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**Datasheet for the decision
of 12 September 2017**

Case Number: T 0227/14 - 3.3.07

Application Number: 04725385.1

Publication Number: 1610822

IPC: A61K47/10, A61K38/24

Language of the proceedings: EN

Title of invention:

Liquid pharmaceutical formulations of FSH and LH together with a non-ionic surfactant

Patent Proprietor:

ARES TRADING S.A.

Opponent:

Ferring B.V.

Headword:

Formulations of FSH/ARES

Relevant legal provisions:

EPC Art. 123(2), 54(2), 83, 56

Keyword:

Late-filed evidence - admitted (yes)

Amendments - allowable (yes)

Sufficiency of disclosure - (yes)

Novelty - (yes)

Inventive step - (yes)

Decisions cited:

T 0488/16



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Case Number: T 0227/14 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 12 September 2017

Appellant: Ferring B.V.
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted on
28 November 2013 concerning maintenance of the
European Patent No. 1610822 in amended form.

Composition of the Board:

Chairman D. Boulois
Members: A. Usuelli
Y. Podbielski

Summary of Facts and Submissions

- I. European patent No. 1 610 822 was opposed on the grounds that its subject-matter lacked novelty and inventive step (Article 100(a) EPC), was not sufficiently disclosed (Article 100(b) EPC) and extended beyond the content of the application as filed (Article 100(c) EPC).

The following documents were among those cited during the first-instance proceedings:

D5: EP 974359

D10: Report dated 19 September 2011 by CR-competence

D18: EP 853945

D20: Luveris - Summary of product characteristics

D23: Experimental report 50269

D29: Report with Tables 1a, 1b, 2a, 2b

D34: Declaration by A. Del Rio and annexed report

- II. By a decision posted on 28 November 2013, the opposition division found that the patent, on the basis of the main request filed on 24 July 2013, met the requirements of the EPC. Claim 29 of this request was amended during the oral proceedings, held on 17 October 2013, to correct an obvious error.

Independent claims 1, 2, 3, 9, 10, 11, 33, 34, 35 of the main request before the opposition division read as follows:

"1. A liquid pharmaceutical composition comprising follicle-stimulating hormone (FSH) or a variant thereof, as well as a surfactant which is Poloxamer 188 and further comprising methionine, a bacteriostatic agent selected from phenol and m-cresol, and sucrose."

"2. A liquid pharmaceutical composition comprising follicle-stimulating hormone (FSH) or a variant and luteinising hormone (LH) or a variant thereof, as well as a surfactant which is Poloxamer 188 and further comprising methionine, a bacteriostatic agent selected from phenol, m-cresol, and sucrose."

"3. A liquid pharmaceutical composition comprising luteinising hormone (LH) or a variant thereof, as well as a surfactant which is Poloxamer 188 and further comprising methionine, a bacteriostatic agent selected from phenol and m-cresol, and sucrose."

"9. An article of manufacture comprising a freeze-dried formulation comprising follicle-stimulating hormone (FSH) or a variant thereof, a surfactant which is Poloxamer 188 as well as methionine and sucrose, the article of manufacture further comprising a solvent for reconstitution containing a bacteriostatic agent selected from phenol and m-cresol."

"10. An article of manufacture comprising a freeze-dried formulation comprising luteinising hormone (LH) or a variant thereof, a surfactant which is Poloxamer 188 as well as methionine and sucrose, the article of manufacture further comprising a solvent for reconstitution containing a bacteriostatic agent selected from phenol and m-cresol."

"11. An article of manufacture comprising a freeze-dried formulation comprising follicle-stimulating hormone (FSH) or a variant thereof as well as luteinising hormone (LH) or a variant thereof, a surfactant which is Poloxamer 188 as well as methionine and sucrose, the article of manufacture further

comprising a solvent for reconstitution containing a bacteriostatic agent selected from phenol and m-cresol."

"33. A method for manufacturing a pharmaceutical composition comprising the step of forming a solution of FSH, a surfactant which is Poloxamer 188 and a liquid diluent and further adding methionine, a bacteriostatic agent selected from phenol and m-cresol, and sucrose."

"34. A method for manufacturing a packaged pharmaceutical composition comprising placing a solution comprising FSH, a surfactant which is Poloxamer 188 and further placing methionine, a bacteriostatic agent selected from phenol and m-cresol, and sucrose, in a vial, ampoule or cartridge."

"35. A method for manufacturing an article of manufacture according to any of claims 9 to 11, comprising the step of forming a mixture of FSH with or without LH, or LH alone as well as a surfactant which is Poloxamer 188 adding methionine and sucrose, and subjecting the mixture to a lyophilisation, and providing a solvent for reconstitution containing a bacteriostatic agent selected from phenol and m-cresol."

III. In its decision, the opposition division held that the subject-matter of the main request complied with the requirements of Article 123(2) EPC and sufficiency of disclosure, and was novel over the disclosure of document D5.

As to inventive step, the opposition division considered that D18 was the closest prior art. This

document disclosed liquid gonadotrophin formulations containing the surfactant Tween 20, whereas the formulations defined in the main request contained Poloxamer 188 as surfactant. The formulations of the main request differed from those of D18 also in the presence of a preservative agent selected from phenol and m-cresol. The objective technical problem was the provision of a gonadotrophin formulation containing a preservative and stable for a long time. The skilled person would have considered adding a preservative agent such as phenol or m-cresol to the compositions of D18. However, as shown by the data submitted by the patent proprietor, these substances were not compatible with Tween-20 and there was no suggestion in the prior art to replace Tween-20 with Poloxamer-188 in order to overcome this problem. Thus, the main request complied with the requirement of Article 56 EPC.

- IV. The opponent (hereinafter: the appellant) lodged an appeal against that decision, requesting that the decision be set aside and the patent be revoked.

- V. By letter dated 6 August 2014, the patent proprietor (hereinafter: the respondent) requested that the appeal be dismissed and that the patent be maintained on the basis of the main request maintained by the opposition division or, alternatively, that the patent be maintained on the basis of one of three auxiliary requests submitted with the same letter. The respondent also filed the following document with the reply to the appeal:

D43: Experimental report N°51150

- VI. With letter dated 30 March 2015, the appellant submitted the following evidence:

D44a-d: Four CD-ROMs containing a video documenting an experimental report

VII. In a communication pursuant to Article 15(1) RPBA issued on 11 July 2017, the Board *inter alia* expressed the opinion that the late-filed evidence D44a-d was not admissible.

VIII. Oral proceedings were held on 12 September 2017.

IX. The appellant's arguments, as far as they are relevant for the present decision, can be summarised as follows:

(a) Admissibility of document D43

The appellant had already pointed out during the first-instance proceedings that the experiments conducted by the respondent were defective in various ways. By filing the experimental report D43 the respondent was trying to respond to these objections. However, this should have already been done during the first-instance proceedings. Document D43 was therefore not admissible.

(b) Article 123(2) EPC

The specific combination of substances included in the pharmaceutical compositions defined in the main request could not be derived from the application as originally filed. Accordingly, the requirement of Article 123(2) EPC was not met.

(c) Sufficiency

The patent did not provide any indication as to the conditions for preparing formulations that did not present problems of turbidity. Thus, the skilled person was not enabled to provide compositions according to

the main request that were suitable as pharmaceutical products.

(d) Novelty

Claim 4 of document D5, referring back to claims 1 to 3, defined formulations comprising FSH that anticipated the subject-matter claimed in the main request.

(e) Inventive step

In accordance with the statement of paragraph [0058] of the patent, Poloxamer 188 was used in the formulation of claim 1 as surfactant in order to avoid the problems of turbidity which occurred when the surfactant Tween-20 was used in combination with a bacteriostatic agent. However, the original application did not contain any experimental data in support of this effect. There was also no evidence that formulations containing a bacteriostatic agent and Tween-20 had problems of turbidity. On the contrary, the experiments of the appellant (documents D10 and D29) indicated that the solutions containing Tween-20 did not present any such problems. This was in line with the information disclosed in D20 that the commercial product Luveris, containing luteinising hormone, was a clear and colourless solution. It was not plausible on the basis of the experimental data contained in the original application that using Poloxamer 188 instead of Tween-20 had the effect of avoiding problems of turbidity.

It followed from decision T 488/16 that post-published evidence could not be taken into account as substantiating a technical effect if such effect was not at least plausible on the basis of the original application. Thus, the respondent's experiments disclosed in documents D23, D34 and D43 were to be

disregarded. The data reported in these experiments were in any case inconsistent, so that they did not support the effects alleged by the respondent regarding reduced turbidity.

Document D18 could be regarded as the closest prior art. The formulations of the main request differed from the formulations of D18 mainly in the presence of a bacteriostatic agent selected from phenol and m-cresol and in the presence of the surfactant Poloxamer 188. Document D5 suggested the use of both phenol and m-cresol as bacteriostatic agent (claim 2) and the use of Poloxamer 188 as additive (paragraph [0081]). Thus, the subject-matter of the main request was obvious in view of the combined teachings of D18 and D5. The same conclusion applied when starting from D5 as the closest prior art. The formulation of the main request was comprised in the general disclosure of this document. In the absence of any particular technical effect this formulation was an obvious selection within the teaching of D5.

X. The respondent's arguments, as far as they are relevant for the present decision, can be summarised as follows:

(a) Admissibility of document D43

Experimental report D43 had been submitted by the respondent in order to address some observations made by the appellant in the grounds of appeal in relation to the previous experiments.

(b) Article 123(2) EPC

The formulation defined in claim 1 was based on the disclosure of original claim 1 in combination with the disclosures of original claims 26, 29 and 30 which referred back to claim 1.

(c) Sufficiency

The experimental data reported in table 8 of the patent showed that the formulation according to claim 1 was clear and stable. This had been confirmed by the additional experiments submitted by the respondent. The requirement of sufficiency of disclosure was met.

(d) Novelty

Document D5 did not disclose any formulation containing the same combination of ingredients as the formulation of claim 1 of the main request. The requirement of novelty was therefore met.

(e) Inventive step

The formulations of the main request differed from the formulation of example 2 of D18 in that a bacteriostatic agent was present and in that they contained Poloxamer-188 as surfactant instead of Tween-20. As observed in example 1 of the patent, formulations containing Tween-20 and a bacteriostatic agent were turbid. In contrast, example 7 of the patent showed that a composition according to claim 1 was stable and clear. Thus, the technical effect underlying the invention, namely reducing the problems of turbidity, was made plausible in the application as originally filed. The situation in the present case was therefore very different from that of case T 488/16. Thus, also the experiments disclosed in documents D23, D34 and D43 could be taken into account in the assessment of inventive step. These experiments showed that in contrast to formulations containing Tween-20 and a bacteriostatic agent, the formulations according to the main request did not present problems of turbidity. The skilled person would have considered adding a bacteriostatic agent to the composition of

D18. However, this would have caused a turbidity problem due to the presence of Tween-20. None of the prior-art documents suggested replacing Tween-20 with Poloxamer-188 in order to avoid these turbidity problems.

XI. The appellant requested that the decision under appeal be set aside and that the patent be revoked. It also requested that document D43 not be admitted into the appeal proceedings.

XII. The respondent requested that the appeal be dismissed, or alternatively that the patent be maintained on the basis of one of the three auxiliary requests filed on 6 August 2014 with the reply to the appeal; it also requested not to admit D44a-d into the appeal proceedings, or, if admitted, that the case be remitted to the opposition division.

Reasons for the Decision

1. Admissibility issues

1.1 The appellant contests the admissibility of document D43, an experimental report submitted by the respondent with the reply to the appeal, arguing that this document should have already been submitted during the first-instance proceedings.

In its submissions of 9 March 2015, the respondent explains that D43 was filed in response to the criticisms of experimental reports D23 and D34 expressed by the appellant in the statement setting out the grounds of appeal.

1.2 The Board notes that according to the appealed decision, the appellant had apparently already contested these experimental reports during the proceedings before the opposition division (points 14 and 21 of the decision). However, whereas during the proceedings before the opposition division it argued that methionine had no effect on the turbidity of the solutions (point 14), in the grounds of appeal it remarked that methionine was not present in the solutions tested although it is mentioned in the claims.

Hence, the filing of D43 is to be regarded, in the Board's view, as a reaction on the part of the respondent to the new arguments put forward by the appellant in the grounds of appeal.

1.3 Moreover, the Board observes that the experimental results reported in D43 are in line with the results disclosed in the patent and in the reports submitted by the respondent during the first-instance proceedings, namely D23 and D34. Hence, the submission of D43 does not result in the introduction of a new line of argument.

1.4 Document D43 is therefore admitted into the appeal proceedings.

1.5 In its communication of 11 July 2017, the Board expressed the opinion that the late-filed evidence D44a-d was not admissible. During the oral proceedings the appellant stated that it no longer wished to rely on this evidence. The video documentation D44a-d is therefore not part of the appeal proceedings.

Main request (request maintained by the opposition division)

2. Article 123(2) EPC

2.1 The subject-matter of claim 1 is based on the combination of original claim 1 with original claims 30 (presence of methionine), 26 (presence of phenol or m-cresol) and 29 (presence of sucrose). Furthermore, the list of four surfactants included in original claim 1 has been limited to Poloxamer-188 (also named Pluronic-F68, see page 12, line 31 of the application) which is the preferred surfactant and is included in most of the compositions exemplified in the description (see third and fourth complete paragraphs of page 12 and Tables 1 to 7 of the original application).

2.2 The Board notes that methionine and sucrose are mentioned as preferred components of the formulation also on page 23 of the original description (lines 7 and 16). Phenol and m-cresol are described as the more preferred bacteriostatic agents on page 18 (line 9). Furthermore, several formulations disclosed in the original application (see Tables 3 to 7) contain the combination of ingredients listed in claim 1.

The specific combination of ingredients of the composition of claim 1 is therefore based on the preferred embodiments and examples of the original application. Thus, claim 1 does not contain subject-matter extending beyond the content of the application as filed.

2.3 The appellant did not substantiate any specific objection under Article 123(2) EPC to the remaining claims of the main request. It remarked however that all the independent claims related to formulations

comprising the combination of several components or to methods for preparing these formulations.

The Board observes that all the independent claims refer to compositions containing the same components included in the formulation of claim 1. For the reasons explained in points 2.1 and 2.2 above, the combination of these components can be derived directly and unambiguously from the application as filed.

3. Sufficiency of disclosure

3.1 The appellant essentially argues that the patent does not provide any indication as to the conditions for preparing formulations that do not present problems of turbidity. In its view, a turbid formulation would not be suitable as a pharmaceutical product, as required by claim 1.

3.2 In this regard the Board notes that the description of the patent explains that turbidity occurs when the formulations contain the surfactant Tween-20 in combination with m-cresol or phenol as bacteriostatic agents (paragraph [0058]). This problem is solved in the patent in suit by using Poloxamer-188 instead of Tween-20 as a surfactant.

Table 8 of the patent shows that the formulation of example 5, which is included in claim 1 of the main request, is free of visible particles. This experiment demonstrates therefore that using Poloxamer-188, as taught in the description of the patent, makes it possible to avoid problems of turbidity.

The appellant's argument is therefore unconvincing. Consequently, the ground for opposition based on

Article 100(b) EPC does not prejudice the maintenance of the patent on the basis of the main request.

4. Novelty

4.1 The appellant has raised an objection of lack of novelty on the basis of claim 4 of document D5.

4.2 The combination of this claim with claims 1 to 3, on which it depends, defines a formulation comprising FSH or an FSH variant, a preservative agent which can be phenol or m-cresol and an isotonicity agent. Paragraph [0040] of D5 indicates that suitable isotonicity agents are for instance methionine and sucrose.

4.3 Thus, the formulations of the main request differ from the composition defined in claim 4 of D5 at least in the requirement of containing Poloxamer-188. This substance is mentioned in paragraph [0081] of D5 in a list of additives that may optionally be included in the formulation. However, D5 fails to disclose compositions comprising Poloxamer-188 in combination with the other components included in the compositions of the main request.

The Board also notes that D5 describes in paragraph [0040] methionine and sucrose as alternative isotonicity agents. There is however no indication to include both substances in the same composition as in the compositions of the independent claims of the main request.

4.4 In the light of the above, the Board concludes that the main request is novel over the disclosure of document D5.

5. Inventive step

5.1 Closest prior art

5.1.1 The patent in suit relates to the problem of providing stable liquid formulations containing the follicle-stimulating hormone (FSH) or the luteinising hormone (LH) or combinations of these hormones (paragraphs [0001] and [0017]). A specific issue addressed in the patent is to avoid precipitation in the formulations resulting in the formation of turbid or milky solutions (see paragraph [0058]).

5.1.2 The Board agrees with the opposition division that document D18 is the closest prior art.

This document relates to liquid gonadotrophin formulations containing *inter alia* Tween-20 (also named Polysorbate-20, see page 4, line 28), sucrose and methionine (see example 2). As explained on page 2 of D18 (lines 5 and 6), gonadotrophins form a family of hormones that includes FSH and LH. The formulations of the main request differ from the formulations of D18 mainly in the presence of a bacteriostatic agent selected from phenol and m-cresol and in the presence of the surfactant Poloxamer-188.

5.1.3 Document D5, proposed by the appellant as alternative closest prior art, is in the Board's view a less suitable starting point for the assessment of inventive step because the specific formulations it discloses do not contain sucrose, methionine and Poloxamer-188 (or any other surfactant). Thus, the compositions of D18 have more features in common with the compositions of the main request than do the compositions of D5.

5.2 Technical problem

- 5.2.1 As discussed in point 3.2 above, according to paragraph [0058] of the description the use of Poloxamer-188 as a surfactant prevents the formation of turbid solutions, a problem that occurs in formulations containing Tween-20 as surfactant and m-cresol or phenol.

To demonstrate this effect the respondent relied *inter alia* on the experimental reports D23, D34 and D43. The appellant countered with the argument that, on the basis of the experimental data reported in the patent, the effect on the turbidity of the solutions discussed in paragraph [0058] of the description was not plausible, and that under these circumstances, in line with decision T 488/16, the respondent could not rely on experiments conducted after the filing date of the patent.

- 5.2.2 The Board does not share this view.

In case T 488/16 the board had to decide whether it was already plausible from the disclosure of the patent that the single compound claimed in the main request (dasatinib) had protein tyrosine kinase (PTK) inhibitory activity (Reasons, points 4.1 and 4.2). The original application was directed to an extremely broad group of compounds (formula I) which were purported to have inhibitory activity toward different types of PTKs (Reasons, points 4.3 and 4.4). In point 4.5 of the Reasons the Board observed that:

"The assays are generically described and refer to the "protein kinase of interest" and the "test compound" or "compounds of interest" to be assayed. No further details are provided in this respect. Nor are any

results, for example IC or Ki values, provided. Indeed, there is no evidence at all in the application as filed that shows that any of the compounds falling within the scope of formula I, let alone dasatinib, is active as an inhibitor for any of the specific protein tyrosine kinases, except a mere assertion on page 50, lines 1 to 2 with (sic) reads that "Compounds described in the following Examples have been tested in one or more of these assays and have shown activity." No further information is provided. No individual values or range of values are given. No information as to whether the observed "activity" is suitable for the intended use, i. e. the treatment of a number of diseases and disorders, is provided".

The board concluded that it had not been made plausible at the filing date that the claimed compounds, in particular dasatinib, had PTK inhibitory activity. As a consequence, the post-published documents relied upon by the proprietor to show that the technical problem was solved could not be taken into consideration.

In the Board's view, the circumstances of the present case are not comparable to those underlying decision T 488/16.

The patent (and the original application) disclose in Table 1 compositions containing recombinant human FSH, a bacteriostatic agent selected from phenol, benzyl alcohol and m-cresol, an excipient selected from sucrose, mannitol and sodium chloride, and a surfactant which is either Poloxamer-188 or Tween-20. Paragraph [0134] of the patent (first sentence of page 33 of the original application) states that from visual examination it was observed that formulations containing Tween-20 and m-cresol or phenol presented a

white opalescent suspension. In contrast, formulations containing Poloxamer-188 and m-cresol or phenol did not exhibit this problem.

Thus, unlike the case underlying decision T 488/16, experimental data in support of the technical effect purported in the description were already present in the application as filed. The Board agrees with the appellant that the formulations of table 2 do not contain methionine, a mandatory ingredient of the composition of claim 1. However, there is no evidence that the addition of this substance may alter the visual appearance of the formulations. Furthermore, as explained in paragraph [0058] of the description, the problems of turbidity are due to the presence of Tween-20 in combination with m-cresol or phenol. Thus, the experiments included in the patent (and in the original application) are sufficient to render it at least plausible that the use of Poloxamer-188 in solutions containing a bacteriostatic agent prevents the formation of turbid solutions, a problem occurring in formulations containing Tween-20.

Thus, decision T 488/16 is not relevant to the present case. It is therefore appropriate to take into consideration in the assessment of inventive step the additional evidence submitted by the respondent during the opposition and opposition-appeal proceedings.

- 5.2.3 Likewise the experiment of the patent which has been illustrated in point 5.2.2 above, also the experiments of reports D23, D34 and D43 relate to a comparison of the turbidity of FSH solutions containing Poloxamer-188 or Tween-20 as surfactant.

For the purposes of the present decision, the Board will focus in particular on the last experimental report submitted by the respondent, namely D43.

In the experiments described in this document, the turbidity of the formulations is determined by nephelometry immediately after their preparation and filtration (time zero) and after storage for 1 week at 2-8°C. Two formulations according to the main request have been tested. They contain FSH, Poloxamer-188, a phosphate buffer, sucrose, methionine and - as a bacteriostatic agent - m-cresol (formulation C1) or phenol (formulation P1). The comparative formulations C2 and P2 differ from formulations C1 and P1 respectively in that they contain Tween-20 instead of Poloxamer-188. The results of the measurements are expressed in NTU units (nephelometric turbidity unit). The higher the NTU value, the more turbid the formulation.

The results concerning the formulations containing m-cresol as the bacteriostatic agent are reported in Table 6. For formulation C1 (according to the main request) the NTU values at time zero and after 1 week's storage are both 1. For formulation C2 (comparative formulation) the NTU values are 17 (time zero) and 14 (after 1 week's storage). The NTU values for the formulations containing phenol as the bacteriostatic agent are disclosed in Table 7. Formulation P1 (according to the main request) has an NTU value of 1 both at time zero and after 1 week's storage. The NTU values for the comparative formulation P2 are 6 (time zero) and 8 (after 1 week's storage).

The above results clearly indicate a strong reduction in turbidity when Tween-20 is replaced by

Poloxamer-188, both immediately after the preparation of the compositions and after 1 week of storage.

- 5.2.4 Experimental data have been submitted also by the appellant with documents D10 and D29.

Document D10 provides data on the turbidity of FSH formulations containing Tween-20, phenol or m-cresol as bacteriostatic agent and an excipient selected from sucrose, mannitol and sodium chloride. The turbidity, expressed in NTU units, is measured after 1 and 2 weeks of storage at room temperature or at 7-8°C.

For most of the formulations tested, the NTU observed is less than 3. These NTU values are well below the values measured by the respondent in D43 for formulations C2 and P2, i.e. the formulations containing Tween-20 as surfactant (see point 5.2.3 above). The appellant concludes that the turbidity data disclosed in D29 indicate that the combination of Tween-20 with phenol or m-cresol does not result in the formation of turbid solutions, contrary to the information reported in the patent and to the respondent's position. Thus, in its opinion, the problem underlying the invention of the patent in suit, namely the avoidance of turbidity in formulations containing Tween-20, does not actually exist.

- 5.2.5 The Board notes the different results reported in D10 and D43 for formulations containing Tween-20 as surfactant. In this regard, during the oral proceedings the respondent explained that the absolute NTU values for the same composition could vary from experiment to experiment.

The Board considers that, in the context of defining the technical problem, what matters is to establish a comparison between Poloxamer-188 and Tween-20 in relation to the issue of turbidity. As explained in point 5.2.3 above, the experiments of document D43 show that formulations containing Poloxamer-188 in combination with phenol or m-cresol provide better results, in terms of reduced turbidity, than formulations containing Tween-20 in combination with phenol or m-cresol. This conclusion is not contradicted by the experiments of D10, in which the turbidity of formulations containing Poloxamer-188 has not been measured.

Moreover, document D10 does not contain any data on the turbidity of the solutions immediately after their preparation (time zero).

- 5.2.6 The experiments disclosed in document D29 relate to solutions containing Poloxamer-188 or Tween-20 as surfactant. However, the solutions contain variable amounts of sucrose and different types and amounts of bacteriostatic agents. Hence, a comparison of the effects of the surfactant on the turbidity of the solution is not possible. Moreover, the Board agrees with the concerns expressed by the opposition division and by the respondent as to the absence in D29 of any detailed information concerning the experimental protocol.
- 5.2.7 Hence, the conclusions drawn in 5.2.3 above on the basis of the results of the experiments made by the respondent hold good also if the experiments of D10 and D29 are taken into consideration.

5.2.8 The appellant pointed to some inconsistencies in the NTU values disclosed in the experimental reports submitted by the respondent. In this regard the Board observes that the respondent's experiments consistently show that solutions containing Poloxamer-188 are less turbid than solutions containing Tween-20. The fact that the same solution may have different NTU values in different experiments may be due to the specific conditions in which each experiment is carried out.

As to the appellant's remark that the commercial product Luveris is a clear and colourless solution despite containing Tween-20, the Board observes that this product does not contain sucrose, which is a mandatory component of the solutions of the main request. In any case, this observation does not invalidate the conclusion that turbidity is reduced when Tween-20 is replaced by Poloxamer-188.

5.2.9 On the basis of the considerations set out in points 5.2.1 to 5.2.8 above, the Board considers that the technical problem underlying the invention can be seen in the provision of a preserved solution containing FSH and/or LH which provides optimal results in terms of absence of turbidity.

5.3 Obviousness

5.3.1 The use of phenol or m-cresol to preserve solutions containing a gonadotrophin hormone is disclosed for instance in document D5 (see paragraph [0014]). Hence, adding one of these substances to the solutions disclosed in D18 in order to prevent their bacterial contamination does not involve any inventive activity.

However, neither D18 nor D5 nor any other document considered by the parties provides any teaching regarding the turbidity of solutions containing a surfactant and a bacteriostatic agent. There is in particular no indication that the turbidity of the solutions of D18, in which phenol or m-cresol has been added as bacteriostatic agent, could be reduced by replacing Tween-20 with Poloxamer-188. Hence, the skilled person confronted with the technical problem defined above would find no hint to replace Tween-20 with Poloxamer-188 in the compositions of D18.

The subject-matter of claim 1 therefore meets the requirements of Article 56 EPC.

- 5.3.2 The same conclusion on inventive step applies to the other independent claims of the main request since they relate to products containing Poloxamer-188 and a bacteriostatic agent selected from phenol or m-cresol or to a method for manufacturing these products.
- 5.4 The Board judges that also when starting from document D5 as the closest prior art the subject-matter of the main request involves an inventive step. This document indicates in paragraph [0081] that the gonadotrophin formulations it discloses can contain various surfactants, including Poloxamer-188 and Tween-20. However, as mentioned in point 5.1.3 above, the specific formulations disclosed in D5 do not contain any surfactant. In the absence of any teaching as to the impact of the surfactant on the turbidity of the solutions, the skilled person seeking to provide a gonadotrophin formulation in which the problem of turbidity is minimised would find no guidance to select Poloxamer-188.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



S. Fabiani

D. Boulois

Decision electronically authenticated