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Datasheet for the decision of 27 November 2014

Case Number: T 1772/11 - 3.3.07

Application Number: 04798566.8

Publication Number: 1694292

IPC: A61K9/12, A61P9/14

Language of the proceedings: EN

Title of invention:
THERAPEUTIC FOAM COMPRISING A SCLEROSING SOLUTION AND A LOW QUANTITY OF GASEOUS NITROGEN

Patent Proprietor:
BTG International Limited

Opponent:
CHEMISCHE FABRIK KREUSSLER & CO. GMBH

Headword:
THERAPEUTIC FOAM COMPRISING A SCLEROSING SOLUTION AND A LOW QUANTITY OF GASEOUS NITROGEN/BTG International Limited

Relevant legal provisions:
RPBA Art. 13
EPC Art. 84, 54, 56

Keyword:
Late-filed document - justification for late filing (no)
Late-filed document - justification for late filing (yes)
Claims - clarity (yes)
Novelty - (yes)
Inventive step - (yes)

Decisions cited:
T 0279/89

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 1772/11 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 27 November 2014

Appellant: (Patent Proprietor)	BTG International Limited 5 Fleet Place London EC4M 7RD (GB)
Representative:	BTG plc Intellectual Property Group 5 Fleet Place London EC4M 7RD (GB)
Respondent: (Opponent)	CHEMISCHE FABRIK KREUSSLER & CO. GMBH Rheingaustrasse 87-93 D-65203 Wiesbaden (DE)
Representative:	Von Kreisler Selting Werner - Partnerschaft von Patentanwälten und Rechtsanwälten mbB Deichmannhaus am Dom Bahnhofsvorplatz 1 50667 Köln (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 10 June 2011 revoking European patent No. 1694292 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	D. Boulois
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. European patent No. 1 694 292 B1 based on application No. 04 798 566.8 was granted on the basis of a set of 30 claims.

Independent claims 1 and 18 as granted read as follows:
"1. A foam comprising a liquid phase and a gas phase wherein the liquid phase comprises at least one sclerosing agent and the gas phase consists of at least one physiologically acceptable gas, physiologically acceptable gases being oxygen, carbon dioxide, nitrous oxide and helium, characterized in that gaseous nitrogen is present in the gas phase in an amount ranging from 0.0001% to 0.8% by volume."

"18. A canister, the contents of which consist of a liquid component and a gas component, maintained at above atmospheric pressure, wherein the liquid component comprises at least one sclerosing agent and the gas component consists of at least one physiologically acceptable gas, physiologically acceptable gas being oxygen, carbon dioxide, nitrous oxide and helium, characterized in that gaseous nitrogen present is present in the gas component in an amount ranging from 0. 0001% to 0.8% by volume."

II. An opposition was filed against the granted patent. The patent was opposed under Article 100(a), (b) and (c) EPC, on the grounds that its subject-matter lacked novelty and inventive step, that it was not sufficiently disclosed, and its subject-matter extended beyond the content of the application as filed.

III. The documents cited during the opposition proceedings included *inter alia* the following:

(1): WO 00/72821

IV. The appeal lies from the decision of the opposition division to revoke European patent application No 1 694 292. The decision was based on 3 sets of claims filed as main request and auxiliary requests 1 and 2 during the oral proceedings of 27 May 2010.

Independent claims 1 and 15 of the main request read as follows, difference(s) compared with claim 1 and 18 as granted shown in bold:
"1. A foam comprising a liquid phase and a gas phase wherein the liquid phase comprises at least one sclerosing agent and the gas phase **being** a physiologically acceptable gas **comprising a mixture of oxygen and carbon dioxide** characterized in that gaseous nitrogen is present in the gas phase in an amount ranging from **0.01%** to 0.8% by volume."

"15. A canister, the contents of which consist of a liquid component and a gas component, maintained at above atmospheric pressure, wherein the liquid component comprises at least one sclerosing agent and the gas component consists of at least one physiologically acceptable gas, physiologically acceptable gas **being a mixture of oxygen and carbon dioxide**, characterized in that gaseous nitrogen present is present in the gas component in an amount ranging from **0.01%** to 0.8% by volume."

The subject-matter of independent claims 1 and 15 of auxiliary request 1 further differed from the subject-matter of claim 1 and 15 of the main request by the specification of the gas composition, by the feature: "a *physiologically acceptable gas* ***which is a mixture of oxygen and 30-50% carbon dioxide***".

The subject-matter of independent claim 1 of auxiliary request 2 read as follows, difference(s) compared with claim 18 as granted shown in bold:
"1. A canister, the contents of which consist of a liquid component and a gas component, maintained at above atmospheric pressure, wherein the liquid component comprises at least one sclerosing agent and the gas component consists of a physiologically acceptable gas **which is a mixture of oxygen and 30-50% carbon dioxide**, characterized in that gaseous nitrogen present is present in the gas component in an amount ranging from **0.01%** to 0.8% by volume, **the canister further comprising a foam generating element with at least one aperture formed therein, the at least one aperture having maximum dimensions ranging from 3 to 10 micron**".

V. According to the decision under appeal, the subject-matter of claim 1 of the main request was not novel; the claimed range of nitrogen of 0.01%-0.8% was not considered a novel selection over the ranges disclosed in document (1).

As regards the first auxiliary request, document (1) did not disclose the newly introduced feature in auxiliary request 1, namely of having 30-50% carbon dioxide.
Document (1) was seen as the closest prior art. The difference was the gas phase composition of the foam.
The problem to be solved was the further reduction of the risk of embolism and reduction of bubble size and numbers.
Although the opposition division concluded that the comparative tests did not demonstrate any effect, it

was argued that even if they did, the solution to the problem of further reducing the risk for embolism and reducing bubble size and number was anyway obvious; the effects observed are bonus effects which result from an obvious way of working for the skilled person.

As regards the second auxiliary request, the difference with the teaching of document (1) was the gas content and the aperture size. The problem to be solved was the improvement of the foam stability in case of low nitrogen content.
Document (1) proposed to use foam generating elements of 5-25 microns, overlapping with the claimed dimensions of 3-10 microns, and indicated that the foam generating elements were used to produce stable foams.
It was concluded to a lack of inventive step over document (1).

VI. The proprietor (appellant) filed an appeal against said decision.
With the statement of grounds of appeal, the appellant submitted a main request and auxiliary requests 1-3.
Annexes I-VII were also submitted.

VII. With the letter dated 22 February 2012, the appellant submitted experimental evidence.

VIII. With the letter dated 30 September 2014, the appellant submitted a new main request and auxiliary requests 1-4.
It submitted also following documents:
(13): Forlee et al., J. Vascular Surg., 2006, 43(1), 162-164: “Stroke after varicose vein foam injection sclerotherapy”
(14): Eckmann/Forlee, J. Vascular Surg., 2006, 44(1), 225.

IX. With a letter dated 17 October 2014, the appellant submitted a new document:
(28): Breu et al, "European Consensus Meeting on Foam Sclerotherapy, April 4-6, 2003, Tegrensee, Germayn", Dermatol. Surg. 30:5, May 2004

X. A Board's communication dated 5 November 2014 was sent to the parties.

XI. With a letter dated 18 November 2014, the appellant withdrew the main request filed previously with letter dated 30 September 2014. The first auxiliary request filed with letter dated 30 September constituted the new main request.

The unique independent claim 1 of the new main request read as follows, difference(s) compared with claim 1 as granted shown in bold:
"1. A foam comprising a liquid phase and a gas phase wherein the liquid phase comprises at least one sclerosing agent and the gas phase consists of a physiologically acceptable gas **which is a mixture of oxygen and 30-50% carbon dioxide**;
characterized in that gaseous nitrogen is present in the gas phase in an amount ranging from **0.01%** to 0.8% by volume."

XII. Oral proceedings took place on 27 November 2014.

XIII. The arguments of the appellant may be summarized as follows:

Documents (13), (14) and (28) were common general knowledge documents and should be admitted into the

proceedings, since they served to support the arguments brought forward during the proceedings.
The experiments filed with letter dated 22 February 2012 were relevant, since they related to a question raised during the opposition phase. They were filed to show that the claimed subject-matter was novel over the teaching of document (1), and thus supported statements in the contested patent over document (1).

As regards the objections of unclarity raised by the respondent, the appellant considered the wording of claim 1 as clear.

As regards novelty, the passage on page 9 of document (1) could not be considered as relevant for novelty, as it concerned the source gas and not the final content of the gas in the microfoam. It was not possible to infer the nitrogen level in the final product from the nitrogen level in the source gases.
Moreover, the product of document (1) had to be the inevitable result of the process used. The experiments filed with letter dated 22 February 2012 showed that the nitrogen content in examples 1 and 2 of document (1) was much higher than the claimed range.
It was not possible to combine parts of the description with the examples, and there was no enabling disclosure in document (1) to arrive to the claimed range of nitrogen, since the processes of preparation were different in document (1) from the process used in the contested patent.

As regards inventive step, the respondent used information derivable only from the contested patent, instead of starting from the closest state of the art and using common general knowledge.

Document (1) did not provide any basis for the problem of controlling the nitrogen levels in the microfoam, and this problem was not known from the common general knowledge.
Document (1) suggested that large volumes of nitrogen must be avoided, hence the volume of injection had to be diminished, and thus the volume of gas injected has to diminished.
The real problem was that blood was already saturated with nitrogen and thus there were three sources of nitrogen which could contaminate the microfoam:
- the source gas
- a contamination by air during the preparation of the microfoam
- a diffusion of nitrogen from the blood into the bubbles of the injected microfoam.
These issues were not known from document (1).

The difference between the claimed subject-matter of claim 1 and the teaching of document (1) was the amount of nitrogen.
The effect provided by this difference was that gas bubbles shrank quicker in the blood, in view of the solubilization of carbon dioxide and oxygen and the low amount of nitrogen. The amount of nitrogen was sufficient to keep the size of bubbles low. The number of incidence of side effects dropped dramatically with the specific claimed gas composition.
Moreover, the claimed product was not achievable by the process disclosed in the prior art (1), and nothing was suggested in this document over a modification of the process.

XIV. The arguments of the respondent may be summarized as follows:

Documents (13), (214) and (28) should not be admitted into the proceedings, because they were late filed, and *prima facie* not relevant.

The experiments filed with letter dated 22 February 2012 should not be admitted into the proceedings, since there were not relevant and they did not show any effect. Moreover, the experiments were deficient, since there was lacking information on several experimental parameters, such as an information on the material used, on the quality of the source gas and how the gas quantity was measured, and under which conditions the experiments were performed.
These experiments should have been provided before the opposition division.

The feature "*a mixture of oxygen and 30-50% carbon dioxide*" in connection with the feature "*a physiologically acceptable gas*" in claim 1 of the main request did not render clear that the claimed gas mixture consisted exclusively in oxygen and carbon dioxide. The corresponding amount of 70-50% of oxygen was indeed not claimed, and it was thus unclear whether the claimed gas mixture might comprise other physiologically acceptable gases. This unclarity was reinforced by the presence of the further term in claim 1 of the main request, namely "*characterised in that gaseous nitrogen is present in the gas phase in an amount ranging from 0.01% to 0.8% by volume*" in claim 1.

As regards novelty, the description of document (1) on page 9, provided the disclosure of gas compositions

comprising oxygen, carbon dioxide and nitrogen. It disclosed in particular a gas composition made from oxygen and carbon dioxide.
In particular, the passage also mentioned a gas composition of 99% of oxygen and 1% of other gases.
The respondent agreed with the opposition division that the skilled person arrived by calculation to a final nitrogen content of 0 to 0.97% in this gas composition.
The claimed range of nitrogen of 0.01%-0.8% was not considered a novel selection over the ranges disclosed in document (1), according to the novelty criteria of decision T279/89. The claimed range of 0.01 to 0.8% of nitrogen could thus not be considered novel over this disclosure.
Example 1 of document (1) showed a composition having the claimed amounts of carbon dioxide and oxygen, and the amounts of nitrogen had to be 0% in this example, in the absence of any counter indication. The experiments provided by the appellant could not prove that the concentration were not really less than 1%, especially given the imprecision of the parameters used in these experiments, such as the nature of the canister, the purity of the source gases, and the experimental conditions.
Document (1) was about avoiding any trace of nitrogen in the microfoams, and the skilled person reading this document would have done everything to avoid the presence of nitrogen.

As regards inventive step, the experiments dated 22 February 2012 could not serve as a comparison basis, since the composition comprising 7% of nitrogen used as a comparative example in these experiments did not correspond to the compositions disclosed in document(1).

The problem in document (1) was clearly to diminish the quantity of nitrogen to be delivered in the microfoam (see page 3, lines 6-9 and page 9, line 5)).
The problem to be solved was the reduction of the quantity of nitrogen in the microfoam, and the solution to this problem was obvious in view of the teaching of document (1). The skilled person would indeed try to reach a level of 0% of nitrogen, as suggested by document (1). He would in particular combine the teaching of examples 1 and 2 of said document, and use the particular process used in example 2 and adapt it to the composition of example 1. The pre-purging step used in example 2 allows indeed a strong reduction of the nitrogen level in the composition.

XV. Requests

The appellant (patent proprietor) requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or, in the alternative, of auxiliary requests 1 to 3 as identified in the letter of 18 November 2014 (the main request corresponding to the first auxiliary request filed with the letter of 30 September 2014).
It further requested that experiments filed with the letter of 22 February 2012 and documents (13), (14) filed with the letter dated 30 September 2014 and document (28) filed with the letter of 17 October 2014 be admitted into the proceedings.

The respondent (opponent 1) requested that the appeal be dismissed.
It further requested that the experiments and documents above mentioned not be admitted into the proceedings.

Reasons for the Decision

1. Admission of documents 13), (14), (28) and of the experiments filed with letter dated 22 February 2012 into the proceedings

1.1 Documents (13), (14) and (28) were filed by the appellant at a late stage in the appeal proceedings and are documents dealing with certain aspects affecting the general common knowledge of the technical field of the contested patent. They do not provide new information and only serve to illustrate the common general knowledge and arguments brought in the proceedings.
The teaching of these documents does thus not present any fundamental importance and is not relevant for the decision.
Documents (13), (14) and (28) are therefore not admitted into the proceedings.

1.2 The experiments of letter dated 22 February 2012 have been filed by the appellant a few months after the statement of grounds of appeal, thus at an early stage of the appeal proceedings. They have been filed in response to questions raised during the opposition proceedings which constituted the basis for the decision of the opposition division. The experiments reproduce indeed the teaching of examples 1 and 2 of document (1) and support important statements of the appellant regarding the teaching of the prior art document (1).
These questions are still pending in the appeal phase, and are possibly relevant for the decision.
The experiments of letter dated 22 February 2012 are therefore admitted into the proceedings.

2. Main request

2.1 Article 84 EPC

The respondent has raised a clarity objection against the term "*...and the gas phase consists of a physiologically acceptable gas which is a mixture of oxygen and 30-50% carbon dioxide*" in claim 1 of the main request.
This feature was not present in the granted claims and is thus open to an objection under Article 84 EPC.

The objection under Article 84 EPC is however unfounded, since the whole claimed feature "*...and the gas phase consists of a physiologically acceptable gas which is a mixture of oxygen and 30-50% carbon dioxide, characterised in that gaseous nitrogen is present in the gas phase in an amount ranging from 0.01% to 0.8% by volume*" in claim 1 of the main request does not present any unclarity or inconsistency.
The term "*consists of*" in fact strictly limits the claimed gas phase to a single physiological gas, which gas comprises several components, namely oxygen, carbon dioxide and nitrogen.

The main request meets the requirements of Article 84 EPC.

2.2 Novelty

2.2.1 Document (1) relates to a composition comprising a sclerosing material, in the form of a dispersion of a gas phase in a liquid in the form of a microfoam. This document does not however directly and unambiguously disclose that nitrogen is present in the gas phase of

the microfoam in an amount ranging from 0.01% to 0.8% by volume and that said amount of nitrogen is inevitably present in the microfoam:

(a) The composition of the gas used in the microfoam compositions of document (1) is given on page 9 of the description (see page 9, lines 1-15), which states that the dispersible gas comprises a large proportion of carbon dioxide and/or oxygen, preferably a mixture of 30-50% of carbon dioxide with oxygen and a "*minor proportion only of nitrogen being preferred*", and even more preferably "*50% vol/vol or more oxygen, the remainder being carbon dioxide, or carbon dioxide, nitrogen and trace gases in the proportion found in atmospheric air*".
This passage not only fails to specify what is meant by a "*minor proportion*" of nitrogen but also relates to the amount of nitrogen in the composition of the source gas, and not to that in the final processed gas phase of the microfoam. The presence of a "*minor proportion*" of nitrogen in the source gas cannot be extrapolated to the final gas phase of the microfoam, particularly in view of the potential for ingress of air or nitrogen during the preparation of the foam. Said passage is therefore not relevant for the question of novelty.

(b) Example 1 of document (1) is the only example showing a microfoam comprising a gas phase made from a mixture. This example discloses a microfoam made by charging half full a canister with a solution of sclerosing agent and pressurising it to 3 atmospheres with a 50:50 mixture of oxygen and carbon dioxide. The example is silent as regards the concentration of nitrogen in the final microfoam.

The experiments filed with the letter dated 22 February 2012 reproduced the teaching of example 1 with regard to the level of nitrogen in the microfoam of examples 1 and 2, and showed that the process used in example 1 led to a final content of nitrogen in the microfoam of around 25% by volume, i.e. outside the claimed range.
Said experiments demonstrated also that the more drastic process used in example 2 of document (1), which included a pre-purging step of the inner chamber of the canister comprising the sclerosing solution with 100% of oxygen, would still lead to a final microfoam with an amount of nitrogen outside the claimed range, since it comprises around 97.5% by volume of oxygen and 2.5% by volume of nitrogen.
These experiments show that a microfoam comprising an amount of nitrogen in the range from 0.01% to 0.8% by volume cannot be produced following the teaching and process used in document (1).

2.2.2 As to the objections of the respondent regarding the imprecision of the conditions under which the experiments were performed, such as the absence of information about the purity grade of the gases used in the tests or about the nature of the canister, purportedly leading the experiments to lack credibility and reproducibility, they fail to convince the Board.

The experiments reproduce reliably the processes of manufacture of a microfoam disclosed in examples 1 and 2 of document (1). The process steps of examples 1 and 2 do not present any particular complexity and are thus easily reproducible, and all equipment or material used in the examples appears to be standard. As regards the gases used, the Board has no doubt that they were

inevitably of pharmaceutical grade, namely having a high degree of purity.
The Board therefore sees no reason to doubt the credibility of the experiments. The respondent had the opportunity to demonstrate the contrary by providing counter tests according to examples 1 or 2.

Moreover, the objections of the respondent that the claimed range of nitrogen of 0.01%-0.8% was not considered a novel selection over the range of 0 to 0.97% of nitrogen disclosed in document (1) is not relevant, since the passage in the description of document (1) mentioning the presence of a theoretical amount of 1% of nitrogen was linked to the further presence of 99% of oxygen, and not to a blend of carbon dioxide and oxygen.

2.2.3 Consequently, the subject-matter of claim 1 of the main request is novel.

2.3 Inventive step

2.3.1 The invention relates to a foam comprising a sclerosing solution, and is suitable for use in the treatment of various medical conditions involving blood vessels (see par. [0001]).
Recent studies have confirmed that air foams cause some complications for certain patient groups. In particular, bubbles have been observed on the left side of the heart in a patient who was subsequently shown to have a minor septal defect, or patient foramen ovale ("PFO"), i.e. a hole in the heart. This is significant because, once on the left side of the circulation system, the bubbles can progress to the brain, where they may cause micro-infarcts (see EP 1 694 292 B1 par. [0028]-[0032]). Screening all patients for even the

most minor PFO is not feasible for an elective procedure such as varicose vein treatment and may not even be possible, since the techniques required are fairly sophisticated and possibly quite invasive.
The present invention thus aims to produce a safe foam product suitable for administration to patients without the need for lengthy PFO screening methodology, especially in the treatment of varicosis in the largest veins, such as the saphenous veins, which necessitates a large amount of microfoam (see par. [0009], [0024]).

2.3.2 Document (1) was seen as the closest prior art by the appellant and the respondent.

Document (1) relates to the generation of an injectable microfoam comprising a sclerosing material. It specifies that large volumes of nitrogen should not be introduced into patients through said foam, since gas embolism with nitrogen remains a possibility (see page 3, lines 6-9).
The preferred gas phase comprises a major proportion of carbon dioxide and/or oxygen, preferably a mixture of 30-50% of carbon dioxide with oxygen and a "*minor proportion only of nitrogen being preferred*", and even more preferably "*50% vol/vol or more oxygen, the remainder being carbon dioxide, or carbon dioxide, nitrogen and trace gases in the proportion found in atmospheric air*" (see page 9, lines 1-16).

Example 1 of document (1) is of particular relevance and shows the preparation of a microfoam comprising a solution of sclerosing agent pressurised to 3 atmospheres with a 50:50 mix of carbon dioxide and oxygen. The repetition of example 1 in the experiments filed with the letter dated 22 February 2012 showed a final amount of around 25.0% of nitrogen.

The experiments filed with the letter dated 22 February 2012 show that the process used in example 2 of document (1), which includes a pre-purging step of the inner chamber of the canister comprising the sclerosing solution with 100% of oxygen for 1 minute, leads to a final microfoam composition comprising 97.5% by volume of oxygen and 2.5% by volume of nitrogen. Document (1), in particular its example (1), therefore does not show microfoam compositions made from carbon dioxide and oxygen in the gas phase, in particular with 0.01% to 0.8% by volume of nitrogen in the gas phase.

2.3.3 According to the patent, the problem to be solved is the provision of a foam that can be injected in relatively large volumes with reduced risks of bubbles entering the arterial circulation and causing emboli, thus providing a higher level of safety.

2.3.4 The solution to this problem is a composition according to claim 1, namely a foam comprising a liquid phase comprising a sclerosing agent and a gas phase consisting of a mixture of oxygen and 30-50% carbon dioxide wherein in particular gaseous nitrogen is present in the gas phase in an amount ranging from 0.01% to 0.8% by volume.

2.3.5 Technical arguments have been put forward by the appellant to demonstrate the beneficial effects.

According to the appellant, the side-effects issue is the size and number of residual bubbles entering the arterial circulation after the treatment. The claimed foam composition produces fewer residual gas bubbles after the sclerosis causes the vein to spasm, and these residual gas bubbles are smaller in size, number and duration.

The foam is indeed injected into a vein such as to displace the blood and cause the vein to spasm, after which any remaining bubbles of the foam must disperse. It appears that the bubbles encountered after the vein has spasmed may change in size. These residual bubbles may enter the arterial circulation and cause unwanted side-effects such as heart or brain emboli. It is the size and the number of residual bubbles entering circulation after treatment which may cause the side-effects.

The gas mixture used to create the bubbles of the microfoam, and in particular the amounts of carbon dioxide and nitrogen in the mixture, is a crucial factor in the existence of these residual bubbles and the consequent formation of emboli. Another important factor is the starting size of the bubbles.
Bubbles made from a high proportion of oxygen and carbon dioxide and a low proportion of nitrogen first gradually decrease in size, since carbon dioxide is highly soluble in the aqueous part of the blood. The resulting bubble following carbon dioxide loss will have a reduced diameter and an increased internal pressure Pi. This internal pressure Pi is indeed strongly influenced by the bubble size: the smaller the bubble, the higher the Pi is likely to be. If Pi is greater than the gas pressure in the blood Po, oxygen also slowly passes into solution or is taken up by haemoglobin.
All that then remains in the bubbles is the relatively insoluble nitrogen, which strongly influences the size of the residual bubble; the amount of nitrogen is sufficient to keep said bubble size low. Nitrogen will gradually be lost until Pi increases to a level where the bubbles break down completely. This breaking down is dependent on the amount of nitrogen.

The fast reduction in bubble size through carbon dioxide dissolution means that the pressure within the bubbles rapidly achieves a level that counters a nitrogen enrichment from the blood, and the bubble is sufficiently small to completely disperse before it can form emboli after passage into arterial circulation. It is thus essential that the amount of nitrogen in the initial foam be very low, and keeping the nitrogen level in the claimed range allows the production of a foam in which the clinical effects of the residual bubbles are effectively eliminated. A low amount of nitrogen allows the bubble pressure Pi to stay higher than the gas pressure in the blood Po.

If nitrogen is present in a greater amount, the bubbles do not decrease in size and may even get bigger, causing a decrease in the internal pressure Pi. The consequence is that external nitrogen may enter from the nitrogen-saturated blood down a pressure gradient into the gas environment of the bubble. This addition of external nitrogen increases further the diameter of the gas bubble, and causes the side effects, in particular emboli.

Thus the presence of low amounts of nitrogen in the gas phase, from which the bubble originate when the microfoam is injected, has a significant technical effect on safety by reducing the diameter, occurrence and number of the residual bubbles.

This technical argumentation renders a beneficial effect credible.

The credibility of these technical arguments is reinforced by the comparison, provided by the appellant in its statement of grounds of appeal, made between a

composition comprising 7% of nitrogen in the gas phase and a composition according to the invention, i.e. comprising 0.01 to 0.8% of nitrogen. Though this experiment cannot serve as a basis of comparison between the teaching of document (1) and the claimed invention in view of the 7% amount of nitrogen in the comparative composition compared to the 25% of example 1 of document (1), it shows nevertheless that a decrease in the amount of nitrogen in a gas phase made from oxygen and carbon dioxide involves a significant decrease in the mean bubble volume (0.20 nl instead of 0.53 nl) and in the number of visible bubbles (2 instead of 27).

The Board is thus convinced that the claimed composition presents an improvement in safety over the closest prior-art compositions, so that the problem is credibly solved.

2.3.6 It remains to determine whether the solution was obvious to the person skilled in the art.

Document (1) addresses in general the problem of making foams for sclerotherapy using physiologically acceptable blood-dispersible gases, and mentions that large volumes of nitrogen should not be introduced into patients through said foam, since gas embolism with nitrogen remains a possibility (page 3, lines 6-9). The measures envisaged in document (1) only relate to the initial composition of the gas phase, which should comprise only a small proportion of nitrogen (page 9, lines 1-15).
Document (1) is in particular silent about the possible contamination of nitrogen by air during the manufacturing process, or about nitrogen diffusing from the blood into the residual bubbles. Nor is there any

teaching in document (1) about the necessity to closely control the process of foam production in order to minimise the effect of air contamination.
The contested patent indeed provides a specific process of preparation of the foams. As nitrogen from air is difficult to exclude totally from a foam, due to the environment in which the foam is prepared (see par. [0020]-[0021]), a small volume of nitrogen in the microfoam is obtained in the contested patent by a process involving multiple oxygen pressurising and depressurising cycles of the canister (see par. [0143], [0171]-[0173]).

For comparison purposes, the experiments filed with the letter dated 22 February 2012 demonstrated that the most drastic process shown in document (1), namely that of example 2, reached a final proportion of nitrogen of 2.5%, thus outside the claimed range. As regards this specific example, it is specified that using a foam with a gas phase consisting of oxygen, irrespective of whether contaminant nitrogen is present, would result in the formation of residual bubbles of significant diameter, in view of the low solubility of oxygen. Moreover, this amount of 2.5% of nitrogen is still above the claimed range. A combination between the teaching of examples 1 and 2 of document (1) would therefore not lead to the claimed solution.

If any problem due to the use of the foam of example 1 of document (1) were perceived, the most obvious solution for the skilled person would have been to look for another solution than the claimed solution, such as reducing the amount of foam injected in each treatment. Document (1) does not mention or suggest adjusting the foam composition, nor that a proper gas composition can solve the problem.

The solution according to the subject-matter of claim 1 is therefore not obvious. The same applies to the dependent claims.

2.3.7 The conditions of Article 56 EPC are met by the main request.

Order

For these reasons it is decided that:

- The decision under appeal is set aside
- The case is remitted to the department of first instance with the order to maintain the patent on the basis of the main request corresponding to the first auxiliary request filed with the letter of 30 September 2014 and a description to be adapted thereto.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated