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Datasheet for the decision of 9 May 2019

Case Number: T 1944/16 - 3.3.07

Application Number: 09712403.6

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IPC: A61K49/10

Language of the proceedings: EN

Title of invention:
PROCESS FOR PREPARING A PHARMACEUTICAL FORMULATION OF CONTRAST AGENTS

Patent Proprietor:
GUERBET

Opponents:
Sanochemia Pharmazeutika AG
European Oppositions Limited
Actavis Group PTC ehf
Jenapharm GmbH & Co KG

Headword:
Contrast agents/ GUERBET

Relevant legal provisions:
EPC Art. 105(1), 56
RPBA Art. 13(3)

Keyword:
Intervention of the assumed infringer - admissible (no)
Late-filed documents - admitted (yes)
Inventive step - main and auxiliary requests (no)

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Office européen des brevets

Beschwerdekammern

Boards of Appeal

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Case Number: T 1944/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 9 May 2019

Appellant: (Patent Proprietor)	GUERBET 15, Rue des Vanesses 93420 Villepinte (FR)
Representative:	Regimbeau 20, rue de Chazelles 75847 Paris Cedex 17 (FR)
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Appellant: (Opponent 3)	Actavis Group PTC ehf Reykjavikurvegur 76-78 222 Hafnarfjordur (IS)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Party as of right: (Opponent 2)	European Oppositions Limited 20 Red Lion Street London WC1R 4PJ (GB)
Representative:	Crooks, Elizabeth Caroline Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)

Party as of right: (Opponent 4)	Jenapharm GmbH & Co KG Otto-Schott-Strasse 15 07745 Jena (DE)
Representative:	Spaltmann, Frank Bayer Intellectual Property GmbH Global IP Litigation Alfred-Nobel-Straße 10 DE-40789 Monheim am Rhein (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 17 August 2016 concerning maintenance of the European Patent No. 2242515 in amended form.**

Composition of the Board:

Chairman	J. Riolo
Members:	A. Usuelli
	C. Schmidt

Summary of Facts and Submissions

I. Three oppositions had been filed against European Patent 2 242 515 on the grounds that its subject-matter lacked novelty and inventive step, was insufficiently disclosed and extended beyond the content of the parent application.

The following documents were among those cited during the first-instance proceedings:

D3: DOTAREM® 0.5 mmol/l, solution for injection
D11: US 5,650,133
D14: US 5,049,667
D15: WO91/10645
D20: Supplemental experimental data
D35: Guidance for Industry - Food and Drug Administration 2004

II. The appeals of the patent proprietor (appellant-patent proprietor) and of opponents 1 and 3 (appellant-opponent 1 and appellant-opponent 3) lie against the decision of the opposition division which found that the patent and the invention according to auxiliary request 2 met the requirements of the Convention. The decision was based on a main request and two auxiliary requests. The main request and auxiliary request 1 were filed on 9 March 2016. Auxiliary request 2 was filed during the oral proceedings held on 11 July 2016.

Claim 1 of the main request read as follows:

"1. 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 macrocyclic chelate being DOTA and said lanthanide being gadolinium, said process comprising the following successive steps:

b) preparation of a liquid pharmaceutical composition containing the complex of macrocyclic chelate with a lanthanide, and 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 free lanthanide, by mixing a solution of free DOTA as the free macrocyclic chelate, and of 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 not all the lanthanide is complexed;
c) measurement in the pharmaceutical formulation obtained in step b) of the concentration of free lanthanide $C_{lan\ l}$; the concentration of free macrocyclic $C_{ch\ l}$ chelate being equal to 0;
d) adjustment of $C_{ch\ l}$ and of $C_{lan\ l}$ by adding to the formulation obtained in step b) the amount of free macrocyclic chelate necessary, firstly, to complete the complexation of the free lanthanide so as to obtain $C_{lan\ l} = 0$, and, secondly, to obtain $C_{ch\ l} = C_{t\ ch\ l}$, 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 the amount of complexed macrocyclic chelate DOTA-Gd in the final liquid pharmaceutical formulation in mol/mol."

Claim 1 of auxiliary request 1 differed from claim 1 of the main request in the indications that the DOTA complex was in the form of a meglumine salt and that step d) comprised at the end an adjustment of the pH and of the volume, with meglumine.

Claim 1 of auxiliary request 2 differed from claim 1 of the main request in the indication in step c) that the measurement of the concentration of free lanthanide was made at pH 7.

III. The opposition division held that the main request and auxiliary request 1 did not comply with the requirement of sufficiency of disclosure since neither the patent nor the common general knowledge would have provided the skilled person with the information required to achieve a concentration of free chelate equal to zero ($C_{ch\ l}=0$) as required in step c) of claim 1.

With regard to auxiliary request 2, the examining division considered that the skilled person would have been enabled to achieve the condition $C_{ch\ l}=0$ by the indication that step c) was to be performed at pH 7.

Document D3 was the closest prior art for the assessment of inventive step. This document disclosed the commercial product DOTAREM®, a formulation obtainable by the process defined in claim 1 of auxiliary request 2. The technical problem was the provision of a process to prepare DOTAREM® in a safe, reliable and reproducible manner which was suitable for industrial scale. None of the documents cited by the opponents considered in combination with the closest prior art would have led the skilled person to the

process of claim 1. Hence, the subject-matter of auxiliary request 2 involved an inventive step.

IV. By letter of 23 November 2016 Jenapharm GmBH & Co. KG requested to intervene in the opposition-appeal proceedings pursuant to Article 105 EPC.

V. In its statement setting out the grounds of appeal filed on 27 December 2016, the appellant-patent proprietor maintained the main request forming part of the basis of the opposition division and filed 15 auxiliary requests designated as auxiliary requests 1 to 7, A and 1a to 7a.

Claim 1 of auxiliary request 1 differed from claim 1 of the main request in the indication that the pharmaceutical formulation was for intravenous injection.

Claim 1 of auxiliary request 2 differed from claim 1 of the main request in the indication that step d) comprised at the end a step of adjustment of the pH and of the volume.

Claim 1 of auxiliary request 3 was identical to auxiliary request 1 forming part of the basis of the decision under appeal (see point II above).

Claim 1 of auxiliary request 4 differed from claim 1 of the main request in the indication that the amount of free macrocyclic chelate in the liquid pharmaceutical formulation was between 0.025% and 0.25%.

Claim 1 of auxiliary request 5 differed from claim 1 of the main request in the indication at the end of step

b) that the free lanthanide/free macrocyclic chelate mol/mol ratio was between 1.001 and 1.3.

Claim 1 of auxiliary request 6 differed from claim 1 of the main request in the indication in step b) that the gadolinium was under the form of Gd_2O_3.

Claim 1 of auxiliary request 7 included all the amendments introduced in auxiliary requests 1 to 3, 5 and 6.

Auxiliary request A was identical to the request that was considered by the opposition division to meet the requirement of the Convention (auxiliary request 2 during the proceedings before the opposition division).

Claims 1 of auxiliary requests 1a to 7a corresponded to auxiliary requests 1 to 7, in which step c) had been limited to a measurement at pH 7.

VI. In a communication pursuant to Article 15(1) RPBA issued on 9 May 2017, the Board expressed the opinion that the notice of intervention filed by Jenapharm GmBH & Co. KG was inadmissible.

In a further communication issued on 15 February 2019, the Board commented on, *inter alia,* inventive step starting from document D3 as the closest prior art. It expressed the view that the subject-matter of the main request did not comply with the requirement of Article 56 EPC having regard to the teaching of the closest prior art in combination with D15.

VII. The following documents were filed by the appellant-patent proprietor by letter of 9 April 2019:

D60: Chem. Rev., 1999, 99, 2293-2352
D61: Inorg. Chem., 2006, 45, 9269-9280.

VIII. Oral proceedings took place as scheduled on 9 May 2019. They were not attended by appellant-opponent 3, who had informed the Board accordingly, and by opponent-2.

IX. The appellant-patent proprietor's arguments on inventive step can be summarised as follows:

The closest prior art D3 disclosed the product DOTAREM® without providing any information as to its preparation. Starting from this document the technical problem was the provision of a process to prepare DOTAREM® in a safe, reliable and reproducible manner which was suitable for industrial scale. As illustrated in document D20, carrying out the reaction of complexation with equimolar amounts of reagents resulted in a too high amount of DOTA in the final composition. In contrast to the methods disclosed in the prior art, in step (b) an excess of gadolinium was used although the aim of the process was to obtain a formulation with an excess of DOTA. In step (c), the amount of free DOTA was measured in order to determine the amount of free DOTA to be added in step (d). The skilled person would not have considered the teaching of example 17 of D15 as suggested by the opponents. This document did not relate to the formation of a complex between gadolinium and DOTA. Example 17 concerned the preparation of a complex in which the chelating agent contained a pyridine moiety. This chelating agent was very different from DOTA. Furthermore, the process of example 17 did not comprise a step of quantitative measurement of the excess of gadolinium and the objective of example 17 was not to provide a pharmaceutical formulation. For all these

reasons, the skilled person would not have considered the teaching of example 17 of D15. None of the other documents disclosed a process similar to the process of the patent in suit. Hence, the main request met the requirements of Article 56 EPC. The subject-matter of the auxiliary requests was inventive substantially for the same reasons as argued in respect of the main request.

X. The appellant-opponents' arguments on inventive step can be summarised as follows:

Starting from the closest prior art document D3, the technical problem was to provide a process for preparing the DOTAREM® formulation. Example 17 of D15 described a process for preparing a gadolinium complex that resulted in the preparation of a composition containing an excess of ligand. Since DOTAREM® also contained an excess of ligand, the skilled person would have considered the teaching of this example of D15. The fact that this example did not relate to the preparation of a DOTA complex was no valid reason for disregarding its teaching. The skilled person would have also considered that to implement the process of D15 at industrial level it was necessary to carry out a quantitative assessment of the amount of free gadolinium. By combining the teachings of D3 and D15, the skilled person would have arrived at the subject-matter of claim 1 of the main request without any inventive effort. Hence, the main request did not comply with the requirements of Article 56 EPC. The auxiliary requests were also not inventive substantially for the same reason as the main request.

XI. The appellant-patent proprietor requested that the decision of the opposition division be set aside and

that a patent be granted on the basis of a main request or one of auxiliary requests 1 to 7, A, 1a to 7a, all filed with the grounds of appeal.

The appellant-patent proprietor further requested that the intervention of Jenapharm GmbH & Co. KG not be admitted.

XII. Appellant-opponent 1 requested that the decision under appeal be set aside and that the patent be revoked. It further requested that documents D60 and D61 not be admitted into the appeal proceedings.

XIII. Appellant-opponent 3 requested in writing that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

1. Request of intervention pursuant to Article 105 EPC

1.1 In its communication of 9 May 2017, the Board informed Jenapharm GmBH & Co. KG that the proceedings referred to in its request to intervene in the proceeding pursuant to Article 105 EPC were neither proceedings for infringement within the meaning of Article 105(1)(a) EPC nor proceedings for non-infringement within the meaning of Article 105(1)(b) EPC.

The Board further stated that the proceedings before the Landgericht München I concerned preparatory measures that might or might not trigger subsequent proceedings as defined in Article 105(1) EPC.

1.2 No reply was filed by Jenapharm GmBH & Co. KG in response to the Board's communication.

Therefore, the Board decides that the notice of intervention pursuant to Article 105 EPC is inadmissible.

2. Admittance of documents D60 and D61.

2.1 Documents D60 and D61 were filed by the appellant-patent proprietor one month before the oral proceedings.

Document D60 is a review that illustrates the common general knowledge in the field of gadolinium complexes. D61 provides information on PCTA complexes. This document was filed by the appellant-patent proprietor in response to the considerations made by the Board in its preliminary opinion of 15 February 2019 in relation to example 17 of D15, which concerns the preparation of a specific PCTA complex.

The introduction into the proceedings of these new documents does not increase the complexity of the case. Therefore, in the exercise of its discretion, the Board decides to admit D60 and D61 into the appeal proceedings (Article 13(3) RPBA).

Main Request

3. Inventive step

3.1 The invention underlying the subject-matter of the main request relates to a process for preparing a liquid pharmaceutical formulation containing a complex of the macrocyclic chelate DOTA with gadolinium and an amount

of free DOTA of between 0.002% and 0.4% (see [0017]). The excess of DOTA is intended to limit the undesired release from the DOTA-gadolinium complex of gadolinium, a potentially toxic substance. The formulation is used as a contrast agent, especially for magnetic resonance imaging (see paragraphs [0001] to [0003] and [0017]).

3.2 The claimed process allows for manufacturing in "one-pot" the DOTA-gadolinium complex and formulating it to obtain the final pharmaceutical formulation. A feature of this process is that in step (b) an excess of free gadolinium is used although the actual aim of the process is to obtain a formulation containing an excess of free DOTA. Step (c) provides a quantitative measurement of the amount of free gadolinium in the reactor upon completion of the complexation. This makes it possible to determine the amount of free DOTA to be added to achieve the final targeted concentration.

3.3 Closest prior art

3.3.1 In agreement with the decision under appeal, the Board considers D3 a suitable starting point for the assessment of inventive step.

3.3.2 D3 is the information leaflet of the commercial product DOTAREM® 0.5 mmol/ml, solution for injection (DOTAREM®). This product contains the meglumine salt of the DOTA-gadolinium complex and an excess of free DOTA (0.12%). As stated in the decision under appeal (see paragraph 6.5.1), DOTAREM® is a product obtainable by the process of claim 1 of the main request.

D3 does not disclose any information as to the preparation of DOTAREM®.

3.4 Technical problem

3.4.1 Example 2 of the patent in suit illustrates a process for preparing a formulation containing a DOTA-gadolinium complex and an excess of free DOTA. The process results in the production of 100 litres of formulation.

On the basis of this example, the Board agrees with the appellant-patent proprietor that the technical problem underlying the invention can be seen as the provision of a process to prepare DOTAREM® in a safe, reliable and reproducible manner which is suitable for industrial scale.

3.5 Obviousness

3.5.1 Document D15 describes novel chelating agents and complexes of these agents with metals. Some of these chelating agents (see example 3) differ from DOTA mainly by the presence of an heterocyclic moiety fused to the macrocyclic structure. Complexes of these chelating agents with gadolinium are disclosed in examples 15 to 20, 22 and 23.

3.5.2 In example 17, the chelating agent of example 3 is complexed with an excess of gadolinium (1.01 equivalent of Gd_2O_3). It is further explained that by using xylenol orange, an indicator of the presence of free gadolinium, further chelate is added until a negative test result is achieved. This step indicates that the free gadolinium present in the solution at the end of the reaction is complexed by the addition of further chelating agent to reach a point in which no free metal is detectable. In the final part of the process, the excess of chelating agent is determined by the addition

of $GdCl_3$ to check that the free chelating agent is less than 0.05%.

Example 17 of D15 therefore discloses a method for preparing a solution of a gadolinium complex that may contain a small amount of free chelating agent.

The process of present claim 1 is essentially based on the approach described in example 17 of D15, i.e. it comprises a step in which an excess of gadolinium is used in the process to form the complex (step b) and an adjustment step (step d) in which the chelating agent is added in an amount sufficient to complex the free gadolinium and to reach the desired concentration of free chelating agent in the solution.

Example 17 does not comprise a step involving a quantitative measurement of the concentration of free gadolinium in the solution in which the complex is prepared. Such a step is present in the method of claim 1 of the main request (step c)). In example 17 of D15, the presence of free gadolinium is monitored in a qualitative manner by using xylenol orange as an indicator. It is nevertheless evident that the skilled person seeking to provide an industrial process for producing a diagnostic agent would have carried out a precise quantitative measurement of the amount of free gadolinium, a potentially toxic substance. D35, a document providing guidance for pharmaceutical industries on matters concerning pharmaceutical development, manufacturing and quality assurance, issued by the Food and Drug Administration, recommends, *inter alia*, the identification and measurement of all critical materials (page 10, fourth paragraph). Thus, step c) does not provide any inventive contribution to the process of claim 1.

3.5.3 The appellant-patent proprietor underlined that D15 disclosed several examples in which the reaction of complexation was carried out using equimolar amounts of reagents. The skilled person would have had no reason to select the sole example in which an excess of gadolinium was used (example 17).

In the Board's opinion, the skilled person confronted with the problem of providing a process for preparing DOTAREM® would, in principle, have considered any process which can be adapted to this end. Example 17 describes the preparation of a solution that may contain, in addition to the gadolinium complex, small amounts of free chelating agent. This is not the case for the other examples of D15 considered by the appellant-patent proprietor. Since DOTAREM® contains a small excess of free DOTA (0.12%), the skilled person would have been motivated to consider the teaching of example 17.

3.5.4 The appellant-patent proprietor also remarked on the structural differences between the chelating agent of DOTAREM®, i.e. DOTA, and the chelating agent used in example 17 of D15, i.e. PCTA. In this regard it referred to documents D60 and D61.

The Board does not dispute that the structural differences between PCTA and DOTA may have an impact on their reactivity. Nevertheless, both chelating agents can react with gadolinium to form a complex. The skilled person facing the problem of preparing a composition containing the gadolinium complex and a small excess of chelating agent would have recognised that the synthetic strategy adopted in example 17 is suitable for providing a solution with a complex and an

excess of ligand. They would also have recognised that this strategy, which is based on the concept of starting with an excess of gadolinium, can, in principle, be applied to the preparation of any gadolinium complex. In other words, the idea of preparing the complex starting from an excess of gadolinium is, in principle, independent of the chemical structure of the chelating agent.

3.5.5 With regard to the experimental data disclosed in D20, the appellant-patent proprietor argued that the inventors of the patent in suit were the first to observe that reacting DOTA and Gd_2O_3 in stoichiometric amounts did not lead to a solution devoid of free entities as expected but to a solution containing high amounts of free DOTA. This previously unknown problem was solved by the provision of the process defined in the main request.

Indeed, the experimental report D20 shows that when DOTA and Gd_2O_3 are combined in stoichiometric amounts to form the gadolinium-DOTA complex, the solution obtained at the end of the complexation reaction still contains some amounts of the starting materials that did not react. In particular, an amount of 0.42% (mol/mol) of free DOTA is still present in the solution. This is, however, unsurprising. Examples 2 and 5 of D14 indicate that the preparation of gadolinium complexes starting from stoichiometric amounts of gadolinium and chelating agent does not necessarily result in a solution free of the starting materials. This behaviour is observed also in D39 with regard to the preparation of the gadolinium-DOTA complex (page 515, "Monitoring the formation of Gd-ligand"). As explained in example 5 of D14, depending on the result of the analysis of the solution after the complexation, it may be necessary to

add ligands. However, the process of claim 1 also involves steps of quantitative measurements and adding ligands (steps c) and d)).

In general terms, no matter whether the complexation is carried out using stoichiometric amounts of the reactants or an excess of gadolinium, it is at some point necessary to analyse the composition obtained after the complexation and possibly to perform an adjustment step. These steps can hardly be dispensed with if the final product is a product to be injected into a patient that may potentially contain a toxic substance such as gadolinium. The strategy adopted by the patent proprietor, starting from an excess of gadolinium, is one option available to the skilled person that does not offer any advantage over carrying out the complexation using stoichiometric amounts of the starting material.

3.5.6 For the above reasons, claim 1 does not comply with the requirements of Article 56 EPC.

Auxiliary requests

4. For the reasons explained below, the amendments made to the auxiliary requests do not substantially alter the above considerations in respect to the main request. The appellant-patent proprietor did not submit any specific arguments for these requests.

4.1 Auxiliary request 1 specifies that the product obtained in claim 1 is for intravenous injection. This indication does not add any further distinguishing feature over D3 since DOTAREM® is also for intravenous injection. Moreover, the arguments in points 3.5.1 to

3.5.6 above apply also to the subject-matter of this request.

4.2 Claim 1 of auxiliary request 2 differs from claim 1 of the main request in the indication that step d) comprises a step of adjusting the pH and the volume. However, such a step is present also in the process of example 17 of D15.

4.3 Compared to claim 1 of auxiliary request 2, claim 1 of auxiliary request 3 further specifies that the pH adjustment is made with meglumine and that the DOTA-gadolinium complex is obtained as meglumine salt. The DOTA-gadolinium complex of DOTAREM® is also a meglumine salt. It therefore would have been obvious to the skilled person to adjust the pH by adding meglumine. The same occurs in examples 2 and 5 of D14.

4.4 Claim 1 of auxiliary request 4 specifies that the amount of free chelate is between 0.025% and 0.25%. Since the amount of free chelate in DOTAREM® is 0.12%, the limitation introduced in auxiliary request 4 does not result in any additional distinguishing feature over the closest prior art.

4.5 Claim 1 of auxiliary request 5 indicates that in step b) the ratio gadolinium/DOTA is between 1.001 and 1.3. In example 17 of D15, the gadolinium/PTCA ratio is 1.01:1.

4.6 Claim 1 of auxiliary request 6 requires that gadolinium is used in step b) in the form of Gd_2O_3. The same occurs in example 17 of D15.

4.7 Claim 1 of auxiliary request 7 is based on the combination of the amendments introduced in auxiliary

requests 1 to 3, 5 and 6. For the reasons explained in points 4.1 to 4.6 above, none of these amendments provide an inventive contribution to the subject-matter of claim 1.

4.8 Claim 1 of auxiliary request A differs from claim 1 of the main request in the indication that in step c) the measurement of the concentration of free gadolinium is made at pH 7. Auxiliary request A corresponds to the request considered by the opposition division to comply with the requirement of the Convention (previous auxiliary request 2). The indication of the pH at which the measurement of the gadolinium is carried out was introduced to overcome the objection for insufficiency of disclosure that led to the refusal of the main and auxiliary request 1 (see point III above).

The appellant-patent proprietor did not submit any argument as to the relevance of this feature with regard to the assessment of inventive step. As noted by appellant-opponent 1 in its statement of grounds of appeal (page 22) in example 2 of D14, the measurement of free gadolinium is made at pH 7.4, i.e. a pH very close to the one specified in auxiliary request A. Thus, claim 1 of auxiliary request A does not involve an inventive step.

4.9 Claims 1 of auxiliary requests 1a to 7a correspond, respectively, to claim 1 of auxiliary requests 1 to 7, in which step c) has been limited to a measurement at pH 7 as in auxiliary request A. Therefore, none of these requests comply with the requirement of Article 56 EPC for the reasons explained in points 4.1 to 4.8 above.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos J. Riolo

Decision electronically authenticated