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D E C I S I O N
of 20 December 1999

Case Number: T 0270/97 - 3.3.2

Application Number: 91810366.4

Publication Number: 0458745

IPC: A61K 49/00

Language of the proceedings: EN

Title of invention:

Polymeric gas or air filled microballoons usable as suspensions in liquid carriers for ultrasonic echography

Patentee:

BRACCO International B.V.

Opponent:

Schering AG
Nycomed Imaging AS

Headword:

Air filled microballoons/BRACCO

Relevant legal provisions:

EPC Art. 83, 54, 52(4)
EPC R. 67

Keyword:

"Main request - novelty (yes): claimed product not inevitably obtained when repeating the process in the prior art"

Decisions cited:

T 0012/81

Catchword:

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Boards of Appeal

Chambres de recours

Case Number: T 0270/97 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 20 December 1999

Appellant: BRACCO International B.V.
(Proprietor of the patent) 7, De Boelelaan
1083 HJ Amsterdam (NL)

Representative: UEXKÜLL & STOLBERG
Patentanwälte
Beselerstrasse 4
D-22607 Hamburg (DE)

Respondent: Schering AG
(Opponent 01) Gewerblicher Rechtsschutz
D-13342 Berlin (DE)

Representative: Lederer, Franz, Dr.
Lederer, Keller & Riederer
Patentanwälte
Prinzregentenstrasse 16
D-80538 München (DE)

Respondent: Nycomed Imaging AS
(Opponent 02) Nycoveien 1-2
PO Box 4220 Torshov
N-0401 Oslo (NO)

Representative: Holmes, Michael John
Frank B. Dehn & Co.
European Patent Attorneys
179 Queen Victoria Street
London EC4V 4EL (BG)

Decision under appeal: Decision of the Opposition Division of the

European Patent Office posted 28 January 1997
revoking European patent No. 0 458 745 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: P. A. M. Lançon

Members: C. Germinario

W. Moser

Summary of Facts and Submissions

- I. European Patent No. 0 458 745 was granted in response to European patent application No. 91 810 366.4 on the basis of a set of 30 claims for all the designated Contracting States.

The claims were directed to air or gas filled microballoons for echography imaging and methods for their preparation.

- II. Notices of opposition were filed by the respondents I and II, respectively opponent I and opponent II, requesting revocation of the patent under Article 100(a) and (b) EPC on the grounds of lack of novelty, lack of inventive step, insufficiency of disclosure and on the further ground that the protection conferred covered subject-matter excluded from patentability pursuant to Article 52(4) EPC.

The following documents were cited, *inter alia*, during the proceedings before the opposition division:

- (1) EP-A-327 490
- (2) WO-A-89/06978
- (3) DE-A-3803972
- (16) DE-A-4219723

Documents (1) and (2) are identical patent applications, though filed under different patent systems and for different contracting states. The two documents were cited as exchangeable during the proceedings. Document (3) is the German patent application corresponding to one of the two priority documents of (1) and (2).

Document (16), although not being part of the state of the art under Article 54(2) or (3) EPC, was cited by respondent I, and was considered by the opposition division as a technical support for interpreting the teaching in document (2).

Additionally a number of declarations and experimental reports were submitted by the parties during the proceedings before the opposition division and the Board.

(17) Schneider declaration and report (25 October 1996),

(18) Nycomed experimental report ER1 (28 October 1996),

(19) Nycomed experimental report ER2 (28 October 1996),

(20) Bussat declaration, Exhibit A, (5 June 1997),

(21) Vauthier declaration, Exhibit B (5 June 1997),

(22) Hopfenberg declaration (2 March 1998),

(23) Schering experimental report (11 November 1998),

(25) Bussat experimental report (22 November 1999).

III. Although a main request, corresponding to the granted claims, and two auxiliary requests had been filed by the appellant (patentee) during the oral proceedings, the opposition division based its decision to revoke the patent only on the auxiliary requests without any consideration of the main request.

The opposition division held that the claimed subject-matter lacked novelty over the microparticles disclosed in examples 2 of document (1) [or (2)]. These microparticles were also cited, as a comparative compound, in late published document (16), which gave additional information, not given in (1) or (2), as to the presence of a membrane surrounding said microparticles and its thickness. The opposition division came to the conclusion that, although (16) was not part of the state of the art, it could be used to show that the microparticles described in the prior documents were actually microballoons and that their characteristics were identical to the characteristics of the claimed product.

IV. The appellant lodged an appeal against this decision, and filed on 22 November 1999 a new main request and four auxiliary requests. During the oral proceedings, held on 20 December 1999, the main request was replaced by the granted claims.

V. In writing and during the oral proceedings, the appellant contested the decision, primarily, on the ground of procedural violation, as the main request had not been considered by the opposition division.

As to the substantive matter, the appellant relied on the experimental works (17), (20), (21) and (25), which all reported unsuccessful attempts to obtain microballoons as claimed by repeating examples 1, 2 and 6 of documents (1) or (2). It further contested the introduction into the proceedings of document (16), firstly because it was published some six months after the publication of the application of the patent in suit, and secondly because it was speculative in its technical content.

- VI. The respondents maintained their objection of lack of sufficiency of disclosure in relation to the porosity of the microballoons.

As to the objection of lack of novelty, they mainly relied on the principle laid down by decision T 12/81 that the teaching of a prior document is novelty-destroying for a product claim if it inevitably leads to the production of the claimed product when its disclosure is followed exactly. The main argument of both respondents was that the claimed microballoons would have been inevitably obtained by reducing to practice examples 1 and 2 of document (1) or (2), as otherwise confirmed by document (16) and by the experimental reports submitted during the opposition and appeal proceedings by respondent II [documents (18), (19) and (22)] and respondent I [document (23)].

The objection under Article 52(4) EPC was not maintained.

- VII. The appellant (patentee) requested that the decision

under appeal be set aside and that the patent be maintained as granted (main request), or that the patent be maintained on the basis of the following documents filed on 22 November 1999:

- (a) first auxiliary request: claims 1 to 27; or
- (b) second auxiliary request: claims 1 to 26; or
- (c) third auxiliary request: claims to 26; or
- (d) fourth auxiliary request: claims 1 to 25.

The respondents (opponents) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible

Main request

2. *Article 83 EPC*

In the respondents' contentions, the skilled person was not in a position to reproduce the claimed microballoons since their porosity was not defined as required, that is, by indicating not only the size of the pores but also the percentage of pores per surface unit.

The Board notes that the porosity of the polymeric

membrane and the size of the pores are not critical features of the invention since they are not cited in any independent claim. As disclosed in the description (column 7, line 53 to column 8, line 4) and in claim 3, the porosity is only a means to achieve the desired biodegradation degree of the microballoon membrane. This feature may move along a wide range of possibilities, namely from biodegradable membranes to the non-biodegradable membrane of claim 14. In the Board's view, the skilled person is provided with sufficient information to control this feature of the microballoons and accordingly the porosity of the membrane, by selecting suitable polymers and additives as disclosed on pages 13 to 15 of the filed application (patent, column 10, line 31 to column 12, line 27). For these reasons, the respondents' arguments do not substantiate the objection of insufficiency of disclosure.

Moreover, it is important to note that, in the attempt to show the lack of novelty of the claimed microballoons, respondent 2 itself reported in document (19) the successful preparation of microballoons by following the instructions given in examples 2 and 3 of the patent in suit. For this reason, the Board considers that the requirements of Article 83 EPC are met.

3. *Novelty*

3.1 The claimed microballoons were considered by the opposition division as anticipated by the ultrasonic contrast agent of document (1) or (2), in particular by the agent produced according to example 2. The contrast

agent described in these prior documents consists of gas and/or liquid filled microparticles made of amylose, preferably cyclodextrine, or of a synthetic biodegradable polymer. The polymeric particles are produced by emulsifying the organic solution of the polymer, copolymer or monomer in aqueous phase and further processing the emulsion in order to obtain a final dry particle material, eg by freeze-drying. Advantageously, the obtained product may be finely milled.

What is undisputed by the Board is that these known microparticles may indeed contain a gas, though not as the only possibility. Nevertheless, whether this gas is included in a hollow structure like a "microballoon" or entrapped within the interstices of a "sponge-like" structure is a feature not explicitly disclosed in documents (1) or (2). For this reason, the prior art documents are open to interpretation.

It is a well established principle laid down in the Case Law, since decision T 12/81 (OJ EPO 1982, 296), that the product inevitably resulting from a process properly defined as to its starting substance and reaction conditions is considered to be disclosed even if it is not cited *expressis verbis* in said document.

- 3.2 Relying on this principle, the respondents stressed that the microparticles inevitably obtained according to examples 1 and 2 of the aforementioned prior documents were "microballoons" as claimed in the patent in suit. This conclusion was corroborated by document (16), which was, as already seen, a late published patent application belonging to respondent I.

3.3 Document (16) discloses gas-containing microparticles, having a hollow structure surrounded by a fine membrane. The document cites, as a comparative product, the microparticles obtained in example 2 of EP-A-0 327 490, which is document (1) in the present proceedings. Table 1 of document (16) illustrates a comparison of some features of the two types of microparticles, ie those according to example 2 of (1) and those according to (16). The table illustrates that the average thickness of the wall of the particles according to document (1) was 180 nm. By relying on this information, respondent I held, as the opposition division also did, that document (16) made it plain that the microparticles obtained in example 2 of document (1), being provided with a wall, necessarily had to be microcapsules or "microballoons".

The Board wishes to stress that document (16) does not provide any evidence showing that the particles obtained according to example 2 of document (1) are indeed in the form of hollow particles. The existence of such a structure was not conclusively shown or made plausible, eg by way of a microscopic picture.

In detail, table 1 of document (16) reports the following features of the particles according to document (1): the particle size, ie 1 μm , the specific weight, ie 0.81 g/cm^3 , the volume of the alleged internal space, ie 0.64 μm^3 , and the thickness of the particle wall, ie 180 nm. Moreover, it is said that the wall thickness of the particles was calculated on the basis of their specific weight, bearing in mind that the polymer specific weight was 1.1 g/cm^3 (see page 2, lines 52 and 53 and footnote to table 1).

The skilled person, knowing the size of the particles, which are assumed to be spherical, could easily calculate their volume. He could also easily calculate the thickness of a particle wall and the volume of the internal space, knowing the specific weight of the particles and that of the polymer in compact form. He would indeed obtain the same values reported in table 1.

However, these simple calculations would be based on the mere presumption that the particle model is indeed that of a hollow spherical capsule surrounded by a compact polymeric wall having a specific weight of 1.1 g/cm^3 . However, the Board is convinced that the same specific weight of 0.81 g/cm^3 , observed for the particles of example 2 of document (1), would not be incompatible with another particle model: namely that of a whole-volume sponge-like particle consisting of a polymeric matrix in porous form entrapping air in its interstices.

For this reason, document (16) merely shows that, supposing that these particles were hollow spheres, then their particle wall would be 180 nm thick. Whether or not these particles actually are hollow spheres or the like, is something which the skilled person cannot infer from document (16).

This document therefore does not offer any reliable contribution to the interpretation of example 2 of document (1). For this reason example 2, which has been indicated by respondent I as the most relevant part of the prior document, has to be considered only within the context of said prior document, which however does

not explicitly disclose, in its general part, any particles, microcapsules or microballoons made of a polymeric membrane surrounding a space filled with a gas.

- 3.4 Considering the text of example 2, it appears evident, first of all, that the method therein disclosed implies an *in situ* emulsion-polymerisation (of the monomer alpha-cyanacrylic acid butyl ester), which is not envisaged in the method according to the patent in suit. A second important aspect is that the text of the example does not report all the experimental details of the method, such as the speed and time of agitation and the polymerisation and freeze-drying conditions.

In an attempt to show that the particles obtained according to example 2 were, or were not, identical to the microballoons of the patent in suit, the appellant and respondent I produced highly contradictory results.

For instance, the appellant reported in (17) failure to obtain any form of particles after four attempts to repeat example 2. It also reported in documents (20) and (21) the production of a lyophilised product showing, upon microscope examination, a disorganised structure comprising polymeric fragments, aggregates and heterogeneous particles, but without any evidence of microballoons.

On the other hand, respondent I declared, in report (23), that it had been able to obtain microballoons by following the teaching of example 2.

Moreover, both the appellant and respondent I contested

the results produced by the opposite party, contending that, by filling in the gap of information, the opposite party had followed arbitrary and not "usual" experimental conditions or procedures not envisaged in the example.

In consideration of these contradictory results and arguments, the Board can only conclude that the experimental conditions not disclosed in example 2 are indeed essential in order to successfully repeat the method therein disclosed, and that, depending on the conditions selected by the skilled person, different products may be obtained. It is therefore evident to the Board that the conditions laid down by decision T 12/81, that is in the specific case that microballoons are inevitably obtained by following the prior known method, are not satisfied. This conclusion is made even more plausible in view of the difference evidenced between the preparing method according to example 2 and that of the patent in suit.

3.5.1 As to example 1, of document (1) or (2), respondent II emphasised that the method therein disclosed was identical to the method according to claim 19 of the patent in suit. For this reason, the lyophilised product obtained according to said example had necessarily to be identical to the microballoons of the patent in suit. To corroborate its arguments, respondent II produced, during the proceedings before the opposition division, two experimental reports [document (19)], concerning a repeat of examples 2 and 3 of the patent at issue, and [document (18)], concerning the repeat of a method said to be identical to the method of example 1 of document (1) [(2)]. In both experimental works production of air-filled microballoons was reported.

3.5.2 The method for making the air or gas filled microballoons according to claims 18 and 19 of the patent in suit comprises the essential step of emulsifying a hydrophobic organic phase in which the polymer is dissolved into a water phase, wherein said hydrophobic phase is selected so that it evaporates substantially simultaneously with the water phase [upon eg lyophilisation]. To achieve this result, evaporation of the hydrophobic phase is performed at a temperature where the partial vapour pressure of said hydrophobic phase is of the same order as that of water vapour (claim 20). This procedure is said to be essential for the achievement of air or gas filled microballoons.

3.5.3 In example 1 of documents (1) or (2), polylactic acid is dissolved in 4 ml of furan and 0.6 ml of cyclohexane, and this solution is emulsified in an aqueous phase of an emulsifier (pluronic F) at a

temperature of below 15°C. Then, the temperature is slowly increased up to evaporation of the organic medium (or solvent). Finally, the suspension obtained is lyophilised.

In the respondent's reading of the text of example 1, the expression in the original language of the document, "Verdampfung des organischen Lösungsmittels", means "evaporation of the organic solvent", ie **one** organic solvent, namely only furan. Thus in the respondent's opinion, example 1 teaches the skilled person that he should carry out a fractionated or partial evaporation in order to remove furan only and to obtain an organic phase enriched with cyclohexane. This latter would remain emulsified in the water phase and would be removed simultaneously with said aqueous phase during lyophilisation. This interpretation reflects the procedure followed in experimental report (18), in which respondent II states that it obtained microballoons by repeating example 1 of document (1) [see document (18), abstract, page 1 and "Content of Furan and Cyclohexane", page 5].

Also Hopfenberg, in his declaration produced by respondent II as document (22), stresses that the slow temperature raising and solvent evaporation step disclosed in example 1 is critical to microcapsule formation, and therefore, one of ordinary skill in the art would control the evaporation process with a view to obtaining a product in microcapsule form.

3.5.4 The Board cannot follow this interpretation of the prior art, which appears to be strongly influenced by hindsight.

While recognising that the heating of the emulsion is indeed the critical passage to obtain hollow particles such as the microballoons according to the patent in suit, the Board emphasises that no part of document (1) [or (2)] explicitly discloses such hollow particles or makes it evident that they are obtainable. For this reason the skilled person, assisted by the general teaching in document (1) and in the attempt to repeat example 1, would have found in this prior document no indication to reproduce the conditions necessary to obtain hollow microparticles, namely to perform the heating of the emulsion in such a way and to such an extent to produce a controlled, partial evaporation of the organic medium with a view to leaving an organic mixture enriched in cyclohexane.

Rather, in the Board's judgement, the definition of the heating step in example 1 is very poor. In fact, beyond the slow increase of the temperature, nothing is said, either in the specific example or in other examples or in the general description of the invention, as to the final temperature, pressure and time of heating. This indicates that the heating step is not at all a critical aspect for the invention of document (1), and that the instruction given by the document to the skilled person is merely that of removing the organic medium in its entirety, ie furan and cyclohexane, and leaving a suspension of fine polylactic particles, which are then lyophilised.

The conclusion of the Board is therefore that the essential feature of the method of making the microballoons of the patent in suit, that is that the hydrophobic phase evaporates substantially

simultaneously with the water phase, is simply not disclosed in prior document (1). Under these circumstances, the respondent's view that in repeating example 1 of document (1) [or (2)], the microballoons of the patent under consideration would be inevitably obtained, is untenable.

Since no other part of prior documents (1) or (2) gives any more explicit teaching in the direction of the invention of the patent in suit, the Board considers that none of them is prejudicial to the novelty of the products and processes claimed in the main request.

4. In view of the outcome of the opposition proceedings, the inventive step involved in the claimed subject-matter was not considered by the opposition division. For this reason, the Board makes use of the power conferred to it by Article 111(1) EPC and remits the case to the first instance for further prosecution. Remittal of the case was also requested, although unofficially, by the appellant during the oral proceedings.

5. *Rule 67 EPC*

As reported in the Minutes of the oral proceedings before the Opposition Division, the appellant requested as main request that the oppositions be dismissed and that the patent in suit be maintained as granted. Auxiliarily, he requested maintenance of the patent in suit on the basis of either of the auxiliary claim requests I and II. However, in the decision under appeal the main request was not dealt with. This failure clearly contravenes Rule 68(2) EPC and thus

constitutes a substantial procedural violation within the meaning of Rule 67 EPC justifying reimbursement of the appeal fee.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the Opposition Division for further prosecution.
3. The reimbursement of the appeal fee is ordered.

The Registrar:

The Chairman:

M. Dainese

P. A. M. Lançon