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Datasheet for the decision of 19 March 2015

Case Number: T 0081/12 - 3.3.07

Application Number: 06778242.5

Publication Number: 1931317

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Language of the proceedings: EN

Title of invention:
PANCREATIN MICROPELLETS SUITABLE FOR ENTERIC COATING

Patent Proprietor:
Abbott Laboratories GmbH

Opponents:
Nordmark Arzneimittel GmbH & Co. KG
Aptalis Pharma S.r.l.

Headword:
PANCREATIN MICROPELLETS SUITABLE FOR ENTERIC COATING/Abbot Laboratories GmbH

Relevant legal provisions:
EPC Art. 56

Keyword:
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Decisions cited:

Catchword:

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Case Number: T 0081/12 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 19 March 2015

Appellant: (Patent Proprietor)	Abbott Laboratories GmbH Freundallee 9A 30173 Hannover (DE)
Representative:	Hart-Davis, Jason Cabinet Beau de Loménie 158, rue de l'Université 75340 Paris Cedex 07 (FR)
Respondent: (Opponent 1)	Nordmark Arzneimittel GmbH & Co. KG Pinnauallee 4 25436 Uetersen (DE)
Representative:	Richter, Joachim RGTH Patentanwälte PartGmbB Neuer Wall 10 20354 Hamburg (DE)
Respondent: (Opponent 2)	Aptalis Pharma S.r.l. Via Martin Luther King 13 20060 Pessano Con Bornago (IT)
Representative:	Gerli, Paolo Botti & Ferrari S.r.l. Via Cappellini, 11 20124 Milano (IT)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 17 November 2011 revoking European patent No. 1931317 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	D. Semino
Members:	D. Boulois
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. European patent No. 1 931 317 based on application No. 06 778 242.5 was granted on the basis of a set of 17 claims.

II. Two oppositions were filed against the granted patent under Article 100 (a) and (b) EPC on the grounds that its subject-matter lacked novelty and inventive step and the patent was not sufficiently disclosed.

III. The present appeal lies from the decision of the opposition division to revoke the patent (Article 101(3)(b) EPC). The decision was based on 6 sets of claims filed with letter of 4 August 2011 as main request and auxiliary requests 1-5.

The subject-matter of independent claim 1 of the then pending main request read as follows:

"1. A process for the manufacture of pancreatin micropellet cores, comprising the steps of:
a. preparing an extrudable mixture comprising:
i. 10% to 95% pancreatin;
ii. 5% to 90% of at least one pharmaceutically acceptable binding agent selected from the group consisting of: polyethylene glycol 1500, polyethylene glycol 2000, polyethylene glycol 3000, polyethylene glycol 4000, polyethylene glycol 6000, polyethylene glycol 8000, polyethylene glycol 10000, hydroxypropyl methylcellulose, polyoxyethylene, copolymers of polyoxyethylene-polyoxypropylene and mixtures of said organic polymers; and
iv. one or more enzyme-friendly organic solvents in an amount sufficient to form an extrudable mixture;

wherein the percentages of components are weight to weight of the pancreatin micropellet cores and the constituents i.) and ii.) add to 100 % by weight;
b. extruding the extrudable mixture to create pancreatin micropellet cores ;
c. forming the pancreatin micropellet cores into approximately spherical or approximately ellipsoidal shape in the presence of additional enzyme-friendly organic solvent; and
d. removing the one or more enzyme-friendly organic solvents from the pancreatin micropellet cores such that the pancreatin micropellet cores are substantially free of the one or more enzyme-friendly organic solvents;
wherein the pancreatin micropellet cores are substantially free of synthetic oils."

IV. The documents cited during the opposition proceedings included *inter alia* the following:
(1): DE 26 26 109 A1
(2): DE 198 48 849 A1
(4): DE 298 24 797 U1
(5): DE 29 23 279 C2
(8): US 2004/0101562 A1
(13): US 4 079 125
(14): US 5 750 104
(15): US 5 302 400
(36): Technical reports on Comparative Examples 1/7-7/7

V. According to the decision under appeal,the main request met the requirements of Article 123(2), 123(3) and 84 EPC.

As regards novelty of the main request, an explicit or implicit unambiguous disclosure of all the features of claim 1, especially the specific binders in document

(1) or (13), and the use of an organic solvent in document (4) was lacking.

Document (1) or equivalently document (13) was seen as the closest prior art with respect to the process of claim 1, the difference lying in the specific binders listed in the claim. From the example of the contested patent, it appeared that the claimed process worked with PEG 4000 and a certain well defined amount of isopropanol. The claimed effect was to provide pellets with properties sufficiently satisfactory that could be further processed, e.g. by coating. The data (36) provided by the patentee showed that several of its examples 1/7-7/7, which were embodiments of claim 1 of the main request with binders of the list and an appropriate amount of isopropanol, had severe processing difficulties. The results of document (36) showed thus that the technical problem was not solved over the whole claimed range. The presence of an inventive step over document (1) could not be acknowledged.

As the only difference in claim 1 of auxiliary request 1 consisted in the deletion of hydroxypropyl methyl cellulose (HPMC) from the list of binders, the considerations on inventive step of the main request applied also to auxiliary request 1.

Auxiliary request 2-5 did not meet the requirements of Article 123(2) EPC.

VI. The proprietor (appellant) filed an appeal against that decision.

VII. With the statement of grounds of appeal, the appellant filed a main request and a new document:

(38): Further Experimental Data

The subject-matter of independent claim 1 of the main request differed from the subject-matter of claim 1 of the main request discussed before the opposition division by the specification of the binding agent (difference(s) shown in bold), namely:
"ii. 5% to 90% of **polyethylene glycol 4000** as pharmaceutically acceptable binding agent;".

VIII. With a letter dated 15 January 2015, the appellant filed auxiliary requests 1 and 2.

The subject-matter of the independent claim 1 of auxiliary request 1 differed from the subject-matter of claim 1 of the main request filed with the statement of grounds of appeal by the following further specifications (difference(s) shown in bold):
"i. **70% to 95%** pancreatin;
ii. **10% to 30%** of polyethylene glycol 4000 as pharmaceutically acceptable binding agent;"

The subject-matter of independent claim 1 of auxiliary request 2 was identical to claim 1 of the main request, this request differing from the main request in the suppression of dependent claim 2.

IX. A Board's communication dated 17 February 2015 was sent to the parties. In this it was stated in particular that document (13) appeared to be the closest state of the art, in particular in view of its example 2. The communication pointed further out that the relevance of the experimental data (36) and (38) would have to be discussed during oral proceedings.

X. Oral proceedings took place on 19 March 2015, in the absence of respondent-opponent 02 as announced with letter dated 18 March 2015.

XI. The arguments of the appellant may be summarized as follows:

Documents (13), (14) or (15) were considered as potential closest prior art. None of these documents disclosed PEG 4000 as binding agent, and it was considered that the binders were not freely interchangeable. It could be seen from the experiments of documents (36) and (38) that it was attempted to vary the relative amounts of pancreatin and binder in order to compare the performance of PEG 4000 with the HPMC and polyvinylpyrrolidone (PVP) binders. Even allowing for variation of the relative amounts of pancreatin and binder, and also allowing a change in the amount of solvent, it was not possible to carry out successful extrusions and spheronization with these binders, in particular with PVP. Moreover, the claimed process offered the advantage to achieve an extrusion process with an unique excipient, and not with supplementary excipients, such as disintegrating agents as in document (13).

As regards document (13), its teaching related to a different problem, namely the protection of pancreatin and its rapid release (see col. 1, lines 27-38). The micropellet core contained thus a binder, but also other excipients, such as a stabilizer and a disintegrating agent (see col. 3, lines 16-28); the presence of such mandatory excipients was not required by the process claimed in claim 1 of the main request. The skilled person, following the teaching of document (13) would thus have considered the use of such

supplementary excipients. Example 2 of document (13) showed an extrusion of pancreatin with a binder, namely PVP, and a disintegrating agent, namely cellulose. Cellulose was not considered as a binding agent, but was rather a disintegrating agent as mentioned in claim 1 of document (13). Example 2 was considered as unworkable. An extrusion with cellulose appeared indeed to be difficult, since cellulose would swell and the resulting mixture would have been too sticky to achieve an extrusion. The comparative data provided by documents (36) and (38) did not repeat exactly the teaching of document (13), but nevertheless showed the existence of a technical effect linked to the use of an unique excipient, namely PEG 4000, in the claimed process. Moreover, documents (36) and (38) showed that excipients such as PVP and HPMC were more difficult to extrude.

The problem was to provide a successful and improved process to produce oil-free, excipient free pancreatin micropellets, since it was not possible to carry out successful extrusion and spheronization with the binders of the closest state of the art. Moreover, the technical problem was considered to be solved over the full scope of the claims. The presence of non-working embodiments, such as example 1/7 of document (36) should not distract from the fact that in essence, and with a large possibility of process variation, shown further in document (38), a technical effect had been demonstrated. Example 1/7 of document (36) was provided to show that the combination of a binding agent with a high amount of solvent would not lead to a successful extrusion process. The skilled person had to optimize the amount of solvent to be used for the extrusion. On that basis, the presence of an inventive step should be acknowledged.

XII. The arguments of the respondents may be summarized as follows:

Respondent-opponent 01 considered that document (5) was the closest prior art and that the claimed process was not inventive over document (5) in combination with documents (1) (2) or (4). As regards document (13), it showed that it was possible to make extrusions without oil. The process disclosed in document (13) included possibly the presence of a disintegrating agent, which had however no effect on the extrusion process. Example 2 of document (13) included excipients which had all binding properties. Moreover, the scope of claim 1 of the main request was very broad, and it was doubtful that a composition comprising the limit values of 90% of PEG 4000 or 95% of pancreatin could be extruded.

Respondent-opponent 02 considered in its written submissions document (13) as the closest prior art, in view especially of its example 2. The difference between the claimed subject-matter and document (13) was that another binding agent, namely PEG 4000, was used instead of PVP and Avicel. In view of document (13), the objective problem was to provide an alternative process to produce oil-free, excipient-free pancreatin micropellets, since no unexpected effect was evident or derivable from the contested patent or from the data of documents (36) or (38). The skilled person knew from document (8) that PEG 4000 could be used as binding agent in the preparation of pancreatin micropellets in oil-free conditions. The subject-matter of claim 1 of the main request was thus obvious over the prior art.

According to respondent-opponent 02, example 1/7 of document (36) furthermore showed that embodiments comprised in the scope of the claim were not able to achieve an extrusion. The performance of the process in the current scope of claim 1 presumed an effective control of special parameters, especially the amount of solvent, which were not defined by the claims or enabled by the patent as a whole. The present patent went thus well beyond a reasonable generalization of the tested examples and failed to provide a solution to the underlying technical problem. In particular, the binding agent was not per se responsible of the technical effect of obtaining an extrudable and/or spheronizable mixture, since this task was accomplished by the solvent if added to the mixture in appropriate amounts. The data (38) provided by the appellant showed examples comprising from 75-85% of pancreatin, 15-25% of PEG 4000, and 22-28% of added 2-propanol, while the claimed process related to a process involving 10-95% of pancreatin, 5-90% of PEG 4000 and no limitation on the solvent. It was not at all evident how to extrude a mixture comprising up to 95% of pancreatin, a very dry and bulky powder, especially since the amounts of the appropriate solvent to be used was not given in the claims or in the description. The patent did not give any guidance on how to adapt the amount of solvent when a certain balance of pancreatin/PEG, other than the one in the examples, was chosen.

XIII. Requests

The appellant (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained on the basis of the set of claims of the main request as filed on 15 March 2012 (statement of grounds), or, alternatively, on the sets of claims of

one of the two auxiliary requests filed with the letter dated 15 January 2015.

Both respondents (opponent 01; opponent 02, in its written submissions) requested that the appeal be dismissed.

Reasons for the Decision

1. Main request - Inventive step

1.1 The claimed invention relates to a process for the manufacture of a medicament containing pancreatin, which is substantially free of synthetic oils. Synthetic oils like paraffins, e.g. liquid paraffins (mineral oils), in particular highly liquid paraffin (light mineral oil) have indeed previously been understood to be a necessary excipient for manufacturing pancreatin micropellet products by extrusion and subsequent spheronisation of the extrudates. There is however a need to provide patients with a pancreatin micropellet product in compliance with the current advice of the health authorities and which does not include synthetic oils such as mineral oil (see par. [0001]-[0004] in the patent).

1.2 The following documents were cited as closest prior art, namely document (5) by respondent-opponent 01, document (13) by respondent-opponent 02, and documents (13), (14) or (15) by the appellant. The opposition division considered documents (1) or (13) as closest prior art.

All cited documents show an oil free extrusion process of pancreatin pellet, and thus relate *de facto* or implicitly to the same purpose as the contested patent.

1.2.1 Document (5) discloses the extrusion of pancreatin alone or with magnesium stearate and does not mention the use of a binding agent (see examples 1 and 2).

1.2.2 Documents (14) and (15) disclose an extrusion process with several excipients, namely a buffering agent, a disintegrant and an adhesive polymer different from PEG 4000 (see document (14), col. 7, lines 1-16 or document (15), col. 5, lines 25-55).

1.2.3 The teaching of documents (1) and (13) is identical, since both belong to the same patent family and differ only in their language; therefore, only the teaching of document (13) will be considered.

Document (13) discloses a process of manufacture of pancreatin pellet with binders generally present in amounts of 0.5% to 10% by weight (see col. 5, lines 58-65). Example 2 of document (13) shows in particular an extrusion process of a composition comprising 90% by weight of pancreatin and respectively 3.0% and 7.0% by weight of polyvinyl pyrrolidone K30 (PVP-K30) and microcrystalline cellulose (Avicel), PVP and Avicel being explicitly identified as binding agents in document (13) (see col. 5, lines 5-6 and 59), and with an amount of isopropanol as solvent of 675 ml per kg of powder blend. Document (13) discloses further that PVP acts both as the binder and as stabilizer for pancreatin and that cellulose has a double function of binding and disintegrating agent (see document (13), col. 5, lines 16-18, line 59 and claim 1). Document (13) does thus not disclose the use of PEG as binding agent, but uses instead a combination of PVP-K30 and Avicel.

1.2.4 As all the cited documents relate to the same purpose and the technical teaching of document (13) shows the largest number of similarities with the claimed subject-matter, this document represents the closest state of the art.

1.3 According to the appellant, the problem is to provide a successful and improved process to produce oil-free, excipient free pancreatin micropellets.

1.4 As a solution to this alleged problem, claim 1 of the main request proposes a process involving in particular as unique excipient and binding agent polyethylene glycol 4000.

1.5 It has to be investigated whether there is sufficient evidence supporting the alleged effect.

1.5.1 The patent in suit provides one example of preparation of a micropellet by an extrusion process, namely by mixing 15.9 kg of pancreatin with 3.975 kg of polyethylene glycol 4000, moistening the mixture with 3.975 kg of 2-propanol and extrusion of the blend (see example 1). The amount of solvent used in this specific example is 25% by weight relative to the amount of pancreatin used. The further examples of the contested patent relate to the coating of said micropellet. Example 1 of the contested patent shows undoubtedly that an oil free extrusion process as claimed is possible and provides a micropellet. This achievement does however not provide a comparison between the process according to present invention and the process according to document (13) or an evidence of the unworkability of the extrusion process of example 2 of document (13).

1.5.2 In order to prove the existence of a beneficial effect over the closest state of the art, the appellant provided experimental data (36) during the opposition proceedings and experimental data (38) during the appeal proceedings.

Document (36) shows 7 comparative examples numbered 1/7 to 7/7. The examples relate to extrusion processes with various binders, such as PEG 4000 (example 1/7), PEG 2000 (example 2/7), PEG 8000 (example 3/7), HPMC (examples 4/7 and 6/7) or PVP (examples 5/7 and 7/7), none of the extrusion processes being shown as satisfactory. Examples 5/7 and 7/7 of document (36) relate in particular to an extrusion process of a mixture of 80% by weight of pancreatin and 20% by weight of PVP-K30 moistened with respectively 27% and 25% of isopropanol by weight relative to the amount of pancreatin used, wherein the extrusion was not possible, in reason of a too high viscosity. All the examples of document (36) are irrelevant for establishing a comparison or for showing the unworkability of the extrusion performed with the components and conditions of example 2 of document (13). The disclosure of examples 5/7 and 7/7 differ in particular in the amount of moistening solvent used and in the nature of the binding agent. Example 2 of document (13) shows indeed a process involving a 10% by weight binding mixture of PVP K30 and cellulose and in particular an amount of moistening solvent, namely isopropanol, of around 675 ml/kg of pancreatin powder (around 67% by weight relative to pancreatin). These specific working conditions, were not reproduced in any of the comparative examples 1/7 to 7/7 of document (36), even when PVP was used as unique binding agent.

Document (38) shows 6 comparative examples with HPMC as binding agent and 6 further comparative examples with 15 to 25% of PVP-K30 as binding agent, with an amount of isopropanol up to 28% by weight relative to the amount of pancreatin used. The examples performed with PVP-K30 not only do not allow a comparison with the process example 2 of document (13) involving an amount of isopropanol of around 67% by weight, but also show a clear trend of improvement of the extrusion process with an increasing amount of isopropanol, the extrusion becoming possible with PVP-K30 as binding agent when moistened with an amount of isopropanol of 28% by weight relative to the amount of pancreatin used.

1.5.3 None of either the example of the contested patent or the further experiments (36) or (38) offer thus sufficient evidence to support the assumptions of the existence of an improvement over the teaching of document (13) or of the unworkability of the extrusion process shown in example 2 of document (13). The assumption on unworkability is particularly further undermined by the experimental results of document (38) which show an improvement of the extrusion properties of the polymer PVP-K30 with an increasing amount of moistening solvent. The trend of an improvement on the extrusion properties of PVP-K30 linked to an increasing amount of solvent shown in document (38) highlights the fact that the skilled person has to adapt a specific amount of solvent to each specific binding agent.

The Board has thus no evidence or credible argumentation to question the teaching of document (13), in particular the workability of the extrusion of example 2.

1.5.4 Further arguments of the appellant

The appellant argued that the claimed process involved the use of an unique necessary excipient, namely the binding agent PEG 4000, instead of several excipients such as in example 2 of document (13), and that a high amount of moistening solvent would in any case prevent the achievement of a satisfactory extrusion process.

The Board could not share this opinion.
As regards the excipients, it has not been made credible or demonstrated by means of experimental evidence that the presence of an excipient other than a binding agent, in particular of a disintegrating agent, hinders or influences the extrusion process. Contrary to binding agents, disintegrating agents do not have a function linked with the manufacture of the galenical form, but rather have an influence on the property of the final product. It is further not credible in view of the binding properties of cellulose.

As to the high amount of moistening solvent, it has been demonstrated in example 1/7 of document (36) that an amount of 60% of solvent based on the pancreatin is detrimental to the extrusion with PEG 4000 as binding agent. An experiment with a high amount of solvent has however not been undertaken for an extrusion performed with PVP and cellulose as binding agent, even less with PVP alone, since the comparative examples of documents (36) and (38) performed with PVP had an amount of moistening solvent of at most 28% by weight relative to the pancreatin powder, thus much less than the 675 ml/kg used in example 2 of document (13). Moreover, as mentioned above, the experiments performed in document (38) show a clear trend of improvement when the extrusion with PVP as binding agent is performed with an increasing amount of solvent. This improvement does

not appear surprising to a skilled person, since the the amount of solvent is a paramount parameter for a successful extrusion, as it makes it possible to moisten the extruding mixture. It is thus to be expected that the necessary amount of moistening solvent be higher for a high viscosity polymer such as PVP-K30 in comparison to a lower viscosity polymer such as PEG 4000.

1.5.5 According to established case law of the boards of appeal, alleged advantages to which the patent proprietor merely refers, without offering sufficient evidence to support the comparison with the closest prior art, cannot be taken into consideration in determining the problem underlying the invention and therefore in assessing inventive step (Case Law of the Boards of Appeal, 7th edition, 2013, I.D.4.2.)

In the absence of experimental or technical evidence or arguments establishing a minimum plausibility, it is not possible to acknowledge the existence of an improvement over the prior art.

1.5.6 The technical problem must therefore be reformulated as the provision of a further process for manufacture of pancreatin micropellet cores. In view of the information found in example 1 of the contested patent, the board is convinced that the problem has been plausibly solved.

1.6 Since the problem consists in the provision of a further process for manufacturing a pancreatin micropellet cores, it belongs to the normal activity of the skilled person to accomplish routine modifications, such as choosing a known alternative binding agent.

The use of PEG 4000 as a binding agent for making microspheres of pancreatin is known from the teaching of document (8). In this document, a microsphere is produced by a process such as fluid bed or granulation involving high energy and heating at a temperature higher than the melting point of said PEG 4000 (see [par.[0022]-[0025] and examples 3, 4). The amount of PEG 4000 as binding agent is preferably comprised between 15% and 40% by weight (see par. [0038]).

The use of PEG 4000 as binding agent in an extrusion process involving pancreatin is therefore seen as an arbitrary choice that would be made as a matter of routine by a skilled person.

1.7 Thus, the subject-matter of claim 1 of the main request is obvious vis-à-vis document (13) taken as the closest prior art.

Consequently, the main request does not meet the requirements of Article 56 EPC.

2. Auxiliary request 1 - Inventive step

The subject-matter of claim 1 of auxiliary request 1 has been amended by the specification of narrower ranges for the amounts of pancreatin and of the binding agent, namely that the mixture comprises:
"i. **70% to 95%** pancreatin;
ii. **10% to 30%** of polyethylene glycol 4000 as pharmaceutically acceptable binding agent;".

Example 2 of document (13) relates to an extrusion process of a mixture of 90% by weight of pancreatin and 10% by weight of the mixture of binding agents, namely 3% by weight of PVP and 7% by weight of cellulose.

Hence, the amendments do not have any incidence on the reasoning and conclusions on inventive step outlined for the main request, which apply *mutatis mutandis* to claim 1 of auxiliary request 1. No inventive step can therefore be seen as a result of the specification of the amounts of pancreatin and binding agent.

Auxiliary request 1 does therefore not meet the requirements of Article 56 EPC.

3. Auxiliary request 2 -Inventive step

Since the subject-matter of claim 1 of auxiliary request 2 is identical to the one of claim 1 of the main request, the same conclusion applies *mutatis mutandis* and the request does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Fabiani D. Semino

Decision electronically authenticated