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**Datasheet for the decision
of 21 November 2008**

Case Number: T 1393/06 - 3.3.03

Application Number: 97201854.3

Publication Number: 0804932

IPC: C08F 20/06

Language of the proceedings: EN

Title of invention:

Contrast media for diagnostic imaging comprising gas filled microspheres

Patentee:

Bristol-Myers Squibb Medical Imaging, Inc.

Opponent:

Alliance Pharmaceutical Corp.
BRACCO IMAGING S.p.A.

Headword:

-

Relevant legal provisions:

EPC Art. 100(c), 76(1)

Relevant legal provisions (EPC 1973):

-

Keyword:

"Divisional application - extension beyond the content of the earlier application as filed (yes) - all requests"

Decisions cited:

-

Catchword:

-



Case Number: T 1393/06 - 3.3.03

D E C I S I O N
of the Technical Board of Appeal 3.3.03
of 21 November 2008

Appellant: Bristol-Myers Squibb Medical Imaging, Inc.
(Patent Proprietor) Route 206 & Provinceline Road
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office dated 9 May 2006 and
posted 4 July 2006 revoking European patent
No. 0804932 pursuant to Article 102(1) EPC
1973.

Composition of the Board:

Chairman: R. Young
Members: W. Sieber
H. Preglau

Summary of Facts and Submissions

I. The mention of the grant of European patent no. 0 804 932, in respect of European patent application no. 97201854.3, in the name of ImaRx Pharmaceutical Corp. (now transferred to Bristol-Myers Squibb Medical Imaging, Inc.), filed on 18 March 1992 as a divisional application of the earlier European patent application no. 92910021.2 and claiming priority from US 680984 (5 April 1991), was published on 16 May 2001 (Bulletin 2001/20). The granted patent contained 27 claims, whereby Claim 1 read as follows:

"A low density gas-filled microsphere having an internal void volume of at least 75% of the total volume of the microsphere, wherein said gas comprises a perfluorocarbon."

II. Notices of opposition were filed by Alliance Pharmaceutical Corp. (opponent 01) and Bracco Imaging S.p.A. (opponent 02) on 18 February 2002. Both opponents requested revocation of the patent in its entirety on the grounds of Article 100(a) (lack of novelty and lack of inventive step), (b) and (c) EPC.

III. With a letter dated 9 March 2006 opponent 01 withdrew its opposition.

IV. By a decision which was announced orally on 9 May 2006 and issued in writing on 4 July 2006, the opposition division revoked the patent.

According to the decision under appeal, the subject-matter claimed in all requests before the opposition

division, namely the main request and auxiliary requests 1-3, had no basis in the earlier European patent application no. 92910021.2, ie the parent application published as WO 92/17514 A (D1). Therefore, all requests contravened Article 100(c)/Article 76 EPC.

- V. On 8 September 2006, the appellant (proprietor) filed a notice of appeal against the above decision with simultaneous payment of the prescribed fee.

With the statement of grounds of appeal, the appellant filed on 14 November 2006 new sets of claims, namely a main request and auxiliary requests I and II, and requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or, in the alternative, one of auxiliary requests I or II.

- (a) The main request was identical to auxiliary request 3 presented before the opposition division at the oral proceedings on 9 May 2006. Claim 1 was as follows:

"A low density gas-filled microsphere having an internal void volume of at least 75% of the total volume of the microsphere,

wherein said gas comprises a perfluorocarbon and

wherein said microspheres comprise thermoplastic synthetic polymers or copolymers prepared from the group of monomers consisting of acrylic acid, methacrylic acid, ethyleneimine, crotonic acid, acrylamide, ethyl acrylate, methyl methacrylate,

2-hydroxyethyl methacrylate, lactic acid, glycolic acid, ϵ -caprolactone, acrolein, cyanoacrylate, bisphenol A, epichlorhydrin, hydroxyalkylacrylates, siloxane, dimethylsiloxane, ethylene oxide, ethylene glycol, hydroxyalkyl-methacrylates, N-substituted acrylamides, N-substituted methacrylamides, N-vinyl-2-pyrrolidone, 2,4-pentadiene-1-ol, vinyl acetate, acrylonitrile, styrene, p-amino-styrene, p-amino-benzyl-styrene, sodium styrene sulfonate, sodium 2-sulfoxyethyl methacrylate, vinyl pyridine, aminoethyl methacrylates, 2-methacryloyloxytrimethylammonium chloride, N,N'-methylenebisacrylamide, ethylene glycol dimethacrylates, 2,2'-(p-phenylenedioxy)-diethyl dimethacrylate, divinylbenzene, triallylamine, and methylenebis-(4-phenyl-isocyanate)."

Independent Claims 2 and 4 were directed to an aqueous suspension of low density gas-filled microspheres according to Claim 1 and to a kit for preparing an aqueous suspension according to Claim 2. However, these claims as well as the dependent claims are not relevant to this decision and will therefore not be discussed in further detail.

- (b) Claim 1 of auxiliary request I limited said gas to a gas comprising "a perfluorocarbon selected from the groups consisting of perfluorocarbons having 1 to 4 carbon atoms and 4 to 10 fluorine atoms".
- (c) The claims of auxiliary request II had been limited to microspheres only. Claims and

embodiments directed to aqueous suspensions and kits had been deleted. However, Claim 1 of auxiliary request II was identical with Claim 1 of the main request.

- (d) The arguments of the appellant presented in the statement of grounds of appeal may be summarized as follows:

Basically, the appellant argued that the heat expansion process described in D1 as a preferred method of preparing microspheres was an implicit basis for the claimed subject-matter. The heat expansion process involved expanding a volatile liquid, *inter alia* a perfluorocarbon, entrapped in the microsphere. The range of perfluorocarbons disclosed in D1 as useful in the heat expansion process included perfluorocarbons which were completely gaseous at room temperature (C₁-C₅ perfluorocarbons), but also included volatile liquids (C₆-C₉ perfluorocarbons). In the latter case, these volatile liquids nevertheless had a gaseous component present because a "volatile liquid" meant a liquid with a high vapour pressure. Consequently, microspheres using volatile perfluorocarbons inevitably included gaseous perfluorocarbon. The heat expansion process disclosed in D1 therefore inevitably led to low density gas-filled microspheres claimed in the main request, ie those wherein the gas comprises a perfluorocarbon. Consequently, the microspheres of Claim 1 were derivable from the parent application as originally filed.

As regards the opposition division's assumption that the perfluorocarbon gas might be lost during the heat expansion process, this assumption was contrary to the disclosure in the parent application as originally filed. The examples of D1 discussed the technical aspects of the heat expansion process in detail. Example 6 of D1 was a substantial repetition of Example 1 of D1, except that the volatile liquid isobutane was replaced with a perfluorocarbon liquid (C₄F₁₀). Example 6 concluded by stating that "the resulting microspheres are filled with perfluorocarbon liquid rather than isobutane". That is to say, Example 6 indicated that both the unexpanded and expanded microspheres obtained were filled with perfluorocarbon liquid. Since the perfluorocarbon liquid was volatile, the expanded microspheres also inevitably contained perfluorocarbon gas, as required by Claim 1. The experimental evidence in D1 therefore demonstrated that the microspheres produced by the heat expansion process of the invention did contain perfluorocarbon gas.

This experimental evidence was entirely consistent with the statements of invention in D1. In one embodiment, D1 provided that the microspheres of the invention (ie microspheres useful for preparing a contrast medium), were "gas-filled". The preferred method of manufacture of microspheres was by a heat expansion process. Therefore, it would be completely contrary to the disclosure of D1 to conclude that the microspheres produced by a heat expansion process or otherwise, would be incapable of holding a gas within the

microsphere. On the contrary, in combination with the evidence provided in the examples, the skilled person would conclude that the gas used in the heat expansion process would remain entrapped within the microsphere.

- VI. With a letter dated 8 June 2008, the respondent (opponent 02) withdrew its opposition.
- VII. Following a summons to oral proceedings, the appellant informed the board with a letter dated 17 July 2008 that it would not attend the oral proceedings scheduled for 24 July 2008, withdrew its request for oral proceedings and requested that the proceedings be continued in writing on the basis of the documents on file.
- VIII. At the oral proceedings on 24 July 2008 where the appellant, as announced, was not present, the board decided to continue the procedure in writing.
- IX. In a communication dated 1 August 2008 accompanying a summons to second oral proceedings, the board raised *inter alia* various objections under Article 100(c)/76(1) EPC against the requests on file.
- X. With a letter dated 21 October 2008, the appellant informed the board that it would not attend the oral proceedings scheduled for 21 November 2008 and withdrew its request for oral proceedings.
- XI. On 21 November 2008, oral proceedings were held before the board at which the only party, ie the appellant, was, as announced, not represented. Since it had been

duly summoned, however, the oral proceedings were continued in its absence in accordance with Rule 115(2) EPC.

Reasons for the Decision

1. The appeal is admissible.

2. It may be convenient to recall at this juncture that the patent in suit is based on European patent application no. 97201854.3 which is a divisional application of the earlier European patent application no. 92910021.2, ie the parent application (D1), and that the subject-matter claimed in all the requests before the opposition division was found to have no basis in D1.

Thus, the decisive issue to be examined in the present case is as to whether or not the subject-matter claimed in the requests before the board now, ie the main request and auxiliary requests I and II, meets the requirements of Article 100(c)/Article 76(1) EPC. In this connection it has to be determined whether or not the claimed subject-matter is clearly and unambiguously derivable from the earlier application as filed.

3. *Main request*
 - 3.1 Claim 1 of the main request (point V(a), above) defines low density gas-filled microspheres having an internal void volume of at least 75% of the total volume of the microsphere, wherein said gas comprises a

- perfluorocarbon and wherein said microspheres comprise specific synthetic polymers or copolymers.
- 3.2 It is a fact that there is no explicit basis for low density gas-filled microspheres, wherein the gas comprises a perfluorocarbon so that the question arises as to whether or not there is an implicit basis for such microspheres.
- 3.3 As regards an implicit basis for the subject-matter of Claim 1, the appellant refers to the heat expansion process described in D1 which allegedly would inevitably lead to the low density gas-filled microspheres as claimed in the main request, ie those wherein the gas comprises a perfluorocarbon and the microspheres comprise the specified polymers or copolymers.
- 3.3.1 The microspheres of D1 may be prepared by various processes (page 5, lines 7-10 of D1), whereby the heat expansion process is the "preferable synthesis protocol" used to prepare microspheres (page 6, lines 1-3 of D1). This process involves "preparing microspheres of an expandable polymer or copolymer which contain in their void (cavity) a volatile liquid" (page 6 lines 8-10). Further it is stated at page 6, lines 10-15: "The microsphere is then heated, plasticising the microsphere and volatilizing the gas, causing the microsphere to expand up to about several times its original size. When the heat is removed, the thermoplastic polymer retains at least some of its expanded shape." Examples of suitable volatile liquids are set out in the passage bridging pages 6 and 7. The final possibility mentioned is "perfluorocarbons such

as those having between 1 and about 9 carbon atoms and between about 4 and about 20 fluorine atoms, especially C₄F₁₀" (page 7, lines 3-6 of D1).

The board notes that these passages are general references to the preparation of microspheres. It is not mentioned that these microspheres are gas-filled.

- 3.3.2 When it comes to gas-filled microspheres, D1 does not refer to the heat extension process but to another process for preparing gas-filled microspheres.

Following the disclosure of the heat expansion process in D1, the text then continues with a new paragraph beginning "In one embodiment, the microspheres of the present invention are gas-filled" (page 8, lines 18-19 of D1). Further, it is stated in the same paragraph (page 8, lines 23-35): "The gas may be any type of gas, such as, for example, carbon dioxide, oxygen, nitrogen, xenon, argon, neon, helium and air. ... The gas-filled low density microspheres may be synthesised under pressure such that gases are solubilised in the liquid employed in microsphere synthesis. When the pressure is removed, the gas comes out of solution to fill the microsphere void. Such microspheres can further be subjected to a heat expansion process, as described above." There is no suggestion that the gas filling the void might be a perfluorocarbon.

- 3.3.3 It is evident from the above analysis that D1 describes two different processes: (i) a process referred to as heat expansion process using volatile liquids, *inter alia* perfluorocarbons, and expandable polymers to produce microspheres which are not called gas-filled

(basically pages 6 and 7 of D1), and (ii) a process which produces gas-filled microspheres where "true" gases are solubilised under pressure in the liquid employed in the microsphere synthesis (page 8, lines 18-25).

In other words, D1 clearly distinguishes between a process (i) for preparing microspheres in a heat expansion process where volatile liquids are used and where nothing is said about the atmosphere in the void volume of the microsphere and a process (ii) for the production of what is considered in D1 to be gas-filled microspheres. The gases referred to in D1 in the latter context do not mention perfluorocarbons.

3.4 In the light of the above detailed analysis of D1, the appellant's reasoning with regard to the heat expansion process as an implicit basis for the subject-matter of Claim 1 of the main request is not convincing for the following reasons:

3.4.1 Claim 1 refers to a low density gas-filled microsphere wherein said gas **comprises** a perfluorocarbon. The word "comprises" is open claim language and allows the presence of further components in the gas. It is, however, not apparent from D1 what other components could be present in the heat expansion process to contribute to the atmosphere in the microspheres. In fact, the disclosure in D1 appears too general definitively to settle this issue. In other words, the rather general disclosure with respect to the heat expansion process in D1 is not suitable clearly and unambiguously to derive from D1 whether the heat expansion process will lead to microspheres with an

atmosphere comprising a perfluorocarbon gas or consisting of a perfluorocarbon gas. Also Example 6, which uses C₄F₁₀ in a heat expansion process to produce microspheres filled with perfluorocarbon "liquid" cannot contribute to clarify this issue.

3.4.2 Nor is the definition for "gas-filled" given on page 8, lines 19-21 of D1 ("By gas-filled, it is meant that at least part of the void volume inside the microspheres is occupied by the gas") and relied upon by the appellant a proper basis for the subject-matter of Claim 1. That definition has been given only in connection with the process (ii) involving the gases carbon dioxide, oxygen, nitrogen, xenon, argon, neon, helium and air but not in connection with the heat expansion process using perfluorocarbons. Thus, the appellant tries to combine elements of two distinctly described processes for which there is no basis in D1.

3.4.3 In fact, the term "gas-filled" has acquired a completely new meaning in the patent in suit. In D1, "gas-filled" is associated with "true" gases, ie substances which are completely gaseous at room temperature, whereas now the term "gas-filled" includes vapour pressure originating from liquids. For example, perfluorononane has a boiling point of 125-126°C but would, according to the appellant's submission, produce a gas-filled microsphere covered by Claim 1.

3.4.4 As regards the assertion to the inevitability of the features based on the disclosed process, this assertion is not supported by any evidence. For example, it appears possible that during the heat expansion process channels form from the void to the outer surface of the

microsphere are formed so that the microsphere does not necessarily contain an atmosphere of the blowing liquid.

Even if the assertion were to be accepted at face value, the fact remains that the term "gas-filled" has been used exclusively in relation to an embodiment which is not relied upon (process (ii) disclosed on page 8 of D1) and in any case provides no basis for perfluorocarbon.

In this connection it may be added that Example 6 does not contribute to clarifying the matter. As set out above, Example 6 of D1 discloses a heat expansion process using C₄F₁₀. The resulting microspheres are described as being "filled with perfluorocarbon liquid", although C₄F₁₀ is, according to the appellant, a gas at room temperature. Hence, this example emphasises the departure from the original language for which there appears to be no justification.

- 3.5 In summary, the subject-matter of Claim 1 of the main request is not clearly and unambiguously derivable from the earlier application D1. Hence, Claim 1 of the main request contravenes Article 100(c) EPC/76(1) EPC.
- 3.6 The finding that gas-filled microspheres as claimed in Claim 1 of the main request have no proper basis in D1 is corroborated by the fact that the patent specification itself contravenes Article 100(c)/76(1) EPC.
- 3.6.1 As set out above, D1 discloses two distinct processes, namely the heat expansion process (i) where there is no reference at all to the atmosphere in the void of the

microspheres, and process (ii) which describes the production of gas-filled microspheres and where perfluorocarbons are not mentioned as possible gases. By declaring perfluorocarbons to be possible gases for the production of gas-filled microspheres, the original distinction between the two different processes (i) and (ii) has at least partly been removed. This is especially apparent from paragraphs [0021] and [0022] of the patent in suit.

3.6.2 Paragraph [0021] of the patent in suit reads as follows:

"[0021] The microspheres of the present invention are gas-filled. By gas-filled, it is meant that at least part of the void volume inside the microspheres is occupied by the gas. Preferably, substantially all of the void volume inside the microspheres is occupied by the gas. The gas-filled low density microspheres may be synthesized under pressure such that gases are solubilised in the liquid employed in microsphere synthesis. When the pressure is removed the gas comes out of solution to fill the microsphere void. Such microspheres can further be subjected to a heat expansion process, as described above."

The basis for paragraph [0021] is found at page 8, lines 18-35 of D1 which reads as follows:

"In one embodiment, the microspheres of the present invention are gas-filled. By gas-filled, it is meant that at least part of the void volume inside the microspheres is occupied by the gas. Preferably, substantially all of the void volume inside the microspheres is occupied by the gas. The gas may be any

type of gas, such as, for example, carbon dioxide, oxygen, nitrogen, xenon, argon, neon, helium and air. Preferably, the gas is carbon dioxide, oxygen, nitrogen, xenon, argon, neon and helium. Most preferably, the gas is inert, that is, a gas that is substantially resistant to chemical or physical action. The gas-filled low density microspheres may be synthesised under pressure such that"

It is evident from that passage in D1 that process (ii) has never been associated with microspheres filled with perfluorocarbon gas or the preparation of such microspheres. D1 exclusively mentions the specific gases carbon dioxide, oxygen, nitrogen, xenon, argon, neon, helium and air. By deleting any reference to the originally mentioned specific gases, paragraph [0021] of the patent in suit reads now on to perfluorocarbons, because that paragraph has to be interpreted in the light of Claim 1 which defines the "microspheres of the present invention". In the end, a new process has been created in paragraph [0021] by turning the volatile liquids of process (i) into the filling gases of process (ii). Paragraph [0021] implies now that the perfluorocarbon gas is solubilised under pressure in the liquid employed. Such a process has never been disclosed in the relevant passage of D1.

3.6.3 The same applies to paragraph [0022] of the patent in suit which reads as follows:

"[0022] For example, to produce the gas-filled microspheres of the invention, one may copolymerize vinylidene and acrylonitrile using one or more of the foregoing procedures, such as phase separation/

coacervation techniques in a pressurized and/or low temperature environment (e.g., at about 300 psi, and/or at about 0°C) with a high concentration of dissolved gas in solution, to form a large microsphere containing the dissolved gas. When the pressure is removed and/or the temperature raised, the gas bubbles come out of solution, forming gas filled microspheres. Such microspheres can further be subjected to a heat expansion process, as described above."

The paragraph bridging pages 8 and 9 of D1 which is the basis for paragraph [0022] of the patent in suit refers to a process "*with a high concentration of dissolved gas (e.g., dissolved nitrogen) in solution*". Again there is no reference to a perfluorocarbon gas in that passage. By deletion of the term "(e.g., dissolved nitrogen)" in paragraph [0022] of the patent in suit, the technical teaching of that paragraph has been shifted to the meaning that a perfluorocarbon gas has to be used, since this paragraph has now to be interpreted in the light of Claim 1.

3.6.4 Hence, technical information has been added to the patent specification itself which is not clearly and unambiguously derivable from D1 contrary to the requirements of Article 100(c)/76(1) EPC.

3.7 In summary, Claim 1 of the main request as well as the patent specification itself do not meet the requirements of Article 100(c)/76(1) EPC. Consequently, the main request is not allowable.

4. *Auxiliary requests I and II*

4.1 Claim 1 of auxiliary request I (point V(b), above) requires a gas comprising a perfluorocarbon selected from the group consisting of perfluorocarbons having 1 to 4 carbon atoms and 4 to 10 fluorine atoms. Thus, this request limits the perfluorocarbons to perfluorocarbons which are gaseous at room temperature.

However, apart from the objection raised in point 3.4.3, above, all objections raised in connection with the main request still apply to auxiliary request I. Consequently, auxiliary request I is also not allowable (Article 100(c)/76(1) EPC).

4.2 Claim 1 of auxiliary request II (point V(c), above) is identical to Claim 1 of the main request. Thus, all objections raised against the main request equally apply to auxiliary request II. Hence, auxiliary request II is also not allowable (Article 100(c)/76(1) EPC).

5. Since none of the requests before the board meets the requirements of Article 100(c)/76(1) EPC, any discussion of further deficiencies of the claims in the various requests is superfluous.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

E. Görgmaier

R. Young