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BARCELONA COMMERCIAL COURT Nº 4

BARCELONA COMMERCIAL COURT OF FIRST INSTANCE

PATENT SECTION

Judges:
Ms Yolanda Ríos López (co-ordinator)
Mr Florencio Molina López
Mr Alfonso Merino Rebollo (*rapporteur*)

Case: Fulvestrant. Interim Inunction nº 24/2016-MI

Claimants and counterclaim defendants: Astrazeneca AB and Astrazeneca Farmacéutica Spain, S. A. (hereinafter, Astrazeneca).
- Procurator: Mr Ángel Quemada Cuatrecasas
- Lawyer: Mr Miquel Montañá Mora

Defendant: Sandoz Farmacéutica, S. A., (hereinafter, Sandoz)
- Procurator: Mr Ignacio López Chocarro
- Lawyer: Mr Miguel Gil Vázquez

RULING 231/16

In Barcelona, on 28 July 2016

BACKGROUND FACTS

ONE.- The procedural representative of the claimants submitted on 11 January 2016 a request for interim injunctions *Inaudita Parte* prior to filing the corresponding complaint for the infringement of industrial property rights, against the entity Sandoz, pursuant to articles 133 *et seq.* of the Patent Act and 721 *et seq.* of the LEC, requesting:

1. That SANDOZ FARMACÉUTICA, S.A., either by itself or through any third party, be provisionally prohibited from manufacturing, using, offering and introducing into trade, and importing and possessing for any of the aforementioned purposes the drug "FULVESTRANT SANDOZ, 250 mg, solución inyectable en jeringa precargada" (Reg. Nº 80254) while patents ES 2.248.272 and ES 2.543.384 are in force.

2. In the event that, before the Court issues a decision, SANDOZ FARMACÉUTICA, S.A., directly or indirectly by means of any third party starts the marketing in Spain of the drug "FULVESTRANT SANDOZ, 250 mg, solución inyectable en jeringa precargada" (Reg. Nº 80254), that SANDOZ FARMACÉUTICA, S.A. be ordered to:

> (a) Provisionally withdraw from commercial trade and from its premises, even if this requires repurchasing from the owners thereof or any other legal business, all the units of the drug "FULVESTRANT SANDOZ, 250 mg, solución inyectable en jeringa precargada" (Reg. Nº 80254).

(b) Provisionally seize the objects produced or imported by infringing the patent rights of ASTRAZENECA AB and the means mainly intended for such production or for the implementation of the infringement and, in particular, the seizure of all the units of the drug "FULVESTRANT SANDOZ, 250 mg, solución inyectable en jeringa precargada" (Reg. Nº 80254).

(c) Officially notify the Ruling ordering the interim injunctions requested for the cessation and/or withdrawal from commercial trade ordered to all the pharmaceutical distributors which, where appropriate, might have acquired units or batches of the drug "FULVESTRANT SANDOZ, 250 mg, solución inyectable en jeringa precargada" (Reg. Nº 80254), so that they might be aware of and respect the precautionary order decreed.

3. That SANDOZ FARMACÉUTICA, S.A. be provisionally ordered to to take any necessary action so that the Ministry of Health, Social Services and Equality might render void of effect the inclusion of the drug "FULVESTRANT SANDOZ, 250 mg, solución inyectable en jeringa precargada" (Reg. Nº 80254) in the pharmaceutical provision of the National Health Service.

4. The provisional notification of the Ruling agreeing the interim injunctions, at the expense of SANDOZ FARMACÉUTICA, S.A., to:

(a) The Spanish Drug Agency (*Agencia Española del Medicamento y Productos Sanitarios*), with address at Parque Empresarial Las Mercedes, Edificio 8, Campezo 1, 28022 Madrid, in order to record the interim injunction Ruling in the Drugs Register.

(b) The Ministry of Health, Social Services and Equality, and in particular its General Directorate on the Basic Portfolio of Services of the National Health Service and Pharmacy and its General Technical Secretary (with address at Paseo del Prado, 18-20, E-28071, Madrid, Fax 91 596 42 94) and the Government Delegate Committee for Economic Affairs (with address at Paseo de la Castellana, 162, Planta 18, 28046, Madrid), in order that:

(i) They might be aware of such decision; and,

(ii) They might take the measures necessary to prevent the "FULVESTRANT SANDOZ, 250 mg, solución inyectable en jeringa precargada" (Reg. Nº 80254) appearing as a drug marketed or marketable in any of the databases administered by such bodies, and so that they might take into account that they should not be considered for the purposes of creating a homogeneous group or the groupings of the reference price system.

(c) The Regional Health Departments, the addresses of which are given below for the Court's ease of reference:

Andalusia: Avda. Innovación, s/n - Edificio Arena 1, 41020 – Seville.

Aragon: Paseo María Agustín, 36, 50071 – Zaragoza.

Asturias: General Elorza, 32, 33001 – Oviedo.

Balearic Islands: Cecili Metelo, 18, 07003 - Palma de Mallorca.
Canary Islands: C/ Alfonso XIII, nº 5, 35071 - Las Palmas de Gran Canaria.
Cantabria: Marqués de la Hermida, 8, 39009 – Santander.
Castilla-La Mancha: Avda. de Burgos, 5, 47014 - Valladolid.
Castilla y León: Avda. de Portugal, 77, 45071 - Toledo.
Catalonia: Travesera de les Corts, 131-158, 08028 - Barcelona.
Extremadura: Avda. del Guadiana, s/n Módulo, B, 06800 - Mérida.
Galicia: Edif. Administrativo San Caetano, s/n, 15771 - Santiago de Compostela.
La Rioja: Villamediana, 17, 26071 - Logroño.
Madrid: O'Donnell, 50, 28009 - Madrid.
Murcia: Ronda de Levante, 11, 30008 - Murcia.
Navarre: Ciudadela, 5, 31001 - Pamplona.
Basque Country: Duque de Wellington, 2, 01011 - Vitoria-Gasteiz.
Valencia: Lauria, 19, 46002 - Valencia.

(d) The General Board of the Spanish Official Medical Associations (with address at Plaza de las Cortes, 11, 28014, Madrid, Fax: 91 431 96 20) so it might notify the various Spanish Official Medical Associations of the decision agreeing the interim injunctions, so that in turn they might notify their members.

TWO.- On 20 January 2016, this Court issued a ruling the operative part of which stated the following:

*"1. – **To partially uphold** the request for interim injunctions requested by the procedural representative of Astrazeneca AB and Astrazeneca Farmacéutica Spain, S.A. against the entity Sandoz Farmacéutica, S.A., without awarding the costs of the proceedings, and by virtue thereof:*

1.1. – To provisionally prohibit SANDOZ FARMACÉUTICA, S.A., either by itself or through any third party, from manufacturing, using, offering and introducing into trade, and importing and possessing for any of the aforementioned purposes the drug "FULVESTRANT SANDOZ, 250 mg, solución inyectable en jeringa precargada" (Reg. Nº 80254), as long as patents ES 2.248.272 and ES 2.543.384 are in force.

*1.2.- Such measure is subject to the provision of a bond for the amount of **800,000 euros** within a period of three **DAYS**, and to the filing of the complaint of the main proceedings within the term legally established".*

THREE.- On 29 February 2016, Mr Ignacio López Chocarro, in the name and on behalf of Sandoz Farmacéutica, S.A., submitted a writ of opposition to the interim injunctions agreed *inaudita parte* by this Court, for the reasons expressed in the corresponding writ.

FOUR.- The opposition hearing was held on 4 and 5 July 2016, where the parties ratified their initial writs of request for interim injunctions and opposition and the claimants replied to the allegations of the opposition in the terms registered in the corresponding recording. Furthermore, the evidence admitted was examined and, after the formulation of the conclusions, the actions were concluded and ready for the corresponding decision.

FIVE.- On 28 July 2016, this legal issue was submitted to the consideration of the Patent Section of the Barcelona Commercial Court of First Instance, consisting of Ms Yolanda Rios López, Mr Florencio Molina López and Mr Alfonso Merino Rebollo, within the framework of the Barcelona Commercial Court of First Instance Statute protocol, approved through an agreement dated 15 July 2014 of the Judicial Council Permanent Commission and reviewed through an Agreement of the Judicial Council Permanent Commission of 18 February 2016.

SIX.- The legal formalities have been observed except for the period for issuing the ruling, due to the workload of these Courts and the legal complexity of this trial.

POINTS OF LAW

ONE.- Undisputed facts.

1. The following facts are relevant in order to resolve this dispute, and they are undisputed by the parties (*ex* art. 281.3 LEC):

1.1 The claimant Astrazeneca AB is holder of European Patent EP 1.250.138 (hereinafter, EP'138) validated in Spain under number ES 2.248.272 (hereinafter, ES'272), entitled "*Formulación de Fulvestrant*" ("Fulvestrant Formulation"), as well as of its Divisional Patent EP 2.266.573 (EP'573) validated in Spain under number ES 2.543.384 (ES'384), entitled "*Formulación de Fulvestrant*" ("Fulvestrant Formulation"). Patent ES '272 was applied for with the European Patent Office (hereinafter, EPO) on 8 January 2001, and will be in force until 8 January 2012. Patent ES'384 will also expire on 8 January 2021.

1.2 Patent EP'138 was applied for on 8.1.2001 and claims the priorities of two British patent applications, dated 10.1.2000 and 12.4.2000. The grant of the patent was published by the EPO on 19.10.2005 and the Spanish Patent and Trademark Office (*Oficina Española de Patents y Marcas*) (hereinafter, OEPM) published its translation into Spanish on 16.3.2006. After opposition proceedings, the EPO published a limited version of the patent on 8.7.2015, the translation of which was published by the OEPM on 19.8.2015.

1.3 Patent EP'573, on being divisional of EP'138, shares its application and priority dates. The grant thereof was published by the EPO on 17.6.2015 and its translation into Spanish was published by the OEPM on 18.8.2015.

1.4 The claimant Astrazeneca Farmacéutica Spain is an entity of the same business group as Astrazeneca AB, which is used by the latter to market the drug FASLODEX® in Spain.

1.5 Patent ES'272 contains 31 claims, with several independent, dependent and multi-dependent claims, the purpose of which is the use of Fulvestrant in the preparation of a pharmaceutical formulation for the treatment of a benign or malignant condition of the breast or reproductive tract with a series of specifics. In turn, patent ES'384 contains three claims, with the first of them being independent and the other two being dependent, also protecting the use of a formulation of Fulvestrant, with the limitation that the only medical indication protected is breast cancer.

1.6 There is a difference between expressing a formulation in units of weight/volume units (w/v) and in volume/volume (v/v).

1.7 The article by McLeskey discloses directly and unambiguously that the pharmaceutical composition of fulvestrant used therein was administered to mice subcutaneously and not intramuscularly.

1.8 Example 3 of patent EP'014 does not include a non-aqueous pharmaceutically accepted ester solvent.

1.9 The general common knowledge in *Avis et. al.* teaches that benzyl benzoate may be used to improve the solubility of steroids in oils, and the general common knowledge in *Wade et. al.* teaches that benzyl benzoate was used as a solubilising agent in intramuscular injections.

TWO.- On the *fumus boni iuris* or appearance of legal standing.

2.1 The Civil Procedure Act (*Ley de Enjuiciamiento Civil*) (LEC) regulates a series of requisites in order to adopt an interim injunction. The first of these requirements is, precisely:

a) Appearance of legal standing *(fumus boni iuris).* This is regulated under art. 728.2 LEC when this states that *the applicant for interim injunctions must also submit any data, arguments and documentary justifications so that the court, without prejudging the merits of the case, can ground a provisional circumstantial opinion in favour of the basis of its request.* In the absence of any documentary evidence, the applicant must offer this by any other means. This requisite consists of a preliminary judicial analysis aimed at evidencing the existence of a sign or initial proof that the main request of the party applying for the interim injunction is apparently well grounded on law. In other words, it offers a probable appearance of legal standing and at first sight does not seem ridiculous, arbitrary or unreasonably grounded.

2.2 The action brought in these interim injunction proceedings by the claimant entities is the so-called "action for prohibition" of acts constituting an infringement of the exclusive right, based on rational indications allowing the imminence thereof to be deduced, this being understood as meaning the forthcoming effective infringement of the patent right in view of the imminent market launch of the drug "FULVESTRANT SANDOZ, 250 mg, solución inyectable en jeringa precargada" by Sandoz when there are still 5 years to go before the expiry of the aforementioned patents.

2.3 Sandoz argues as the main reason for the opposition to the interim injunctions granted by means of the ruling dated 20 January 2016 the lack of *fumus boni iuris* of the claimants, since the patents invoked, EP'138 and EP'573, are allegedly invalid due to the lack of novelty and, in any case, of inventive step.

2.4 For these purposes, we will first analyse the scope of protection of patents EP'272 and ES'384 and, subsequently, we will proceed to suitably judge the validity of such patents.

Scope of protection of patents EP'272 and ES'384

2.5 Patent ES'272 object of these proceedings has 31 claims. We consider that it is necessary, for the purposes of resolving this opposition to the interim injunctions, to proceed only to analyse in detail the first of such claims. The literal wording thereof is as follows:

"A pharmaceutical formulation comprising fulvestrant in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks".

2.6 The technical characteristics of such claim are:

a) The use of the Fulvestrant in the preparation of a pharmaceutical formulation;
b) For the treatment of a benign or malignant condition of the breast or reproductive system;
c) By means of intramuscular administration;
d) In which the formulation comprises:
   i) Fulvestrant,
   ii) A ricinoleate vehicle,
   iii) A pharmaceutically accepted non-aqueous ester solvent, and
   iv) A pharmaceutically accepted alcohol

e) The formulation is adjusted in order to obtain a therapeutically significant concentration of Fulvestrant in blood plasma for at least 2 weeks.

2.7 Patent ES'384 object of these proceedings has 3 claims, and the literal wording of the first and single independent claim is as follows:

"A pharmaceutical formulation for use in the treatment of breast cancer by intramuscular injection, wherein the pharmaceutical formulation comprises fulvestrant, a pharmaceutically-acceptable alcohol being a mixture of 10 % weight of ethanol per volume of formulation and 10 % weight of benzyl alcohol per volume of formulation, and the formulation contains 15 % weight of benzyl benzoate per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45 mgml-1 of fulvestrant, wherein the ricinoleate vehicle is castor oil, and wherein the total volume of the formulation is 6 ml or less".

2.8 The technical characteristics of such claim are that it is a pharmaceutical formulation:

a) To be used for the treatment:
   i) Of breast cancer;
   ii) By intramuscular injection;
b) It comprises:
   i) Fulvestrant,
   ii) A pharmaceutically acceptable alcohol which is a mixture of:
      (1) 10% weight of ethanol by volume of the formulation, and
      (2) 10% weight of benzyl alcohol by volume of the formulation;
   iii) 15% weight of benzyl benzoate by volume of the formulation, and
   iv) A sufficient amount of a ricinoleate vehicle which is castor oil in order to prepare in this way a formulation of at least 45 mg/ml of Fulvestrant.
c) In which the total volume of the formulation is of 6 ml or less.

2.9 In view of the above, we can conclude that the elements comprising these claims can be gathered into four broad groups, as the parties have been indicating in these interim

injunctions. Namely:

a) formulation (a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent and a pharmaceutically acceptable alcohol)

b) therapeutic indication (mainly breast cancer in both patents).

c) administration route (intramuscular injection).

d) deposit effect (therapeutically significant concentrations and duration of fulvestrant).

THREE.- On the (lack of) novelty of the patents.

3.1 We will now proceed to analyse the validity of patents ES'272 and ES'384, starting in the first place with the novelty. It should be recalled, as regards the examination of the requisites of patentability within the framework of injunction proceedings such as those at hand, that Section 15 of the Barcelona Court of Appeal (among other Rulings those of 29 March 2016, 24 January 2011, 20 July 2009 and 4 January 2006) decided the following: "*...for the purposes of a provisional circumstantial opinion, it is inadmissible to analyse the validity of the patent in terms of certainty. As we pointed out in such decisions, "the Court can not, within the strict framework of opinion supposed by the assessment of the requisite of the fumus boni iuris of the interim injunctions adopted (art. 728.2 LEC), fully judge the validity of the said patent, but only circumstantially, which is decisively influenced by the registration of the patent in favour of the claimant". But we added subsequently that "this does not mean that this exception will not be invoked, but only that the decision thereon will be also circumstantial, and may not be used to replace the subsequent decision taken in the main proceedings, and that in this circumstantial decision, the starting point in favour of the validity of the patent is its registration, especially if, in order to obtain it, a previous examination process has been followed, as is the case in hand, on this being t a European patent. It will be the defendant who has to submit very clear and evident indications that allow the possible invalidity to be observe provisionally and circumstantially".*

A) Legal and jurisprudential configuration of novelty.

3.2 Art. 52 of the Convention of 5 October 1973 on the Grant of European Patents (EPC), establishes that European patents will be granted for new inventions which involve inventive step and are susceptible of industrial application .

3.3 Thus, the first of the requisites of patentability of an invention is the novelty thereof, with the aim of it being impossible to patent anything forming part of the state of the art again.

3.4 Art. 54.1 tells us that *"an invention shall be considered to be new if it does not form part of the state of the art"*. In addition, the second paragraph of this precept clarifies that *"the state of the art will be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way"*.

3.5 For these purposes, the third paragraph of the said article 54 specifies that *"the content of European patent applications as filed, of which the dates of filing are prior to the date referred to in paragraph 2 and which were published under Article 93 on or after that date, will be considered as comprised in the state of the art"*.

3.6 An invention lacks novelty when a document, which forms part of the state of the art, anticipates directly and unambiguously, in other words, without leaving any doubt, each one

of the elements claimed by the patented invention.

3.7 The method described by the Guidelines for Examination in the EPO and the Guidelines of the Spanish Patent Office in order to assess the novelty of a patent includes three stages:

(1) The first consists of determining the elements of the invention claimed, in order to compare them with the document or documents of the state of the art.

(2) The second consists of determining whether the document under study forms part of the state of the art.

(3) The third consists of assessing whether the anticipatory document on the date of its publication disclosed explicitly or implicitly for the person skilled in the art, in combination, all the elements or stages of the invention claimed.

3.8 The first fundamental rule in order to determine the *state of the art* is that it is not permitted to combine different documents of the state of the art in order to compare their teachings with the elements of the invention claimed, and therefore the comparison must be made separately document by document, between those which form part of the state of the art and the invention claimed, in order to determine whether the elements claimed are disclosed or not.

3.9 It is not even possible to combine elements of different embodiments executed within the same document unless this combination is suggested. This first rule has an exception when a document (the main document) refers explicitly to another document in order to provide more details on such characteristic. In such case, the disclosure by this said document is considered to be part of the main document, if the aforementioned document is available to the public on the date of publication of the main document (T153/85, OJI-2/1988, 1) *(Guidelines for Examination, Section C, 7.1).*

3.10 The technical teaching of a document forming part of the state of the art must be considered in full, as a person skilled in the art would consider it. It is not justified to isolate arbitrarily different parts of a document from their context, in order to extract certain technical information which may be different or even contradictory to the disclosure made by the document considered in full (T 56/87).

3.11 However, the Technical Board of Appeal of the EPO has also maintained that in order to assess the novelty, several passages of a same document may be combined, since there is no reason to prevent a skilled person from doing so, for example T 332/87.

3.12 The disclosure of the state of the art will be such that it permits the person skilled in the art to reproduce the invention claimed. To such end, the knowledge acquired somewhere other than from the document of the state of the art may be used.

3.13 In the third stage we find the participation of an imaginary figure or prototype of a skilled person, which is the person skilled in the art or the technical field to which the object of the invention refers; this is a practical person in such technical field, who has the common knowledge thereof on the relevant date, as well as the common means in order to carry out the routine experiment work. The special characteristic of this archetypal skilled person is that they have access to all the knowledge defining the state of the art and, specifically, to those documents which will be compared to the invention claimed *(Guidelines for Examination, Section C,* 9.3).

3.14 Therefore, in order to make this assessment between what has been disclosed and what is being claimed, we need to start from what such skilled person would have considered disclosed by reading the anticipatory document. Logically, pursuant to the provisions of art. 335 LEC, that knowledge has to be submitted to the court by the skilled persons participating as experts in the proceedings, but that figure can not be identified with any of the experts, but must be imaginarily created by the judge, who is layman in the matter, starting from the knowledge the experts provide to him. The function of the experts is thus to provide the judge with the correct identification, reading and assessment of the documents forming part of the state of the art.

3.15 The elements of the claims of a patent may have been disclosed by a prior document either explicitly or implicitly.

(1) Express disclosures:

A document forming part of the state of the art deprives the claimed invention of novelty if, after the reading thereof by a skilled person, all the elements claimed are clear to them (T 450/89, T 465/92), directly and unambiguously (T 204/83, T 56/87), in other words, without any doubt. It is important to specify that those characteristics implicit for the skilled person of all those elements which are explicitly mentioned in the document are likewise deemed disclosed. What can not be done, when assessing the novelty, is to include equivalents which are already known, since this kind of interpretation of the document belongs to the analysis of the inventive step (Guidelines for Examination, Section C, 7.2).

The elements described in a document will only be considered disclosed to the public when a person skilled in the art, on the relevant date of the document, from the information provided to them by such document and with the common knowledge they are supposed to have, could have put into practice that technical teaching. Furthermore, a chemical compound, the formula of which is mentioned in a document of the state of the art, will not be considered to have been disclosed unless the information of the document, together with the general knowledge available on the date of the document, allow sit to be prepared and separated or, in the case of natural products, only separated *(Guidelines for Examination, Section C,* 7.3a).

As a general rule, it can be said that a general teaching or disclosure does not deprive a more specific invention of novelty; however, a specific disclosure, in contrast, might deprive the general one of novelty *(Guidelines for Examination, Section C,* 7.4).

(2) Implicit disclosures:

In the event of a priority document, the lack of novelty might be clear from what is expressly stated in the document. However, this lack of novelty might also be implicit when the person skilled in the art inevitably obtains a result which falls within the scope of the claim when executing the teaching of the document (Guidelines for Examination, Section C, 7.5).

In order for an implicit disclosure to exist, the explicit evidence on which the examiner is based will clearly establish that the descriptive elements missing are necessarily present in the reference documents, and that they would be known as such by the person

skilled in the art, without the need for any probabilities or possibilities, and without such aspect being likely to be deduced from a certain group of circumstances.

3.16 These rules are completed with others directly taken from decisions of the Board of Appeals:

(i) No part of the document will be interpreted in isolation from the rest of the document, in such a way that, even though one part of the document could seem to have a particular meaning when interpreted literally in isolation from the rest of the document, the true meaning of such part of the document might be different within the context of the rest of the document (T 312/94). As a consequence, the isolated reference to the previous document does not involve a clear and unequivocal disclosure if it is inconsistent with the key ideas or teachings of the rest of the document CT 450/89).

(ii) The determination by a skilled person of which teachings are implicit is not something they can do freely, but this is subject to a requirement for immediacy and clarity related to a system based on legal certainty: the previous document will destroy the novelty if the subsequent invention is immediately apparent to a skilled person reading the document CT 204/93), if it can be directly und unequivocally inferred from the description CT 56/87), since it is not sufficient for upholding the lack of novelty of the claimed elements that they might have derived from the document of the state of the art. There should have been a clear and unequivocal teaching of the claimed elements CT 677/91). For this reason, when it is stated that the lack of novelty might be implicit because a person skilled in the art could have inevitably obtained a result comprised in the terms of the claim, the Boards specify that the word inevitably means indefectibly, certain to occur, something that will happen or so true as to prevent any alternative solutions. Therefore, it is clear that the inevitability prevents the existence of valid and alternative results or options: in other words, it is equivalent to 100% probability CT 793193, repeated by T 396/89).

B) On the alleged lack of novelty of C1 of ES'272 and ES'384.

3.17 The defendant Sandoz maintains that the C1 are invalid due to a lack of novelty, based on the expert reports of Mr Armin Buschauer and Mr Claus-Michael Lehr. Such lack of novelty is based on the following document:

- Tamoxifen-resistant fibroblast growth factor-transfected MCF-7 cells are cross-resistant in vivo to the antiestrogen ICI 182,780 and two aromatase inhibitors, by McLeskey *et al.*, published in 1998 in Clinical Cancer Research. Hereinafter, this is referred to as the "McLeskey article".

3.18 The parties to the dispute disagree on whether such McLeskey article discloses and, therefore, anticipates the four technical characteristics of the Cl which we summarised in point 2.9. Therefore, we will now proceed to analyse them separately.

a) Formulation.

3.19 Sandoz maintains that the document McLeskey discloses the same excipients and the

same proportions as the pharmaceutical composition of fulvestrant object of the patents. In addition, the claimants disagree since they understand that McLeskey does not define whether the percentages of ethanol, benzyl benzoate and benzyl alcohol are expressed in weight/volume (w/v) units or in volume/volume units (v/v).

3.20 Both patents under dispute on page 14 thereof include the following example of formulation:

"The amounts of each one of the formulation compounds are chosen according to the specification of the required formulation and the examples are previously described. For example, amounts of each one of the compounds are added in order to prepare a formulation containing

10 % w/v benzyl alcohol

1 0 % w/v ethanol

1 5 % w/v benzyl benzoate

250 mg of fulvestrant for each 5 ml of the finished formulation, and the remaining amount as castor oil".

3.21 The McLeskey article on its page 2, right-hand column, indicated the following:

"Drugs. ICI 182780 was kindly donated by Mr Alan Wakeling of Zeneca Pharmaceuticals (Macclesfield, England) and was administered s.c in a dose of 5mg in 0.1 ml of vehicle every week. For the experiment depicted in Fig. 1, powdered drug was first dissolved in 100% ethanol and spiked into warmed peanut oil (Eastman Kodak, Rochester, NY) to give a final concentration of 50 mg/ml. In the experiments depicted in figure 1, B and C, 50 mg/ml pre-formulated drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil, was supplied by B. M. Vose (Zeneca Pharmaceuticals).

3.22 We should start from the information consistent of it not being the same for the formulation to be expressed in weight/volume units (w/v) or in volume/volume units (v/v), as the parties to the dispute and their respective legal experts recognise (ex art. 281.3 LEC). From the reading of McLeskey, in its entirety, and from the transcribed passage, in particular, it is not disclosed to a person skilled in the art clearly (T 450/89, T 465/92), directly and unambiguously (T 204/83, T 56/87), in other words, without any doubt, that the percentages of ethanol, benzyl benzoate and benzyl alcohol are expressed in w/v. Furthermore, according to the indications of the expert Mr Pedro Gascon (document 55 of the claimant, page 7) all of the compounds of the formulation are liquid, which might lead to the understanding that the concentrations of the formulation are expressed in v/v.

3.23 With the caution required at this procedural stage, we can state that this characteristic is not anticipated in McLeskey for patent ES'384. However, it would be anticipated for ES'272, since it only claims the formulation without indicating the exact percentages.

b) Therapeutic indication (mainly breast cancer in both patents).

3.24 Sandoz also considers that McLeskey discloses this characteristic for the following reasons:

- such article is published in Clinical Cancer Research and the authors thereof, as indicated in the article, belong to the Lombardi Center Cancer of the University of Georgetown (Washington).

- the article explains that its object is to study a possible mechanism by which resistance to tamoxifen is generated in the treatment of breast cancer. One of the tools used in order to analyse such resistance is fulvestrant, of which it is said that it has been used in the treatment of breast cancer.

- because it was known that formulations of fulvestrant were efficient for the treatment of breast cancer.

3.25 In order to resolve this point, it is worth transcribing several passages of the document by McLeskey:

- The title of the article reads *"Tamoxifen-resistant fibroblast growth factor-transfected MCF-7 cells are cross-resistant in vivo to the antiestrogen ICI 182780 and two aromatase inhibitors."*

- The abstract on its page 1: *"Although the antiestrogen tamoxifen has been the mainstay of therapy for estrogen receptor (ER)-positive breast cancer, successful treatment of responsive tumors is often followed by the acquisition of tamoxifen resistance. Subsequently, only 30-40% of patients have a positive response to second hormonal therapies. This lack of response might be explained by mechanisms for tamoxifen resistance that sensitize ER pathways to small amounts of estrogenic activity present in tamoxifen or that bypass ER pathways completely. To elucidate one possible mechanism of tamoxifen resistance, we treated ovariectomized tumor-bearing mice injected with fibroblast growth factor (FGF)-transfected MCF-7 breast carcinoma cells with the steroidal antiestrogen ICI 182,780 or one of two aromatase inhibitors, 4-OHA or letrozole. These treatments did not slow estrogen-independent growth or prevent metastasis of tumors produced by FGF-transfected MCF-7 cells in ovariectomized nude mice. FGF-transfected cells had diminished responses to ICI 182,780 in vitro, suggesting that autocrine activity of the transfected FGF may be replacing estrogen as a mitogenic stimulus for tumor growth. ER levels in FGF transfectants were not down-regulated, and basal levels of transcripts for estrogen-induced genes or of ER-mediated transcription of estrogen response element (ERE) luciferase reporter constructs in the FGF expressing cells were not higher than parental cells, implying that altered hormonal responses are not due to down-regulation of ER or to FGF-mediated activation of ER. These studies indicate that estrogen independence may be achieved through FGF signaling pathways independent of ER pathways. If so, therapies directed at the operative mechanism might produce a therapeutic response or allow a response to a second course of antiestrogen treatment."*

- Its introduction: *"Because conventional therapy is not usually curative in clinical breast cancer, development of tamoxifen resistance, in which breast tumors previously growth-inhibited by tamoxifen become refractory, represents an important therapeutic dilemma". [...] "As mentioned, in each of these three instances, substitution of a hormonal therapy different from tamoxifen might result in a clinical response. Two such alternative therapies used in this report are steroidal estrogen antagonists, such as ICI 182,780, which lack the partial agonist activity of tamoxifen, and aromatase inhibitors, which inhibit endogenous estrogen production by all tissues, depriving the ER of its ligand. Although the mechanisms of tamoxifen resistance described above should be amenable to alternative hormonal therapy, early results for small numbers of tamoxifen-resistant patients have shown that only about 30-40% of such patients have a positive response to subsequent ICI 1*

82780 or aromatase inhibitor therapy (13-20). These data imply alternative mechanisms for tamoxifen resistance". [...] "In contrast to what was seen with ERB-B signaling pathways, we report that FGF-mediated pathways appear to provide an alternative growth stimulatory signal that is not dependent on ER activation."

- It ends with the following conclusion: *"In contrast to some of the models mentioned above, which may mimic tamoxifen-resistant breast tumors that would respond to a second hormonal therapy, we predict that tumors in which FGF receptor-mediated signalling drives autonomous growth would be refractory to alternative hormonal therapies, as well as to tamoxifen. Therapy of such tumors with agents directed against the autocrine or paracrine effects FGFs (53) might result in beneficial effects in such cases and might result in the restoration of antiestrogen sensitivity."*

3.26 The studies described by McLeskey are intended to clarify a possible mechanism of resistance to tamoxifen and not to evidence the activity of fulvestrant in breast cancer, as evidenced from the passages transcribed and from the statements of the legal expert of the defendant Mr Armin Buschauer (document 39 of the reply, page 3). With the aforementioned purpose of discovering a mechanism of resistance to tamoxifen, fulvestrant (referred to as ICI 182780) or one or two aromatase inhibitors were used to treat ovariectomized mice with tumours into which fibroblast growth factor (FCF) transfected MCF-7 cells had been injected. The study showed that tumour growth independent from estrogens is not inhibited by means of the treatment with pure or aromatase inhibiting antiestrogens. It concluded that these studies point to the fact that independence from estrogen can be obtained through the signalling pathways of FGF which are independent of the ER pathway, which determines that the treatments intended for the operating mechanism could produce a therapeutic response or enable the response to a second cycle of a treatment with antiestrogens. McLeskey discloses that the formulation of fulvestrant was used as a tool in order to study a signalling pathway in the case of resistance to tamoxifen, in other words, as a therapeutic alternative to tamoxifen.

3.27 On the basis of the above, we can conclude, on a provisional basis at this stage of the proceedings, that McLeskey does not disclose this characteristic required by both parties to the dispute.

3.28 Furthermore, the Opposition Division of the EPO in its decision of 11 February 2015 (document 24 *bis* of the claimant) considers that D13 (numbering used to refer to McLeskey) "*does not disclose the use of the formulation for the treatment of a benign or malignant condition of the breast or of the reproductive tract by means of an intramuscular injection. The subject-matter object of these claims is therefore considered to contain novelty in view of the document D13".* And the Judgments handed down on 19/2/2016 by the Dusseldorf Regional Court (documents 58 *bis* and 59 *bis* of the claimant) stated that: *"the skilled person does not find in the reference cited* [corresponding to McLeskey] *any indication that the formulation described in the group of characteristics 2 is going to be used for the treatment of a benign or malignant condition of the breast or of the reproductive system or by means of intramuscular administration.* These judgments also indicated that *"it is also not obvious whether a skilled person would infer the characteristics not expressly disclosed",* in this case, the aforementioned document by McLeskey.

c) Administration route (intramuscular injection)

3.29 Sandoz recognizes that "in the article by McLeskey, the pharmaceutical composition of fulvestrant was administered to mice subcutaneously"; however, it maintains that for any

skilled person it was implicit that such pharmaceutical composition would be likewise administered intramuscularly. It maintains that any skilled person would have understood that the administration to mice in the McLeskey experiment was made subcutaneously because the intramuscular administration of drugs to small animals is usually a difficult task which is hardly recommended and thus has it been tacitly recognized by Astrazeneca according to its allegations and actions during the proceedings of patent EP'138 before the EPO.

3.30 The legal expert Mr Lehr declared in his opinion (doc. 38 of the defendant) that the person skilled in the art knew that both subcutaneous and the intramuscular administration were equally valid for *depot* injections and that the intramuscular administration was preferred if administered to human beings, especially in the case of oily solutions. The expert Mr Armin Buschauer declared in similar terms during the hearing.

3.31 The administration route of a drug is especially important, to the point that an invention consisting of a new therapy with a different administration route might lead to a patent of second use, as revealed by Decision T51/93 of the Case Law of the Boards of Appeal of the European Patent Office. Both parties to the dispute and their legal experts recognized that the article by McLeskey discloses directly and unambiguously the fact that the pharmaceutical composition of fulvestrant therein used was administered to the mice subcutaneously and not intramuscularly.

3.32 We must ask ourselves at this point whether McLeskey implicitly discloses the administration of fulvestrant intramuscularly. For these purposes, it should be recalled that when stating that the lack of novelty could be implicit because a person skilled in the art would have inevitably obtained a result comprised within the terms of the claim, the Boards specify that the word inevitably means indefectibly, certain to occur, something that will happen or appear, so true as to prevent any alternative solutions. Therefore, it is obvious that the inevitability prevents the existence of any valid alternative results or options: in other words, it is equivalent to 100% probability (T 793/93, repeated by the T 396/89). The subcutaneous route and the intramuscular route are different and can not be interchanged, as pointed out by the legal expert Ms Karin Schaupp (doc. 56 of the claimant), since the biological environment of the site of the injection differs fundamentally between the two kinds of administration, and therefore the administration route has an influence on the simplicity of the therapeutic use, affecting the release of the drug and the blood plasma concentration profile. During the hearing, this legal expert declared that the fact that the mice are administered the drug subcutaneously does not mean that, in the case of administration to human beings, the intramuscular route will always be used, adding that if McLeskey had had the intention of studying the intramuscular route, he would have chosen a different animal for the experiment. She also maintained that the subcutaneous route is also used with human beings and it is the preferred route if there is the option, since it provides advantages such as it might be directly applied by the actual patient. The legal expert Mr Armin Buschauer declared during the hearing that the subcutaneous route in mice might mean that, in the case of administration to human beings, the intramuscular route should be applied. However, this legal expert spoke in terms of probability and not certainty. All of the above leads us to conclude that McLeskey does not implicitly disclose the use of the intramuscular route.

3.33 Furthermore, we have already indicated in point 3.28 that the Opposition Division of the EPO in its decision of 11 February 2015 considered that McLeskey does not disclose the use of the formulation for the treatment of a benign or malignant condition of the breast or

reproductive tract by means of an intramuscular injection. The subject-matter object of these claims therefore is considered to contain novelty in view of document D13. Moreover, the Judgments given on 19/2/2016 by the Dusseldorf Regional Court maintained that the skilled person did not find in McLeskey any indication (either directly or indirectly) that the formulation described in the group of characteristics 2 was going to be used for the treatment of a benign or malignant condition of the breast or reproductive tract by means of intramuscular administration.

3.34 Having reached this point, after having concluded that the article by McLeskey does not disclose several of the technical characteristics of C1 of the patents ES-272 and ES-384, it makes no sense to proceed to analyse the fourth requisite regarding the deposit effect, especially in interim injunctions where, as we have pointed out, the validity of the said patents are not being judged in full, but only circumstantially.

c) On the alleged lack of novelty of C2 and C3 of ES'384.

3.35 At this stage, after having declared the circumstantial novelty of C1, which is the only independent claim of patent ES'384, there is no need to proceed with the analysis of the rest of the alleged claims, since C2 is a dependent claim of the C1 and C3 depends in turn on C2. One of the maxims of patent law consists of the fact that if an independent claim is new, by definition all of the other claims depending on it will also be new. Thus is it stated by the Examination Guidelines of the OEPM (section 3.3, page 55), on declaring "*if the subject-matter of the independent claim is new, that of the dependent claims will also be considered new for search purposes*". In addition, the EPO Guidelines for Examination (Part G - Chapter VII-13, version from November 2015, pages 79-80), indicate the following:

"13. Dependent claims; claims in different categories

If the subject-matter of an independent claim is new and non-obvious, there is no need to investigate the novelty and non-obviousness of the subject-matter of any claims dependent thereon, except in situations where the subject-matter of a dependent claim has a later effective date than the independent claim and intermediate documents are to be considered (see F-VI, 2.4.3).

Similarly, if the subject matter of a claim to a product is new and non-obvious there is no need to investigate the novelty and non-obviousness of the subject matter of any claims for a process which inevitably results in the manufacture of that product or of any claims for a use of that product. In particular, analogy processes, i.e. processes which themselves would otherwise not involve an inventive step, are nevertheless patentable insofar as they provide a novel and inventive product (see T 119/82). It should, however, be noted that in cases where the product, process and use claims have different effective dates, a separate examination as to novelty and inventive step may still be necessary in view of intermediate documents.

D) On the alleged lack of novelty of C2 to C31 of ES'272.

3.36 The same reasons as set forth in the foregoing point (3.35) are applicable to claims 3, 5 to 17, 20 to 22 and 25 to 31 on being dependent or multi-dependent on C1, with only the novelty of the independent claims 2, 4, 18, 19, 23 and 24 pending analysis.

3.37 C2, 4, 18, 19, 23 and 24, among other characteristics, require the use of fulvestrant in

the preparation of a pharmaceutical formulation for the treatment of a benign or malignant condition of the breast or reproductive system by means of intramuscular administration. We have already pointed out (points 3.24 to 3.33) that these two characteristics are not disclosed in McLeskey, based on circumstantial evidence, and therefore we can not conclude that they meet the requisite of novelty.

FOUR.- On the (lack of) inventive step of the patents.

4.1 The following issue we must analyse regarding the validity of the patents in dispute is whether they meet the requisite of inventive step. Such examination will equally be circumstantial on being related to the interim injunctions and not terms of certainty.

A) Previous legal and jurisprudential considerations on the examination of inventive step.

4.2 Examining inventive step involves the analysis of the merit of the invention so that it can be considered as such, for which purpose it must be asked whether a person skilled in the art, based on the previous descriptions and depending on their own knowledge, would be capable of obtaining the same result, without using their inventiveness.

4.3 In this sense, Art. 8 of the Patent Act states that *"an invention is considered to involve inventive step if it is not obvious from the state of the art to a person skilled in the art"* .

4.4 A useful method for analysing the requisite of inventive step is the problem and solution approach, which is the one usually used by the examiner of the European Patent Office, although it is not the only process capable of assessing inventive step.

4.5 The said method, used by the EPO in the analysis of the inventive step of a patent application and known under the name of the "problem and solution approach", is fundamentally intended to avoid an *ex post facto* assessment of the inventive step. The intention of this is to objectivize the analysis of the obviousness on the date on which the priority of the patented invention is claimed, in other words, before the description of the invention was made public, as required by art. 8.1 of the Patent Act and art. 56 EPC.

4.6 The Boards of Appeal, in order to find a legal basis for this test, are usually supported by Regulation 40(1)c() (Implementing Regulation of the EPC, currently adapted by decision of the Administrative Council from 7 December 2006), according to which the description of the request will: *"disclose the invention, as claimed, in such terms that the technical problem, even if not expressly stated as such, and its solution can be understood"*. It thus turns out that the technical problem and its solution are elements of any invention.

4.7 The application of the method involves having to follow three steps: a) the determining of the closest state of the art; b) the definition of the technical problem intended to be solved with the new invention; and c) based on these two elements, assessing whether the invention claimed was obvious to a person skilled in the art, which supposes, on the one hand, for the skilled person to have questioned the problem the invention tries to solve, and, on the other hand, which proposed solution would have seemed obvious to them.

4.8 As we have just said, there are other methods used to assess the inventive step of a patent. For example, the British courts do so by following the method described by the judge Lord

Oliver in the Judgment of the United Kingdom Court of Appeal from 25 April 1985 in the case of Windsurfing International Inc. v. Tabur Marine (G. B.) Ltd., reformulated by the judge Lord Jacob in the Judgment from 22 June 2007 also before the Court of Appeal in the case Pozzoli SPA v. BDMO SA. According to this method, there would be four steps that should be analysed in order to reply to the answer of whether an invention has inventive step. These steps are:

a) determining the inventive concept of the patent,
b) the court should assume the role of the average skilled person but without imagination on the priority date of the patent, and attributing to them the general knowledge on such date,
d) identifying the differences between what is known in the state of the art and the invention,
d) the court should question whether, viewed without any knowledge of the invention, these differences determined in the third step constitute steps that would have been obvious to a person skilled in the art or whether, in contrast, they would require any degree of inventiveness.

4.9 Furthermore, in the United States the requisite of inventive step is called the "non-obviousness requirement", and their assumptions are analogous to it. In that country, there are two landmark cases of the Supreme Court which explain the basis for the analysis of the requisite of inventive step. These are the case Graham v. John Deere from the year 1996 and the case KSR v. Teleflex from the year 2007. According to these decisions, the factors that must be determined in order to know whether an invention is obvious are the following:

a) the level of the person skilled in the art
b) the scope and content of the state of the art
c) the differences between the invention claimed and the state of the art
d) any secondary considerations.

4.10 Both the Supreme Court and Section 15 of the Barcelona Court of Appeal and Section 28 of the Madrid Court of Appeal accept the method of the EPO of the problem and solution approach in order to resolve the requisite of the inventive step of an invention. However, they recognise that it is not the only possible method. Such bodies agree in that the important thing is to analyse whether the person skilled in the art, based on the disclosures of the state of the art and on the common general knowledge, is capable of obtaining the invention protected by the claim whose validity is in dispute. Supreme Court Judgment n° 182/2015, of 14 April, stated the following: "*There is not just one single method for judging inventive step, but the one to be followed must ensure that the judgment takes into account the decisive factors. In the judgment 434/2013, of 12 June, we corroborated the validity and suitability of the method to be followed by the court of instance of the "problem and solution approach", or the three- step method, according to which the first thing to do is to determine the closest state of the art, subsequently establishing the objective technical problem to be solved; and, finally, to consider whether the invention claimed would have been obvious to a skilled person in view of the closest state of the art and the technical problem. Such method, which is consistent with regulation 27 of the Implementing Regulation of the Convention, is used generally by the European Office and has been embraced by courts of other States which are part of the Convention as a useful method in most cases in order to assess inventive step*'".

4.11 Furthermore, both sections defend that the parties to the legal proceedings should use a system for the analysis of the requisite of inventive step which enables the avoidance of any *ex post facto* approaches. In this sense, Section 28 of the Madrid Court of Appeal maintains that, without such system, it is practically impossible to carry out a legal control of the analysis which could be made by a legal expert participating in the legal proceedings. Thus, its Judgment nº 283/2011, of 3 October 2011, declared the following:

"... that this person is limited in his position as skilled person, regarding the analysis of the inventive step, to providing an obvious opinion according to his criteria. In other words, he shares the result of his reflections, but without making in his report (in which, moreover, on occasions he does not distinguish between whether he is dealing with the analysis based on a different premise such as novelty, which was then criticised by such expert and which not even the party suggesting it now defends that it did not concur) any assessment of the requisite of inventive step according to the method of the problem and solution approach. This court considers that the opinion of such expert is respectable, considering his brilliant curriculum, but this is not sufficient for us to consider it as a decisive evidence if it is does not comply with a method we can submit to legal assessment, as otherwise we would be considering uncritically an argument of authority and would be leaving the solution to the dispute in the hands of a subject different from the judge. Furthermore, we consider that there is an obvious risk that, if the legal expert acts in that way, making continuous references to what he considers broadly known, he could be unconsciously committing an "ex post facto" analysis, affected by the embodiment of a retrospective view towards what has been invented from some knowledge which was years old after the moment when the patent registration was requested".

4.12 The entity Sandoz formulates its opposition to the interim injunctions without developing the steps of the problem and solution approach and without following the system required by such method. The allegations it makes are more typical of an assessment of the novelty in which several documents are combined, an issue which is not permitted in the analysis of novelty. This lack of system does not permit us to make a judicial control of the requisite of inventive step through any of the three methods mentioned, which would simply lead us to observe that in the patents under dispute, the requisite of inventive step exists and, therefore, we would dismiss this ground for opposition. However, we will proceed to the analysis of the inventive step, which will lead us to the same result mentioned.

B) Legal and jurisprudential configuration of inventive step

4.13 As we were saying, the application of the problem and solution approach involves following several steps (point 4.7).

B.1) The determining of the closest state of the art

4.14 In order to determine the closest state of the art, the Boards of Appeal of the EPO follow different criteria, starting generally from the fact that such state of the art is represented by a priority document meeting a series of characteristics. In the first place, it is a state of the art aimed at the same purpose or effect as the disputed invention (T 606/89, T 686/91, T 650/01). In the second place, it must be a document related to the same or similar technical problem as the invention in dispute, or at least to the same or similar technical field as the patent in dispute (T 909/93, T 1203/97, T 263/99). In the third place, it must constitute, for a person skilled in the art, the most promising starting point in order to reach the invention in dispute

(T 254/86, T 282/90,70/95, T 644/97, T656/90).

4.15 The Guidelines for Examination of the EPO (version 16/9/2013, Part G. Chapter VII, 5.1) set out that: *"The closest prior art is that which in one single reference discloses the combination of features which constitutes the most promising starting point for a development leading to the invention".*

4.16 When analysing novelty, the relevant date is that of the disclosure of the background document, and not that of the priority of the patent challenged, whilst in order to assess inventive step, the relevant date is the priority date of the patent in question. As declared by the case law of the Boards of Appeal of the EPO "The closest prior art must be assessed from the skilled person's point of view on the day before the filing or priority date valid for the claimed invention (T 24/81, DO 1983, 133 by the legal expert, T 772/94, T 971/95, Guidelines G-VII, 5.1 – version June 2012).

8.2) The technical problem to be solved with the new invention.

4.17 The second step of the test applied consists of identifying the objective technical problem to be solved with the new invention.

4.18 The Examination Guideline C-VII, 5.2 sets out: *"In the context of the problem-and-solution approach, the technical problem means the aim and task of modifying or adapting the closest prior art to provide the technical effects that the invention provides over the closest prior art. The technical problem thus defined is often referred to as the "objective technical problem".*

B.3) The assessment of obviousness.

4.19 Once the closest state of the art and the problem to be solved by the invention have been determined, the final step of the problem and solution approach will be taken, which is the assessment of whether the solution suggested by the patent questioned is obvious to a hypothetical person skilled in the art.

4.20 In this regard, it should be recalled that this person skilled in the art has certain common features in all cases, which we should define:

a) The person skilled in the art is a person (or a team of persons) who has experience in the matter to which the invention refers, possesses certain common knowledge in the corresponding technical or scientific field and, at the time when the application is submitted, is an average professional who has the common knowledge for this kind of profession.

b) The skilled person is attributed the knowledge of all the documents forming the state of the art, which they have carefully read and, of course, those cited in the report on the state of the art.

c) Our skilled person has the common means and capacity to carry out both routine work and experiments.

d) They are a skilled person in the field of the state of the art corresponding to the invention (Boards of Appeal EPO T 641/00, OJ 2003, 352), but do not have any inventive

capacity (T39/93, OJ 1997, 134). It is precisely this kind of capacity which differentiates the inventor from the person skilled in the art.

e) In order to choose the ideal skilled person, we need to start from the technical problem dealt with and intended to be solved by the invention, and not from the solution (T 422/93).

4.21 At this point, following the "could-would" test, it should be recalled that it is not about whether the person skilled in the art "could have" obtained the invention in dispute. It is obvious that a skilled person could have obtained it by carrying out the same routine experiments carried out by the patent holder. However, this analysis would be an *ex post facto* analysis of the inventive step, in other words, knowing the starting point (the closest state of the art) and the destination point (the invention in dispute), without considering that, on the priority date of the patent, the skilled person was not familiar with the invention which solves the problem.

4.22 The determining factor in order to assess whether the invention is obvious or not is whether the skilled person would have done so, in other words, we need to ask whether, starting from the closest state of the art, the skilled person would have reached the solution suggested. This "would have" is what turns what is otherwise inventive into obvious.

C) On the alleged lack of inventive step of C1 of ES'272 and ES'384.

C.1) <u>The determining of the closest state of the art</u>.

4.23 The defendant Sandoz maintains that the closest state of the art could be determined based on three different starting points, the first being the document by McLeskey submitted as document 1 by the opposition, the second being the document by Howell (doc. 10 of the opposition) and the third being patent EP'014 (doc. 12 of the opposition). For its part, the claimant disagrees over considering McLeskey or Howell as the closest state of the art. The claimant declares that the closest state of the art would be patent EP'014.

4.24 Sandoz alleges a judgment issued by this Court on 20-10-2014 (Celocoxib case) as the basis for its argument in order to take those documents as the starting point.

4.25 The aforementioned judgment issued by this Court declared the following:

"14. Art. 126 of the Patent Act establishes that it is the duty of the defendant to allege the total or partial invalidity of the patent of the claimant, and art. 217 LEC adds that he has the duty of proving such facts on which he grounds his allegations ("it is up to the defendant (...) to prove the facts that, according to the rules applicable to him, prevent, extinguish or aggravate the legal efficacy of the facts referred to in the section above").

15. If it is up to the defendant to allege the invalidity (by way of a plea or a counterclaim), it is also up to him to select the facts on which such pretension is based. My function in this point consists of verifying the existence of such facts and assessing the certainty or falsity of his conclusions. Therefore, if the defendant chooses a document as being the closest to the relevant state of the art, I will start my analysis from such selection.

16. In this case, the claimant admits that EP'845 Fujisawa (compound of example 25), forms part of the state of the art and is the closest document for the compounds of claims 1, 2 and 3 of patent ES'795, but adds that the closest state of the art document regarding claim 4, which describes Celecoxib, would be the compound of example 29.3 of patent application EP'829 Fujisawa, since it would structurally be the compound most similar to Celecoxib.

17. As recognized by the Guidelines mentioned, there could be several documents constituting starting points which are equally valid, in which case the examiner of the Office will apply the problem and solution approach starting from each one of them, since his objective is to assess whether the patent will be granted or not.

18. However, in the case of a legal action for invalidity against a patent which has been already granted, the judge in his judgment is limited to assessing the alleged facts which have been proven by the parties as a ground for invalidity as a requirement of congruence, art. 218 LEC. From a procedural point of view, I must start from the document alleged by the defendant, since it is him, as I have said, who bears the burden of proving the facts on which he grounds his plea or request for invalidity. If the defendant has chosen a document which is further away than the one he has chosen, he will be responsible for his possible mistake in the analysis of the inventive step, but I can not disregard such assessment due to the simple fact that there is a closer document to the relevant state of the art.

19. The problem and solution approach is only one legal method for analysing the obviousness of an invention, the application of which never has true or false premises, but rather more or less reasonable premises. If the party requesting the invalidity of the patent starts, as I have said, from a compound described in the state of the art requiring more structural modifications than another, it will be more difficult for him to justify the obviousness of the invention in question, but I think it does not make much sense to become obsessed with a discussion on whether the document proposed by the holder is the closest or not: the important thing will always be whether the document chosen by the defendant is part of the relevant state of the art.

20. Logically, the holder of the patent, when opposing the request for invalidity, can deny that the document is part of the relevant state of the art or that it constitutes the most promising starting point, but from the point of view of the procedure it makes no sense to analyse whether there is a closer state of the art document than the one suggested by the defendant.

21. As a consequence, I will start from example 25 Fujisawa as alleged by the defendant in his counterclaim, regardless of the consequences that could derive from the teachings of the second patent of Fujisawa EP'829 when assessing the obviousness of the solution suggested by ES'727".

4.26 The defendant who has alleged the invalidity of the patents bears the burden of proving it, and therefore, on the basis of what has been already decided in the judgment of this Court transcribed above, we must start from the documents alleged by Sandoz as the closest state of the art.

C.2) The technical problem to be solved with the new invention.

4.27 The problem to be solved by the patents object of these proceedings, according to their wording, is the following:

"The finding is surprising since the solubility of fulvestrant in non-aqueous ester solvents - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in non-aqueous ester solvents than the solubility of fulvestrant in castor oil.

Therefore, we present as a feature of the invention a pharmaceutical formulation comprising fulvestrant (preferably fulvestrant is present at 3-10% w/v, 4-9% w/v, 4-8% w/v, 4-7% w/v, 4-6% w/v and most preferably at about 5% w/v) in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Another feature of the invention is a pharmaceutical formulation comprising fulvestrant in which the formulation is adapted for intra-muscular injection into a human and which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks. (page 8 lines 32-22 and page 9 lines 1-11, of ES'272). ES'384 states similarly, but referring only to the treatment of breast cancer.

4.28 We have already pointed out during the examination of novelty that the studies carried out in McLeskey are intended to clarify a possible mechanism of resistance to tamoxifen and not to prove the successful activity of fulvestrant in the actual treatment of breast cancer in human beings. Therefore, McLeskey does not have the same purpose and does not seek the same objective as the patents at hand.

4.29 Howell analyses the pharmacokinetics, pharmacologic and antitumour effects of the specific steroid antiestrogen ICI 182780 in 19 patients with advanced breast cancer with resistance to tamoxifen. The agent was administered once a month by means of a depot intramuscular injection. ICI 182780 was administered as a long-term formulation contained in a vehicle based on castor oil on a monthly basis by means of an i.m. injection (5ml) in the buttock. Therefore, Howell has neither the same purpose nor is intended for the same objective as the patents at hand.

4.30 The document consisting of patent EP 0346014 is the European equivalent of US patent US'814. It refers the treatment of peri- and post-menopause states with pure antiestrogen, including fulvestrant. Within this patent, the closest state of the art would be formed by its example 3, which reads as follows:

"Example 3

The pure antiestrogen used was 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

Each of a series of selected doses of this compound was dissolved in a mixture of castor oil and benzyl alcohol and given by intramuscular injection to a group of 5 mature rats. The formulation contained 50 mg of the test compound, 400 mg of benzyl alcohol and

sufficient castor oil to bring the solution to a volume of 1 ml. In each case a second dose was administered two weeks after the first dose. Two weeks after the second dose the weights of the uteri of the test groups of rats were determined. In addition, the femurs were dissected and analysed for Gross Femur Density as in Example 1."

C.3) The assessment of obviousness.

4.31 In McLeskey, as we have concluded, the problem to be solved would be different than the one solved in the patents at hand. Furthermore, in McLeskey, the fulvestrant used, together with other substances, is a mere working tool in order to study a possible signalling pathway. McLeskey does not make a study of the treatment in human beings, instead it makes a study on rats using the subcutaneous route and not the intramuscular one as in ES'272 and ES'384. Likewise, as we have stated in the examination of novelty, McLeskey does not disclose the same formulation or identical therapeutic indication or the same administration route. As a consequence, the skilled person, based on the McLeskey, would not have arrived at the solution suggested by the patents subject-matter of these proceedings, not even by combining such document with any of the others cited, as we will now proceed to analyse.

4.32 Howell publishes the results of a clinical study for the treatment of breast cancer carried out in 19 patients to whom fulvestrant was administered formulated in castor oil via the intramuscular route. However, this document does not disclose a formulation comprising a pharmaceutically acceptable non-aqueous ester solvent or a pharmaceutically acceptable alcohol. In view of this fact and of what we have explained in the point above, we understand that the skilled person would have not been interested in combining Howell and McLeskey in order to find an alternative formulation to the one described by Howell since, as we have said, McLeskey does not refer to individuals and its purpose is a study on the sensitivity of FCF-transfected MCF-7 breast cancer cells to several substances, including fulvestrant.

4.33 Example 3 of patent EP'014 does not include a pharmaceutically acceptable non-aqueous ester solvent, as recognised by Sandoz. Patent ES'272 itself refers to this example in the following terms: *"Example 3 of the document US 5.183.814 describes an oil based injection formulation of fulvestrant, which comprises 50 mg of fulvestrant, 400mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. The manufacture at a commercial scale of a formulation as described in US 5.183.814 will be complicated due to the high alcohol concentration. Therefore, there is a need to lower the alcohol concentration in fulvestrant formulations whilst preventing precipitation of fulvestrant in the formulation."* (page 8, lines 1-6). Further on it indicates: *"As can be appreciated, the fulvestrant is significantly more soluble in castor oil than in any of the other oils tested"* (lines 10-11). However, it maintains that *"even when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically significant release rate.* (lines 15-18). As a consequence, the patent has found it *"surprising that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 mgml^{-1} - see Table 3 below. The finding is surprising since the solubility of fulvestrant in non-aqueous ester solvents - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in non-aqueous ester solvents than is the solubility of fulvestrant in castor oil. Therefore, we present as a feature of the invention a pharmaceutical formulation comprising*

fulvestrant (preferably fulvestrant is present at 3-10% w/v, 4-9% w/v, 4-8% w/v, 4-7% w/v, 4-6% w/v and most preferably at about 5% w/v) in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks. Another feature of the invention is a pharmaceutical formulation comprising fulvestrant in which the formulation is adapted for intra-muscular injection into a human and which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks" (page 8, lines 29-33 and page 9, lines 1-11, of ES'272). ES'384 pronounces similarly. Therefore, the patents at hand seek how to increase the solubility of fulvestrant in an intramuscular formulation and for this purpose they propose the solution of adding a non-aqueous ester solvent. For its part, patent EP'014 describes the addition of fatty esters only in relation to water in oil emulsions, which are only known as oral formulations, and it does not suggest the addition of a non-aqueous ester solvent to the formulation for intramuscular use (page 5, lines 18-57). The article by McLeskey reports a study that intends to determine the sensitivity of certain breast cancer cells which are resistant to tamoxifen compared to different substances, among them, fulvestrant, where the fulvestrant is administered subcutaneously to mice. Therefore, the skilled person based on EP'014 and facing the problem consisting of increasing the solubility of fulvestrant in an intramuscular formulation would have not found any incentive to pay attention to McLeskey in order to solve the problem.

4.34 Sandoz also considers that if we start from EP'O14, the skilled person would have combined the common general knowledge embodied in the handbook by Avis, Lieberman and Lachman (doc. 19 of the opposition) or with that found in Wade and Weller (doc. 20 of the opposition). Avis *et. al.* teaches that benzyl benzoate might be used in order to improve the solubility of steroids in oils and Wade *et. al.* discloses that benzyl benzoate was used as a solubilizing agent in intramuscular injections, *ex* art. 281.3 LEC. However, we consider that even if the person skilled in the art started from EP'014 and combined it with the common general knowledge existing in Avis *et. al.* or in Wade *et. al.*, they would have not obtained the solution suggested by ES'272 or ES'384, since such documents do not contain any technical teachings on the treatment of breast cancer or on the release of fulvestrant in such a way that a therapeutically significant concentration of Fulvestrant is obtained in blood plasma for at least 2 weeks.

D) On the alleged lack of novelty of tC2 and C3 of ES'884 and C2 to C31 of ES'272.

4.35 The same reasons described in point (3.35) are applicable to claims 2 and 3 of ES'384 and those set forth in points 3.35 and 3.36 to claims 3, 5 to 17, 20 to 22 and 25 to 31 on being dependent or multi-dependent on C1, with only the novelty of independent claims 2, 4, 18, 19, 23 and 24 pending analysis.

4.36 Regarding C2, 4, 18, 19, 23 and 24, the defendant entity does not specify whether they are also invalid due to the lack of inventive step, since the analysis thereof is only made using the document by McLeskey mentioning that this scientific paper discloses the characteristics required in such claims. Even if we understood that Sandoz also requests the invalidity thereof due to a lack of inventive step, the defendant dos not use any of the methods described for judging inventive step (points 4.2 to 4.12). This lack of system does not enable us to carry out a judicial control of the requisite of inventive step by means of any

of the three methods described, which simply leads us to observe that the requisite of inventive step exists in such claims.

4.37 In short, we may conclude, with the caution required by this procedural stage, that patents ES'272 and ES'384 are not invalid. This means that the requisite of the *fumus boni iuris* exists and implies the dismissal of the opposition to the interim injunctions in respect of this point.

FIVE.- On the working of the patents in dispute.

5.1 The second and final ground for opposition to the interim injunctions, alleged by Sandoz, is the lack of *fumus boni iuris* of the claimants due to a failure to work the invention. Specifically, Sandoz maintains that Astrazeneca has not evidenced the exploitation of claims 2, 4-19, 23-26, 30 and 31 of patent EP'138 or any of the three claims of patent EP'573.

5.2 Article 133 of the Patent Act states that: "Any party bringing or about to bring an action from among those set out in this act might ask the court hearing it to adopt interim injunctions aimed at ensuring the effectiveness of such actions, provided that they justify the working of the patent object of the action under the terms of article 83 of this act, or that they have made serious effective preparations for such purposes". Therefore, in order to obtain provisional protection, it is necessary to justify the working of the patent or the start of preparations intended for such working. This obligation of exploitation must be met in the terms of article 83 PA, according to which the holder of the patent is obliged to work the invention patented, either itself or through a person authorized by it, by means of the execution thereof in Spain or within the territory of a member of the World Trade Organization, in such a way that such exploitation is sufficient to satisfy the demand of the domestic market.

5.3 Ruling nº 141/2012of Section 28 of the Court of Appeal stated that compliance with the working of the invention may take place not only when such exploitation is made in Spain, but also in a member state of the European Union or the World Trade Organization.

5.4 The requirement of the said rules is only aimed at the exploitation of the invention of the patent, and not at the requirement to exploit all the claims included in the patent, especially when, in this case, Sandoz is recognising, in the opposite sense, that Astrazeneca is exploiting several claims of patent ES'272, among them C1.

5.5 With regard to patent ES'384, Sandoz alleges that, to date, none of its claims have been exploited. Article 83.2 PA states that "the exploitation must be made within a period of four years from the date of submission of the patent application, or three years from the date on which the grant thereof is published in the Official Industrial Property Bulletin (BOPI), subject automatically to whichever term expires last". These terms have not yet elapsed for patent ES'384, since the date of publication in the BOPI took place in 2015. We understand that if the holder of the patent is granted the said periods terms for complying with the obligation to exploit, it does not seem reasonable to requiring such exploitation when it is requesting interim injunctions before the conclusion of the periods granted to it by the legal system for meeting the obligation of working the patent.

5.6 Therefore, we may conclude that the requisite of exploitation has been met by both patents, which implies the dismissal of the opposition to the interim injunctions.

SIX.- On the costs.

6.1 Art. 741.2 LEC states that if the interim injunctions agreed were maintained, the opposing party shall be ordered to pay with the costs of the opposition.

6.2 Pursuant to such regulation, the dismissal of the opposition to the interim injunctions obligatorily involves the awarding of the costs against the defendant, in this case, the entity Sandoz.

DECISION

WE HEREBY AGREE:

1.- **To dismiss** the opposition brought by Mr Ignacio López Chocarro, in the name and on behalf of Sandoz Farmacéutica, S.A., against the interim injunctions agreed by means of the ruling of 20 January 2016, maintaining them, with the express awarding of the costs against the entity Sandoz.

2.- That the parties should be informed that this ruling is not final and an appeal may be filed against it, without suspending effects, to be filed by means of a writ submitted to this court within a period of 20 days from the notification thereof, pursuant to the provisions of arts. 455 *et seq.* of the LEC, by evidencing the deposit of the amount of 50 euros in the deposits and consignments account of this Court. The appeal will not be admitted unless such requirements are met (!5th Additional Provision of the Law on the Judiciary, pursuant to the regulation given by Organic Law 1/09, of 3 November).

3.- To include the original ruling to the registry book of final decisions, including a record in the proceedings and proceeding to close the file, once final.

Thus do I, Mr Alfonso Merino Rebollo, Senior Judge of this Court n° 4, order and sign, having submitted this ruling to the consideration of the Patent Section of the Barcelona Commercial Court of First Instance, consisting of Ms Yolanda Ríos López (co-ordinator), Mr Florencio Molina López and Mr Alfonso Merino Rebollo, within the framework of the Barcelona Commercial Court of First Instance Statute protocol approved by the agreement of 15 June 2014 of the Judicial Council Permanent Commission.

PUBLICATION.- The resolution above has been read and published on the day of its date by the judge issuing it with a public hearing having been held. I attest