For information purposes only

**PARIS DISTRICT COURT**

3rd Chamber 2nd section

General List No.:

**15/12348**

MINUTE No.:

**JUDGMENT**

**Handed down on 23 March 2018**

Summons of:

29 July 2015

**PLAINTIFF**

**The company BAYER PHARMA AKTIENGESELLSCHAFT**

Mullerstrasse 170

13342 BERLIN (GERMANY)

represented by Maître Dariusz SZLEPER of the AARPI SZLEPER HENRY Attorneys, attorneys at the PARIS bar, robing room #R0017

**DEFENDANT**

**The company GUERBET**

15 rue des Vanesses

BP 57400

93420 VILLEPINTE

represented by Maître Raphaëlle DEQUIRE-PORTIER of the AARPI GIDE LOYRETTE NOUEL AARPI, attorneys at the PARIS bar, robing room #T0003

**Enforceable copies**

**issued on:**

**COMPOSITION OF THE DISTRICT COURT**

Francois ANCEL, First Deputy Vice Presiding Judge

Marie-Christine COURBOULAY, Vice Presiding Judge

Françoise BARUTEL, Vice Presiding Judge

assisted by Jeanine ROSTAL, acting as Clerk to the court

**PROCEEDINGS**

At the hearing of 02 February 2018 held in open court before François ANCEL, Françoise BARUTEL, reporting judges, who, without opposition from the attorneys, held the hearing alone, and, after having heard counsels for the parties, reported to the District Court, in accordance with the provisions of Article 786 of the French Code of Civil Procedure.

**JUDGMENT**

Handed down publically by delivery

In the presence of the parties

At first instance

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**FACTS, PROCEEDINGS AND CLAIMS OF THE PARTIES:**

The company BAYER PHARMA, a Germany company founded in 1863, presents itself as having as activity pharmaceutical and medical products and in particular in the field of pharmaceutical formulations of contrast agents which are used for magnetic resonance imaging (MRI).

The company GUERBET, founded in 1926, presents itself as a specialist in medical imaging and indicates that it sells a wide range of contrast products to hospitals, clinics and radiologists in private practice.

It sells in particular a gadolinated contrast agent under the name DOTAREM for which it obtained a marketing authorization in 1989.

It is the proprietor of several patents protecting the process for producing this product, which is of use as pharmaceutical contrast agent in medical imaging, in particular, in MRI and in particular:

- French patent No. 2 927 539 (referred to below as patent FR 539) granted on 30 July 2010 and having the title “Process for preparing a pharmaceutical formulation of contrast agents”;

- European patent No. 2 242 515 (referred to below as patent EP 515) filed on 18 February 2009 under priority of patent FR 539 and granted on 2 April 2014. On the basis of this European patent EP 515, the company GUERBET also filed four divisional European patent applications, namely patent applications E 2 799 089, EP 2 799 090, EP 3 159 014 (still undergoing examination) and EP 2 591 807 (application rejected by the EPO on 24 January 2017), two of which are entitled to the priority date of 18 February 2009 (European patent No. 2 799 089 granted on 3 August 2016 and No. 2 799 090 granted on 29 June 2016).

The process covered by Claim 1 of patent FR 539 corresponds to that of patent EP 515, the process covered by Claim 2 of patent FR 539 corresponds to that of No. 2 799 089.

By virtue of a writ of 29 July 2015, the company BAYER PHARMA served a summons against the company GUERBET for a nullity of all of the claims of patent FR 539.

The company GUERBET filed an application for limitation of its patent with the INPI [French Patent Office], which was accepted on 17 May 2016.

**In its most recent consolidated pleadings, notice of which was filed electronically on 31 January 2018, the company BAYER PHARMA**, pursuant to Article L. 613-25 of the French Intellectual Property Code, asked the District Court in these terms to:

DISMISS the company GUERBET’s application for rejection of the pleadings and exhibits of the company BAYER of 30 January 2018 as being in no way able to be considered since they were late;

DISMISS from the proceedings GUERBET’s exhibits No. 19, 20 and 33 as not meeting the requirements of means of proof as defined in particular by Article 201 et seq. of the French Code of Civil Procedure;

DECLARE inadmissible and in any event unfounded all the applications, arguments and pleadings of the company GUERBET; dismiss them from the proceedings.

In the light of Article L. 613-25 of the French Intellectual Property Code,

TO PRONOUNCE the nullity of Claims 1 to 11 of patent FR 08 51055 on the grounds of insufficiency of disclosure and also on the grounds of absence of novelty and of inventive step, and also Claim 2 et seq. on the grounds of extension of their subject matter;

TO ORDER the judgment to be handed down to be entered in the National Patent Register;

TO ORDER the company GUERBET to pay the company BAYER PHARMA compensation of € 85000 by application of the provisions of Article 700 of the French Code of Civil Procedure;

TO ORDER the company GUERBET to pay the entire costs that it will be possible for Maître Dariusz SZLEPER, instructed attorney, to recover directly in accordance with the provisions of Article 699 of the French Code of Civil Procedure.

**In its most recent consolidated pleadings, notice of which was filed electronically on 31 January 2018, the company GUERBET**, pursuant to Article 6§1 of the European Convention on Human Rights and Articles 15, 16, 135, 779, 783 and 907 of the French Code of Civil Procedure, L. 612-5, L. 611-11 and L. 611-14 of the French Intellectual Property Code, asks the District Court in these terms to:

*In limine litis*, DISMISS from the proceedings the pleadings No. 4, notice of which was served by Bayer Pharma AG on 30 January 2018, and exhibits No. 28 to 30;

DISMISS the application for nullity of French patent No. 2 927 539 made by the company Bayer Pharma AG;

ORDER the company Bayer Pharma AG to pay the company Guerbet the sum of 96000 euros, by application of Article 700 of the French Code of Civil Procedure;

ORDER the company Bayer Pharma AG to pay the entire costs, a deduction to be made therefrom to the benefit of Maître Raphaëlle Dequiré-Portier, by application of Article 699 of the French Code of Civil Procedure;

Before the opening of the proceedings, the District Court, wishing to be able to be in possession of the company GUERBET’s elements of reply from all parties regarding the most recent pleadings produced by the company BAYER PHARMA, proposed referral of the case in order to allow the company GUERBET to file pleadings regarding these most recent elements. After consultation with its client opposed to referral of the case, the company GUERBET’s attorney indicated that he was abandoning his application to have the latest written proceedings from the company BAYER PHARMA dismissed so that the case can be held and pleaded as it is.

The pretrial review was closed before opening of the proceedings.

**GROUNDS FOR THE DECISION**

**Regarding the presentation of the patent**

Patent FR 539 relates to a “*Process for preparing a pharmaceutical formulation of contrast agents*”. It relates to a process for preparing a liquid pharmaceutical formulation which is of use as a pharmaceutical contrast agent in medical imaging, in particular in magnetic resonance imaging (MRI), the contrast agent being a substance which makes it possible to visualize, by an increase in contrast, an anatomical structure (an organ for example) or a pathological condition (a tumour for example) which naturally shows little or no contrast, and which otherwise would be difficult to distinguish from the neighbouring tissues.

The description of the patent indicates that “*the invention relates to pharmaceutical formulations of contrast agents, in particular complexes of chelates with paramagnetic ions, in particular for Magnetic Resonance Imaging, and industrially effective processes for producing these formulations*”.

The chelates (such as DOTA) bind with a metal, such as gadolinium, so as to form the “*complex*”. The metal of the lanthanide family, when it is free, that is to say when it is not complexed with a chelate, is toxic to human beings such that it is impossible to inject it directly into the human body.

For this reason, in order to prevent lanthanides from “*escaping*” from the complexes after they have been administered and being found in the free state in the body, the pharmaceutical formulations described in patent FR 539 also comprise between 0.002 and 0.4% mol/mol of excess “*free*” macrocyclic chelate. The role of this excess, as stated by the patent, is to “*capture*” the lanthanide atoms that would be free. Thus, the role of the patent is to prevent an unwanted release of gadolinium in the human body.

The patent discloses that an undesired release of gadolinium in the human body presents risks that a person skilled in the art has sought to solve and that several approaches “*for improving the tolerance of complexes of chelates with gadolinium are described in the prior art*” and in particular the production of formulations comprising an excess of free chelate so as to complex any unwanted subsequent release of lanthanide.

However, the excess of chelates presents risks of toxicity to the human body such that the inventor demonstrated for macrocyclic chelates “*the advantage of the use of an amount of free chelate particularly advantageous in terms of tolerance*” and shows that by “*using a very low amount of excess free chelate (between 0.02 and 0.4%), “resulting terms of tolerance” are obtained (…) which are “very advantageous””*.

The inventor thus manages to determine not only an excess of macrocyclic chelate that is sufficient to make it possible to complex any fortuitous release of gadolinium, but also sufficiently low to prevent any toxicity associated with the presence of free chelates (DOTA).

However, the description of the patent indicates that “*in view of this low amount, a new problem arises, unknown from the prior art, namely the need for extremely precise and difficult control, on the industrial scale, of the concentrations of free chelate and therefore of the production of the product in order to achieve this range of target values of free amount of free chelate, these values having to be stable, including after storage for several months or years*”.

It is in fact specified that the inventor “*had to develop a preparation process which makes it possible to guarantee the reliability and the reproducibility of the composition of batches which are sold*” after having noted that the mixing of the theoretical amounts of the reagents (DOTA and Gd) *does not make it possible to obtain, in a manner that is satisfactory enough on the industrial scale, the respective amounts of complex of chelate with the lanthanide and of free chelate at low concentration in the pharmaceutical formulation*”. This problem makes it necessary to carry out several analysis steps, “*which can take several hours, and significantly increase the industrial cost price of the product*” and the “*applicant’s process makes it possible, on the contrary, in particular to prepare in advance and to optimize the analytical device which is important, by virtue of its impact on the quality of the final product*”.

The patent indicated that the problem was solved by the applicant by virtue of the use of at least one step of measuring, in the liquid pharmaceutical composition, the concentrations of free macrocyclic chelate and/or of free lanthanide and of at least one step of adjusting so as to obtain the desired concentration.

It specifies that the invention therefore relates to a process for preparing a liquid pharmaceutical formulation containing a complex of macrocyclic chelate with a lanthanide (Gd-DOTA), with an amount of free macrocyclic chelate (DOTA) between 0.002 and 0.4% mol/mol (Claims 1 and 2, and also dependent Claims 3 to 6), to the liquid pharmaceutical formulation that can be thus obtained (Claims 7 to 9), and to the uses thereof for preparing a diagnostic composition for medical imagery (Claims 10 and 11).

**Regarding the application for rejection of exhibits 19, 20 and 33 produced by the company GUERBET;**

The company BAYER PHARMA requests rejection of exhibits 19, 20 and 33, which consist of a report entitled “Supplemental Experimental Data” and the free translation thereof, of a report from the company GUERBET regarding the carrying out of example 2 of patent EP 515 and the free translation thereof and of a report by the company GUERBET regarding the carrying out the process described in patent EP 2 799 089.

However, there is no reason to immediately dismiss these exhibits, of which the company BAYER PHARMA contests essentially their prohibitive force, said force having to be assessed by the District Court in the context of the examination of the present case on the merits thereof.

**Regarding the application for nullity of patent FR 539 on the grounds of lack of novelty;**

It is established that, while in the enacting terms of its most recent consolidated pleadings, the company BAYER PHARMA persists in requesting that the District Court pronounce the nullity of Claims 1 to 11 of patent FR 08 51055 “*on the grounds of lack of novelty*”, the evidence drawn from the nullity based on the lack of novelty is in no way discussed in the grounds of these pleadings and that this information clearly constitutes material error.

Consequently, there will be no ruling regarding this application.

**Regarding the application for nullity of Claims 2 to 11 of patent FR 539 on the grounds of extension of the subject matter thereof beyond the content of the patent application;**

The company BAYER PHARMA submits that Claim 2 intends to protect a process which is not contained in the text of the application as filed since it provides that the pharmaceutical composition contains, in step b), freed lanthanide while at the same time requiring that all the lanthanide be complexed and that, independently of the clear inconsistency which exists between these two requirements, such a composition is not found in the initial application of patent FR 539, the description of which at no time describes a pharmaceutical composition that would meet this double cumulative requirement of step b), namely the presence of free lanthanide and the complexation of all the lanthanide. It adds that Claims 3 to 11 include the subject matter of Claim 2 such that Claims 2 to 11 extend beyond the content of the patent application as filed and should be invalidated in accordance with the provisions of Article L. 613-25, c), French Intellectual Property Code. In reply to the company GUERBET, the company BAYER PHARMA considers that, in the text of the patent application as filed, the passages reproduced in the table produced by the company GUERBET were not connected to one another, or intended to be so, and in particular that the passage of the description which describes a “*preparation of a liquid pharmaceutical composition containing, on the one hand, the complex of macrocyclic chelate with a lanthanide and, on the other hand, free macrocyclic chelate and/or free lanthanide*” cannot be connected to Claim 5 since said Claim relates solely to the embodiment of the process according to case B, wherein all the lanthanide is complexed, and that this passage relates to the general process described in the patent application, which encompasses three different embodiments. It considers that, in combining a feature specific to case B only, with features relating to the general process, the company GUERBET performs an intermediate generalization which is not admissible according to the established case law of the EPO which considers that it is only admissible if a person skilled in the art can without any doubt deduce from the application as filed that these features are not closely linked to the other features of the embodiment, but that they apply directly and unambiguously to the more general context, which could not be the case in the case in point, since this combination results in an impossibility since, during step b), the formulation must contain both an excess of gadolinium while all the gadolinium must be complexed.

In reply, the company GUERBET recalls that the assessment of the extension of the subject matter of patent beyond the content of its application simply involves assessing whether the subject matter claimed by the patent granted or subsequently amended was indeed included in the application taken as a whole and that, in the case in point, the comparison of the patent application with the limited patent makes it possible to note that Claim 2 and more particularly all of the features of step b) correspond to the combination of Claims 1, 2, 3 and 5 as filed, such that all of the features of step b) of claim 2 of the limited patent were disclosed in the claims and the description as filed and that the subject matter of step b) of Claim 2 does not therefore extend beyond the content of the application.

***On the basis of this;***

By application of Article L. 613-25 of the French Intellectual Property Code, “*the patent shall be declared invalid by legal decision: (…) c) If the subject matter thereof extends beyond the content of the application as filed or, when the patent was granted on the basis of a divisional application, if the subject matter thereof extends beyond the content of the initial application as filed*”.

***With regard to the nullity of Claim 2;***

Claim 2 of the limited patent is thus drafted: “*Process for preparing a liquid pharmaceutical formulation containing a complex of macrocyclic chelate with a lanthanide and a mol/mol amount of the free macrocyclic chelate of between 0.002 and 0.4%, advantageously between 0.02 and 0.3%, very advantageously between 0.025 and 0.25%, the macrocyclic chelate being DOTA, and the lanthanide being gadolinium, said process comprising the following successive steps:*

*a) determination of a theoretical target concentration of free macrocyclic chelate Ctcl in the final liquid pharmaceutical formulation;*

*b) preparation of a liquid pharmaceutical composition containing, on the one hand, the complex of macrocyclic chelate with a lanthanide and, on the other hand, free macrocyclic chelate and/or free lanthanide by mixing a solution of free macrocyclic chelate and of free lanthanide so as to obtain the complexation of the lanthanide by the macrocyclic chelate, the amounts of free macrocyclic chelate and of free lanthanide being added being such that there is a difference between the amounts of free macrocyclic chelate and of free lanthanide added and the stoichiometric proportions, and such that all the lanthanide is complexed and that Ccl > Ctcl, the macrocyclic chelate/lanthanide (mol/mol) ratio advantageously being less than 1.2;*

*c) measurement, in the pharmaceutical formulation obtained in step b), of the concentration of free macrocyclic chelate Ccl, the concentration of free lanthanide Cll being equal to 0; d) adjustment of Ccl so as to obtain Ccl = Ctcl and Cll being equal to 0, by elimination of free macrocyclic chelate and/or by addition of free lanthanide and/or by pH modification*”.

It results from the comparison between the initial patent application and the limited Claim 2, that all of the features of step b) of the latter are found in the combination of Claims 1, 2, 3 and 5 as filed:

Thus, the recalled preamble of Claim 2 above is stated in the preamble of Claim 1 of the patent application which describes a “*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%, advantageously between 0.02 and 0.3%, very advantageously between 0.025 and 0.25%, the macrocyclic chelate advantageously being selected from DOTA, NOTA, DOTA.GA, D03A, BT D03A, HP D03A and PCTA, preferably DOTA, said process comprising the following successive steps: (…)*”, the circumstance that other chelates are targeted in the initial application being of no consequence in this regard since said application in any event targets the chelate finally retained in the limited claim (DOTA).

Likewise, step a) of the limited Claim 2 was presented in Claim 1.a) filed, according to which this step also consists of the “*determination of a theoretical target concentration of free macrocyclic chelate Ctcl in the final liquid pharmaceutical formulation*”.

In addition, step b) of the limited Claim 2 is clearly described, on the one hand, in Claim 1.b) and on page 5 of the description (lines 12 to 14) which targets a “*preparation of a liquid pharmaceutical composition containing, on the one hand, the complex of macrocyclic chelate with a lanthanide and, on the other hand, free macrocyclic chelate and/or free lanthanide*”; on the other hand, in Claim 2 of the initial application which discloses a “*Preparation process according to Claim 1, characterized in that step b) consists in mixing a solution of free macrocyclic chelate and of free lanthanide so as to obtain the complexation of the lanthanide by the macrocyclic chelate*”; in Claim 3 of the initial application which discloses a “*Preparation process according to Claim 2, characterized in that, in step b), there is a difference between the amounts of free macrocyclic chelate and of free lanthanide added and the stoichiometric proportions*”; and, finally, in Claim 5 of the initial application and lines 12 to 15 on page 11 of the description which disclose a “*preparation process according to Claim 3, characterized in that, in step b), the amounts of free macrocyclic chelate and free lanthanide added are such that all the lanthanide is complex and that Ccl > Ctcl, the macrocyclic chelate/lanthanide (mol/mol) ratio advantageously being less than 1.2*”.

Thus, Claim 5 of the patent application precisely discloses a process for preparing the pharmaceutical formulation, characterized in that, in step b), the amounts of macrocyclic chelate and free lanthanide added are such that “*all the lanthanide is complex*”, like that which is envisaged in Claim 2 of the limited patent.

While this functional feature is explicitly mentioned for one of the three variants of the production process (case “B”), without being envisaged in cases A and C, it nevertheless remains the case that it is clearly envisaged as an option disclosed in the initial application of which the title, which relates to a process for producing a formulation, can lead a person skilled in the art, a chemist used to combining various formulae, not to consider that this feature was excluded from all other embodiments, the fact that this requirement of Claim 2 of the limited patent can contradict another feature of this same claim (namely the presence of free lanthanide) stemming, as appropriate, from a lack of clarity but not from an undue extension of the subject matter of the patent.

Consequently, the application for nullity of Claim 2 on the grounds of undue extension of the subject matter shall be dismissed.

***Regarding the nullity of Claims 3 to 11;***

Since the company BAYER PHARMA submitted nullity on the grounds of undue extension of Claims 3 to 11 as the result solely of the nullity of Claim 2, because these Claims 3 to 11 include the subject matter of Claim 2, without further explaining this evidence claim by claim, this application will consequently also be dismissed, Claim 2 having been validated.

**Regarding the application for nullity on the grounds of insufficiency of disclosure of Claims 1 and 2;**

The company BAYER PHARMA submits that the invention which is the subject matter of Claims 1 and 2, which are independent claims, is not sufficiently disclosed in the text of the patent for a person skilled in the art to be able to be reproduced.

As regards Claim 1, the company BAYER PHARMA specifies that a person skilled in the art who implements exactly the teaching of the GUERBET patent and in particular example No. 2 is not able, by simply applying the recommendations of the patent and his general knowledge, to obtain, at the end of step b) the solution comprising only the Gd-DOTA complex and the free gadolinium such that the patent does not allow a person skilled in the art to carry out the claimed invention in its entirety.

The company BAYER PHARMA thus reveals that the only example intended to illustrate the implementation of the alleged invention of Claim 1 of patent FR 539, namely example No. 2, describes a process for preparing a Gd-DOTA complex starting from an amount of gadolinium (in the form of gadolinium oxide) which is slightly higher than the amount of DOTA and that two experts attempted, independently of one another, to reproduce this example No. 2. It specifies that the results of their tests show that Claim 2 is insufficiently disclosed since a large amount of DOTA is not complexed at the end of step b) since a considerable amount of gadolinium necessarily remains in the free state. It thus considers that it is not possible to achieve complete complexation of the gadolinium, as required by steps b) and c) of Claim 2.

It adds that the interpretation of Claims 1 and 2 by the company GUERBET, wherein the measurement step c) carried out on a sample taken from the reactor is not supposed to represent the state of the formulation at the end of step b), but instead the “fictitious” state of this formulation, is taught neither by the text, nor by examples, nor by claims of the patent FR 539. It considers that, contrary to what the company GUERBET asserts, a person skilled in the art does not know, on the basis of his general knowledge, at what pH the complexation reaction is complete and, as a result, the invention is therefore insufficiently disclosed.

As regards Claim 2, the company BAYER PHARMA emphasizes that it cannot be considered to be sufficiently disclosed while the description of the patent comprises no example illustrated in this claim. It adds that the reports by Messrs WELZIG and HAHN make it possible however to demonstrate that it is not possible to obtain complete complexation of the DOTA with the gadolinium at the end of step b), unless the pH is adjusted with meglumine, and that the same would be true if, instead of starting from an amount of gadolinium higher than that of DOTA, one started from reverse proportions.

It specifies that Claim 2 nevertheless explicitly requires that step b) be carried out in the absence of free gadolinium such that Claim 2, which does not specify the pH at which step b) should be carried out, covers embodiments which cannot be reproduced. It also considers that exhibit No. 33 entitled “Production of a pilot batch of a liquid pharmaceutical formulation according to the process in patent EP 2 799 089” introduced by the company GUERBET does not even satisfy the minimum conditions of form for being able to be considered admissible in proceedings relating to the sufficiency of disclosure of a patented invention while it appears to have been carried out internally by the company GUERBET, even if there is no indication as to the author of this note or as to the individuals who would have carried out the alleged implementation of the process which is the subject matter of Claim 2 of patent FR 539 after limitations such that it does not meet the requirements of Articles 201 and 202 of the French Code of Civil Procedure. It adds that this exhibit is not relevant because it contains no indication regarding the pH of step b), said step having been carried out without meglumine, although it has been established that, without adjustment of the pH, it was impossible for all the gadolinium to be complexed during step b).

The company BAYER PHARMA also emphasizes that Claim 2 also provides that the adjustment of the DOTA is carried out by elimination of the amount of free DOTA in excess relative to the amount of free DOTA targeted and that this elimination is carried out by passage over an ion exchange resin, such as anionic resins, and submits that it is materially impossible with an ion exchange resin to remove only a part of the free DOTA, so as to maintain, in the pharmaceutical formulation, the precise amount of free DOTA targeted. It considers, under these conditions, that it would therefore have been necessary for the patent to illustrate the feasibility of such a process, by explaining the parameters (size of the filtration column, flow rate, retention tongue, etc.) that a person skilled in the art could have followed, in order to make such a process plausible and that, in the absence of such data, it is impossible for a person skilled in the art to reproduce this embodiment, which is merely speculative, it being specified that the report produced by the company GUERBET entitled “Report on the efficiency of resin for removing a small amount of free DOTA” does not give the parameters such as filtration column size, flow rate, etc., that would have allowed a person skilled in the art to produce DOTAREM.

The company BAYER PHARMA consequently considers that Claims 1 and 2, and also Claims 3 to 11 which refer thereto, cover embodiments which cannot be reproduced, such that they are insufficiently disclosed and should be invalidated.

In reply, the company GUERBET pleads that this evidence of nullity should be dismissed and emphasizes that the reasoning by the company BAYER PHARMA is based on three erroneous premises according to which the complexation should be total in the reactor in step b), the process of Claim 1 supposedly excludes any pH adjustment, and a person skilled in the art could not place himself under the conditions required in step c).

It recalls that step b) covers both embodiments in which the complexation is total in step b), and embodiments in which the reaction conditions are such that the complexation has reached equilibrium, but is not complete, which depends, as a person skilled in the art knows, on the pH at which step b) was carried out, it being known that the complexation equilibrium is shifted towards total formation of the complex only if the pH is sufficiently high.

It recalls that the company BAYER PHARMA cannot submit that the process of Claim 1 would exclude any pH adjustment on the basis of the fact that, on page 12, line 17 of the patent, this process is denoted as “without adjustment by the pH”, while this information makes it possible only to distinguish the process of Claim 1 from another process (not claimed) comprising a step b1 with a very specific pH adjustment since it involves increasing it up to 12 and since the process of Claim 1 does not comprise such a step b1, it being specified that example 2 expressly describes a pH adjustment in the reactor during step d.

The company GUERBET specifies that, contrary to what is alleged by the company BAYER PHARMA, it is only in step c) that the complexation must be total in order for it to be possible for the concentration of free gadolinium to be measured, since Claim 1 contains a functional feature obliging a person skilled in the art to work, during step c), under conditions such that the concentration of free DOTA is zero, this requirement not applying to the solution present in the reactor, but to the solution taken as sample.

The company GUERBET recalls that, in order to assess whether a patent is sufficiently disclosed, it is necessary to combine its teaching with the general knowledge of a person skilled in the art and that it is not required for a patent to again disclose information already known to a person skilled in the art and that, in the case of point, at the priority date, several articles described the conditional constants of formation of the Gd-DOTA complex at all pHs making it possible to determine the pH range in which the complexation is complete such that, with regard to such a formation, a person skilled in the art can without difficulty determine the conditions required for measuring the free Gd in the claimed step c) and said person skilled in the art subsequently knowing how to comply with such conditions, that is to say to work at a pH between 4 and 7, he in fact knows how to modify as appropriate the pH of the solution contained in the sample in order to achieve the pre-determined pH range. The company GUERBET thus considers that, with regard to the books, the new articles and the tests introduced into the proceedings, it is established that a person skilled in the art knows how to determine, by virtue of these documents or through experimentation, the pH conditions required for the measurement of step c) and that he can therefore, without undue difficulty, carry out the process of Claim 1.

The company GUERBET adds that the reports produced in the proceedings by the company BAYER PHARMA are ineffectual since they do not seek to carry out the patent in process in its entirety, but by reproducing only step b), limit themselves to showing that the complexation is not total at the end of step b) when example 2 is reproduced, whereas, contrary to what the company BAYER PHARMA submits, Claim 1 does not require that the complexation be total in step b).

Finally, the company GUERBET specifies that it carried out tests with industrial amounts and that these tests that were carried out in its own laboratory by an independent expert, such as Professor Guillon, all give the same indications and demonstrate that a person skilled in the art is in a position, by virtue of the teachings of the patent and of his general knowledge, to carry out the process of Claim 1 of the patent FR 539 and that the process claimed makes it possible to obtain the target concentration of free DOTA.

As regards Claim 2, the company GUERBET emphasizes that the fact that no example illustrates the embodiment of Claim 2 is not of a nature to demonstrate that this claim is insufficiently disclosed since it is in no way necessary, in order for a patent to be sufficiently disclosed, for it to comprise its examples, nor *a fortiori* for each embodiment of the claimed invention to be accompanied by an example, it being observed that the process which is the subject matter of Claim 2 comprises the same steps as Claim 1, with the only difference being that the respective roles of the DOTA and of the gadolinium are reversed, the DOTA then being in excess during the formulation in step b) so that all the results obtained during the implementation of the process of Claim 1 can be directly extrapolated to the process of Claim 2. It adds that it introduced into the proceedings tests carried out on a pilot scale showing that the process of Claim 2 can easily be reproduced by a person skilled in the art and solves the technical problem.

The company GUERBET adds that Claim 2 expressly provides for the possibility of the presence of free lanthanide during step b) and that there is no contradiction in that it would also require that the complexation be totalled during this step even though there cannot be both a presence of free lanthanide and total complexation of the lanthanide, provided that it is never required that all the lanthanide be complexed during step b) and that total complexation was required only during the measurement phase c) and not in step b). Finally, the company GUERBET considers that the company BAYER PHARMA cannot submit that it would not be possible to carry out step d) of Claim 2 in its variant consisting in eliminating free macrocyclic chelate since, in the description, this elimination is carried out by a passing over an ion exchange resin, and that, while the patent does not contain an example in this regard, this does not, per se, make it insufficiently disclosed due to being speculative, since a speculative patent is a patent which is not supported by any research work or any beginning of research work, and that, in the case in point, the claimed process is illustrated by an example.

***On the basis of this;***

By application of Article L. 612-5 of the French Intellectual Property Code, the invention must be disclosed in the patent application sufficiently clearly and completely for it to be possible for a person skilled in the art to carry it out.

It also emerges from Article L. 613-25 of this same code that a patent “*is declared invalid by legal decision (…) b) if it does not disclose the invention sufficiently clearly and completely for it to be possible for a person skilled in the art to carry it out*”.

The requirement of sufficiency of disclosure, the purpose of which is to guarantee the possibility for a person skilled in the art, defined as the person who possesses the normal general knowledge of the art in question, to carry out the invention without excessive burden by virtue of the information provided by the whole of the patent and his own technical knowledge, is met provided that the description indicates the means which give a person skilled in the art, who has the capacities and the knowledge that one is entitled to expect of him, the possibility of carrying out or implementing the invention by making a reasonable effort of reflection, for example routine tests.

In the case in point, a person skilled in the art should be likened to a chemist having experience in particular in process chemistry.

***Regarding the insufficiency of the disclosure of the limited Claim 1;***

In the case in point, Claim 1 which relates to a process for preparing the pharmaceutical formulation containing a complex of gadolinium with the macrocyclic chelate DOTA (Gd-DOTA), this formulation containing an excess of free DOTA macrocyclic chelate of 0.002% to 0.4% mol/mol, expressly describes the “successive steps” that this process comprises in these terms:

*“a) determination of a theoretical target concentration of free macrocyclic chelate Ctcl in the final liquid pharmaceutical formulation;*

*b) preparation of a liquid pharmaceutical composition containing, on the one hand, the complex of macrocyclic chelate with a lanthanide and, on the other hand, free macrocyclic chelate and/or free lanthanide, by mixing a solution of free macrocyclic chelate and free lanthanide so as to obtain the complexation of the lanthanide by the macrocyclic chelate, the amounts of free macrocyclic chelate and free lanthanide added being such that a difference exists between the amounts of free macrocyclic chelate and of free lanthanide added and the stoichiometric proportions, and such that not all the lanthanide is complex, the lanthanide / macrocyclic chelate (mol/mol) ratio advantageously being less than 1.2;*

*c) measurement, in the pharmaceutical formulation obtained in step b), of the concentration of free lanthanide Cll, the concentration of free macrocyclic chelate Ccl being equal to 0;*

*d) adjustment of Ccl by addition to the formulation obtained in step b) of the amount of free macrocyclic chelate required in order, on the one hand, to complete complexation of the free lanthanide so as to obtain Cll = 0 and, on the other hand, to obtain Ccl = Ctcl*”.

It emerges from this claim that said claim describes the four steps which allow a person skilled in the art to carry out the invention, step a) having the objective of determining a theoretical target concentration of free macrocyclic chelate (free DOTA) Ctc in the final liquid formulation; step b) having the objective of mixing the free macrocyclic chelate (DOTA) and the free lanthanide (gadolinium) in order to obtain, by adjusting the amounts, an excess of free gadolinium (Claim 1) – or an excess of free DOTA (Claim 2); step c) consisting in measuring, in the formulation obtained in step b), the concentration of free macrocyclic chelate or the concentration of free lanthanide under conditions such that the concentration of free DOTA (Claim 1) or free gadolinium (Claim 2) is equal to 0; and step d) having the objective of adjusting the formulation obtained in step b) on the basis of the measurement carried out in step c) in such a way that it no longer contains free lanthanide and that it contains a concentration of free macrocyclic chelate equal to the theoretical target concentration defined in step a).

In this regard, although step a) is intellectual in nature since it aims to theoretically set the concentration of free chelate in the final formulation, it cannot be dismissed by the company BAYER PHARMA on the ground that it supposedly has no technical nature, since this target concentration must be included in the range which is described in the preamble of the claim, thereby conferring on it a technical nature, and since, in any event, as regards in the case in point assessing a possible insufficiency of disclosure of the invention, this step participates precisely in the overall understanding by a person skilled in the art of the process of implementing the invention and therefore of the description thereof.

In addition, it is also established that the patent comprises, in its description, an example of implementation of Claim 1 (example 2), it being observed that it is in no way required, in order for an invention to be sufficiently disclosed, for all the embodiments to be represented in the patent.

In substance, the company BAYER PHARMA considers that the invention is insufficiently disclosed because its example 2 cannot be carried out by a person skilled in the art on the grounds that it is not possible to achieve total complexation at the end of step b) without adding meglumine and that this step is neither disclosed nor claimed.

In support of this evidence, it produces a report by Dr WELZIG according to which example 2 of the patent supposedly does not comply with Claim 1 since a very large amount of free DOTA supposedly remains at the end of step b), although said claim postulates, according to the company BAYER PHARMA, that there is total complexation of the DOTA at the end of this step, otherwise it would not be possible to measure, in step c), the concentration of free Gd in the formulation of step b), but instead a content of gadolinium other than that contained in the formulation of step b).

However, it should be observed that Claim 1 does not in any way expressly describe that the complexation of the DOTA must be total at the end of step b), no mention being produced in order to corroborate this restrictive interpretation of the patent. While, in the description of the patent, it is indicated “*consequently, at the end of this step b), the pharmaceutical formulation will typically comprise macrocyclic chelate-lanthanide complex and either free macrocyclic chelate or free lanthanide*”, this insertion is not intended to be generalized, the use of the adverb “typically” allowing the person skilled in the art to consider that this is a possibility that is not limiting.

In addition, should this interpretation be retained, it would render needless step c), which has precisely the objective of measuring the concentration of free lanthanide in the pharmaceutical formulation obtained in step b) under conditions such that the concentrations of free DOTA is equal to zero, which requires all the DOTA to be complexed by the gadolinium. It necessarily results from this that step c) thus comprises a functional feature – achieving total complexation of the DOTA – in order to carry out the measurement of the free gadolinium that will precisely be performed on the sample taken during this step c), and that would be of no use if the complexation of the DOTA had to be total at the end of the step b) as submitted by the company BAYER PHARMA.

Thus, even though step c) of Claim 1 does not exclusively disclose that it involves a modification of the sample taken, this modification implicitly results from the functional feature that it imposes for carrying out the desired measurement, namely a concentration of free macrocyclic chelate Cc1 which must be equal to zero.

This being so, a person skilled in the art will understand that the total complexation thus sought for measuring the free gadolinium will be that which results from the sample and will not necessarily be that which is present in the mixture of the tank from step b). This interpretation is corroborated by example 2 of the description which describes a step 5 corresponding to the adjustment step d) of Claim 1 and under the terms of which it is specified that this step comprises an “adjustment of the pH and of the density” with introduction of meglumine into the tank.

Incidentally, it is precisely what Dr WELZIG did under the terms of the report produced by the company BAYER PHARMA, since said Dr, having noted that the complexation was not complete at the end of step b) and specified that an “*adjustment of the free DOTA in the reaction mixture by addition of solid DOTA or of a solution was consequently not possible*”, added meglumine, which results in an increase in the pH and allowed, as noted by this expert, a reduction in free DOTA content and therefore complete complexation, which tends to precisely establish that a person skilled in the art, who knows that the pH can have an impact on complexation, and who is confronted with the same difficulty, will act likewise in order to be able to carry out the invention.

In addition, while a person skilled in the art does not have available the pH range allowing complete complexation, the company GUERBET provides evidence that this information ensues from an article devoted to “stable bifunctional metal chelates used in radiotherapy” by Mr Min K. Moi et al., presented during a conference on radioimmunodetection, which comprises a graph disclosing the conditional constants at all pHs of Gd-DOTA complexation and, in addition, that the formulae for calculating the conditional constant as a function of the pH are described in a manual published in 2001 in Belgium intended for university undergraduate and postgraduate students, entitled “*chemical equilibria in solution*” which presents itself as having the “*objective of describing various situations of chemical equilibria, which are first simple and then increasingly complex depending on the number of reactions involved*” and from which it emerges that “*variations in pH can have a considerable and direct effect on complexation equilibria*” such that this is therefore general knowledge of a person skilled in the art.

It is therefore impossible to agree with the company BAYER PHARMA when it indicates that “*a person skilled in the art, when reproducing example 2 in accordance with the description of the patent, must not make a pH adjustment in order to push the reaction until it is complete, otherwise he will distort the teaching of the patent at the time of preparation of the pharmaceutical composition*”.

Apart from the fact that this interpretation ignores the fact that a person skilled in the art seeking to reproduce the invention must also favour a reading of the patent which gives him an effect to the detriment of that which causes him to produce none, this amounts to prohibiting him from making use of his general knowledge in order to carry out an invention.

With regard to these elements, in the case in point, a person skilled in the art who knows that the invention comprises, as recalled by the patent description, “at least one measurement step” and “at least one adjustment step”, understands that it can only be imagined in several steps which are not necessarily autonomous with respect to one another, but that, on the contrary, the complexation may, where appropriate, be obtained only at the end of all these steps, once the dissolution, measurement and adjustment operations described by steps b), c) and d) have been carried out.

The plea relating to insufficiency of disclosure of the limited Claim 1 will consequently be dismissed.

***Regarding the insufficiency disclosure of Claim 2;***

The limited Claim 2 is thus drafted:

*“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 between 0.002 and 0.4%, advantageously between 0.02 and 0.3%, very advantageously between 0.025 and 0.25%, the macrocyclic chelate being DOTA, and the lanthanide being gadolinium, said process comprising the following successive steps:*

*a) determination of a theoretical target concentration of free macrocyclic chelate Ctcl in the final liquid pharmaceutical formulation;*

*b) preparation of a liquid pharmaceutical composition containing, on the one hand, the complex of macrocyclic chelate with a lanthanide and, on the other hand, free macrocyclic chelate and/or free lanthanide, by mixing a solution of free macrocyclic chelate and free lanthanide so as to obtain the complexation of the lanthanide by the macrocyclic chelate, the amounts of free macrocyclic chelate and free lanthanide added being such that a difference exists between the amounts of free macrocyclic chelate and of free lanthanide added and the stoichiometric proportions, and such that all the lanthanide is complexed and that Ccl > Ctcl, the macrocyclic chelate / lanthanide (mol/mol) ratio advantageously being less than 1.2;*

*c) measurement, in the pharmaceutical formulation obtained in step b), of the concentration of free macrocyclic chelate Ccl, the concentration of free lanthanide Cll being equal to 0;*

*d) adjustment of Ccl so as to obtain Ccl = Ctcl and Cll being equal to 0, by elimination of free macrocyclic chelate and/or by additional free lanthanide and/or by pH modification*”.

It is established that Claim 2 is not illustrated by an example in the patent.

However, it emerges from Claim 2 that the latter comprises the same implementation steps as Claim 1 for preparing the pharmaceutical formulation, the respective roles of the DOTA and of the gadolinium being reversed, an excess of DOTA being envisaged for step b) in this claim, contrary to Claim 1 which envisages an excess of gadolinium.

Consequently, a person skilled in the art who is able to carry out Claim 1 as indicated above, and for the same reasons which should be referred to, is able to carry out Claim 2 by making use in particular of his general knowledge, such that the absence of an example to illustrate this claim is not of a nature to cause it to have an error of lack of disclosure.

In this regard, the wording of Claim 2 actually suggests, as observed by the company BAYER PHARMA, that, during step b), the complexation of the lanthanide is complete since it discloses a “*preparation of a liquid pharmaceutical composition containing, on the one hand, (…) and, on the other hand, (…) so as to obtain the complexation of the lanthanide by the macrocyclic chelate, the amounts of free macrocyclic chelate and free lanthanide added being such (…) that all the lanthanide is complexed (…)*”.

However, this same step clearly envisages the presence, on the one hand, of a complex of macrocyclic chelate with a lanthanide and, on the other hand, free macrocyclic chelate “and/or free lanthanide” and it emerges from the general knowledge of the person skilled in the art that it is not possible to find both the presence of free lanthanide and the total complexation of the lanthanide, such that reading said patent with the objective of giving an effect of the patent, which provides for various steps of carrying out the process for dissolution, measurement and adjustment, he will understand that the total complexation of the lanthanide may be carried out subsequently and that this circumstance is not of a nature to make it impossible to reproduce the claim, which supposes envisaging carrying out Claim 2 in its entirety without stopping at only one of its steps without taking the others into account.

Finally, in step d), an adjustment of the preparation “*by elimination of free macrocyclic chelate*” is envisaged. This embodiment is clearly explained in the description of the patent which specifies that “*Advantageously, the elimination of free lanthanide is carried out by passing over an ion resin. It is thus possible, for example, to use a styrene/divinylbenzene copolymer resin which contains immunodiacebate ions acting as a chelating group for the binding with the metal ions*”. While the company BAYER PHARMA emphasizes that this is impossible, with an ion exchange resin, to eliminate only a part of the free DOTA, it does not justify this allegation with any evidence introduced into the proceedings, even though the burden of proof of this speculative nature of the patent with regard to this point is its responsibility.

As these pieces of evidence stand, the plea in relation to the insufficiency of disclosure of Claim 2 will also be dismissed.

***Regarding the insufficiency of disclosure of Claims 3 to 11;***

Since the company BAYER PHARMA did not develop and argue the nullity on the grounds of insufficient disclosure of Claims 3 to 11 other than by specifying that this nullity results from said claims all referring to Claim 1, this plea was submitted by BAYER PHARMA as regards Claims 3 to 11 will also be dismissed.

**Regarding the lack of inventive step of Claim 1;**

The company BAYER PHARMA, which recalls that the pharmaceutical formulations that are of use as contrast agents, based on the complexes formed from a chelate and from gadolinium and comprising a slight excess of free chelate were perfectly known to a person skilled in the art well before 19 February 2008, which is the date of filing of patent FR 539, since this is the case with the DOTAREM product of the company GUERBET, authorized in France in 1989 and also patent US 5 876 695 by the company SCHERING, the priority date which is 1986 and which describes, in example 2 thereof, the preparation of a pharmaceutical formulation comprising a complex of gadolinium with DPTA, submits that the process of Claim 1 is not inventive.

It sets out that, for the purpose of preparing such a product, a person skilled in the art (a process chemist) would necessarily carry out known processes for the production of contrast agent formulations, this being with an at the very least reasonable expectation of success. It emphasizes that the steps envisaged in Claims 1 and 2, which comprise a complexation step b) wherein non-equal amounts (differing from the stoichiometry) of DOTA and of gadolinium are used, followed by a step of measuring the excess of either the DOTA or the gadolinium, and a step of adjusting this excess so as to achieve the desired concentration of free DOTA and to obtain a pharmaceutical formulation known to a person skilled in the art, is a routine procedure for a person skilled in the art, as demonstrated by several prior art documents, HAGAN et al., WO 91/10645, US 5 049 667 and AIME et al.

It also considers that the technical problems brought to the fore by the patent relating to the use of stoichiometric amounts of chelate and of gadolinium that would pose specific weighing problems, in order to obtain formulations comprising a slight excess of chelate, and to the fact that the chelates comprise acid functions which can bind water, for example atmospheric water (this is why these products are termed “hygroscopic”) distort the weighing, were solved by a person skilled in the art, well before the date of the GUERBET patent, since a person skilled in the art who uses stoichiometric amounts on an industrial scale, will quite simply control, in the reaction reading, the amounts of each of the reagents and, if one of the two reagents is in excess, he will simply adjust his concentration by adding an appropriate amount of the other reagent so as to achieve the desired pharmaceutical formulation. It thus sets out that such a control and such an adjustment are nothing other than the measurement step c) and the adjustment step d) of Claims 1 and 2 of the GUERBET patent such that this company raised, in the description of its patent, artificial technical problems that a person skilled in the art could easily solve by applying routine methods and that it did not demonstrate that, if these problems were to exist, the processes claimed make it possible to solve them in a manner which involves an inventive step.

It specifies in particular that the steps of the process of Claim 1 are identical, in their combination, to those of example 17 of PCT application WO 91/10645, the claimed process being different only in terms of the nature of the chelate used, which is merely a simple process by analogy with respect to that described in example 17. It considers that such a process by analogy is not inventive as long as it results in a known product and that a person skilled in the art who, at the date of filing of patent FR 539, had knowledge of the DOTAREM formulation as described in the DOTAREM notice, and who was seeking a process for producing it, merely had to carry out the process described in example 17 of document WO 645, while adapting it in an obvious manner so as to achieve the process which is the subject matter of Claim 1.

The company BAYER PHARMA adds that Claim 1 of the GUERBET patent lacks inventive step with respect to the teaching of the DOTAREM notice combined with example 2 of patent US 5 049 667. It in fact considers that a person skilled in the art wishing to produce DOTAREM merely has to follow example 2 of this American patent and to make two routine adjustments consisting in using DOTA instead of the dimethylated derivative of DOTA and in adding a sufficient amount of chelate to reach the excess of 0.12% of DOTA of the DOTAREM product.

The company BAYER PHARMA also emphasizes that the feature according to which its process is supposedly particular owing to the determination of a target concentration of free chelate to be achieved in the final formulation (step a)), has no bearing on the assessment of the alleged inventive step of the process according to Claim 1 since it is a non-technical element because it is purely theoretical, and that a person skilled in the art was aware of this feature through the disclosure of the DOTAREM notice well before the priority date of the GUERBET patent.

It considers that the fact of using, in the initial formulation, an excess of gadolinium is a feature that was perfectly disclosed in the prior art, as attested to by the prior publications introduced into the proceedings, and in particular example 17 of the prior publication WO 645, in which the complexation reaction is carried out with an excess of gadolinium relative to the ligand and the fact that the measurement must be quantitative and not only qualitative is a perfectly ordinary feature for a person skilled in the art, specializing in pharmaceutical products, who must every day deal with precise amounts of substances capable of affecting the health of patients and verify these substances not only qualitatively, but also quantitatively.

In reply, the company GUERBET states that the documents constituting the closest prior art, namely the DOTAREM notice and patent US 5 876 695, do not allow a person skilled in the art to achieve the invention in an obvious manner and that no document presented by the company BAYER PHARMA relates to the problem of the production, on an industrial scale, of a contrast agent comprising a low excess of free macrocyclic chelate, nor teaches how to reliably and reproducibly obtain a predetermined low excess of free chelate. It considers that the prior art taught only, for laboratory processes, to firstly synthesize the “stoichiometric” complex of Gd-DOTA in order to obtain the intended pharmaceutical formulation, as indicated in example 22 and in the description of application WO 91/10645, and that these processes made it possible to obtain a solution without gadolinium excess but did not allow any control of the final excess of free chelate, such that it was therefore obvious for a person skilled in the art to arrive at the specific steps of the process of Claim 1. It specifies in particular that it was not obvious for a person skilled in the art to come to imagine that a single step of measurement and adjustment, under the specific conditions claimed, could make it possible to solve the technical problem.

The company GUERBET emphasizes that the prior art documents cited by the company BAYER PHARMA are based on a reconstruction *a posteriori* that is totally prohibited in terms of assessment of inventive step since a person skilled in the art would not have been prompted to specifically consult such documents in order to solve the technical problem because they relate to an industrial process, this being even though the description of the patent clearly emphasizes the fact that the implementation of the process on an industrial scale is an essential parameter of the technical problem. It specifies in this regard that the DOTAREM notice contains only the information relating to the DOTAREM composition solved by it and that this document does not in any way teach a person skilled in the art how to achieve this result and in particular not the steps of the production process which makes it possible to obtain a product composed of a Gd-DOTA complex and 0.12 mol/mol of excess of free DOTA, it being observed that, starting from only the formulation of the product, it is not possible for a person skilled in the art to determine the process for producing same.

It adds that the objective of application WO 645 is to provide new chelating agents having better stability, solubility in water and better selectivity or better biodistribution than the prior art chelates, in particular DOTA, and that it proposes to solve this difficulty by means of new compounds which have a particular structure, such that the solution to this technical problem is in no way presented as lying in the particular formulation of these new compounds and specifies that example 17 of this document, the starting proportions of which are not stoichiometric, does not describe a precise quantitative measurement as taught in step c) of the invention, that the objective of application WO 645 at the stage of the synthesis of the active ingredient is merely to be sure of the absence of any gadolinium and is not to obtain a solution comprising any excess of free chelate and that the solution of example 17 is not presented as a directly injectable pharmaceutical formulation. The company GUERBET adds that the objective is therefore the disappearance of the free gadolinium and not the obtaining of an excess of free chelate, it being specified that the method of successive additions is not controlled, that it is therefore impossible to predict whether an excess of chelate will be obtained and in what amount, and that it is verified that the possible excess does not exceed 0.05% such that one is therefore far removed from the controlled adjustment which makes it possible to obtain a predetermined excess as claimed in step d) of Claim 1.

The company GUERBET thus considers that application WO 645 does not have the objective of providing a process that can be used on an industrial scale of a chelate/gadolinium complex.

The company GUERBET also states that each of the steps of the processes of Claims 1 and 2 are not conventional steps for a person skilled in the art that are merely routine work: it being specified that the company BAYER PHARMA cannot rely on application WO 645 and on patent US 667 to illustrate this alleged general knowledge and that, as regards the document entitled “Guidance for industry PAT – a framework for innovative pharmaceutical development, manufacturing of quality assurance”, it precisely underlies the need to design mechanisms of control for each pharmaceutical product, which means that it is impossible to systematically apply, for all processes for producing a pharmaceutical formulation, the same mechanisms of measurement, of controls and of adjustment, but that it is necessary to develop them case by case.

The company GUERBET considers that the company BAYER PHARMA distorts Claims 1 and 2 and the teachings of the prior art documents since the processes of Claims 1 and 2 do not boil down to complexation processes comprising a step of complexation followed by measurements and adjustments, and omits to recall the fact that it is a question of industrial processes carrying out, in a single step, the synthesis of the active ingredient and the formulation of the final pharmaceutical composition, that is to say ready to be injected into the patient; the determination of a target concentration of free chelate to be achieved in the final formulation; the fact of deliberately moving away from the target by deciding to obtain an excess of gadolinium or a target excess of free chelate different from the target concentration with a specific proportion of the starting products; the conditions under which the measurement of free entities must be carried out; at a zero concentration of the free chelate (Claim 1) of free gadolinium (Claim 2); the fact that this measurement must be quantitative and not only qualitative; the fact that the concentration of free chelate determined at the convening of the process is reliably and reproducibly obtained.

The company GUERBET thus submits that none of the documents cited by the company BAYER PHARMA mentions the problem of the patent or, *a fortiori*, proposes a solution to solve it, since no cited document relates to an industrial process, and that no document seeks to obtain a precise concentration of excess of free DOTA in the final formulation.

It also considers that the company BAYER PHARMA does not in any way provide evidence that the claimed processes supposedly do not solve the stated problem and that, since the problem of hygroscopy distorts the measurements of the starting products, the fact of moving away from the stoichiometric proportions supposedly does not solve the problem, whereas, on the contrary, the choice of the starting amounts, of the measurement conditions and of the time at which the adjustment is made makes it possible to dispense with the problem of hygroscopy. It specifies that a single step of measurement and adjustment is necessary in order to achieve this result and that this measurement step carried out in a sample is essential and innovative since it allows a person skilled in the art to perform an extremely precise and reliable measurement in order to be able to reproduce, also extremely precisely and reliably, the conditions measured in the reactor, which allows a person skilled in the art to reproduce, on an industrial scale, the conditions of the formulation during a single overall step of pharmaceutical formulation such that it is not necessary, as in the prior art, to proceed by trial and error by successively and randomly adding small amounts of free chelate.

The company GUERBET emphasizes that a person skilled in the art would have consulted the DOTAREM notice which indicated to him the objective to be obtained, then document US 695, since it is the only document that mentions the problem of the *in vivo* gadolinium release and describes a process for producing a formulation with an excess of chelate and that he would not have consulted documents WO 645 and US 667 which mention neither *a fortiori* nor solve the technical problem in question. It specifies that, with regard to the DOTAREM notice and patent US 695, a person skilled in the art was prompted to adopt a process very different from the process of Claim 1 in order to solve the technical problem, such that a person skilled in the art would not in an obvious manner come to the subject matter of Claim 1 which therefore involves an inventive step.

It also considers that Claim 1 is also inventive with regard to the combination of the DOTAREM notice and of WO 645 cited by the company BAYER PHARMA, since none of the examples of WO 645 relates to a process for obtaining a final composition ready to be administered to the patient, with the exception of example 22, which would have led a person skilled in the art to firstly synthesize the “stoichiometric” Gd-DOTA complex, and to mix this stoichiometric complex with the target excess of free DOTA in order to obtain the intended pharmaceutical formulation, as indicated in example 22 and in the description of application WO 91/10645, and that this process is different from the process of Claim 1 of which it discloses none of the steps, such that it was not obvious for a person skilled in the art, starting from a process disclosing none of the steps of Claim 1, to come to the specific sequence of the steps of the claimed process. The company GUERBET adds that, even if a person skilled in the art had been prompted to consult example 17, even though it describes no step of the claimed process, this example does not make it possible to solve the technical difficulty since it does not make it possible to reproducibly and reliably obtain a predetermined excess of free chelate, but proceeds by trial and error and random additions of amounts of chelates and even though it is thus impossible to know whether this concentration is indeed greater than 0.002%, advantageously than 0.02% and very advantageously than 0.025%, or even if any excess of free chelate exists, this uncertainty being contrary to the objective of the patent, which is precisely to make it possible to ensure, at each reproduction of the process, that the formulation contains a specific and predetermined excess of free chelate.

Finally, the company GUERBET submits that Claim 1 is inventive with regard to the DOTAREM notice combined with patent US 667 on the grounds that the objective technical problem is that of providing a safe and reliable process for the preparation on industrial scale of a liquid pharmaceutical formulation of a Gd-DOTA complex comprising a predetermined small excess of free DOTA, such as DOTAREM, the concentrations of the Gd-DOTA complex and of free DOTA having to be stable, including after storage for several months or years, and that patent US 667 teaches, in order to obtain a chelate/gadolinium complex on an industrial scale, starting from stoichiometric amounts of gadolinium and of DOTA so as to obtain a solution comprising only the complex without free gadolinium or free chelate, and describes none of the steps of the process of Claim 1 nor, *a fortiori*, the specific sequence thereof, such that it is difficult to see what would have allowed a person skilled in the art, starting from a process different from the one claimed, to arrive at the latter without the prior art giving him the slightest indication in this sense.

***On the basis of this;***

It emerges from Article L. 613-25 a) of the French Intellectual Property Code that a patent is declared invalid by legal decision if its subject matter is not patentable under the terms of Articles L. 611-10, L. 611-11 and L. 611-19.

By application of Article L. 611-10 of the French Intellectual Property Code, “*normal inventions involving an inventive step (…)*” are patentable.

According to Article L. 611-14 of French Intellectual Property Code, “*an invention is considered to involve an inventive step if, for a person skilled in the art, it does not follow obviously from the prior art”*.

Thus, in order to assess the inventive step of a patent, it is necessary to determine, on the one hand, the objective technical problem to be solved, and on the other hand, the closest prior art and, finally, to examine whether the claimed invention, starting from the closest prior art and from the objective technical problem, would have been obvious for a person skilled in the art, who in the case in point must be likened, as indicated above, to a chemist with experience in particular in process chemistry.

***Regarding the objective technical problem to be solved;***

It results from the description of patent FR 539 that the object of said patent is to determine not only an excess of macrocyclic chelate that is sufficient to make it possible to complex any fortuitous release of gadolinium, but also sufficiently low to avoid any toxicity associated with the presence of free DOTA and that “*in the light of this low amount, a new problem arises, unknown from the prior art, namely the need for extremely precise and delicate control, on an industrial scale, of the concentrations of free chelate and therefore of the production of the product in order to achieve this range of target values of amount of free chelate, these values having to be stable, including after storage for several months or years*”.

It is in fact specified that the inventor “*had to develop a preparation process which makes it possible to guarantee the reliability and the reproducibility of the composition of the batches sold*” after having noted that the mixing of the theoretical amounts of the reagent (DOTA and Gd) “*does not make it possible to obtain, in a manner that is sufficiently satisfactory on an industrial scale, the respective amounts of complex of chelate with the lanthanide and of free chelate in low concentration in the pharmaceutical formulation*”.

In this regard, the company GUERBET introduces several documents and tests which, without being contradicted by other documents in the opposite sense by the company BAYER PHARMA, and in particular an article dated 2006 entitled “*How to determine free Gd and the free ligand in a solution of Gd chelates.*”, established that the mixing under stoichiometric conditions of DOTA and gadolinium results in a final solution comprising an excess of DOTA of 0.42% mol/mol and therefore that it is not possible to use the theoretical amounts of the reagents from the industrial application.

As these elements stand, the technical problem to be solved aims to propose a process for the preparation of the DOTAREM product, which makes it possible to reliably determine the respective amounts of complex of chelate with the lanthanide and of free chelate in low concentration in the pharmaceutical formulation, in order for it to be reproducible and for it to enable an application on an industrial scale.

***With regard to the closest prior art to be taken into account;***

*With regard to the relevance of the combination of the DOTAREM notice and international PCT patent application No. WO 91/10645 as closest prior art;*

It should be noted that the company BAYER PHARMA, which cites several documents, does not expressly specify what, in its opinion, constitutes the closest prior art. However, as long as it cites firstly a lack of inventive step of Claim 1 with respect to international application WO 91/10645 in combination with the DOTAREM notice, it can be considered that it is this combination that the company BAYER PHARMA intends to use in opposition to the company GUERBET as being the closest prior art.

There is reason to agree with the company BAYER PHARMA when it selects the DOTAREM notice, since the object of Claim 1 is to disclose a process for preparing a pharmaceutical formulation comprising a Gd-DOTA complex having a very low excess of DOTA of between 0.002% and 0.4% mol/mol and since the notice of the DOTAREM product sold on the French market as early as 1989 describes a pharmaceutical composition for injection, comprising an excess of DOTA corresponding to this range, this point not being contested.

However, this sole document which discloses the product is not sufficient to disclose the process for preparing the pharmaceutical formulation thereof in such a way that a person skilled in the art would be prompted personally to look for a document which discloses a pharmaceutical formulation preparation process.

This is not the case with PCT document WO 91/10645 cited by the company BAYER PHARMA, since this international publication published on 25 July 1991, entitled “Chelants”, relates to “*certain novel chelating agents, in particular polyamines, and the uses thereof, in particular the medical uses thereof*” and notes that there is “*a general and continuous need for polyamine-based chelating agents which form metal chelates of low toxicity, of improved stability or of improved water-solubility or which have improved biodistribution characteristics*”, and proposes “*now a new class of polyamine-based chelating agents, which incorporate within their structure at least one 5- or 6-membered heterocyclic ring*”.

Thus, a person skilled in the art who is already in possession of the composition of the formulation for which he seeks only to carry out the process, has no objective reason to consult a document, which was furthermore published many years beforehand (in 1991), of which he has absolutely no need for his invention.

The combination of the DOTAREM notice and of PCT international application WO 91/10645 cited by the company BAYER PHARMA cannot be retained as being the closest prior art, such that all the developments by the BAYER PHARMA with respect to this combination are irrelevant for assessing inventive step.

*Regarding the combination between the DOTAREM notice and patent US 5 049 667;*

The company BAYER PHARMA considers secondly that Claim 1 lacks inventive step with respect to patent US 5 049 667 in combination with the DOTAREM notice.

Patent US 5 049 667, granted on 17 September 1991, is entitled “*Nitrogen-containing cyclic ligands*” and relates to an invention which “*relates to nitrogen-containing cyclic ligands and metal complexes formed by these ligands, the uses of these complexes as magnetic resonance imaging (MRI) agents, as X-ray contrast agents and as chemical shift reagents in vivo*” and also in addition “*a process for the preparation of the ligands*”.

However, firstly, this patent does not relate to a process for preparing a liquid pharmaceutical formula ready to be injected into the human body, as proposed by patent FR 539. Secondly, it relates only to a process for “*the preparation of the ligands*”, such that this point corresponds only partially to the search that must be carried out by a person skilled in the art who wishes to carry out an invention relating to a production process which does not relate only to the ligands.

Finally, in any event, assuming that it constitutes the closest prior art in that example 2 of this document describes a complexation reaction in which stoichiometric amounts of a DOTA derivative and of gadolinium are reacted together, then subsequently the free gadolinium is determined in order, finally, to add macrocyclic chelate in order to achieve complete complexation of the residual gadolinium, the subject matter of this example is “*the overall determination of the gadolinium in the solution*”, this being in order to correct the excess thereof and not, as in Claim 1, to define a very small precise amount of macrocyclic chelate in the final formulation by choosing a lanthanide/chelate ratio of less than 1.2.

It emerges from these elements that a person skilled in the art will not have been prompted to consult this document, such that it cannot be considered to be relevant for assessing the inventive step of the contested patent.

*Regarding the combination of the DOTAREM notice with patent US 5 876 695;*

Patent US 5 876 695, granted on 2 March 1999, is entitled “*Metal* *complex-containing pharmaceutical agents*” and relates to an invention which “*relates to improved metal complex-containing pharmaceutical agents which, as an additive, contain one or more complexing agents and/or one or more weak metal complex(es) or mixtures thereof*”. It is specified that this invention also relates to “a method for producing” such a pharmaceutical agent.

In addition, the description of this patent specifies “*the question of long-term tolerance of these substances containing heavy metals must be given great attention*” and mentions that “*furthermore, in vivo, a concurrence of different ions is involved in the bond to the complexing agents so that the probability for the undesired and sometimes dangerous release of heavy metal ions in the organism increases*” and that “*thus, for diverse purposes, there is a need for better tolerance agents in which a release of the heavy metal ion in question from the complex compound is prevented as much as possible*”.

It emerges from these elements that the object of patent US 695 is to solve a problem close to that of patent FR 539 aimed at designing a process for producing an agent which makes it possible to ensure that the metal complex-based pharmaceutical formulations are less harmful to the human body, such that, combined with the DOTAREM notice, which discloses the composition of the pharmaceutical formulation to be achieved, it must be considered to be the closest prior art in order to assess the inventive step of patent FR 539.

***Regarding the assessment of the inventive step of patent FR 539;***

By way of introduction, it should be noted that the DOTAREM product was marketed in 1989 and that no process making it possible to obtain the pharmaceutical formulation of DOTAREM was disclosed before the process of patent FR 539 filed on 19 February 2008 and granted on 30 July 2010, that is to say close to 20 years later, which makes it possible to characterize per se an index of inventivity of said patent, it being additionally added that none of the documents produced by the company BAYER PHARMA envisages the abovementioned objective technical problem.

*With regard to the likening of the steps of the patented process to routine operations for a person skilled in the art;*

While the steps of a process for preparing a liquid composition, comprising a complex of a macrocyclic chelate with a lanthanide, a step of measurement, followed by a step of adjustment can be considered to be part of the general knowledge of a person skilled in the art as emerges in particular from the article from 1988 by J. HAGAN et al., entitled “*Fluorescence detection of gadolinium chelates separated by reversed-phase high-performance liquid chromatography*” which describes a method for detecting a small amount of gadolinium ion in an aqueous medium in a chelate solution, this document does not in any way disclose the features of Claim 1, namely the fact that it requires a preparation of a chelate/gadolinium complex under conditions which are not stoichiometric, the determination of a target excess of chelate and the fact of starting from a lanthanide/chelate ratio of less than 1.2 or else the operation consisting in carrying out a quantitative measurement of the free lanthanide under conditions such that the concentration of free DOTA is equal to zero.

In this regard, the company BAYER PHARMA cannot, without reversing the burden of proof, submit that the company GUERBET “*does not demonstrate why a person skilled in the art would not have had a “reasonable expectation of success””* by carrying out the processes of the prior art that were perfectly available to a person skilled in the art in order to achieve the processes of Claims 1 and 2.

The only consideration, that is commonplace for a chemist, of carrying out measurement and adjustment operations is not sufficient to summarize the invention of the contested patent, since the company BAYER PHARMA did not specify how the determination of the abovementioned conditions for achieving the desired result would not be the fruit of an inventive step, even though, as the company GUERBET observes, the claimed process does not comprise any step of dissolving the starting products, or any measurement step.

*With regard to the absence of technical effect alleged by the company BAYER PHARMA*;

It is to no greater degree relevant for the company BAYER PHARMA to submit that the company GUERBET does not provide evidence that the claimed process is more effective than another process, the process of patent FR 539 having been the first to be disclosed, such that there is no reason to wonder, for assessing the inventive step, whether or not there is an effect that is improved by this patent compared with other processes.

In any event, it is established in particular by tests that the process can be carried out on a larger industrial scale than that in example 2 of the contested patent and that the amount of excess of free DOTA in the final composition of DOTAREM is always controlled, which tends to demonstrate that the process can effectively be carried out safely, reliably and reproducibly and is compatible with industrial amounts.

While the company BAYER PHARMA criticizes these tests for the reason that no step of adjustment of the amounts of DOTA or of gadolinium was carried out after the dissolution step, this criticism is irrelevant since the sole objective of these tests was to show the reality of the problems of lack of reliability of the use of stoichiometric amounts mentioned in the patent, and not to illustrate the behaviour of a person skilled in the art.

With regard to these elements, the company BAYER PHARMA does not provide the evidence to contest the inventive step of the absence of technical effect of the invention, although it is incumbent upon BAYER PHARMA to do so.

*With regard to the inventive step of Claim 1 with respect to the closest prior art;*

With respect to patent US 695 and specifically example 2 thereof and the application thereof to the production of DOTAREM, patent FR 539 differs therefrom in that it does not provide for the mixing of stoichiometric amounts of the starting compounds (chelate and ligand), but, on the contrary, an excess of gadolinium, and in that it also does not explicitly provide for a step of measuring this substance.

While the company BAYER PHARMA considers that a person skilled in the art knew, by virtue of the prior publication consisting of example 17 of PCT application WO 91/10645 15, that, in order to prepare a pharmaceutical formulation based on a complex of Gd with a chelate, he could start from a mixture containing an excess of the same gadolinium, it should be observed, on the one hand, that, as indicated above, a person skilled in the art would not have been prompted to consult this document, and that, on the other hand, said document does not in any way intentionally claim the choice of non-stoichiometric conditions or explain the reasons for this choice, such that it cannot be deduced from this that a person skilled in the art, wishing to solve the technical problem of the contested patent, would consider that it is necessary to start from non-stoichiometric amounts.

Thus, it is not demonstrated how this approach, which is nevertheless counter-intuitive, which consists whereas the final result is according to the patent to obtain an excess in small measurable amount of free chelate (DOTA), of beginning the preparation with a step consisting in introducing an excess of gadolinium, would lack inventiveness.

In addition, the combination of these documents does not prompt a person skilled in the art to anticipate a step of measuring the free gadolinium corresponding to step c) of Claim 1 under the conditions such that the concentration of free DOTA is equal to zero.

It results from these elements that the process described by Claim 1, in that it departs not only from the stoichiometric amounts but also from the predetermined target amounts, is not merely the result of implementing operations known to a person skilled in the art, but is the arrangement of several steps corresponding to precise conditions which do not emerge from the data of the prior art.

Consequently, it is necessary to dismiss the application for nullity on the grounds of lack of inventive step of Claim 1.

**With regard to the lack of inventive step of Claim 2**

The company BAYER PHARMA states that the process of Claim 2 is not inventive since the article by AIME et al. describes a process for preparing a complex between gadolinium and a DOTA derivative and since the steps of the process of the Claim 2 comply in all respects with those described in the article by AIME et al., the claimed process being different from that of the article by AIME et al. only in terms of the nature of the chelate used and the concentration of this chelate that is free in the final formulation (0.49% instead of 0.4%). It specifies that the claimed process is merely a simple process by analogy with respect to that described in AIME et al. and that such a process by analogy is not inventive, as long as it results in a known product, since it requires only simple adjustments (in the case in point, using DOTA in the process of AIME et al. instead of a derivative thereof).

The company GUERBET emphasizes in reply that the objective technical problem solved by the process of Claim 2 is exactly the same as that solved by Claim 1, such that the documents constituting the closest prior art are the same, namely the DOTAREM notice and patent US 695, and considers that, if the company BAYER PHARMA cites a different prior art document in order to attempt to demonstrate the lack of inventive step of Claim 2, it is because it is carrying out a reasoning *a posteriori*. It states that, with regard to the DOTAREM notice and document US 695, a person skilled in the art was not prompted to provide for amounts of starting reagents such that they make it possible to obtain an excess of free DOTA greater than the target excess of the final formulation. It specifies that the AIME document thus does not describe a process on an industrial scale, but only experiments on a laboratory scale, and never teaches how to obtain any excess of free chelate, but only how not to obtain an excess of gadolinium, such that a person skilled in the art seeking a process which makes it possible, on an industrial scale, to reliably and reproducibly obtain a pharmaceutical formulation with a specific excess of free DOTA therefore had no reason to consult this document in order to solve this technical problem. It considers that a person skilled in the art has even less reason to focus particularly on example 6a and that the document AIME et al., on the contrary, prompted a person skilled in the art to adopt a process different from that of Claim 2, since it incites him to develop a process comprising the steps of preparation of a complex, of purification of the complex by filtration, of isolation in solid form, and of formulation by dissolution of the Gd-DOTA complex in solid form, and of free DOTA, in the final aqueous solution. It explains that this process differs from the process which is the subject matter of Claim 2 which has the advantage, in addition to providing a very precise control of the excess of free chelate, of combining the steps of synthesis and formulation, which results in a process that is both robust and economical on an industrial scale.

***On the basis of this,***

It is established that Claim 2 is dependent on Claim 1 and discloses the same steps of the process and differs therefrom in that step b), the object of which is to react amounts of free macrocyclic chelate (DOTA) and of free lanthanide (gadolinium), aims to this time obtain an excess of free DOTA (and not, as in Claim 1, an excess of free gadolinium) such that the formulation will comprise free gadolinium in the event of incomplete complexation.

In addition, the object of step c) is to measure the concentration of free chelate (DOTA) under conditions such that the concentration of free gadolinium is equal to zero (whereas, in Claim 1, step c) aims to measure the concentration of free gadolinium under conditions such that the concentration of free DOTA is equal to zero).

Thus, as indicated above, the company BAYER PHARMA does not explain how, for the examination of the inventive step of Claim 2, whereas said claim is presented as the mirror image of Claim 1, there would be reason to take into account a new document as closest prior art and more specifically the document by S. AIME from 1992, since this document does not relate to the implementation of a process for producing a pharmaceutical formulation, but to the synthesis of two new ligands of DOTA type and the gadolinium complexes thereof, only example 6a of this document mentioning a preparation of a complex between gadolinium and a DOTA derivative, which comprises steps of mixing, measurement and adjustment.

In addition to the fact that this document does not in any way aim to solve the same technical problem as the contested patent, such that a person skilled in the art would not be prompted to consult it, it also does not in any way aim to obtain an excess of chelate (the mentioning of an excess of chelate of 0.49% in the pleadings by the company BAYER PHARMA not in any way emerging from said document), nor does it disclose the addition of DOTA above an initially determined target value, or a measurement of the free chelate under conditions such that the concentration of free gadolinium is equal to zero.

As these elements stand, assuming that a person skilled in the art was prompted to consult this document, he would not have managed, by simple implementing measures, to imagine the invention presenting the characteristics of Claim 2 comprising a succession of precisely arranged steps.

The application for nullity of Claim 2 on the grounds of lack of inventive step shall consequently be dismissed.

**Regarding the nullity of the dependent process claims (Claims 3, 4, 5, 6, 7, 8, 9, 10, 11) on the grounds of lack of inventive step;**

It is not contested that Claims 3, 4, 5 and 6 are dependent on Claims 1 and 2, such that the validity of these two main claims with respect to inventive step necessarily leads to the conclusion of an inventive step for the dependent claims, and that the application for nullity filed by the company BAYER PHARMA shall consequently be dismissed.

As regards Claims 7 and 8, said claims are drafted in the following way: “*7. Pharmaceutical formulation which can be obtained by a process according to Claim 6, characterized in that the formulation contains between 0.02 and 0.08% mol/mol of amount of free DOTA*”. “*8. Pharmaceutical formulation which can be obtained by a process according to Claim 6, characterized in that the formulation contains between 0.15 and 0.25% mol/mol of amount of free DOTA*”.

In addition to the fact that these claims are dependent on the process of Claim 6, which is itself inventive, the company BAYER PHARMA does not demonstrate how the fact precisely of moving away from the value of excess of free DOTA disclosed in the DOTAREM notice, in order to choose a particular range either of 0.02 to 0.08% mol/mol of excess of free DOTA, or of between 0.15 and 0.25% mol/mol, would lack inventive step.

Claim 9 is drafted in the following way: “*Pharmaceutical formulation according to Claim 7 or 8, characterized in that it contains an amount of calcium of less than 15 ppm, advantageously less than 10 ppm*”.

Claim 10 is drafted in the following way: “*Use of a pharmaceutical formulation according to any one of Claims 7 to 9 for the preparation of a diagnostic composition for medical imaging*”.

Claim 11 is drafted in the following way: “*Use according to Claim 10, characterized in that the medical imaging is Magnetic Resonance Imaging and in that the diagnostic composition is intended for intravenous administration in saline solution*”.

As regards Claims 9 to 11, since they are dependent on Claims 7 and 8, the inventive step of which has been acknowledged, the application for nullity filed by the company BAYER PHARMA shall consequently be dismissed.

**With regard to the costs and irrecoverable expenses**

There is cause to order to company BAYER PHARMA, the losing party, to pay the costs, which will be recovered in accordance with the provisions of Article 699 of the French Code of Civil Procedure.

In addition, it shall be ordered to pay the company GUERBET, which has had to incur irrecoverable expenses in order to assert its rights, compensation pursuant to Article 700 of the French Code of Civil Procedure that it is equitable to set at the sum of 90 000 euros.

**ON THESE GROUNDS**

**The District Court, ruling in open court by decision submitted to the Clerk’s Office, handed down at first instance after hearing both parties,**

- STATES that there is no cause to dismiss from the proceedings exhibits 19, 20 and 33 produced by the company GUERBET;

- STATES that there is no cause to rule on the application for nullity of the patent on the grounds of lack of nullity;

- DISMISSES the company BAYER PHARMA’s applications for nullity of French patent No. 2 927 539;

- ORDERS the company BAYER PHARMA to pay the company GUERBET the sum of 90 000 euros pursuant to Article 700 of the French Code of Civil Procedure;

- ORDERS the company GUERBET to pay the costs, which will be recovered in accordance with the provisions of Article 699 of the French Code of Civil Procedure.

**Done and judged in Paris on 23 March 2018**

**Clerk of the Court Presiding Judge**