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Datasheet for the decision of 24 January 2019

Case Number: T 1680/17 - 3.3.01

Application Number: 10180667.7

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Language of the proceedings: EN

Title of invention:
Fulvestrant formulation

Patent Proprietor:
AstraZeneca AB

Opponents:
Hexal AG
Actavis Group PTC ehf
Fresenius Kabi Deutschland GmbH
Intas Pharmaceuticals Ltd.
Teva Pharmaceutical Industries Ltd.

Headword:
Fulvestrant/ASTRAZENECA

Relevant legal provisions:
EPC Art. 100(c), 123(2), 76(1), 100(b), 100(a), 54(2), 56

Keyword:
Inventive step - (yes) - reasonable expectation of success (no)

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Case Number: T 1680/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 24 January 2019

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Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 20 July 2017 revoking European patent No. 2266573 pursuant to Article 101(2) and Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	M. Pregetter
	M. Blasi

Summary of Facts and Submissions

I. European patent no. 2 266 573 was filed as patent application no. 10 180 667.7 (document (37)). It is a divisional application of the parent application no. 05 016 921.8 (document (38)), published as EP1 669 073 A1, which in turn is a divisional application of the root application no. 01 900 186.6, filed as an international application which was published as WO 01/51056 (document (39)).

II. Independent claim 1 of the patent in suit as granted reads as follows:

"1. A pharmaceutical formulation for use in the treatment of breast cancer by intra-muscular 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."

III. In addition to those appearing in point I, the following documents, cited during the opposition/appeal proceedings, are referred to below:

(1) McLeskey et al., Clinical Cancer Research, 1998, 4, 697-711

(4) Howell et al., Br. J. Cancer, 1996, 74, 300-308

(5) Howell et al., Lancet, 1995, 345, 29-30

(7) EP 346 314 B1

(9) Riffkin et al., J.Pharm.Sci., 1964, 891-895

(10) O'Regan, J. Nat. Cancer Inst., 1998, 90(20), 1552-1558

(11) Howell et al., Eur. J. Cancer, 1998, 34, S19

(14) DeFriend et al., Cancer Res., 1994, 54(2), 408-414

(15) Wade and Weller (eds.), Handbook of Pharmaceutical Excipients, 2nd edition, 1994, pages 7-9 and 38-39

(21) Avis, Lieberman and Lachman (eds.), Pharmaceutical Dossage Forms: Parenteral Medications Volume 1, 2nd edition, 1992, pages 173, 174 and 192

(23) Declaration of Dr Schaupp, 22 October 2015, 10 pages

(34) Dukes et al., J. Endocr., 1992, 135, 239-247

(35) Robertson et al., Clin Pharmacokinet, 2004, 43(8), 529-538

(43) Press release, thepharmaletter, printout from internet: "Zeneca Allays Fears of Near-Term Product Gap", 4 December 1997, 3 pages

(44) Press release, Pink Sheet, printout from internet: "Zeneca faslodex Phase III trial v. tamoxifen to start in early 1998, with approval target in 2001; casodex

early prostate cancer trial is 80% enrolled",
8 December 1997, 5 pages

(45) Sucker et al. (eds.), Pharmazeutische Technologie, 1978, pages 551-553

(46) Wang et al., J Parenteral Drug Association, 1980, 34(6), 452-462

(47) Kranz, Vademecum für Pharmazeuten, 1995, 16th ed., pages 83/84

(48) Martindale, The Extra Pharmacopoeia, 1978, 27th ed., pages 331, 332, 1235, 1400, 1401, 1409, 1529, 1536

(52) Fischer et al. (eds.), Die Pharmaindustrie, 2003, page 97

(54) Karzel et al., Allgemeine Pharmakologie, 1977, pages 88-89

(63) Declaration of Dr Illum, 18 January 2015, 156 pages, including Appendix A, in total 193 pages

(64) Valium®, Fachinformation des Arzneimittel-Kompendium der Schweiz®, dated 1 December 2015, printout from internet on 6 March 2017, 6 pages

(65) Gupta and Brazeau (eds.), Injectable Drug Development, pages 215-266, 401-421

(66) Lopatin et al., Use of nonaqueous solvents to prepare injection solutions, 1973, 724-733

(69) Howell (ed.), Endocrine Therapy of Breast Cancer

VI, 1994, pages 55-60

IV. The appeal lies from the decision of the opposition division to revoke the patent. The subject-matter of the patent as granted (main request) was found to fulfil the requirements of Articles 54, 76(1), 83 and 123(2) EPC. However, the subject-matter of the main request and of auxiliary requests 1 to 3 was found to lack an inventive step.

V. The patent proprietor lodged an appeal against this decision, maintaining its requests and requested acceleration of the appeal proceedings.

VI. The board granted the request for acceleration. Oral proceedings were held before the board on 23 and 24 January 2019.

VII. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Extension of subject-matter

The description as filed was identical to the description of the parent and grandparent applications as filed. The description as filed related to pharmaceutical formulations containing fulvestrant (see page 1, first paragraph and page 2, lines 5 to 8, of the grandparent application as filed) and described the treatment of breast cancer as the preferred treatment (see page 15, lines 21 to 31). There were several disclosures of the formulation claimed in claim 1 of the main request found in the description of the grandparent application as filed (see page 9, lines 20 to 21, page 10, line 16, page 11, lines 5 to 6, and the only example). The preferred embodiment relating to

total volume and concentration was described on page 8, lines 21 to 22. The combination of the claimed features was thus prioritised in the application as filed. The same basis was found in the parent application and the present applications as filed.

Sufficiency of disclosure

Respondent 1's reference to document (1) was not a valid argument to prove that the claimed invention was insufficiently disclosed. There was no valid argument on file.

Novelty

Document (1) did not directly and unambiguously disclose the fulvestrant formulation of claim 1 of the main request. Furthermore, nor did it disclose the treatment of breast cancer or intramuscular administration.

Inventive step

Document (4) was a non-enabling disclosure. Its teaching was not reproducible since the document did not disclose the actual fulvestrant formulation used in the experiments. At the priority date of the patent in suit, no fulvestrant formulation that had been proven to be safe and effective in a clinical setting for treating breast cancer was known. Small changes in excipients could result in large changes in *in vitro* and *in vivo* results. Not all oily injections containing fulvestrant provided the same effects of therapeutic efficacy and tolerability. Consequently, common general knowledge could not have provided the skilled person with information on the fulvestrant formulation that

was used in document (4).

According to the case law of the boards of appeal, an embodiment that was not workable did not usually qualify as the closest prior art document. When taking document (4) as the closest prior art, the deficiencies in disclosure had to be properly taken into consideration.

Document (4) described results which were not questioned as such. However, these results were not accessible to the public since document (4) did not disclose the formulation used. There was no evidence that every castor oil-based formulation would provide the results of document (4). As a consequence, the results of document (4) were not state of the art.

The technical problem underlying the patent in suit was to provide a fulvestrant formulation - for the first time - that was suitable for treating breast cancer, i.e. that was effective and safe and showed an even release of therapeutically significant fulvestrant levels over a prolonged period of time following intramuscular injection.

Concerning the formulation of the technical problem the concentration must not be included in the formulation of the technical problem since it was not part of the problem but an element of the solution. In view of the non-reproducible disclosure of document (4), the safe and effective treatment had to be included in the formulation of the technical problem since it represented the core of the invention. The long-term action also had to be included. It was a characteristic linked to the fulvestrant formulation itself (whose formulation was not disclosed in document (4)).

The problem had been solved, as could be seen from the patent in suit and from document (35). Reference was made to figures 1-3 of document (35) showing the pharmaceutically significant blood plasma fulvestrant concentrations after intramuscular administration of the claimed formulation. More importantly, it was stated in paragraph [0036] of the patent in suit that intramuscular administration of this formulation led to the release of fulvestrant over an extended period of time. As described in paragraph [0040] an extended release of fulvestrant at therapeutically significant levels was found. The successful solution was not only due to the castor oil but also to the other excipients (see paragraph [0044] and table 4, which compare the effects of formulations F1 and F3 on the precipitation of fulvestrant at the injection site). Reference was also made to paragraph [0049], which described the even release profile and the absence of precipitation of fulvestrant at the injection site. The complete formulation was thus responsible for the even release and the suitability for intramuscular administration.

The solution, as claimed in claim 1 of the patent in suit, was not obvious since neither common general knowledge nor document (1) would have provided the skilled person with a reasonable expectation of success.

Document (4) did not disclose whether fulvestrant was to be administered in solution or as a suspension. Prior art fulvestrant formulations for animal tests were either solutions or suspensions. Although a large number of excipients were known from, for instance, documents (46) and (63), no commercial preparation for human administration comprising 3 co-solvents existed.

As could be seen from document (9), especially from the data in tables V and VI, the same vehicle with a different drug, or the same drug in a slightly different vehicle, led to different responses with regard to irritation (see also page 894, left column, second paragraph). The effects of excipients were thus unpredictable. Furthermore, the claimed combination of excipients would have been perceived as exotic. Ethanol in the claimed high concentration would have been considered to cause pain and to be relatively toxic. Ethanol in such a high concentration would normally only be used in aqueous rapid release compositions (e.g. Valium, see document (64)). Benzyl benzoate, although generally and widely used (see document (21)), even at higher concentrations (see document (9)), was a bad solvent for fulvestrant and would thus not have been considered suitable. Benzyl alcohol was known to be toxic and act as an irritant (document (66), table 3). There was thus no pointer in the general prior art towards the claimed combination.

A skilled person would not have sought information about formulation development in document (1), which mentioned formulations only in passing and focused on basic research far removed from therapeutic applications. A skilled person would not have found any information on safety and tolerability of any formulation in document (1). Document (1) did not use an animal model that could show the efficacy of fulvestrant in the treatment of breast cancer. The shown anti-oestrogenic effect, which was shown in a different animal model, was not enough to prove efficacy in breast cancer treatment. Also, it was not disclosed which fulvestrant formulation was used. Furthermore, no information on even release could be obtained due to the lack of pharmacological data and

the administration of very high amounts of fulvestrant in weekly intervals. Finally, document (1) could also not have been taken to show a suitability for intramuscular administration. In sum, a skilled person, having in mind the problem formulated above, would not have turned to document (1) for finding a solution, since document (1) concerned an animal cancer model and administration of a very high dose of fulvestrant at weekly intervals subcutaneously to mice.

Furthermore, document (1) did not describe the physical state of the formulation. Document (1) did not even disclose the claimed combination as it did not disclose whether w/v% or v/v% was used.

In addition, a skilled person would not have looked specifically for a formulation containing 50 mg/ml fulvestrant. Having in mind the information on drug accumulation from document (4) (page 305, left column, end of second paragraph of "Discussion"), the skilled person would have looked for formulations comprising less fulvestrant. Less fulvestrant would furthermore have been considered advantageous since such formulations would have needed less excipients.

Overall, the skilled person would have been careful about the amounts and number of different excipients in a pharmaceutical formulation and would have only used as few as necessary. A warning could be found in document (46), page 462, last paragraph. This was backed up by the statement in document (65), page 414, second paragraph, which discussed co-solvents in the context of tissue damage and pain. Furthermore, it was known from document (66), table 3, that benzyl alcohol was toxic and an irritant in concentrations of 5% and that ethanol had a low LD_{50} of about 8 g/kg. In this

context, it noted that table 1 of the patent contained errors. For the last two entries, two columns had been shifted, creating the impression that those entries related to formulations comprising three co-solvents, whereas only two co-solvents were present.

Furthermore, the effects, especially the therapeutic effects, of a particular formulation given by a particular mode of administration were not predictable.

In sum, starting from the deficient disclosure of document (4), the skilled person would not have arrived at the claimed subject-matter, even when aware of document (1). The subject-matter of claim 1 of the main request involved an inventive step.

VIII. The respondents' (opponents 1 to 5) arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Extension of subject-matter

The subject-matter of claim 1 as granted extended beyond the application as filed and also beyond the parent and grandparent applications as filed. A new combination of a specific combination of excipients, a specific medical use and a specific volume of the formulation had been created. Selections of several lists had to be made, the first list being the 3 alternative formulations of claims 1, 2 and 4 of the grandparent application as filed. The second selection was from the various combinations of alcohol- and ester solvents in different concentrations from claims 5-16 and 20 of the grandparent application as filed. The third selection was the medical indication "breast cancer" on page 15, lines 20-30. The combination of the

specific combination of excipients in the amounts as claimed and the total volume of the formulation was not originally disclosed. Also, claim 1 as granted did not define the formulation as an extended release formulation. The deficiency was even more apparent when looking for a basis in the parent application as selections from more claims had to be made.

Sufficiency of disclosure

Respondent 1 raised a conditional objection for lack of sufficiency of disclosure of the patent in suit: Should the proprietor argue that it was not clearly and unambiguously derivable from document (1) that the composition under consideration was suitable for the treatment of breast cancer, then the patent in suit, based on comparable experimental data, should be considered insufficiently disclosed. Respondent 1 took the position that it was clearly and unambiguously derivable from document (1) that its formulation was suited for the treatment of breast cancer.

As a consequence of doubting the suitability of the formulation of document (1), which is the same as the formulation defined in claim 1 of the main request, the same doubts would automatically also be extended to the subject-matter of the main request.

Novelty

Document (1), in the context of mechanistic considerations of breast cancer treatment, disclosed a preformulated formulation as defined in claim 1 of the main request. The introduction of document (1) referred to the use of fulvestrant in human breast cancer treatment ("introduction", page 697, right column to

page 698, left column). Intramuscular administration of the fulvestrant formulation was implicitly disclosed to the skilled person by document (1). It was mandatory to inject fulvestrant intramuscularly for human use (see document (10), paragraph bridging pages 1552/1553). Also, document (9) taught to administer oily steroid formulations by intramuscular administration to humans. This mandatory administration via the intramuscular route would have been immediately complemented by the skilled person when reading document (1) and was therefore unmistakably disclosed to the skilled person in document (1). Document (1) disclosing all technical features of claim 1 of the main request was thus novelty destroying for the subject-matter of this claim.

Inventive step

Document (4) represented the closest prior art. The skilled person would have understood the teaching of document (4) as a technical reality. The document confirmed the suitability of fulvestrant for the treatment of breast cancer in a clinical phase II setting. The outcome of the study was positively received by the community and the public (see also press releases (43) and (44)). Document (4) would have provided a wealth of information to the skilled person. Apart from the confirmation that fulvestrant could be used to treat breast cancer when the gold standard tamoxifen failed, it provided information on the concentration (50 mg/ml), including the amount (250 mg) and volume (5 ml), the administration mode (intramuscular), the monthly dosage regimen, and the indication that the formulation was castor oil-based (the skilled person would have understood from the term "based" that further excipients were present) (page

301, right column, first paragraph). The document taught that 250 mg fulvestrant administered in 5 ml was a suitable dose to achieve the necessary threshold levels in serum, which were also disclosed (page 305, left column, second paragraph of "Discussion"). Furthermore, it was stated that no serious side effects were observed (page 303, right column, "Side-effects"). In sum, document (4) described a highly promising treatment.

There was no disclosure of the complete formulation administered. Not all excipients were derivable from document (4) However, the most important excipient, castor oil, which was responsible for the extended release, was disclosed. The distinguishing feature was the missing part of the formulation, i.e. a situation arose where it was necessary to simply "fill in the gap". The term "enabling disclosure" should be confined to novelty objections, the appropriate term in the context of inventive step would be "deficient disclosure", which did not apply to document (4). The missing piece of information relating to the exact formulation used would not have kept the skilled person from considering the valuable information regarding the formulation in general terms and its successful use derivable from document (4). Furthermore, the burden of proof to show that document (4) was not enabling was on the appellant.

The respondents formulated the following technical problems:

Respondent 1:
The problem resided only in the provision of a castor oil-based fulvestrant injection formulation allowing the solubilisation of a higher concentration of

fulvestrant for a complete monthly dose of around 250 mg to be solubilised in the recommended injection volume for intramuscular administration of no more than 5 ml in a single injection.

Respondents 2 and 5:
The problem was to provide a fulvestrant formulation based on castor oil, containing fulvestrant in a concentration of 50 mg/ml and being suitable for intramuscular administration.

Respondent 3:
The problem was to provide an exact formulation based on castor oil and having 50 mg/ml fulvestrant.

Respondent 4:
The problem resided in the provision of a castor oil-based formulation suitable for the administration of 250 mg fulvestrant by intramuscular administration of 5 ml.

Concerning the formulation of the technical problem the respondents stressed that it was important to include the specific concentration of fulvestrant in the formulation of the problem since this concentration had been shown to work in document (4) and to be suitable to be given by one injection and would thus have been an integral part of the formulation sought for by the skilled person. The mere mention of drug accumulation in document (4) would not have led the skilled person away from a monthly dose of 250 mg fulvestrant since no negative effects were reported to be linked to this drug accumulation. An "even release" profile should not be part of the technical problem since it was not reflected in the patent in suit. The extended release was entirely due to the castor oil. Thus, there was no

need to include it in the formulation of the technical problem. It was irrelevant whether terms like "safe and effective" were included in the formulation of the technical problem since these terms were already implied when talking about the treatment of breast cancer. There was, furthermore, no question of particular levels of safety or efficacy. Concerning the treatment of breast cancer, the respondents argued that the skilled person would have known from document (4) that treatment had been achieved. Also, the solvents were not responsible for obtaining the effects. No effects should therefore be included in the formulation of the technical problem. In sum, the skilled person would have aimed at providing fulvestrant in a formulation based on castor oil in the concentration described in document (4).

The solution was obvious. A skilled person, in the form of a team of a pharmacologist and a formulator looking for a solution, would have had in mind that the solution involved a castor oil-based formulation at 50 mg/ml suitable for injection by intramuscular administration. When looking at what was available for parenteral administration in general and for fulvestrant in particular the skilled person would have considered document (1).

Document (1) related to the same active, fulvestrant, in the context of cancer research, especially breast cancer research, and even cited document (4). The pharmacologist in the team would have immediately recognised that document (1) was relevant for breast cancer treatment, while the formulator in the team would not have missed the fulvestrant formulation described in document (1), especially since it was castor oil-based and had exactly the concentration of

active sought. The fulvestrant formulation of document (1) was sophisticated in that it comprised several excipients. Knowing that fulvestrant was difficult to formulate, the skilled person would have seriously considered the formulation of document (1), especially since it had been provided by Zeneca and was labelled "preformulated".

It was also generally known that AstraZeneca was developing a castor oil based fulvestrant formulation for human application: Document (34), in 1992, described a castor oil based fulvestrant solution as "prototypic" of a long-acting formulation for intramuscular injection (page 245, left column). Document (14), in 1994, stated that studies were "now in progress" (page 413, last paragraph before "Acknowledgements"). In 1995, document (5) disclosed a monthly castor oil-based formulation (page 29, right column). In 1996, document (4) was published, followed in 1997 by document (1). Also in 1997, Faslodex was announced (see document (43) and (44). Finally, document (11), published in 1998, relates to the phase III clinical study. All these documents were initiated by Zeneca or referred to Zeneca. The skilled person would thus have seriously considered any complete, full formulation provided by Zeneca. The obtention of a sample of a drug or a drug formulation from the drug producer was normal, and the skilled person would have considered that such a drug or drug formulation would work (see document (23), page 4, last paragraph).

Furthermore, the skilled person would have had a reasonable expectation of success (neither a guarantee of success nor a predictability of the outcome being necessary, see established case law) when employing the formulation disclosed in document (1). Document (1)

established the presence of an anti-oestrogenic effect due to the administration of the fulvestrant formulation, thus demonstrating that this formulation inherently had the properties that were underlying its effectiveness in breast cancer treatment. Document (1) used fulvestrant explicitly as an anti-oestrogen (abstract) and proved its anti-oestrogenic activity by the "uterus test" (paragraph bridging pages 701 and 702). The skilled person (i.e. the team of the pharmacologist and the formulator) would not separate the pharmacological information from the formulation used in document (1). When looking at the formulation itself, the skilled person would have been aware that all the excipients in the formulation were well known in the art, e.g. from commercial products, i.e. from formulations that work. This perception would have been supported by statements in document (46), page 452, "introduction" and document (65), page 406, third paragraph. Furthermore, document (46), last paragraph, pointed to the importance of selecting proper excipients and using them at optimal concentrations.

The addition of the further excipients, which were co-solvents or solubilisers, such as benzyl benzoate (see document (15), page 38, left column, middle paragraph), was necessary to provide a solution of fulvestrant. The patent showed no further effects for these co-solvents. Moreover, the formulation of document (7) had been rejected by the patent proprietor merely due to manufacturing reasons (see patent in suit, paragraph [0014]).

The co-solvents themselves and the amounts to be employed were well known for the intramuscular administration of steroids. Document (9) described that castor oil led to a prolonged release and that further

solvents increased the solubility of the steroids (abstract). Annex A of document (63) provided a list of commercially available products. Not even one page was taken up by parenteral formulations in oily solutions, these solutions having a very limited number of excipients, namely, benzyl benzoate, benzyl alcohol, ethanol and cholesterol. No oily suspensions were disclosed for steroids. Oil-based formulations for intramuscular administration were thus common in the art. The skilled person would have been aware that the presence of several co-solvents allowed for a formulation having favourable characteristics. Further relevant documents discussing the use and activity of these excipients (ethanol, benzyl alcohol and benzyl benzoate), often teaching to use several in combination in lipophilic vehicles for intramuscular administration, included documents (9) (paragraph bridging pages 893 and 894), (45) (table 5.22), (47) (page 84), (48) (excerpts referring to formulations comprising the excipients under consideration for administration by intramuscular injection) and document (65) (table 11-1 and page 217, first and third paragraph). The explanation by the appellant that table 1 of the patent contained errors and did not disclose a formulation having more than two co-solvents was accepted. Furthermore, document (1) already provided a complete formulation. Since a complete formulation was given, the skilled person would not have considered the solubility of fulvestrant in the individual components (e.g. benzyl benzoate) of this formulation.

The skilled person would have been well aware that, while subcutaneous administration differed from intramuscular administration, the same formulations could be used for these two types of administration (see document (54), point 5.5).

Finally, fulvestrant was known to be difficult to formulate. Consequently, the skilled person, aware of the disclosure of document (1), which described a complete fulvestrant formulation, would have started with this formulation and verified its suitability by some routine tests. They would not have tried to make up a formulation from scratch.

The drug-accumulation effects described in document (4) would not have been a concern to the skilled person since no negative effects were attributed to the accumulation. Optimisation by routine experiments would also have always been a consideration.

Furthermore, the subject-matter of claim 1 of the main request was rendered obvious by combining the teaching of document (4) with the common general knowledge. All excipients were known for use in combination with castor oil (see commercial products). Some simple routine experiments were sufficient to find the claimed formulation when starting from the information available in document (4).

There was also no reason to have considered the formulation of document (1) to be suitable only for animal use. Formulations used in animal studies were usually the same as the ones used for clinical studies. It was furthermore well known that higher doses were used in animal studies than in clinical studies (see document (52), page 97, left column, paragraph 4). Also, the proprietor's expert, Mr Wakeling, derived a reasonable expectation of success from experiments in animal models (document (69), page 58, paragraph bridging the columns).

Therefore, the subject-matter of claim 1 of the main request did not involve an inventive step.

IX. The appellant requested that the decision under appeal be set aside and the patent be maintained as granted, i.e. that the oppositions be rejected, or alternatively, that the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 1 to 3, re-submitted with the statement of grounds of appeal.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Extension of subject-matter (Article 100(c) EPC)*

The wording of the passages of the description relevant for the assessment of whether the ground for opposition under Article 100(c) EPC prejudices the maintenance of the patent as granted is identical in the application as filed (document (37)) and in the two earlier applications as filed (i.e. in the "grandparent" application EP 01 900 186.6, document (39), and the parent application EP 05 016 921.8, document (38)). The following passages refer exclusively to document (37), the corresponding passages in documents (38) and (39), which are in some instances shifted by a couple of lines, are not identified.

On page 15, lines 20 to 27, the treatment of a benign or malignant disease of the breast or reproductive tract, preferably the treatment of breast cancer, is described. Breast cancer is thus clearly identified as

the preferred treatment. The treatment is carried out by intramuscular injection of an extended release ricinoleate vehicle based pharmaceutical formulation comprising at least 45 $mgml^{-1}$ fulvestrant. This vehicle contains 35% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation and at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation. A limitation to the most preferred formulation (see e.g. last entry in the table on page 11, or the formulation according to the invention in table 4 ("Formulation F1") or the formulation of the "Formulation Example" on page 16, line 23, to page 17, line 11) does not add subject-matter. An appropriate volume to administer the at least 45 $mgml^{-1}$ fulvestrant intramuscularly is disclosed in the passage on page 8, lines 18 to 21, where it is stated that for preferred pharmaceutical formulations the total volume of the formulation is 6 ml or less and the concentration of fulvestrant is at least 45 $mgml^{-1}$. The volume of 6 ml or less is thus the only selection to be made to arrive at the subject-matter of claim 1 of the main request. The claimed formulation has been shown to have an extended release (see figure 1), a definition of the formulation by the term "extended release" is thus not necessary.

Consequently, the ground for opposition under Article 100(c) EPC does not prejudice the maintenance of the patent.

3. *Sufficiency of disclosure (Article 100(b) EPC)*

Respondent 1 has raised a conditional objection for lack of sufficiency of disclosure of the patent in suit: Should the proprietor argue that it was not

clearly and unambiguously derivable from document (1) that the composition under consideration was suitable for the treatment of breast cancer, then the patent in suit, based on comparable experimental data, should be considered insufficiently disclosed.

In its statement setting out the grounds of appeal, the appellant stated that "No experiment is reported in D1 that would lead a skilled person to conclude that any of the formulations tested would be suitable for a safe and effective therapy as described in D4" (page 28, paragraph 3).

The patent in suit depicts the release profile of fulvestrant *in vivo* over five days from the composition under consideration following intramuscular administration in rabbits (figure 1). This figure shows that the claimed composition is suitable for achieving the required plasma profiles. The suitability of fulvestrant in the treatment of breast cancer has not been questioned as such. Consequently, the data presented in the application as filed and depicted in the published patent renders it plausible that the claimed composition is suitable for use in the treatment of breast cancer. Post-published evidence, in the form of document (35), was filed as confirmation.

Hence, the invention as defined in the claims is sufficiently disclosed in the patent and the ground for opposition under Article 100(b) EPC does not prejudice the maintenance of the patent.

4. *Novelty (Article 100(a) and Article 54(1) EPC)*

Document (1) does not provide a direct and unambiguous disclosure of the feature of intramuscular injection

and is thus not novelty-destroying for the subject-matter of claim 1.

Respondent 1 has argued that the skilled person would have understood the disclosure of document (1) as referring to intramuscular administration. The board cannot accept this line of argument since document (1) discloses the formulation under consideration solely for animal studies. In animal studies a subcutaneous administration is a common mode of administration which is, however, distinct from intramuscular administration. Therefore, intramuscular administration is not directly and unambiguously disclosed.

The board notes that document (1) does not disclose any concrete formulations in the context of the therapeutic treatments discussed in the passages of the "introduction" (page 697, right column, first paragraph to page 698, left column, first paragraph).

The ground for opposition under Article 100(a) and Article 54 EPC does therefore not prejudice the maintenance of the patent.

5. *Inventive step (Article 100(a) and Article 56 EPC)*

5.1 Preliminary remarks

The boards of appeal of the European Patent Office generally apply the problem-solution approach to assess inventive step. In accordance with the problem-solution approach, it is first necessary to identify the closest prior art, then to determine in the light of the disclosure of the closest prior art the technical problem which the claimed invention addresses and successfully solves, and finally to examine whether or

not the claimed solution to this problem is obvious for the skilled person in view of the state of the art. The problem-solution approach was developed to ensure an objective assessment of inventive step and to avoid *ex post facto* analysis of the prior art (see "Case Law of the Boards of Appeal of the EPO", 8th edition 2016, I.D.2).

5.2 Closest prior art

5.2.1 The decision under appeal relies on document (4) as the closest prior art. Furthermore, all respondents have chosen document (4) as the closest prior art. Document (4) is thus the only document that has been invoked as the starting point for the assessment of inventive step in the appeal proceedings.

The patent in suit is based on the premise that oestrogen deprivation is fundamental to the treatment of many benign and malignant diseases of the breast and reproductive tract (paragraph [0002]) and consequently provides a sustained release pharmaceutical formulation comprising fulvestrant for the treatment of breast cancer (paragraph [0001]). Document (4) relates to the same problem.

5.2.2 Document (4) concerns the pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer (title). ICI 182780 is fulvestrant. The agent was administered as a monthly depot intramuscular injection. Out of the 19 patients participating in the study, 13 responded, seven of which had partial responses while the other six had "no change" responses (abstract). No serious drug-related adverse events were reported. The formulation was well tolerated locally at

the site of injection (page 303, "Side-effects"). Of the 19 patients treated, five patients were still in remission and continued treatment after 30-33 months (page 304, "Response"). There was evidence of drug accumulation after multiple dosing, such that after 6 months of treatment, there was an 80% increase in mean end of month drug levels and a 50% increase in the AUC compared with data from month 1. These data were interpreted as suggesting that lower doses of drug may be effective in maintaining therapeutic serum drug levels (page 305, left column, paragraph 3). In the section "Study design", on page 301, right column, first paragraph, information relating to the administration of fulvestrant can be found. It is stated that "ICI 182780 was administered as a long-acting formulation contained in a castor oil-based vehicle by monthly i.m. injection (5 ml) into the buttock. For appraisal of drug safety, the first four patients received escalating doses of ICI 182780, starting with 100 mg in the first month and increasing to 250 mg i.m. from the second month onwards, following confirmation of lack of local or systemic drug toxicity at the 100 mg dose". This passage provides information on the administration mode, i.e. intramuscular, the administered volume, i.e. 5 ml, the amount of active, i.e. 250 mg, and gives an indication that the vehicle comprises castor oil. No further information is given on other excipients.

In document (4), there is thus no disclosure of the complete formulation used in the clinical study. Information on further excipients is not provided, i.e. is not been made available to the public.

5.2.3 Next, the consequences of the missing information must be assessed.

In the absence of a disclosure of the complete formulation used in the study, the study cannot be directly reworked, i.e. reproduced. The question to be answered in the context of the problem-solution approach is: What exactly had been made accessible to the skilled person?

To answer this question, the link between formulation and effects must be examined. The literature cited in this respect mainly relates to the side effects due to the presence of excipients. Of particular relevance is document (9). Entitled "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones", document (9) discusses the use of co-solvents to render castor oil-based steroid formulations suitable and acceptable for parenteral administration.

The initial consideration to be made according to document (9) is the solubility of the active in the vehicle. The high concentrations of active in solution sought by the clinicians required the addition of co-solvents to castor oil (abstract, paragraph bridging pages 893 and 894). The skilled person would thus have been aware that the physical state of a formulation, i.e. the form of solution or suspension, was linked to the amount of active and the specific solvents/co-solvents used. Furthermore, it was common general knowledge that the physical state of a formulation had an influence on the bioavailability of active agents.

The authors of document (9) then point to the fact that the presence of side effects is linked to the specific formulation. On page 894, left column, second paragraph, it is stated that the irritative response depended on the particular hormone, its concentration

in the formulations, and/or the composition of the vehicle. As can be seen in the data presented in tables V and VI, different vehicles were acceptable for 17-hydroxyprogesterone caproate and for estradiol valerate. While a vehicle comprising 58% castor oil, 40% benzyl benzoate and 2% benzyl alcohol was accepted for estradiol valerate (adverse reactions in 2.67%), the same vehicle was rejected for 17-hydroxyprogesterone caproate (adverse reactions in 23.2%).

The skilled person would thus have been aware, when reading in document (4), page 303, right column, second paragraph, that the formulation of fulvestrant used appeared well tolerated locally at the site of injection and that such a good tolerance was not to be expected for any castor oil-based fulvestrant formulation. Or, put another way, the skilled person would have had in mind that the lack of side effects would have been due to a particular formulation, including a certain amount of a certain active in combination with certain excipients in certain concentrations. In sum, there is strong evidence in the literature that side effects are linked to specific formulations. There is no reason to believe that other effects, e.g. effects in the context of efficacy of treatment, would not be similarly linked.

This finding must be reflected in the assessment of the overall information obtainable from document (4). Based on the foregoing, the disclosure of document (4) would have told the skilled person that:

- Fulvestrant was a potent agent in the treatment of breast cancer.
- Intramuscular administration was a suitable mode of

administration.
- A vehicle of choice would contain castor oil.

When using document (4) as the starting point in the assessment of inventive step, i.e. as the closest prior art, the next steps of the problem-solution approach must therefore be based only on the disclosure as set out above.

5.2.4 The fact that the missing information does not concern only the formulation as such but also the achievability of the effects described in document (4) has direct consequences on the correct formulation of the technical problem.

5.3 Technical problem

5.3.1 The following technical problems have been formulated by the parties:

Appellant:
The problem is to provide a fulvestrant formulation - for the first time - that is suitable for treating breast cancer, i.e. that is effective and safe and shows an even release of therapeutically significant fulvestrant levels over a prolonged period of time following intramuscular injection.

Respondent 1:
The problem resides only in the provision of a castor oil-based fulvestrant injection formulation allowing solubilisation of a higher concentration of fulvestrant for a complete monthly dose of around 250 mg to be solubilised in the recommended injection volume for intramuscular administration of no more than 5 ml in a single injection.

Respondents 2 and 5:
The problem is to provide a fulvestrant formulation based on castor oil, containing fulvestrant in a concentration of 50 mg/ml and being suitable for intramuscular administration.

Respondent 3:
The problem is to provide an exact formulation based on castor oil and having 50 mg/ml fulvestrant.

Respondent 4:
The problem resides in the provision of a castor oil-based formulation suitable for administration of 250 mg fulvestrant by intramuscular administration of 5 ml.

5.3.2 For the following reasons, the board cannot adopt any of these wordings.

The board concurs with the respondents that the inclusion of the terms "safe and effective" for characterising the treatment of breast cancer is meaningless in the absence of a certain "level" or "benchmark" qualifying these terms. The terms "treatment of breast cancer" are taken to imply that patients with breast cancer benefit from the administration of the formulation under consideration, i.e. that the administration of the formulation has a positive influence on their condition in the absence of intolerable side effects.

However, having come to the conclusion that the achievement of effects is linked to the actual formulation (see point 5.2.3 above), the therapeutic indication as such must be part of the technical

problem.

Document (4), on two occasions (first on page 305, left column, third paragraph, and second in the concluding remarks on page 306, right column, last paragraph) discloses that drug accumulation has been observed in the patients. Drug accumulation is generally not considered favourable by the skilled person. It is thus questionable whether the skilled person would have limited themselves exclusively to formulations comprising 50 mg/ml or 250 mg total dose when starting from document (4) as the closest prior art. Consequently, the concentration or dose of fulvestrant must not be included in the formulation of the technical problem.

5.3.3 The technical problem is thus as follows:

The technical problem is the provision of a castor oil-based vehicle for a fulvestrant containing composition allowing for treatment of breast cancer by intramuscular injection.

5.4 Solution of the technical problem

The patent specification provides the information that the claimed fulvestrant composition, upon intramuscular administration, leads to plasma levels which are considered effective (see figure 1 of the patent in suit). In paragraph [0049] it is stated that there was no evidence of precipitation of fulvestrant at the injection site. It is thus plausible that the claimed formulation leads to the treatment of breast cancer. This has not been contested by the respondents.

5.5 Obviousness

In the following it will be examined whether the solution as defined in claim 1 of the main request was obvious. One point arising in this context is the skilled person's expectation of success. It will thus be examined, *inter alia*, whether the skilled person, in the expectation of solving the technical problem, would have arrived at the claimed subject-matter, in particular, at the claimed fulvestrant formulation.

5.5.1 Two approaches will be analysed in detail. The first approach focuses on the knowledge of the skilled person in view of the preparation of a castor oil-based intramuscular formulation containing a steroid as an active agent. The second approach considers the state of the art concerning the formulation of the active agent under consideration, i.e. fulvestrant. Document (7), fulfilling both criteria, will be addressed in the second approach.

5.5.2 Various documents deal with castor oil as solvent for steroids in the context of parenteral administration, some also explicitly in the context of intramuscular administration.

Documents (9) and (63) have extensively been discussed by the parties in this context. Document (9) is silent on fulvestrant. It relates to castor oil-based vehicles for parenteral administration of steroid hormones (title). Castor oil is combined either with benzyl alcohol at 2 to 5%, benzyl benzoate at 20 to 50% or with both. Tables V and VI show that different vehicles were acceptable for 17-hydroxyprogesterone caproate and for estradiol valerate. While a vehicle comprising 58% castor oil, 40% benzyl benzoate and 2% benzyl alcohol

was accepted for estradiol valerate, the same vehicle was rejected for 17-hydroxyprogesterone caproate. The respondents have furthermore invoked Appendix A of document (63) listing several commercially available oil-based solutions for parenteral administration.

Document (45), a textbook on pharmaceutical technology, discusses solvents and dispersing aids in parenteral formulations. It lists solvents, including castor oil, ethanol, benzyl benzoate and benzyl alcohol, for parenteral formulations and provides indications for their concentrations, including, however, both hydrophilic and lipophilic vehicles (table 5.22). Although combinations of alcohols are suggested, no details on such combinations are disclosed (page 552, last paragraph).

Document (47) lists solvents for peroral, parenteral and cutaneous administration. This list includes, *inter alia*, ethanol, said to be suitable in concentrations up to 30% for all three modes of administration; castor oil, also suitable for all three modes of administration; and benzyl benzoate, listed only for parenteral administration without any indication as to its concentration. Ethanol is listed as being miscible with castor oil, benzyl benzoate is to be used exclusively in mixture with an oil, especially in mixture with sesame oil (table on pages 83 and 84). No concrete formulation is disclosed.

Document (48), comprising entries in the Martindale Pharmacopoeia, provides excerpts on various drugs. It shows that intramuscular formulations may contain one or more of the excipients under consideration. No formulation comprising a combination of castor oil,

ethanol, benzyl benzoate and benzyl alcohol is disclosed.

Document (65), a textbook entitled "Injectable Drug Development", discusses various aspects of co-solvents. A list of co-solvent compositions for various formulations is shown in table 11-1. It can be seen that mixtures of ethanol and benzyl alcohol are mainly used in aqueous-based formulations for intravenous administration. The importance of the selection of appropriate co-solvents is stressed. On the one hand co-solvents are considered powerful tools for providing the required solubility (page 217, first and third paragraph). On the other hand, they may cause side effects (page 245, second paragraph and page 414, second paragraph).

It is, however, not clear to what extent these passages can be applied to fulvestrant. As acknowledged by all parties, fulvestrant is difficult to formulate. Not all general guidelines for steroids can be applied directly to fulvestrant. Document (21), for example, teaches to add benzyl benzoate to castor oil to increase the solubility of the active agent in the form of a steroid (page 192, paragraph 4, last three lines), and document (15) provides guidance to generally use benzyl benzoate in formulations for intramuscular administration at concentrations of 0.01 to 46.0% (page 38, left column, middle paragraph). Fulvestrant is however less soluble in benzyl benzoate than in castor oil. A skilled person would have had no incentive to add a worse solvent to increase solubility.

Furthermore, the documents relied upon by the parties in this context do not suggest using a combination of the three co-solvents/excipients ethanol, benzyl

benzoate and benzyl alcohol.

In sum, the documents considered above do not point towards a formulation for intramuscular administration of a steroid having the claimed combination of excipients in the required concentrations. Such a combination would thus not have been rendered obvious by common general knowledge.

5.5.3 Several documents refer to fulvestrant formulations. However, only two of these documents disclose complete formulations. While documents (5) ("castor oil based vehicle"), (10) (ethanol spiked into peanut oil), (11) (no information on vehicle) and (14) (propylene based vehicle) mention fulvestrant formulations, they do not disclose a complete castor oil-based formulation. Complete castor oil-based fulvestrant formulations are disclosed in documents (1) and (7).

Document (7) deals with various steroids. Example 3 relates to a formulation of fulvestrant for intramuscular administration. The formulation comprises fulvestrant, benzyl alcohol and castor oil in certain concentrations. Although breast cancer is not mentioned in document (7), the document relies on the anti-estrogenic effects of its actives. This can also be seen from example 3, which describes that the/a "uterus test" is carried out. In sum, document (7) discloses a formulation that could have been adopted by the skilled person. The formulation was, however, rejected by the inventors of the patent in suit (see paragraph [0014] of the patent in suit relating to the US family member of document (7)).

The only other concrete composition comprising fulvestrant to be found in the cited documents is

described in document (1), which is a scientific paper. Document (1) is titled: "Tamoxifen-resistant Fibroblast Growth Factor-transfected MCF-7 Cells Are Cross-Resistant *in Vivo* to the Antiestrogen ICI 182,780 and Two Aromatase Inhibitors". It aims to elucidate mechanisms underlying an acquired tamoxifen resistance in the therapy for estrogen receptor-positive breast cancer (abstract). To find information underlying the mechanism(s) or tamoxifen resistance, FGF-transfected MCF-7 cells were used. Such cells do not rely on an estrogen receptor based mechanism and thus allow for the examination of other pathways. There is no doubt that treatment, or rather the failure of treatment, of breast cancer by tamoxifen, is the cause of the experiments on which document (1) is based. However, the purpose of document (1) is the elucidation of a biochemical mechanism. Document (1) does not aim at the provision of a therapy.

In the context of these mechanistic studies, four drugs, ICI 182,780 (fulvestrant), 4-OHA (4-hydroxyandrostenedione), letrozole and tamoxifen, were used in 5 different vehicles. Fulvestrant was used in two different vehicles. Firstly, powdered fulvestrant was dissolved in ethanol and spiked into peanut oil. Secondly, preformulated drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil was used. The latter formulation is said to have been provided by "B. M. Vose (Zeneca Pharmaceuticals)". The two fulvestrant formulations were administered subcutaneously at a dose of 5 mg in 0.1 ml of vehicle every week. For the experiments depicted in figure 1, the first formulation was used, while for the experiments used in figure 1, *B* and *C*, the second formulation was used. For other experiments, such as

the "uterus test", which of the two fulvestrant formulations was used is not disclosed (page 698, right column, paragraph 3).

Thus, there is no doubt that document (1) discloses the use of, *inter alia*, a fulvestrant formulation that has the same excipients as defined in claim 1 of the main request.

5.5.4 To determine whether the claimed invention, starting from the closest prior art and the technical problem formulated above (see point 5.3.3 above) would have been obvious to the skilled person, it must be determined whether the skilled person would have used the fulvestrant formulation of document (1) which is described as "preformulated drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil". The skilled person would have used this formulation, if they had a reasonable expectation of success that it would solve the problem defined above.

5.5.5 Therefore, it is now necessary to have a closer look at the context and the detailed disclosure of document (1).

Document (1) is a scientific research paper. It pertains to the domain of basic research. References to therapeutic applications are made merely to put the basic research into context. The document aims at elucidating a mechanism of tamoxifen resistance on the level of molecular pathways, in particular, looking at whether estrogen receptor pathways are implicated. Experiments in basic research are done with formulations that primarily aim at ensuring that the compound tested will be present at the location where

it was hypothesised to exert its activity. This is supported by the disclosure of document (1). After negative results were obtained for the hypothesised mechanism, the authors of document (1) went on to carry out the "uterus test" to verify whether the compounds tested (fulvestrant, 4-hydroxyandrostenedione and letrozole) could exert their activity in the test system. A formulation in basic research is thus geared to ensure that a high concentration will reach the required location. Such research requires no considerations on the pharmacologically suitable concentration, the safety and tolerability, or the suitability for administration in a clinical setting are necessary. Thus, a skilled person would have had no incentive to turn to document (1), a scientific paper dealing with basic research, to provide a formulation for administration in a clinical situation.

The respondents have pointed to the fact that document (1) cites document (4). Document (1), on page 698, left column, line 5, cites 8 references (references 13-20) relating to the response of tamoxifen-resistant patients to subsequent fulvestrant or aromatase inhibitor therapy. One of these 8 references is document (4). These references are cited in the context of considerations relating to mechanisms of tamoxifen resistance. Formulations are not even mentioned. The fact that document (4) is cited would have thus not caused the skilled person to assess the formulations of document (1) in a different way.

It has been argued that the relevant formulation of document (1) has been highlighted by three facts: Firstly, the skilled person would have considered the combination of a solvent (castor oil) with three co-solvents to be "sophisticated". Secondly, the skilled

person would have been made aware that the formulation was the result of a targeted development process due to the term "preformulated". Finally, the skilled person would pay special attention to a complete formulation obtained by "Zeneca", which was known to develop a fulvestrant based medicament.

The formulation of document (1) contains three co-solvents in addition to the base oil. Commercially available steroid formulations for parenteral administration usually contain one or two co-solvents, the exception being "Syncortyl®", which contains three further excipients in the form of cholesterol, benzyl alcohol and ethanol (Appendix A of document (63)). Cholesterol, having a melting point of 148°C, is not a classical "co-solvent". The commercially available compositions listed in table 1 of the patent include, at most, two further solvents (note that the two last entries of table 1 contain errors, two columns being shifted). Document (65) states on page 217, first paragraph, that co-solvents are powerful tools to reduce irritation and have advantages over other techniques for solubilisation of water-insoluble compounds. The document goes on to teach that the solubility of a compound should be maximised to lower the total amount of solvents needed and thus to reduce potential side effects (page 217, third paragraph). Reduction of pain and irritation at the injection site can be obtained by using appropriate co-solvents (page 245, second paragraph). Document (46) describes an ideal formulation as containing no excipients at all. It is however acknowledged that excipients are necessary to preserve potency, elegancy and safety. Nevertheless, extreme caution should be used in selecting proper excipients (page 462, last paragraph). Having in mind these statements, the skilled person

would have had certain reservations against the use of the formulation of document (1) in a clinical setting.

The respondents have argued that the term "preformulated" would have directed the skilled person towards this composition since they would assume that this composition was the result of extensive development. This is mere speculation. The term "preformulated" in the context of document (1) simply refers to the fact that an active has been provided to the researchers in dissolved form. The reason for the provision of fulvestrant in a solvent mix, in contrast to the second part of fulvestrant used in document (1), which was obtained as a powder, is not known. Several different explanations are possible.

It does not come as a surprise that the "preformulated" formulation, as well as the powdered fulvestrant, was obtained from "Zeneca". Given the history of fulvestrant, to which the respondents have pointed several times, the obtaining of the compound from Zeneca was to be expected, since Zeneca was the company in possession of fulvestrant (after the transfer of, *inter alia*, the pharmaceutical sector of ICI in 1993 (AstraZeneca only being founded in 1999)). Thus, no pointer can be derived from the fact that fulvestrant was obtained from Zeneca. This view is supported by expert declaration (23) stating that active ingredients were usually obtained from the producer of the active ingredient (page 4, last paragraph).

5.5.6 Thus, having analysed document (1) in detail, a conclusion must be reached whether the skilled person, having in mind the problem defined above (see point 5.3.3), would have considered the disclosure of document (1) and adopted one of the fulvestrant

formulations disclosed in it with a reasonable expectation of success of solving the problem. The respondents have asserted that a person skilled would not have required certainty of success to adopt a certain route. The board agrees with this statement. However, in the present case, no expectation of success can be admitted by the board when assessing the approach proposed by the respondents. This absence of an expectation of success is due to the following reasons:

Firstly, document (1) is a scientific paper dealing with basic research. The board considers that the skilled person would not have turned to formulations used in basic research when aiming at providing a formulation for therapeutic treatment. The requirements of a formulation to be used in basic research are fundamentally different from the requirements of a formulation to be administered to a patient. While in basic research merely the availability of the active at the test site is of relevance, in a clinical situation aspects such as safety/tolerability and bioavailability over the treatment period are decisive factors.

Secondly, even if the skilled person would have paid particular attention to the formulations used in document (1), they would have had reservations about using a formulation having a combination of an unusually high number of excipients in unusual concentrations in a clinical trial.

Thirdly, the formulation under consideration of document (1) is not particularly preferred. This can be seen in that it was not used in all the experiments carried out in document (1).

Consequently, the skilled person would have had no reasonable expectation of success when using the formulation of document (1) in the treatment of breast cancer. Such a use would thus not have been obvious.

5.5.7 Further arguments

(a) It has been argued that the skilled person was a team of a pharmacologist and a formulator. The pharmacologist would have studied the introductory parts of document (1) and concluded that it concerns certain aspects of breast cancer. Having been pointed to document (1), the formulator would have immediately spotted the formulation under consideration for the reasons set out above.

The board cannot accept this argument. The skilled person may well be a team of specialists of neighbouring technical fields. However, in the present case, considering a pharmacologist and a formulator as suggested by the respondents, the proper "work sharing" of the team would be for the pharmacologist to identify document (4) as a promising springboard and for the formulator to look for a formulation allowing the carrying out of a therapeutic treatment. The approach adopted by the respondents can either be seen as an *ex post facto* analysis or as an approach taken by researchers of inventive skill.

(b) The respondents have argued that the skilled person, being aware that the formulation of document (1) had anti-estrogenic properties as shown by the "uterus test", would have had a high expectation of success when using this formulation for solving the technical problem. The anti-

estrogenic properties are the properties of fulvestrant that underlie its anti-breast cancer effect.

However, document (1) discloses not one but two fulvestrant formulations. Which of the two fulvestrant formulations was used in the "uterus test" is not disclosed. Furthermore, the simple fact that an active agent has been shown to retain its known activity under animal test conditions in a mechanistic study cannot be seen as an incentive for the skilled person to use such a formulation in a clinical setting.

(c) The respondents have argued that it was usual to use similar or closely related formulations in animal studies and in clinical studies. This argument is pertinent when considering preclinical animal studies carried out to assess the treatment of a disease by a certain active. However, in the present case, the situation is different since document (1) pertains to the domain of basic research far removed from preclinical situations.

In this context, it is important to stress that the absence of an expectation of success by the skilled person is (at least in part, see above) due to the fact that document (1) is a scientific paper relating to basic research. The mere fact that animal models are used cannot be seen as a deterrent for a skilled person to consider a document in the context of therapeutic treatments, such as the animal studies mentioned in document (69). The animal studies referred to in document (69), page 58, paragraph bridging the columns, relate to pharmacological effects and

anti-tumour acting in animal models, i.e. clearly to preclinical studies. However, this passage merely reports that "a variety of oil-based formulations" of fulvestrant were used.

(d) Castor oil-based fulvestrant formulations have been identified as being "prototypic" of long-acting formulations for intramuscular injection (document (34), page 245, left column). This statement is in line with the fact that document (4), i.e. the closest prior art, relies on castor oil-based fulvestrant formulations. However, no further information or pointer can be gained from the qualification of castor oil-based formulations as being "prototypic".

(e) The argument that the "The skilled person would use the formulation, because it is there" amounts to an *ex post facto* analysis. Although it sounds like a compelling and simple approach when having in mind the claimed formulation, it attains these attributes only with the knowledge of the claimed solution. According to established case law, it is necessary to identify objective factors which would have motivated the skilled person to combine the teaching of documents. Such a pointer cannot be seen in the fact that a formulation was merely disclosed.

5.6 The subject-matter of claim 1 of the patent in suit involves an inventive step and, therefore, the ground for opposition under Article 100(a) and Article 56 EPC does not prejudice the maintenance of the patent.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The oppositions are rejected.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated