of D18, emulsifiers were used for the purpose of stabilising the emulsion droplets. According to the patent in suit, the emulsifiers were also intended to aid the release and pharmaceutical delivery of the active substance from the granulate and, to that end, were employed at fairly substantial concentrations of at least 10 wt.%. Since much lower concentrations were sufficient for the purpose mentioned in D18, the person skilled in the art would have found no incentive in the teaching of D18 to increase the level of emulsifier employed in the process.

XIV. The appellant - patent proprietor requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed with letter dated 6 October 2017 or, alternatively, one of auxiliary requests I to III, all filed with that same letter.

XV. The appellant - opponent had requested in writing that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

1. Main request - inventive step

Patent in suit

1.1 The patent in suit (see paragraphs [0001] and [0002]) seeks to provide a process for the preparation of a granulate containing a pharmaceutically active substance. In paragraph [0018] of the patent specification, the term "granulate" is defined as "a particulate material that consists of discrete particles".

1.2 Such a granulate can be prepared by the process according to claim 9 of the present main request, which starts from a pumpable emulsion having a continuous phase which contains a polar solvent and a dispersed phase which contains the pharmaceutically active substance and an emulsifier. The process involves combining and mixing the emulsion with an extractant comprising a supercritical, subcritical or liquefied gas, and allowing the formation of granules.

The claim further specifies that the polar solvent is substantially more soluble in the extractant than the emulsifier. Presumably, the extractant is meant to extract polar solvent from the continuous phase during the mixing step of the process, but this is not explicitly mentioned in the claim as a process feature.

The board considers that any solvent with some degree of polarity may be regarded as a "polar solvent" within the meaning of the patent in suit (which does not give a more restrictive definition). Water, C_{1-6} alcohols and ketones are mentioned as examples

of suitable solvents (see paragraph [0056] of the patent specification).

1.3 Example 3 of the patent in suit (see paragraph [0071] of the patent specification) describes a specific process embodiment:

An autoclave was heated to 40°C and brought to 30 bar with carbon dioxide (the extractant). An O/W emulsion containing 10 wt.% of a pharmaceutically active substance (melted THC), 30 wt.% of an emulsifier (sucrose stearate) and 60 wt.% of water was sprayed into the vessel by means of a syringe pump (ISCO 260D) through a two-fluid nozzle consisting of two concentric tubes of specified dimensions. The emulsion was fed via the inner tube at 0.3 ml/min, and carbon dioxide pre-heated to 40°C was fed via the outer tube at 500 g/min. The powder that formed within the vessel was collected on a filter at the bottom of the vessel.

Starting point in the prior art

1.4 It was not contested by the appellant - patent proprietor that the pre-published international application D18 was a conceivable starting point for assessing the inventiveness of the process defined in claim 9.

1.5 Document D18 (see claims 1 and 3 and paragraphs [0004] to [0008]) relates to a method of producing particles, e.g. particles containing a pharmaceutically active substance. The method (process) according to D18 involves supercritical fluid extraction of an emulsion. The dispersed phase of the emulsion contains a solute (in particular, a poorly water-soluble drug, see D18: paragraphs [0039], [0049]) dissolved in a solvent. The solvent is extracted from the dispersed phase into

the supercritical fluid, causing the solute to precipitate. The emulsion preferably comprises an emulsifier ("surfactant"; see D18: paragraphs [0038] and [0039]). No general concentration range is specified for the emulsifier.

D18 (see paragraph [0047]) also describes a specific embodiment in which the emulsion contains a partially water-soluble solvent and water (both being polar solvents within the meaning of the patent in suit). As explained in D18, the partially water-soluble solvent, present in equilibrium in both phases of the emulsion, is extracted from the aqueous continuous phase by a supercritical fluid. The extraction disturbs the thermodynamic equilibrium between the organic solvent in the emulsion droplets and the aqueous phase, resulting in a transfer of the organic solvent from the droplets into the aqueous phase. Particles are formed due to supersaturation as the supercritical fluid extracts the solvent from the emulsion.

The process embodiment according to paragraph [0047] of D18 comes close to the process of the patent in suit in terms of technical features and will be used in what follows as the starting point for the assessment of inventive step.

Technical problem and solution

1.6 Within the framework of the problem-and-solution approach employed as a rule by the boards for assessing inventive step, the objective technical problem is determined on the basis of a technical effect achieved by the claimed subject-matter when compared with the subject-matter which is the starting point in the prior art. In doing so, an alleged advantage in the form of a technical effect can only be taken into account if said

effect is reflected in the technical features of the claim under consideration and is based on a technical feature distinguishing the claimed subject-matter from the disclosure which is the starting point in the prior art, and if the technical effect in question is obtained over the entire scope of the claim.

1.7 To apply these criteria, it must first be established which technical features and technical effects can be taken into account in the formulation of the technical problem. On that basis, the technical problem will then be defined.

1.8 In support of inventive step, the appellant - patent proprietor relied upon the following technical features which in its opinion distinguished the claimed process from the process disclosed in document D18: the removal of the continuous phase of the emulsion, the direct production of a powder granulate in the extraction step, and the use of high emulsifier levels of at least 10 wt.%.

According to the appellant - patent proprietor, the claimed process had the following advantages over the process of D18:

- Since the continuous phase was removed during the extraction step, a powder granulate was obtained *in situ*, thus avoiding further process steps involving filtration/centrifugation and drying.

- The high emulsifier levels employed served to facilitate the rapid release of the pharmaceutically active substance from the particles upon application.

- The claimed process provided better control of particle size, resulting in greater homogeneity.

The appellant - patent proprietor further argued that the process described in example 3 of the patent in suit illustrated the essence of the invention, in particular with regard to the direct *in situ* formation of a powder granulate resulting from the removal of the continuous phase with the help of the extractant.

1.9 Extraction and granule formation

1.9.1 The appellant - patent proprietor emphasised in particular that the claimed process involved the *in situ* production of a powder granulate (as opposed to a suspension of particles) in one single step, due to the continuous phase being extracted and replaced by the extractant. Claim 9 could not be construed other than to the effect that the process yielded a dry powder.

1.9.2 However, the board considers that the removal of the continuous phase of the emulsion and the *in situ* production of a powder granulate are neither defined as explicit or implicit mandatory technical features of the process of claim 9, nor inevitably achieved as technical effects over the entire scope claimed, for the following reasons:

(a) The claim relates to a "process for the preparation of a granulate". Accepting the appellant - patent proprietor's argument that the term "granulate" designates a particulate powder material (as opposed to a suspension of particles in a liquid) and that such a material is the end product of the process, the claim still does not specify explicitly that this desired material is directly obtained *in situ* when the emulsion is mixed with the extractant.

(b) The "*in situ*" production of a powder granulate is not implicit in the definition of the process steps, either:

The process embodiment described in example 3 of the patent in suit involves a defined emulsion composition and specific apparatus features and process conditions which apparently resulted in the complete removal of the continuous emulsion phase (water) and the *in situ* formation of a dry powder granulate (see point 1.3 above). While example 3 may well describe a process embodiment which is encompassed within the scope of present claim 9, it should be borne in mind that claim 9 itself is silent as to specific apparatus requirements and process conditions. Its scope is therefore not restricted to the process conditions described in example 3, nor to other process conditions which would inevitably result in the *in situ* formation of a dry powder granulate.

Instead, claim 9 merely states that the emulsion is combined with the extractant "under mixing conditions", whereupon granules are formed, which are then collected and separated from the extractant. It is not possible to infer from such a general description that the liquid continuous phase must be completely removed during the mixing stage.

Moreover, the wording chosen in claim 9: "the process comprising the successive steps of ..." and "collecting the granules" does not exclude from the scope of the process other measures which may bring about the desired end-result of obtaining a powder granulate, since the process may comprise steps or measures which are not explicitly mentioned, and

granules may be collected in different ways. Such further measures may thus include filtration or centrifugation of a suspension of particles and drying of the collected particles.

1.9.3 In view of these considerations, the board has come to the conclusion that the wording of claim 9 also covers process embodiments wherein the particles (or granules) are obtained, at first, in a liquid suspension as a result of the mixing/extraction step, as in the process disclosed in D18. Hence the alleged simplification of the process regarding ease of particle recovery is not achieved over the entire scope claimed and cannot be taken into account in the formulation of the objective technical problem.

1.10 Control of particle size

1.10.1 The patent in suit mentions, in a general way, that the process according to the invention makes possible the preparation of a granulate with a very homogeneous particle size (see paragraph [0044] of the patent specification). In the context of example 3 (see paragraph [0071]), it is mentioned that the particle size can be varied within a wide range by varying flow rates and the nozzle parameters.

1.10.2 However, the patent in suit does not provide any comparative experimental data about this, and the definition of claim 9 does not indicate any precise mixing conditions or features of the apparatus to be employed. Hence it cannot be confirmed that there is any mandatory technical feature distinguishing the claimed process from the process of D18 and resulting in a better control of particle size and a more homogeneous particle size. In any case, it is routine work for the person skilled in the art to optimise

process conditions. Thus, like the patent in suit, D18 mentions in a general way that selecting parameters such as solvent, solute and supercritical fluid type, as well as other process parameters, can determine and control particle size (see D18: paragraphs [0048] and [0121]).

1.10.3 Hence, applying the criteria mentioned in point 1.6 above, the technical effect of superior process control and particle homogeneity alleged by the appellant - patent proprietor cannot be taken into account in the formulation of the objective technical problem, since no corresponding technical feature has been identified in claim 9 which is causally linked to such a technical effect.

1.11 Concentration of the emulsifier

1.11.1 It is common ground that the use of emulsifier at a level of at least 10 wt.% is a technical feature distinguishing the claimed process from the disclosure in D18.

1.11.2 There is no evidence on file to show that a process employing a pumpable emulsion with an emulsifier content of 10 wt.% in the dispersed phase will provide particles with different properties compared to a process employing a pumpable emulsion with less than 10 wt.% of emulsifier in the dispersed phase (such as, for instance, 9 wt.%), and that this is the case irrespective of the nature of the emulsifier.

1.11.3 In the absence of any evidence of a specific technical effect, the technical problem is to be seen as being to provide a further process for the preparation of a granulate containing a pharmaceutically active substance.

1.12 That problem is solved by the process as defined in present claim 9, in which the dispersed phase of the emulsion contains at least 10 wt.% of emulsifier.

Obviousness of the solution

1.13 While an emulsifier (surfactant) is used in preferred embodiments of D18 as an emulsion stabiliser (see D18: paragraph [0039]), and while lower concentrations may typically be sufficient to fulfil that function, there is no actual technical teaching in D18 which would deter or prevent the person skilled in the art from using emulsifier concentrations around 10 wt.%. The board thus takes the view that emulsifier concentrations of at least 10 wt.-% in the dispersed phase, while not specifically disclosed, are not outside the general scope of document D18.

1.14 Nor is the board aware of a technical prejudice against high emulsifier levels which might be derived from the cited prior art or from common general knowledge. On the contrary, it was known that increased wettability, which can be achieved by the incorporation of amphiphilic substances (i.e. surfactants/emulsifiers), may improve the dissolution properties of solid particles (see D16: page 1948: introduction, page 1949: column 1, lines 6 to 29). Thus the person skilled in the art might have had an incentive to use higher emulsifier levels in order to obtain this known advantage.

1.15 In conclusion, starting from the teaching of D18 to provide a further process for the preparation of a granulate containing a pharmaceutically active substance, it would not have required inventive skill to employ the emulsifier at a level encompassed within

the general scope of D18, viz. at least 10 wt.% of the dispersed phase.

1.16 As a consequence, the subject-matter of claim 9 of the main request does not involve an inventive step within the meaning of Article 56 EPC.

2. Auxiliary requests I to III - inventive step

2.1 The independent process claim is identical in all pending requests (see points I and X above).

2.2 Hence the subject-matter of claim 9 of auxiliary request I, claim 1 of auxiliary request II and claim 9 of auxiliary request III does not involve an inventive step within the meaning of Article 56 EPC, for the same reasons as explained in section 1 above.

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:

S. Fabiani J. Riolo

Decision electronically authenticated