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D E C I S I O N
of 17 September 2004

Case Number: T 0309/99 - 3.3.2

Application Number: 88120371.5

Publication Number: 0324938

IPC: A61K 49/00

Language of the proceedings: EN

Title of invention:
Concentrated stabilized microbubble-type ultrasonic imaging agent and method of production

Patentee:
MOLECULAR BIOSYSTEMS, INC.

Opponent:
Andaris Limited

Headword:
Ultrasonic imaging agent/MOLECULAR BIOSYSTEMS

Relevant legal provisions:
EPC Art. 56, 57, 83, 100, 106(1), 113(1)
EPC R. 71(2)

Keyword:
"Auxiliary request containing amended claims prima facie inadmissible for late-filing but capable of maintaining patent revoked at first instance - right of other party to be heard - interest of third parties in certainty - suspensive effect of appeal - admissibility of request conditional as patentee's undertaking not to bring infringement proceedings until board's decision issued"

"Main request, first and second auxiliary requests: inventive step (no) - insufficient evidence that the objective problem was solved over the whole range claimed"

"Third auxiliary request - inventive step (yes) - problem solved over the whole range claimed, proposed solution was not obvious"

Decisions cited:
G 0012/91 T 0020/81, T 0181/82, T 0124/84, T 0152/93, T 0912/94, T 0615/95, T 0325/97, T 1051/97

Catchword:
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Case Number: T 0309/99 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 17 September 2004

Appellant: (Proprietor of the patent)	MOLECULAR BIOSYSTEMS, INC. 10030 Barnes Canyon Road San Diego California 92121 (US)
Representative:	Goldin, Douglas Michael J.A. KEMP & CO. 14 South Square Gray's Inn London WC1R 5JJ (GB)
Respondent: (Opponent)	Andaris Limited Unit 21 Whitemoor Court Nuthall Road Nottingham NG8 5BY (GB)
Representative:	Bassett, Richard Simon Eric Potter Clarkson Parkview House 58 The Ropewalk Nottingham NG1 5DD (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 28 January 1999 revoking European patent No. 0324938 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: G. F. E. Rampold
C. Rennie-Smith

Summary of Facts and Submissions

I. This appeal is against the decision of the opposition division posted on 28 January 1999 to revoke European patent No. 0 324 938 ("the patent") based on European patent application No. 88 120 371.5 and concerning a "Concentrated stabilized microbubble-type ultrasonic imaging agent and method of production". Opposition was filed by the respondent **against product claims 1 to 9 as granted,** which all are directed to an ultrasonic imaging agent as such, on the grounds of lack of inventive step (Articles 56 and 100(a) EPC), lack of industrial applicability (Articles 57 and 100(a) EPC), and insufficient disclosure (Articles 83 and 100(b) EPC). None of the **method claims 10 to 14** have been attacked in the notice of opposition. The claims of the patent as granted read as follows:

"1. A concentrated room-temperature stable ultrasonic imaging agent comprising a parenterally administrable aqueous medium containing a dispersion of microspheres at least 80% of which have diameters in the range of 1 to 9 μm, said microspheres consisting of gas microbubbles encapsulated in a water-insolubilized heat-denaturable biocompatible protein, said imaging agent having a homogeneously dispersed concentration of greater than 100 x 10^6 microspheres per ml and maintaining this concentration for over 4 weeks at a temperature of 20 to 25°C.

2. The imaging agent of claim 1 which has a homogeneously dispersed concentration of said microspheres greater than 200 x 10^6 microspheres

per ml and which maintains this concentration for over 4 weeks at a temperature of 20 to 25°C.

3. The imaging agent of claim 1 in which said microbubbles are encapsulated with human serum albumin.

4. The imaging agent of claim 1 in which said microspheres are suspended in an aqueous solution of the same protein in which the microbubbles are encapsulated.

5. The imaging agent of claim 4 which has a homogeneously dispersed concentration of from 300 to 600 x 10^6 microspheres per ml, and which maintains such concentration for at least 8 weeks at a temperature of 20 to 25°C.

6. The imaging agent of claim 4 or claim 5 in which said protein is human serum albumin.

7. The imaging agent of claim 4 or claim 5 in which 90% or more of said microspheres have diameters in the range from 2 to 8 μm.

8. A concentrated room-temperature stable ultrasonic imaging agent for intravenous administration, comprising a sterile aqueous solution of human serum albumin containing a dispersion of microspheres at least 80% of which have diameters in the range of 1 to 9 μm, said microspheres consisting of a bubble of air encapsulated in a water-insolubilized layer of said albumin, said imaging agent having a homogeneously-dispersed concentration of from 300 to 600 x 10^6 microspheres per ml and maintaining this concentration for at least 8 weeks at a temperature of 20 to 25°C.

9. The imaging agent of claim 8 in which at least 90% of said microspheres have diameters in the range of 2 to 8 μm.

10. A method of producing a dispersion of microspheres according to any of claims 1 to 9 for use as an ultrasonic imaging agent in which an aqueous solution of a heat-denaturable biocompatible protein is subjected to sonication to form gas microbubbles while heating said solution to insolubilize a portion of the protein, wherein the improvement comprises: during an initial sonication phase directly contacting the tip of the sonicator horn with said solution and carrying out the sonication and heating of said solution without appreciable foaming, then withdrawing the sonicator horn to a position in the ambient atmosphere proximate to the surface of said solution and foaming the solution to increase the population of microbubbles, and encapsulating the microbubbles with denatured protein to obtain a dispersion of stabilized microspheres of increased concentration.
11. The method of claim 10 in which said protein is human serum albumin.
12. A method of producing a concentrated dispersion of microspheres for use as an ultrasonic imaging agent in which a solution of human serum albumin is subjected to a sonication process according to claim 10, wherein the improvement comprises holding a body of the thus-obtained microsphere dispersion without agitation for sufficient time to permit the microspheres to rise therein and concentrate in an upper layer above the clarified albumin solution, and separating a portion of the clarified albumin solution from the concentrated layer to obtain a dispersion of greater microsphere concentration.

13. The method of claim 12 in which said dispersion of greater concentration is fractionated by withdrawing a dispersion containing most of the microspheres while leaving behind a microsphere fraction containing the largest size microspheres which had collected near the upper surface of the dispersion.

14. The method of claim 12 in which at least 80% of said microspheres have diameters in the range from 1 to 9 μm but include microspheres of larger diameters, which method includes the further steps of holding a body of the microsphere dispersions without agitation for sufficient time to permit at least the microspheres of larger than 10 μm diameter to rise therein and concentrate in an upper layer, and withdrawing a dispersion from beneath said upper layer containing most of the microspheres of less than 10 μm diameter while leaving behind a microsphere fraction containing most of the microspheres of larger than 10 μm diameter."

II. Of the numerous documents cited in the course of the first instance opposition and subsequent appeal proceedings, the following are referred to in this decision:

(4) EP-A-0 224 934;

(5) M. W. Keller et al, "Successful left ventricular opacification following peripheral venous injection of sonicated contrast agent: An experimental evaluation", Am. Heart J. 114, 1987, pp 570-575.

III. At the close of the oral proceedings, held on 7 December 1998, the opposition division decided that the claimed subject-matter in the patent as granted, although complying with Articles 57 and 83 EPC and being novel, lacked an inventive step. The essence of the reasoning in the opposition division's decision was as follows:

There was general agreement that citation (4) represented the closest state of the art. This citation disclosed a contrast agent for ultrasonic imaging in the form of an aqueous protein solution comprising microbubbles (microspheres) produced by subjecting an aqueous solution of human serum albumin (HSA) to high-frequency ultrasonic energy. Of the microbubbles produced, approximately 9.5×10^6/ml of solution were in the 2-6 micron range, and relatively negligible amounts of microbubbles in the range above 6 microns were formed (see (4) especially bottom of page 7). As an alternative to denaturation of the protein layer of the microbubbles already resulting from development of heat during sonication, the protein could be further denaturated and the microspheres stabilized by an additional heat treatment at a temperature in the range of 50 to 60°C. The microspheres formed from a 5% aqueous albumin solution which had been sonicated and stabilized existed for 48 hours or longer (see (4), page 8, penultimate paragraph). Such microspheres could successfully be used for left ventricular opacification following peripheral venous injection and eliminated the air embolism toxicity risks inherent in this diagnostic method.

Citation (5), of which the inventor of (4) was a co-author, also reported successful left-ventricular opacification by the injection of microspheres obtained by a sonication process similar to that descried in (4). The mean particle size of the microspheres of (5) was below 9 μm and the mean concentration 22 x 10^6 microspheres/ml, although even higher concentrations up to 30-50 x 10^6 microspheres/ml would appear to be achievable by the sonication method disclosed in (5).

The opposition division then specifically pointed to the following statements in (5), namely that "the indicator-dilution analysis used indicated a linear relationship between bubble concentration and ultrasound backscatter" and that "further development and standardization techniques will certainly yield microbubbles more uniform in size and more stable".

The opposition division found that the only difference between the claimed subject-matter and the prior art of (4) and (5) was the higher concentration of microspheres/ml in the ultrasonic imaging agent in the patent. It emphasised that, according to the respondent's own submissions, a direct relationship between stability and concentration of the microspheres existed. This led the opposition division to infer in the decision under appeal that the "*figures of concentration and stability duration are arbitrarily chosen over those known from the prior art*" (see bottom of page 11 of the decision.

On the basis of its analysis of the cited state of the art the opposition division reached the conclusion that citation (4) had disclosed the use of high

concentrations of microbubbles in ultrasonic imaging agents and that citation (5) clearly suggested to those skilled in the art that even higher concentrations might be highly desirable to improve the ultrasonic contrast. Moreover, in the opinion of the opposition division, those citations had already taught that a direct relationship existed between the stability of the microspheres and their concentration in the ultrasonic imaging agent. The opposition division concluded therefrom that the claimed ultrasonic imaging agent was the result of an obvious combination of the teachings of citations (4) and (5) and thus devoid of an inventive step. This was all the more so, because the use of a similar type of microbubbles was reported in (4) to eliminate the air embolism toxicity risks inherent in the administration of ultrasonic contrast agents and therefore the alleged technical prejudice against using the claimed contrast agents in the patent no longer existed.

IV. The proprietor (appellant) filed a notice of appeal and paid the appeal fee on 18 March 1999 and filed a statement of grounds of appeal on 28 May 1999. The respondent requested a two month extension of time to respond to the statement of grounds of appeal in a letter of 27 September 1999 and a further two month extension of time in a letter of 22 November 1999.

V. By a letter dated 1 December 1999, the Registrar of the board notified the parties of the board's refusal of the respondent's request for a second extension of time. In a communication of 10 December 1999, sent in response to a telephone call of 10 December 1999 by the respondent's representative to the Registrar, detailed

reasons were given why the board had decided not to grant the further extension.

VI. In response to the summons to oral proceedings, scheduled for 22 January 2003, the respondent's representative informed the board in a letter of 16 December 2002 that the respondent would neither be present nor represented at those oral proceedings.

VII. In advance of the oral proceedings the appellant filed by facsimile of 10 January 2003, less than two weeks before the date fixed for the hearing before the board, further observations and three amended sets of claims forming its first, second and third auxiliary requests.

VIII. The independent product claim 1 of the **first auxiliary request** reads as follows, with the sole amendment indicated below in bold italic letters:

"1. A concentrated room-temperature stable ultrasonic imaging agent comprising a parenterally administrable aqueous medium containing a dispersion of microspheres at least 80% of which have diameters in the range of 1 to 9 μm, said microspheres consisting of gas microbubbles encapsulated in **human serum albumin**, said imaging agent having a homogeneously dispersed concentration of greater than 100 x 10^6 microspheres per ml and maintaining this concentration for over 4 weeks at a temperature of 20 to 25°C.

The independent product claim 1 of the **second auxiliary request** reads as follows, with the sole amendment indicated below in bold italic letters:

"1. A concentrated room-temperature stable ultrasonic imaging agent comprising a parenterally administrable aqueous medium containing a dispersion of microspheres at least 80% of which have diameters in the range of 1 to 9 μm, said microspheres consisting of gas microbubbles encapsulated in a water-insolubilized heat-denaturable biocompatible protein, said imaging agent having a homogeneously dispersed concentration of greater than **200** x 10^6 microspheres per ml and maintaining this concentration for over 4 weeks at a temperature of 20 to 25°C."

IX. The product claims 1 to 5 of the **third auxiliary request** read as follows, with the amendments in claim 1 indicated below in bold italic letters:

"1. A concentrated room-temperature stable ultrasonic imaging agent comprising a parenterally administrable aqueous medium containing a dispersion of microspheres at least 80% of which have diameters in the range of 1 to 9 μm, said microspheres consisting of gas microbubbles encapsulated in a water-insolubilized heat-denaturable biocompatible protein, **and being suspended in an aqueous solution of the same protein in which the microbubbles are encapsulated**, said imaging agent having a homogeneously dispersed concentration of **from 300**

to 600 x 10^6 microspheres per ml and **which maintains such concentration for at least 8 weeks** at a temperature of 20 to 25°C.

2. The imaging agent of claim 1 in which said microbubbles are encapsulated with human serum albumin.

3. The imaging agent of claim 1 in which 90% or more of said microspheres have diameters in the range from 2 to 8 μm.

4. A concentrated room-temperature stable ultrasonic imaging agent for intravenous administration, comprising **a sterile aqueous solution of human serum** albumin containing a **dispersion** of microspheres at least 80% of which have diameters in the range of 1 to 9 μm, said microspheres consisting of a bubble of air **encapsulated in a water-insolubilized layer of said albumin,** said imaging agent having a homogeneously-dispersed concentration of from 300 to 600 x 10^6 microspheres per ml and maintaining this concentration for at least 8 weeks at a temperature of 20 to 25°C.

5. The imaging agent of claim 4 in which at least 90% of said microspheres have diameters in the range of 2 to 8 μm."

The method claims 6 to 10 correspond to the method claims 10 to 14 as granted, with the dependencies amended as necessary.

X. Oral proceedings before the board were held in the absence of the respondent as provided for in Rule 71(2) EPC. At the end of the hearing, the board decided to continue the proceedings in writing, in accordance with directions to be given in a communication, in order to

give the absent respondent the opportunity to present its comments on the appellant's late-filed auxiliary requests.

XI. In the said communication, sent on 27 January 2003, the board informed the parties that it had become clear during the oral proceedings that the board would be unlikely to allow the appellant's main request filed with the statement of grounds of appeal (maintenance of the patent in the form as granted), or its first or second auxiliary request. In the board's judgment, it appeared unclear whether, in assessing inventive step using the problem/solution approach, the problem as discussed during the oral proceedings had, according to claim 1 of the above-mentioned requests, been shown to be solved across the whole range. As a result of the discussion of the case at the hearing, it appeared, however, that the above objection would not arise as regards the claims of the third auxiliary request. However, the board considered the auxiliary requests filed with the appellant's facsimile of 10 January 2003 to be *prima facie* inadmissible by reason of being filed so late that, if one of those requests was indeed held to be admissible without giving the respondent an opportunity to comment on them, it might be said the respondent had been prejudiced.

The board made the following directions in its communication:

"1. The proceedings shall be continued in writing only for the purpose of giving the respondent an opportunity to comment on the allowability of the auxiliary requests. If it so wishes, it should

file written observations to be received no later than two months after the deemed date of receipt of this communication.

2. If the respondent does file such observations, the appellant should file any observations in reply, and limited to replying thereto, to be received within two month after the deemed date of receipt from the board of the respondent's observations.

3. The time limits in 1 and 2 above will not be extended.

4. No submissions of any kind and no new evidence or requests (including requests for further oral proceedings) from either party will be considered.

5. The board's decision will include an order for apportionment of costs so that the appellant pays any costs incurred by the respondent after 10 January 2003. It follows from the above that those costs will be limited to only those reasonable costs properly incurred by the respondent in complying with these directions.

6. Since the continuation of the appeal proceedings will have the effect of continuing the period during which the effect of the decision under appeal is suspended (Article 106(1) EPC), the appellant has undertaken not to start any infringement proceedings on the patent in suit until the effective date of the board's decision."

XII. In its reply of 24 March 2003 to the board's communication (i.e. the first submission of the respondent in the course of the appeal proceedings), the respondent argued essentially as follows:

The first and second auxiliary requests did not appear to improve the appellant's position over the main request, since the only enabling disclosure in the patent was to a process that inevitably resulted in a suspension of the protein microcapsules in the protein solution that had been sonicated. The microcapsules could not be separated from the solution and either presented dry or suspended in another liquid. A suspension of the microcapsules in a solution of their own protein was the only product for which the appellant had any evidence of stability. This issue applied to albumin in accordance with the first auxiliary request just as much as to any other protein. In addition, as the respondent's experimental reports had shown, concentrations at the lower end of the concentration range (ie below 300 x 10^6/ml) in claim 1 as granted were not stable. Hence, the second auxiliary request was also not acceptable.

However, the respondent did not wish to object to claims 1 to 3 of the appellant's third auxiliary request (see IX above). However, it did object to claims 4 and 5 of the third auxiliary request (again, see IX above), since they were, in the respondent's opinion, not limited to the microspheres being suspended in a solution of the same protein as was used to prepare and encapsulate the microbubbles. It appeared that the omission of this feature from claims 4 and 5 of the third auxiliary request was an

oversight, since the appellant's description of this claim request on page 2 of its letter of 10 January 2003 indicated that the request was supposed to be "*a combination of claims 1, 4 and 5 as granted*" and that "*the microspheres are stated as being suspended in an aqueous solution of the same protein (in) which the microbubbles are encapsulated*".

If the appellant amended its third auxiliary request to delete claims 4 and 5, or to make these dependent on claim 1, and made this his only claim request, then the respondent would withdraw its opposition.

XIII. In a further communication of 16 March 2004 the board repeated its view that the main request (maintenance of the patent with the claims as granted) and the first and second auxiliary requests would not appear to be acceptable for the reasons summarised in paragraph 2 of its previous communication of 23 January 2003. In this second communication, the board also remained of the view that the claims of the third auxiliary request did not suffer from this objection and were potentially allowable. In this respect the board noted that the respondent had submitted it would withdraw its opposition if the third auxiliary request was amended as set out in XII above, last paragraph.

The board communicated to the parties its opinion that, if the matter was capable of resolution on terms the parties could agree and which the board could in the public interest approve, then such a resolution should be advanced. Further, if the parties agreed on a single request, the board would have to give effect to that agreement by ending the appeal proceedings (T 615/96 of

13 November 2001, unpublished in OJ EPO). Although the respondent had indicated it would withdraw its opposition and thus cease for almost all purposes to be a party to the proceedings, it should remain a party in order for the condition of identity of pending requests to be satisfied. Both parties should also find it in their interest to have a formal decision and order - in the respondent's case to be able to enforce the order for an apportionment of costs and, in the appellant's case, to have confirmation that its undertaking of 22 January 2003 (not to take infringement proceedings until the effective date of the board's decision) was discharged.

Accordingly, the board's previous direction that no further requests would be considered was modified to the extent necessary to accommodate the following further directions: "Within two months of the deemed date of receipt of this communication:

- the appellant, if it so wishes, should file a request (called "sole request") in the form of the third auxiliary request filed on 10 January 2003 amended in one of the ways indicated by the respondent, withdraw its other requests and file its written consent to an order being made by the board in the terms of the annexed draft;

- the respondent, if it so wishes, should file its written consent to the "sole request" and to an order being made by the board in terms of the annexed draft."

The draft order annexed to the communication read as follows:

"1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the claims in the request entitled "sole request" filed on (..... full date to be inserted when known).

3. The respondent's costs shall be apportioned so that the appellant pays to the respondent £ 494 (the sum to be paid was expressed in pounds sterling since it appeared the parties had agreed a sum in that currency).

4. The undertaking given to the board by the appellant on 22 January 2003, not to start any infringement proceedings on the patent in suit until the effective date of the board's decision, is hereby discharged (the effective date of the decision and thus the date of the discharge of the undertaking, would be the date the decision is given to the EPO postal service, see G 12/91, OJ EPO 1994, 285)."

At the end of this communication, the board made it unambiguously clear that, if the above directions were not complied with within the time indicated above, it would proceed to prepare and issue a decision on the basis of the materials then on file.

XIV. In its reply of 6 May 2004, the appellant indicated that there were four requests on file. These were the main request and its first, second and third auxiliary requests. It emphasised, however, that it would be prepared to file the third auxiliary request as a sole request (but not amended in one of the ways indicated by the respondent), if this assisted the board in these proceedings. It further noted that claim 4 of the third auxiliary request was originally claim 8 in the granted patent and it seemed that the respondent only commented on the third auxiliary request when invited to do so by the board in January 2003. It likewise appeared that the board had not specifically commented either, in a positive or negative manner, on the patentability of claim 4 of the third auxiliary request.

The respondent essentially argued in its reply to the board's communication that the technical feature of keeping the microspheres in a solution of the same protein from which they were made appeared to be essential for stability. This feature was present in claim 1 of auxiliary request 3 but was, in the respondent's opinion, not present in independent claim 4 of auxiliary request 3. This was why it continued to oppose it and could not withdraw the opposition.

XV. In view of the foregoing the following requests are on file:

The appellant requests that the decision under appeal be set aside and that the patent be maintained on the basis of its main request or its first, second or third auxiliary request in that order.

The respondent requests that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Introductory remarks

2. From the history of the case it is clear that the need to continue these proceedings in writing resulted solely from the late introduction of the appellant's first, second and third auxiliary requests with its facsimile of 10 January 2003, i.e. only 12 days before the hearing before the board on 22 January 2003, without giving any previous warning or any sound reasons or explanation for such lateness. The board's conclusion was that these requests were *prima facie* inadmissible by being filed so late that if one of them was held admissible without giving the respondent an opportunity to comment on them, it might justifiably be said that the respondent had to been prejudiced by violation of its rights guaranteed in Article 113(1) EPC.

2.1 Both during the oral proceedings and subsequently in its communications of 23 January 2003 and 16 March 2004, the board clearly expressed its view that the appellant's main request (maintenance of the patent with the claims as granted) and likewise its first and second auxiliary requests could not be allowed for the reasons summarised, *inter alia*, in the said communications. The board made it similarly clear that

the only justification for exercising its discretion in favour of the appellant and for admitting the late-filed requests into the proceedings lay in the fact that the claims of the appellant's third auxiliary request appeared, in the board's preliminary opinion, *prima facie* allowable, provided the respondent's written submissions in reply to the official communications would not lead the board to adopt a different opinion.

2.2 One reason for holding late-filed requests (or other submissions) inadmissible is the delay which would otherwise be caused to the proceedings. Such delay may not only prejudice other parties to the case but also parties to other pending cases and, in a more general sense, sections of the public who have an interest in the outcome of a appeal in that the existence or not of a patent, or the scope of a patent, may affect their commercial activities. Such delay may be made worse by the suspensive effect of an appeal (Article 106(1) EPC), which may mean that a patent revoked at first instance remains "alive" even beyond the date of the oral proceedings in the appeal simply because a patentee has filed new requests at a very late stage. In that sense it may be said the system encourages the withholding by patentees until a late stage of the requests most likely to succeed. If however one of those requests has some merits, a finding of inadmissibility, and thus upholding of the first instance revocation decision, may be seen as harsh. The question thus becomes how to balance procedural and substantive fairness.

2.3 That was the position with which the board was faced in the present case. The immediate injustice to the

respondent which might have been caused by finding the late-filed requests admissible could be mitigated by an apportionment of costs in the respondent's favour. There remained however the further possible injustice, to both the respondent and the public, arising from the combination of delay and the suspensive effect. The board avoided this injustice by requiring the appellant to give an undertaking to the board not to commence infringement proceedings on the patent in suit until a decision in the present appeal proceedings was issued. Such a requirement may appear harsh but, in the board's opinion, this is a situation which calls for "tough justice" - the patentee who files a late request is allowed the chance to pursue that request, and thereby to save its patent, but at the price of not being able to enforce the patent in the meantime. Of course, if the possibility of such an undertaking being required persuades patentees to file the requests most likely to succeed at an early stage of proceedings, so much the better for both other parties and the public.

2.4 It may be asked, what is the value of such an undertaking when the board, unlike national courts, has no sanctions at its disposal to use in the event of a breach of the undertaking? While the board has no enforcement procedures of its own, the undertaking will none the less have its intended effect - any party sued for infringement of the patent will inspect the EPO file and thereby discover the existence of the undertaking and bring it to the attention of the national court in which the infringement proceedings are pending. That court will thus be able to hold that the patentee has invoked its jurisdiction in breach of

an undertaking not to do so with the result that the national proceedings may be suspended or dismissed.

2.5 In view of the impact such an undertaking may have, it is important that its cessation is clearly shown on the file and the board considers this is best done by making a specific order for its discharge. Thus even when, as at one point seemed possible in this case, proceedings may be capable of termination by agreement, the patentee should request an appropriate order which, if agreed by the other party or parties, should be no more than a formality.

Closest prior art - problem and solution: main request, first and second auxiliary requests

3. There was general agreement that the sonication-produced, albumin-based ultrasonic imaging agents disclosed in citation (4) or (5) represent the closest and therefore the most relevant state of the art. These ultrasonic imaging agents contain in an aqueous medium a dispersion (suspension) of microspheres consisting of gas microbubbles which are encapsulated with the heat-denaturable biocompatible protein human serum albumin (hereinafter referred to HSA) and are suspended in an aqueous solution of the same protein (HSA) in which the microbubbles are encapsulated.

3.1 The appellant maintained that, although the sonication-produced microbubble imaging agents disclosed in (4) or (5) represented an important advance in this art, their stability of 24 to 48 h was insufficient for commercial manufacture. In the appellant's view the technical problem to be solved by the claimed invention was

therefore the provision of a microbubble-type ultrasonic imaging agent showing improved stability.

3.2 The solution to the problem proposed in the **main request** is the provision of:

- a concentrated room-temperature stable ultrasonic imaging agent comprising a **parenterally administrable aqueous medium** containing a **dispersion** of microspheres <.....> (**main request; claim 1 as granted - see I above);**

3.3 The solution to the problem proposed in the **first auxiliary request** is the provision of:

- a concentrated room-temperature stable ultrasonic imaging agent comprising **a parenterally administrable aqueous medium** containing a **dispersion** of microspheres at least 80% of which have diameters in the range of 1 to 9 μm, said microspheres consisting of gas microbubbles encapsulated in **human serum albumin** <.....>; (**first auxiliary request; claim 1 - see VII above);**

3.4 The solution to the problem proposed in the **second auxiliary request** is the provision of:

- a concentrated room-temperature stable ultrasonic imaging agent comprising a **parenterally administrable aqueous medium** containing a **dispersion** of microspheres at least 80% of which have diameters in the range of 1 to 9 μm, said

microspheres consisting of gas microbubbles encapsulated in a water-insolubilized heat-denaturable biocompatible protein, said imaging agent having a homogeneously dispersed concentration of greater than **200** x 10^6 microspheres <.....>;
(**second auxiliary request; claim 1 - see VII above);**

4. In its reply of 6 May 2004 to the board's communication of 16 March 2004, the appellant declared clearly and unequivocally that, if it assisted the board in theses proceedings, it would file the current third auxiliary request as the sole request so that the third auxiliary request, in its present (unamended) form, would exist as the only request of the appellant. It further declared that this would mean that the EPO and respondent need only to concentrate on, and decide on, one single sole request, i.e the third auxiliary request (see appellant's letter of 6 May 2004, page 2, second full paragraph.

4.1 Having regard to the appellant's above declaration, no lengthy explanation is required as to why the board remains of the view that neither the main request, nor the first and secondary auxiliary requests, should be allowed. As has already been explained in the official communications, in the board's judgment it appears at least unclear and highly uncertain whether, in assessing inventive step using the problem/solution approach, the technical problem as discussed during the oral proceedings before the board and repeated in 3.1 above, has, according to claim 1 of any one of the main request, first or secondary auxiliary request, been

shown to be adequately solved across the whole range claimed.

4.2 The application as filed and the patent as granted explain and exemplify the preparation of the claimed ultrasonic imaging agent only by a process which necessarily results in a dispersion (suspension) of microspheres consisting of gas or air microbubbles which are suspended in an aqueous solution of the same protein in which the microbubbles are encapsulated or, differently expressed, from which they were prepared by the proposed sonication, concentration and fractionation procedures. There is no enabling disclosure that the microbubbles could be separated from the protein solution that has been sonicated and either presented dry or suspended in another liquid (see especially patent specification page 5, line 30 to page 6, line 50).

Contrary to the appellant's assertion, the patent does not refer to the possibility of "redispersion" of the microbubbles in the sense that they are suspended in a solution which is different from the aqueous solution of the protein in which the microbubbles are encapsulated. References in the patent to "redispersion" of the microbubbles are always meant to indicate a dispersion to achieve an essentially homogeneous suspension (dispersion) of the microbubbles **in the aqueous solution of the same protein in which the microbubbles are encapsulated and from which they were made:**

- see page 5, lines 16 to 17:" For example, one-half or three-fourths of the solution [i.e the aqueous

solution of the same protein in which the microbubbles are encapsulated and from which they were obtained by sonication] can be removed. However, it is desirable to retain sufficient solution volume to permit redispersion of the concentrated microspheres";

- see page 5, line 20: "Fig.4 illustrates the microsphere concentrate with the microspheres redispersed" [in the aqueous solution of the same protein in which the microbubbles are encapsulated];

- see page 5, line 21: "After redispersion to an essentially homogeneous condition, fractionation may <.....>";

- see page 5, line 53: "If required for redispersion, concentration may be adjusted with 5% HSA",[i.e. exactly the aqueous solution in the same concentration of the same protein in which the microbubbles are encapsulated.]

4.3 From the language of the claims it is sufficiently clear that none of the main or first or second auxiliary requests **are limited** to an ultrasonic imaging requiring and stipulating that the microspheres are suspended in an aqueous solution of the same protein in which the microbubbles are encapsulated, or differently expressed, from which they were obtained by sonication. An ultrasonic imaging agent of this kind, i.e. a suspension or dispersion of the microspheres in an aqueous solution of the same protein in which the microbubbles are encapsulated, **is, however, the only**

product for which any evidence of the alleged improved stability over the cited closest state of the art has been provided in the entire course of the opposition and appeal proceedings (see patent specification, page 6, Table B).

4.4 However, claim 1 of the main request and the first and second auxiliary requests covers imaging agents in which the microspheres may be suspended in any conceivable parenterally administrable **aqueous medium** which may be entirely **different** from the solution of the protein in which the microbubbles are encapsulated and from which they were made. It is, however, immediately evident to a person skilled in the art that the **chemical and physico-chemical nature** of **that aqueous medium** (solution) such as, for example the chemical and physical properties of the solute (protein), the density, polarity, concentration, osmolarity, osmalility, surface tension, etc. of that aqueous medium (solution) are essential to the stability of gas or air microbubbles encapsulated in a tiny shell or layer of a water-insolubilized heat-denaturable protein. Therefore the conclusion must be drawn that, in the case of the main, first and second auxiliary requests, the available evidence is insufficient to establish plausibly that the stated technical problem was solved by the suggested solution **over the whole range of the claims** and that the alleged advantageous properties such as improved stability of the microspheres could be achieved **over the whole range of the claims.**

4.5 According to the boards' established case law, 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 (see T 20/81, OJ EPO, 1982,217; T 181/82, OJ EPO, 1984, 401; T 124/84, T 152/93; T 912/94; T 284/98; T 325/97, T 1051/97). Since the advantages referred to by the appellant have not been properly demonstrated over the whole range claimed (see 4.3, 4.4 above), the problem underlying the subject-matter of the main, first and second auxiliary requests can only be seen in the provision of a simple alternative to the microbubble-type ultrasonic imaging agents disclosed in (4) or (5), having about the same properties and capabilities as those known from the cited state of the art. The claimed alternatives are obvious to a person skilled in the art and lack an inventive step.

Third auxiliary request

5. The solution to the problem proposed in the **third auxiliary request** is the provision of:

- a concentrated room-temperature stable ultrasonic imaging agent comprising a **parenterally administrable aqueous medium** containing a **dispersion** of microspheres at least 80% of which have diameters in the range of 1 to 9 μm, said microspheres consisting of gas microbubbles encapsulated in a water-insolubilized heat-denaturable biocompatible protein, **and being suspended in an aqueous solution of the same protein in which the microbubbles are encapsulated** <.....>;

(**third auxiliary request; claim 1 - see VII above);**

- a concentrated room-temperature stable ultrasonic imaging agent for intravenous administration, comprising **a sterile aqueous solution of human serum albumin** containing a **dispersion** of microspheres at least 80% of which have diameters in the range of 1 to 9 μm, said microspheres consisting of a bubble of air **encapsulated in a water-insolubilized layer of said albumin**, said imaging agent having a homogeneously-dispersed concentration of from 300 to 600 x 10^6 microspheres per ml and maintaining this concentration for at least 8 weeks at a temperature of 20 to 25°C. (**third auxiliary request; claim 4 - see VII above).**

5.1 The board notes the respondent has submitted that it did not wish to object to claims 1 to 3 of the third auxiliary request. However, it objected to independent claim 4 and dependent claim 5 of the third auxiliary request, since these claims were, in the respondent's opinion, not limited to an imaging agent in which the microspheres are suspended in an aqueous solution of the same protein in which the microbubbles are encapsulated or, differently expressed, from which the microbubbles were obtained by the sonication method described in the patent.

5.2 The board is unable to agree with the respondent's objection and its interpretation of claim 4. Thus, claim 4 clearly states that the microspheres are suspended in **an aqueous solution of human serum albumin**

(see .... imaging agent <.....> comprising a sterile aqueous solution of human serum albumin containing a dispersion of microspheres <.....>") and also clearly states that **said microspheres are suspended in an aqueous solution of the same protein, in which the microbubbles are encapsulated** (..... said microspheres consisting of a bubble of air **encapsulated** in a water-insolubilized layer of **said albumin**.....").

5.3 From the foregoing it appears to the board unambiguously clear that the technical feature of suspending the microspheres in the same protein in which the microbubbles are encapsulated and from which they were made is equally present in both independent product claims 1 and 4 of the third auxiliary request. As already mentioned this feature appears to be a key feature essential for stability. Therefore the conclusion must be drawn that in the case of the third auxiliary request the available evidence, in particular tabulated test results from Table B on page 6 of the patent, are sufficient to make it plausible that the stated technical problem was solved by the suggested solution **over the whole range of the claims**.

5.4 Even upon careful study of the state of the art available in the proceedings, the skilled reader is given no hint or suggestion leading him to the conclusion that the problem posed could successfully be solved and the stability of the claimed ultrasonic imaging agents could substantially be improved in comparison with the closest state of the art by the specific methods of sonication, concentration and fractionation used in the patent. The claimed subject-matter in the third auxiliary request is therefore

considered to involve an inventive step in accordance with Article 56 EPC. The conclusions above apply not only to claims 1 and 4 but also to claims 2, 3 and 5 which append on the afore-mentioned claims. The method claims 6 to 10 in the third auxiliary request correspond to method claims 10 to 14 in the patent as granted, which have not been attacked in the notice of opposition, and are therefore also allowable.

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 with the order to maintain the patent on the basis of claims 1 to 10 in the third auxiliary request filed on 10 January 2003 and a correspondingly adapted description.

3. The respondent's costs shall be apportioned so that the appellant pays to the respondent £ 494.

4. The undertaking given to the board by the appellant on 22 January 2003, not to start any infringement proceedings on the patent in suit until the effective date of the board's decision, is hereby discharged.

The Registrar: The Chairman:

A. Townend U. Oswald