Facts and submissions

I. The European patent EP 2 266 573 B1; based upon European patent application 10180667.7; filed as a divisional application divided from the earlier European patent application 05016921.8 (EP 1 669 073); in turn divided from the earlier European patent application 01900186.6 (EP 1 250 138); date of filing: 08.01.2001; priorities: 10.01.2000 (GB 0000313) and 12.04.2000 (GB 0008837); date of publication and mention of the grant of the patent: 17.06.2015 (Bulletin 2015/25);

Proprietor: AstraZeneca AB, 151 85 Södertälje (SE)

has been opposed by:

Opponent 1: Hexal AG, 83607 Holzkirchen (DE)

Opponent 2: Actavis Group PTC ehf, 220 Hafnarfjördur (IS)

Opponent 3: Fresenius Kabi Deutschland GmbH, 61352 Bad Homburg (DE)

Opponent 4: Intas Pharmaceuticals Ltd., 380009 Ahmedabad (IN)

Opponent 5: Teva Pharmaceutical Industries Ltd., Petach Tikva 49131 (IL)

II. With notice of opposition dated 29.10.2015, filed on same day, the Opponent 1 requested revocation of the patent in its entirety on the grounds of Art. 100(a) EPC for lack of novelty (Art. 54 EPC) and lack of an inventive step (Art. 56 EPC). Alternatively, oral proceedings were requested (Art. 116 EPC).

III. With notice of opposition dated 16.02.2016, filed on same day, the Opponent 2 requested revocation of the patent in its entirety on the grounds of Art. 100(a) EPC for lack of novelty (Art. 54 EPC) and lack of an inventive step (Art. 56 EPC); on the grounds of Art. 100(b) EPC for lack of sufficient disclosure (Art. 83 EPC); and on the grounds of Art. 100(c) EPC for extension of the subject-matter (Art. 76(1) and 123(2) EPC). Alternatively, oral proceedings were requested (Art. 116 EPC). Further, the Opponent 2 requested accelerated examination of the opposition in view of revocation actions pending before national courts.

IV. With notice of opposition dated 08.03.2016, filed on same day, the Opponent 3 requested revocation of the patent in its entirety on the grounds of Art. 100(a) EPC for lack of novelty (Art. 54 EPC) and lack of an inventive step (Art. 56 EPC). Alternatively, oral proceedings were requested (Art. 116 EPC).

V. With notice of opposition dated 17.03.2016, filed on same day, the Opponent 4 requested revocation of the patent in its entirety on the grounds of Art. 100(a) EPC for lack of novelty (Art. 54 EPC) and lack of an inventive step (Art. 56 EPC); and on the grounds of Art. 100(c) EPC for extension of the subject-matter (Art. 76(1) and 123(2) EPC). Alternatively, oral proceedings were requested (Art. 116 EPC).

VI. With notice of opposition dated 16.03.2016, filed on same day, the Opponent 5 requested revocation of the patent in its entirety on the grounds of Art. 100(a) EPC for lack of an inventive step (Art. 56 EPC); and on the grounds of Art. 100(c) EPC for extension of the subject-matter (Art. 76(1) and 123(2) EPC). Alternatively, oral proceedings were requested (Art. 116 EPC).

VII. With letter dated 17.03.2016, filed on same day, the Opponent 1 added the grounds for opposition of Art. 100(b) EPC for lack of sufficient disclosure (Art. 83 EPC); and the grounds of Art. 100(c) EPC for extension of the subject-matter (Art. 76(1) and 123(2) EPC). Further, the Opponent 1 requested accelerated processing of the opposition in view of infringement proceedings against the opponent brought in by the Patentee.

VIII. With letter dated 16.03.2016, filed on 21.03.2016, the Swiss Federal Patent Court requested acceleration of the proceedings before the EPO in view of pending Swiss proceedings regarding the patent in suit.

IX. With letter of reply dated 08.09.2016, filed on same day, the patent Proprietor requested rejection of the oppositions and maintenance of the patent as granted (Main request). Alternatively, oral proceedings were requested (Art. 116 EPC) in the event that the Opposition Division would be unable to grant this request on the basis of the written proceedings.

Moreover, in view of several pending national proceedings involving the opposed patent, or family members thereof, the Patentee made the following procedural requests:

i) to accelerate the proceedings;

ii) to issue an early substantiated preliminary opinion by the Opposition Division on all issues in dispute.

X. With letter dated 06.10.2016, filed on same day, the patent Proprietor as a precaution submitted Auxiliary requests 1 to 3.

XI. With letter dated 17.11.2016, filed on same day, the Opponent 4 raised objections of lack of clarity (Art. 84 EPC, G 3/14) against claim 1 of Auxiliary requests 2 and 3, and stated that also an objection in view of Art. 83 EPC could be raised.

XII. With letter dated 18.11.2016, filed on same day, the Opponent 5 submitted that the claims of Auxiliary requests 1 to 3 do not meet the requirements of Art. 76(1) and 123(2) EPC. Furthermore, the Opponent 5 submitted that the grounds of lack of an inventive step (Art. 56 EPC) equally apply to the claims of Auxiliary requests 1 to 3.

XIII. With letter dated 24.11.2016, filed on same day, the Opponent 1 submitted that the Auxiliary requests 1 to 3 do not meet the requirements of Rule 80 EPC, because the amendments are not suited to overcome the deficiencies under Art. 123(2) EPC. Furthermore, the Opponent 1 submitted that the grounds of lack of novelty (Art. 54 EPC), lack of an inventive step (Art. 56 EPC), and lack of sufficient disclosure (Art. 83 EPC) equally apply to the claims of Auxiliary requests 1 to 3.

XIV. As requested by the parties, and by the Swiss Federal Patent Court, the opposition was dealt with under acceleration.

XV. With official communication dated 30.11.2016, the Opposition Division gave a substantiated preliminary, non-binding opinion on all issues in dispute and summoned to oral proceedings.

In the preliminary opinion, it was emphasised by the Opposition Division that the present opposition was to be examined on its own merits, independently from any other previous or pending national proceedings involving the opposed patent, and also independently from any previous EPO or national proceedings involving the patent EP 1 250 138 (grandparent of the opposed patent). It was particularly stressed that the present Opposition Division was not bound by the reasons for the decision taken in opposition proceedings before the EPO involving the patent EP 1 250 138.

In the preliminary opinion, the Opposition Division expressed the view that claim 1 of the opposed patent as granted did not meet the requirements of Art. 56 EPC, and that this conclusion appeared to apply entirely also to Auxiliary requests 1 to 3.

XVI. With letter dated 02.05.2017, filed on same day, the Opponent 1 submitted that Auxiliary requests 2 and 3 should not be admitted into the proceedings since the amendments to claim 1 lead to *prima facie* lack of clarity (Art. 84 EPC, G 3/14).

XVII. Oral proceedings before the Opposition Division took place on 08.05.2017.

At the beginning of the oral proceedings, the parties confirmed their requests made in writing.

During the oral proceedings, the parties made no comments with regard to the questions of novelty (Art. 54 EPC), sufficiency (Art. 83 EPC), and extension of the subject-matter (Art. 76(1) and 123(2) EPC). They expressly referred to their submissions in writing. Only the question of inventive step (Art. 56 EPC) was discussed.

After the discussion of the Main request, the patent Proprietor stated that he wanted to proceed with the discussion of the Auxiliary request 2 only.

The parties made no comments with regard to the objections under Rule 80 and Art. 84, 83 and 54 EPC raised in their written submissions. Only the representative of Opponents 2 and 5 stated that the objections under Art. 76(1) and 123(2) EPC made in writing were maintained.

Then, the question of inventive step (Art. 56 EPC) in connection with the Auxiliary request 2 was discussed.

After deliberation of the Opposition Division, the decision was announced that the Main request (claims as granted) as well as the Auxiliary requests 1 to 3 do not meet the requirements of Art. 56 EPC.

XVIII. In the course of the proceedings, the following documents were submitted as evidence by the parties (see Annex A):

D1-D16, D16A, D17, D17A, D18-D23, D23A, D24, D24A, D25, D25A, D26, D26A, D27-D67, D68 (comprising 6 annexes), D69, D70: See consolidated list of cited documents attached (Annex A, pages 1/4 to 4/4).

XIX. The arguments submitted by the parties and relevant for the present decision may be summarized as follows:

Extension of subject-matter (Art. 76(1) and 123(2) EPC)

The Opponents 1, 2, 4 and 5 essentially argue that the combination of a) specific excipients, b) specific medical use, and c) specific volume of the formulation in claim 1 of the patent as granted represents a new combination of features which was not directly and unambiguously derivable from the earlier (grandparent) application as originally filed (WO 01/51056 A1), but requires a selection from at least two lists. The same applies with regard to the parent application as filed (EP 1 669 073).

The patent Proprietor argues that there is no selection from multiple lists, claim 1 as granted being based on the combination of features of original claims 4, 17, 20 and 22, wherein the medical use has been limited to the only preferred embodiment “breast cancer”.

Novelty (Art. 54 EPC)

The Opponents 1, 3 and 4 argue that D1 is prejudicial to novelty of claim 1 as granted, because D1 discloses the use of a preformulated 50 mg/ml fulvestrant injection composition comprising castor oil, ethanol (10%), benzyl benzoate (15%) and benzyl alcohol (10%) in the treatment of breast cancer. The use by *intramuscular injection* in breast cancer patients is *implicit,* so the Opponents.

The Opponent 1 further argues that the experiments described in D1 using a preformulated 50 mg/ml fulvestrant injection composition demonstrate a *public prior use* by the authors of D1 of the formulation claimed in the opposed patent.

The Opponent 2 further alleges a *public prior use* of the fulvestrant formulation claimed in the opposed patent through the phase III clinical trials of “Faslodex”.

The Patentee alleges that D1 discloses neither the specific fulvestrant formulation defined in claim 1 of the opposed patent, nor a safe and effective treatment of breast cancer.

Sufficiency (Art. 83 EPC)

The Opponents 1 and 2 allege that, *if* the 50 mg/ml castor oil-based fulvestrant formulation disclosed in D1 is regarded as not suited for the treatment of breast cancer patients, *then* the invention as defined in the claims of the opposed patent *must* be considered insufficient by the same token.

The patent Proprietor submits that the Opponents' objection is not substantiated by verifiable facts raising serious doubts.

Inventive step (Art. 56 EPC)

The Opponents 1 to 5 submit that claim 1 of the opposed patent as granted lacks an inventive step in view of the combination of D4 with D1. The Opponents argue that D4 is the closest prior art. From D4, it would have been obvious for the skilled person to try the fulvestrant injection formulation comprising castor oil, ethanol (10%), benzyl benzoate (15%) and benzyl alcohol (10%) disclosed in D1 as being suited for use in the treatment of breast cancer patients by intramuscular injection, because the prior art provides the skilled person with a reasonable expectation of success.

The Patentee contends that D4 is *not enabling* and only provides an incomplete and vague disclosure of the formulations actually used. Further, the Patentee argues that the technical problem was the provision of a therapeutically effective fulvestrant injection formulation for treatment of breast cancer patients having, in particular, *good tolerability*, i.e. not causing skin irritation or inflammation due to precipitation of solid particles of the active agent at the site of injection. According to the Patentee, D1 does not disclose a safe and therapeutically effective fulvestrant injection formulation for humans; nor is D1 directed to an intramuscular administration. D1, so the Patentee, only discloses a formulation *for animals*, and it does not teach anything about the therapeutic efficacy in breast cancer, nor about the tolerability of the fulvestrant injection formulation comprising benzyl benzoate and benzyl alcohol in humans. Therefore, according to the Patentee, the skilled person would have had *neither a motivation* to combine D4 with D1, *nor a reasonable expectation of success* due to a complete lack of predictability regarding the efficacy and the tolerability in humans of the formulation disclosed in D1.

XX. The text of the claims under consideration in form of the Main request (Annex 1) and the Auxiliary requests 1 to 3 (Annexes 2-4) is appended to this decision.

Reasons for the decision

1. The oppositions, filed in due time, in proper form, and supported by reasoned statements, are formally admissible (Art. 99(1) and 100 EPC, and Rules 3(1) and 76 EPC).

Main request

2. Extension of subject-matter (Art. 76(1) and 123(2) EPC)

In the Opposition Division view, the allegations of the Opponents 1, 2, 4 and 5 are without merit.

Claim 1 of the opposed patent as granted is drafted in the second medical use claim format pursuant to Art. 54(5) EPC, and is directed to:

A pharmaceutical formulation comprising:

(a) at least 45 mg/ml fulvestrant

(b1) a castor oil vehicle

(b2) 10% w/v ethanol

(b3) 10% w/v benzyl alcohol

(b4) 15% w/v benzyl benzoate

(c) having a total volume of 6 ml or less

(d) for use in the treatment of breast cancer by intramuscular injection.

The earliest (grandparent) application as originally filed (WO 01/51056 A1) unambiguously discloses a castor oil-based vehicle comprising the features (b1) to (b4) as being the preferred vehicle for a pharmaceutical formulation adapted for intramuscular injection of fulvestrant (see page 7 lines 6-16; page 9 lines 20-21; page 10 line 16), this being supported by the exemplary formulation of the invention "F1" (page 14 lines 45-46; page 17 lines 6-13).

WO 01/51056 A1 also discloses without ambiguity that a pharmaceutical formulation having a total volume of 6 ml or less (c) and a concentration of fulvestrant of at least 45 mg/ml (a) represents a preferred form of the invention (page 8 lines 21-22).

Thus, the combination of features (a), (b1) to (b4) and (c), as defined in claim 1 of the opposed patent, cannot add subject-matter extending beyond the contents of WO 01/51056 A1, simply because it represents a clearly *preferred* formulation of the invention.

This preferred formulation is also defined in claims 17 and 20 of WO 01/51056 A1, taken in combination.

As regards the feature (d), the use of the formulation of the invention by intramuscular injection in the treatment of benign or malignant diseases of the breast, preferably treating breast cancer by administration by intramuscular injection, is disclosed throughout WO 01/51056 A1, and this applies *especially* to the most preferred formulation of the invention comprising 45 mg/ml of fulvestrant (see page 15 lines 20-24).

No selection-combination of features from WO 01/51056 A1 is needed in order to arrive at the subject-matter of claim 1 of the opposed patent as granted. To the contrary, claim 1 defines the very core of the invention as disclosed in WO 01/51056 A1.

For analogous reasons, claims 2 and 3 of the opposed patent as granted find their basis on page 8 lines 23-26 of WO 01/51056 A1. These preferred embodiments of the formulation of the invention are also defined in claims 18 and 19 of WO 01/51056 A1, taken in combination with claim 20.

Since the description of the parent application 05016921.8 (EP 1 669 073) as originally filed is identical to the description of WO 01/51056 A1, it follows that the requirements of Art. 76(1) EPC are met.

Further, since the description of the application 10180667.7, corresponding to the opposed patent, is also identical to the description of WO 01/51056 A1, it follows that the requirements of Art. 123(2) EPC are equally met.

3. Novelty (Art. 54 EPC)

3.1 D1 has been cited by the Opponents 1, 3 and 4 as being novelty-destroying for claim 1 of the opposed patent.

D1 discloses the treatment of ovariectomized tumor-bearing mice (injected with MCF-7 breast carcinoma cells) with the steroidal anti-estrogen ICI 182,780 (fulvestrant) in form of a preformulated injection composition having a concentration of fulvestrant of 50 mg/ml, and comprising a vehicle consisting of castor oil, ethanol (10%), benzyl benzoate (15%), and benzyl alcohol (10%).

This formulation is administered to mice by subcutaneous (s.c.) injection at a dose of 5 mg in 0.1 ml weekly (see page 698, right-hand column, "Drugs").

However, D1 does not disclose the administration of this formulation to patients by intramuscular injection.

Thus, the question which arises is whether the different mode of administration (namely intramuscular injection instead of subcutaneous injection) represents a different *specific* use in a method of treatment from which novelty of the pharmaceutical formulation over D1 can be derived pursuant to Art. 54(5) EPC).

The Opposition Division's view is that this question must be answered in the affirmative, because, even in an animal model, a different site and mode of administration might be a critical factor in a method of treatment by virtue of e.g. a different release and absorption profile of the drug. This might be especially relevant in the case, as the present one, of depot injection formulations comprising a hydrophobic oil vehicle.

3.2 The Opponents 1, 3 and 4 allege that the use of the preformulated fulvestrant injection composition by *intramuscular injection in breast cancer patients* is implicit to the disclosure of D1.

The Opposition Division does not agree.

It is true that, as the Opponents allege, parenteral administration of steroids in oily formulations was typically performed at the priority date of the opposed patent by the intramuscular route as common practice.

Moreover, it is also true that the use of fulvestrant by intramuscular injection, more specifically depot intramuscular injection, administered to patients (women) with breast cancer, in particular tamoxifen-resistant breast cancer, in clinical settings was

well known at the date of priority of the opposed patent. This is demonstrated by D4 (page 301, "Patients and methods"), D5 (abstract), D10 (paragraph bridging pages 1552-1553), and D14 (page 408, "Patients and methods").

Further, fulvestrant intramuscular injections ("Faslodex") had undergone phase III clinical trials in the treatment of tamoxifen-resistant advanced breast cancer (ABC) well in advance of the priority date of the opposed patent (see D11 page S19, abstract 74).

This is to be considered as common knowledge of the skilled person in the art at the date of priority.

In particular, D4 discloses the use of fulvestrant in the treatment of tamoxifen-resistant advanced breast cancer (ABC) at dose levels of 100 mg or 250 mg monthly administered by intramuscular injection in the form of a long-acting castor oil-based depot formulation. D4 is referenced in D1 (see D1 page 709, literature reference #19).

However, the skilled person's knowledge regarding the administration of fulvestrant to breast cancer patients by depot intramuscular injection (as demonstrated by D4, D5, D10 and D14) cannot be intentionally *incorporated* into the skilled person's reading of D1 in order to make D1 *"implicitly"* disclose what it does not.

The fact remains that D1 does not directly and unambiguously disclose the *intramuscular administration* route in breast cancer patients, but only describes the administration of the preformulated fulvestrant composition by subcutaneous injection in an animal model (mice).

In the Opposition Division's view, this gap must be dealt with under the viewpoint of *obviousness*, not under the viewpoint of an *implicit* anticipation. Whether or not the preformulated fulvestrant composition disclosed in D1 *would be suitable* for intramuscular injection administration in breast cancer patients is therefore a question of inventive step (see discussion of inventive step, point 5 below).

3.3 For these reasons, D1 is not prejudicial to novelty of claims 1-3 of the opposed patent as granted.

3.4 Additional remarks regarding D1

The Opposition Division further notes that a great deal of controversy has been generated in the present opposition proceedings, as well as in various national injunction proceedings, as to what is the disclosure which D1 actually makes available to a person skilled in the art.

In this regard, the patent Proprietor alleges that D1 neither relates to the treatment of breast cancer nor discloses the specific fulvestrant formulation defined in claim 1 of the opposed patent.

These allegations do not hold true.

It is essential for the ruling in this case to investigate which is the actual teaching of D1, as this has implications for the subsequent analysis of inventive step.

For the sake of clarification, the Opposition Division takes the following position regarding the disclosure of D1:

3.4.1 Treatment of breast cancer

D1 reports on the results of basic research designed to elucidate one possible mechanism of tamoxifen resistance in the clinical treatment of breast tumors (see "Introduction" lines 1-5). For this purpose, ovariectomized tumor-bearing mice injected with FGF-transfected MCF-7 breast carcinoma cells are used as an animal model.

First of all, the Opposition Division emphasises that mice bearing tumors produced by the injection of MCF-7 breast carcinoma cells are an accepted animal model for breast cancer in humans.

In this context, D1 discloses that successful treatment of estrogen receptor-positive breast tumors with the anti-estrogen tamoxifen is often followed by the acquisition of tamoxifen resistance, so that subsequently only *30-40% of patients have a positive response* to second hormonal therapies. This lack of response [to second hormonal therapies] might be explained by mechanisms for tamoxifen resistance (see "Abstract" lines 1-7).

Then, D1 explains in more detail that, according to the knowledge at the time of the research in 1998, tamoxifen resistance would not preclude successful treatment with an alternative hormonal therapy (see "Introduction" lines 10-13), and substitution of a hormonal therapy different from tamoxifen might result in a clinical response. One such alternative therapy studied in D1 is the use of the steroidal estrogen antagonist ICI 182,780 (fulvestrant) lacking the partial agonist activity of tamoxifen (see "Introduction" lines 21-25).

In other words, the animal model study described in D1 was aimed at elucidating a possible mechanism of tamoxifen resistance which could explain the lack of response to second hormonal therapies *in some patients*, in particular second hormonal therapy with fulvestrant, which was well-known at that time to be an alternative hormonal therapy to tamoxifen in the clinical treatment of women with breast cancer which had become refractory.

This aim is explicitly disclosed in D1 (page 697, right-hand column, last line, and page 698, on top of the left-hand column): *"Although the mechanism 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 182,780 therapy"*.

In this regard, D1 quotes several literature citations dated back in 1995 and 1996. The literature reference #19 cited in D1 is precisely the document D4 disclosing the use of fulvestrant in form of a castor oil-based depot intramuscular injection as second-line anti-estrogen treatment for women with advanced breast cancer having tamoxifen resistance (ABC).

In summary, D1 demonstrates that the use of fulvestrant as second hormonal therapy for the effective therapeutic treatment of breast cancer with positive response in at least 30-40% of tamoxifen-resistant patients was well-known to the person skilled in the art since the mid 1990s, well before the priority date of the opposed patent. D1 elaborates on that previous knowledge.

An average person skilled in the art gathers from the disclosure of D1 not only basic research information regarding the elucidation of one possible mechanism of tamoxifen resistance explaining the lack of response to second-line fulvestrant therapy in a percentage of patients. Rather, the elucidation of such a mechanism is inevitably associated with the treatment of breast cancer patients, as it serves to understand the clinical limitations of the second-line hormonal therapy with fulvestrant of breast cancer patients exhibiting tamoxifen resistance, and to predict the clinical cases in which breast tumors would be refractory to second hormonal therapy as well as to tamoxifen (see page 708, bottom of right-hand column).

3.4.2 Fulvestrant formulation

D1 discloses a preformulated injection composition of fulvestrant at a concentration of 50 mg/ml comprising a vehicle consisting of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, *brought to volume* with castor oil.

This formulation is identical to the one defined in claim 1 of the opposed patent except that D1 does not explicitly disclose whether the percentages (per volume) of ethanol, benzyl alcohol and benzyl benzoate are by weight (% w/v) or by volume (% v/v).

The patent Proprietor alleges that the disclosure of the castor oil-based formulation of fulvestrant in D1 is therefore *"incidental, vague and ambiguous"*, and that, for this reason, it cannot anticipate the formulation defined in claim 1 of the opposed patent.

This is not true.

First, the composition of the fulvestrant injection formulation is accurately disclosed in D1 in *percent per volume* amounts.

Secondly, the information content which D1 makes available to the skilled person concerning the composition of the injection formulation is not *vague* or *ambiguous*, because the skilled person is well aware that the % (per volume) amounts disclosed in D1 can only be by weight or by volume, i.e. only two interpretations are possible: either the percentages are % w/v units, or they are % v/v units.

In other words, the information content which D1 makes available, implicitly but also directly and unambiguously, to the skilled person consists of a well-defined, limited list of only two possible options.

Therefore, the only relevant point to be decided upon is whether or not the injection formulation defined in claim 1 of the opposed patent *can be distinguished* from the injection formulation disclosed in D1.

According to the long-standing case law of the EPO, the mere individualisation of one element chosen out of a list of only two options, wherein both options are disclosed in an equally individualised (though implicit) manner, cannot render that element a new one.

Therefore, the composition of the fulvestrant injection formulation, as defined in claim 1 of the opposed patent, cannot be considered to be different from the preformulated injection disclosed in D1.

3.5 Alleged public prior use by authors of D1

As explained above, claim 1 of the opposed patent as granted is novel over D1 because it differs from D1 in the use of the fulvestrant formulation for intramuscular injection administration to breast cancer patients. The fulvestrant formulation *per se*, as defined in claim 1 of the opposed patent, is not distinguishable from the preformulated fulvestrant composition disclosed in D1.

Therefore, the question of whether or not the experiments described in D1 using said preformulated fulvestrant composition demonstrate a *public prior use* by the authors of D1 of the formulation claimed in the opposed patent, as alleged by the Opponent 1, is redundant, because *any person* following the disclosure of D1 could have *reproduced* said fulvestrant formulation before the priority date of the contested patent.

In other words, the fulvestrant formulation defined in claim 1 of the opposed patent is anticipated in D1 because it is *disclosed to the public* in that document in a detailed and enabling manner, not because of a *prior use*.

In this regard, it is established case law of the EPO that an allegation of public prior use in opposition has to be sufficiently substantiated as to all the circumstances involved, including the question of *how* the alleged public prior use took place.

On the other hand, it is also established case law that a different mode of administration of a medicament (e.g. intramuscular injection instead of subcutaneous injection) amounts to a different *specific* use in a method of treatment from which novelty of a claim pursuant to Art. 54(5) EPC can be derived.

Accordingly, *if* D1 demonstrates a public prior use of the preformulated fulvestrant composition by the authors of the paper, as alleged by the Opponent 1, *then* this use was only a use by subcutaneous injection in mice, i.e. a different use from the use by intramuscular injection in breast cancer patients defined in claim 1 of the opposed patent; and therefore the alleged prior use cannot be prejudicial to claim 1 of the opposed patent which derives its novelty under Art. 54(5) EPC precisely from a different *specific* use in a method of treatment.

Finally, whether or not the authors of D1 received some information from the pharmaceutical company handing over the preformulated fulvestrant composition about its in-house plans for development of an intramuscular depot formulation is pure speculation. The controversial question of confidentiality is, in this regard, completely irrelevant to the present proceedings.

3.6 Alleged public prior use in clinical trials

The Opponent 2 alleges a *public prior use* of the fulvestrant formulation claimed in the opposed patent through the phase III clinical trials of “Faslodex” performed prior to the priority date (see D11).

However, as explained above, substantiation of an allegation of public prior use requires clarification of all the circumstances involved in the alleged public prior use, namely *what* was made available to the public through the clinical trials on selected patients, *how*, and *when*.

These points have not been clarified.

In particular, as regards the question of *what* was made available to the public through the phase III clinical trials of “Faslodex”, it is out of question that the medicament tested in the clinical trials (an injection to be administered by a

practitioner) was not commercially available, and that the patients participating in the clinical trials were not in a position to inspect, analyse and find out by themselves the chemical composition of said medicament.

Whether or not the patients were handed over the fulvestrant injection or could have taken it home with them is only pure speculation.

4. Sufficiency (Art. 83 EPC)

The Opponents 1 and 2 raise a *conditional* objection under Art. 83 EPC.

They allege that, *should* the Opposition Division take the view that the 50 mg/ml castor oil-based fulvestrant formulation disclosed in D1 is not suited for the treatment of breast cancer, *then* the invention as defined in the claims of the opposed patent *must* be considered insufficiently disclosed by the same token, because the experimental data supporting the achievement of that therapeutic effect in the opposed patent does not exceed the information provided in this regard in D1.

The Opposition Division cannot follow this way of reasoning.

The Opponents' allegation of insufficiency is neither substantiated through verifiable facts demonstrating serious doubts as to the reproducibility of the invention (T 19/90), nor has such a *conditional* objection any substantive merits.

First, the assessment of the teaching of D1, on the one hand, and the question of whether or not the opposed patent contains sufficient guidance for a skilled person to carry out the invention as claimed without undue burden, on the other hand, are two separate issues, with no bearing on one another, which must be judged independently.

Whether or not the skilled person would consider obvious to try the 50 mg/ml castor oil-based fulvestrant formulation disclosed in D1 as being suited for the treatment of breast cancer patients is a question for the inventive step analysis.

Secondly, as explained in paragraph 3.2 above, the use of fulvestrant in the treatment of breast cancer patients by depot intramuscular injection, specifically in the form of a long-acting castor oil-based depot formulation, was well known in the art at the date of priority of the opposed patent, as demonstrated by D4, D5, D10, D11 and D14.

Claim 1 of the opposed patent as granted is drafted in the second medical use claim format pursuant to Art. 54(5) EPC. According to Art. 54(5) EPC, a pharmaceutical substance or composition known in the art can derive its novelty from a previously *unknown specific* use in a method of medical treatment referred to in Art. 53(c) EPC.

However, the opposed patent does not address any further (*unknown*) *specific* use of castor oil-based formulations of fulvestrant in the treatment of benign or malignant diseases of the breast by depot intramuscular injection going beyond the state-of-the-art use in the treatment of breast cancer demonstrated in D4, D5, D10, D11 and D14. The claims of the opposed patent only recite said known use (see discussion of inventive step, point 5 below).

Therefore, the state of the art itself proves that treatment of breast cancer patients by intramuscular injection administration of a long-acting castor oil-based depot formulation of fulvestrant, as defined in claim 1 of the opposed patent, can be effectively carried out by a skilled practitioner with no undue burden.

Furthermore, the opposed patent confirms the achievement of therapeutically significant plasma levels of fulvestrant *in vivo*, well above the therapeutic threshold, which are sustained for at least five days after intramuscular injection of the castor oil-based formulation in rabbits (see Figure 1 of the patent specification), which is an animal model sufficiently indicative for a corresponding effect in humans.

Thus, the disclosure in the opposed patent supplemented with the knowledge of the skilled person in the art at the date of priority is sufficiently enabling with regard to the effective attainment of the therapeutic goal defined in claim 1 of the opposed patent.

As regards the reproducibility of the castor oil-based fulvestrant injection formulation comprising specific amounts of ethanol, benzyl alcohol and benzyl benzoate, as defined in claim 1 of the opposed patent, its preparation is described in full detail in paragraphs 59 and 60 of the specification. The skilled person finds no difficulty or burden in following these detailed manufacturing instructions.

Therefore, the contested patent meets the requirements of Art. 83 EPC.

5. Inventive step (Art. 56 EPC)

5.1 Closest prior art

5.1.1 In their written submissions, the Opponents and the Patentee started the analysis of inventiveness either from D1 or D4 as closest prior art.

It has been explained above that D1 reports on results of basic research experiments carried out on an animal model, whereas D4 reports on results of clinical tests in a real medical treatment of breast cancer patients with demonstrated positive response.

Already for this reason alone, D4 is a more promising starting point for the evaluation of inventive step than D1.

However, the Opposition Division expressly rejects, for the reasons explained under point 3.4 above, the Patentee's allegation that D1 neither relates to the treatment of breast cancer nor discloses the fulvestrant formulation defined in claim 1 of the opposed patent. The only reason why D4 is the closest prior art is because it discloses the real, effective clinical treatment of women with advanced breast cancer, which is the medical use pursuant to Art. 54(5) EPC to which the claims of the opposed patent are directed.

With his submissions dated 08.09.2016, the patent Proprietor stated that D7 is another plausible starting point.

However, D7 is not at all concerned with the treatment of breast cancer. Therefore it cannot be the closest prior art.

During the oral proceedings held on 08.05.2017, all parties expressed the view that D4 represents the closest prior art, and there was mutual agreement on that point.

5.1.2 D4 discloses the use of ICI 182,780 (fulvestrant) as second-line anti-estrogen therapy in women with advanced breast cancer having tumors resistant to tamoxifen (see page 300, bottom of right-hand column to page 301, left-hand column).

In this regard, claim 1 of the opposed patent does not define any further (*unknown*) *specific* medical use pursuant to Art. 54(5) EPC, but it only recites the well-known use of fulvestrant in the treatment of breast cancer patients by depot intramuscular injection.

Accordingly, the technical contribution of the opposed patent can only lie in the pharmaceutical formulation of the intramuscular injection *per se*, but not in the therapeutic application pursuant to Art. 54(5) EPC.

5.1.3 In D4, fulvestrant was administered as a long-acting (monthly) depot formulation comprising a castor oil-based vehicle by intramuscular (i.m.) injection of 5 ml into the buttock. Patients received escalating doses of fulvestrant starting with 100 mg in the first month and increasing to 250 mg as from the second month. Some patients received 250 mg fulvestrant already from the first month (see page 301, on top of right-hand column).

D4 does not directly and unambiguously disclose the fulvestrant concentration of the 5 ml intramuscular injection; nor how many injections were necessary to administer the monthly dose.

However, as the Patentee correctly pointed out during the oral proceedings, D4 discloses that "therapeutic levels of ICI 182,780 (...) can be achieved and maintained for one month following a single i.m. injection of the long-acting formulation" (page 305, "Discussion", first paragraph). Further, D4 also discloses that "the long-acting formulation of ICI 182,780 used in this study appeared well tolerated locally at the site of injection despite the relatively large volume (5 ml) administered" (page 303, "Side-effects", first paragraph).

Since the patients received an injection volume of 5 ml, a single monthly injection would imply a fulvestrant *concentration of 50 mg/ml* for the patients at the 250 mg/ month dose level; but by the same token it would imply a *concentration of 20 mg/ml* for those patients at the 100 mg/month dose level.

5.1.4 The patent Proprietor argues that D4 does not provide information on the *actual composition* of the fulvestrant formulation because the expression *"a castor oil-based vehicle"* (page 301, on top of right-hand column) indicates that the formulation contained *some other* undisclosed excipients further to castor oil. According to the patent Proprietor, it is therefore unclear what kind of fulvestrant formulation was actually used in D4. Hence the disclosure of D4 is *"incomplete"*, so the Patentee, to fully qualify as closest prior art with no hesitation.

Further, during the oral proceedings the patent Proprietor alleged that if castor oil were the only excipient in the intramuscular injection formulation of D4, which is, so the Patentee, a possible interpretation, then the 5 ml injection comprising 100 mg of fulvestrant would be a solution, but the 5 ml injection comprising 250 mg of fulvestrant would have the form of a *suspension*, because the solubility limit of fulvestrant in castor oil (20 mg/ml at 25°C; see Table 2 of the specification of the opposed patent) would be exceeded.

The Opposition Division takes the view that the Patentee's arguments in this regard are purely speculative. This is explained below.

5.1.5 With his written submissions dated 08.03.2017, the patent Proprietor further argued that, for the above reasons, D4 does not fulfil the EPO's standard for an *enabling disclosure*.

This allegation must fail.

The disclosure of D4 with regard to the composition of the fulvestrant injection is not *"unclear and vague"*, as alleged by the Patentee, only because D4 *"does not disclose which, if any, other components are present in the castor oil-based vehicle"*, i.e. *"which fulvestrant formulation in a castor oil-based vehicle is useful (i.e. safe and effective) in the treatment of breast cancer"*.

Whether or not the fulvestrant injection formulation of D4 comprises *"other components"* further to castor oil can only qualify as speculation in particular in the light of the fact that D4 also discloses a 5 ml injection comprising 100 mg of fulvestrant which is soluble in castor oil alone (concentration of 20 mg/ml), with no need for additional components or co-solvents, as the opposed patent itself confirms (see Table 2 of the specification of the opposed patent).

The fact remains, however, that D4 does not directly and unambiguously disclose any other components of the intramuscular injection formulation besides castor oil.

It is precisely due to the fact that D4 does not disclose the *other components* of the intramuscular injection formulation defined in claim 1 of the opposed patent besides castor oil that D4 does not represent an anticipating disclosure. Yet this does by no means diminish the suitability of D4 as closest prior art for the evaluation of inventiveness.

The Patentee overinterprets the requisites for an *enabling disclosure* in the context of the evaluation of inventive step, and goes as far as to require that D4 should disclose *all* the composition features necessary to achieve the alleged effects of safety and therapeutic efficacy according to the opposed patent in order for the disclosure of D4 to qualify as closest prior art. However, this is as much as to require that D4 be novelty-destroying.

It is out of question that the castor oil-based fulvestrant formulation used in D4 is both safe and has therapeutic effectiveness (positive response) in the treatment of women with advanced breast cancer (see point 5.2 below). In particular, the good tolerability locally at the site of injection without serious adverse events is discussed on page 303 of D4 ("Side-effects").

As correctly pointed out by the Opponent 1, D4 thus discloses a *safe and effective* castor oil-based fulvestrant formulation, and in providing the basis of the injection vehicle (castor oil) and the desired concentration of fulvestrant (20 mg/ml or 50 mg/ml), the information furnished in D4 to the skilled person by far exceeds the information a formulator would typically have at his hands when starting to develop a safe and effective formulation.

In this regard, the Opposition Division emphasises that *"a castor oil-based vehicle"* is an injection vehicle in which castor oil is the sole or the major component. Castor oil as a vehicle for parenteral administration of steroid hormones by intramuscular injection, possibly comprising additions consisting of benzyl alcohol and benzyl benzoate for increasing drug solubility and concentration per dose, has been known in the art for more than 50 years, as demonstrated by D9 (see page 892, bottom of left-hand column and table IV to VI), and this forms part of the skilled person's common general knowledge.

The disclosure of D4 regarding the castor oil-based fulvestrant formulation is therefore perfectly enabling for a skilled person in the art.

The skilled person, furnished with his common general knowledge, can prepare a fulvestrant formulation in a castor oil-based vehicle. He can also reproduce, for the reasons explained in point 4 above, the effective treatment of advanced breast cancer as described in D4 using said castor oil-based fulvestrant formulation with no undue burden.

Also from D4, the skilled person aiming at developing *a particular* castor-oil based formulation eventually meeting some *specific demands* can start that development. In this regard, attaining *a particular degree* of safety or therapeutic efficacy should be considered as the effects deriving from the distinguishing composition features of that particular castor oil-based formulation over the castor oil vehicle disclosed in D4, i.e. as the technical contribution made by that development over D4 (see point 5.2 below), not as a pre-requisite for the disclosure of D4 to be enabling.

For these reasons, the Patentee's contention that D4 is not to be considered as the closest prior art for lack of an enabling disclosure as regards the composition of the castor oil-based fulvestrant formulation is plainly wrong in the application of the problem-solution approach, and therefore it must be rejected.

Furthermore, the Opposition Division notes that during the oral proceedings the patent Proprietor did no longer pursue this argument. Although he expressed some hesitation as to the completeness of the disclosure in D4, as explained above, he expressly conceded that D4 can be the closest prior art.

5.1.6 In summary, with regard to the evaluation of inventive step, the only relevant point, apart from speculative considerations, is that the disclosure of D4 provides the most promising springboard and allows an unambiguous identification of the distinguishing feature(s) of claim 1 of the opposed patent as granted, namely: that the castor oil-based fulvestrant injection formulation additionally comprises 10% w/v

ethanol, 10% w/v benzyl alcohol, and 15% w/v benzyl benzoate, and has a concentration of at least 45 mg/ml of fulvestrant, because these technical features are not directly and unambiguously disclosed in D4.

5.1.7 The Opposition Division also emphasises that the *dose* of fulvestrant and the *dosing* interval are no distinguishing feature of claim 1 of the opposed patent over D4.

Claim 1 indicates that the formulation for injection may have any possible volume of 6 ml *or less*, and it does not define any dosage regimen in particular.

5.2 Technical problem

5.2.1 D4 discloses that fulvestrant levels in serum were well above the therapeutic threshold at day 28 after dosing, i.e. that a slow release of the drug from the long-acting castor oil-based depot formulation was maintained over one month after dosing (see page 302, bottom of left-hand column, Table II, and Figure 2), thus allowing effective treatment in patients with advanced breast cancer who had previously relapsed on tamoxifen.

The therapeutic threshold had been determined in a previous phase I study where it was predicted that serum levels of fulvestrant in the range of 2-3 ng/ml were consistent with a therapeutic effect in patients with advanced breast cancer (see D4, page 305, left-hand column, third paragraph).

In the opposed patent, *"therapeutically significant levels"* of fulvestrant are also meant to be blood plasma concentrations of at least 2.5 ng/ml (see paragraph 41 of the patent specification).

5.2.2 In Figure 2 of D4, it is shown that (taking into account the confidence intervals) the mean serum Cmax values, even during the first month of treatment ("on entry"), are well above the 2.5 ng/ml level at day 28 after injection of the first dose, even at the 100 mg/month dose level.

Thus, the question of providing a long-acting (sustained release) depot formulation of fulvestrant adapted for administration by intramuscular (i.m.) injection of a small volume containing the complete recommended monthly dose of fulvestrant and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks, and even 4 weeks, has already been addressed and solved in D4 by means of a castor oil-based formulation.

5.2.3 Furthermore, in Figure 2 of D4 it is shown that the blood concentration profile between time 0 and day 5 is substantially identical to the blood concentration profile demonstrated in the contested patent for the "Formulation F" according to the invention (see Figure 1 of the patent specification).

In particular, it has to be emphasised that in Figure 2 of D4 no burst effect is observed following injection, i.e. the maximum plasma concentration of fulvestrant of about 7.5 ng/ml is reached steadily after 8-9 days from the first injection ("profile at entry"), and it remains below 10 ng/ml for the profile after 6 months of treatment.

Thus, if the problem addressed in the contested patent was to achieve *"a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site"* (paragraphs 48 and 49 of the specification) thereby avoiding a fulvestrant plasma peak after injection (as demonstrated in Figure 1 of the contested patent for the comparative oil formulations comprising Miglyol 812 or sesame seed oil), then this problem was already solved in D4 by means of a castor oil-based formulation.

5.2.4 Moreover, in Table II of D4 it is shown that serum fulvestrant levels above the therapeutic threshold are attained in the first month even in patients at the 100 mg/ month dose level "on entry", i.e. those who received a single 5 ml injection of 100 mg fulvestrant during the first month (patients 1 to 4).

5.2.5 Accordingly, the technical contribution over D4 made in the opposed patent resides only in the provision of a castor oil-based injection formulation allowing solubilization of a higher concentration of fulvestrant for a complete monthly dose of around 250 mg to be solubilized in the recommended injection volume for intramuscular administration of no more than 5 ml in a single injection (see paragraph 18 of the patent specification).

This was the objective technical problem to be solved.

5.2.6 During the oral proceedings, the Opponents expressed their agreement with this formulation of the technical problem proposed in its preliminary opinion by the Opposition Division.

5.2.7 The Patentee, however, argues that the technical problem has to be more ambitiously formulated as:

"To provide fulvestrant (a) in solution, (b) in the required high concentration (50 mg/ml), (c) having good tolerability (safe; no tissue irritation; no precipitation at site of injection), and (d) having effective drug release over an extended period of time".

According to the patent Proprietor, the opposed patent addresses the questions of providing satisfactory release of fulvestrant over an extended period of time at therapeutically significant levels with an even release profile (paragraphs 40, 49, Figure 1 and second part of Table 4 of the patent specification), as well as avoiding tissue irritation or inflammation at the site of injection due to precipitation of solid particles of the active agent (paragraphs 36 and 37 of the patent specification).

Therefore, these key issues must be incorporated, so the Patentee, as part of the formulation of the technical problem solved.

5.2.8 The Opposition Division cannot agree with these allegations.

First, as explained above, whether or not the castor oil-based 5 ml injection of D4 comprising 250 mg of fulvestrant is in the form of a suspension is pure speculation. The fact remains that D4 does not explicitly disclose any *"suspensions"*, and that at least the 5 ml injection comprising 100 mg of fulvestrant can be solubilized in castor oil alone (solubility limit 20 mg/ml) with no need of any other co-solvents or excipients, this being recognized in the opposed patent itself (see Table 2). Thus, D4 already provides fulvestrant *in solution* in a castor oil vehicle.

Secondly, with regard to the questions of *tolerability/safety* and *therapeutically effective extended drug release,* it has already been explained in paragraph 5.1.5 above that the castor oil-based fulvestrant formulation used in D4 has both good tolerability and therapeutic effectiveness over an extended period of time for the treatment of women with advanced breast cancer.

The opposed patent provides *in vivo* experimental data regarding the fulvestrant plasma profile over five days following intramuscular administration of the castor oil-based fulvestrant formulation according to the invention in rabbits (paragraph 49 and Figure 1 of the patent specification).

In this regard, no further technical contribution is demonstrated in the opposed patent going beyond the proven therapeutic efficacy with an even release of therapeutically significant levels of the active agent over a prolonged period of time demonstrated in D4 (Figure 2) for the castor oil-based depot intramuscular injections of fulvestrant.

On the other hand, the opposed patent contains no experimental data regarding the question of tolerability (in terms of tissue irritation) of the fulvestrant injection in breast cancer patients *in vivo*.

The only source of possible tissue irritation/inflammation is attributed in the opposed patent to the presence of fulvestrant in form of solid particles locally at the injection site, which is also identified as the cause of poor release profile (paragraph 37 of the specification).

According to the opposed patent, *"precipitation of fulvestrant"* intramuscularly was determined *in vivo* in rabbits, and *"no evidence of precipitation of fulvestrant at the injection site"* was shown for the castor oil formulation according to the invention (paragraphs 48 and 49 of the specification).

From this, the Patentee draws the conclusion that the castor oil-based fulvestrant injection according to the invention has *good tolerability/safety* in terms of *reduced tissue irritation*.

Yet the fact is that the opposed patent contains no data at all regarding any measurement of tissue irritation or inflammation, and that it is not even apparent from the patent specification how the *"degree of precipitation"* of fulvestrant at the injection site was determined *in vivo* in rabbits (see second part of Table 4 of the patent specification), let alone whether, and to which extent, the alleged precipitation at the injection site would translate in some noticeable tissue irritation or inflammation when employed in humans.

Nor has the patent Proprietor provided any supplementary experimental evidence in the course of the opposition proceedings regarding the question of tolerability in terms of tissue irritation or inflammation at the injection site *in breast cancer patients*. Since the Patentee attributes to the question of tolerability an "utmost importance", this is very surprising.

In this regard, the Opposition Division emphasises that in D4 it is explicitly disclosed that the castor oil-based depot intramuscular injection of fulvestrant had *acceptable tolerability without serious adverse events*. According to D4, one patient (out of 19) developed bruising over the buttock; a second patient developed tenderness at the injection site; and a third patient had local erythema at the injection site; on one occasion each. The occurrence of these single events is however compatible with the finding that the long-acting castor oil-based formulation of fulvestrant used in D4 was *"well tolerated locally at the site of injection despite the large volume (5 ml) administered*" (see page 303, "Side-effects").

If the cause of local tissue irritation is to be attributed to the presence of solid fulvestrant particles at the site of injection, the findings of D4 regarding good local tolerability of the castor oil-based injection would therefore demonstrate that, contrary to what the Patentee argues, the formulations of D4 are <u>not</u> suspensions.

In summary, no additional technical effect regarding local tolerability or tissue irritation of the castor oil-based fulvestrant intramuscular injection formulation is demonstrated in the opposed patent going beyond the findings of D4.

In the opposed patent (paragraph 37 of the specification), it is stated that the castor oil formulations according to the invention were compared to previously tested aqueous suspension injections of fulvestrant administered intramuscularly, and that the latter were found to cause extensive local tissue irritation/inflammation at the injection site, as well as poor release, due to the presence of solid particles of the active agent.

However, an aqueous suspension referred to in paragraph 37 of the specification is not the relevant comparison for the problem-solution approach starting from D4.

Nor are the Miglyol-based or the sesame seed oil-based formulations described in Table 4 of the patent specification the relevant comparison, either.

Starting from D4, the acceptable local tolerability of castor oil-based depot intramuscular injections of fulvestrant was already known, and the opposed patent does not demonstrate any improvement over D4 in this regard.

In conclusion, although therapeutic efficacy, release profile and tolerability/safety are aspects which must of course be taken into consideration for the evaluation of obviousness, they cannot be incorporated into the formulation of the objective technical problem.

5.3 Obviousness

5.3.1 D4 teaches intramuscular injection of a single monthly dose of either 100 mg or 250 mg of fulvestrant in form of a depot formulation having a *volume of 5 ml*.

It is also recognized in the specification of the contested patent that current guidelines recommend *no more than 5 ml* of a long-acting depot formulation to be injected intramuscularly in a single injection (see paragraph 18 of the specification).

Starting from D4, the skilled person trying to dissolve a 250 mg fulvestrant monthly dose in castor oil would realize through simple routine experiments that it would be necessary to use more than 5 ml of the injection vehicle.

Therefore, D4 itself provides the incitation for the skilled person to look for ways of increasing the solubility of fulvestrant in castor oil, and hence the concentration of the castor oil-based fulvestrant injection formulation, so as to accommodate a complete monthly dose of 250 mg in a single 5 ml injection.

5.3.2 Confronted with the objective technical problem as formulated in paragraph 5.2.5 above, and following the motivation provided by D4, the skilled person *would have indisputably considered* the use of castor oil-based vehicles comprising co-solvents such as benzyl alcohol and benzyl benzoate.

As already explained above, the use of castor oil as a vehicle for parenteral administration of steroid hormones by intramuscular injection comprising co-solvent additions of benzyl alcohol and benzyl benzoate for increasing drug solubilization and concentration per dose was well known in the art, and formed part, at the date of priority, of the skilled person's common general knowledge, represented by D9 (see tables IV to VI) and D21 (see page 192 paragraph 3).

5.3.3 So, the relevant question to be answered in the present opposition proceedings is whether the skilled person, under consideration of all the relevant issues and furnished with his common general knowledge, would have had *a motivation to look into D1* for a solution to the objective technical problem.

The answer can only be in the affirmative.

5.3.4 As explained in paragraph 3.4.1 above, D1 is a scientific paper in the area of clinical cancer research. It relates to the study of mechanisms underlying the therapy of tamoxifen-resistant breast cancer, in particular the second hormonal therapy with fulvestrant. Already for this reason alone, the skilled person would have had knowledge of D1, and he would have looked into it.

5.3.5 The patent Proprietor alleges that at the priority date of the opposed patent the skilled person *"could not have found D1 in an ordinary literature search"* because the title and the abstract of D1 do not provide any indication that D1 could contain information on formulations of fulvestrant.

This allegation is untenable.

First, whether or not it was difficult to retrieve D1 in an *"ordinary literature search"*, whatever this means, is irrelevant. The only crucial point is, as correctly underlined by the Opponents 2 and 5 during the oral proceedings, that at the priority date of the opposed patent D1 was *publicly available* and the skilled person could have gained knowledge of it.

Secondly, the title of D1 clearly refers to "ICI 182,780" and to research with tamoxifen-resistant MCF-7 breast carcinoma cells in tumor-bearing mice. As explained above, the skilled person in the area of breast cancer research would have had a motivation

to look into D1 for this reason alone, and he would have expected that a study in clinical research with an animal model would contain experimental information on the administered formulations.

5.3.6 D1 describes the composition of a fulvestrant injection formulation having a concentration of *50 mg/ml* of fulvestrant (page 698, right-hand column, "Drugs").

This is precisely *the concentration* that the skilled person is seeking to achieve in order to accommodate a monthly dose of 250 mg fulvestrant in an injection volume of no more than 5 ml of castor oil-based vehicle.

5.3.7 D1 *discloses how to achieve this concentration*, namely by using "a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil" (page 698, right-hand column, "Drugs").

5.3.8 With his submissions dated 08.03.2017, the Patentee argued that due to the *"physicochemical properties of fulvestrant, the person skilled in the art would have expected a worsening of the solubility of fulvestrant as a result of adding benzyl benzoate to a castor oil fulvestrant formulation"*, and therefore *"he would have refrained from using benzyl benzoate as an excipient in vehicles as mentioned in D9"*.

However, the Patentee has not substantiated this allegation with any evidence whatsoever, and the Patentee's statements cannot contradict *the fact* that in D1 a concentration of 50 mg/ml of fulvestrant is effectively achieved by using 15% benzyl benzoate in the castor oil vehicle.

Thus, following the teaching of D1 the skilled person would have not refrained from using benzyl benzoate as an excipient in a castor oil vehicle for fulvestrant, but the contrary is true.

5.3.9 The only remaining question is therefore whether the skilled person would have considered the *50 mg/ml* fulvestrant injection formulation comprising castor oil, 10% ethanol, 15% benzyl benzoate and 10% benzyl alcohol disclosed in D1 *to be suitable for trying* in patients with breast cancer by intramuscular injection, as disclosed in D4, with a reasonable expectation of success.

5.3.10 The patent Proprietor alleges that this question has to be answered in the negative because: (a) the skilled person had *no motivation* to combine D4 with D1; and (b) because there was no reasonable expectation of success due to a complete *lack of predictability* regarding efficacy and tolerability of the formulation of D1 in humans.

5.3.11 With regard to (a)

This allegation is rejected for the reasons already explained in paragraphs 5.3.4 to 5.3.8.

D1 is concerned with clinical breast cancer research, and its conclusions are ultimately directed to the treatment of breast cancer patients, in particular tamoxifen-resistant breast cancer. This has been already explained in paragraph 3.4.1.

This said, it is true, as the Patentee argues, that D1 does not disclose the treatment of breast cancer patients (women) with the preformulated 50 mg/ml fulvestrant injection formulation comprising castor oil, 10% ethanol, 15% benzyl benzoate and 10% benzyl alcohol by intramuscular administration.

However, this argument completely misses the point.

The case law of the EPO has consistently established that the answer to the question of what the skilled person *would do* depends on *what he is set out to achieve* when confronted with the objective technical problem to be solved.

In the present case, as explained in 5.2.5 above, this problem was the provision of a castor oil-based injection formulation of fulvestrant having higher concentration of the active agent allowing a complete monthly dose of 250 mg to be solubilized in the recommended injection volume (5 ml) for intramuscular administration.

In this regard, whether or not D1 teaches an *effective and safe* treatment of breast cancer patients with the preformulated 50 mg/ml fulvestrant injection formulation is irrelevant, because the effective and safe treatment of women with advanced breast cancer by using castor oil-based intramuscular injections of fulvestrant belongs to what the skilled person already knows from D4, which is his springboard (see paragraphs 5.1.2 and 5.1.3 above).

Starting from D4, the skilled person is set out to develop a castor oil-based injection formulation having higher concentration of fulvestrant *for use in the known* breast cancer treatment, and he finds such a formulation in D1, which is a closely related document in the field of clinical breast cancer research.

In order to be motivated to consider D1, the skilled person does not expect *also* D1 to disclose an *effective and safe* treatment of breast cancer in women. It appears that the Patentee would only recognize a motivation for the skilled person to resort to D1, if D1 itself explicitly disclosed the treatment of breast cancer patients with the preformulated 50 mg/ml fulvestrant injection formulation. But then D1 would simply take away novelty. The Patentee is stretching the criteria for D1 to be combinable with D4 beyond the limits of a correct application of the problem-solution approach.

5.3.12 Further, the Opposition Division emphasises that D1 does not present the skilled person with any *prejudice against* the use of the preformulated 50 mg/ml fulvestrant injection formulation comprising castor oil, 10% ethanol, 15% benzyl benzoate and 10% benzyl alcohol in the treatment of breast cancer patients.

The Patentee alleges that D1 clearly and unambiguously teaches that the use of the formulation in the experiments of D1 resulted in *"no effect"*.

However, the fact that in D1 fulvestrant treatment did not prevent tumor progression produced by FGF-transfected MCF-7 breast carcinoma cells, i.e. the specific FGF-transfected cell line studied in D1, does by no means contradict the well-known clinical efficacy of castor oil-based depot intramuscular injections of fulvestrant in the treatment of tamoxifen-resistant advanced breast cancer in women, demonstrated by D4, D5, D10, D11 and D14, which is also recognized in D1 (page 698, left-hand column, lines 2-5).

The experiments with a specific FGF-transfected cell line reported in D1 are designed precisely to explore one possible mechanism of tamoxifen resistance which *may explain the lack of response* to fulvestrant *in a percentage of patients* developing tamoxifen resistance.

In this regard, the experimental results in D1 cannot be *"discouraging"*, as the Patentee alleges, for a skilled person who is set out to develop a castor oil-based injection formulation having higher concentration of fulvestrant for use in tamoxifen-resistant patients *who do show a positive response* to second hormonal therapy with fulvestrant (D1, page 698, left-hand column, first paragraph).

5.3.13 In D1, the preformulated 50 mg/ml fulvestrant injection formulation is used *subcutaneously in a mouse model*, not intramuscularly in breast cancer patients.

Yet this fact does not lead the skilled person away from D1, as alleged by the patent Proprietor, but the contrary is true, precisely because of the basic reason that tests in a well-accepted animal model (ovariectomized tumor-bearing mice injected with breast carcinoma cells) are regarded by the skilled person as predictive for humans, this being the reason why the animal model is used in clinical cancer research.

In this regard, the Opposition Division emphasises that it does not share the conclusions reached in the opposition proceedings involving the grand-parent patent EP 1 250 138 (point 5.3 of the decision dated 11.02.2015; see D2).

The Patentee has alleged with his submissions dated 08.09.2016, as well as during the oral proceedings, that the fulvestrant formulations used in D1 are *"animal formulations"*, i.e. formulations in a vehicle *"for animal use only"*.

This is not true.

D1 does not relate to the *"treatment of animals"*, but uses a generally accepted animal model in basic clinical cancer research aimed at investigating possible reasons for the lack of response to fulvestrant of a percentage of patients developing tamoxifen resistance (D1, page 698, left-hand column, first paragraph).

The authors of D1 postulate the possible role of FGF signaling in the estrogen-independent growth of breast tumors, and they study the estrogen-independent and tamoxifen-resistant growth of FGF-transfected MCF-7 breast carcinoma cell lines injected into mice used as an animal model for *in vivo* experiments. They conclude that, as expected in their postulated model, tumor growth is unaffected by the treatment with fulvestrant (D1, page 698, paragraph bridging columns).

From this, the skilled person does by no means draw the conclusion that the preformulated 50 mg/ml castor oil-based fulvestrant injection supplied to the authors of D1 by a pharmaceutical company is a formulation *"designed and suitable only for animal experiments"* which *"would not be usable in humans"*, as the Patentee argues.

To the contrary, the skilled person is well aware from D4, D5, D10, D11 and D14 that fulvestrant depot intramuscular injection formulations, in particular in a castor oil-based vehicle, are well suited for use in safe and effective treatment of breast cancer patients.

As correctly pointed out by the Opponent 1, castor oil-based solutions of fulvestrant were regarded at the priority date as *prototypic* of long-acting intramuscular injection formulations of fulvestrant for breast cancer treatment (see D34, page 245, left-hand column).

Further, the skilled person was also well aware that, as underlined by the Opponents 1, 2 and 5, benzyl benzoate and benzyl alcohol are entirely standard excipients of commercial parenteral medicaments for humans (see D46, Table I); and that benzyl benzoate and benzyl alcohol are used as components of *prototypic* castor oil-based depot intramuscular injection formulations of steroid hormones (see D9; D63-Appendix A, page 1).

In particular D9, representing the common general knowledge of the person skilled in the art, demonstrates that oil-based depot intramuscular injection formulations of steroid hormones comprising castor oil, benzyl benzoate and benzyl alcohol having different degrees of tolerability in terms of local irritation at high concentrations of benzyl benzoate were well known in the art at the date of priority (see page 892, right-hand column and table IV to VI).

Also, it was common general knowledge at the date of priority that benzyl benzoate is a standard excipient for use as solvent in intramuscular injections at high concentrations of up to 46% v/v (see D15, page 38, point 7).

Further, it was also common knowledge of the skilled person that the combination with benzyl alcohol had additional advantages relating to favourable viscosity for injection, as well as preservative and local anaesthetic effect (see D9, page 894, on top of left-hand column).

The skilled person also knew from D46 (Table I, page 453) that the use of benzyl alcohol in concentrations as high as 10% was not *"unprecedented"*, as the Patentee alleges.

The *general acceptability* of the castor oil/benzyl benzoate/benzyl alcohol vehicle for intramuscular injection in humans is explicitly confirmed in D9 (see page 895, on top of left-hand column).

For these reasons, the skilled person reading D1 would not draw the conclusion that the preformulated 50 mg/ml castor oil-based fulvestrant injection comprising ethanol, benzyl benzoate and benzyl alcohol is *"for animal use only"*.

To the contrary, he would recognize that, as correctly pointed out by the Opponents 2 and 5, the castor oil-based formulation of D1 comprising *typical excipients of intramuscular oil-based injections* satisfies the basic requisites of a prototypic castor oil-based formulation suitable for intramuscular injection in humans as used in D4.

Nor would the *subcutaneous route* of administration in mice described in D1 discourage the skilled person, or teach him away, from the *well-known intramuscular route of administration* of castor oil-based depot formulations of fulvestrant in the treatment of patients with advanced breast cancer, as demonstrated by D4, D5, D10, D11 and D14, which is also recognized in D1 (page 698, left-hand column, lines 2-5).

In this regard, the Patentee's allegation that D1 contains *"no pointer to intramuscular injection"* but discloses a different mode and schedule of administration (for mice) is totally irrelevant, because the skilled person *starting from D4* does not have to *"extrapolate"* from D1 the conditions (mode and schedule of administration) for a safe and efficient use in patients with advanced breast cancer already known from D4.

5.3.14 The Patentee also argues, referring to the declaration D32, that a skilled person would have *prima facie* considered the incorporation of large amounts of benzyl alcohol (such as 10% w/v) in a castor oil-based formulation of fulvestrant to be unsuited for intramuscular injection in humans, and *"contrary to precedent"*, since benzyl alcohol at high concentration is known to cause tissue irritation and damage. According to the Patentee, such a concentration of benzyl alcohol is *"rather unusual"* and *"not conventional"* in products on the market, because it is *"potentially intolerable"* (D65, page 229; D66, Table 3).

However, in D32 itself it is recognized that benzyl alcohol in commercialized oil-based intramuscular injectable formulations is *"almost always"* in preservative concentrations of about 2%, but it is also sometimes present in concentrations of up to about 5%, or even *"higher concentrations"* (see D32, point 23).

It is self-evident that in the cases referred to in D32 where benzyl alcohol is present in concentrations of about 5%, or even higher (see e.g. D46, Table I, page 453), benzyl alcohol is not used as a preservative, but has a co-solvent function. Therefore, the list of literature citations provided in D32 where benzyl alcohol is merely used *as a preservative* at low concentration does by no means demonstrate a *universally accepted prejudice* against the use of benzyl alcohol in concentrations of 5% or even higher in cases where its use *as a co-solvent* might be necessary due to extremely low drug solubility in the oil injection vehicle.

In the latter cases, as in the present one, the skilled person, while being perfectly aware of the potentially compromising tissue irritating or even toxic effect of benzyl alcohol, may indisputably have good reasons to prioritize its solubilizing effect, and to seek an acceptable balance between both.

Therefore, the Opposition Division takes the view that the skilled person would indisputably find in D1 an *incentive to try* the preformulated 50 mg/ml castor oil-based fulvestrant injection comprising 10% ethanol, 15% benzyl benzoate and 10% benzyl alcohol in the treatment of women with tamoxifen-resistant advanced breast cancer by intramuscular administration known from D4.

5.3.15 With regard to (b)

The Patentee argues that the *therapeutic efficacy* and *tolerability* (tissue irritation at the site of injection) in humans of the castor oil-based formulation of D1 comprising 10% ethanol, 15% benzyl benzoate and 10% benzyl alcohol was *"completely unpredictable"*.

The patent Proprietor alleges that D9 (tables V and VI) demonstrates the *general unpredictability* as regards tolerability of vehicles for steroid hormone injections comprising castor oil, benzyl benzoate and benzyl alcohol. Further, the patent Proprietor alleges that D63 demonstrates the unpredictability of *in vivo* performance of castor oil-based fulvestrant formulations regarding release rate after intramuscular injection, precipitation in the muscle, and lack of irritation at the injection site.

However, the Opposition Division emphasises again that, starting from D4 and in view of the objective technical problem to be solved, the skilled person was not set out to achieve *any particular degree of therapeutic efficacy* going beyond the therapeutically significant levels over an extended period of time already demonstrated in D4 (Figure 2); or beyond the increased therapeutic levels resulting from an increase of the fulvestrant concentration of the depot intramuscular injection, also demonstrated in D4 (Figure 2).

Nor was the skilled person set out to achieve *any particular degree of tolerability* in terms of tissue irritation *in vivo* in breast cancer patients going beyond the acceptability levels which result from avoiding the precipitation of solid particles of fulvestrant at the site of injection.

In particular, in the opposed patent no concern is expressed and nothing is said about a potential tissue irritation effect *in vivo* in breast cancer patients *attributable to the different concentrations of ethanol and benzyl alcohol* used in the various formulations tested (see Table 3). The only source of potential tissue irritation identified in the patent is associated with the presence of solid particles of fulvestrant precipitated at the site of injection (see paragraph 37).

This has already been explained in paragraph 5.2.8 above.

Therefore, the skilled person would not need any particular *degree of predictability*, let alone certainty, in this regard, because the skilled person would not act *in the expectation of achieving some particular degree* of therapeutic efficacy or tolerability, much less in the expectation of developing a formulation *devoid of skin irritation*, but only in the expectation of solving the objective technical problem of providing a higher fulvestrant concentration of the once-monthly castor oil-based injection *while*

maintaining an acceptable balance of safety/tolerability appropriate for intramuscular injection in humans in the context of the breast cancer treatment as already confirmed in D4.

In this regard, D1 indisputably provides the skilled person not only with a clear *incitation to try* the preformulated 50 mg/ml fulvestrant injection formulation in breast cancer patients by intramuscular administration, but also with *every expectation of success* to solve the technical problem of accommodating a complete monthly dose of around 250 mg of fulvestrant in a single injection having the recommended volume for intramuscular administration (no more than 5 ml), because D1 promises a castor oil-based injection formulation of fulvestrant in form of solution having a concentration as high as 50 mg/ml of the active agent, which is precisely the concentration that the skilled person is seeking to attain. Furthermore, this concentration is achieved by using excipients commonly employed in oil-based intramuscular injections for humans, against which no generally-accepted prejudice in the art has been demonstrated.

Additionally, the superior fulvestrant solubilizing ability of the castor oil-based vehicle described in D1 also gives the skilled person a founded expectation of simultaneously achieving both adequate therapeutic efficacy over an extended period (because of the higher fulvestrant concentration injected) as well as acceptable tolerability in terms of avoiding precipitation of solid particles of fulvestrant at the injection site (because of the increased solubility).

5.3.16 Consequently, in the light of all the relevant circumstances, the Opposition Division comes to the conclusion that the skilled person would have regarded the 50 mg/ml fulvestrant injection formulation comprising castor oil, 10% ethanol, 15% benzyl benzoate and 10% benzyl alcohol disclosed in D1 (equally whether % w/v or % v/v) as suitable for intramuscular injection in humans, and he would have tried it in the treatment of breast cancer patients according to D4 as an obvious course of action with a reasonable expectation of success, thereby exercising no inventive effort.

Auxiliary requests 1 to 3

6. The above conclusions on inventive step apply in their entirety to claim 1 of each of the Auxiliary requests 1 to 3.

6.1 Claim 1 of the Auxiliary request 1 differs from claim 1 as granted in that *"the total volume of the formulation is 5 ml"* and comprises *"250 mg fulvestrant"*.

6.2 Claim 1 of the Auxiliary request 2 differs from claim 1 as granted in that *"the formulation is capable after injection of attaining blood plasma fulvestrant concentration of at least 2.5 ng/ml for at least two weeks"*.

6.3 Claim 1 of the Auxiliary request 3 differs from claim 1 as granted in that *"the total volume of the formulation is 5 ml"* and comprises *"250 mg fulvestrant"*; and *"the formulation is capable after injection of attaining blood plasma fulvestrant concentration of at least 2.5 ng/ml for at least two weeks"*.

6.4 These amendments can do nothing to change the above conclusions as regards the formulation of the objective technical problem and the evaluation of obviousness, in particular in view of the fact that the closest prior art D4 explicitly discloses an *injection volume of 5 ml comprising 250 mg* of fulvestrant (D4, page 301, right-hand column); as well as the attainment of mean serum concentrations of fulvestrant well above 3 ng/ml for longer than two weeks after a single injection (D4, Figure 2).

In this regard, during the discussion of the Auxiliary request 2 at the oral proceedings, the Patentee argued that D1 discloses no pharmacokinetic data and provides no hint towards the plasma levels of fulvestrant claimed.

However, these allegations are of no merit, because the plasma fulvestrant concentration defined in claim 1 of the Auxiliary requests 2 and 3 is nothing more than a recitation of the *therapeutic threshold* known from the prior art to be necessary for a significant therapeutic effect in patients with advanced breast cancer (D4, page 305, left-hand column, third paragraph) and which is already *exceeded by* the castor oil-based formulations of D4 *even at the 100 mg dose level* (see Figure 2).

In this regard, it is noted that the minimum plasma fulvestrant concentration defined in claim 1 of the Auxiliary request 2 is not even associated with a dose of 250 mg of fulvestrant, nor with any particular dose level, because claim 1 indicates that the injection of a 45 mg/ml fulvestrant formulation may have any possible volume of 6 ml *or less*. In other words, this functional requirement does not result from the administration of a particular dose of fulvestrant, but only corresponds to the minimum plasma fulvestrant level known in the prior art to be effective for the treatment of

advanced breast cancer. D4 already demonstrates that this minimum plasma fulvestrant concentration is both mandatory and attainable by intramuscular injection even at a 100 mg dose level. This is not a contribution of the opposed patent.

Thus, starting from D4, the relevant question remains whether the skilled person would regard the 50 mg/ml fulvestrant injection formulation disclosed in D1 as suitable for trying in patients with breast cancer by intramuscular injection.

This question must be answered in the affirmative for all the reasons explained in point 5.3 above.

Furthermore, with regard to the Auxiliary request 3, it is emphasised that by being able to administer an injection formulation according to D1 having higher solubility and concentration of fulvestrant (50 mg/ml), accommodating a complete monthly dose of 250 mg in a single injection volume of 5 ml, the skilled person would also have every expectation of success in exceeding the blood plasma fulvestrant concentration of at least 2.5 ng/ml for at least two weeks already attained in D4 with castor oil-based injections of lower dose and concentration (100 mg; 20 mg/ml).

6.5 At the oral proceedings, the patent Proprietor also argued, referring to Figure 2 of D4, that the problem to be solved was to attain the plasma fulvestrant level defined in claim 1 of the Auxiliary request 2 not just in average but *for each and every* patient, i.e. to ensure that, taking into account the inter patient variability, no single patient is below the 2.5 ng/ml level.

Yet nothing of the sort is disclosed or suggested in the opposed patent. Therefore, this allegation is dismissed as mere speculation.

Decision

7. Since none of the requests meets the requirements of Art. 56 EPC, the patent is revoked.