Internal distribution code:
(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 10 October 2013

Case Number: T 0499/09 - 3.3.04

Application Number: 01130213.0

Publication Number: 1188444

IPC: A61K38/24, A61K47/10, A61K47/18

Language of the proceedings: EN

Title of invention:
Stable FSH and FSH variant formulations

Patent Proprietor:
Ares Trading S.A.

Opponent:
Sandoz AG

Headword:
Multi-use FSH formulations/ ARES TRADING

Relevant legal provisions:
EPC Art. 56, 114(2)
RPBA Art. 13(3)

Keyword:
Main request and auxiliary requests 2 to 6 - inventive step (no) - "try and see"
Auxiliary request 1 - inadmissible

Decisions cited:
T 1241/03, T 0380/05, T 1599/06, T 1149/09

Catchword:

Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0499/09 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 October 2013

Appellant I: (Patent Proprietor)	Ares Trading S.A. Zone Industrielle de l'Ouriettaz 1170 Aubonne (CH)
Representative:	Weiss, Wolfgang Weickmann & Weickmann Patentanwälte Postfach 86 08 20 81635 München (DE)
Appellant II: (Opponent)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Breuer, Markus Henkel, Breuer & Partner Patentanwälte Erika-Mann-Straße 23 80636 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 23 December 2008 concerning maintenance of the European Patent No. 1188444 in amended form.**

Composition of the Board:

Chairman	C. Rennie-Smith
Members:	G. Alt
	M. Montrone

Summary of Facts and Submissions

I. The appeals of both the patent proprietor (hereinafter the "appellant-patentee" and the opponent (hereinafter the "appellant-opponent") are against the decision of the opposition division by which it announced its intention to maintain the European patent EP 1 188 444 on the basis of the third auxiliary request. The patent has the title: *"Stable FSH and FSH variant formulations"*.

II. "FSH" is the abbreviation for "follicle stimulating hormone". In the present decision the term "FSH" is also used as an abbreviation for the expression "FSH and FSH variant". "M-cresol" is the abbreviation for "meta-cresol", *i.e.* 3-methylphenol.

III. The following documents are cited in the present decision:

D1 US 5,162,306

D2 WO 92/22568

D6 J. Radioanal.Nucl.Chem. Letters, 102 (2), 1986, pages 102-116, Pimpalkhute, M. et al.

D7 USP XXI; Pharmaceutic Ingredients; USP and NF Pharmaceutic Ingredients, listed by Categories; page 49

D8 Pharmaceutical Technology; May 1984; pages 36-46; Akers, Michael J.

D9 Vidal; 69e edition, 1993

D10 printout of http://home.mtekom.com/pharm/akromed/api-mj.html: "A.P.L. Injection 5000 IU. A.P.L. Injection 10 000 IU"

D11 Rote Liste 1997; pages with entries 50 003 to 50 014

D12 WO 94/03198

D13 US 4,847,079

D15 US 5,661,125

D17 WO 97/17087

D19 EP 0 853 945

D20A Remington's Pharmaceutical Sciences 18; Chapter 84; Parenteral Preparations

D22 International Journal of Pharmaceutics, 140 (1996), pages 155-168, Maa, Y.F. and Hsu, C.C.

D23 "Development of pharmaceutical parenteral dosage forms" (1977), pages 116-121; Bontempo

IV. The patent was opposed on the grounds of Article 100(a) EPC in combination with Articles 54 and 56 EPC, of Article 100(b) EPC and on the ground provided for in Article 100(c) that the subject-matter of the European patent extended beyond the content of the application as filed.

V. The opposition division rejected the **main request** because its claims 10, 11 and 20 contravened the requirement of Article 54 EPC. It rejected

auxiliary request 1 because the subject-matter of its claim 1 lacked an inventive step. Claim 1 read: *"1. A formulation comprising FSH or a FSH variant, containing an alpha and beta subunit, and a preservative which is m-cresol, in an aqueous diluent, for therapeutic use."*

The opposition division considered document D1 as the closest prior art document. It related to multi-use FSH formulations and differed from the subject-matter of claim 1 by the use of thymol instead of m-cresol as a preservative. In the absence of comparative data with thymol-containing formulations the problem to be solved was considered as the provision of alternative stable FSH formulations.

The prior art could not be considered as establishing a prejudice against the combination of FSH with m-cresol. On the one hand documents D19, D22 and D23 demonstrated that m-cresol was problematic when used in combinations with certain proteins that were structurally different from FSH. On the other hand documents D8 and D11 disclosed the use of m-cresol in commercially available insulin- and human growth hormone-containing products. Thus, the disclosure in the prior art concerning the combination of m-cresol with proteins different from FSH was conflicting. Moreover, no document explicitly raised doubts concerning the compatibility of m-cresol with FSH. The fact that document D1 disclosed that thymol was chosen from a list of usual preservatives and that this preservative was compatible with FSH did not allow the implicit conclusion that other common preservatives, as for example disclosed in document D7 and including m-cresol, would not be compatible. The skilled person would therefore turn to the usual preservatives as disclosed in documents D7 or D8. M-cresol was one of them that would be obvious to try

with a reasonable expectation of success, leading the skilled person to the claimed solution.

The opposition division did not allow **auxiliary request 2** because its claims 1 and 9 contravened the clarity requirement of Article 84 EPC. The expression *"in a single solution vial"* did not define whether the claim related to the solution as such or to the vial containing the solution. Claim 1 read: *"1. A formulation comprising FSH or a FSH variant, containing an alpha and beta subunit selected from [...] in an aqueous diluent, which is a multi-use formulation in a single solution vial for therapeutic use."*

Finally, the opposition division considered that **auxiliary request 3** with its independent claims 1 and 7 and six dependent claims complied with the requirements of the EPC. Claim 1 of auxiliary request 3 read: *"1. Use of a formulation comprising FSH or a FSH variant, containing an alpha and beta subunit, and a preservative which is m-cresol in an aqueous diluent which is a multi-use formulation, for the manufacture of a medicament for human therapeutic use, wherein the concentration of FSH or a FSH variant is 5.0 mg/ml to 200mg/ml, and wherein said FSH or FSH variant and preservative are in solution."*

The opposition division accepted an inventive step for the subject-matter of all claims of auxiliary request 3 for the following reasons. Document D11 represented the closest prior art document. It disclosed lyophilized FSH and a solvent, both without preservative and to be mixed before use. Neither of documents D1, D2, D6 or D19 could be regarded as the closest prior art document. Whereas claim 1 was restricted to human therapy, document D1 did not relate to use in humans

and moreover only disclosed multiple uses over a 4-day period which was insufficient for human therapy. Document D2 did not contain any particular information regarding the stability of FSH solutions with preservatives and only mentioned on page 27 benzyl alcohol or methyl paraben as possible preservatives. Document D6 related to radioactive FSH and addressed a different technical problem and document D19 concerned the stability of a liquid FSH solution without preservative, but not the influence of preservatives on the stability of FSH.

Consequently, in view of document D11 the problem to be solved was the provision of FSH formulations that were more convenient for administration. The subject-matter of claim 1 solved this problem in that it provided a formulation with long shelf-life and the possibility of multiple uses.

The claimed solution was not obvious in view of documents D9 and D10. Although both related to a heterodimeric protein, human chorionic gonadotropin, the preparations were two-vial products consisting of a solid and a solution, and benzyl alcohol was used as a preservative. Moreover, the product disclosed in document D10 had to be stored in the refrigerator, whereas the claimed product was stable at 23°C for 237 days.

If at all, the skilled person would have been guided by the teaching in document D10 to use benzyl alcohol as a preservative, which according to the patent had inferior properties when compared to m-cresol. There was no incentive apparent from the prior art to replace benzyl alcohol with m-cresol. Thus, m-cresol was a non-obvious alternative to benzyl alcohol.

VI. With its statement of grounds of appeal the appellant-patentee filed a new main and four auxiliary requests as well as six new documents D24 to D28. Auxiliary request 4 corresponded to auxiliary request 3 considered by the opposition division to meet the requirements of the EPC.

With its reply dated 18 November 2009 the appellant-opponent filed document D29 and argued that none of the newly filed requests fulfilled the requirements of Articles 56, 83, 84, 123(2) EPC. With regard to Article 56 EPC the appellant-opponent referred to the reasons already provided in its own statement of grounds of appeal.

VII. In its statement of grounds of appeal the appellant-opponent had argued that not only claim 1 of auxiliary request 3, but also its independent claim 7 - a claim which was not dealt with in the decision under appeal - did not comply with the requirements of Article 56, 83, 84 and 123(2) EPC.

With its reply dated 25 August 2009 the appellant-patentee filed an amended main and amended auxiliary requests 1 to 4, corresponding essentially to the requests filed with its statement of grounds of appeal, but comprising the following amendments: the addition of a comma after the word *"subunit"* in the wording *"FSH or a FSH variant, containing an alpha or beta subunit and a preservative"* - this was to overcome a combined objection under Articles 83 and 84 EPC - and the replacement of the wording in claim 7 of auxiliary request 4 *"...for the manufacture of a medicament in the treatment of infertility in a patient in need thereof, ..."* by the wording *"...for the manufacture of*

a medicament in the treatment of infertility in a ***human*** *patient in need thereof, ..."* - this was in relation to an objection under Article 56 EPC (emphasis added).

VIII. With its reply dated 3 March 2010 to the appellant-opponent's submission dated 18 November 2009 (see section VI above) the appellant-patentee filed a main and five auxiliary requests. They corresponded to the requests filed with the submission dated 25 August 2009 (see section VII above) except that in claims 1 to 5 and 10 of auxiliary request 2 the term *"multi-use"* was used to qualify the *"formulation"* or *"solution"*, respectively, instead of the *"medicament"*. Auxiliary request 5 corresponded to the main request except that the term *"multi-use"* was deleted in claims 1, 5, 9, 10, 14, 18 and 19.

IX. The board summoned the parties to oral proceedings - which both had requested on an auxiliary basis - to be held on 10 October 2013. In a letter of 24 May 2013 the appellant-opponent announced that it would not be represented, whereas the appellant-patentee notified the board by letter dated 7 June 2013 that it would be represented at the oral proceedings.

In a communication the board informed the parties that the oral proceedings would be held as scheduled and set out, issues to be dealt with at the oral proceedings in relation to inventive step, *inter alia* whether or not document D19 represented the closest prior art document. The appellant-patentee filed arguments in response to the board's communication.

X. Oral proceedings were held on 10 October 2013. The appellant-patentee was represented.

The appellant-patentee filed a new auxiliary request 1 and renumbered its previous auxiliary requests 1 to 5 as auxiliary requests 2 to 6.

Accordingly, the wording of claim 1 of each of the requests pending at the oral proceedings read as follows:

Main request: *"1. A multi-use formulation comprising FSH or a FSH variant, containing an alpha and beta subunit, and a preservative which is m-cresol, in an aqueous diluent, for human therapy."*

Auxiliary request 1: *"1. A multi-use formulation comprising FSH or a FSH variant, containing an alpha and beta subunit, and a preservative which is m-cresol, in an aqueous diluent, for human therapy, wherein the formulation further comprises a physiologically acceptable phosphate buffer."*

Auxiliary request 2: *"1. A multi-use formulation comprising about at least 85% pure FSH or an about at least 85% pure FSH variant, containing an alpha and beta subunit, and a preservative which is m-cresol, in an aqueous diluent, for human therapy."*

Auxiliary request 3: *"1. Use of a multi-use formulation comprising FSH or a FSH variant, containing an alpha and beta subunit, and a preservative which is m-cresol, in an aqueous diluent, for the manufacture of a medicament for human therapy."*

Auxiliary request 4: *"1. Use of a formulation comprising FSH or a FSH variant, containing an alpha and beta subunit, and a preservative which is m-cresol, in an aqueous diluent, for the manufacture of a*

medicament for human therapy, wherein said FSH or a FSH variant and preservative are in solution."

Auxiliary request 5: *"1. Use of a formulation comprising FSH or a FSH variant, containing an alpha and beta subunit, and a preservative which is m-cresol, in an aqueous diluent, which is a multi-use formulation, for the manufacture of a medicament for human therapeutic use, wherein the concentration of FSH or a FSH variant is 5.0 ug/ml to 20 ug/ml, and wherein said FSH or a FSH variant and preservative are in solution."*

Auxiliary request 6: *"1. A formulation comprising FSH or a FSH variant, containing an alpha and beta subunit, and a preservative which is m-cresol, in an aqueous diluent, for human therapy."*

At the end of the oral proceedings the chairman announced the board's decision.

XI. The appellant-patentee's arguments, as far as they are relevant for the present decision, may be summarized as follows:

Inventive Step (Article 56 EPC)

Document D11 was the closest prior art document. It disclosed an FSH-containing composition suitable for a single administration in human therapy. It was packaged in two vials, one containing the diluent, the other the active compound, both to be mixed immediately prior to injection and thereafter to be discarded.

The problem to be solved was the provision of an FSH-containing formulation that was suitable for multiple

administrations in human therapy, that was therefore protected against microbial infection and that maintained biological activity during the length of the treatment cycle. The solution to this problem according to the claims was an FSH-containing formulation comprising m-cresol as a preservative.

The required treatment period with FSH, for example in the course of an infertility treatment, was 7 to 14 days. Thus, there was a need for a multi-use FSH formulation.

The skilled person knew that (a) regulatory authorities required preservatives to be encompassed in multi-use formulations (see document D20A), (b) preservatives generally had a destabilizing effect on proteins due to their properties as partly surface-active molecules and partly organic solvents (see documents D22 or D23), and (c) in general proteins tended to be more unstable at low concentrations and that this was in particular so with heterodimeric proteins such as FSH where the two subunits were held together by weak non-covalent bonds.

At the priority date of the patent, and in the more than 30 years before that date, commercially available FSH-formulations had been provided only as single-dose formulations without preservative in the form of a lyophilized substance for immediate reconstitution with sterile solvent prior to each use and with any potentially remaining solution to be discarded after use. During the same period of time a product structurally similar to FSH, human chorionic gonadotropin, had been marketed as a preparation including a preservative, namely benzyl alcohol. It could only be concluded from these circumstances that the skilled person would not have attempted at all to

provide the urgently needed FSH multi-use formulation because he or she had considered that the exposure of FSH to the destabilizing effects of preservatives would result in a therapeutically useless FSH.

The skilled person's view would not have been changed by the disclosure in document D2 - the allusion on page 27 to *"multiple dose vials"* was of a completely theoretical nature - or in document D19 on page 5 which related to a special device for multi-use administration (*"pen-type injector"*) which device would in principle work without a preservative and moreover the formulation included a special buffer, *i.e.* one containing a polycarboxylic acid or salt thereof, such as sodium citrate (page 3, lines 15 to 23).

If the skilled person had attempted to provide an FSH multi-use formulation, he or she knew that generally there was only a small number of preservatives available (and authorized) for use in human therapy, but that reliable predictions of a particular preservative's destabilising effect on a particular protein in a formulation, *i.e.* predictions about which protein-preservative combination was good, could not be made. Therefore, the skilled person would not have proposed the combination of FSH with m-cresol in an obvious manner.

If the skilled person would have envisaged making predictions and therefore would have, for example, sought inspiration from other preservative-containing protein formulations, he or she would not have turned to those containing, for example, insulin or human growth hormone because these proteins were monomeric proteins *i.e.* structurally completely different from FSH. Moreover, m-cresol was the second worst of the

tested preservatives for human growth hormone formulations (see abstract of document D22) and the stabilizing effects of m-cresol on insulin were due to specific spatial interactions which were not present in other proteins. Rather the skilled person would have turned to formulations which contained heterodimeric, non-covalently bound proteins, as for example gonadotropins, which were structurally related to FSH and approved for human therapy, in particular human chorionic gonadotropin. Benzyl alcohol or phenol and not m-cresol were used in these formulations (see document D10).

Finally, and as it was surprisingly shown in the patent, m-cresol was superior to benzyl alcohol as a preservative in an FSH-containing formulation.

For all these reasons, an inventive step for the subject-matter of claim 1 had to be acknowledged.

Auxiliary request 1

Admissibility

Although filed only at the oral proceedings in response to the board's decision that claim 1 of the main request lacked an inventive step, this request should be admitted, because the newly added feature *"wherein the formulation further comprises a physiologically acceptable phosphate buffer"* overcame the reasons why the board had found that claim 1 of the main request lacked an inventive step.

Auxiliary requests 2 to 6

Inventive step (Article 56 EPC)

Arguments in addition to those provided with respect to the main request were not submitted with regard to these requests.

XII. The appellant-opponent's arguments, as far as they are relevant for the present decision, may be summarized as follows:

Inventive Step (Article 56 EPC)

The closest prior art document was either document D1 or D2. Document D1 disclosed a multi-use formulation containing FSH and thymol as a preservative. Document D2 disclosed multi-use formulations containing FSH and suggested to add benzyl alcohol or methyl paraben as preservatives.

Since no effect was provided by replacing thymol, benzyl alcohol or methyl paraben with m-cresol the problem to be solved was the provision of an alternative FSH-containing formulation which was suitable for multiple uses.

The long time period during which FSH had been commercialized only as a single-dose medicament was not an indication that the skilled person would have considered that it was not feasible to use any of the common preservatives for providing a stable multi-use formulation of FSH. There might also be other reasons for the long-term absence of a product from the market. Besides, documents D2 and D19 suggested the generation of multi-use FSH-containing formulations.

The skilled person knew for example from document D8 that for obtaining marketing authorisation for a multi-use product a preservative had to be mandatorily included in the formulation and moreover that the number of preservatives that were available to be included into a formulation for human use was rather limited. Documents D7 and D8 disclosed such preservatives and m-cresol was amongst them. In fact, m-cresol was among the preservatives most often used in commercial products (see document D20A, page 1550, left-hand column and document D8, Table III). Documents D12, D15 and D17 disclosed combinations of human growth hormone, erythropoietin and nerve growth factor with m-cresol. Thus, m-cresol was a potential candidate for inclusion in a FSH-containing solution. And if the skilled person would not have been inspired by prior art preparations, he or she would have established the actual utility of m-cresol by routine experimentation, *i.e.* the skilled person would have tested the few candidates and seen that m-cresol (as well as others) was suitable. According to established case law, as for example decision T 1599/06 such an approach was not consistent with an inventive step.

The patent did not establish that m-cresol was superior to phenol or benzyl alcohol because the shelf-life of products containing chorionic gonadotropin was compared to that of products with FSH, *i.e.* formulations of different products were compared.

XIII. Requests

The appellant-patentee requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed with

the letter dated 3 March 2010 or on the basis of the new auxiliary request 1 filed during the oral proceedings or on the basis of auxiliary requests 2 to 6 filed as auxiliary requests 1 to 5 with the letter of 3 March 2010.

The appellant-opponent requested in writing that the decision of the opposition division be set aside and that the patent be revoked.

Reasons for the Decision

Main request

1. In view of its decision regarding the requirements of Article 56 EPC, decisions on any of the other grounds of opposition raised in the present proceedings need not be taken.

Inventive Step (Article 56 EPC)

2. For assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the Boards of Appeal of the European Patent Office apply the "problem and solution" approach, a practice to which the board adheres in the present case (Case Law of the Boards of Appeal 6th edition 2010, I.D.2).

This approach involves as a first step identifying the closest prior art which normally is a document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention. A secondary criterion is the commonality of technical features (Case Law of the Boards of Appeal 6th edition 2010, I.D.3.1). As for the determination of

the disclosure content of any document, it is made by taking account of the skilled person's understanding of the information content of a document as a whole (Case Law of the Boards of Appeal 6th edition 2010, I.C.2.1, second paragraph).

The invention

3. The present invention is directed to a pharmaceutical formulation comprising FSH or a FSH variant. In its ready-to-use form the aqueous formulation is protected against microbial contamination by the preservative m-cresol and is therefore suitable for multiple uses. According to the patent, paragraph [0002], FSH-containing formulations are used in the course of the treatment of infertility, for example by inducing superovulation for assisted conception (see also document D11, for example entries Nos. 50 004 and 50 005).

The closest prior art

4. The appellant-patentee considered document D11 and the appellant-opponent either document D1 or document D2 as the closest prior art document.

Document D11 is an extract from the the so-called *"Rote Liste"* of the year 1997, an index of pharmaceutical preparations registered in Germany in that year. It discloses as entry numbers 50 004 and 50 005 the commercially available, FSH-containing products *"Fertinorm HP 75"* and *"Fertinorm HP 150"* as well as *"Gonal-F 75"* and *"Gonal-F 150"*. The products are packaged in two ampoules, one containing the active substance in dry form and the other containing a solvent. It is undisputed that prior to their

administration the products are to be reconstituted, that only a single dose is to be drawn from the vial with the reconstituted product and that any reconstituted, non-used product is to be discarded.

Both documents D1 and D2 disclose or suggest FSH compositions containing preservatives, but this is not the main teaching that the skilled person would derive from these documents. Document D1, a US patent, teaches that formulations containing FSH and luteinizing hormone in a particular ratio produce optimal superovulation. Document D2, an international patent application, teaches the regions in, for example, FSH that are responsible for luteinizing hormone and FSH receptor binding and that it is possible to provide FSH with altered receptor binding affinity and specificity by making modifications in these regions.

In the board's view, the disclosure in document D11, and not that in documents D1 and D2, is related to the effect to be achieved by the present invention, because the FSH preparations disclosed in document D11 are prevented from microbial contamination by their administration regimen, *i.e.* they are formulations foreseen for a single use. Therefore, the board considers that among the three documents referred to, document D11 represents the closest prior art.

Problem and solution

5. Treatment with FSH generally requires multiple administrations. For a common infertility treatment administrations for a period of about 7 to 14 days are necessary (see for example the patent, paragraph [0002]). Thus, using the two-vial products disclosed in document D11 requires, firstly, reconstituting the

dried product with the diluent before each use, and secondly, discarding the vial with the left-over solution after each use. These are circumstances which could be considered as undesirable, especially for patients who are self-dosing at home, because reconstitution is inconvenient and may lead to dosage errors resulting in undesirable consequences for the treatment.

Thus, in the light of document D11 the problem to be solved is to simplify the treatment with FSH-containing formulations.

According to claim 1 the solution to this problem is the provision of an aqueous multi-use formulation comprising FSH or FSH variant and m-cresol as a preservative.

Obviousness

6. Two main questions arise in this context in view of the appellant-opponent's argumentation. The first is whether or not the skilled person would have been motivated to provide FSH as an aqueous multi-use formulation and the second is whether or not the skilled person would have been motivated to include m-cresol as a preservative into such a multi-use formulation.

Provision of a multi-use formulation

7. It is undisputed that in view of the necessary administration regimen of several consecutive applications for up to 14 days based on his or her general knowledge the skilled person would have considered a multi-use formulation as a solution to the

problem underlying the present invention (see in particular section XI above).

8. However, the appellant-patentee argues that the skilled person would not have been motivated to put this theoretically conceived solution into practice. The skilled person knew that (i) regulatory authorities required a multi-use formulation to contain a preservative, (ii) preservatives generally had a destabilizing effect on proteins due to their properties as partly surface active molecules and partly organic solvents and (iii) proteins tended generally to be unstable at low concentrations and that this concerned in particular heterodimeric proteins such as FSH where the two subunits were held together by non-covalent bonds. Therefore, the skilled person would have considered that the combination of FSH with a preservative would result in inactive, *i.e.* therapeutically useless, FSH. Evidence that this was indeed the skilled person's perception was apparent, on the one hand, from the fact that at the priority date, and in the more than 30 years before this date, commercially available FSH-formulations had always been provided only as single-dose formulations without preservative while, on the other hand, during the same period of time another structurally related heterodimeric protein, namely chorionic gonadotropin, had been marketed as a multi-use preparation including benzyl alcohol or phenol as a preservative.

8.1 With regard to this line of argument the board notes that there is no explicit evidence on file showing either that the skilled person assumed it to be impossible to provide therapeutically active FSH in the presence of a preservative or that the reason for the absence of multi-use FSH-formulations from the market

was in fact the skilled person's perception that such formulations could not be made because FSH would be de-activated in the presence of any preservative.

The board considers that the long time period during which only FSH single-dose preparations were commercially available but during which preparations with structurally related proteins were marketed as multi-dose preparations including a preservative cannot necessarily be considered as an implicit indication that the skilled person would have considered that FSH was too unstable to be used in a preservative-containing, multi-use preparation or that the skilled person would encounter other obstacles when attempting to make it into a multi-use preparation. This is so because the reasons for which the dosage format of a commercially available medicament remains unchanged for a long time may be unrelated to properties of the product. Possible reasons may be, for example, of an economic nature, namely the manufacturer's wish to retain its existing production facilities or not to get involved in regulatory issues related to the change of an already approved formulation.

8.2 Thus, the board comes to the conclusion that at the priority date the circumstances depicted in point 8.1 above would not have deterred the skilled person from attempting to make a multi-use FSH-containing formulation.

9. Given this conclusion and that it is undisputed that the skilled person would have considered a multi-use formulation as a desirable solution to the problem underlying the present invention (see point 7 above), whether or not the teaching in documents D2 or D19

suggested the preparation of multi-use FSH-containing formulations is not decisive.

10. Hence, at the priority date of the patent the skilled person would have been motivated to provide a multi-use FSH-containing formulation as a solution to the problem formulated in point 5 above.

M-cresol as a preservative

11. The presence of a preservative is required in aqueous multi-use formulations in order to protect the formulation from inadvertent bacterial or fungal contamination while withdrawing a portion of the contents of the vial (see for example document D8, page 36, first full sentence of second column to third column; document D20A, page 1550, first column, first sentence; or document D23, page 116, under "H. Antimicrobials (Preservatives)"). In view of their function, preservatives are necessarily chemically very reactive compounds. Yet, their reactivity does not differentiate between the micro-organisms to be inactivated and the ingredients in the formulation, such as the therapeutically active product. Therefore, as noted above, preservatives tend to destabilize the therapeutic proteins in aqueous formulations and thus may have a negative effect on their activity.

12. As to the compounds used as preservatives in general, and in particular in pharmaceutical preparations for human use, the following evidence is available.

Under the heading *"Antimicrobial Preservative"* document D7 lists 24 different compounds amongst them *"Cresol"*.

Document D8 lists in Table III phenol, benzyl alcohol, chlorobutanol, benzalkonium chloride, thimerosal, phenylmercuric nitrate and acetate, parabens and also m-cresol as preservatives which are used in about 120 different commercially available parenteral products.

Document D12 mentions multiple-use packaging of human growth hormone and states on page 6, second paragraph: *"Preservatives include phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben benzalconium chloride, and benzethonium chloride."*

Document D15 states in relation to pharmaceutical preparations containing erythropoietin in column 6: *"Concerning the use of phenol as a preservative, it may be used in amounts ranging [...]. Other derivatives of phenol, in addition to the ones mentioned above, also may be used as preservatives. As examples of such derivatives, metacresol (m-cresol) and chlorocresol are used in compositions shown below [...]."*

Document D17 discloses in the paragraph bridging pages 4 and 5 about preservative-containing nerve growth factor formulations: *"Suitable preservatives include those known in the pharmaceutical arts. Benzyl alcohol, phenol, m-cresol, methylparaben and propylparaben are preferred preservatives."*

Document D20A discloses on page 1550 in the first paragraph with regard to antimicrobial agents contained in multiple-dose containers: *"Among the compounds most frequently employed with the concentration limits prescribed by the USP, are: Phenylmercuric nitrate and thimerosal 0.01%. Benzethonium chloride and benzalkonium chloride 0.01%; Phenol or cresol 0.5%. Chlorobutanol 0.5%."*

Document D22 discloses in its first paragraph: *"In pharmaceutical protein development, antimicrobial preservative agents such as phenol, m-cresol, methylparaben, and resorcinol, are often added to liquid formulations to ensure its sterility during shelf life and multiple use."*

Document D23 mentions on page 116 under the heading *"H. Antimicrobials (Preservatives)"* in relation to the development of multi-dose formulations: *"The most common preservatives used in pharmaceuticals and biopharmaceutical injectable products are phenol, benzyl alcohol, chlorobutanol, metacresol, and parabens."*

It appears that only one of the relevant documents available to the board, document D13, discloses that cresol was not included in assays testing 28 preservative compounds for compatibility with an interferon-containing preparation (see Table 1).

12.1 The board concludes that at the priority date of the present patent there was only a limited number of preservatives used in pharmaceutical or biopharmaceutical products destinated for use in human therapy (see also document D8, page 37, first column, first paragraph). M-cresol was one of them.

13. The interplay between a particular preservative and a particular formulation (which often contains constituents in addition to the therapeutic protein) and thus the nature and degree of reactivity, is characteristic for each preservative-formulation combination. Thus, there are preservatives which are better suited for one particular formulation than

others. The appellant-patentee argues that the skilled person had no means to make any valuable predictions as to the suitability of a particular preservative for a particular formulation. The absence of any hints or the possibility of any rational predictions had the consequence, in its view, that the combination of m-cresol with FSH had to be considered as non-obvious.

13.1 There is in fact ample evidence on file demonstrating that the skilled person would not have selected a preservative on the basis of "predictions", *i.e.* theoretical considerations, such as for example, known physico-chemical properties of the preservative or compounds in the formulation or extrapolations from other multi-use formulations even if they contained structurally similar proteins. However, in the board's view, the same evidence also demonstrates what the skilled person's normal approach to finding a suitable preservative was, *i.e.* he or she would have carried out routine experiments with the limited number of available preservatives in order to find a suitable one.

The following is stated in documents D8, D13, D15 and D20A:

Document D8, page 46, first column, fourth full paragraph: *"In the development stages of a parenteral product formulation, however, there is the need to assess the efficacy of various preservative system possibilities rapidly and economically. Several screening methods have been described in the literature."*

Document D13, last paragraph of column 1, first and last paragraph of column 2: *"Various preservatives and preservative combinations have been tested,[...]. [...]"*

Document D15, column 4, last full paragraph: *"The examples show aspects of the invention and include results of stability testing and microbial challenge [...]."*

Document D20A, page 1550, first column, third paragraph: *"Antimicrobial agents must be studied with respect to compatibility with all other components of the formula. In addition, their activity must be evaluated in the total formula. It is not uncommon to find that a particular agent will be effective in one formulation but ineffective in another."*

14. There are cases where the Boards of Appeal considered claimed subject-matter as non-obvious because it could not be "predicted" and therefore there was no reason to expect that what was claimed was a solution to the problem posed.

There are other cases, however, where the lack of predictability or the lack of reasons for expecting success that a certain technical effect would be achieved did not have the consequence that the claimed subject-matter was held to be non-obvious by the Boards. This was so, for example, when the skilled person was considered to be in a "try and see" situation. Such a situation had occurred if, in view of the teachings in the prior art, the skilled person had envisaged a group of compounds and then determined by routine tests which of those had the desired effect (Case Law of the Boards of Appeal, 6th edition 2010,

I.D.6, paragraphs 6 and 7 and additionally, for example, decisions T 1241/03, points 30 and 31 of the reasons; T 380/05, point 8.5 of the reasons; T 1599/06, point 20.2 of the reasons; T 1149/09, point 27 of the reasons).

14.1 In the light of the case law and given the circumstances of the present case the board considers that in the present case the skilled person is in a "try and see" situation.

There is a number of potentially suitable compounds - and even a relatively small one; they are all known to have a preservative activity; and there are routine tests to determine the compound which is most suitable for the given FSH formulation (points 12 and 13 above).

There is no evidence on file indicating that the skilled person would have considered not to find a preservative for the FSH-containing formulation among the ones normally used (see point 8.1 above) or that he or she would generally not have included m-cresol in the preservatives to be tested (see point 12 above).

Moreover, in the present case, the available prior art shows that the selection of suitable preservatives for pharmaceutical formulation is in fact an empirical exercise (see point 13 above), which demonstrates that the skilled person would be motivated to follow a "try and see" approach.

Thus, in conclusion, by carrying out routine testing, the skilled person would have identified in an obvious manner m-cresol as a preservative compatible with FSH or a FSH variant-containing formulation.

15. In these circumstances, and assuming in the appellant-patentee's favour that m-cresol would be more suitable than benzyl alcohol, this superiority of m-cresol is not an effect which could justify the finding of non-obviousness because, if the skilled person works according to a "try and see" approach, such a superior property cannot be considered as "surprising" or "unexpected", but is a inevitable result of the skilled person's course of action.

16. Hence, the subject-matter of claim 1 of the main request is obvious and therefore does not involve an inventive step. The main request does not fulfil the requirements of
Article 56 EPC.

Auxiliary request 1

Admissibility

17. This request was submitted during the oral proceedings as a reaction to the board's decision on the main request. It is therefore to be considered as "late-filed" and consequently its admissibility is an issue to be assessed (Article 114(2) EPC; Article 13(3) RPBA).

Claim 1 of auxiliary request 1 differs from that of the main request in that at the end of the claim the feature *"wherein the formulation further comprises a physiologically acceptable phosphate buffer"* is added.

In deciding on the admissibility of this new request, the board has in the first place taken into account whether or not an inventive step could *prima facie* be accepted for the amended subject-matter.

18. The board was not persuaded by the appellant-patentee's submission that the feature regarding the use of a phosphate-buffer in an FSH-containing preparation would justify the acknowledgement of an inventive step. The board considers that (i) phosphate buffers are one of the most frequently employed buffers in aqueous therapeutic formulations (see for example document D7, under the heading "Buffering Agent"; document D20A, page 1550, first column, *"Buffers"*); that (ii) solvents of commercialized, single-dose FSH products contained phosphate ions (see document D11, item 50 005 *"Gonal F"* where the solvent includes *"Natriummono-hydrogenphosphat, Natriumdihydrogenphosphat, Phosphorsäure"*); that (iii) although document D19 discloses citrate as a stabilizer of, *inter alia*, FSH-containing solutions, it is not derivable from the overall teaching of this document that phosphate buffers would be incompatible with FSH-containing preparations; and that finally (iv) there is no evidence of any surprisingly advantageous properties arising from the presence of a phosphate buffer in the FSH formulation.

19. Thus, the board decided not to admit auxiliary request 1 into the proceedings.

Auxiliary requests 2 to 6

Inventive step (Article 56 EPC)

20. These requests had been filed during the written proceedings as auxiliary requests 1 to 5. The appellant-patentee has not made any submissions either during the written proceedings or at the oral proceedings explaining why the amendments, in

particular to claim 1 of any of these requests (for their wording see section X above), generated subject-matter for which, in contrast to the subject-matter of claim 1 of the main request, an inventive step should be acknowledged. *Prima facie* the board cannot see any such reasons and therefore concludes that the subject-matter of claim 1 of each of auxiliary requests 2 to 6 lacks an inventive step for the same reasons as claim 1 of the main request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith

G. Alt
(as foreseen by
Article 8(3) RPBA)

Decision electronically
authenticated