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D E C I S I O N
of 9 September 2003

Case Number: T 0803/01 - 3.3.3

Application Number: 97202586.0

Publication Number: 0816413

IPC: C08G 63/90

Language of the proceedings: EN

Title of invention:
Purified polylactide and pharmaceutical composition thereof

Patentee:
Novartis AG

Opponent:
-

Headword:
-

Relevant legal provisions:
EPC Art. 54, 56, 84
EPC R. 29(1)

Keyword:
"Claims - clarity (yes)"
"Novelty - purity of a polymeric compound a new element (yes)"
"Inventive step (yes)"

Decisions cited:
G 0002/88, T 0012/81, T 0204/83, T 0205/83, T 0206/83, T 0450/89, T 0012/90, T 0595/90 ,T 0990/96, T 0100/00

Catchword:
The question of whether a degree of purity of a compund provides a new element over the prior art must be sought in the concrete technical context concerned (reasons, point 4.6)

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Case Number: T 0803/01 - 3.3.3

D E C I S I O N
of the Technical Board of Appeal 3.3.3
of 9 September 2003

Appellant: Novartis AG
Lichtstrasse 35
CH-4056 Basel (CH)

Representative: -

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 24 October 2000 refusing European application No. 97202586.0 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: R. Young
Members: W. Sieber
J. Van Moer

Summary of Facts and Submissions

I. European patent application No. 97 202 586.0, filed in accordance with Article 76 EPC as a divisional application of the earlier application 91 112 725.6 (29 July 1991), claiming GB priorities of 1 August 1990 (9016882 and 9016840) and published under No. 0 816 413 on 7 January 1998, was refused by a decision of the examining division issued in writing on 24 October 2000.

II. The decision was based on a set of Claims 1 to 32 where the independent claims read as follows:

"1. A polylactide being an ester of a polyol containing at least 3 hydroxyl groups and being in a purified state, which meets the requirements of

- the colour strengths of reference solutions B_2-B_9 of the brown colour test of the European Pharmacopoeia, 2nd Edition (1980) part I, Section V, 6.2 and

- containing one or more metals in cationic form, the metal ion(s) having a concentration of at most 10 ppm.

6. A polylactide in a purified state, which meets the requirements of

- the colour strengths of reference solutions B_2-B_9 of the brown colour test of the European Pharmacopoeia, 2nd Edition (1980) part I, Section V, 6.2 and

- containing one or more metals in cationic form, the metal ion(s) being residues of catalysis and having a concentration of at most 10 ppm.

27. A pharmaceutical composition containing a polylactide according to any one of claims 1-26 as a matrix for a drug compound.

32. Process for the preparation of the pharmaceutical composition of any one of claims 27-31, which comprises working up the polylactide of claims 1-26 with the drug compound to form an implantate or a microparticle."

Claims 2 to 5, 7 to 26 and 28 to 31 were dependent claims directed to elaborations of the subject-matter of Claims 1, 6 and 27, respectively.

III. According to the decision, the application was refused since the requirements of Articles 84, 54 and 56 EPC were not met:

(a) Claims 1 to 26 were not clear (Article 84 EPC) since the claimed chemical compound was not defined by features inherent to this compound but by features attributable to impurities, ie the concentration of a metal cation or the colouration of the compound originating from the presence of these impurities.

(b) It was also not clear whether or not metal cation-free polylactide was covered by the wording of Claims 1 to 6 (Article 84 EPC). Even if the claims had to be read as requiring the presence of some metal cation, they would still be unclear since the lower limit of the concentration of the metal cation would depend on an unspecified analytical method.

(c) Furthermore, the decision objected against the claimed subject-matter under Articles 54 and 56 EPC. In particular, reference was made to the following documents:

D1: EP-A-283 925;

D2: GB-A-2 145 422;

D3: EP-A-0 171 907; and

D5: Patent Abstracts of Japan Vol. 10, No. 296 (C-337) & JP-A-62111326.

IV. On 20 December 2000, a notice of appeal against the above decision was filed by the applicant (hereinafter referred to as the appellant) with simultaneous payment of the prescribed fee.

The statement of grounds of appeal, filed on 28 February 2001, was accompanied by three sets of claims forming a main request and a first and second auxiliary request.

V. In a communication dated 26 June 2003 accompanying a summons to oral proceedings, the board raised objection against some of the claims filed on 28 February 2001 under Articles 123(2) and 84 EPC.

VI. In reply, the appellant filed on 8 August 2003 a new set of Claims 1 to 10 (main request) and, as an auxiliary request, an alternative Claim 1.

VII. Oral proceedings were held on 9 September 2003, in the course of which the discussion focussed on the question of whether the claims filed on 8 August 2003 met the requirements of Articles 123(2) and 84 EPC. In view of this discussion, the appellant withdrew all the previous requests and filed as its sole request a set of Claims 1 to 8 which read as follows:

"1. A pharmaceutical composition comprising a polylactide in a purified state which polylactide is an ester of a polyol containing at least 3 hydroxyl groups and which meets the requirements of

- the color strenght [sic] of reference solutions B_2-B_9 of the brown color test of the European Pharmacopeia [*sic*], 2nd Edition (1980) part I, Section V, 6.2 and

- containing one or more metals in cationic form, the metal ion(s) having a concentration of at most 10 ppm,

and

a hydrophilic or lipophilic drug.

2. The pharmaceutical composition according to claim 1, wherein the polylactide is a polylactide-co-glycolide and/or the polyol is glucose.

3. The pharmaceutical composition according to claim 2, wherein the monomer molar ratio of the lactide/ glycolide units in the polylactide is 100-25/0-75, preferably 60-40/40-60.

4. The pharmaceutical composition according to any of the preceding claims, wherein the polylactide has a mean molecular weight M_w of from 10000 to 200000, preferably from 25000 to 100000, more preferably from 35000 to 60000.

5. The pharmaceutical composition according to any of the preceding claims, wherein the polylactide has a polydispersity M_w/M_n of from 1.7 to 3.0, preferably from 2.0 to 2.5.

6. The pharmaceutical composition according to any of the preceding claims, wherein the polylactide further comprises
monomer in a content of at most 1% by weight of polylactide,
water in a content of at most 1% by weight of polylactide,
organic solvent in a content of at most 1% by weight of polylactide,
ash in a content of at most 0.1% by weight of polylactide,
ethyl hexanoate in a content of at most 0.5% by weight of polylactide,
and which acid number is at most 10.

7. The pharmaceutical composition according to any of claims 1 to 6, comprising bromocriptine, octreotide or an acid addition salt or a derivative thereof as drug substance.

8. The pharmaceutical composition according to claim 7 in form of an implant or microparticles."

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of Claims 1 to 8 filed as the sole request at the oral proceedings.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 EPC and Rule 64 EPC and is therefore admissible.

2. *Amendments*

2.1 Claim 1 is a combination of

- Claim 1 as originally filed (polylactide in a purified state),

- Claim 13 as originally filed (the polylactide being an ester of a polyol containing at least 3 hydroxyl groups), and

- page 9, lines 26 to 34 of the application as originally filed (pharmaceutical composition).

2.2 Claim 2 is based on Claim 9 as originally filed and on page 5, lines 13 to 14 of the application as originally filed.

2.3 Claim 3 is based on Claims 10 and 12 as originally filed.

2.4 Claim 4 is based on Claim 17 as originally filed and on page 5, lines 23 to 25 of the application as originally filed.

2.5 Claim 5 is based on Claim 18 as originally filed and on page 5, lines 25 to 26 of the application as originally filed.

2.6 Claim 6 is based on Claims 7 and 8 as originally filed.

2.7 Claim 7 is a combination of Claims 23 and 26 as originally filed.

2.8 Claim 8 is based on Claim 27 as originally filed.

2.9 Thus, the board is satisfied that the amended claims meet the requirements of Article 123(2) EPC.

3. *Clarity*

3.1 According to Claim 1, the matter for which protection is sought is constituted by a pharmaceutical composition requiring the presence of two components, namely a polylactide and a drug, whereby the polylactide is further defined by its structure (an ester of a polyol containing at least three hydroxyl groups) and by its degree of purity, ie the colour of the polylactide and the metal cation concentration therein. The coloration of the polylactide is due to a certain amount of brown coloured decomposition by-products which have been formed in the polymer preparation process and the metal cations basically are the remnants of the catalyst normally employed in the

preparation process (paragraph bridging pages 1 and 2 of the application as originally filed).

3.2 In the decision under appeal, the examining division objected to the parameters relating to the degree of purity under Article 84 EPC since it was not allowable to define a chemical product by parameters not inherent to the product but attributable to the presence of certain impurities. In this context, reference was made to T 205/83 (OJ EPO 1985, 363).

3.3 Although Claim 1 is not directed to a polylactide *per se* any more, the polylactide is, nevertheless, a component of the now claimed composition, and defined in the same way which was refused by the examining division.

3.3.1 The board takes note that there is no statement whatsoever in T 205/83 which prohibits the presence of parameters relating to impurities in a claim for reasons of clarity. Moreover, the statement in T 205/83 (point 3.2.3 of the reasons) relied upon by the examining division, namely to disregard properties which are not attributable to the substance parameters of the product itself, eg impurities, was reached in the assessment of novelty. This issue is dealt with in point 4.3 to 4.6, below.

3.3.2 Thus, the argument, in the decision under appeal, that the definition of a chemical product by parameters not inherent to the chemical product is not allowable in view of Article 84 EPC goes without justification beyond the finding in the case law relied upon.

3.3.3 Furthermore, the application in suit has at its heart the purification of polylactides. The two parameters relating to the purity of the polylactides are therefore technical features of the invention in line with Rule 29(1) EPC according to which "The claims shall define matter for which protection is sought in terms of the technical features of the invention". This is considered to be a relevant criterion for the assessment of the extent to which the use of purity parameters in a product claim is allowable from the point of view of clarity (Article 84 EPC) (see G 2/88, point 2.5 of the reasons).

3.3.4 It follows from the above, that parameters relating to purity do not in principle contravene the requirements of Article 84 EPC.

3.4 As regards the metal cation concentration, there was a discussion as to the meaning of the wording "polylactide ... containing one or more metals in cationic form, the metal ion(s) having a concentration of at most 10 ppm". According to the appellant, this wording left no doubt as to the presence of metal cation(s). Furthermore, it was impossible completely to remove the remnants of the metal catalyst employed in the polymer preparation.

3.4.1 If a metal catalyst is used in the preparation of the polylactide it is certainly true that it is not possible for thermodynamical reasons to purify a polylactide so that it is - in the strict sense - totally free of metal cations. However, Claim 1 is not restricted to the use of polylactides prepared in the presence of a catalyst. In fact, as is apparent from

page 2 of the application as originally filed, polylactides could be prepared in the absence of a catalyst.

3.4.2 Furthermore, as mentioned in point 3.3.3 above, the application in suit is concerned with the purification of polylactides. It is the purpose of this purification to remove the catalyst, together with the brown impurities, as far as possible (page 2, lines 11 to 12 of the application as originally). In other words, the aim of the purification is a limitless removal of the metal ions with the consequence that they are not detectable any more by analytical means. Example 1b, for instance, reports a tin content of less than 1 ppm, which means, according to the submissions of the appellant of 14 March 2000, point 3, "that tin was not detectable within the limits of the analytical method".

3.4.3 Hence, in the board's view, in the context of the description, the wording "containing at most" in Claim 1 should be interpreted as embracing not only polylactides comprising still impurities within the limits of Claim 1, but also the possibility of metal cation-free polylactides, namely in the sense of not containing metal cations at all (since no metal catalyst was used during the preparation of the polylactides) and in the sense of not containing analytically detectable amounts of metal cations (since the polylactides have been purified to such a high degree).

3.5 As regards the second requirement of the polylactide, the colour, there is no doubt that it is possible clearly and reliably to define this parameter since the exact method of measurement is indicated in Claim 1.

3.6 In summary, the board is satisfied that Claim 1, and in particular with regard to the definition of the polylactide, meets the requirements of Article 84 EPC.

4. *Novelty*

4.1 D1 relates to a process for purifying polymers, in particular resorbable polyesters, where the polymer is dissolved in a solvent and the polymer solution is subsequently brought into intimate contact with a precipitation agent under the effect of high shear forces in a turbulent shear field, so that the polymer precipitated is divided up into minute particles. D3 to D5 disclose copolymers prepared from glycolic acid and/or lactic acid and glycolide and/or lactide, respectively. However, none of documents D1 and D3 to D5 discloses a polylactide with a structure required in Claim 1, ie an ester of a polyol containing at least three hydroxyl groups.

4.2 The only document which, in the board's view, is sufficiently close to the claimed subject-matter to enter into consideration as possibly being of relevance for novelty is D2.

4.2.1 According to D2, there is disclosed an ester of a polyol, that polyol containing at least three hydroxyl groups and having a molecular weight of up to 20,000, at least one hydroxyl group in that polyol being in the

form of an ester with a poly- or copolylactic acid residue each having a molecular weight of at least 5,000 (Claim 1). Not only have the polylactides of D2 the structure required in Claim 1, they are also used as a depot matrix material for a pharmaceutically active agent (Claim 26), such as bromocriptine (Claim 27) which is a lipophilic drug. Whilst it is stated in D2 at page 2, line 47 that the formed polyol ester "may be purified and isolated in a conventional manner" and a detailed purification procedure is given in the examples, in particular Examples 1 and 6, D2 is silent on the colour and metal ion content of the obtained products.

4.2.2 Hence, the only feature of the subject-matter of Claim 1 which is not literally disclosed in D2 is the degree of purity of the polylactide, in particular the colour and the metal cation content. Therefore, it has to be examined whether the degree of purity is suitable to establish novelty over D2.

4.3 The first question to be answered in this respect is whether a degree of purity of a chemical compound is in principle a suitable distinguishing feature over relevant prior art.

4.3.1 T 205/83 rejected evidence of novelty involving properties which were not attributable to the substance parameters of the product itself, in that case absence of monomer impurities with an unwanted odour (see point 3.3.1, above).

4.3.2 On the other hand, the European Patent Convention contains no such restriction with regard to novelty. Article 54(1) EPC stipulates that an invention shall be considered to be new if it does not form part of the state of the art, whereby state of the art is according to Article 54(2) EPC held to comprise everything made available to the public before the date of filing of the European patent application. As regards the interpretation of the words "made available to the public", the boards of appeal took the view that, for the purposes of destroying novelty, an earlier document has to contain not only a clear and unmistakable disclosure of the subject matter of the later invention, including implicit features (eg T 204/83 OJ EPO 1985, 310; T 450/89 of 15 October 1989; T 100/00 of 7 March 2003, the latter two decisions not published in OJ EPO), but must contain also a so-called "enabling disclosure" (T 206/83 OJ EPO 1987, 005).

4.3.3 Basically it is the purpose of Article 54(1) and (2) EPC to prevent the state of the art being patented again, and therefore, the decisive question to be asked in any assessment of novelty is whether the later inventor has really given the public something new, or, in other words, whether there is a new element which imparts novelty over the prior art. This approach applies to all novelty situations, including selection inventions (T 12/81 OJ EPO 1982, 296, headnote) and cases of overlap (T 12/90 of 23 August 1990, not published in OJ EPO). It goes without saying that the ascertainment of what has been made available by a prior art document has to be made according to the circumstances of each individual case.

4.4 In the board's judgement, this approach is also applicable to the present case where the novelty of a pharmaceutical composition is at issue which differs from compositions of the prior art only by the degree of purity of one of its components.

4.5 It appears that T 990/96 (OJ EPO 1998, 489) followed the above-mentioned approach and examined the question as to whether a feature which represented a specific degree of chemical purity of a low molecular organic compound (in particular a diastereomeric purity) constituted a "new element" in the sense of decisions T 12/81 and T 12/90 (point 5 of the reasons). In that case, novelty of a low molecular organic compound having a specific degree of purity was denied since, in a situation where conventional methods of purification of low molecular organic reaction products are within the common general knowledge of those skilled in the art, a document disclosing a low molecular compound and its manufacture in general makes available this compound to the public in the sense of Article 54 EPC in all desired grades of purity (point 7 of the reasons).

4.5.1 The implication of this statement, in the board's view, is, however, that each and every purification method is presumed, provided it is "conventional" but regardless of the extent of purification desired to be achieved, to be automatically available to the public, and this in a fully enabling way, so as to amount to an effective novelty-destroying disclosure (point 4.3.2, above).

4.5.2 Thus, the "new element" required for the establishment of novelty is presumed, according to the above decision, not to exist, the burden of proof that an exceptional situation, such as that "all prior attempts to achieve a particular degree of purity by conventional purification processes had failed" lying with the defending party - here the appellant (point 8 of the reasons).

4.5.3 Quite apart from the question of whether this presumption amounts to a reversal of the burden of proof, and whether the specific exception exemplified amount to an excessively stringent criterion, since it requires the proof of a negative, both share the quality of being tied to the concept of the availability of purification processes or methods which are "conventional".

4.5.4 As stated in decision T 100/00 (*supra*) in this connection, however, the term "conventional" can only mean "conventional in view of the concrete technical context concerned" (point 4.15(ii) of the reasons).

4.6 In view of the above considerations, therefore, the question of whether the degree of purity for the polylactide required in Claim 1 provides a new element over the prior art must be sought in the concrete technical context concerned.

4.6.1 In Example 1 of D2, the crude reaction product is first treated with methylene dichloride. The combined dark-brown solutions are then further purified with a filtering agent, an aqueous HCl-solution (to remove the catalyst), water, magnesium sulphate and methanol. A

further purification by membrane filtration is described in Example 6. In the oral proceedings, the appellant stated, however, that none of these purification measures would significantly lighten the colour of the product. As regards the membrane filtration mentioned in Example 6, only the unreacted monomers or other low molecular weight components would be removed but not the coloured impurities which had a molecular weight very close to the polylactide and would therefore be above the exclusion size of the membrane.

4.6.2 Furthermore, even if the purification method disclosed in D1 were applied to the so-called "star-shaped" polymers of the application in suit (ie polyol with three hydroxyl groups as a central moiety), the required degree of purity could not be reached. This argument of the appellant was supported by a declaration of witness, signed by M. Schneider and filed on 8 August 2003.

4.6.3 Thus, it is credible to the board, that the methods of purification described in D2 - which must be regarded as the relevant "conventional purification processes" in the concrete technical context concerned - will not succeed in providing the required degree of purity. Nor is there, on the balance of probabilities, any ground for concluding that other "conventional" methods of purification would be capable either of delivering the required degree of purity. On the contrary, on the basis of the existence of the application in suit itself (which has as its purpose the achievement of a degree of purity hitherto not achieved), the declaration of the appellant that previously known

purification methods were not effective and the complete absence from D2 of any reference to a lightening of the coloured product, the board perceives a new element in the feature of a defined level of purity as set out in Claim 1.

4.7 In summary, the subject-matter of Claim 1 and, by the same token, the subject-matter of Claims 2 to 8 is novel over D2 (Article 54 EPC).

5. *Inventive step*

5.1 Beyond all doubt, D2 is the closest state of the art disclosing polylactides not only having the structure required in the application in suit but also being used in pharmaceutical compositions. The impurities remaining in the polylactides can, however, give rise to local irritation reactions of the body tissue and, eg depending on the catalyst used, to instability of the matrix and thus possibly to accelerated drug compound release (page 2 of the application as originally filed).

5.2 Thus, the objective technical problem to be solved by the application in suit is to be seen in the provision of a pharmaceutical composition which overcomes the disadvantages of the prior art. This problem is solved by the provision of a pharmaceutical composition wherein one component, ie the polylactide, has a desired degree of purity. As can be seen from the examples in the application in suit, the brown impurities and the metal cations originating from the catalyst are indeed removed to the desired level.

Therefore, the board is satisfied that the application in suit solves the above problem.

5.3 In practice, the purity of a product will depend on the purification process for the product concerned, so that the assessment of inventive step of a product defined in terms of its purity is inseparably linked to the purification process itself. This applies even if the process characteristics are not features of the product claim.

5.3.1 In this respect, the present case bears a resemblance to the situation described in T 595/90 (OJ EPO 1994, 695) where the subject-matter of the product claim was only concerned with a known desideratum. That decision held that "a product which can be envisaged as such with all characteristics determining its identity together with its properties in use, ie an otherwise obvious entity, may become nevertheless non-obvious and claimable as such if there is no known way or applicable (analogy) method in the art to make it and the claimed methods for its preparation are therefore the first to achieve this in an inventive manner" (point 5, last paragraph, of the reasons).

5.3.2 Therefore, in analogy to T 595/90, the decisive question in the present case is whether the polylactide in the claimed degree of purity was achievable at the priority date of the application in suit or whether there was an obvious way leading to it.

5.3.3 However, as explained in point 4.6, above, the higher degree of purity could not in fact be reached by either the purification processes disclosed in D2 or the process of D1, if applied in analogy to polylactides having the required structure. This finding is also consistent with the fact that the parent application which is directed to a purification method leading to the polylactides of present Claim 1 resulted in the grant of a European patent.

5.4 In summary, the subject-matter of Claim 1 and, by the same token, the subject-matter of Claims 2 to 8, is not derivable in an obvious manner from the prior art and thus involves an inventive step (Article 56 EPC).

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 grant a patent on the basis of Claims 1 to 8 filed as the sole request at the oral proceedings and after any necessary consequential amendment of the description.

The Registrar: The Chairman:

E. Görgmaier R. Young