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D E C I S I O N
of 13 December 2005

Case Number: T 0032/05 - 3.3.08

Application Number: 94926817.1

Publication Number: 0742902

IPC: G01N 33/53

Language of the proceedings: EN

Title of invention:
A method of assaying collagen fragments in body fluids, a test kit and means for carrying out the method and use of the method to diagnose the presence of disorders associated with the metabolism of collagen

Patentee:
Osteometer Biotech AS

Opponent:
Ostex International, Inc.

Headword:
Collagen fragments/OSTEOMETER

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 87

Keyword:
"Main request (filed as auxiliary request 5)"
"Added matter (no)"
"Clarity (yes)"
"Novelty (yes)"
"Inventive step (yes)"
"Sufficiency of disclosure (yes)"

Decisions cited:
T 0840/93

Catchword:
-

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Case Number: T 0032/05 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 13 December 2005

Appellant I: (Proprietor of the patent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 17 November 2004 concerning maintenance of European patent No. 0742902 in amended form.

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
S. Perryman

Summary of Facts and Submissions

I. The appeal lies from the interlocutory decision of the opposition division posted on 17 November 2004, whereby the European patent No. 0 742 902 (based on European patent application No. 94 926 817.1, published as WO 95/08115) with the title "A method of assaying collagen fragments in body fluids, a test kit and means for carrying out the method and use of the method to diagnose the presence of disorders associated with the metabolism of collagen" was maintained in amended form. The patent had been opposed on the grounds of Article 100(a), in particular lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), Article 100(b) and 100(c) EPC.

II. In the decision under appeal, the opposition division found that, whereas the main request (claims as granted) and the auxiliary requests 1 to 11 then on file were in breach of Article 123(2) EPC and the amendments to claim 9 of the auxiliary request 13 offended against Article 84 EPC, the set of claims filed at oral proceedings as auxiliary request 13A (claims 1 to 6) and a description amended accordingly met the requirements of the EPC, in particular those of Articles 123(2) and (3), 84, 83, 87, 54 and 56 EPC.

III. The proprietor of the patent (appellant I) and the opponent (appellant II) each lodged an appeal against the interlocutory decision of the opposition division. With its statement of grounds of appeal dated 17 March 2005, appellant I filed four new sets of claims, a main request and three auxiliary requests, which replaced the requests considered by the opposition division.

Expedited handling of the appeal was requested due to an infringement action in Germany by appellant I *versus* appellant II.

IV. On 24 March 2005, appellant II filed an statement of grounds of appeal which included new documents D11 to D16.

V. Each party was given the opportunity to comment on the grounds of appeal of the other party. With its comments, appellant I filed new documents D17P and D18P.

VI. Since both appellants had requested oral proceedings under Article 116 EPC in the event that the board did not intend to grant their respective requests, on 29 September 2005 the parties were summoned to oral proceedings. In a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal attached to the summons, the board informed the parties that the request for expedited handling had been granted. Furthermore, the board drew attention to matters which seemed to be contentious, in particular matters in connection with Article 123(2) EPC.

VII. On 18 October 2005, appellant II requested a postponement of the oral proceedings on the grounds that neither of the two representatives handling the case for this appellant would be available at the dates scheduled for the proceedings. Appellant I opposed the postponement.

VIII. In a communication dated 25 October 2005 sent by telefax, the board drew attention to the Notice of the Vice-Presidents Directorates-General 2 and 3 dated

1 September 2000 concerning oral proceedings before the EPO (OJ EPO 2000, 456), and asked the representatives of appellant II to provide evidence for the alleged circumstances.

IX. Documentary evidence for the circumstances alleged by one of the representatives was received with fax letter dated 26 October 2006. No evidence was filed for the second representative. In a further communication dated 4 November 2005, the board informed the parties that, in view of the circumstances of the case the request for postponement of the oral proceedings could not be granted.

X. At oral proceedings, which took place as scheduled on 13 December 2005, both appellants were represented. The parties presented their arguments in connection with the requests then on file. At the end of the discussion, appellant I submitted new auxiliary requests 4 and 5, the introduction of which into the proceedings was opposed by appellant II arguing that the requests were late-filed. The board, having heard the parties on this issue, decided to admit auxiliary request 5 (claims 1 to 6) into the proceedings. After discussion, appellant I made the auxiliary request 5 its main request and withdrew all its previous requests. An amended description adapted to the new claims was also filed.

XI. Claims 1 and 2 of the **main request** (filed as auxiliary request 5 during the oral proceedings) read as follows:

"1. A method of assay for collagen Type I fragments in a body fluid, in which collagen fragments in a said

body fluid and a synthetic peptide **having a sequence derived from collagen and having a potential site for cross-linking but** containing no collagen crosslink structure immobilised on a solid surface are contacted with an immunological binding partner which is immunoreactive with the immobilised synthetic peptide and with collagen fragments in said body fluid, wherein the immunological binding partner **has been raised against a peptide consisting of the amino acid sequence Gln-Tyr-Asp-Gly-Lys-Gly-Val-Gly and** is immunoreactive with an immobilised peptide consisting of the amino acid sequence Gln-Tyr-Asp-Gly-Lys-Gly-Val-Gly.

2. A method as claimed in Claim 1, comprising:

(a) contacting a sample of the body fluid with a synthetic peptide immobilised on a solid support and with an immunological binding partner which is immunologically reactive with said immobilised synthetic peptide **and which has been raised against a peptide consisting of the amino acid sequence Gln-Tyr-Asp-Gly-Lys-Gly-Val-Gly**, wherein the collagen fragments compete with said synthetic peptide for binding with the immunological binding partner; and

(b) quantifying the amount of collagen fragments in the body fluid by measuring the amount of binding of said immunological binding partner with said synthetic peptide;

wherein

said immunological binding partner is immunologically reactive with a peptide immobilised on a solid support

and consisting of the amino acid sequence Gln-Tyr-Asp-Gly-Lys-Gly-Val-Gly; and

said immobilised synthetic peptide **is derived from collagen,** contains no collagen cross-link structure but **contains a potential site for cross-linking** and is immunologically reactive with said immunological binding partner."
(wording introduced into the claims as granted has been emphasized by the board)

Dependent claims 3 to 6, which concerned various embodiments of the methods of claims 1 and 2, were identical to the corresponding claims as granted.

XII. The following documents are referred to in the present decision:

D1: WO 91/08478;

D3: WO 94/03813;

D4: D.A. Hanson et al., Journal of Bone and Mineral Research, 1992, Vol. 7, No. 11, pages 1251 to 1258;

D15: M.H.V. Van Regenmortel, Ann. Biol. Clin., 1993, Vol. 51, pages 39 to 41.

XIII. The submissions made by appellant I, as far as they are relevant to this decision, may be summarized as follows:

Article 123(2) EPC

There was no limitation in the application as filed to an assay in which the competitive peptide and the peptide used to raise antibodies were the same. This was supported by the statements on page 19, lines 1 to 3, and page 22, lines 9 to 16 of the application as filed. The only constraint imposed in the application on the competitor peptide was that it should be a competitor, ie that it also was reactive with the antibody so as to compete with the collagen fragments in the body fluid for binding to the antibody.

The application explicitly described the peptide Gln-Tyr-Asp-Gly-Lys-Gly-Val-Gly as one to use for raising antibodies (cf. page 19, line 18). Thus, the use of antibodies reactive with that peptide was explicitly envisaged.

Article 54 EPC

The burden of proof lay on the opponent to demonstrate beyond reasonable doubt that practising the teaching of D3 would inevitably lead to an assay as claimed. This would involve naming the peptide relied upon and showing that D3 teaches its use in raising antibodies and also proving the technical fact that the use of that peptide inevitably produces the required antibody response. There was no teaching in D3 to raise antibodies against the specific sequence recited in claim 1.

Article 56 EPC

Figure 9 of D1 demonstrated that the monoclonal antibody 1H11 did not recognise two linear peptides derived from the collagen fragment used to raise the antibody, and in particular the human α2(I) telopeptide fragment comprising the peptide recited in claim 1. Furthermore, it was stated on page 31, lines 1 to 3 that the linear peptides demonstrated little, if any, significant competitive binding. This was confirmed by document D4 (cf. page 1255), in which it was established that the epitope recognised by 1H11 was not simply a linear peptide by synthesising the two linear peptides used in D1 and "showing that these did not compete in the inhibition assay". Furthermore, the experiment reported with reference to Figure 9 in D1 related to the binding of the antibody to a peptide in solution, whereas the claims required binding to an immobilised peptide.

Article 83 EPC

The information provided in the patent allowed the skilled person to carry out an assay in which the competitive peptide was not identical to the peptide used to raise the antibody. The specification taught at paragraph 0062 that it was possible to add or omit one or more amino acid residues from the given sequence. Minor changes of this nature required no more than a small amount of trial and error in order to be accomplished.

XIV. The submissions by appellant II were as follows:

Article 123(2) EPC

The claims defined a particular combination of immunological binding partner and competitive peptide which was never contemplated nor disclosed in the application as originally filed.

No sequence information whatsoever was provided for the synthetic immobilised peptide, which was only defined as having a sequence derived from collagen and having a potential site for cross-linking, but containing no collagen crosslink structure. The term "potential site for cross-linking" should be interpreted as meaning that those synthetic peptides had a potential site for cross-linking that was found in the collagen breakdown products, namely lysine (or hydrolysine). Any broader interpretation would so seriously lack clarity and support under Article 84 and add matter under Article 123(2) EPC that it could not be intended.

The opposition division erred in concluding that the introduction of the term "a potential site for cross-linking" dealt with the objection under Article 123(2) EPC satisfactorily, unless that term was interpreted to mean "lysine".

The application as filed did not disclose an assay in which an immunological binding partner to one peptide was used with a second and different peptide immobilized on a solid surface. In the application as filed, in particular in the statements on page 13, lines 12 to 33, which constituted the core of the

disclosure, no distinction was drawn between competitive peptides and the peptides used in order to define the immunoreactivity of the immunological binding partner used in the assay.

Furthermore, the application as filed did not define the immunological binding partner according to its immunoreactivity with an immobilized peptide, except where the same peptide was used as a competitive peptide. Moreover, no basis was found in the application as filed for the use of an immunological binding partner defined according to its immunoreactivity with the peptide Gln-Tyr-Asp-Gly-Lys-Gly-Val-Gly, except where this peptide was also used as a competitive peptide.

Article 87 EPC

For the same reasons given in connection with Article 123(2) EPC, the claimed subject-matter went beyond the disclosure of the priority document. Accordingly, the claims were not entitled to the claimed priority date, but only to the filing date of the application.

Article 54 EPC

The disclosure of document D3 included a clear and explicit reference to the use of peptides corresponding to the amino terminal telopeptide sequences, and explicitly stated that the peptide could overlap with the cross-linked region of the corresponding collagen molecule. D3 therefore provided an explicit disclosure of a subset of peptide sequences i.e. those surrounding

the cross-linked sequence of the N-terminal telopeptide of type I collagen. Moreover, D3 disclosed that peptides containing 8 to 20 amino acids were especially preferred. Thus, a very large number of individual experiments using different peptides derived from the region indicated in D3 would inevitable result in an antibody which was immunoreactive with the particular peptide recited in the claims of the patent in suit, particularly if polyclonal antibodies were used.

Article 56 EPC

Since the claims were not entitled to priority, document D3 constituted prior art under Article 54(2) EPC and had to be considered for the assessment of inventive step. But, even if the disclosure of document D3 was ignored, having regard to document D1 in combination with the common general knowledge at the priority date - as exemplified in document D15 -, the claimed subject-matter did not involve an inventive step. Document D1 disclosed an immunological assay aimed at the determination of type I collagen fragments in body fluids, and provided a monoclonal antibody ("1H11") which was suitable for the detection of a cross-linked degradation product containing the particular N-terminal telopeptide sequence recited in the claims of the patent in suit. In addition, document D1 disclosed that one fragment of the collagen degradation products from the N-terminus of type I collagen found in body fluids also contained, as part of its structure, that very same peptide. Thus, all the materials required for carrying out the method of claim 1 were available from D1.

The problem to be solved over document D1 was how to formulate an alternative assay for the determination of type I collagen degradation products. The solution to the problem, ie conducting a competition assay using the components described in D1, would have been immediately apparent to the skilled person on reading the same document. Figure 9 in D1 showed that the monoclonal antibody 1H11 was immunologically reactive with the peptide specified in claim 1. In this figure, competitive binding of this peptide against the peptide used to raise the antibody was shown.

Article 83 EPC

There was lack of sufficiency with respect to both producing the necessary antibodies and conducting the assays for the determination of collagen type I fragments in a body fluid in which the competitive peptide was other than the peptide Gln-Tyr-Asp-Gly-Lys-Gly-Val-Gly. Furthermore, the required competitive peptide lacked enablement, because for the vast majority of competitive peptides falling within the scope of the claims there would be no cross-reactivity with a suitable immunological binding partner. Even if the claim was intended to be functionally limited such that it only encompassed the use of peptides which were immunoreactive with the immunological binding partner, the possibilities were endless and the scope of the claim could not be determined without undue burden.

XV. Appellant I (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained on the basis of:

- claims 1 to 6 filed as auxiliary request 5 at the oral proceedings on 13 December 2005,
- description: page 5 as filed at the oral proceedings on 13 December 2005, and pages 2 to 4 and 6 to 22 as granted, and

- Figures: as granted.

XVI. Appellant II (opponent) requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Admission of auxiliary request 5 into the proceedings

1. Appellant II objected to the introduction into the proceedings of the auxiliary request 5 (claims 1 to 6) on the grounds of it being late-filed. This request was filed, in fact, at a very late stage of the appeal proceedings, namely during the oral proceedings before the board. According to the practice of the boards of appeal, requests submitted during the appeal procedure - in particular those filed at oral proceedings - are admitted and considered by the board only if such requests represent *bona fide* attempts to overcome objections raised in the proceedings (cf. T 840/93, OJ EPO 1996, 335; points 3.1 and 3.2.1 of the Reasons).

2. With the amendments introduced into claims 1 and 2 of this additional request, appellant I intended to overcome various objections under Article 123(2) EPC raised by appellant II. Thus, even if filed at such a late stage of the proceedings, the amendments should not have taken appellant II by surprise. It is true that the objections had been raised already at an early stage of the appeal proceedings, ie either in appellant II's statement setting out the grounds of appeal or in its observations in respect of the appeal of the other party; however, their significance might have become clear to appellant I only when they were discussed during the oral proceedings with regard to the requests then on file.

3. The board considered the amendments introduced to claims 1 and 2 of the auxiliary request 5 and found them to be appropriate and necessary to take account of the grounds for opposition invoked by appellant II under Article 100(c) EPC. Furthermore, the claims did not give rise to new objections under Article 123(2) EPC and were, *prima facie*, allowable. Their admission into the proceedings was not likely to cause a substantial procedural complication. Therefore, the board, availing itself of its discretionary power, decided to admit auxiliary request 5 into the proceedings. After withdrawal of all other claim requests on file, the auxiliary request 5 became appellant I's main request.

Article 123(2) and (3) EPC

4. According to Article 123(2) EPC, a European patent application or a European patent may not be amended in

such a way that it contains subject-matter which extends beyond the content of the application as filed. Amendments to the claims of a European patent introduced during opposition proceedings and the subsequent appeal proceedings are not allowed, if the protection conferred by the patent is extended (Article 123(3) EPC).

Claim 1

5. The method of assay according to claim 1 at issue differs from the method of claim 1 as granted in that (i) the synthetic peptide immobilized on a solid surface **has a sequence derived from collagen and a potential site for cross-linking,** but contains no collagen crosslink structure, and (ii) the immunological binding partner **has been raised against a peptide consisting of the amino acid sequence Gln-Tyr-Asp-Gly-Lys-Gly-Val-Gly** and is immunoreactive with an immobilised peptide consisting of the same sequence.

6. The additional features introduced to further characterize the synthetic peptide used in the claimed assay have a basis in the application as filed, *inter alia*, in the passages on page 17, lines 29 to 30 ("*...contacting the sample with a synthetic peptide having a sequence derived from collagen...*"); page 13, lines 24 to 26 ("*Also, the synthetic peptides ... will have potential sites for cross-linking...*"); page 14, lines 30 to 33 ("*In a representative procedure, synthetic peptides containing potential sites for cross-linking, are used for the raising of antibodies and subsequently incorporated in the assay...*"); and on

page 18, lines 22 to 23 under the heading "Preparation of synthetic peptides" ("*Sequences of interest include potential sites for cross-linking.*").

7. The new feature introduced to further characterize the immunological binding partner is derivable from the combination of the passage on page 17, lines 34 to 35 of the application as filed, where it is indicated that the antibody is raised against a synthetic peptide, with the passage on page 19, line 18, where the specific peptide with the amino acid sequence Gln-Tyr-Asp-Gly-Lys-Gly-Val-Gly (also referred to as α1(I)N1 peptide) is disclosed as an example of amino acid sequences to be used as a basis for synthetic peptides. Furthermore, an antibody raised using the specific α1(I)N1 peptide as immunogen is described in Example 1 of the application as filed. This antibody is said to be immunoreactive with the α1(I)N1 peptide conjugated to gelatine and coated onto the solid surface of a microtiter plate (see page 26, lines 6 to 35 and Figure 3).

8. Thus, the amendments introduced into claim 1 comply with Article 123(2) EPC.

9. In its statement of grounds of appeal, appellant II raised various other objections under Article 123(2) EPC, some of which were overcome by the amendments introduced to the claims during the oral proceedings (see Section XIV and points 6 and 7 above). *Inter alia*, appellant II maintained that, whereas the application as filed disclosed only a competitive assay in which the synthetic peptide used to raise the immunological binding partner and the competitive peptide used in the

assay were identical, claim 1 as amended encompassed also an assay in which an immunological binding partner to one peptide was combined with a different peptide immobilized on a solid surface. In appellant II's view, such an assay lacked a basis in the application as filed.

10. The board disagrees with this view. It is true that in the assay described in the examples of the application (see Example 4) the immunogenic peptide used to raise the antibody and the competitive peptide are identical. However, the application clearly teaches that "*it is not necessary to use the same peptide as the immunogen and the competitor in the assay*" (see page 19, lines 1 to 3). Moreover, on page 22, first paragraph under the heading "Conduct of Immunoassays" it is stated that:

> "*The specificity for the desired collagen in the biological fluid is supplied by the antibody in combination with the use of a synthetic peptide (**against which the antibody was raised or in any event with which the antibody is immunochemically reactive**) in the assay construction.*" (emphasis added by the board)

11. It follows from the passages cited above that the invention disclosed in the application as filed is not restricted to assays in which the peptide used for raising the immunological binding partner and the competitive peptide are identical. Rather, different peptides are envisaged in the application, provided that both peptides are capable of immunoreacting with the same immunological binding partner.

12. Furthermore, appellant II argued that the application as filed did not define the immunological binding partner according to its immunoreactivity with an **immobilized** peptide, except where the competitive peptide and the peptide used for raising the immunological binding partner were the same peptide. In this respect, the board notes that on page 14, lines 12 to 17 of the application as filed it is stated that:

> "*In a representative assay, collagen fragments in the patient's body fluid and a synthetic peptide* ***immobilized*** *on a solid surface are contacted with an immunological binding partner which is immunoreactive with* ***the*** *synthetic peptide.*" (emphasis added by the board)

It follows from this passage of the application as filed that, according to the invention, the immunological binding partner must be immunoreactive with the immobilized synthetic peptide. No explicit or implicit general limitation of this disclosure to the effect that the immunological binding partner has to be raised against a synthetic peptide identical to the immobilized peptide, is found in the application as filed. Thus, the objection cannot be accepted.

13. Appellant II contended that no basis could be found in the application as filed for the use of an immunological binding partner defined according to its immunoreactivity with a synthetic peptide having the amino acid sequence Gln-Tyr-Asp-Gly-Lys-Gly-Val-Gly, except where this peptide was also used as a competitive peptide. The board disagrees. In Table 1 of the application as filed (see page 19, in particular

line 18), the specific amino acid sequence recited in claim 1 is disclosed as one of the possible sequences to be used as a basis for synthetic peptides, ie either as an immunogen to raise the immunological binding partner or as a competitive peptide in the assay. The application as filed teaches that, where the synthetic peptide is used as an immunogen, antibodies raised against it are screened for immunoreactivity (see page 21, lines 28 to 31, and Example 1). Furthermore, it follows from the teachings in the application as filed that, if a particular peptide is to be used as a competitive peptide in an assay according to the invention, it must be immunoreactive with the immunological binding partner, so as to be able to compete with collagen fragments present in the sample of body fluid. Thus, it is unambiguously derivable from the description of the application that the immunological binding partner used in the assay of the invention must be in any case immunoreactive with the specific synthetic peptide recited in claim 1.

Claim 2

14. Claim 2, which depends on claim 1, relates to a quantitative assay with essentially the same features as the method of assay of claim 1, even though their respective wording differs slightly. Both the amendments introduced into claim 2 on appeal (see Section XI above) and the objections raised by appellant II (see Section XIV above) are mainly the same as for claim 1. Thus, the reasons given in respect of claim 1 (see points 6 to 13 above) apply *mutatis mutandis* also to claim 2.

15. A further amendment introduced into claim 2 consisted in the deletion of the feature "*spans a region of a sequence of Type I collagen at which in nature a said cross-link structure would form*" referring to the immobilised synthetic peptide used in the assay. By this amendment, the objection under Article 123(2) EPC discussed in the appealed decision (see point 18 of the decision) is overcome. No objection under Article 123(3) EPC was raised by appellant II against the amended claim 2, and the board is satisfied in this respect.

16. Summarizing the above: none of appellant II's arguments in respect of Article 123(2) EPC was convincing. Neither the amendments to claims 1 and 2 nor those introduced into page 5 of the description, which correspond essentially to the amendments to the claims, extend the claimed subject-matter beyond the content of the application as filed. The board thus concludes that claims 1 to 6 meet the requirements of Article 123(2) EPC.

17. Since the amendments introduced to claims 1 and 2 are of limiting nature, the protection conferred by the claims is not extended (cf. Article 123(3) EPC).

Article 84 EPC

18. In its statement of grounds of appeal, appellant II discussed various interpretations of the feature "*having a potential site for cross-linking*" present both in the claims on the basis of which the opposition division intended to maintain the patent and in the present claims. Appellant II concluded that there was only one interpretation of this feature which is

technically consistent with the teachings of the patent, namely that the potential site for cross-linking in the synthetic peptides must be a site found in collagen. However, at oral proceedings appellant II insisted that, for the sake of clarity, the definition of the terms "crosslinkable sites" and "crosslinkable peptides" contained in the application as filed but no longer present in the patent as granted, should be reintroduced.

19. For the following reasons, the board cannot accept this argument. Firstly, appellant II has put forward no arguments as to why the introduction of the original definitions of the terms "crosslinkable sites" and "crosslinkable peptides", which as such are not present in the claims, would contribute to define more clearly the matter for which protection is sought. And secondly, the board is convinced that, even in the absence of these definitions, an objective assessment of the matter of the claims within the meaning of Article 84 EPC is possible in the light of the description of the patent. In respect of the interpretation of the feature "*having a potential site for cross-linking*" in claims 1 and 2, the board believes that paragraph [0051] of the description, in particular its last sentence ("*...the synthetic peptides have a potential site for cross-linking at the lysine incorporated in the structure.*") provides a clear guidance which allows to determine the meaning of this feature in the context of the present claims. Thus, the objection under Article 84 EPC is rejected.

Article 87 EPC

20. In the decision under appeal, the opposition division found that the priority claimed in the patent in suit was valid and that, therefore, document D3, which was published between the priority date and the filing date of the application from which the patent was granted, was not comprised in state of the art under Article 54(2) EPC (see point 14 of the decision). This finding was contested by appellant II.

21. Having considered the arguments put forward on appeal (see Section XIV above), appellant II's view on the limited disclosure content of the priority document cannot be shared. On the contrary, the board is convinced that the skilled person neither could nor would derive from the priority document a general limitation to methods of assay in which the competitive peptide is identical to the synthetic peptide used as immunogen to raise the immunological binding partner. This is not in contradiction with the fact that claim 3 of the priority application is directed to such a specific method, since the subject-matter of this claim represents only one particular embodiment of the invention claimed in claims 1 and 2, from which claim 3 depends. Neither claim 1 nor claim 2 include the alleged general limitation. Nor can appellant II's allegation be supported by the passage of the priority document to which appellant II has referred (see paragraph bridging pages 10 and 11), as this passage indicates that, in a representative assay, the body fluid and a synthetic peptide immobilised on a solid surface are contacted with an immunological binding partner **which is immunoreactive with the synthetic**

peptide. There is no indication whatsoever that the immunological binding partner has necessarily to be raised against the competitive peptide with which is immunoreactive.

22. Since the claimed subject-matter and the subject-matter disclosed in the priority document are the same and represent the "same invention" within the meaning of Article 87(1) EPC, claims 1 to 6 are entitled to the priority of the earlier application (17 September 1993). Consequently, document D3 is not comprised in the state of the art under Article 54(2) EPC and cannot be taken into account in deciding whether there has been an inventive step. Being comprised in the state of art under Article 54(3)(4) EPC, D3 can however be taken into account for the assessment of novelty of the claimed subject-matter.

Novelty (Article 54 EPC)

23. No arguments were put forward by appellant II at oral proceedings on the issue of novelty of the claims 1 to 6 as presently on file. The board notes that, whereas document D3 teaches generally the use of any peptide derived from telopeptide sequences of Type I collagen in a competitive assay for determining collagen Type I fragments in a body fluid, no specific disclosure is found in this document for methods of assay using an immunological binding partner raised against and immunoreactive to the particular peptide recited in claim 1. Thus, the subject-matter of claim 1 as well as that of claims 2 to 5, which depend directly or indirectly on claim 1, is considered to be novel.

Inventive step (Article 56 EPC)

24. Document D1 is considered to be the closest prior art. This document describes a method of detecting collagen degradation by contacting a body fluid with a specific binding partner to telopeptides derived from collagen. For this purpose, a monoclonal antibody (1H11) is described, which was raised against a specific telopeptide derived from the N-terminal telopeptide domain of Type I collagen and has a 3-hydroxypiridinium cross-link (telopeptide P1 of Formula III; see page 10 of D1). The antibody 1H11 recognized an epitope which included chemical features of the two telopeptide sequences (which are referred to as α1(I) and α2(I) N-telopeptides) embodied in the structure of the telopeptide P1 (see page 30, last paragraph, lines 4 to 6), whereas it was not able to recognize either the linear α2(I) N-telopeptide or the α1(I) N-telopeptide. It should be noted that the sequence of the α2(I) N-telopeptide is nearly identical to the sequence of the synthetic peptide specified in claim 1, the only difference being an additional cysteine residue at the carboxy terminus of the telopeptide.

25. The results described in this passage of D1 were obtained by contacting the free peptides competing against plated-out telopeptide P1 or directly as binding partners conjugated to BSA and plated out. In comparison to free P1, which competed with immobilized P1 for binding to the monoclonal antibody 1H11, the α2(I) and α1(I) N-telopeptides demonstrated little if any significant competitive binding with 1H11 (see page 31, lines 1 to 3). The results of these binding experiments are shown as a graph in Figure 9.

26. In view of D1, the objective technical problem to be solved is to provide an alternative immunological assay for detecting collagen fragments in body fluids.

27. This problem is solved by a method of assay according to claim 1. The assay method is based on the competitive binding of collagen fragments in body fluids and synthetic peptides derived from collagen, to an immunological binding partner which has been raised against and is immunoreactive with a synthetic peptide having the sequence Gln-Tyr-Asp-Gly-Lys-Gly-Val-Gly.

28. Appellant II alleged that, starting from the results described in D1 and with a view to providing an alternative immunological assay to detect collagen fragments, it would have been obvious for a skilled person to prepare antibodies against one of the two linear peptides present in the telopeptide fragment P1, specifically against the α2(I) N-telopeptide, and to use these antibodies and the synthetic peptide in a competitive assay to detect collagen fragments in body fluids. For the following reasons, the board considers that this conclusion could only be reached with the hindsight knowledge of the present invention.

29. Firstly, neither document D1 nor the further prior art documents cited by appellant II would motivate the skilled person to try to obtain antibodies against a synthetic peptide having the amino acid sequence of **one** of the two linear peptides of the telopeptide fragment P1, in particular against the α2(I) N-telopeptide. The results described in D1 (see point 25 above) indicated that the P1 epitope

recognised by the antibodies was a conformational epitope including features of the **two** cross-linked peptides. Thus, in view of these results the skilled person would rather be discouraged from using only one of the peptides as immunogen, since he/she would recognize that, the epitope being possibly incomplete, the antibodies raised may not immunoreact with telopeptide fragments in the natural cross-linked form found in body fluids.

Document D4, a scientific publication authored, *inter alia*, by the identified inventor of D1, does not contain more relevant information than the closest prior art, but merely confirms the observations in document D1 (cf. D4, page 1255, paragraph bridging the left and right columns). Accordingly, no hint in the direction of the claimed invention can be expected from this document.

Document D15 in fact suggests the use of synthetic peptides that mimic the antigenic determinants of proteins for the preparation of antibodies (see first sentence of the Summary). However, if the skilled person were to follow the advice given in D15, he/she, being aware of the information on the recognised epitope provided in document D1, would try to mimic this epitope by combining in the immunogenic synthetic peptide amino acid sequences from each of the linear cross-linked peptides in P1, thus departing from the solution proposed in the patent. Hence, the combination of the teachings of documents D1 and D15 would fail to motivate the skilled person to try to use the α2(I) N-telopeptide and antibodies raised against it in an

assay for determining collagen fragments in a body fluid.

Secondly, should the skilled person nevertheless have tried to determine collagen fragments present in body fluids by an assay based on the **competition** between the collagen fragments and a synthetic peptide (competitive peptide) which contains no collagen crosslink structure, he/she would not have had any expectation of succeeding. As stated above (see point 25), in the experiment reported in the paragraph bridging pages 30 to 31 of document D1 the antibody 1H11 (raised against the telopeptide P1 having a crosslink structure) failed to recognize the linear synthetic α2(I) N-telopeptide and, consequently, "little if any" significant competitive binding of the synthetic telopeptide to the antibody was observed (see experiment described in the paragraph bridging pages 30 to 31 of D1). The same result is reported in document D4. In view of these results and, in particular, the conclusions reached by the authors of document D1, the skilled person would not have reasonably expected that antibodies raised against a **linear** peptide as specified in claim 1 would be able to recognize cross-linked structures in which the epitope includes features of **two** different peptides being **cross-linked**, the immunological binding partner being immunoreactive not only with the peptide used to raise it, but also with both the collagen fragments **and** the competitive peptide. Thus, an inventive step is acknowledged.

Article 83 EPC

30. No evidence has been provided by appellant II to support its allegation of lack of sufficient disclosure, and the board has no reason to question the disclosure of the patent with respect to the obtention of antibodies against the peptide recited in claims 1 and 2. Moreover, appellant II's allegation with respect to the functional limitation of the required competitive peptide to those being immunoreactive with the immunological binding partner (see Section XIV above) cannot be accepted. The patent discloses that synthetic peptides to be used as competitive peptide in the claimed assay can be obtained by omission or addition of one or more amino acid residues from (or to) the sequences indicated in the patent, in particular the sequence specified in claims 1 and 2, as long as the peptide retains its ability to inhibit the binding of the immunological binding partner to the native fragment (see paragraph [0062] of the patent). Even if the skilled person may have to carry out binding experiments in order to determine whether or not the modified peptide is still able to compete with the collagen fragments present in the body fluid, the board considers that the required amount of experimentation would not represent an undue burden. Thus, the requirement of Article 83 EPC is met.

31. The board concludes that none of the grounds of opposition invoked by appellant II prejudices the maintenance of the patent on the basis of claims 1 to 6 as filed during the oral proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of:

   – claims 1 to 6 filed as auxiliary request 5 at the oral proceedings on 13 December 2005,

   - description: page 5 as filed at the oral proceedings on 13 December 2005, and pages 2 to 4 and 6 to 22 as granted, and

   - Figures: as granted.

The Registrar: The Chairman:

A. Wolinski L. Galligani