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# D E C I S I O N
# of 29 January 2002

**Case Number:** T 0247/97 - 3.3.4

**Application Number:** 88302782.3

**Publication Number:** 0285370

**IPC:** A61K 35/50

**Language of the proceedings:** EN

**Title of invention:**
Injectable soft tissue augmentation materials from the placenta and their method of manufacture

**Patentee:**
INSTITUT CLAYTON DE LA RECHERCHE

**Opponent:**
IMEDEX

**Headword:**
Augmentation materials from the placenta/INSTITUT CLAYTON DE LA RECHERCHE

**Relevant legal provisions:**
EPC Art. 54, 56, 123(2)(3)

**Keyword:**
"Main request: novelty (yes); Inventive step (no)"
"Auxiliary request: added subject-matter (no); extension of scope of protection (no), novelty (yes), inventive step (yes)"

**Decisions cited:**
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**Catchword:**
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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0247/97 - 3.3.4

**D E C I S I O N**
**of the Technical Board of Appeal 3.3.4**
**of 29 January 2002**

**Appellant:** (Proprietor of the patent)
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**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted 20 February 1997 revoking European patent No. 0 285 370 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chairwoman:** U. M. Kinkeldey
**Members:** R. E. Gramaglia
V. Di Cerbo

## Summary of Facts and Submissions

I. The appeal is against the decision of the opposition division revoking European patent No. 0 285 370 (application No. 88 302 782.3), which had been opposed by the respondent (opponent) on the grounds of lack of novelty and inventive step. Independent claims 1 and 8 as granted read as follows:

"1. An injectable soft tissue augmentation material comprising a sterilised mixture of type I and type III collagen extracted by proteolytic digestion of insoluble amnion, soluble amnion, soluble chorion from human placenta, and combinations thereof, homogenised to pass through a surgical needle.

8. A method of making an injectable soft tissue augmentation material comprising, sterilising a mixture of type I and type III collagen extracted by proteolytic digestion of insoluble amnion, soluble amnion, soluble chorion from human placenta, and combinations thereof, and homogenising the material sufficiently to pass through at least a 0.556 mm diameter (25 gauge) surgical needle."

Claims 2 to 7 and 9 to 13 related to specific embodiments of the injectable soft tissue augmentation material of claim 1 or of the method of claim 8, respectively.

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

(D1): Marie Claire, No. 410, page 360 (October 1986);

(D2): Madame Figaro, No. 1311, pages 172 to 176 (October 1986);

(D3): Tardy M. et al., Enjeux, No. 74, pages 79 to 82 (November 1986);

(D4): EP-A1-0 083 868;

(D5): US-A-4,485,096.

III. On 28 January 2002, the appellant submitted claims 1 to 13 of an auxiliary claim request, wherein claims 1 and 8 read as follows:

"1. An injectable soft tissue augmentation material comprising a sterilized mixture of type I and type III collagen in a ratio of type I to type III of 57:43, extracted by proteolytic digestion of insoluble amnion or soluble amnion from human placenta, and combinations thereof, homogenised to pass through a surgical needle.

8. A method of making an injectable soft tissue augmentation material comprising, sterilizing a mixture of type I and type III collagen in a ratio of 57:43, extracted by proteolytic digestion of insoluble amnion or soluble amnion from human placenta and combinations thereof, and homogenising the material sufficiently to pass through at least a 0.556 mm diameter (25 gauge) surgical needle."

Claims 2 to 7 and 9 to 13 were as granted.

IV. With a letter dated 25 January 2002, the respondent withdrew the opposition.

V. Oral proceedings were held on 29 January 2002.

VI. The submissions by the appellant can be summarized as follows:

*Main request*

*Novelty (Article 54 EPC)*

- Documents (D1) and (D2) were non-technical publications which provided no specific details about what particular part of the placenta (amnion/chorion) one had to start with, the type(s) of collagen to be used and the process of production. Document (D3) did not disclose injectable augmentation material comprising type I and type III collagen. Document (D4) related to collagen derived from bovine or porcine sources. Therefore these documents failed to disclose a product having all the technical features recited in claim 1.

*Inventive step (Article 56 EPC)*

- The problem to be solved was to improve the injectable augmentation materials of bovine origin such as Zyderm® (referred to in document (D4), on page 1, line 26 and in the patent in suit, eg on page 3, lines 20 to 22) and Zyplast® (see page 3, lines 28 to 29 of the patent in suit). The solution provided were the compositions according to claim 1 which, compared with these known augmentation materials, achieved the following unexpected advantageous effects: (i) a reduction in adverse immunological reactions (see page 5, lines 24 to 25

of the patent in suit) ; (ii) a longer persistence at six months (see Table 2 on page 8); (iii) a greater fibrocytic ingrowth and neovascularisation vis-à-vis the bovine collagen implants and adipocytes deposition in the implant (see page 8, lines 5 to 10 and 46 to 57).

- While the skilled person might have learned from documents (D1) and (D2) the vague idea that human placenta collagen could be an alternative to products derived from bovine sources, he/she would not have arrived at the claimed subject-matter on the following grounds:

  - Although the prior art bovine products (such as Zyderm®) were based on type I/type III collagen mixtures, the skilled person would not have selected the type I/type III collagen fraction from human placenta because there were differences in composition between type I/type III collagen mixtures obtained from human placenta and those obtained from bovine sources.

  - Documents (D1) and (D2) were magazines which merely mentioned that collagen from the human placenta could be used to fill up wrinkles with reduced allergenicity. No details were given about the process of production or what particular part of the placenta (amnion/chorion) one had to start with.

  - Document (3) reviewed the biomaterials obtainable from human placenta, including two fractions of collagen (collagen type IV and a mixture of collagen type I and collagen

type III). The only injectable materials mentioned were solutions of type IV collagen useful in ophthalmology. No injectable preparations comprising the type I/type III collagen mixture were disclosed but merely solid gels for use in healing ("cicatrisation"), surgical haemostasis, reconstitution of (possibly burned) living skin and tissue repair. There was thus no suggestion in document (D3) to use a type I/type III collagen mixture from human placenta as an injectable composition for augmentation (eg filling up wrinkles). On the contrary, there were good reasons for the reader of document (D3) to avoid using a type I/type III collagen mixture from human placenta for augmentation. In fact, document (D3) pointed towards type IV collagen from human placenta as injectable collagen. Moreover, it was emphasised in this document that a problem arose upon colonisation of type I/type III collagen mixtures from human placenta by fibroblasts: the length of the applied gel contracted by a factor of 5.

*Auxiliary request*
*Novelty*

- Documents (D1) to (D4) failed to disclose all the technical features recited in claim 1, including the ratio of collagen type I to type III of 57:43.

*Inventive step (Article 56 EPC)*

- The amendments to independent claims 1 and 8 resulted in a restriction of the placental source of

type I and type III collagen to the amnion of human placenta (the wording "soluble chorion" had been deleted). As an effect of this restriction, the ratio of type I to type III collagen in the mixture was 53:47, as mentioned in the patent in suit on page 9, line 9.

- The use of amnion-derived collagen (having thus a ratio of type I to type III of 53:47) gave rise to the unexpected advantageous effects (i) to (iii) already pointed out in relation to the main request.

- No prior art document suggested the proportion 53:47 recited in claim 1. While documents (D1) and (D2) were silent about this specific ratio, document (D3) taught that one had to start from whole placenta (see Table 2: "tissu placentaire"), thus leading to a different ratio of type I to type III collagen than the one stated in claim 1.

VII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained as granted (main request) or on the basis of claims 1 to 13 filed with the letter dated 28 January 2002 (auxiliary request).

## Reasons for the Decision

1. The appeal is admissible.

*Main request*
*Novelty*

2. Documents (D1) and (D2) do not provide specific

technical details inter alia about which collagen type(s) among the possible types I, III, IV, V, VI (see Table 1 of document (D3)) have to be present in the augmentation material and about what particular part of the placenta (amnion/chorion) one had to start with.

Document (3) reviews the biomaterials obtainable from human placenta, including two fractions of collagen (collagen type IV and a mixture of collagen type I and collagen type III ). The only injectable material mentioned in this document is a solution of type IV collagen useful in ophthalmology (see central column on page 81). No injectable preparation comprising a type I/type III collagen mixture is disclosed but merely solid gels for use in healing ("cicatrisation"), surgical haemostasis, reconstitution of (possibly burned) living skin. It is true that reference is made on page 81, r-h column to "comblement" (filling), however, it is in the context of a porous solid collagen structure comprising fibrin and growth factors (PDGF, â-TGF) to be used for promoting healing. There is thus no disclosure in document (D3) of the use of a type I/ type III collagen mixture from human placenta as an injectable composition for augmentation (eg filling up wrinkles).

Document (4) discloses injectable soft tissue augmentation material comprising collagen from bovine or porcine corium (skin).

In view of the foregoing, it must be concluded that none of documents (D1) to (D4) discloses all the technical features of the material of claim 1 and the method of claim 8. Therefore these claims and dependent

claims 2 to 7 and 9 to 13 are found to satisfy the requirements of Article 54 EPC.

*Inventive step (Article 56EPC)*

3. The appellant considers that the compositions according to claim 1 provide a solution to the problem of improving (see patent in suit, bottom of page 3) the known injectable augmentation materials of bovine origin such as Zyderm® (referred to in document (D4), on page 1, line 26 and in the patent in suit, eg on page 3, lines 20 to 22) and Zyplast® (ibidem, page 3, lines 28 to 29). It is argued that the claimed compositions, compared with these augmentation materials based on bovine collagen, achieve the following unexpected advantageous effects: (i) a reduction in adverse immunological reactions (see page 5, lines 24 to 25 of the patent in suit); (ii) a longer persistence at six months (ibidem, Table II on page 8); (iii) a greater fibrocytic ingrowth and neovascularisation and adipocytes deposition in the implant (ibidem, page 8, lines 5 to 10 and 46 to 57).

4. As for advantageous effect (i) above, in the board's opinion, collagen from human placenta, unlike bovine collagen, is not "xenogeneic" (patent in suit, page 5, line 24). Hence it is obvious to the skilled person that it induces less adverse immunological effects, if at all. Technical effect (i) has thus to be treated as an obvious and expected effect, also in view of documents (D1) and (D2) (see eg the third column on page 176 of document (D2): "[le collagène tiré du placenta humain est] anallergique car tout à fait identique à notre propre collagène").

As regards advantageous effect (iii) above, the appellant admits that it is a mere explanation of effect (ii) rather than a technical effect per se (see point 13 of the Grounds for Appeal: "This [effect (iii)] leads to greater persistence for the claimed implants"). The board agrees as well that effect (iii) can be merged with effect (ii).

In view of this, the only technical effect left, possibly giving rise to a problem to be solved vis-à-vis the bovine implants of the prior art, is effect (ii) above (longer persistence at six months).

5. As evidence that the claimed compositions exhibit technical effect (ii), the appellant points to Table 2 on page 8 of the patent in suit, dealing with the persistence of implants from human placenta after six months.

Yet the board observes that "Groups 8 and 10" listed in column 1 of Table 2, relating to two compositions according to claim 1 based on (or comprising) soluble chorion from human placenta, turn out to be comparable or worse than Zyderm® and Zyplast® as to the persistence at six months. For these reasons the board is not ready to accept that the problem to be solved by the claimed subject-matter is to prepare a better product (exhibiting longer persistence at six months) than Zyderm® and Zyplast®.

6. In the absence of any advantageous technical effect, the objective problem solved by the claimed subject-matter has to be restated to meet a less ambitious objective, namely the provision of a further or alternative augmentation material, differing from

Zyderm® and Zyplast® by the fact it is extracted by proteolytic digestion of insoluble amnion and/or soluble amnion from human placenta. The remaining technical features of this further augmentation material are common to Zyderm® and Zyplast®, since these also comprise a mixture of type I and type III collagen (see page 9, line 9 of the patent in suit) and have also been sterilised and homogenised to pass through a surgical needle. The question to be answered is whether or not it would have been obvious for the skilled person to arrive at something falling under the terms of claim 1.

7. Thus, there was an incentive for the skilled person to turn to collagen from human placenta in view of its lower immunogenicity (as confirmed by documents (D1) and (D2)), in particular to a fraction thereof possibly comprising a mixture of type I and type III collagen as in Zyderm® and Zyplast®.

But Table 2 of document (D3) already taught the skilled person how to obtain this fraction. This Table was a flow chart relating to the proteolytic digestion of whole human placenta yielding a first fraction being a mixture of collagen type I and type III and another fraction being collagen IV. Document (D3) also warned that pepsin digestion was the only way to extract collagen without denaturation (see page 80, r-h column, lines 5 to 8).

In the board's judgement, once the skilled person put the extraction process of Table 2 into practice by departing from whole placenta ("tissu placentaire"), he/she would of necessity arrive at "a mixture of type I and type III collagen extracted by proteolytic

digestion of insoluble amnion, soluble amnion, soluble chorion from human placenta, and combinations thereof" as worded in claim 1 at issue. This is because human placenta consists mainly of amnion and chorion (see Figure 3 on page 14 of priority document GB 8708009 underlying the patent in suit; this Figure is no longer present in the patent specification). It is true that this material had still to be sterilised and homogenised to pass through a surgical needle, in order for it to exhibit all the features of present claim 1, but these were routine steps if one wished to get an injectable soft tissue augmentation material.

8. According to the appellant, the reader of document (D3) would have avoided using a type I/type III collagen mixture from human placenta for augmentation in view of the problem arising upon colonisation of type I/type III collagen mixtures from human placenta by fibroblasts (contraction of the length of the applied gel by a factor of 5). In the board's view, though, the passage of document (D3) on page 81, r-h column, last paragraph pointed out by the appellant relates to artificial skin production (Reference [16] in this passage deals with "The reconstitution of living skin"). A similar passage in document (D5), column 3, lines 45 to 46, also relates to the preparation of "a tissue equivalent useful in the treatment of burns". It is the board's view that reconstitution of living skin for treating burns or other skin wounds is a different field than filling up wrinkles with hypodermic syringes. The skilled person would thus not conclude that a problem turning up when making artificial skin with a mixture of type I/type III collagen **and** skin fibroblasts would also arise when using a type I/type III collagen

mixture alone for augmentation.

9. In view of the foregoing, it must be concluded that it was obvious for the skilled person to arrive at something falling under the terms of claim 1. The appellant's main request is thus not allowable under the terms of Article 56 EPC.

*Auxiliary request*
*Article 123(2) and (3) EPC*
*Claims 1 and 8*

10. Claims 1 and 8 are based on claims 1 and 8 as granted with the introduction of the wording "in a ratio of type I to type III of 57:43" and the deletion of "soluble chorion" (see paragraph III supra). The wording "in a ratio of type I to type III of 57:43" finds a basis in the published application as filed on page 8, lines 6 and 7. Furthermore, the claims are narrower than the granted claims since they are limited to injectable soft tissue augmentation material (and a method for making it) comprising (or starting from) collagen extracted from the amnion of human placenta, while the granted claims were not so limited. In conclusion, the claims of the auxiliary request do not infringe Article 123(2) and (3) EPC.

*Novelty (Article 54 EPC)*

11. The conclusion arrived at by the board in relation to the main request (see point 2 supra) also applies to the claims of this request, differing therefrom by the deletion of "soluble chorion" and the introduction of "in a ratio of type I to type III of 57:43". The documents of the prior art (D1) to (D4) indeed fail to

disclose all the technical features recited in independent claims 1 and 8, let alone the ratio of collagen type I to type III of 57:43.

*Inventive step (Article 56 EPC)*

12. The appellant maintains that the use of amnion-derived collagen having the above ratio of type I to type III collagen gives rise to the unexpected advantageous effects (i), (ii) and (iii) already pointed out in relation to the main request.

13. Bearing in mind that effect (ii) (persistence at six months) is the only technical effect to be possibly taken into account (see point 4 supra), the board agrees that Table 2 of the patent in suit illustrates a longer persistence at six months of amnion-derived collagen implants having a ratio of type I to type III of 53:47 . "Groups 2, 4 and 6" listed in column 1 of Table 2 , relating to three such compositions, perform indeed equally well as Zyderm® and Zyplast® (the latter is bovine collagen cross-linked with glutaraldehyde: see page 3, line 29 of the patent in suit), however at a lower collagen concentration (compare 37.2 mg/ml, 22.2 mg/ml and 40.5 mg/ml with 65 mg/ml and 35 mg/ml) or without the need for cross-linking. The board is thus ready to accept that the problem to be solved by the claimed subject-matter is to prepare a better product (exhibiting longer persistence at six months) than Zyderm® and Zyplast®.

14. In the board's judgement, no prior art document suggests that the solution to the above problem lies with selecting the proportion 53:47 recited in claims 1 and 8. While documents (D1) and (D2) are silent about

this specific ratio, document (D3) teaches that one has to start from whole placenta (see Table 2: "tissu placentaire"), thus leading to a different ratio of type I to type III collagen than the one stated in claims 1 and 8. Consequently, these claims and dependent claims 2 to 7 and 9 to 13 satisfy the requirements of Article 56 EPC.

15. The board concludes that the appellant's auxiliary request has to be accepted.

## 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 13 filed with the letter dated 28 January 2002, and pages 4 to 7 and 10 of the description filed at the oral proceedings and pages 2, 3, 8 and 9 as granted.

The Registrar: The Chairwoman:

P. Cremona U.M. Kinkeldey