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Datasheet for the decision of 9 October 2018

Case Number: T 1896/15 - 3.3.07

Application Number: 07726820.9

Publication Number: 1996163

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Language of the proceedings: EN

Title of invention:
PROCESS FOR PRODUCING A SOLID DISPERSION OF AN ACTIVE INGREDIENT

Patent Proprietor:
Abbott GmbH & Co. KG

Opponent:
Bühler, Dirk

Headword:
PROCESS FOR PRODUCING A SOLID DISPERSION / ABBOTT

Relevant legal provisions:
EPC Art. 56
RPBA Art. 13(1), 13(3)

Keyword:

Inventive step - main request (no)
Late-filed auxiliary request - submitted during oral proceedings - admitted (no)

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Case Number: T 1896/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 9 October 2018

Appellant: (Opponent)	Bühler, Dirk Maiwald Patentanwalts -und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstraße 3 80335 München (DE)
Representative:	Bühler, Dirk Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstraße 3 80335 München (DE)
Respondent: (Patent Proprietor)	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden (DE)
Representative:	Reitstötter Kinzebach Patentanwälte Sternwartstrasse 4 81679 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 16 July 2015 rejecting the opposition filed against European patent No. 1996163 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	S. Albrecht
	C. Heath

Summary of Facts and Submissions

I. European Patent No. 1 996 163 was granted on the basis of a set of 13 claims.

Independent claim 1 as granted read as follows:

"A process for producing a solid dispersion of a biologically active ingredient which comprises feeding the active ingredient and a matrix-forming agent to an extruder and forming a uniform extrudate, wherein the extruder comprises at least two rotating shafts (2), each of the shafts (2) carrying a plurality of processing elements disposed axially one behind the other, the processing elements defining

(i) a feeding and conveying section (A),
(ii) at least one mixing section (B), and
(iii) a discharging section (E),
wherein the processing element(s) defining the mixing section (B) comprise(s) a mixing element (11, 12, 13) that is derived from a screw type element,
characterized in
that the basic shape of the mixing element (11, 12, 13) is that of a screw element, but which has been modified such that it exerts a compounding or mixing effect in addition to a conveying effect,
that the mixing element (11, 12, 13) has recesses formed in the screw flight of the screw type element, and
that the mixing element (11, 12, 13) has a plurality of concentric ring portions (16; 25) formed by grooves turned into the screw type element."

II. An opposition against the patent was filed on the grounds that its subject-matter lacked inventive step

(Article 100(a) EPC) and was not sufficiently disclosed (Article 100(b) EPC).

The documents filed during the opposition proceedings included the following:

O3: EP 0 580 860 A1

O5: WO2004/009326 A1

O6: US 5,318,358

O8: Understanding Compounding, R.H. Wildi, C. Maier, Hanser Publishers, Munich 1998, pages 103 to 110

O10: J. Breitenbach, European Journal of Pharmaceutics and Biopharmaceutics, 2002, 54, pages 107 to 117

O13: Experimental report "Extrusion of lopinavir/ ritonavir combinations based on the teaching of WO 2007/104747 A2"

III. The appeal by the opponent (hereinafter the appellant) lies against the decision of the opposition division to reject the opposition.

IV. According to the decision under appeal, the claimed invention fulfilled the requirements of sufficiency of disclosure.

As regards inventive step, the opposition division considered O3 as the closest prior art, from which the subject-matter of claim 1 differed in terms of the mixing element of the extruder. As the opponent had not demonstrated that the claimed method did not lead to

the alleged technical effect of reduced degradation of the active agent, the objective technical problem was seen as the provision of a process minimising degradation of the active agent while enabling sufficient mixing or homogenisation of the active agent. The solution provided by the subject-matter of claim 1 was considered to be inventive. In particular, although the claimed mixing elements were generally known from O5, O6, O8, none of these disclosures provided the skilled person with an incentive to select the mixing element of claim 1 in order to solve the objective technical problem.

V. With the statement setting out the grounds of appeal the appellant requested that the decision under appeal be set aside and that the patent be revoked. It also submitted the following new evidence:

O17: Experimental report "Extrusion of lopinavir/ ritonavir combinations based on the teaching of WO 2007/104747 A2" (i.e. second experimental report following O13 and having eight pages in total)

O18: Summary of the data of the patent, O13 and O17 (two pages in total)

O19: Supplementary expert declaration of Prof. Dr. Steffens (nine pages in total)

VI. With the reply to the statement setting out the grounds of appeal filed on 13 June 2016, the patent proprietor (hereinafter the respondent) requested that the appeal be dismissed. It also submitted the following evidence:

P2: Experimental report "Evaluation of two different screw configurations (Kneading Block/Segmented

Elements)" (four pages in total)

P3: Statistical evaluation of O17 (three pages in total)

VII. In a communication pursuant to Article 15(1) RPBA issued on 27 August 2018, the Board expressed its preliminary opinion on *inter alia* inventive step of the main request and raised the question of the breadth of the subject-matter of claim 1 in this respect (see point 2.2.1, paragraph 4 of the Board's communication).

VIII. With letter dated 17 September 2018, the respondent provided further arguments why the claimed subject-matter was inventive based on the closest prior art document O3 taken in combination with either O6 or O8.

IX. Oral proceedings took place on 9 October 2018 in the presence of both parties. In these proceedings, the respondent filed an auxiliary request (hereinafter auxiliary request 1). This request differed from the main request only in that the biologically active ingredient of claim 1 was specified to be shear- and temperature-sensitive.

X. The appellant's arguments, as far as they are relevant for the present decision, can be summarised as follows:

(a) The subject-matter of claim 1 of the main request differed from the closest prior art in terms of the mixing element of the extruder. As claim 1 did not impose any restrictions on the biologically active agent to be processed, it included any such agent including thermostable agents which did not present any problems of thermal degradation during the

extrusion process in the first place. Accordingly, the technical effect of minimised degradation of the active agent did not exist over the whole scope of claim 1, and could therefore not be taken into account for the formulation of the objective technical problem. The latter was thus to be worded as the provision of an alternative process for producing a solid dispersion of a biologically active ingredient in a matrix-forming agent by means of extrusion. The proposed solution, i.e. the process of claim 1, was obvious in the light of the closest prior art O3 taken in combination with *inter alia* O5.

(b) Auxiliary request 1 should not be admitted into the proceedings. In particular, there were no valid reasons for filing this request so late in the proceedings, as the appellant's line of argument that the technical effect of minimised degradation of the active agent did not exist over the whole area claimed had already been mentioned in the course of the written appeal proceedings. Furthermore, the amendments made to claim 1 gave rise to an objection of lack of clarity, and were not suitable to overcome the lack of inventive step observed for the main request.

XI. The respondent's arguments, as far as they are relevant for the present decision, can be summarised as follows:

(a) The distinguishing feature between the subject-matter of claim 1 and the closest prior art O3, i.e. the mixing element of the extruder, provided the technical effect of reduced degradation of the active agent.

This effect existed for all active agents including thermostable agents, albeit to a lesser extent than in the case of thermolabile compounds. What was more, the appellant had not provided any evidence to the contrary.

The objective technical problem was therefore the provision of a process for producing a solid dispersion of a biologically active ingredient in a matrix-forming agent, in which the active ingredient was homogeneously dispersed and/or dissolved in the matrix-forming agent such as to attain high bioavailability, and which process minimised degradation of the active ingredient and/or the matrix-forming agent.

The claimed solution was inventive. In particular, even though the claimed mixing elements were generally known from O5, this document lacked any incentive to select these particular elements in order to solve the objective technical problem as posed.

The same conclusions applied in the event that the objective technical problem was considered to be the provision of an alternative process for producing a solid dispersion of a biologically active ingredient in a matrix-forming agent by means of extrusion. In particular, the skilled person would not have taken into account document O5 for solving this technical problem, as it was a very general disclosure which did not mention any pharmaceutical applications, let alone the preparation of solid dispersions of a biologically active ingredient in a matrix-forming agent. Furthermore, common general knowledge would not

have led the skilled person either to consider that the generally known principles of melt extrusion technology elaborated in other technical fields such as plastics would equally apply to melt extrusion processes involving pharmaceutical agents.

(b) Auxiliary request 1 should be admitted into the proceedings. Its submission constituted a legitimate reaction to the appellant's argument that the technical effect of minimised degradation did not exist for thermostable active agents, which had been mentioned by the appellant for the first time in the oral proceedings. Furthermore, the introduction of the term "shear- and temperature sensitive" into claim 1 did not pose any problems in terms of clarity, as it had a generally recognised meaning in the art.

XII. Requests

The appellant requested that:
- the decision under appeal be set aside and the patent be revoked;
- auxiliary request 1 not be admitted into the proceedings.

The respondent requested that the appeal be dismissed, in the auxiliary that the decision under appeal be set aside and the patent be maintained on the basis of auxiliary request 1 filed during oral proceedings.

Reasons for the Decision

Main request

1. Article 100(a) EPC in conjunction with Article 56 EPC

1.1 The closest prior art

1.1.1 The Board agrees with the parties and with the decision under appeal that document O3 represents the closest prior art.

1.1.2 This document describes in particular a process for producing a solid dispersion of a drug dissolved in a polymer, wherein a twin-screw extruder equipped with paddle means or kneading blocks as mixing element is employed (see page 2, lines 35 to 47; example 1 and claim 1 of O3; paragraph [0004] of the patent in suit).

1.1.3 It was not disputed by the parties that the difference between the subject-matter of claim 1 and that of O3 lies in the mixing element forming part of the mixing section of the extruder.

The Board sees no reason to deviate from the approach followed by the parties.

1.2 *Technical problem and solution*

1.2.1 The problem addressed in the patent in suit is to provide a process for producing a solid dispersion of a biologically active ingredient in a matrix-forming agent by means of extrusion, in which degradation of the active ingredient is minimised (see paragraphs [0012] and [0020]).

1.2.2 As evidence of the achievement of this objective, the respondent referred to

(a) example 2 of the patent,
(b) to the experimental data comprised in document P2, and
(c) to the statistical data disclosed in P3 in connection with formulation B, which is based on the experimental data described in table 6 of O17.

All of the experiments were performed with formulations comprising the biologically active agent ritonavir, and included the determination of the amount of the major degradation products of this compound in the extrudates. These data show *inter alia* that ritonavir is indeed subject to thermal degradation during melt extrusion.

1.2.3 Claim 1, on the other hand, is not limited to any specific type of biologically active agent, and merely requires that a solid dispersion of this agent is produced by means of the claimed process.

Accordingly, the question arises whether the technical effect of reduced degradation relied upon by the respondent can be achieved substantially across the whole scope of claim 1 by using the claimed extruder, i.e. for substantially all biologically active agents.

1.2.4 In his reply to the grounds of appeal, the respondent indicated that the known melting methods for producing solid dispersions of biologically active ingredients could pose problems in connection with thermolabile ingredients, in that the heat stressing shear forces applied in these processes caused the active substance to be thermally degraded (see points 4, 6 and 9 of the

reply). Hence, the aim of the claimed invention was to develop a process which allowed for the preparation of solid dispersion products of thermolabile poorly soluble drugs with minimised thermal degradation (see point 10 of the reply).

In so far as other active agents were concerned, such as for instance thermostable agents which were readily soluble in the melt, the respondent considered that these would also undergo thermal degradation during melt extrusion, albeit in a less pronounced manner. Accordingly, in the respondent's view, it was fully credible that the claimed process provided for the technical effect of reduced thermal degradation throughout the entire range covered by claim 1, i.e. with regard to any type of biologically active ingredient. The fact that the degree of improvement obtainable by the claimed process might be less pronounced and more difficult to detect in the case of thermostable compounds than in the case of thermolabile substances, did not, however, imply that the technical effect of reduced thermal degradation did not exist at all in the former case.

1.2.5 Nevertheless, the Board disagrees with the respondent's argumentation for the following reasons:

It is undisputed that the technical effect relied upon by the respondent can only occur if the biologically active agent is actually prone to thermal degradation.

The respondent also did not dispute that the scope of claim 1 encompassed any type of biologically active agent, provided that it formed a solid dispersion with a matrix-forming agent by means of the claimed process. The active agent as claimed might range from a fairly

thermolabile ingredient to a virtually indestroyable ingredient and included *inter alia* thermostable compounds such as paracetamol (see points 22 and 23 of respondent's reply to the grounds of appeal).

Accordingly, the respondent's argumentation can only succeed if each and every biologically active agent will undergo thermal degradation in some form or another, when being subjected to melt extrusion methods.

However, the Board does not find this credible, in so far as the claimed process involves the use of biologically active ingredients which are thermostable or "virtually indestroyable". Furthermore, even if for the sake of argument it were assumed that these types of active agents underwent some minor form of thermal degradation upon melt extrusion, the degree of improvement obtainable by means of the claimed process in comparison with the process of the closest prior art would be so marginal that it could, if detectable at all, not constitute any valid support for the attainment of the purported technical effect substantially across the whole scope of claim 1.

1.2.6 Accordingly, in the Board's judgement, the technical effect of reduced thermal degradation is not achievable over the whole area claimed, and can thus not be taken into account for the formulation of the objective technical problem.

1.2.7 The technical problem over O3 must therefore be formulated as the provision of a further process for producing a solid dispersion of a biologically active ingredient in a matrix-forming agent by means of extrusion.

1.2.8 The solution proposed to this problem is a process in accordance with claim 1.

1.3 *Obviousness*

1.3.1 Document O5 generally relates to the technical field of extruders, and addresses in particular the problems associated with the kneading blocks of these extruders (see page 1, lines 14 to 24). To solve these problems, O5 proposes to replace these kneading blocks with another type of mixing element as shown in figures 2 and 5 of O5. This element corresponds to an embodiment of the mixing element of claim 1 of the main request (see paragraph [0035] of the patent in suit).

Hence, O5 relates to the same type of twin screw extruders as those mentioned in the closest prior art O3, specifically discusses the disadvantages associated with these and provides a solution for these problems which falls within the scope of claim 1 of the main request.

1.3.2 The respondent argued that O5 was only concerned with the mixing of liquid, viscous, plastic or particulate substances in general, whereas it did not mention any pharmaceutical applications. Furthermore, it solely referred to extrusion processes of a single compound, whereas the process of claim 1 was aimed at the preparation of a solid dispersion of a biologically active ingredient in a matrix-forming agent. Accordingly, the skilled person would not take into account document O5 for solving the objective technical problem as posed.

1.3.3 This appears unconvincing, given the fact that it was generally known at the priority date of the patent in

suit that melt extrusion processes, originally developed for the plastic industry, in the mean time have found their place in an array of pharmaceutical manufacturing operations such as *inter alia* the preparation of a variety of dosage forms including solid dispersions (see review article O10, in particular the title and the abstract thereof).

1.3.4 In the respondent's view, the skilled person would not apply the principles of melt extrusion technology of the plastic industry to melt extrusion processes aimed at the preparation of solid dispersions involving pharmaceutical agents. In particular, he would not consider any extruder employed in the plastic industry to be suitable for melt extrusions involving pharmaceutical agents, given the fact that the pharmaceutical area was subject to much stricter regulations than the field of plastics, for instance with regard to the maximum permissible content of impurities.

1.3.5 This argument is not found convincing, either. O10 mentions on page 114, column 2, second paragraph that the drawbacks of the melt extrusion technology in the pharmaceutical area (i.e. the degradation of drugs and excipients caused by high energy input, the latter being mainly related to shear forces and temperature), may be overcome by a proper design of screw assemblies and extruder dies. As a result thereof, even drugs which were sensitive to elevated temperatures could be processed successfully.

1.3.6 Therefore, in the Board's judgement, the skilled person, having at his disposal the common general knowledge reflected by O10, would consider the melt extrusion technology applied in the plastic industry to

be closely related to the melt extrusion processes of the pharmaceutical field. Accordingly, he would take document O5, and in particular the solution proposed therein, into account for solving the objective technical problem as posed, thereby arriving at the subject-matter of claim 1 in an obvious manner.

Hence, the subject-matter of claim 1 does not comply with the requirements of Article 56 EPC.

Auxiliary request 1

2. Admission of this request into the proceedings

2.1 The respondent filed this request in the oral proceedings after the announcement of the Board's conclusion on inventive step of the main request. Claim 1 of this request differs from claim 1 of the main request only by the fact that the biologically active ingredient is shear- and temperature-sensitive.

2.2 Since this request was filed after the filing of the respondent's reply to the grounds of appeal, it constitutes an amendment to the case in the sense of Article 13(1) RPBA. Under this article, the Board is given discretion in admitting and considering such an amendment.

2.3 When the amendment is filed in the course of the oral proceedings only, the generally accepted practice of the Boards of Appeal when exercising their discretion is as follows: unless good reasons exist for filing amendments so late into the procedure, e.g. when these are occasioned by developments during the proceedings, they are only admitted if clearly or obviously allowable.

2.4 This means that it must be immediately apparent to the Board, with little investigative effort on its part, that the amendments successfully address the problems to be overcome without giving rise to new ones.

2.5 Accordingly, it first needs to be determined, if good reasons exist on the part of the respondent for filing the amendments so far into the procedure. The respondent argued in this regard that the submission of the auxiliary request constituted a legitimate reaction to the appellant's line of argument that the technical effect of minimised degradation did not exist for thermostable active agents, this argument having been put forward by the appellant for the first time in the oral proceedings.

However, the Board holds that this argument has already been mentioned in the course of the written appeal proceedings. Accordingly, no new issues have been raised during the oral proceedings which could justify the submission of a new request at this late stage of the proceedings.

2.6 Furthermore, the Board agrees with the appellant that the auxiliary request raises prima facie new issues. Among others, the feature "shear- and temperature sensitive" introduced into claim 1 is a relative term which is neither defined in the patent in suit itself nor appears to have a generally recognised meaning in the art. Hence, this amendment gives prima facie rise to an objection of lack of clarity of claim 1.

2.7 Accordingly, the Board exercises its discretion under Article 13(1) and 13(3) RPBA not to admit auxiliary request 1 into the proceedings.

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