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**Datasheet for the decision
of 8 February 2018**

Case Number: T 1599/16 - 3.3.07
Application Number: 03104219.5
Publication Number: 1417972
IPC: A61K38/29, A61K47/10, A61K9/08,
A61K47/26
Language of the proceedings: EN

Title of invention:
Stabilized teriparatide solutions

Patent Proprietor:
Eli Lilly & Company

Opponents:
TEVA PHARMACEUTICAL INDUSTRIES, LTD.
Aechter, Bernd
Helm AG
CADILA HEALTHCARE LIMITED

Headword:
Stabilized teriparatide solutions/Eli Lilly & Company

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

Keyword:

Main request -Amendments (yes)

Main request - Sufficiency of disclosure (yes)

Main request - Novelty (yes)

Main request - Inventive step (yes)

Decisions cited:

Catchword:



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Case Number: T 1599/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 8 February 2018

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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
4 July 2016 concerning maintenance of the
European Patent No. 1417972 in amended form.**

Composition of the Board:

Chairman A. Usuelli
Members: D. Boulois
P. Schmitz

Summary of Facts and Submissions

- I. European patent No. 1 417 972 was granted on the basis of a set of 31 claims.

Independent claims 1, 19 and 30 as granted read as follows:

"1. A sealed vial or cartridge containing a storage stable pharmaceutical composition in the form of a sterile solution ready for parenteral administration in an human patient, which solution comprises PTH(1-34), a buffer to maintain a pH from 3 to 7 and a polyol stabilizing agent, and which solution has not been reconstituted from a lyophilisate."

"19. A process for preparing a pharmaceutical composition in the form of a sterile solution ready for parenteral administration, said process comprising: mixing human PTH(1-34), a buffering agent and an excipient to form an aqueous solution containing PTH in a concentration range from 25µg/mL to 1000µg/mL, which is then sterile-filtered and filled into a vial or cartridge for use, wherein the excipient comprises a polyol stabilising agent".

"30. A pharmaceutical composition in the form of a stabilized solution comprising: (a) a therapeutically effective amount of human PTH(1-34); (b) an effective amount of a polyol stabilizing agent; (c) a buffering agent in an amount sufficient to maintain the pH of the composition within a range of about 3-7; (d) a parenterally acceptable preservative; and (e) the balance being water."

- II. Four oppositions were filed against the granted patent under Article 100(a), (b) and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, the patent was not sufficiently disclosed, and its subject-matter extended beyond the content of the application as filed.
- III. The appeal by the opponents OP1, OP2 and OP3 (hereinafter appellants 01, 02 and 03) lies from the decision of the opposition division that the patent in amended form based on auxiliary request 19 filed during oral proceedings met the requirements of the EPC.
- IV. The documents cited during the opposition proceedings included the following:
- D1: WO95/17207
 - D2: WO94/08613
 - D3: Kimmel et al, *Endocrinology*, 1993, 132(4), 105-112
 - D8: US5578567
 - D9: Bontempo, *Preformulation development of parenteral biopharmaceuticals*, p. 91-142, 1997
 - D12: J. Reeve et al, *Calcified Tissue Research*, 1976, vol. 21, p. 469-477
 - D21: WO97/14429
 - D39: Tong et al, *Journal of Biological Chemistry*, 2000, vol. 275(38), p. 29894
 - D41: Translation of JP 83-60940 (D41a: original; D41b: certified translation)
 - D46: Experimental report
 - D47: *J. Parenteral Science and Technology*, 1988, 42(suppl.), S3-S26
- V. According to the decision under appeal, the main request comprised subject-matter extending beyond the

content of the original and parent applications contrary to Articles 123(2) EPC and 76(1) EPC. Auxiliary requests 1-7 did not comply with the requirements of Article 123(3) EPC. Auxiliary requests 8-17 did not meet the requirements of Articles 76(1) and 123(2) EPC. Auxiliary request 18 was not admitted into the opposition proceedings under Rule 80 EPC.

In auxiliary request 19, claims 1-18 and 31 had been deleted, and the requirements of Articles 123(3), Art. 84, A76(1) and 123(2) EPC and Rule 80 EPC were met by this request.

Process claim 1 corresponded to claim 19 as granted with the further feature "and wherein said composition further comprises a parenterally acceptable preservative". Product claim 11 was identical to claim 30 as granted.

The subject-matter of the claims of auxiliary request 19 was considered to be new *inter alia* over D1.

As regards inventive step, D21 was considered to represent the closest prior art; it related to the problem of stabilizing PTH, and PTH(1-34) was mentioned. The formulations according to D21 contained PTH with a basic amino acid such as arginine, in particular for injection or infusion with a pH of 4-8. D1 and D2 could not be considered as an appropriate starting point, since these documents did not specifically relate to human PTH(1-34). D12 related to human PTH(1-34) but did not refer to a buffer or preservative and did not recognize any particular stability of the disclosed formulations. Neither did D39 and D41 recognize any particular stability associated with the disclosed compositions.

The difference between D21 and the claimed subject-matter concerned the presence of a buffer in combination with a polyol and the addition of a parenterally acceptable preservative as defined in the contested claims. The problem to be solved in the light of D21 was the provision of an alternative stable liquid formulation of human PTH(1-34), which was ready for administration and suitable for use as a multi-dose formulation. The claimed subject-matter was not considered obvious to the skilled person from D21.

VI. With its statement of the grounds of appeal dated 2 November 2016, appellant 03 requested an accelerated appeal proceedings.

VII. With a letter dated 28 March 2017, the patent proprietor (hereafter the respondent) filed a main request (corresponding to auxiliary request 19 maintained by the opposition division) and auxiliary requests 1-20.

The subject-matter of claim 1 of the main request corresponded to claim 19 as granted with the further specification "and wherein said composition further comprises a parenterally acceptable preservative". The product claim 11 was identical to claim 30 as granted.

VIII. A communication from the Board was sent to the parties. The Board mentioned in particular that documents D41 and D2 appeared to be as closer on a technical point of view to the claimed invention than D1 or D21, and that these documents could be the closest prior art for assessing inventive step.

- IX. Oral proceedings took place on 8 February 2018. Nobody was present on behalf of appellant 01 and appellant 02, and on behalf of opponent 04.
- X. The arguments of the appellants, as far as relevant to the present decision, may be summarised as follows:

Article 76(1) EPC and 123(2) EPC

Appellant 03 argued that the description on page 6 of the parent application or of the application of the contested patent, disclosed that the treatment of osteoporosis was linked with the concentration feature of from 25 to 1000 µmL, and that the absence of said feature for treating osteoporosis in claim 1 infringed Article 76(1) EPC.

Insufficiency of disclosure

According to appellant 03, claim 11 was restricted to compositions having storage stability. The patent did not contain sufficient information to allow a person skilled in the art to carry out the invention within the whole area that is claimed. D46 showed compositions falling under the claimed scope which were not stable when tested at 50°C during 14 days, and less stable than the compositions comprising only a buffer as shown in example 2 of the contested patent. Thus the patent did not disclose how a PTH(1-34) solution at pH 3 and 6 could be stabilized.

Novelty

According to appellants 01, 02 and 03, D1 was novelty-destroying for the subject-matter of the composition claim 11.

Inventive step

According to appellant 01, D41 was the closest prior art. The differences with the claimed subject-matter were the stabilizing polyol, the buffer and the preservative. The problem was seen as identifying a class of stabilising agents and a suitable pH for a hPTH(1-34) solution which might be used in a multi-dose format. The use of a polyol was obvious in view of D1 and D41, and the pH was known from D1. The inclusion of a preservative was also known.

If D1 was used as closest prior art, the only difference was the type of PTH, and the problem was seen as identifying a particular form of PTH(1-34). The object of claim 11 was obvious in view of D1.

According to appellant 01, D2 was also a potential closest prior art, and the problem was thus seen as identifying a particular form of PTH(1-34) for use in a multi-dose formulation. The use of a preservative was obvious in view of D41 and the solution was seen as obvious.

According to appellant 02, D1 had to be considered as closest prior art, since it disclosed directly and unambiguously human PTH(1-34). The process of claim 1 differed from the process of D1 in that the PTH(1-34) is sterile filtered and not the mixture containing PTH. No technical effect derived from this difference. The sterilisation method was commonly known and the claimed subject-matter could not be inventive. Additionally, the composition of claim 1 of the opposed patent, comprised a preservative, which presumably minimized microbial growth. Preservatives were however

typical ingredients for parenteral solutions and the solution was also obvious.

If D21 was taken as closest prior art, claims 1 and 11 differed in that human PTH(1-34) was used in combination with a buffer, a polyol stabilizing agent, and a preservative. As no effect was shown, the problem was to be formulated as a process for providing an alternative stable liquid formulation of human PTH(1-34), ready for parenteral administration, less susceptible to microbial growth and suitable as multi-dose formulation. The solution was obvious in view of D21 and D1.

Appellant 03 considered both D1 and D21 as closest prior art. The difference between the composition of claim 11 and D21 laid in the presence of a stabilizing agent, a buffering agent and a preservative instead of a basic amino acid. The problem was seen as the provision of an alternative liquid formulation of PTH(1-34), ready for administration and suitable for use as a multi-dose formulation. The solution was obvious in view of D21 itself, but also D1, D34, D47. As regards D1, the objective technical problem was seen as the provision of PTH(1-34) in a form that is more convenient for parenteral administration. The solution was obvious, since the use of a parenteral solution was always preferred.

XI. The arguments of the respondent, as far as relevant to the present decision, may be summarised as follows:

Article 76(1) EPC and 123(2) EPC

The patent related to pharmaceutical compositions and the passage on page 6 cited by appellant 03 was not specific to osteoporosis treatment.

Insufficiency of disclosure

D46 showed that compositions according to the claimed subject-matter at pH 3.1 or 5.9 showed a 93.6% or 86.1% stability at 30°C for 30 days. The results in D46 confirmed that the combined use of a polyol and a buffer provides stability relative to buffer alone.

Novelty

D1 did not unambiguously disclose a liquid composition which contained non-lyophilised PTH and a preservative.

Inventive step

Documents D2, D21, D41 were mentioned as closest prior art for the process claim 1.

The differences between claim 1 and D2 were the filtration step, the preservative, the lyophilisation step, and the claimed dosage. The effects were that the liquid solution was sterile, could be used in repeated doses, that the liquid solution was stabilised by the polyol and did not need to be reconstituted from a lyophilisate, and the product included a specific dose of hormone. The problem was the provision of a process for preparing a multi-dose sterile composition which could be administered more conveniently. Since D2 related to a single dose composition, there was no reason to modify its teaching to arrive at the claimed process.

The differences between claim 1 and D21 were that the claimed process uses human PTH(1-34) rather than PTH(1-37), a preservative, a buffer and a polyol. The

effect was the provision of a stable formulation of PTH(1-34) which permitted administration of multiple doses from the same sterile solution. D21 taught away from using additives such as a buffer, a polyol and a preservative, and the claimed process was inventive for this reason.

The differences between claim 1 and example 2 of D41 was the dose, the presence of a polyol, a preservative, and the use of a vial or cartridge, rather than an ampoule. The effects were a more concentrated solution, an increased stability of PTH due to the polyol, and a multiple use due to the preservative and the vial or cartridge. The technical problem was seen as the provision of a process for preparing a multi-dose sterile composition which had a longer shelf-life and could be administered repeatedly and more conveniently. The solution was not obvious in view of D1 or D41.

Documents D1, D2, D21, D41 were mentioned as closest prior art for the product claim 11. D1 and D2 could not be the closest prior art, since they related to lyophilised compositions.

The differences between claim 11 and example 5 of D2 were the presence of hPTH(1-34), the buffer for a pH of 3-7, the polyol and the preservative. The problem was the provision of an improved stable composition useful for repeated use in treating a chronic condition by multiple dose administration of hPTH(1-3). There was no incentive in the prior art to take a multi-dose solution and the skilled person would have had no reason to add a preservative to the solutions of D2.

The differences between claim 11 and the liquid composition of D21 were the use of hPTH(1-34), of a

polyol, a buffer and a preservative. The effect was the provision of a composition useful for repeated use in treating a chronic condition by the administration of multiples doses from the same stable solution of PTH(1-34). Since D21 stated that an amino acid was essential for the stabilisation, whereas a polyol should not be added (see page 3 of D21), the solution was not obvious.

The differences between claim 1 and example 2 of D41 was the presence of a polyol and a preservative, a pH between 3-7, and that the claimed composition did include a tonicity agent. The problem was the provision of improved compositions for repeated administration of hPTH(1-34) from the same composition over an extended period. The claimed solution was not suggested by D41 and was not obvious.

XII. Requests

Appellants 01, 02 and 03 (opponents 01, 02 and 03) request that the decision under appeal be set aside and that the patent be revoked.

Respondent (patent proprietor) requests that the appeals be dismissed, i.e. that the patent be maintained on the basis of auxiliary request 19 filed during the oral proceedings before the opposition division (main request), or that the patent be maintained on the basis of one of auxiliary requests 1 to 20 filed with letter of 28 March 2017.

Reasons for the Decision

1. Main request - Articles 123(2) and 76(1) EPC

- 1.1 Appellant 03 objected to the subject-matter of claim 1 under Articles 76(1) and 123(2) EPC, in that the claimed concentration of PTH(1-3), namely "*in a concentration range from 25µg/mL to 1000µg/mL*", was disclosed only in relationship with the treatment of osteoporosis, in view of the description of the parent application EP 98 123 225 on page 6 or of the application document EP 1 417 972 A1 of the contested patent on paragraph [0022]. According to appellant 03, the absence of any reference to the treatment of osteoporosis in claim 1 resulted in an unallowable generalization.

- 1.2 Since the parent application EP 98 123 225 and the published application EP 1 417 972 A1 of the contested patent have an identical content, both objections will be treated simultaneously on the basis of the published application document 1 417 972 A1.

- 1.3 Paragraph [0022] of the application EP 1 417 972 A1 discloses in its preamble that "*the PTH solution and composition of the present invention incorporate PTH in a medically effective amount*". It then further mentions the usual dose of human PTH(1-34) for treating osteoporosis, namely that "*osteoporosis therapy entails administration of the reconstituted preparation by injection, desirably subcutaneous injection, in unit doses that reflect the prescribed treatment regimen but are, by way of example, for human PTH(1-34), within the range from 25 µg PTH/mL of injected solution to 1000 µg/mL of injected solution per patient, with injection volumes being desirably from 0.02 to 1.3 mL*". Paragraph [0022] concludes in its last sentence that "*accordingly, the purified PTH is desirably incorporated with the buffering agent and excipient to form an aqueous solution containing PTH in a*

concentration range from 25 µg/mL to 1000 µg/mL, preferably 100 µg/mL to 500 µg/mL, which is then sterile-filtered and filled into a vial or cartridge for use".

Consequently, the last sentence of paragraph [0022] constitutes as such an explicit basis for the claimed concentration, since the claimed concentration of "25 µg/mL to 1000 µg/mL" is disclosed directly and unambiguously therein without any link with the specific treatment of osteoporosis. Moreover, it appears also clearly from the wording of the remaining part of paragraph [0022] that PTH(1-34) must be in an effective medical amount, and that the treatment of osteoporosis is only taken as reference for determining the concentration necessary in the vials or cartridges for reaching said dosage; it is not possible to deduct from this passage an unwavering link between the disclosed dosage and the treatment of osteoporosis.

- 1.4 The requirements of Articles 76(1) and 123(2) EPC are therefore met by the main request.
2. Main request - Article 100(b) EPC - Sufficiency of disclosure
 - 2.1 According to appellant 03, claim 11 was restricted to a composition having storage stability, namely "*a stabilized solution*", without sufficient information to allow a person skilled in the art to carry out the invention.
 - 2.2 Claim 11 refers indeed to "*a stabilized solution*", but without further restrictive feature relating to the stability in term of time or nature of stability. It appears difficult to see in this term a restrictive and

problematic feature as regards the preparation of the compositions of claim 11.

There is thus no reason to doubt the possibility to prepare the claimed stabilized solutions, all the more so as the description of the contested patent provides enough teaching showing how to obtain them and how to measure their storage stability. The description of the contested patent gives indeed sufficient information as regards the nature and amounts of the polyol, buffering agent and preservative to be used to prepare the claimed stabilized solution (see par. [0013]-[0015]). Additionally, examples 1 and 2 of the contested patent show convincing data relating to the stability of the compositions as claimed comprising a polyol, a buffer and a preservative. Example 2 gives also a teaching as how the stability may be measured, namely by determining the amount in % of hPTH(1-34) after a certain time; said example shows that the combination of the claimed excipients provide a stability of the obtained compositions of 96% after 30 days at 30°C.

2.2.1 Appellant 03 further used document D46 to support its argumentation as to the lack of stability of the claimed compositions.

The stability of the pH of compositions of PTH(1-34) comprising a polyol, a preservative, and buffers, at the values of 3.1 and 5.9 was determined in document D46 at 30°C after 30 days and after 14 days at 50°C.

The residual amounts of PTH(1-34) at 30°C after 30 days were respectively 93.6% and 86.1% for the compositions at pH 3.1 and 5.9, these results being comparable and in line with the results obtained in example 2 of the

patent. D46 confirms thus undeniably the stability of the claimed compositions.

As to the tests performed in D46 at 50°C, the residual amounts of PTH(1-34) at 50°C after 14 days were respectively 69.5% and 45.31% for the compositions at pH 3.1 and 5.9. The arguments of appellant 03, namely that the compositions falling under the claimed scope were not stable, as demonstrated by D46 when tested at 50°C after 14 days, and anyway less stable than the compositions comprising only a buffer as shown in Table 1 of example 2 of the contested patent, could however not be followed by the Board.

When it comes to the stability of a composition, the skilled person does indeed never expect an absolute or total stability of any composition, which is technically not realistic. Consequently, a term such as "*a stabilized solution*" cannot mean that the stability is absolute when measured under any conditions, even under drastic conditions; such interpretation of the term would be distorted and fallacious. It is thus to be expected that testing a composition under drastic conditions leads to poorer stability results. In the present case, testing a composition which is presumably stored in a fridge, at 50°C during 14 days represents harsh conditions, for which it may be expected that a decrease in stability occurs.

As to the doubts expressed by the appellant regarding the comparison of the results obtained in D46 at 50°C for 14 days with the better results obtained for a composition with only a buffer and without polyol shown in Table 1 of example 2 of the contested patent, this point might relate to the question of inventive step and not to sufficiency of disclosure. The Board

notes however that said results at 50°C are contradicted by all storage test results obtained at 30°C comparison between the results obtained at 30°C, as shown in example 2 of the contested patent or in D46.

2.2.2 Thus, the skilled person would find no difficulty in preparing the claimed compositions. Consequently, the invention is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC).

3. Main request - Novelty

3.1 Document D1 has been cited as relevant for novelty by appellants 01, 02 and 03.

3.2 D1 discloses freeze-dried parathyroid hormone preparations that exhibit storage stability. PTH(1-34) is mentioned in a list in the description, wherein it is mentioned that the PTH may be of human, porcine or bovine origin and different fragments, such as PTH(1-34), PTH(1-37) or PTH(1-38) (pages 4 and 5, 2nd paragraph); the composition comprises also a buffer to maintain the pH between 3,5 to 7,5 and mannitol as excipient (see page 6). The use of a bacteriostatic agent is also suggested on page 10 of D1. The preferred and exemplified embodiment of D1 is a freeze-dried composition comprising PTH(1-84), as shown on pages 8, 11 and in the claims.

Thus, D1 does not disclose directly and unambiguously a composition comprising hPTH(1-34) or the process for preparing it, even less in liquid state and with a preservative. The combination of all these features is not derivable directly and unambiguously from D1.

The content of a prior art document should not be taken as a reservoir from which it would be permissible to draw features belonging to distinct or alternative embodiments to artificially create a particular embodiment that would destroy novelty, unless the document itself suggests such a combination. This is clearly not the case within document D1, where it is not possible to combine the disclosure of specific embodiments with general statements of the description.

3.3 The main request meets the requirements of Article 54 EPC.

4. Main request - Inventive step

4.1 This invention relates to stabilized liquid pharmaceutical solutions containing hPTH(1-34), in particular to solutions exhibiting storage stability in terms of hormone composition and activity.

4.2 Several documents were presented by the appellants as potential closest prior arts. Appellant 01 considers indeed D41, D1 or D2 as the potential closest prior art documents, while appellant 02 expresses a preference for D1 or D21, and appellant 03 chooses D1, D2 and D21 with a preference to D21, which was according to appellant 03, the best starting point. The choice of the opposition division in its decision was also D21.

4.2.1 D1 relates to PTH formulations in powder form having improved storage stability, but does not disclose directly and unambiguously a composition comprising human PTH(1-34), although its presence was derived by the appellants from the disclosure on pages 4 and 5 of D1, which mentions the human, bovine and porcine forms

of *inter alia* PTH(1-34), PTH(1-37), PTH(1-38) and PTH(1-84). Said compositions are provided in freeze-dried powder form (see page 5, 2nd paragraph; see examples of pages 8 and 11 and claims). The addition of a polyol is envisaged to yield a quality cake, as well as a non-volatile buffer that can buffer the pH of the preparation between 3.5 to 7.5 (see page 6). The incorporation of a bacteriostatic is envisaged in the case a multi-dose vial is provided, and D1 mentions that "the formulation remaining after administration of each dose can be refrigerated for subsequent use within a time frame of several days". The specific examples and embodiments show freeze-dried powders of PTH(1-84), with mannitol and buffer.

D1 does therefore not disclose a composition comprising human PTH(1-34), even less a liquid composition, said liquid composition comprising a polyol, a buffer and a preservative and the process for preparing it.

4.2.2 D2 shows in all examples 1-6 injectable formulations comprising *inter alia* an unspecified PTH, a polyol, a buffer for a pH of 2.5-3 and further excipients. Said PTH might be PTH, PTH(1-34), PTH(1-13), PTH(38-64), PTH(67-86) and PTHrP. The compositions comprise a stabilizing agent such as albumin, peptone, PVP and are preferably lyophilized with an appropriate support in case of a lyophilised product, such as lactose or mannitol (see page 6); example 1-6 are injectable compositions, example 3 showing a composition of unspecified PTH with mannitol, PVP and a buffer for a pH of 2,5-3,0 and example 5 showing a composition with PTH, albumin and a buffer to pH 2.5-3. This document does not disclose a sterilization step.

Consequently, D2 does not disclose the explicit presence of human PTH(1-34), a preservative as claimed in claim 1 and the further presence of a buffer for pH 3-7 as claimed in claim 11 of the main request.

- 4.2.3 D21 discloses stabilized compositions of human PTH, and its fragments such as PTH(1-34), (1-35), (1-36), (1-38) and other shortened fragments, but more particularly PTH (1-84) and PTH(1-37), as mentioned on page 2, lines 15-30; said passage mentions further that PTH(1-37) is particularly labile, in view of its structure and conformation. Examples 2-12 show lyophilized compositions of PTH(1-37) or PTH(1-84) in combination with an amino acid or saccharose, a buffer for pH 7.4, and an acid. Example 1 shows a liquid composition of PTH(1-37) with arginine at pH 6.5, sterilized by filtration and packaged in a vial with a nitrogen gas filling.

D21 does not disclose therefore in example 1 the explicit presence of human PTH(1-34), a preservative and a polyol, and said solution comprises further an inert gas. The other examples are all with PTH(1-37) in a freeze-dried composition.

- 4.2.4 D41 discloses in example 2 a liquid injectable composition which has been sterile filtered and which comprises hPTH(1-34) at a concentration of 10 µg/ml, with an unspecified buffer, a tonicity agent and a stabilizer; example 1 discloses a freeze-dried injectable composition of hPTH(1-34), mannitol and a stabilizer (see examples 1 and 2 of the translation D41b).

D41 does not specify the nature of the buffer and the stabilizing agent used in example 2, and does not

disclose the presence of a preservative and a concentration of 25 to 1000 µg/ml as claimed in claim 1.

- 4.2.5 Documents D1 and D21 are in the Board's view less promising starting points for the assessment of inventive step, since they do not disclose compositions comprising the specific hPTH(1-34), and they emphasize or disclose exclusively the use of lyophilised compositions, instead of liquid compositions. However, given the choice of D21 and D1 by the appellants and the fact that the decision of the opposition division used D21 as closest prior art, the relevance of D21 will be assessed first; the relevance of the other documents D1, D2 and D41 will then be assessed thereafter.

D21 as closest prior art

- 4.3 Appellant 02 defined the problem over D21 as the provision of a process for providing an alternative liquid formulation of PTH(1-34), ready for parenteral administration, less susceptible to microbial growth. Appellant 03 saw the problem as the provision of an alternative stable liquid formulation of human PTH(1-34), suitable as multi-dose formulation.
- 4.4 As regards the subject-matter of claim 1, the solution is a process of preparation of a liquid composition involving the use of hPTH(1-34), a buffer, a polyol, and a preservative. As regards claim 11, the solution is the provision of a liquid composition comprising hPTH(1-34), a polyol, a preservative and a buffer to pH 3-7.

- 4.5 Examples 1 and 2 of the contested patent disclose compositions and their preparations showing undoubtedly a storage stability at 30°C linked with the combination of a polyol and a buffer.
- 4.6 The question is whether the skilled person, starting from the teaching of D21, would arrive at the subject-matter of claims 1 and 11 of the main request in an obvious manner in order to solve any of the problem posed.
- 4.6.1 D21 focuses on the stabilisation of compositions comprising hPTH(1-84) or hPTH(1-37), and mainly the stabilisation of compositions in lyophilised state, as explicitly disclosed in examples 2-12. Only example 1 shows a liquid composition of PTH(1-37) with arginine at pH 6,5 and under inert gas atmosphere.
- 4.6.2 It is common general knowledge that lyophilisation allows for long-term storage of proteins with very little threat of degradation and that it generally results in improved stability profiles; preservation is possible because the greatly reduced water content inhibits the degradation of proteins.

It is also commonly known that a storage in liquid form is not always feasible given the susceptibility of proteins to denaturation, especially in presence of water, which can make the liquid formulation unsuitable for long-term storage. Usually water mediates reactions such as hydrolysis and oxidation of the proteins, and these reactions are accelerated under aqueous conditions, making frequently a formulation in liquid form unsuitable for long-term storage. Accordingly, a storage in liquid form is usually not seen as a first storage choice for proteins, and cannot be considered

as an obvious alternative to a storage in lyophilised form. In the same order of ideas, a skilled person would not be considered that stabilising a composition in dry state as an equivalent or possible alternative for a stabilisation in liquid state.

In the present case, PTH is mentioned in the description of the contested patent as a very labile protein, since particularly sensitive to oxidation, deamidation and hydrolysis; said PTH protein requires that its N-terminal and C-terminal sequences remain intact in order to preserve bioactivity (see paragraph [0006] of the contested patent). Accordingly, a storage in liquid form of PTH cannot be seen a priori as a first choice of storage, and even less as an obvious alternative to a storage in lyophilised form.

This is also the reason why the teaching of D1 relating to lyophilised compositions and their preparation cannot be seen as a reasonable starting point for the assessment of inventive step of a liquid composition or the preparation thereof.

Accordingly, the subject-matter of claims 1 and 11 of the main request constitutes already a non-obvious alternative over the teaching of D21 as regards the lyophilised state of the compositions and their preparation disclosed in D21.

- 4.6.3 Moreover, D21 emphasizes the preparation of compositions comprising PTH(1-84) and PTH(1-37). D21 points out that the hPTH(1-37) fragment is particularly labile, reminding implicitly that all hPTH show different structure and conformations and afferent properties; accordingly, it is not possible to conclude that the methods used for stabilising one particular

fragment of PTH will also necessarily work for another different fragment, such as PTH(1-34).

It is therefore not possible to deduct from the general teaching of D21 and particularly from examples 1 or 2-12 that the stabilizing compositions proposed therein, whether they are in lyophilised state or in liquid state, would also be effective for hPTH(1-34).

Consequently, the preparation of a composition comprising a definite PTH fragment different from PTH(1-34) cannot constitute an incentive or an obvious alternative for the preparation or composition comprising hPTH(1-34).

4.6.4 A combination with the teaching of D1 as suggested by appellant 03, would not lead to the subject-matter of claim 1, since D1 also relates only to freeze-dried compositions and not specifically to hPTH(1-34).

4.7 The solution claimed in claims 1 and 11 of the main request constitutes therefore a non-obvious alternative over the teaching of D21.

D1 as closest prior art

4.8 According to appellant 01, the problem over D1 was seen as the identification of a particular form of PTH(1-34) (*sic*). Appellant 02 defined the problem as the provision of an alternative sterilization step in the process of preparing a solution comprising hPTH(1-34) and the provision of solution comprising hPTH(1-34), which is less susceptible to microbial growth and is suitable for use as a multi-dose formulation. Appellant 03 saw the problem as the provision of a hPTH(1-34) in a form that is more

convenient for parenteral administration, and which improved the patient compliance.

In view of the absence of disclosure of hPTH(1-34) and of a liquid composition in D1, it appears necessary to the Board to reformulate the problem *ad minima* as the provision of an alternative stable composition of PTH(1-34) and of a process for preparing it.

- 4.9 In view of the disclosure of liquid compositions of hPTH(1-34) and their preparation and stability testing disclosed in examples 1 and 2 of the contested patent, the Board has no reason to doubt that the problem as defined is not solved by the claimed subject-matter
- 4.10 The question is whether the skilled person, starting from the teaching of D1, would arrive at the subject-matter of claims 1 and 11 of the main request in an obvious manner in order to solve the problem posed.
- 4.10.1 D1 relates to PTH preparations exclusively in powder form which storage stability is obtained by freeze-drying the compositions (see for instance page 3, par. 3-5). As mentioned above in point 4.6.2, a storage in liquid form of PTH cannot be seen as a first choice, and even less as an obvious alternative to a storage in lyophilised form.

Said document D1 appears furthermore even to teach away from the possibility of storage in liquid state, since it recommends to use the reconstituted liquid composition within a time frame of several days and to store it refrigerated, in the case where a multi-dose vial is provided, this despite the potential presence of a bacteriostatic (see page 10).

Already for this reason, the solution claimed in claims 1 and 11 of the main request appears to be non-obvious over D1.

- 4.10.2 As regards the nature of the active ingredient, the preparation of D1 desirably incorporates hPTH(1-84) (see pages 4, 8 and 11).

Alternatives to PTH(1-84) are exclusively mentioned on pages 4 and 5 of D1, such as the human, bovine or porcine forms of PTH, such as PTH(1-34), PTH(1-37), PTH(1-38), PTH(1-41) and "other PTH alternatives incorporating from 1 to 5 amino acid substitutions that improve PTH stability and half-life". Said passage, which is the only passage of D1 mentioning alternatives to PTH(1-84), can however only be seen as a general statement and does not identify specific alternatives for PTH(1-84), in particular not hPTH(1-34).

- 4.10.3 A combination with the teaching of D21 and D41 as argued by appellant 03, does also not appear to be realistic, in view of the use of PTH(1-84) and PTH(1-37) in D21, mostly in freeze dried state, and the absence of clear disclosure of a stabilising composition in D41.

- 4.10.4 A liquid composition of hPTH(1-34) and its process of preparation cannot be seen as an obvious alternative to the compositions disclosed in D1.

As for D21 above, D1 cannot be seen as a realistic starting point for assessing inventive step, and the teaching of other potential complementary document cannot overcome the fundamental deficiency of disclosure of D1 as regards the invention claimed in claims 1 and 11 of the main request.

4.11 The solution claimed in claims 1 and 11 of the main request is therefore non-obvious vis-à-vis of D21.

D2 as closest prior art

4.12 According to appellant 01, the problem over D2 is the identification of a particular form of PTH(1-34) for use in a multi-dose formulation.

During oral proceedings, appellant 03 saw the problem as the provision of an alternative process and composition for PTH(1-34).

4.13 As already mentioned above, there is no reason to doubt that the problem(s) have been solved by the claimed invention, as illustrated by examples 1 and 2 of the contested patent.

4.14 It remains to determine whether the claimed solution was obvious.

4.14.1 D2 discloses in examples 1-6 injectable compositions of undefined PTH or one of its fragment. Among these examples, example 3 was considered as particularly relevant by appellant 03.

As is clear from document D21, all human PTH show different structure and conformations and different afferent properties; accordingly, it is not possible to conclude that the methods used for stabilising one particular fragment of PTH will also necessarily work for another different fragment, such as hPTH(1-34). It appears thus difficult to conclude from the teaching of examples 1-6 of D2 that the compositions disclosed therein are effective for all PTH or PTH fragments.

It is also clear from the teaching of D2 that the compositions of at least examples 1-4 and 6 as disclosed in D2 are lyophilised. The description of D2 mentions indeed that "*the injectable pharmaceutical form in which the active ingredient is in the liquid phase or, better yet lyophilized, with the presence eventually of a appropriate stabilizing agent (albumin, peptone, PVP, et...), an appropriate support (in case of lyophilized product: lactose, mannitol, glycine, etc...)*". As discussed above under point 4.6.2, a storage in liquid form of PTH cannot be seen as an obvious alternative to a storage in lyophilised form.

As regards the disclosure of example 5, which relates to a composition comprising PTH, albumin and a buffer to pH 2.5-3, the absence of a support for lyophilisation casts doubts on the final state of the composition, and a storage under liquid state cannot be excluded. However, there is no incentive or suggestion in D2 to use a polyol as stabilising agent for a liquid composition, even less for the specific hPTH(1-34). Moreover, the argument of the respondent that it was generally known that a buffer at pH 2.5-3, as used in all examples 1-6 of D2, was not able to stabilise a liquid composition comprising PTH, has not been contested or counter-argued by the appellants.

There is therefore no incentive in the teaching of D2 to arrive to a process for preparing a composition comprising hPTH(1-34), a polyol, a buffer, a preservative as claimed by claim 1 and the resulting composition of claim 11. A combination with the teaching of D1, as argued by appellant 03, is also not possible in view of the freeze-dried compositions disclosed therein, and the absence of any disclosure of PTH(1-34).

4.15 Consequently, the subject-matter of claims 1 and 11 is not obvious in view of the teaching of D2.

D41 as closest prior art

4.16 According to appellant 01, the problem over D41 is the identification of a class of stabilising agents and a suitable pH range for a hPTH(1-34) solution formulation which may be used in a multi-dose format.

The respondent considered the problem as the provision of an improved composition for repeated administration of hPTH(1-34) from the same composition over an extended period of time.

4.17 The solution of any of the problems posed by appellant 01 or by the respondent, as regards claim 1 of the main request, is a process of preparation of composition comprising a polyol, a preservative and PTH(1-34) at a concentration of 25 to 1000 µg/ml, and a composition comprising a stabilising system comprising a polyol, a buffer for a pH of 3-7 and a preservative as regards claim 11 of the main request.

4.18 There is no incentive or suggestion in D41 to adapt the concentration of hPTH(1-34) to the claimed concentration, to add a preservative to the solution, and to fill it in a vial or cartridge. The choice of an ampoule in combination with a concentration of 10 µg/ml in D41 and the absence of a preservative means that repeated dosing from a single container was not envisaged in D41.

Moreover, the addition of polyol to a buffer was shown in examples 1 and 2 of the contested patent to improve

the stability of the liquid composition over liquid compositions comprising only a buffer (see Table 2).

Thus, even if the polyols were generally known as potential protein stabilisers, as mentioned in D47 or D9, it remains that the choice of a polyol had to be made among a list of potential other stabilisers, such as surfactants, amino acids, fatty acids, as mentioned in D9, on page 114, and that it was not expected to show an unexpected improvement in stability of liquid formulations of hPTH(1-34) in combination with a buffer at a stabilising pH.

No other cited document mentions the possibility to prepare a multi-dose liquid formulation for storage comprising a polyol and a preservative.

Consequently, the simultaneous adjustment of the concentration, the addition of a preservative and of a polyol, in order to prepare a multi-dose composition having an improved stability in liquid state cannot be derived from the teaching of D41, and constitutes a non-obvious solution.

4.19 Consequently, the subject-matter of claims 1 and 11 is not obvious in view of the teaching of D41.

4.20 The subject-matter of the main request is inventive over the prior art and meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar:

The Chairman:



S. Fabiani

A. Usuelli

Decision electronically authenticated