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# D E C I S I O N
## of 28 February 2001

**Case Number:** T 0294/96 - 3.3.4

**Application Number:** 82300416.3

**Publication Number:** 0058481

**IPC:** A61K 37/02

**Language of the proceedings:** EN

**Title of invention:**
Continuous release pharmaceutical compositions

**Patentee:**
Syngenta Ltd.

**Opponents:**
Takeda Chemical Industries, Ltd.
Debiopharm S.A.
Schering Corporation
Société de Conseils de Recherche et d'Applications Scientifiques (S.C.R.A.S.)
Akzo Pharma B.V.
Boehringer Ingelheim GmbH
Ares-Serono N.V.
Abbott Laboratories
E.I. Du Pond de Nemours and Company

**Headword:**
Continous release pharmaceutical compositions/SYNGENTA LTD.

**Relevant legal provisions:**
EPC Art. 56, 83, 12(2)(3)

**Keyword:**
"Added subject-matter (no)"
"Extension of the scope of protection (no)"
"Sufficiency of disclosure (yes)"
"Inventive step - last main request (yes)"

**Decisions cited:**
T 0004/80

**Catchword:**
-

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**Case Number:** T 0294/96 - 3.3.4

**D E C I S I O N**
**of the Technical Board of Appeal 3.3.4**
**of 28 February 2001**

**Appellant:** (Proprietor of the patent)
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**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted 8 March 1996 revoking European patent No.0 058 481 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chairman:** U. M. Kinkeldey
**Members:** A. L. L. Marie
S. C. Perryman

## Summary of Facts and Submissions

I. The appeal lies from the decision of the opposition division, by which European Patent No. 0 058 481, with the title "Continuous release pharmaceutical compositions" was revoked.

II. The patent application had been originally filed with inter alia the following claims reading:

"1. A pharmaceutical composition comprising a polylactide, as hereinbefore defined, and an acid-stable polypeptide, which, when placed in an aqueous physiological-type environment, releases polypeptide into said aqueous physiological-type environment in a continuous manner, as hereinbefore defined, until essentially all of the polypeptide has been released."

"2. A pharmaceutical composition comprising a polylactide, as hereinbefore defined, and an acid-stable polypeptide, and exhibiting two successive phases of release of polypeptide when placed in an aqueous physiological-type environment, the first phase being released by matrix diffusion and the second phase being released consequent upon degradation of the polylactide, characterized in that the diffusion phase and the degradation-induced phase overlap in time."

"3. A pharmaceutical composition comprising a polylactide as hereinbefore defined and an acid-stable polypeptide, which, when placed in an aqueous physiological-type environment absorbs water in a continuous manner, as hereinbefore defined, until the polylactide has been degraded and essentially all of the polypeptide has been released into said aqueous

physiological-type environment."

"15. A pharmaceutical composition as claimed in claim 1, 2 or 3 comprising from 5 to 50% by weight of ICI.118,630 and from 50 to 95% by weight of a polylactide wherein the ratio of glycolide to lactide units is 0.8 to 3, and which has an inherent viscosity of more than 0.5."

"16. A pharmaceutical composition as claimed in claim 1, 2 or 3 comprising from 5 to 50% by weight of ICI.118,630 and from 50 to 95% by weight of a polylactide wherein the ratio of glycolide to lactide units is 0.2 to 3, and which has an inherent viscosity of 0.2 to 0.5."

"17. A pharmaceutical composition as claimed in claim 1, 2 or 3 comprising from 0.1 to 50% by weight of ICI.118,630 and from 50 to 99.9% by weight of a polylactide wherein the ratio of glycolide to lactide units is 0 to 3, and which has an inherent viscosity of less than 0.2."

III. The patent had been granted with inter alia the following claims reading:

"2. A pharmaceutical composition, comprising a polylactide, which is a polymer of lactic acid alone, a copolymer of lactic and glycolic acids, a mixture of such polymers, a mixture of such copolymers or a mixture of such polymers and copolymers, and an acid-stable polypeptide, which is not significantly hydrolysed under the conditions encountered within the composition during the period of use envisaged, which composition, when placed in an aqueous physiological-

type environment, exhibits two successive phases of release of the polypeptide, the first phase being released by matrix diffusion and the second phase being released consequent upon degradation of the polylactide, characterised in that the diffusion phase and the degradation-induced phase overlap in time, and release of polypeptide occurs over a period of at least one week; but excluding a composition in microcapsule form comprising at least one polypeptide which is a naturally occurring luteinising hormone releasing hormone (LH-RH), a synthetically prepared material of the same type or synthetically prepared analogues of naturally occurring LH-RH which act in some manner on the anterior pituitary gland to affect the release of luteinising hormone (LH) and follicle stimulating hormone (FSH)."

"15. A pharmaceutical composition as claimed in claim 1, 2 or 3 comprising from 5 to 50% by weight of ICI.118,630

(Pyro-Glu-His-Trp-Ser-Tyr-D-Ser(O-tBu)-Leu-Arg-Pro-Azgly-$NH_2$)

and from 50 to 95% by weight of a polylactide wherein the ratio of glycolide to lactide units is from 0.8 to 3, and which has an inherent viscosity of more than 0.5 dl/g (1 g per 100 ml in chloroform or dioxan)."

"16. A pharmaceutical composition as claimed in claim 1, 2 or 3 comprising 5 to 50% by weight of ICI.118,630

(pyro-Glu-His-Trp-Ser-Tyr-D-Ser(O-tBu)-Leu-Arg-Pro-Azgly-$NH_2$)

and from 50 to 95% by weight of a polylactide wherein the ratio of glycolide to lactide units is from 0.2 to 3 and which has an inherent viscosity of 0.2 to 0.5 dl/g (1 g per 100 ml in chloroform or dioxan)."

"17. A pharmaceutical composition as claimed in claim 1, 2 or 3 comprising from 0.1 to 50% by weight of ICI.118,630

(pyro-Glu-His-Trp-Ser-Tyr-D-Ser(O-tBu)-Leu-Arg-Pro-Azgly-$NH_2$)

and from 50 to 99.9% by weight of a polylactide wherein the ratio of glycolide to lactide units is from 0 to 3, and which has an inherent viscosity of less than 0.2 dl/g (1 g per 100 ml chloroform or dioxan)."

IV. The Board issued a communication pursuant to Article 11(2) of the rules of procedure of the Boards of Appeal giving its preliminary, non-binding opinion.

V. Oral proceedings were held on 27 and 28 February 2001.

VI. Before and during the oral proceedings the appellant/patentee submitted several main and auxiliary requests, which were finally all withdrawn and replaced by a sole request with the following single claim:

"1. A solid pharmaceutical composition for subdermal implantation comprising a polylactide, which is a copolymer of lactic and glycolic acids made by a ring opening polymerisation of a mixture of cyclic dimer of lactic acid and cyclic dimer of glycolic acid in the presence of chain stopping agent or a mixture of such copolymers, and an acid stable polypeptide which is not

significantly hydrolysed under the conditions encountered within the composition during the period of use envisaged, which composition, when placed in an aqueous physiological-type environment, exhibits a release profile which has two successive phases of release of the polypeptide as an aqueous solution, the first phase being released by matrix diffusion and the second phase being released consequent upon degradation of the polylactide until essentially all of the polypeptide has been released, characterised in that the diffusion phase and the degradation phase of the release profile overlap in time, and the release of the polypeptide occurs over a period of at least one week, the composition being adapted to achieve the release profile by varying the polylactide composition, particularly the proportion of lactic acid to glycolic acid, by choosing the weight average molecular weight of the polylactide and its polydispersity, by choosing the proportion of the polypeptide to polylactide or by choosing the geometry of the solid formulation for implantation to provide the release profile when taking account of the molecular weight of the polypeptide and interaction of basic polypeptides with the terminal carboxylic-acid groups of the polylactide and wherein either (a) the composition comprises from 5 to 50% by weight of ICI.118,630 (Pyro-Glu-His-Trp-Ser-Tyr-D-Ser(O-tBu)-Leu-Arg-Pro-Azgly-$NH_2$) and from 50 to 95% by weight of polylactide wherein the ratio of glycolide to lactide units is from 0.2 to 3, and which has an inherent viscosity of 0.2 to 0.5 dl/g (1g per 100 ml in chloroform) or (b) the composition comprises from 0.1 to 50% by weight of ICI.118,630 (Pyro-Glu-His-Trp-Ser-Tyr-D-Ser(O-tBu)-Leu-Arg-Pro-Azgly-$NH_2$) and from 50 to 99.9% by weight of a polylactide wherein the ratio of glycolide to lactide units is up to 3, and which has an

inherent viscosity of less than 0.2 dl/g (1g per 100ml in chloroform) and excluding a composition in microcapsule form comprising at least one polypeptide which is a naturally occurring luteinising hormone releasing hormone (LH-RH), a synthetically prepared material of the same type or synthetically prepared analogues of naturally occurring LH-RH which act in some manner on the anterior pituitary gland to affect the release of luteinising hormone (LH) and follicle stimulating hormone (FSH)."

VII. Among all the documents relied on by the appellant and the respondents during the appeal procedure, the following ones are cited in this decision:

(1) EP-0 021 234;

(4) EP-0 052 510;

(13) US-3,773,919.

VIII. In respect to the sole remaining request the arguments of the opponents can be summarized as follows:

**Procedural matters**: respondent IV argued that the restriction of the sole claim of the last main request to the ICI.118,630 molecule has taken him by surprise, because it had only been the subject of dependent claims in the former requests and stated that putting now the accent on it would amount as defining a technical problem underlying the patent in suit totally different from that one considered up to this stage of the procedure. This created a new case which should be considered by two instances.

**Article 123(2) EPC**: objection was raised against the reference to chloroform as a solvent for the determination of the inherent viscosity and against the expression "*...essentially all the polypeptide has been released...*".

**Article 84 EPC**: at the onset of the oral proceedings, the respondents indicated that they no longer intend to object under Article 84 EPC.

**Article 83 EPC**: it was argued that the expression "*...taking account of the molecular weight of the peptide and interaction of the basic polypeptides with the terminal carboxylic-acid groups of the polylactide...*" did not define a clear technical teaching and hence offended the requirements of Article 83 EPC.

**Article 54 EPC**: no objection was raised under Article 54 EPC against the sole claim of the last main request.

**Article 56 EPC**: the respondents submitted that document (13), the closest prior art, was not only concerned with the same technical problem as the patent in suit, ie. the continuous release of a given drug over a certain period of time, but also disclosed a process leading to a copolymer having the same structural features, such as composition, lactide/glycolide ratio, inherent viscosity, etc. and hence the same properties as that of the patent in suit, in particular the same release profile by adaptation of the same parameters. Peptides were mentioned as a class of molecules susceptible to be

introduced in said copolymer in order to be continuously released. The technical problem was seen in the replacement, in the context of the teachings of document (13), of the molecules exemplified as a drug to be continuously released by the ICI.118,630 molecule. No inventive contribution was seen in the solution proposed by claim 1 of the last main request, since the skilled man would have found with few routine experiments the suitable conditions for the continuous release of said ICI.118,630 molecule.

IX. The appellant's arguments can be summarized as follows.

**Procedural matters**: a pharmaceutical composition containing the ICI.118,630 molecule in connection with the lactide-glycolide polymer in order to obtain the claimed release profile had already been the subject of claims 15 to 17 of the application as filed and of claims 5 and 6 of the main request submitted on 26 January 2001, so that the respondents could not be considered as having been taken by surprise.

**Article 123(2) EPC**: chloroform had been used as the sole solvent for the determination of the viscosity in the specification of the patent in suit up to Tables 1 and 2, so that the skilled man would have assumed that this was also the case for said Tables 1 and 2.

Further, the expression objected to was to be found in the application as filed on page 12, lines 1 to 9.

**Article 83 EPC**: the expression objected to should not be considered as conveying a technical teaching, but far more as a warning defining the background, in which the adaptation of the various parameters of claim 1

should be made.

**Article 56 EPC**: document (13), as the closest prior art, did not disclose a process leading to a copolymer having the same features as that of the patent in suit. In particular, the appellant expressed doubts on document (13) in view of the methods used for the viscosity determinations and the values obtained, the method of preparation of the copolymer and the possibility of introducing a peptide into the copolymer by the methods described therein. Furthermore, the appellant stressed the fact that the ICI.118,630 molecule had never been described in the cited prior art.

X. The appellant requested that the decision under appeal be set aside and the patent maintained on the basis of the claim of the last main request.

XI. The respondents requested that the appeal be dismissed.

## Reasons for the Decision

*Procedural matters*

1. The application as filed and as granted contained claims 15, 16 and 17 directed to a pharmaceutical composition comprising ICI.118,630. Of the nine examples (examples 14 to 20, 30 and 31) relating to pharmaceuticals, five related to ICI.118,630. All requests filed during the opposition and appeal proceedings had claims directed specifically to ICI.118,630. In these circumstances the Board considers

that any opponent should have reasonably anticipated that the patentee might seek to defend the patent on the basis of claims making ICI.118,630 an essential feature, and have put on file any material on which he wishes to challenge even such restricted claims. The Board thus considers it legitimate that such a limited request be put forward, and sees no reasons for not itself dealing with all the issues arising. It is within the discretion of the Board under Article 111 EPC whether it deals with the matter itself or remits it to the first instance: there is no right to have every request considered by two instances. In view of the age of the patent and the time already spent by all parties on the matter, the Board considers it appropriate to decide on this request itself.

*Added subject-matter, extension of the protection (Article 123(2)(3) EPC)*

2. The reference to chloroform as solvent for the determination of the inherent viscosity as mentioned in the sole claim of the last main request under the points (a) and (b) is directly derived from Table 2, examples 14 and 15 of the application as filed. No reference to a solvent for the determination of the inherent viscosity can be found in said Tables 1 and 2. However, as indicated by the appellant, up to this point of the description, the measurement of the inherent and/or reduced specific viscosities have always been made in chloroform. It is true that two specific embodiments, namely, the suspension formulation (page 21, lines 20 to 33) and certain copolymers (page 24, lines 6 to 21), use benzene and dioxan for the determination of the inherent and/or reduced specific viscosities. These embodiments,

however, are only mentioned later in the specification and do not have a link to Tables 1 and 2. The Board is of the opinion that the skilled person, seeing the disclosure of the application as filed in its respective context, would have had no doubt that the inherent viscosities of Tables 1 and 2 have also been determined in chloroform.

3. The expression "...*essentially all the polypeptide has been released...*" can be found in the application as filed on pages 4, lines 17 to 25 and 12, lines 1 to 9 and in claim 1.

4. Further, the features now mentioned in the sole claim of the last main request can be found in the application as filed and in the claims as granted.

5. The disclaimer excluding a composition in microcapsule form is restrictive in nature, introduces no uncertainty as to the scope of the claim and fulfils the requirements for allowability of a disclaimer in view of Article 123(2) EPC defined in e.g. T 4/80 (OJ EPO 1982, 149). It excludes from the scope of the protection a hypothetical teaching of document (1) having its origin in Example 8.B.2, which has not been carried out as shown by the use of the expression "*...would be...*" (document (1), page 17, line 50). It also excludes the content of document (4), which brings the Example 8.B.2 of document (1) to completion and describes in Example 1 the use of a lactide-glycolide copolymer in the form of microcapsules for the controlled, sustained release of a LHRH analogue. This disclaimer can also be found in claims 1-3 as granted. Moreover, the appellant argued that its removal may provoke an objection under Article 123(3) EPC, since

the expression "solid pharmaceutical composition for subdermal implantation" might possibly be considered as still encompassing microcapsules. The Board agrees with the appellant's view.

The Board is therefore of the opinion that the requirements of Article 123(2)(3) EPC are not offended.

*Disclosure of the invention (Article 83 EPC)*

6. The expression "*...taking account of the molecular weight of the peptide and interaction of the basic polypeptides with the terminal carboxylic-acid groups of the polypeptide...*" has been objected to, but was considered by the appellant as being a warning drawing the attention of the skilled man to the background or context, within which the adaptation of the parameters has to be done, if the claim of the last main request embraced several peptides, each of them requiring specific conditions. However, the claim is now restricted to the ICI.118,630 molecule and the points (a) and (b) define quite precisely how the various parameters have to be adapted. Therefore, it can be concluded that in the specific context of the claim of the main request, this expression considered together with points (a) and (b) defines a precise technical teaching, which fulfils the requirements of Article 83 EPC.

*Novelty (Article 54 EPC)*

*7.* The respondents have not raised a novelty objection against the claim of the last main request, which essentially differs from the cited prior art as far as it concerns a specific peptide analogue, namely

ICI.118,630 and defines specific conditions for its slow release over a period of time of at least one week.

*Inventive step (Article 56 EPC)*

8. The Board agrees with the position of the parties that among the prior art documents cited against the patent in suit, document (13) is to be considered as the closest prior art. It discloses compositions for subdermal implantation based on a lactide-glycolide copolymer and a given drug, the controlled, sustained release of which over a predetermined period of time is desired. A list of drugs susceptible to be used in said compositions and specifying polypeptides, such as bacitracin, polymyxin B sulfate, sodium colistimethate and trypsin is mentioned in column 2 (lines 37 to 70). Examples showing the preparation of such subdermal implantation devices are only concerned with steroid hormones which are to be melted into the lactide-glycolide copolymer. There is no disclosure for the preparation of such devices as far as the release of polypeptides is concerned.

Starting from document (13), the technical problem to be solved can be seen as the provision of alternative slow release implants to the exemplified steroid hormones.

The information in the patent in suit shows that a solution to this problem is the composition now claimed. But the question remains whether the skilled person could derive this particular solution in an obvious manner from the prior art.

9. No document cited discloses the ICI.118,630 molecule. Document (1) indeed discloses a family of molecules referred to by a generic formula, which does not embrace the ICI.118,630 molecule, since the substituent "R" on the D-amino acid and the COOH-terminal amino acid, which is glycinamide in document (1) and Azglycinamide in the patent in suit, are different.

Document (13) refers to bacitracin, polymixin B sulfate, sodium colistimethate and trypsin, but gives no working example concerning peptides. For the broad class of peptides as a whole, the skilled person might be confident that at least some known peptides could be got to work. The skilled person would start with known, readily available peptides. There is no reason for the skilled person to start trying peptides analogues, such as ICI.118,630. This would be to embark on a quite new research project, which is in the established case law of the Boards of Appeal considered to involve inventive step.

The Board thus considers that the claim of the last main request meets the requirements of 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 maintain the patent on the basis of claim 1 submitted as last main request at oral proceedings on 27 and 28 February 2001 and a description yet to be adapted.

The Registrar: The Chairwoman:

U. Bultmann U. Kinkeldey