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D E C I S I O N
of 7 March 2006

Case Number: T 0460/03 - 3.3.02

Application Number: 92919150.0

Publication Number: 0605477

IPC: A61K 49/00

Language of the proceedings: EN

Title of invention:
Gaseous ultrasound contrast media

Patentee:
GE Healthcare AS

Opponent:
Acusphere, Inc.
BRACCO S.p.A.

Headword:
Gaseous Ultrasound Contrast Media/GE HEALTHCARE

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"Admissibility of late-filed request (yes): direct response to a late raised objection"
"Novelty (yes): state of the art does not disclose in an individualized form a composition encompassed by claim 1"
"Inventive step (yes): the proposed solution is not obvious in the light of the prior art"

Decisions cited:
T 0176/84

Catchword:
-



Case Number: T 0460/03 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 7 March 2006

Appellant: GE Healthcare AS
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 13 February 2003
revoking European patent No. 0605477 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: M. C. Ortega Plaza
P. Mühlens

Summary of Facts and Submissions

- I. European patent EP-0 605 477, based on European application No. 92 919 150.0, which was filed as international application WO 93/05819, was granted on the basis of 10 claims.

Claim 1 as granted read as follows:

"1. Contrast media for ultrasound image-enhancement comprising microbubbles of a biocompatible gas or a combination of gases in a biocompatible aqueous liquid vehicle, the gas or gases being selected from hexafluoropropylene, octafluoropropane, octafluoro-2-butene, hexafluoro-2-butyne, hexafluorobuta-1,3-diene, octafluorocyclobutane and decafluorobutane."

Claim 2 as granted read as follows:

"2. Contrast media for ultrasound image-enhancement comprising microbubbles of a biocompatible gas or a combination of gases in a biocompatible aqueous liquid vehicle, the gas or gases comprising dodecafluoropentane."

Claim 6 as granted read as follows:

"6. Use of one or more of hexafluoropropylene, octafluoropropane, octafluoro-2-butene, hexafluoro-2-butyne, hexafluoro-buta-1,3-diene, octafluorocyclobutane and decafluorobutane for the production of contrast-enhancing media for ultrasound imaging."

Claim 7 as granted read as follows:

"7. Use of dodecafluoropentane for the production of contrast-enhancing media for ultrasound imaging."

II. The following documents inter alia were cited during the proceedings:

- (2) D. P. Swanson, "Pharmaceuticals in Medical Imaging", Macmillan Publishing Co., Inc., March 1990, pages 682-687
- (3) H. Lincoff, Arch. Ophtalmol., 98, 1610-1611, 1980
- (4) H. Lincoff, American Academy of Ophtalmology, 90, 546-551, 1983
- (5) C. M. Vygantas, Arch. Ophtalmol., 90, 235-236, 1973
- (11) US-A-4 276 885
- (12) US-A-4 265 251
- (13) WO 92/17514
- (15) WO 91/12823
- (18) M. C. Ziskin, Invest. Radiol., 67, 500-505, 1972
- (24) Copy of the declaration by Mr R. Skurtveit made in relation to the appeal case T 274/02
- (25) Declaration of Mr Debenedetti dated 29 August 2002
- (28) Bruce D. Butler, J. Clin. Ultrasound 14, 408-412, 1986
- (29) Declaration of Mr J. Lai dated 12 November 1996
- (33) Dupont "Freon" Fluorocarbons
- (34) Summary of PFC's in form of a table, filed by opponent 1

III. Opposition was filed and revocation of the patent in its entirety was requested pursuant to Article 100(a), (b) and (c) EPC.

- IV. The appeal lies from the decision of the opposition division revoking the patent under Article 102(1) and (3) EPC.
- V. The opposition division considered that the main request (filed during the oral proceedings before the opposition division) did not meet the requirements of Article 123(2) EPC. In particular, the opposition division considered that the introduction of the term "gaseous" in claim 7 was unallowable.

The opposition division considered that the first auxiliary request (filed during the oral proceedings before the opposition division) extended beyond the content of the application as filed (Articles 100(c) and 123(2) EPC), in particular independent claim 2.

As regards the second auxiliary request (filed during the oral proceedings before the opposition division), the opposition division considered that it contravened the requirements of Article 123(2) EPC, in view of the introduction of the term "polyoxyethylene (20) sorbitan monolaurate".

According to the opposition division's findings, claim 5 of the third auxiliary request (filed during the oral proceedings before the opposition division) lacked support in the description (Article 84 EPC).

As regards the fourth auxiliary request (filed during the oral proceedings before the opposition division), the opposition division considered that it met the requirements of Articles 84 and 123(2) and (3) EPC.

In the opposition division's view, the subject-matter claimed in the fourth auxiliary request was novel over the cited prior art.

The opposition division considered document (2) to represent the closest prior art since "it provid(ed) the more detailed and comprehensive overview of ultrasound enhancement agents, including microbubble comprising media". The opposition division defined the problem to be solved as to provide advantageous gases for use in microbubble contrast media.

The solution claimed was considered to be obvious by the opposition division since document (2) already mentioned that incorporation of an insoluble gas, such as nitrogen, resulted in precision microbubbles with substantially longer persistence than the use of more soluble gases. Therefore, in the opposition division's view the solubility/insolubility of a gas was known as a relevant criterion for its selection when looking for suitable gases for microbubble contrast agents. Additionally, perfluorocarbons were further mentioned in document (2) as suitable gases for contrast media.

- VI. The patent proprietor (appellant) lodged an appeal against said decision and filed grounds of appeal in which it added additional technical calculations. It also filed an amended set of claims as its main request (sole request).

- VII. The respondent (opponent 1) filed counterarguments to the grounds of appeal accompanied by additional technical calculations.

- VIII. A board's communication dated 3 June 2005 which conveyed the rapporteur's preliminary opinion was sent to the parties.
- IX. The appellant filed with its letter of 10 August 2005 further arguments and an amended set of claims as main request.
- X. The summons to oral proceedings was sent on 27 September 2005.
- XI. The respondent sent by fax a letter dated 17 January 2006 in which it conveyed its opinion about the set of claims of the main request filed with the letter of 10 August 2005.
- XII. The appellant filed with its letter of 7 February 2006 a first and a second auxiliary requests, further arguments and additional technical calculations.

Each of the two sets of claims of the auxiliary requests contained six claims (claims 2, 5 and 7 as granted were deleted).

Claim 1 of the first auxiliary request read as follows:

"1. Contrast media for ultrasound image-enhancement comprising microbubbles of a biocompatible gas or a combination of gases in a biocompatible aqueous liquid vehicle, the gas or gases being selected from octafluoropropane, octafluorocyclobutane and decafluorobutane."

Claim 4 of the first auxiliary request read as follows:

"4. Use of one or more of the gases octafluoropropane, octafluorocyclobutane and decafluorobutane for the production of contrast-enhancing media for ultrasound imaging in the form of suspensions of microbubbles of said gas or gases."

Claim 1 of the second auxiliary request differed from claim 1 of the first auxiliary request in that the expressions "or a combination of gases" and "of gases" were deleted. Claim 4 of the second auxiliary request differed from claim 4 of the first auxiliary request in that the expression "or more" was deleted.

XIII. Oral proceedings took place on 7 March 2006. At the beginning of the oral proceedings the appellant announced the withdrawal of its main request filed with its letter dated 10 August 2005 and renumbered its first and second auxiliary requests filed with its letter of 7 February 2006 as main request and first auxiliary request respectively. It also filed a second and third auxiliary requests, both containing only three claims (i.e. these requests related to amended versions of the sets of claims of the main request and first auxiliary request in which the use claims were deleted).

All these late-filed sets of claims were admitted by the board into the proceedings.

Further, during the oral proceedings a discussion about the reading of the independent claims took place and as

a result the board raised an objection of lack of novelty vis-à-vis document (13).

As a consequence of the objection of lack of novelty two amended sets of claims (each containing only two claims) were filed by the appellant.

Claim 1 of the amended main request incorporated the features of claim 3 as granted and read as follows:

"1. Contrast media for ultrasound image-enhancement comprising microbubbles of a biocompatible gas in a biocompatible aqueous liquid vehicle, the gas being selected from octafluoropropane, octafluorocyclobutane and decafluorobutane, said microbubbles having a diameter of less than 8 μm ."

Claim 1 of the amended first auxiliary request differed from claim 1 of the main request in that the option "decafluorobutane" was deleted.

These two sets of claims were also admitted into the proceedings. These sets of claims replaced all previous sets of claims, which were withdrawn.

Following a discussion on inventive step based on these two late-filed requests, the debate was closed and the board conferred for about two hours. Afterwards the proceedings were resumed and the board reopened the debate and requested the parties to address directly the option concerning the gas "octafluorocyclobutane", which had not been specifically discussed by the parties previously.

As an immediate reaction to the board's request, the appellant filed an amended set of claims based on the last main request in which the option "octafluoro cyclobutane" was deleted. After a positive decision by the board on admissibility, the appellant withdrew all its previous requests and made its latest request its main and sole request.

Claim 1 of the set of claims of the main and sole request (which appears as an annex to the minutes of the oral proceedings) contains only two claims.

Claim 1 of the main request (sole request) reads as follows:

"1. Contrast media for ultrasound image-enhancement comprising microbubbles of a biocompatible gas in a biocompatible aqueous liquid vehicle, the gas being selected from octafluoropropane and decafluorobutane, said microbubbles having a diameter of less than 8 μm ."

Claim 2 is a dependent claim of claim 1 and corresponds to claim 4 as granted.

XIV. The appellant justified the filing of its latest request immediately after the reopening of the debate as anticipating an objection not yet raised by the board in respect of the option concerning perfluorocyclobutane (octafluorocyclobutane), since Lai's studies (29) did not use this specific gas. Such an objection had not been raised in the written proceedings and had not as yet been discussed during the oral proceedings. Therefore, this very late-filed request was a clear and direct response to a very

late-raised objection. The amendment was very simple and clear, namely it merely related to the deletion of the questioned option. The thus amended claim did not require further discussion since it raised no new issues and hence did not delay the proceedings.

The appellant's reading of claim 1, in particular in view of the use of the term "comprising" was as follows: the claim required the presence of microbubbles of a specific biocompatible gas, but it did not exclude the possibility of a gel coating of the gas microbubble. Each of the examples of Lai's studies (29) concerning the specific gases claimed supported the subject-matter claimed. Claim 1 was not restricted to a two-phase system with free gas microbubbles suspended in the biocompatible aqueous liquid vehicle. The possibilities of microbubbles stabilised or encapsulated by e.g. albumin was not excluded by the claim's wording. A technically meaningful reading of the claim by the skilled person would immediately make evident the existence of a transition region or barrier layer between the liquid vehicle and the gas. This would not impair the improved persistence caused by the selection of the gas.

The appellant also cited paragraphs [29] and [53] of the patent as granted and pointed out that the microbubble compositions were made by known methods and hence this did not exclude encapsulation. However, the appellant specified that the claim encompassed a three-phase system in which there is a transition phase which would allow diffusion but it did not include spheres which would not allow diffusion. This was an extreme case, not meant to be included.

The appellant stated that although the environment of the gas microbubbles affected the scattering, the primary effect was caused by the nature of the specific perfluorocarbon gas defined in the claim.

In respect of the novelty assessment, the appellant acknowledged that document (13) formed part of the state of the art within the meaning of Article 54(3) EPC. The appellant stated that there was no unambiguous disclosure of any specific gas microbubbles in an aqueous medium in document (13). The only related disclosure was that on pages 7 and 17 (example 6), but example 6 clearly stated "perfluorocarbon liquid" and was to be understood in conjunction with example 1. It would not be possible to carry it out because of too low a boiling point. The opposition division had correctly established that the disclosure of document (13) was non-enabling. If the only technical meaningful reading possible of example 1 was that the isobutane gas dissolved in the liquid medium, when speaking of "isobutane liquid" a "solution of the gas" would be understood. Therefore, in the appellant's view, whatever argument was correct, the preferred gas was merely an expanding gas in a solvent. It was however not unambiguously derivable from the disclosure of document (13) that the gas which was used to inflate the microbubbles was still present in the bubble when the composition was used as contrast media, especially in view of the temperature used for the expansion step. Moreover, in the appellant's opinion, there was a long list of possible expanding gases given in document (13) including some very toxic options. When document (13) "wanted to talk about gas" it drew a distinction as

shown on page 8, line 17 onwards in which microspheres filled with an inert gas were disclosed. Additionally, examples 1-7 were mentioned in document (13) as "prophetic examples". Finally, page 5 disclosed various particle sizes going from about 1 to about 1000 microns. Even if the respondent were right to assume a suitability as contrast media one would still need to select a specific microsphere size in the lowest range. The specific sizes on page 5 could not be read in combination with the specific examples. Such specific sizes were not an inevitable result of the process employed. Finally, the most preferred size disclosed in document (13) was 50 microns. This was in accordance with the use disclosed in document (13).

As regards the inventive step issue, the appellant's arguments may be summarised as follows: document (2) could be taken as the closest prior art since it belonged to the same technical field. Whether document (2) or document (11) was considered as the starting point did not change the definition of the problem, which was to provide microbubbles for ultrasound contrast media with improved stability capable of passing through the lung. It cited paragraphs [13], [14], [15], [41] and [47] of the patent in suit.

The solution related to microbubbles containing specific gases which had increased persistence, i.e. longer life.

As regards the question of plausibility in respect of the proposed solution, the appellant referred to example 3, especially page 15, of the patent in suit

and to Lai's declaration (29). Example 3 showed that the bubbles had survived the passage through the lungs.

Lai's studies (29) showed undeniably that the microbubbles filled with perfluoropropane or perfluorobutane had an unexpectedly higher persistence than the microbubbles filled with other inert gases of the state of the art, in particular nitrogen.

The appellant stressed that the respondent's position on inventive step was based on an ex post facto analysis of the prior art and that the respondent's reading of document (2) (primarily a review document of other's people work) was made with hindsight with knowledge of the claimed invention.

The passages of document (2) cited by the respondent had to be read within their context. For instance, the teaching about the incorporation of nitrogen "into the manufacturing process" was incomplete without reading the quoted document (28). Document (28) did not mention any other "insoluble" inert gases as an alternative to nitrogen, which was used as a minor gas in conjunction with another more soluble gas. Although document (28) mentioned adding nitrogen as the primary gas in order to obtain a longer life for the bubbles, it did not disclose that nitrogen would lead to bubbles with longer life in comparison to oxygen bubbles. In the appellant's view, Lai's experiments (29) demonstrated that this was not the case.

Furthermore, there was nothing in the cited prior art to suggest looking at other gases. The mention of perfluorocarbons on page 685 of document (2) related to

those which are liquid (and not gas) at room temperature. These volatile liquids were not suitable for use in the process of document (28). Indeed, the passage on page 685 did not tell anything about low solubility. The document referred to therein was document (18), which dealt with ether (a soluble gas) and did not even mention perfluorocarbons. Hence, the two passages of document (2) mentioned by the respondent could not be combined.

The appellant further argued that even if the skilled person were to be looking for other gases, he would have looked at document (11) but certainly not at documents (3) to (5) since they did not relate to the same technical field as the invention. Their technical teaching was not relevant to the present invention since they had nothing to do either with contrast media or with microbubbles.

In the appellant's opinion, the disclosure of document (11) suffered from the same problem as document (2) since it only disclosed nitrogen or one of the slow-dissolving noble gases. The skilled person would not recognise that nitrogen was not good enough and there was no incentive to look at perfluorocarbon gases.

In the appellant's view, documents (12) (nothing about solubility) and (15) (liquid higher fluorocarbons) did not represent general knowledge. Moreover, none of these document provided an incentive to select a perfluorocarbon gas as solution to the stated problem.

XV. The respondent contested the admissibility of the appellant's latest request since it was extremely

late-filed. In its opinion, it was immaterial for the admissibility check whether or not a particular part of the claim had been directly attacked since a patentee should always have prepared in at earlier stage a fallback position by way of an auxiliary request.

The respondent also contested the admissibility of the calculations filed with the appellant's letter of 7 February 2006. These calculations included inter alia propane and butane which could not be considered as biocompatible inert gases.

When questioned by the board about the main claim's wording, the respondent made a more restrictive reading than the appellant, namely the respondent considered that the claim encompassed free microbubbles and microbubbles stabilised by a surfactant but it certainly did not encompass encapsulated microbubbles. In the respondent's view, such a possibility was not contemplated by the original description, which related to the problem of gas dissolution and not to gas dispersion through a membrane. In this context it referred to document (24), point 15, as meaning that the critical pressure was affected by the precise nature of the encapsulated microbubbles (microvesicles) and not necessarily by the nature of the gas.

Moreover, the respondent denied that the effects were only dependent on the nature of the gas in case of encapsulated microbubbles. It cited in this context Mr Debenedetti's declaration (25), in which it was stated that the equation concerning the Q-factor was only applicable to free gas bubbles and not to encapsulated bubbles. The reason lay in the fact that

the equation did not reflect the existence of any barrier between liquid and gas. In this context the respondent disagreed with the appellant's interpretation of the contents of paragraphs [29] and [53] of the patent in suit and stressed that in the light of their wording only free gas microbubbles were meant.

The respondent accepted that there would be diffusion through a shell, but that its existence should have been taken into account for the Q-factor equation.

The respondent did not raise any objection within the meaning of Articles 100(c), 123, 84 or 83 EPC against the main request.

The respondent's comments in respect of document (13) were as follows: there was a clear disclosure for the combination of the teaching of examples 1 and 6 which ends up in a product falling within the scope of claim 1. The resulting particles would contain the perfluorobutane gas, since some gas would remain after expansion. In the absence of a step for eliminating the gas in example 1, the blowing gas expands in the void and at least some remains in it.

The respondent contested the validity of the appellant's attempt to overcome a lack of novelty objection when arguing a non-enabling disclosure without providing any technical evidence in order to bring reasonable doubts about the contents of document (13). With respect to the feature concerning the aqueous vehicle, it cited page 10, lines 13-15, and with respect to the size of the microspheres it cited

page 5, lines 3-4. These features were part of the general disclosure and hence it was allowed to combine them with the specific disclosure. Such compositions were encompassed by claim 1 of the main request since they were suitable as contrast media for ultrasound imaging (for instance of the gastrointestinal tract). Claim 1 of the main request was a product claim not restricted to the use. Finally, claim 1 had an open worded language since the expression "comprising" did not limit the claim to particles having overall the size now specified.

The respondent's arguments in respect of inventive step may be summarised as follows: Document (2) represented the closest prior art since it was in the same technical field as the invention. The contents of document (2), page 384, related to the problem of increased stability of microbubbles for contrast media in ultrasound. Document (2) taught that the stability of gas bubbles in a solution was dependent, inter alia, on the nature of the gas. Moreover, document (2) taught how varying the composition of the bubbles by incorporation in the manufacturing process of an insoluble gas, such as nitrogen, resulted in bubbles of virtually any desired size range and stability. Hence, document (2) contained the teaching to incorporate an insoluble gas for achieving improved stability. Document (28) was cited in document (2), but the reader of document (2) would read it on its own without its cross-references. Furthermore, the last passage on page 411 of document (28) had to be read within the context of the avoidance of systemic embolization, since document (28) also disclosed very big bubbles (80 μm) which would block the blood vessels. In such a

case nitrogen was not to be considered. Additionally, on page 685 of document (2), still under the heading "Microbubbles", the use of perfluorocarbons that are liquid at room temperature but that vaporize at body temperature was disclosed. If the skilled person was looking for a microbubble that persists for longer, then he would read these two passages of document (2) together, since it does not matter whether or not the bubbles are created in situ or in vivo. Microbubbles containing nitrogen gas last longer as a consequence of the fact that nitrogen is less soluble. The skilled person was taught by document (2) to use an insoluble gas and document (2) further suggested using a perfluorocarbon. The skilled person knew which perfluorocarbons are in the gas form at body temperature and was aware of their solubility ranking. In this context, the respondent cited document (34). These two parameters allowed the skilled person to select the adequate gases.

Moreover, the respondent agreed with the analysis made by the opposition division which considered that the skilled person would have taken into consideration those perfluorocarbon gases which had been previously used in medicine, as shown by documents (3) to (5). In this context the respondent cited published decision T 176/84, OJ EPO, 1986, 50, in order to support the view that the skilled person would also have considered the state of the art relevant in a neighbouring field.

The respondent also stated that there had been extensive discussion during the written proceedings about the calculations in relation to the correlation of persistence versus (reverse) solubility. The

respondent contended that it had conclusively demonstrated that the Q factor was not better than the solubility of a gas when selecting a gas for bubbles with higher persistence. The improved persistence was predictable when considering the correlation with the reverse solubility.

The respondent also stated that the patent in suit did not contain data in vivo with the exception of example 3, which merely corresponded to a safety evaluation in a dog.

The respondent cited the Case Law of the Boards of Appeal of the EPO, 4th edition 2001, Section I.D.4.4, and stated that alleged advantages cannot be taken into consideration for the assessment of inventive step. There was a lack of in vivo data showing any improvement.

In the respondent's view, the problem vis-à-vis document (2) was how to put into practice, i.e. in vivo, its teaching of finding gases for microbubbles with longer persistence. Fifteen years after filing of the application there was still no in vivo data available nor had a product been developed which could be used by clinicians. The problem of producing a product for clinical trials had not been yet solved. The respondent stated that the patentee had withdrawn its product containing perfluoropentane before FDA authorities.

The respondent contested the interpretation by the appellant of the data in Lai's declaration (29) since the particle size varied. The bigger bubbles would last longer than smaller bubbles. Therefore no true

side-by-side comparison was possible. Moreover, some of the bubble sizes were now outside the scope claimed. Finally, the tests did not contemplate all possible comparisons.

The respondent stressed that document (2) and not document (28) was the closest prior art and that document (2) clearly taught the use of a less soluble gas for longer life, and this had been done. Microbubbles filled with nitrogen were the closest prior art.

The respondent also cited documents (12) (especially, freon gases as Dupont's freons) and (15) (in particular page 10, example 4, as double emulsion) in order to show that fluorocarbons had already been used in contrast media.

XVI. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the main request filed in the oral proceedings.

The respondent (opponent 1) requested that the appeal be dismissed.

Reasons for the decision

1. The appeal is admissible.

2. *Procedural matters, admissibility of the late-filed main request (sole request)*

2.1 As a matter of fact, the positive decisions on admissibility progressively taken by the board during the oral proceedings, which concerned the several requests filed by the appellant either with its letter of 7 February 2006 or during the oral proceedings, implied that the amendments introduced were considered by the board to relate to a direct response to recently introduced (arguments or) objections and/or as being of a clear and simple nature (deletion of claims, deletion of option(s), incorporation of dependent claim 3 as granted), not extending the scope of discussion but reducing it in a considerable way.

2.2 During its deliberation on the then main and first auxiliary requests of the appellant, the board came to the conclusion that the claims were not allowable because it had not been demonstrated that the technical problem underlying the invention could be solved by using the substance "octafluorocyclobutane" contained in claim 1 of both requests. The reason is that the Lai's declaration (29) shows no experiments with that substance.

Apart from this, the main request was found to be allowable. Thus, the appeal had to be dismissed only because of the presence of "octafluorocyclobutane" in respective claims 1.

However, this lack of experimental data for the particular option "octafluorocyclobutane" had never been addressed before, either in writing or in the oral

proceedings before the board. Consequently, the appellant had not been given the opportunity to defend the mentioning of that substance in the claims or, if he deemed it appropriate, to amend the claims accordingly, i.e. by deleting the item. Thus, dismissing the appeal for this reason alone would have taken the appellant by surprise and therefore amounted to a violation of the right to be heard (Art. 113(1)EPC). Given this situation, the board had to continue the debate.

2.3 The very late filing by the appellant of its latest request, renamed afterwards as main and sole request, was an immediate reaction to the continuation of the debate for addressing directly the question of inventive step in respect of the option concerning perfluorocyclobutane (octafluorocyclobutane), which had not been discussed in the previous debate.

2.4 It is not necessary to decide about the admissibility of the technical calculations submitted by the appellant with the letter of 7 February 2006, since the appellant did not base its arguments in favour of inventive step on these calculations. Moreover, they are not relevant for the ruling of the present case.

3. *Main request (sole request)*

3.1 The respondent has not raised any objection within the meaning of Articles 123, 84 and 83 EPC against the set of claims of the main request.

3.2 Claim 1 of the main request no longer includes those options which were contested on the ground of opposition pursuant to Article 100(c) or 123(2) EPC. Moreover, the amendments introduced, all relating to restrictions and deletions of alternative options, do not contravene the requirements of Article 123 EPC.

Additionally, the main request no longer contains the claims found by the opposition division to contravene the requirements of Article 84 EPC.

The sufficiency of disclosure of the subject-matter now claimed has not been challenged by the respondent. The board is also satisfied that the requirements of Article 83 EPC are met.

3.3 As regards the subject-matter claimed in claim 1, the appellant's reading of the claim's wording is linguistically (due to the use of the word "comprising") and technically meaningful. The board cannot follow the more restrictive reading made by the respondent, since even if accepting the argument that the description specifies more limited microbubble compositions than those encompassed by the claim, it is the claim's wording which defines the claimed invention. Furthermore, the disputed wording belongs to the granted claim version and cannot be questioned under Article 84 EPC (support in the description) in opposition appeal proceedings.

Therefore, the board is satisfied that claim 1 is not restricted to two-phase systems, where free microbubbles are suspended in a biocompatible aqueous liquid vehicle, but it **generically** includes other

(stabilised) options on condition that they comprise microbubbles of either octafluoropropane or decafluorobutane in a biocompatible aqueous liquid vehicle and that the said microbubbles have a diameter of less than 8 μm .

3.4 Novelty

- 3.4.1 Document (13), with an earlier priority date than the first priority date of the patent in suit, forms part of the state of the art within the meaning of Article 54(3) EPC. This has not been disputed by the parties.

Document (13) discloses contrast media for computer tomography imaging comprising a substantially homogeneous aqueous suspension of low density microspheres (page 2, lines 34-36). The microspheres are small spheres having a central void cavity (page 3, lines 25-26).

Document (13) states: "The microspheres of the present invention are low density [microspheres] [sic]. By low density, it is meant that the microspheres of the invention have an internal void (cavity) volume which is at least about 75% of the total volume of the microspheres." (page 4, lines 30-34)

Furthermore, document (13) states: "The microspheres may be of varying size, provided they are low density. Suitable microspheres include those ranging from between about 1 and about 1000 microns in outside diameter, preferably between about 5 and about 70 microns in outside diameter. **Most preferably, the**

microspheres are about 50 microns in outside diameter."
(page 5, lines 1-6) (*emphasis added*)

Document (13) further states: "in general terms, the heat expansion process is carried out by preparing microspheres of an expandable polymer or copolymer which contain in their void (cavity) a volatile liquid. The microsphere is then heated, plasticising the microsphere and **volatilizing the gas**, causing the microsphere to expand to up to about several times its original size." (page 6, lines 7-13) (*emphasis added*)

Among the long list of "volatile liquids" useful in the heat expansion process perfluorocarbons, especially decafluorobutane, are mentioned. (page 7, lines 3-6)

Furthermore, document (13) also states: "For example, to produce microspheres of the present invention, vinylidene and acrylonitrile may be copolymerized in a **medium of isobutane liquid** using one or more of the foregoing modified or unmodified literature procedures; such **that isobutane becomes entrapped within the microspheres**. When such microspheres are then heated to between about 80°C and about 120°C, the **isobutane gas** expands, which in turn expands the microspheres."
(page 7, lines 23-30) (*emphasis added*)

Further on page 7 it is acknowledged that isobutane is used for illustrative purposes. (page 7, lines 35-36)

Document (13) also states: "The present invention is further described in the following Examples. Examples 1-7 are prophetic examples ... and **describe the preparation of microspheres by a heat expansion**

process" (page 14, lines 34-35, page 14, line 37, page 15, line 1). "Examples 8-9 are actual examples that describe the **preparation of contrast media** of the invention." (page 15, lines 1-3) (*emphasis added*)

Example 6 states: "The procedures of Example 1 are substantially repeated with the exception that the volatile liquid isobutane is replaced with perfluorocarbon liquid (C₄F₁₀). **The remainder of the process is similar.** The resulting microspheres are filled with perfluorocarbon liquid rather than isobutane." (page 17, lines 4-9) (*emphasis added*)

Moreover, example 1 clearly includes, for a portion of the microspheres, the expansion step (achieved by heating) in which the isobutane gas expands. Therefore, the process illustrated by example 6 includes, by analogy, both the production of unexpanded microspheres filled with the so-called perfluorocarbon liquid and of expanded microspheres in which the perfluorocarbon expands in the form of gas from the liquid medium contained in the microspheres. However, although examples 1 and 6 disclose the preparation of expanded microspheres filled in their void by means of the expansion with a mixture of liquid and gas, none of these examples discloses the preparation of contrast media containing a suspension of the expanded microspheres in a biocompatible aqueous vehicle. Examples 8 and 9, concerning the preparation of contrast media, do not use the microspheres of example 6.

Additionally, the size of the microspheres prepared according to example 6 is left open. The exchange in the nature of the expanding gas is essential for the size of the expanded microspheres obtained. Hence, the sizes obtained in the process of example 1 when using isobutane as expanding gas cannot be interpolated into the sizes of microspheres obtained in example 6.

Consequently, document (13) does not disclose in an individualised form compositions comprising expanded microspheres filled in their void by decafluorobutane, said microspheres having a diameter of less than 8 μm , in a biocompatible aqueous vehicle.

- 3.4.2 The respondent's argument that document (13) discloses in a direct and unambiguous manner compositions falling within claim 1 of the main request does not apply, since, when taking example 6, where perfluorobutane is specifically used, it is required to perform an additional step (not disclosed in document (13) in combination with example 6) in order to achieve suspensions in a biocompatible aqueous vehicle. Moreover, in addition to that, one has previously to select or to adjust the means of the initial process in order to specifically obtain **expanded** microspheres having a diameter of less than 8 μm . These specific means are not disclosed in combination with example 6 in document (13).

Therefore, even if considering the general disclosure of document (13) which states that in order to obtain suitable contrast media the microspheres have "to be mixed in a solution in a substantially homogeneous suspension. This can be achieved by using thickening

and suspending agents." (page 9, lines 19-23), the selection of **expanded** microspheres such as those having the lowest diameter possible, combined with the selection of the specific expanding gas as perfluorobutane is not specifically disclosed in document (13). Indeed, the most preferred diameter value disclosed in document (13) is of about 50 microns.

- 3.4.3 In view of the above conclusions (cf. points 3.4.1-3.4.2) it is not necessary to discuss the appellant's arguments in relation to an alleged non-enabling disclosure of document (13).
- 3.4.4 None of the other cited documents was relevant for the novelty assessment of the claimed subject-matter. Hence the subject-matter of the main request meets the requirements of novelty (Article 54 EPC).
- 3.5 Inventive step
 - 3.5.1 Document (2) relates to "Enhancement Agents for Ultrasound: Fundamentals" and under the heading "Microbubbles", reviews the history, chemistry and clinical considerations of contrast media for ultrasound comprising gas-liquid emulsions containing microbubbles.
 - 3.5.2 Document (2) reports on the problems found in the background art, owing to the hand-injection technique, of providing microbubbles able to survive the passage through the capillary bed of the lung (end of right-hand column on page 683) and then expresses a prognosis in connection with more recent production processes: "The availability of preformed microbubbles

of reduced size (i.e., 4-7 microns) and increased stability **may** not only result in more reliable and improved echogenic enhancement of the right heart following their intravenous injection, but **may** also permit capillary transmission to allow noninvasive enhancement of ultrasonic studies of the left heart and/or the evaluation of tissue perfusion." (page 684, left column, lines 2-11)

- 3.5.3 Document (2) further states "The stability of gas bubbles in a solution is dependent on several factors including bubble size, the surface tension of the solution, and the nature of the gas (Butler BD, 1986)" (i.e. document (28)). (page 684, left-hand column, beginning of second paragraph)
- 3.5.4 Document (2) also states: "Reducing the surface tension of the aqueous solution that constitutes the external phase of a gas-liquid emulsion increases bubble stability. Hence, aqueous solutions of various proteinaceous, alcoholic, or carbohydrate surfactants (e.g. gelatin, albumin, glycerin, sorbitol, saccharin, dextrose, glucose) have been used to produce sonicated or hand-agitated microbubbles with increased resistance to vascular collapse". (page 684, left-hand column, third paragraph)
- 3.5.5 Furthermore, document (2) states "Preformed microbubbles of a specific size, quantity, and composition can be manufactured using gas injection techniques (Butler BD, 1986). (i.e. document (28)) Compared to gas bubbles produced by the previously described cavitation approaches (i.e., hand injection or agitation, sonication), **these** "precision" or

"calibrated" microbubbles offer advantages related to their known and controlled size range and concentration and the ability to vary their composition to increase stability... (*emphasis added*) For example, incorporation of an insoluble gas, such as nitrogen into the manufacturing process results in precision microbubbles that demonstrate a substantially longer intravascular bubble life than that observed with the use of air, carbon dioxide, oxygen, or other soluble gases (Butler BD, 1986). (*i.e. document (28)*) Such manipulation of gas or surfactant solution composition during manufacturing can result in "precision" microbubbles of virtually any desired size range or stability, thus ensuring reliable and reproducible echogenic enhancement for a variety of clinical applications". (page 684, right-hand column, first paragraph)

- 3.5.6 In the last paragraph under the heading "CLINICAL CONSIDERATIONS" document (2) states: "**Another approach** to microbubble enhancement of ultrasound studies involves the administration of agents that react in vivo to form bubbles. For example, materials (e.g. ether, perfluorocarbon) that are liquid at room temperature but that vaporize at body temperature may represent effective intravascular ultrasonic enhancement agents provided they are non toxic (Ziskin MC, et al, 1972)" (*i.e. document (18)*). (*emphasis added*)
- 3.5.7 Both parties considered document (2) to represent the closest prior art.

The board agrees with this choice insofar as the teaching of document (2) concerns contrast media for ultrasound comprising microbubbles of nitrogen.

In this context it has to be stated that the nitrogen microbubbles specifically disclosed in document (11) are too big (38, 80 and 140 microns) to be considered as the objective starting point (would not be suitable for passing through normal capillaries).

Therefore, in the light of the closest prior art the problem to be solved can be seen in the provision of contrast media comprising microbubbles of a biocompatible gas having increased persistence.

The solution relates to the choice of octafluoropropane (perfluoropropane) or decafluorobutane (perfluorobutane) as the biocompatible gas.

- 3.5.8 The question of whether the proposed solution actually solves the technical problem needs to be investigated.

The appellant cited the experiments in Lai's declaration (29) in order to demonstrate that the problem was plausibly solved.

The experimental results in Lai's declaration concern several comparisons between microbubbles of one of the biocompatible gases according to claim 1 and other gases, in particular nitrogen.

The results shown in Table 5 allow a direct comparison between microbubbles (4.6 μm mean diameter) of perfluorobutane and of nitrogen. The microbubbles of

perfluorobutane show a much longer (by a factor of almost 10x) persistence ($T_{1/2}$, sec) than those of nitrogen. The slightly bigger microbubbles of perfluoropropane (5.3 μm mean diameter) have an increased persistence of more than twice that of the microbubbles of nitrogen.

The data in Table 4 show that even if smaller microbubbles (6.9 μm mean diameter versus 9.8 μm) are taken, for which a shorter life is to be expected when compared to bigger microbubbles, the microbubbles of perfluoropropane show a much longer (by a factor of almost 5x) persistence ($T_{1/2}$, sec) than those comprising microbubbles of nitrogen.

The results in Table 3 show that the slightly bigger microbubbles of either perfluoropropane or perfluorobutane (9.3 or 9.5 μm mean diameter respectively) than nitrogen microbubbles (8.1 μm mean diameter) have a much longer persistence (by a factor of more than 10x and about 18x, respectively).

Therefore, these test results support the assumption that the choice of perfluoropropane or perfluorobutane as the biocompatible gas in the microbubbles, instead of nitrogen, is linked to a relevant increase in the persistence of the microbubbles. Moreover, the tests which cover a palette of variations in respect of the constitution of the microbubble compositions show that it is plausible for the positive influence in the persistence caused by the two specific gases chosen to be sufficiently important to be reflected in the contrast media encompassed by claim 1.

Accordingly, the board is convinced that in the light of the experiments shown in Lai's declaration (29), and discussed in some detail above, the problem has been plausibly solved.

- 3.5.9 It remains to be assessed whether the proposed solution appears obvious in the light of the cited prior art.

There was exhaustive discussion between the parties during the written proceedings as to whether or not there is a correlation between persistence and gas solubility (or its reverse).

However, even if the respondent's calculations (and corrected calculations) were to be considered as a valid demonstration that there is a certain correlation between persistence and the inverse of solubility for certain gases, the question to be answered is whether such a teaching was part of the prior art. Moreover, it also has to be answered whether there was a clear pointer in the prior art for choosing the gases of claim 1 as the solution to the problem.

Therefore, it has to be investigated which is the objective teaching of document (2) in this respect. It is a fact that document (2) teaches that one of the factors on which the stability of gas bubbles in a solution depends is the nature of the gas (cf. second paragraph on page 684, left-hand column, reproduced above).

It is also undeniable that the section of document (2) dedicated to microbubbles emphasises the usefulness of the manufacturing process of document (28) (which leads

to "calibrated" microbubbles) over previously used techniques such as sonification or in situ generation of bubbles by means of the hand-injection technique, for which the use of surfactants had proved to be necessary to increase resistance to vascular collapse of the bubbles. Indeed, it is within this context that document (2) reports that the incorporation **into the manufacturing process** of an insoluble gas such as nitrogen results in "precision microbubbles" with longer life than that observed with the **use** of air, carbon dioxide, oxygen or other soluble gases. This statement in document (2) is immediately followed by a reference to document (28) (cf. passage quoted in paragraph 3.5.5. above). Leaving aside the fact that document (2) leaves open to interpretation whether this assertion by the author was based on any particular self-performed experiments, or on other non-cited documents, the only technical information remaining is the actual content of document (28).

An inspection of document (28) leaves no doubt about the fact that the process disclosed therein concerns the use of two gases, namely a primary gas and a diluent gas: "The combination of carbon dioxide as the diluent gas and either nitrogen or oxygen as primary gas can be used in this system." (page 410, left-hand column, paragraph under the heading "Gases and Solutions"). Document (28) specifies how modification in the procedure can lead to different microbubble sizes and how certain combinations of gases influence the life of the bubbles: "By using gas mixtures of carbon dioxide and oxygen or other soluble gases, the life of the bubbles can be limited to a few minutes. Longer life would necessitate **the use of nitrogen as a**

primary gas. These variables can be altered using the technique described so as to customize the microbubbles according to each particular need." (page 411, left-hand column, end of first paragraph)

Hence, there is in document (28) no teaching whatsoever in respect of a possible correlation between the (inverse of) solubility and the persistence of microbubbles. Moreover, there is no hint or indication in document (28) of other insoluble gases or perfluorocarbons.

Therefore, the disputed passage in document (2) reproduced in point 3.5.5 above has to be read on its own merits as a statement of a general nature which merely confirms the assumption that the choice of gas plays a role in the stability of the microbubbles obtained by the manufacturing process of document (28). This passage, however, cannot be extrapolated as disclosing a teaching of general applicability.

As regards the passage reproduced in point 3.5.6 above, the following has been considered. Apart from the fact that the said passage only mentions perfluorocarbon as an example of a material that is liquid at room temperature (i.e. the perfluorocarbon gases are not concerned), the technique and the compositions involved are so different from those concerning compositions containing microbubbles in a biocompatible vehicle that the skilled person would not be able to extract any valuable teaching in its search for a solution to the problem. Moreover, the choice of the liquid agent is made on the basis of its volatility and no teaching is shown in relation to its solubility.

Inspection of further documents (3), (4) and (5), shows that none of them relates to the field of contrast media for ultrasound or includes any teaching in respect of microbubbles. Hence their contents cannot be considered to be useful for the skilled person when looking for a solution to the above-stated problem. The only valuable information they provide is that some perfluorocarbons are suitable for use in the medical field.

Document (15) relates to the production of hollow microcapsules having preferably as their core a water-immiscible oil which can be volatilised (page 1, third paragraph, and page 3, first paragraph). The products are double emulsions. Among the preferred volatile liquids, some perfluorocarbons liquids at room temperature are disclosed (page 3, example 4). Although document (15) relates to the preparation of echogenic materials, it does not contain any indication relating to either the choice of perfluoropropane or perfluorobutane or to any teaching about persistence and solubility.

The microbubble precursors disclosed in document (12) as being useful for measuring pressure by sonic signals preferably contain carbon dioxide gas trapped in a solid (column 3, line 46). "Freon" is an option mentioned among other gases in document (12) (column 6, line 66). However, it becomes evident from document (33) that neither perfluoropropane nor perfluorobutane are "freon" fluorocarbons. Moreover, document (12) gives no indication to the skilled person of how to solve the problem of an increased persistence.

Finally, document (11) does not disclose the use of perfluorocarbons and does not contain any teaching about persistence and solubility.

Consequently, none of the cited documents teaches the skilled person about a correlation between persistence and the *reciprocal* of solubility and none of the prior art documents gives any indication to the skilled person that he should choose perfluoropropane or perfluorobutane as the solution to the problem.

3.5.10 The respondent sought another definition of the technical problem in the light of a hindsight interpretation of the teaching of document (2), since document (2) does not teach that there is a correlation between the persistence of the microbubbles and the reverse of the solubility of the gas.

Additionally, the respondent did not contest the results of the tests shown in Lai's declaration (29), but merely that the tests could serve as a support for inventive step. However, the only requirement when applying the problem-solution approach is that the tests serve to show that the problem has been plausibly solved by the claimed subject-matter, and this is the case (cf. point 3.5.8 above).

With respect to the respondent's argument that the increase in persistence was to be expected by the skilled person, a distinction has to be drawn between an effect which can be explained after being proven to exist and an effect to be expected in the light of the

prior art. The first case relates to an ex post facto analysis with knowledge of the invention.

Furthermore, as shown by the established jurisprudence of the boards of appeal, there is no requirement for a patent in order to be granted to provide in vivo essays, since in vitro essays or laboratory tests may suffice for showing that the proposed solution has been plausibly solved. Moreover, the patent in suit contains an in vivo experiment which shows the suitability of the microbubble compositions for attaining both the right and the left ventricular chamber (cf. example 3).

Additionally, the argument that the Q-factor is no better than solubility for choosing the gas for the microbubbles is not relevant for the appreciation of the obviousness of the proposed solution, since such appreciation has to be made in the light of the objective contents of the available prior art. Moreover, document (34) concerns a table of several properties for certain perfluorocarbons chosen by the respondent after acquiring knowledge of the patent in suit. This document does belong to the prior art.

The board in principle agrees with the respondent's argument that the effects of increased persistence are not just dependent on the nature of the gas, but the tests provided by the appellant have shown that it is plausible that the two particular gases of the claim contribute in an essential and relevant manner to the relevant increase in persistence over a palette of variations of possible microbubble compositions. The respondent has not provided any experimental data to support any counterarguments.

Finally, the respondent cited decision T 176/84 in order to support its allegation that the skilled person would look at the contents of documents (3) to (5). These documents do not belong to the same technical field, but they also do not concern the same or related technical problems, i.e. persistence of microbubbles.

3.5.11 Therefore, in view of the above, the board concludes that the subject-matter claimed in the main (sole) request meets the requirements of Article 56 EPC.

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 in amended form on the basis of the main request filed in the oral proceedings and a description to be adapted.

The Registrar:

The Chairman:

A. Townend

U. Oswald