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Process for preparing a pharmaceutical formulation of contrast agents

Patent Proprietor:
GUERBET

Opponents:
Agfa HealthCare N.V.
Bayer Pharma Aktiengesellschaft
Sanochemia Pharmazeutika AG

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Case Number: T 1820/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 8 November 2022

Appellant: (Patent Proprietor)	GUERBET 15, Rue des Vanesses 93420 Villepinte (FR)
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Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 23 April 2019 revoking European patent No. 2799089 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	A. Jimenez

Summary of Facts and Submissions

I. The appeal was filed by the patent proprietor (appellant) against the decision of the opposition division to revoke European patent 2 799 089 (hereinafter "the patent").

II. The patent had been granted with 12 claims on the basis of a divisional application. Claim 1 of the patent read as follows:

"Process for preparing a liquid pharmaceutical formulation containing a complex of macrocyclic chelate with a lanthanide and a mol/mol amount of free macrocyclic chelate of between 0.002% and 0.4%, said process comprising the following successive steps:

b) preparation of a liquid pharmaceutical composition containing the complex of macrocyclic chelate with a lanthanide, free macrocyclic chelate that is not under the form of an excipient X[X',L] in which L is the macrocyclic chelate and X and X' are a metal ion, in particular chosen independently from calcium, sodium, zinc and magnesium, and/or free lanthanide,
by mixing a solution of free DOTA as the free macrocyclic chelate and of free gadolinium as the free lanthanide, so as to obtain complexation of the lanthanide by the macrocyclic chelate,
the amounts of free macrocyclic chelate and of free lanthanide being such that all the lanthanide is complexed and that $C_{ch\ l} > C_{t\ ch\ l}$, with $C_{ch\ l}$ representing the concentration of free macrocyclic chelate and $C_{t\ ch\ l}$ representing the target concentration of the free macrocyclic chelate in

the final liquid pharmaceutical formulation, $C_{t\ ch\ l}$ being selected in the range of between 0.002 % and 0.4 % mol/mol;
c) measurement in the pharmaceutical formulation obtained in step b) of $C_{ch\ l}$, the concentration of free lanthanide $C_{lan\ l}$ being equal to 0;
d) adjustment of $C_{ch\ l}$ and of $C_{lan\ l}$ by eliminating free macrocyclic chelate from and/or by adding free lanthanide to and/or by modifying the pH of the formulation obtained in step b) so as to obtain $C_{ch\ l} = C_{t\ ch\ l}$ and $C_{lan\ l} = 0$,
wherein $C_{t\ ch\ l}$ is the target concentration of the free macrocyclic chelate in the final liquid pharmaceutical formulation and is selected in the range of between 0.002 % and 0.4 % mol/mol,
wherein the amount of free macrocyclic chelate in the final liquid pharmaceutical formulation corresponds to the proportion of free macrocyclic chelate relative to amount of complexed macrocyclic chelate DOTA-Gd in the final liquid pharmaceutical formulation in mol/mol,
wherein the macrocyclic chelate is DOTA and the lanthanide is gadolinium."

III. Three oppositions had been filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the (earlier) application as filed.

IV. The opposition division's decision to revoke the patent was based on:
- the patent as granted as the main request,
- auxiliary requests 1-5 submitted during the oral proceedings before the opposition division,

- auxiliary requests 6-10 filed (as auxiliary requests 2-4, 6 and 7) on 27 October 2017, and
- auxiliary requests 11-14 filed (as auxiliary requests 8-11) on 5 December 2018.

V. The decision cited the following documents among others:

D1: "DOTAREM® 0.5 mmol/ml, solution for injection vials, Pre-Filled Syringes", 1 June 2007, pages 1-4, XP003028305, URL:http://www.health.gov.il/units/pharmacy/trufotialonim/3768.pdf
D2: Aime et al. *Inorg. Chem.* 1992, 31, 12, 2422-2428
D7: US 5,650,133
D8: Gries, *Topics in Current Chemistry*, vol 221, 1-24 (2002)
D13: Guidance for Industry PAT, FDA, 2004
D30: US 5,049,667
D32: Data submitted by patentee on September 3, 2015
D37: Repetition of Example 2 (switching the role of Gd and DOTA) at the industrial scale
D51: Declaration by Caroline Robic and Monique Sabatou illustrating step d) carried out by pH modification
D56: Experimental data submitted by O2 on 5 December 2018
D57: WHO Guidelines for GMP dated 2007
D58: G.L. David et al. *Analytical Chemistry* 2001, p 5
D59: Tweedle, M.F. et al. *Magnetic Resonance Imaging*, Vol. 9, pp. 409-415, 1991

VI. The opposition division considered that the main request and auxiliary request 1 did not comply respectively with Article 83 and Rule 80 EPC. It further decided that auxiliary requests 2, 3 and 5-14 did not comply with Article 56 EPC.

Starting from D1 as closest prior art, the process of claim 1 of auxiliary request 2 differed by steps b) mixing DOTA and Gd, c) measuring free DOTA and d) adjusting free DOTA concentration. The technical problem was the provision of a safe, reliable and accurate process suitable for industrial scale production of a pharmaceutical composition according to D1. The claimed solution was obvious in particular in light of the common general knowledge as reflected by D8. Auxiliary request 4 was not admitted into the proceedings.

VII. With the statement setting out the grounds of appeal, the appellant defended its case on the basis of the patent as granted as the main request, and filed main request a1, main request a2, auxiliary requests 1-13, main request b and auxiliary request 1bis-13bis.

The main requests a1 and a2 differed from the main request in that step d) of claim 1 was respectively amended as follows: "and~~/or~~ optionally by modifying the pH" or "and~~/or~~ optionally ~~by~~ modifying the pH" (additions and ~~deletions~~ emphasized by the Board).

Auxiliary requests 2-4 differed from the main request in that step b) of claim 1 was respectively amended as follows:
- auxiliary request 2: "the added amounts of free macrocyclic chelate and of free lanthanide [...]";
- auxiliary request 3: "the amounts of free macrocyclic chelate and of free lanthanide added are such that the free macrocyclic chelate / free lanthanide mol/mol ratio is between 1.001 and 1.3";
- auxiliary request 4: "wherein the complexation reaction of step b) is performed by using a difference between the stoichiometric proportions and the amounts

of free lanthanide and of free macrocyclic chelate added in step b),"

Auxiliary requests 1 and 5-7 corresponded to the main request and auxiliary requests 2-4, wherein claim 10 was deleted.

Auxiliary requests 8 and 9 respectively differed from the main request in that claim 1 mandated that the formulation be injectable or that, in step b), Gd be added as Gd_2O_3.

Claim 1 of auxiliary requested 10 additionally specified that the measurement step c) be performed "at pH 7".

Claim 1 of auxiliary request 11 differed from claim 1 of the main request in that it related to a process "for preparing an industrial amount of a liquid pharmaceutical formulation".

Auxiliary request 12 differed from the main request in that the adjustment step d) of claim 1 additionally comprised "at the end a step of adjustment of the pH and of the volume with meglumine", and in that "the pharmaceutical formulation is a pharmaceutical formulation of the mecglumine salt of a DOTA-gadolinium complex".

In claim 1 of auxiliary request 13, step d) was limited as follows: "by eliminating the appropriate amount of free macrocyclic chelate from ~~and/or by adding free lanthanide to~~".

The main request b and auxiliary requests 1bis-13bis corresponded to the main request and auxiliary requests

1-13 wherein the alternative "and/or by modifying the pH" in step d) of claim 1 was deleted.

VIII. The following documents were submitted during the appeal proceedings:

D60: Declaration of Pr Guillon

D61: Declaration by Monique Sabatou

D62: Hernandez G. et al., *Proton Magnetic Relaxation Dispersion in Aqueous Glycerol Solutions of $Gd(DTPA)^{2-}$ and $Gd(DOTA)^{-}$*, Inorg. Chem. 1990, 29, 5109-5113.

IX. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.

X. Oral proceedings were held before the Board. During the oral proceedings, the appellant withdrew auxiliary requests 1 and 4-7.

XI. The appellant requests that the decision under appeal be set aside and that the patent be maintained as granted (main request), or, alternatively, that the patent be maintained on the basis of one of the main request a1, main request a2, auxiliary requests 2, 3 or 8-13, main request b or auxiliary request 1bis-13bis.

The appellant further requests that neither D59 nor D62 be admitted into the proceedings.

XII. Opponent 1 (respondent 1) and opponent 2 (respondent 2) both request that the appeal be dismissed.

Respondent 1 further requests that auxiliary requests 11-13 not be admitted into the proceedings.

Respondent 2 additionally requests that the main request a2 and auxiliary requests 2, 1bis-5bis, 8bis, 9bis, 11bis and 13bis, as well as documents D60 and D61, not be admitted into the proceedings. Respondent 2 also requests that D59 be admitted in case the appellant would dispute the fact that the one skilled in the art knew that DOTA is hygroscopic.

Opponent 3 (respondent 3) made no request.

XIII. The appellant's arguments can be summarised as follows:

(a) Admittance of D59-D62

Both D60 and D61 should be admitted, because D60 was highly relevant to the question of inventive step and because D61 was submitted in reply to the reasoning in the appealed decision. Both D59 and D62 were late-filed and not *prima facie* pertinent, and were not to be admitted.

(b) Main request, inventive step

The problem underlying the invention was the preparation of a liquid pharmaceutical formulation containing DOTA-Gd and 0.002-0.4% free DOTA reliably and reproducibly, and in a time and cost efficient manner, in particular at industrial scale. The patent addressed the problem of unpredictable deviations in the final concentrations due, among other factors, to the uncertainty of weighing and the variability of the hygroscopic characteristics of DOTA.

- Interpretation of claim 1

Step (b) of claim 1 consisted in mixing free DOTA and free Gd in amounts such that there was an initial deliberate excess amount of free DOTA beyond the targeted excess, i.e. it did not cover the use of stoichiometric amounts. The complexation reaction was not necessarily complete. The subsequent quantitative measurement step (c) was carried out under conditions mimicking what occurred in the reactor upon completion of the reaction. Finally, an adjustment step (d) was carried out to obtain the target pharmaceutical formulation. The claimed process was a one-pot preparation process wherein steps b), c) and d) were inextricably carried out together.

- Inventive step

Starting from the closest prior art D1, the problem was the provision of a safe, reliable, and accurate process suitable for industrial scale production of a pharmaceutical formulation according to D1 in a cost and time efficient manner.

The reaction between DOTA and Gd was unpredictable, as shown in D56 and D60. However, the skilled person was not aware of this unpredictability before the filing date, and would have implemented the preparation method by first preparing DOTA-Gd using stoichiometric amounts and then formulating the complex by adding the desired excess of free DOTA, as in D8. D2 or/and D7 would not have been consulted by a skilled person seeking to prepare the product of D1, as they did not relate to DOTA and aimed at the preparation of the complex in solid form. Hence the criteria of inventive step were met.

(c) Auxiliary requests, inventive step

In auxiliary request 2, the word "added" introduced in claim 1 clarified that the amounts mentioned in step b) related to the amounts of free DOTA and free Gd added in the complexation step.

The limitation in claim 1 of auxiliary request 3 to amounts of free DOTA and free Gd added in a mol/mol ratio of between 1.001 and 1.3 made it clear that there was an initial free DOTA excess. This limitation, and likewise the requirement in auxiliary request 4 that the amounts differ from the stoichiometric proportions, excluded pseudo-stoichiometric processes.

The limitation in claim 1 of auxiliary request 8 that the final product be injectable entailed that a precise measurement of the final concentrations was required.

As a result of the feature of claim 1 of auxiliary request 11 relating to an "industrial scale", the teaching of documents D2, D7 and D30 was no longer relevant to the invention.

In claim 1 of auxiliary request 12, the additional step of adjustment of the pH and of the volume with meglumine made clear that step b) was not complete.

The same arguments applied to the main request b and auxiliary requests 1bis-13bis, which only differed by the deletion of the alternative "and/or by modifying the pH" in step d) of claim 1.

XIV. The arguments of the respondents can be summarised as follows:

(a) Admittance of D59-D62

D59 had been submitted in the course of the opposition proceedings. The reports D60 and D61 were late filed and not relevant, and were not to be admitted into the proceedings. D62 was *prima facie* relevant to question whether the skilled person was aware of the unpredictability of the formation of a DOTA-Gd solution, and was thus to be admitted.

(b) Main request, inventive step

Claim 1 was to be interpreted such that no free Gd was left in the formulation obtained at the end of step b). Furthermore, claim 1 covered the use of pseudo-stoichiometric amounts of DOTA and gadolinium, i.e. amounts considered stoichiometric when weighted, but which were in fact not stoichiometric.

Before the priority date, the skilled person was aware of the unpredictability of the reaction between DOTA and Gd (e.g. in view of D7 and D30), and knew that DOTA was hygroscopic and that this could induce weighing errors (in view of D58 and D59). The one-pot synthesis of a Gd complex was commonly known (see D8). The need for process control and adjustments was also part of the common general knowledge, as shown in D57 and D13.

The closest prior art D1 disclosed a pharmaceutical composition obtainable by the process of claim 1. Claim 1 differed by the process comprising steps b), c) and d).

No improvement with regard to safety, reliability or accuracy had been demonstrated. The problem was therefore to provide an alternative process for the preparation of a composition as defined in claim 1. The claimed solution was obvious in light of the prior art, especially D2 or D7. The skilled person was motivated by D1 to use an excess of DOTA, and would have understood the teaching of D2 or D7 to be applicable to DOTA.

Accordingly, the main request infringed Article 56 EPC.

(c) Auxiliary requests, inventive step

The additional word "added" in claim 1 of auxiliary request 2 did not change the assessment of inventive step.

Regarding auxiliary request 3, it was obvious to use an excess of DOTA to obtain the DOTA excess of the formulation of D1. The excess defined by the free DOTA : free Gd ratio of 1.001-1.3 was not associated with any effect and was arbitrary.

D1 already disclosed injectable solutions, and the presence of meglumine and a pH of 6.5-8.0, such that the limitations of auxiliary requests 8 and 12 did not modify the assessment of inventive step. As to auxiliary request 11, no effect was associated with the feature "industrial scale".

Hence none of the auxiliary requests met the requirement of inventive step either.

Reasons for the Decision

1. Admittance of D59-D62

The appellant filed D60 and D61 with the grounds of appeal dated 22 August 2019. D62 was filed by respondent 1 with the reply to the grounds of appeal. Lastly, D59, initially submitted during the proceedings before the opposition division, was relied upon by respondent 2 in its reply to the grounds of appeal (see page 18).

The admittance of each of D59-D62 is subject to the provisions of Article 12(4) RPBA 2007.

The Board decided to take into account each of D59-D62 for the following reasons:
- the opposition division did not take any decision as to the admittance of D59. Thus D59 is not a document which could have been presented or was not admitted in the first instance proceedings, such that Article 12(4) RPBA 2007 is not a bar to its admittance.
- In addition, each of D59-D62 is relevant to the questions of unpredictability of the reaction of DOTA with Gd, and of the skilled person's awareness of this fact. The submission of these documents is therefore seen as an appropriate reaction to the reasoning in the appealed decision and as a legitimate attempt by the parties to further support the arguments they had already presented in the first instance proceedings.

2. Main request (patent as granted), inventive step

2.1 The claimed invention

2.1.1 The patent pertains to a process for preparing a liquid pharmaceutical formulation containing gadoteric acid (DOTA-Gd), i.e. the complex formed between the macrocyclic chelate DOTA and the lanthanide gadolinium (Gd). The formulation is used as a contrast agent, especially for magnetic resonance imaging (see paragraph [0001] of the patent).

As explained in the patent (see paragraphs [0003], [0005] and [0010]), in the body, the complexes of chelates with lanthanide are in a situation of chemical equilibrium, which may lead to a risk of undesired release of the toxic free lanthanide. The toxicity of the free chelate (i.e. DOTA which is not under the form of an excipient X[X',L] as defined in claim 1) was also known. In order to solve the problem of tolerance in the patient, the formulation thus contains a very low excess of free chelate DOTA of 0.002-0.4%, so as to increase the scavenging capacity for potential free lanthanide Gd.

In view of this low amount of free DOTA excess, the patent seeks to address the problems of precise and delicate industrial-scale control of the concentrations of free DOTA, and of providing a preparation process ensuring the reliability, reproducibility and stability of the composition, considering in particular the uncertainty of weighing at the industrial scale and the variability of the hygroscopic characteristics of DOTA (see paragraphs [0011]-[0013]).

2.1.2 Claim 1 of the main request accordingly relates to a process for preparing a liquid pharmaceutical formulation containing DOTA-Gd and 0.002-0.4% free DOTA, comprising in summary the following steps:

b) preparation of a liquid pharmaceutical composition by mixing a solution of free DOTA and of free Gd in amounts such that
- all Gd is complexed and
- $C_{ch\ l} > C_{t\ ch\ l}$,

c) measurement in the pharmaceutical formulation obtained in step b) of $C_{ch\ l}$,
$C_{lan\ l}$ being equal to 0;

d) adjustment of $C_{ch\ l}$ and of $C_{lan\ l}$ so as to obtain $C_{ch\ l} = C_{t\ ch\ l}$ and $C_{lan\ l} = 0$,

wherein
$C_{ch\ l}$ is the concentration of free DOTA,
$C_{lan\ l}$ is the concentration of free Gd,
$C_{t\ ch\ l}$ is the target concentration of free DOTA and is selected in the range of 0.002-0.4%.

2.2 Interpretation of claim 1

2.2.1 According to the appellant, claim 1 allows for the complexation reaction to be incomplete and for free Gd to be present at the end of step b). The amounts recited in step (b) would refer to the input amounts of free DOTA and free Gd entering step b), and would not define a result to be achieved with respect to amounts of free DOTA and free Gd at the output of said step. Furthermore, the subsequent quantitative measurement step c) would be carried out under conditions mimicking what occurred in the reactor upon completion of the reaction, namely by modifying the pH. The contradictory statements in claim 1 would make it necessary to use the description to interpret them, thus leading to the

above claim construction, following the principles summarised in the Case Law of the Boards of Appeal (10th edition, 2022, see II.A.6.3.2).

2.2.2 The Board does not adopt the appellant's interpretation, and construes claim 1 as requiring the absence of free Gd in the pharmaceutical formulation obtained in step b).

Firstly, step b) of claim 1 is a step of mixing a solution of free DOTA and of free Gd "so as to obtain complexation of the lanthanide by the macrocyclic chelate". It is therefore not a mere dissolution step, as the appellant argued, but a step in which complexation occurs. Furthermore, step b) mandates that the amounts of free DOTA and free Gd added as starting material are "such that all the lanthanide is complexed". It is therefore a feature of step b) that all Gd is complexed.

Secondly, in the subsequent measurement step c), claim 1 specifies "the concentration of free lanthanide $C_{lan\ l}$ being equal to 0". Since the wording of step c) clearly relates to a "measurement in the pharmaceutical formulation obtained in step b)", this requirement that the concentration $C_{lan\ l}$ of free Gd be zero can only apply to the pharmaceutical formulation obtained in step b). The appellant's interpretation, whereby $C_{lan\ l}$ is different from zero in the formulation obtained in step b) and only becomes zero after modifying the pH of the sample taken from this formulation, is not compatible with the wording of claim 1.

2.2.3 It is a fact that claim 1 still generally defines step b) as a step of preparing a composition containing DOTA-Gd, free DOTA, "and/or free lanthanide". This

appears to allow, in one alternative, for the *presence of free Gd* in the composition resulting from step b), which contradicts the *absence of free Gd* required by the statements of claim 1 mentioned above (see 2.2.2). However, in the Board's opinion, the skilled reader would resolve this inconsistency by considering that this optional presence of free Gd in the formulation of step b) is ruled out by the subsequent mandatory features of claim 1 mentioned above.

Thus, what appears at first sight to be an inconsistency in claim 1 can be resolved by the skilled reader on the basis of the claim alone. The appellant cannot rely on this inconsistency to give a interpretation to claim 1 which runs counter to its clear technical meaning, namely that the pharmaceutical formulation obtained in step b) contains no free Gd.

2.2.4 In addition, and contrary to the appellant's opinion, this interpretation is not contradicted by the description. The reference example 2 is not according to claim 1, as it is carried out in the presence of an excess Gd in step b), and is thus not relevant to its interpretation. Paragraph [0037] mentions a difference between the amounts of free DOTA and of free Gd added and the stoichiometric proportions, but does not call into question the requirement of claim 1 that this difference be such that all Gd is complexed. Paragraphs [0044]-[0048] pertain to the possibility, in step d), of adjusting the pH so as to shift the reaction equilibrium, but do not indicate that step b) may or must be incomplete or lead to free Gd in the formulation. The description of possible tests for the presence of free DOTA or free Gd, involving preferably a pH 5 buffer medium (see the end of paragraph [0021] and paragraph [0022] on page 7) cannot lead to this

conclusion either, because there is no indication in these passages that the testing conditions necessarily modify the tested concentrations or bring the complexation to completion. On the contrary, in the reaction scheme in paragraph [0019], the first step is shown to lead to DOTA-Gd and free DOTA but not to free Gd. Thus paragraph [0019], as well as paragraph [0043], support the Board's interpretation. The appellant's arguments are thus not persuasive.

2.3 The closest prior art and differentiating features

2.3.1 The closest prior art is the information leaflet D1 of the commercial product DOTAREM® 0.5 mmol/ml, solution for injection. This product is indicated for use in magnetic resonance imaging, and contains gadoteric acid, i.e. DOTA-Gd, corresponding to 20.246 g DOTA and 9.062 g gadolinium oxide (i.e. Gd_2O_3). These amounts correspond to an excess of free DOTA of about 0.12% mol/mol (see paragraph 72 of the appealed decision). The liquid formulation for injection of D1 further contains meglumine and has a pH of 6.5 to 8.0.

Thus, D1 discloses a product obtainable by the process of claim 1 of the main request.

D1 does not disclose any information as to the preparation of DOTAREM®.

2.3.2 The subject-matter of claim 1 of the main request thus differs from D1 by steps b)-d) of the process.

2.4 Objective technical problem

2.4.1 According to the appellant, the claimed process is safe, reliable and accurate, and is suitable for

industrial scale production of a pharmaceutical composition according to D1. The appellant further submits that the process is a one pot procedure eliminating the need for isolating the intermediate solid complex prior to formulating the final product, and that it is cost- and time-effective.

However, technical advantages cannot be taken into account in the formulation of the technical problem if it is not made credible that they are indeed achieved as a result of the steps of the claimed process. The fact that the closest prior art D1 does not disclose any preparation process, making a side-by-side comparison with the claimed process impossible, does not mean that any quality alleged by the appellant has to be accepted even in the absence of any evidence. The burden of proof for this rests with the appellant.

The Board finds that no such advantageous technical effect has been shown to arise from the claimed process.

No such evidence is present in the patent or the application as filed. The application as filed (see page 16) equally considered carrying out the complexation step b) with:
- an excess of lanthanide relative to the macrocyclic chelate (i.e. case A), or
- an excess of macrocyclic chelate (case B) leading either to $C_{ch\ l} < C_{t\ ch\ l}$ or to $C_{ch\ l} > C_{t\ ch\ l}$.
The patent however does not comprise any example of the alternative chosen in claim 1 of the main request, where $C_{ch\ l} > C_{t\ ch\ l}$. There is thus no basis for the appellant's assertion that starting from a deliberate initial excess of free DOTA above the target is advantageous. The appellant did not explain either why

such conclusion should be drawn by analogy from reference example 2.

D37 describes a single reproduction of the process of claim 1 on pilot scale, and is thus not suitable to demonstrate any level of reproducibility or reliability: considering the appellant's argument that the complexation of Gd with DOTA is characterised by a high variability, the single experiment of D37 cannot be regarded as proof that this problem has been solved. Furthmore, D37 is not carried out on industrial scale, and thus does not demonstrate that the claimed process would overcome any difficulty associated with such production quantities.

The protocol followed in D51 does not correspond to the subject-matter defined by claim 1 of the main request. In particular, there is no indication that step b) of D51 led to a formulation in which all Gd is complexed and $C_{ch\ l} > C_{t\ ch\ l}$.

D32 does not show any reproduction of the claimed process including the measurement and adjustment steps c) and d).

D56 does not indicate any difference in the outcome of the process when starting from an excess of DOTA or an equimolar amount (see reactions 1, 2 and 3).

No effect as to cost- and time-effectiveness can be acknowledged either: contrary to the appellant's position, carrying out the adjustment step d) by incremental additions is not ruled out by the wording of claim 1.

Lastly, no effect associated with the composition of the formulation itself, such as the narrow range of 0.002-0.4% free DOTA, may be taken into account, because this composition is already known from D1. In particular, no link is shown between any long term storage stability and the steps of the process.

2.4.2 Accordingly, the objective technical problem starting from D1 is to provide a process for making the composition of D1.

2.5 Obviousness

2.5.1 The synthesis of DOTA-Gd by complexation of Gd with DOTA, the toxicity of free Gd and the need to ensure, as in D1, a small excess of ligand in the formulation, were part of the skilled person's common general knowledge (see D8, scheme 3, page 21 lines 7-9 and page 22, chapter 4.2). The textbook D8 further discloses an exemplary one-pot synthesis of a gadolinium complex (see the paragraph spanning pages 20-21, using a related chelate). The skilled person was therefore aware of the possibility of a one-pot process for providing a pharmaceutical composition of a gadolinium-based contrast agent.

The Board considers that the skilled person was also aware that the reaction of DOTA with Gd was unpredictable and that the initially weighted amounts of macrocyclic chelate and Gd did not necessarily result in the intended and calculated ratio, at least because the skilled person knew of the hygroscopic nature of DOTA and the ensuing potential for weighing error (see D58 and D59). In addition, the skilled person would have found confirmation of this fact, in the case of structurally related chelates, in D2 (see

page 2424, left column, "Gd-5a Complex (6a)"), D7 (see example 2) and D30 (see example 2).

Thus, the skilled person knew of the critical importance of controlling the concentrations of free DOTA and free Gd in the complex formulation, and the particular uncertainty associated with the complexation reaction, especially in view of DOTA hygroscopicity and weighing error.

The appellant, relying on the post-published evidence D32, D56 and D61, submits that, even taking into account the hygroscopic character of DOTA, the reaction remains unpredictable. The Board considers this not to be decisive. The skilled person knew of the unpredictability of the reaction already for the reasons given above. Therefore, irrespective of further unelucidated factors contributing to this unpredictability, the skilled person would have been prompted to take the required steps when preparing this type of complexes.

2.5.2 Furthermore, it is generally part of the commonly known good manufacturing practices in the pharmaceutical field to control all critical attributes of the manufacturing process (see D13, page 10, section c; see also D57, page 16, point e), in particular to:

- identify and measure critical material and process attributes,
- design a process measurement system to allow real time monitoring of all critical attributes, and
- design process controls that provide adjustments to ensure control of all critical attributes.

2.5.3 The skilled person, starting from the closest prior art D1 and seeking to prepare the DOTA-Gd solution for

injection with an excess of free DOTA as indicated therein (see 2.3.1 above), would logically consider carrying out the complexation reaction between Gd and DOTA using an excess of free DOTA reagent. Then, in view of the known critical importance of controlling the concentration of free DOTA in the formulation, and the expected uncertainty of the complexation reaction, the skilled person is led, by its common general knowledge, to carry out steps of measuring (c) and adjusting (d) this concentration.

2.5.4 The sole remaining question is whether the skilled person would use, in the complexation step b), amounts of reagents (free Gd and free DOTA) leading to a concentration of free DOTA $C_{ch\ l}$ which is higher than the target concentration $C_{t\ ch\ l}$ (the target concentration being here the concentration of free DOTA in the formulation of D1).

The Board notes firstly that using a (deliberately) higher excess of DOTA than necessary in the complexation step b) is not associated with any technical effect (see 2.4.1 above). Furthermore, it follows from the reasoning above that the skilled person would in any case carry out the steps c) and d) of measurement and adjustment, such that the extent of the intermediate excess in free DOTA $C_{ch\ l}$ would anyway be corrected to the target excess.

Hence the skilled person, which is already led to use an excess of DOTA by the closest prior art D1, would immediately realise that using an excess above the target concentration of D1 would still lead to the same outcome. The Board concludes that the claimed solution is obvious in light of the above common general knowledge.

In these circumstances, a pointer to the specific alternative defined in claim 1 of the main request, whereby $C_{ch\ 1} > C_{t\ ch\ 1}$, is not needed, because this alternative is not associated with any advantageous properties and is equally suited as the others to obtain the desired DOTA-Gd formulation of D1.

Nonetheless, the Board adds that this strategy is illustrated by D2, which describes the preparation of a closely related Gd-macrocyclic chelate complex comprising the steps of mixing an excess of chelate 5a with free Gd (Gd_2O_3) to obtain complexation, measuring the concentration of free chelate, and adjusting by adding further free Gd to the reaction mixture without resulting in an excess of free Gd. The Board agrees with the appellant that D2 relates to the preparation of a different Gd complex on a laboratory scale. Nonetheless, this document shows that the general approach followed by the present inventors was known in the art.

Accordingly, the subject-matter of the main request does not meet the requirements of Article 56 EPC.

3. Auxiliary requests, inventive step

3.1 It is not necessary to assess the admittance of the main request a2 and auxiliary requests 2, 11-13, 1bis-5bis, 8bis, 9bis, 11bis and 13bis under Article 12(4) RPBA 2007, because these requests can in any case not be allowed for lack of inventive step.

3.2 The alternative "and/or by modifying the pH" in step d) of claim 1 is reformulated in the main requests a1 and a2, and is deleted in the main request b (as well as in

auxiliary requests 1bis-13bis). These amendments to step d) are immaterial to the issue of inventive step discussed above.

3.3 In auxiliary requests 2, 2bis, 3, 3bis and 4bis, step b) of claim 1 is amended as follows:
- auxiliary requests 2 and 2bis: "the added amounts of free macrocyclic chelate and of free lanthanide being such that[...]";
- auxiliary requests 3 and 3bis: the mol/mol ratio of the added free DOTA : free Gd amounts is between 1.001 and 1.3;
- auxiliary request 4bis: the amounts of free Gd and of free DOTA added are different from the stoichiometric proportions.

These amendments were introduced in order to exclude an interpretation of claim 1 covering the use of (pseudo-)stoichiometric ratios. They do not modify the assessment of inventive step given for the main request, since the reasoning above is not dependant on such an interpretation. As indicated above (see 2.5.3), an excess of free DOTA is already indicated in the closest prior art, such that it was obvious to depart from stoichiometric amounts and to perform the complexation reaction with an excess of (added) free DOTA. The excess defined by the free DOTA : free Gd ratio of 1.001-1.3 is not associated with any effect and is arbitrary.

3.4 Claim 1 of auxiliary requests 1bis and 5bis-7bis is identical to claim 1 of the main request b and auxiliary requests 2bis-4bis, such that the same considerations apply.

3.5 The features introduced in claim 1 of auxiliary requests 8, 8bis, 9 and 9bis, mandating that the formulation be injectable or that Gd_2O_3 be used, do not establish any additional difference over the closest state of the art D1 (see 2.3.1 above).

3.6 Regarding auxiliary requests 10 and 10bis, the feature of claim 1 that the measurement step c) be carried out at pH 7 does not modify the interpretation of claim 1, because the mere indication of this measurement condition does not entail that step b) be incomplete (see 2.2.4 above). This limitation to a pH of 7 for the measuring step is not associated either with any effect on the outcome of the process. The Board agrees with the opposition division that this amendment does not overcome the objections of lack of inventive step (see paragraph 113 of the appealed decision).

3.7 Claim 1 of auxiliary requests 11 and 11bis relates to a process "for preparing an industrial amount of a liquid pharmaceutical formulation". As indicated above for the main request (see 2.4.1), it has not been made credible that the claimed process leads to any technical effect beyond the formation of the formulation of D1, whether on industrial scale or otherwise. Furthermore, the finding of lack of inventive step for the main request is not based on documents limited to smaller amounts, such that the limitation in auxiliary requests 11 and 11bis does not establish an inventive step.

3.8 With respect to auxiliary requests 12 and 12bis, as reasoned in the appealed decision (see paragraph 110), the addition of a step of "adjustment of the pH and of the volume with meglumine", leading to a "formulation of the meglumine salt of a DOTA-gadolinium complex", does not overcome the objection of lack of inventive

step, seeing that the composition of D1 already comprises this meglumine salt. The skilled person seeking to produce the formulation of D1 would add meglumine to the formulation, and the addition of this basic compound would modify the pH.

3.9 In claim 1 of auxiliary requests 13 and 13bis, the adjustment step d) is carried out "by eliminating the appropriate amount of free macrocyclic chelate". In the Board's view, where the complexation reaction leads to a relative concentration in free DOTA above that of the target formulation of D1, the elimination, by undefined means, of this excess free DOTA is one way to obtain the desired formulation. As concluded by the opposition division (see paragraph 112 and 112.1 of the appealed decision), this amendment does not modify the assessment given above for the main request.

3.10 Accordingly, none of the auxiliary requests meet the requirements of inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated