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D E C I S I O N
of 3 December 1999

Case Number: T 0079/99 - 3.3.2

Application Number: 91113152.2

Publication Number: 0526666

IPC: A61K 9/51

Language of the proceedings: EN

Title of invention:
Solid lipid microspheres having a narrow size distribution and method for producing them

Patentee:
Gasco, Maria Rosa

Opponent:
Yamanouchi Europe B.V.

Headword:
Solid lipid microspheres/GASCO, MARIA ROSA

Relevant legal provisions:
EPC Art. 123(2)(3), 84, 83, 111(1)

Keyword:
"Article 123(2) - yes - derivable feature"
"Article 84 - yes - meaning depending on the circumstances of the case"
"Sufficiency of disclosure - yes"
"Remittal to the first instance - yes"

Decisions cited:
-

Catchword:
When considering requests for extension of time, the Board will take into account not only any reasons put forward but also the number of previous extensions (if any), the views of the other party or parties (if known), the effect of delays on other appeals pending before it and the general principle that all delays are to be avoided where possible. Similar considerations apply to requests to adjourn oral proceedings. In these cases however, the Board will also take account of the fact that, once a date has been accepted, exceptional reasons may be required to justify a postponement. (See Reasons, point 2.2)

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Case Number: T 0079/99 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 3 December 1999

Appellant: (Proprietor of the patent)
Gasco, Maria Rosa
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10153 Torino (IT)

Representative:
Gervasi, Gemma, Dr.
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Corso di Porta Vittoria, 9
20122 Milano (IT)

Respondent: (Opponent)
Yamanouchi Europe B.V.
Elisabethhof 19
2350 AC Leiderdorp (NL)

Representative:
-

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 26 November 1998 revoking European patent No. 0 526 666 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
C. Rennie-Smith

Summary of Facts and Submissions

I. European Patent No. 0 526 666 based on application No. 91 113 152.2 was granted with 15 claims of which independent claim 1 read as follows:

"1. Solid lipid microspheres having an average diameter lower than one micron and a polydispersion of between 0.06 and 0.90."

II. The respondent opposed the patent under Article 100(b) EPC for insufficiency of disclosure and under Article 100(a) EPC for lack of novelty and inventive step.

The following documents were cited inter alia during the proceedings before the Opposition Division and the Board of Appeal:

(4) T. de Vringer et al., J. Pharm. Sci., 84(4), pages 466 to 472, 1995

(7) Journal of colloid and interface Science, 67, No. 3, pages 543 to 547, 1978

(11) "Zetasizer II C User Manual" (November 1986)

(15) Pharmazie 47 (1992), H. 2, pages 119 to 121.

III. The decision of the Opposition Division pronounced on 29 October 1998, posted on 26 November 1998 revoked the patent under Article 102(1) EPC for insufficiency of disclosure.

Independent claim 1 filed during the oral proceedings

before the Opposition Division reads:

"1. Solid lipid microspheres having an average diameter lower than one micrometer and a polydispersion of between 0.06 and 0.90, characterized in that said microspheres are in powder form and substantially free from surfactants and co-surfactants."

As regards the feature "in powder form" introduced in claim 1, the Opposition Division was of the opinion that a powder form of the microspheres was the inevitable effect of the lyophilisation step on microspheres of the type defined in the contested patent. It therefore concluded that this feature did not contravene Article 123(2) EPC although not *expressis verbis* disclosed in the original application.

It also took the view that the disclosure in the application (eg page 5, lines 13 to 20) was sufficient to support the new feature 2substantially free of surfactants and co-surfactants" of amended claim 1.

Concerning the opponent's objections under Article 100(b) EPC with respect to the technique of determination of polydispersion, the Opposition Division considered that, having regard to document (4), the degree of dilution of the polydispersion appeared to be an essential factor when using the Malvern Zetasizer II C method referred to in the patent.

As the dilution factor was not disclosed in the patent, it concluded that the method for measuring the polydispersion of the claimed solid lipid microspheres was not sufficiently disclosed contrary to the

requirements of Article 83 EPC.

As regards the opponent's other Article 100(b) objection, the Opposition Division expressed the opinion that the selection of appropriate conditions for carrying out the diafiltration technique mentioned in the patent could be easily derived from document (7), which described this technique in latex studies where the impurities were of the same nature.

IV. The appellant (proprietor) lodged an appeal against that decision.

V. In a communication dated 28 October 1999, the Board drew the appellant's attention the requirements of Article 123(2) and (3) EPC with respect to the added feature "in powder form" of amended claim 1 and the term "optionally" in amended claim 5.

The Board also rejected the appellant's request to postpone the date of the oral proceedings, which had already been agreed by both parties.

VI. By a letter dated 18 November 1999 the appellant filed a new set of 12 claims.

Claim 1 of this set of claims reads as follows:

"1. Solid lipid microspheres having an average diameter lower than one micrometer and a polydispersion of between 0.06 and 0.90, characterized in that said microspheres are in lyophilized form and substantially free from surfactants and co-surfactants."

Also, in claim 5 the term "optionally" was deleted as

it did not conform with the original disclosure.

VII. Oral proceedings were held before the Board on 3 December 1999.

VIII. The appellant's submissions both in the written procedure and at the oral proceedings can be summarised as follows:

As regards the amendments in claim 1, the feature "substantially free from surfactants and co-surfactants" was allowable since the original application clearly stated that "the washing by diafiltration leads to the elimination of all substances present in the dispersing aqueous phase (surfactant, co-surfactant and free drug not included in the microsphere)". In support of this view, the appellant's expert (a physical chemist who has experience of using the process of the invention) described the technical background of the invention and provided further explanation of the absence of surfactants and co-surfactants in the solid lipid microspheres.

The appellant also observed that the percentages of lipids in the liposphères reported in the examples (which ranged from 75% to 97%) were in fact the percentages of the lipid components transformed into microspheres, ie the yields, so that, contrary to the respondent's allegation in its reply to the grounds of appeal, it could not be concluded from these percentages that surfactants or co-surfactants or any other substances were also present beside the microspheres.

The appellant also maintained that document (15), filed by the respondent during the appeal procedure in order to demonstrate the presence of co-surfactant in the solid lipid microspheres, was in fact irrelevant as it did not concern a co-surfactant but a lipophilic complex ie an entity which did not have the characteristics of a co-surfactant. Accordingly, she claimed that the feature "substantially free from surfactants and co-surfactants" was clear and supported by the description.

Concerning the objection of insufficient disclosure with respect to the technique for measuring polydispersion, the appellant contended that, unlike the particles of document (4), the particles of the patent in suit did not necessitate a particular preliminary dilution as they were substantially pure and that it was therefore sufficient just to follow the instructions of the "Zetasizer II C User Manual" (document 11). She also filed experimental test results demonstrating that the measurement of the mean diameter and polydispersion of the particles did not change with the degree of dilution.

The appellant also argued that, as demonstrated by document (7), diafiltration was a known technique and since the patent in suit clearly stated that diafiltration was used in the step of washing the dispersion in cold water to eliminate the substances present in the dispersing phase, this step was merely a common operation practiced by every laboratory worker.

IX. The respondent (opponent) contested these arguments as follows:

The feature "substantially free from surfactants and co-surfactants" in claim 1 was not allowable under Article 123(2) EPC. The passage in the application relied on by the appellant was not a proper basis for the amendments as it referred only to the substances present in the dispersing aqueous phase.

It maintained that it was not understandable why the solid microspheres did not include surfactants and co-surfactants whereas they contained drugs having totally different properties, particularly as very significant amounts (up to 30%) of surfactants and co-surfactants were used in the process for the preparation of the microspheres. The respondent also suggested the diafiltration technique removed only the dissolved surfactants but not those present at the interface between the microspheres and the water phase nor those within the microspheres, as evidenced by document (7).

In that respect, it also pointed out that document (15), relating to solid lipid microspheres prepared by the process of the patent in suit, made clear that a co-surfactant was present in the microspheres together with the drug as an ion pair. The respondent was therefore of the opinion that it was very doubtful whether lipospheres "substantially free from surfactant and co-surfactants" were obtained by the process disclosed in the contested patent and that the interpretation of "substantially free" was ambiguous.

It was however conceded by the respondent that it could not be concluded from the percentage yields of lipids given in the examples of the patent that substantial amounts of the components of the microspheres were not specified in the examples.

Concerning the objection of insufficiency of disclosure, the respondent contended that, although document (7) demonstrated that diafiltration was a known technique, the disclosure in the patent did not identify which mode of the diafiltration apparatus was to be used in order to achieve the benefits of the process described in the patent.

In the light of the evidence regarding the measurement of polydispersity, the respondent withdrew its insufficiency objection to that feature.

X. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the set of 12 claims filed with her letter of 18 November 1999.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Procedural matters*

2.1 As mentioned above (supra, paragraph 5), the appellant sought a postponement of the oral proceedings. This resulted from the late filing by the respondent of its written submissions on the Grounds of Appeal which were received on 25 March 1999 and copied to the respondent by a registered letter of 6 April 1999 requiring the respondent's observations within four months. Accordingly, the respondent's written submissions were (by virtue of Rule 78(3) EPC) due to be received by the

Board of Appeal no later than 16 August 1999, a period of four months and ten days.

On 16 August 1999, i.e. the last day of that period, the respondent sent a fax to the Board asking for a further two month period in which to file observations on the Grounds of Appeal. Although no reasons for this request were given, it was granted. The period for the respondent to file its written submissions was thereby extended until 18 October 1999 (16 October being a Saturday).

On 18 October 1999, again the last day of the period in question, the respondent by a further fax asked for a further extension of "a few days" - the exact time sought was, somewhat unhelpfully, not specified. However, on this occasion reasons were given - the illness "during the major part of the extension period" (that is, the previous two months) of a person whose advice the respondent deemed necessary followed by the illness of the respondent's representative. A further short extension until 3 November 1999 was allowed and communicated to the parties by faxes of 25 October 1999.

In the meantime the Board had, after the usual consultation with the parties, fixed 3 December 1999 as the date for oral proceedings and formal summonses to oral proceedings on that date were sent on 10 September 1999, although the parties had known of that date since 27 August 1999 when they received faxes from the Registrar proposing either that date or the day before. It is to be noted that the respondent had agreed to, or at least had not disagreed with, the date for oral proceedings only shortly after its first request for an

extension of time to file its written submissions had been made and agreed.

On receipt of the Board's fax of 25 October 1999 confirming the second extension of time to 3 November 1999, the appellant, by a fax also of 25 October 1999, asked for the oral proceedings to be postponed. The appellant said that, in the light of the further extension of time granted to the respondent, she would not have time to file her own further observations in reply sufficiently in advance of the hearing on 3 December 1999. The Board had some sympathy with the appellant who, having filed her own written submissions in time, had to wait several months to learn the exact case put by the respondent. Clearly, the respondent did not deal with this matter as expeditiously as it should - while it may have encountered difficulties due to illness during the period of the first extension, no explanation was given for not filing its submissions during the initial period of over four months; and both requests for extensions, the second for an unspecified period of a few days, were requested on the very last days of the expiring periods and, in the case of the second, some considerable time after the respondent knew of the arrangements made for oral proceedings.

However, when asked for either extensions of time or postponement of oral proceedings, the Board has to consider not only the interests of each of the parties but also the overall interest in the expeditious prosecution of appeals and the delays to other cases in the event of postponements. In the present case a second extension of only twelve working days was granted and the loss of that time to the appellant could be more than compensated for by not imposing the

usual requirement that all written submissions be filed at least four weeks before the oral proceedings. The Board also observed that, if the appellant had been put to any other inconvenience, she could make an application for apportionment of costs under Article 104(1) EPC. Accordingly, the Board decided that all interests would be best served in the present case by maintaining the date appointed, and agreed by the parties, for the oral proceedings and also directed that the respondent ensure that its written submissions were indeed received by the end of the second extension of time and copied directly to the appellant, and that the appellant might have until the date of the oral proceedings to prepare her response (if any) to the respondent's submissions.

That decision and those directions were notified to the parties by the Communication of 28 October 1999. In the event, the respondent filed its submissions within the extended time and apologised for the earlier delay. The appellant then managed to respond in writing by 18 November 1999 and did not make an application for apportionment of costs. While both parties thus demonstrated commendable speed in progressing the appeal following receipt of the Board's Communication, that very speed suggests that the earlier delays may have been in large part avoidable.

2.2 The Board takes this opportunity to remind parties that, while some delay arising from the volume of pending appeals is inevitable, additional delays caused by parties themselves are often avoidable and are in principle undesirable. Such additional delays can affect not only the particular cases in which they occur but also other pending appeals the parties to

which have complied with the usual time limits. It is also the case that most initial time limits under the EPC and the procedure of the Boards (for example, four months for an appellant to file its Grounds of Appeal and four months for a respondent to reply thereto) are generous by comparison with corresponding provisions of the laws of many contracting states.

Parties should not consider extensions of time as being available for the asking. Requests for extensions of time should only be made sparingly. Such requests should be made as soon as the possibility of the need for extra time becomes apparent and not at the last moment. Only the period of time actually and reasonably required should be sought. The more extensions a party seeks, or the longer the time sought for any one extension, the more important it is to provide reasons. It is also prudent to consult other parties to the appeal in advance - if they agree to an extension, the Board is more likely to agree also; if they disagree, the Board can then be made aware of their views.

When considering requests for additional time, the Board will take into account not only any reasons put forward but also the number of previous extensions (if any), the views of the other party or parties (if known), the effect of delays on other appeals pending before it and the general principle that all delays are to be avoided where possible. Similar considerations apply to requests to adjourn oral proceedings. In these cases however, the Board will also take account of the fact that, in accordance with the usual procedure, the parties will have been offered alternative dates and agreed on one of those dates. Once a date has been accepted and agreed, exceptional reasons may be

required to justify a postponement.

3. *Article 123(2) and (3) EPC*

3.1 The subject-matter of claim 1 of the main request differs from that originally filed in that the solid lipid microspheres are "in lyophilized form" and "substantially free from surfactants and co-surfactants".

The feature "in lyophilized form" is allowable as it is clear from the disclosure in the application as originally filed (page 3, step c) that the microspheres prepared according to the process of the patent in suit undergo a final lyophilisation step.

As regards the second amendment, the Board agrees it is not disclosed *expressis verbis* in the application. In these circumstances, it must decide whether the skilled person could derive this feature directly and unambiguously from the whole teaching of the original application.

The Board appreciates that the passage (see supra, paragraph VIII) in the application relied on by the appellant as the basis for the amendment merely refers to the elimination of the substances present in the dispersing phase and that, as contented by the respondent, the words "not included in the microspheres", which are part of the passage in brackets, could be understood as referring either just to "free drug" or also to "surfactant and co-surfactant".

However, in the light of the sentence following this

passage, which reads "Said compositions afford therefore an improved control on the action and effectiveness of the drug and minimize possible effects due to the simultaneous undesired administration of auxiliary substances such as surfactant", the Board is satisfied that it would be clear to the skilled person reading the application that the present invention aims to provide solid lipid microspheres which are free from surfactants and co-surfactants.

As regards the technical arguments put forward by the respondent (see supra paragraph IX), the appellant's expert stressed that, although it was indeed true that the first step of the process for the preparation of the solid lipid microspheres involved the use of a large amount of surfactants and co-surfactants, only an insignificant amount of these were present at the interface between the lipid microspheres and the water phase since the surfactant shell encasing the microspheres was made of a molecular monolayer of surfactant and co-surfactant molecules.

Moreover, the expert pointed out that the polar heads of the surfactants and co-surfactants molecules would prevent these entities from entering the lipid droplets. In addition, the rapid freezing of the lipid droplets during the second step of the process would also prevent any diffusion of the surfactants and co-surfactants in the microspheres as the diffusion process was time-dependant. Additionally he said this surfactant and co-surfactant molecular monolayer separated from the microspheres during this freezing step.

As regards the diafiltration technique disclosed in

document (7), the expert noted that it merely recited that the removal of adsorbed species such as surfactants "may be much slower than the removal of dissolved species" and that, in any case, the latex particles and their adsorbed materials described in (7) could not be compared with lipid microspheres encased within a molecular monolayer of surfactants and co-surfactants.

Against this, the respondent did not provide any experimental or other technical evidence beyond its submissions summarised above (see supra, paragraph IX). The Board was thus presented on the one hand by the respondent with the assertion that surfactants and co-surfactants remain after diafiltration within the microspheres and/or at the interface of the microspheres and the water phase and, on the other hand, by the appellant with a technically plausible explanation from an expert who has worked the invention of why that is not the case. In those circumstances, the Board is compelled to accept the views of the expert witness. This happens to be in keeping with the fact that scientific certainty is only achieved by actually proving the presence of a substance in a complex mixture.

Concerning document (15), the Board notes that this is not part of the state of the art. It can however form technical evidence in the proceedings. With respect to this document, the Board shares the appellant’s analysis that the lipophilic complex described in (15) represents a different chemical entity from a co-surfactant.

The Board accordingly finds no basis in the

respondent's submissions for an objection under Article 123(2) with respect to the introduction of the feature "substantially free from surfactants and co-surfactants" in independent claim 1.

3.2 In conclusion, all the amendments introduced into present claim 1 by the main request are adequately supported by the original application and thus comply with Article 123(2) EPC.

3.3 Compared with the independent claim 1 (see paragraph I supra) as granted, the corresponding independent claim 1 as amended is limited in view of the additional technical features. The amendments to present claim 1 are therefore also acceptable under Article 123(3) EPC.

4. *Article 84 EPC*

4.1 The meaning of particular words or expressions in the context of Article 84 EPC nearly always depends on the circumstances of the case, and in particular the specific technical field and the content of the description. Therefore, no general quantitative definition can be given for the expression "substantially free", the meaning of which should be construed on the basis of the description. In the present case the Board takes the view that it merely means that the solid lipid microspheres should be as free of surfactants and co-surfactants as is practically and realistically feasible.

4.2 It remains however questionable whether any claimed solid lipid microspheres would fulfil all the requirements of independent claim 1 since both the inventor herself as well as her expert stressed during

the oral proceedings that only the selection of specific lipids in combination with specific surfactants and co-surfactants would realise the benefit of the invention. The claim to, in effect, "[any] solid lipid microspheres" in claim 1 has not previously been considered. Whether a claim of that breadth is allowable is an issue which should be considered initially by the first instance, if only so that the parties may have the opportunity of a further appeal (see also infra paragraph 6).

5. *Sufficiency of disclosure*

5.1 The only objection of the respondent under Article 83 EPC which remained in issue at the oral proceedings was the allegation that the skilled person could not find any relevant information as to which mode of the diafiltration apparatus to use during the process of preparation of the solid lipid microspheres.

It is undisputed that document (7) discloses that the diafiltration apparatus can be used for concentrating, cleaning, equilibrating or fractioning a sample (see page 543, left column, lines 30 to 42).

It is however noted that, as the publication date of document (7) shows, the diafiltration technique had been well-known for more than twenty years at the filing date of the contested patent.

Furthermore, the original application unambiguously teaches that diafiltration is used for washing the microsphere dispersion with water ie exclusively for a cleaning purpose (see e.g. page 3, lines 1 and 2; examples).

The skilled person is also taught the result to be expected by this cleaning technique: the application (at page 5, lines 13 to 16) discloses that washing by diafiltration is carried out to eliminate all the substances present in the dispersing phase (surfactant, co-surfactant and free drug). Accordingly, the Board is satisfied that, knowing the nature of the products to be eliminated, the skilled person has sufficient information to use the diafiltration apparatus in its appropriate mode.

Against this, the respondent failed to provide any evidence or argument demonstrating that such washing by diafiltration is not a common operation practiced by laboratory workers.

5.2 In conclusion, the Board’s judgement is that the invention is disclosed in a manner sufficiently clear and complete for it to be carried out by a skilled person and the patent therefore meets the requirements of Article 83 EPC and accordingly the ground of opposition under Article 100(b) EPC is not made out.

6. *Remittal to the first instance*

6.1. Although Article 111(1) EPC, which gives the Boards of Appeal the powers of the first instance departments, does not guarantee parties an absolute right to have all the issues in a case considered by two instances, it is well recognised that there are occasions when consideration by both instances is appropriate. The essential function of an appeal in inter partes proceedings is to consider whether the decision of the first instance department is correct. If, as here, the appeal is from a first instance decision taken solely

upon only one or some of the issues and that appeal is successful, the outstanding issues should then be the subject of examination and decision by the first instance department, with a possible further appeal on those issues thereafter.

6.2. In the present case, the Opposition Division decided that claim 1 was not patentable on the grounds of insufficiency of disclosure (Article 83 EPC), but left open the essential issues of novelty (Articles 52(1), 54 EPC) and inventive step (Articles 52(1), 56 EPC). The Board has thus concluded that, in those circumstances, the case should now be remitted to the Opposition Division for further prosecution on the basis of the set of 12 claims filed with the appellant’s letter dated 18 November 1999 and received on 19 November 1999.

6.3 While it is not for the Board to dictate to the Opposition Division how it should deal with the remaining issues, it is clear that the treatment of those issues by the parties is currently spread across a number of written submissions on both sides. Those submissions also deal with issues which have, by this decision, now been finally decided. The Board suggests it would be appropriate for each of the parties to summarise its case on novelty and inventive step in one document and file such summaries with the Opposition Division. The sooner that is done, the sooner no doubt the further consideration of this case can be undertaken.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance for further prosecution.

The Registrar: The Chairman:

M. Dainese U. Oswald