

Internal distribution code:

- (A) [] Publication in OJ
(B) [] To Chairmen and Members
(C) [X] To Chairmen

D E C I S I O N
of 18 January 2001

Case Number: T 0965/95 - 3.3.2

Application Number: 87304570.2

Publication Number: 0251476

IPC: A61K 9/22

Language of the proceedings: EN

Title of invention:

Controlled release of macromolecular polypeptides

Patentee:

SYNTEX (U.S.A.) INC.

Opponent:

- (I) Boehringer Mannheim GmbH Patentabteilung
(II) TAKEDA CHEMICAL INDUSTRIES, LTD.

Headword:

Lactide/SYNTEX

Relevant legal provisions:

EPC Art. 54, 56, 111(1), 123(2), (3)
TRIPS Art. 32

Keyword:

"Main request - novelty (no): Implicitly disclosed features"
"First auxiliary request - (no): Added subject-matter"
"Second auxiliary request - (no): Obvious modification of the composition"
"Third auxiliary request - (yes): Not suggested modification of the preparation method"

Decisions cited:

-

Catchword:



Case Number: T 0965/95 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 18 January 2001

Appellant: Boehringer Mannheim GmbH
(Opponent I) Patentabteilung
Sandhofer Strasse 116
D-68298 Mannheim (DE)

Representative: -

Appellant: TAKEDA CHEMICAL INDUSTRIES, LTD.
(Opponent II) 1-1, Doshomachi 4-chome, Chuo-ku
Osaka 541 (JP)

Representative: Keller, Günter, Dr.
Lederer, Keller & Riederer
Patentanwälte
Prinzregentenstrasse 16
D-80538 München (DE)

Respondent: SYNTEX (U.S.A.) INC.
(Proprietor of the patent) 3401 Hillview Avenue
Palo Alto
California 94303 (US)

Representative: Armitage, Ian Michael
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP (GB)

Decision under appeal: Interlocutory decision of the Opposition Division
of the European Patent Office posted
13 November 1995 concerning maintenance of
European patent No. 0 251 476 in amended form.

Composition of the Board:

Chairman: U. Oswald
Members: C. Germinario
C. Rennie-Smith

Summary of facts and submissions

- I. European Patent No. 0 251 476 was granted pursuant to European patent application No. 87 304 570.2 on the basis of a set of 15 claims for all the designated Contracting States except AT, GR and ES and an additional set of 15 claims for AT, GR and ES.
- II. Notice of opposition was filed by appellant I under Article 100(a) and (b) EPC alleging lack of novelty, inventive step and sufficiency of disclosure, and by appellant II under Article 100(a) alleging lack of novelty and inventive step.

The following documents were cited, *inter alia*, during the proceedings before the opposition division:

(6) EP-A-0 134 318

(7) US-A-3 773 919

(8) EP-A-145 240

(22) Tice et al. "Pharmaceutical Technology",
November 1984, pages 26 to 36.

- III. The opposition division maintained the patent in amended form with two sets of 13 claims including an amended claim 1 and a newly filed claim 12 for the different contracting states.

The opposition division found that the amended claims complied with the requirements of Articles 83 and 123(2) and (3) EPC and expressed the view that appellant I had not produced any convincing evidence to

the contrary.

The opposition division also found the subject-matter of independent claim 1 and 13 novel over the prior art documents as none of them disclosed individualised compositions having all the essential features of claim 1, specifically the particle size and the retained biological activity.

Moreover, the opposition division held that none of the possible combinations suggested by the appellants of the closest prior art (either document (7) or (8) combined with other documents) could be prejudicial to the inventive step involved in the claimed subject-matter.

IV. The appellants both lodged appeals against this decision. After filing the statement setting out its grounds of appeal containing new comparative tests (Koll), appellant I withdrew its opposition and appeal by a letter dated 8 May 1998.

Appellant II filed new experimental results (Ogawa) with the statement setting out its grounds of appeal.

The respondent submitted on different dates counter-arguments supported by three sworn statements (including experimental reports) by L. M. Sanders, J. S. P. Lollar and J. J. Holbrook.

The Board issued two communications on 11 November 1999 and 17 May 2000 in which it discussed and clarified some preliminary matter under Articles 123(2)(3) and Rule 57(a) EPC.

As a reaction to the Board's first communication, the respondent filed on 22 March 2000 two amended sets of 12 claims (for the different contracting states), which form the respondent's main request. Claim 1 of both sets remained in the form maintained by the opposition division. A first, a second and a third auxiliary requests were also filed on 23 September 2000.

Oral proceedings took place before the Board on 25 October 2000, during which the respondent filed new first and second auxiliary requests.

- V. The text of claim 1 according to the main request and to the first and second auxiliary requests for the contracting states other than AT, GR and ES, and according to the third auxiliary request for all the contracting states reads as follows:

Main request

"An active agent delivery system for the controlled administration of a macromolecular polypeptide to a mammal, which system comprises a polymeric matrix comprising not more than about 30 percent by weight of particles of denaturable macromolecular polypeptide of a molecular weight greater than 10,000 and other optional water-soluble components, dispersed in a polyactide (sic), wherein substantially all of the particles of polypeptide and other water-soluble components have diameters of 10 μm or less and are uniformly and discretely dispersed throughout the matrix, and wherein the polypeptide retains at least about 50 percent of the biological activity which it possessed prior to manufacture of the matrix."

First auxiliary request

(See claim 1 of the main request) "... matrix comprising not more than **about 20 percent** by weight of particles..." (emphasis added)

Second auxiliary request

(See claim 1 of the main request) "... matrix comprising not more than **10 percent** by weight of particles..."

Third auxiliary request

"A method for producing an active agent delivery system for the controlled administration of a macromolecular polypeptide to a mammal, which system comprises a polymeric matrix comprising not more than about 30 percent by weight of particles of denaturable macromolecular polypeptide of a molecular weight greater than 10,000 and other optional water-soluble components, dispersed in a polyactide (sic), wherein substantially all of the particles of polypeptide and other water-soluble components have diameters of 10 μm or less and are uniformly and discretely dispersed throughout the matrix, and wherein the polypeptide retains at least about 50 percent of the biological activity which it possessed prior to manufacture of the matrix; **said method comprising preparing a microsuspension of the polypeptide, and other optional water-soluble components, in the polylactide solution, and spray-casting or atomizing the microsuspension.**" (emphasis added).

The word "polyactide" in the cited texts should read

"polylactide".

All the requests were re-submitted by telefax on 23 September 2000.

VI. The parties' arguments

Both appellants objected to the repeatability of the invention when using polypeptides other than interferon. Basis for this objection was found in the experimental report by H. Koll. However, the sole appellant remaining in the proceedings, ie appellant II, withdrew the objection during the oral proceedings.

The novelty of the subject-matter of claim 1 according to the main request was objected to, firstly, in the light of document (8). Appellant II argued that a product having all the features characterising the delivery system of claim 1, namely the amount of the active polypeptide, the particle size, the uniform and discrete dispersion and the retained activity, would have been obtained by the skilled person directly by following the preparation method disclosed in document (8), specifically example 5. In support of its arguments, the appellant relied on the experimental report of Ogawa, which was an attempt to repeat example 5 of document (8).

The appellant also contended that in so far as claim 1 of any auxiliary request had to be regarded as novel over document (8) because of the lower amount of active polypeptide, the claim would not imply an inventive step, firstly because no advantage over document (8) was shown and secondly because document (22) already

suggested that the release of the drug from a lactide-glycolide matrix could be managed by modifying the loading of the drug.

As to the method for producing the delivery system according to claim 1 of the third auxiliary request, the appellant argued that methods implying the step of spray-casting or atomising a suspension of a delicate polypeptide was unambiguously suggested by document (7).

The respondent objected to the admissibility of all the comparative tests (Koll) and other experimental reports (Ogawa) since they were only produced by the appellants on appeal.

As to the novelty of the delivery system, the respondent reiterated that document (8) either was silent on or undermined the criticality of a number of essential features of the invention, namely the molecular weight, the particle size and the uniform and discrete dispersion of the active polypeptide within the matrix. Moreover the document did not recognise the importance of the retained polypeptide activity. The very correctness of the activity values reported in examples 5 and 10 was questioned since the document did not describe any method for assessing such activity. Therefore the reported results had to be interpreted in terms of "take up" of the protein rather than in terms of real recovered activity. On the other hand, the attempt by Ogawa to repeat example 5 of document (8), to show that the products thereby obtained had all the features of the claimed system, failed because Ogawa did not use the same polypeptide as that used in example 5.

The respondent also stressed that the main scope of the invention concerned production of a delivery system, and a method for its preparation, capable of efficiently preserving polypeptide activity, and characterised by a regular release profile of the drug. Since neither document (8) nor any other cited document was directed to such a system and method, the claimed subject-matter had to be recognised also as involving an inventive step.

In addition to the substantive issues, the respondent also raised a number of preliminary legal points concerning the requirements of Article 32 of the TRIPS Agreement. In summary the respondent maintained that a decision of the Board to reverse the opposition division's decision and revoke the patent would be contrary to the provision of Article 32 of the TRIPS Agreement, unless there was an opportunity for the Board's decision to be judicially reviewed. This possibility was however excluded by the EPC, as confirmed by the Enlarged Board of Appeal in the case G 1/97 (OJ EPO 2000, 322 - ETA). For this reason, in the event that the Board contemplated the revocation of the patent, remittal of the case to the department of first instance should be considered.

VII. The appellant (opponent) requests that the decision under appeal be set aside and that the European patent No. 0 251 476 be revoked.

The respondent (patentee) requests that the decision under appeal be set aside and that the patent be maintained in accordance with its main request filed on 22 March 2000 or alternatively its first or second auxiliary requests as filed during the oral proceedings

or alternatively its third auxiliary request filed on 23 September 2000. (All re-submitted on 23 September 2000)

The respondent also requests that the case be remitted to the department of first instance, if the Board envisaged revocation of the patent on the basis of the newly filed evidence.

Reasons for the decision

1. The appeal is admissible.

2. *Admissibility of the new evidence*

New comparative tests (Koll) and a report of experiments (Ogawa) were produced by the appellants with their grounds of appeal. The admissibility of this new evidence was challenged by the respondent as being too late. The respondent argued that introducing on appeal of any new evidence not filed during the opposition proceedings meant taking the appeal as a continuation of the opposition proceedings rather than as a review of the decision terminating those proceedings.

Although such arguments may be understandable, they are based on a somewhat misconceived view of the "Board of Appeal" which is not simply a "Cour de Cassation" but a judicial second instance which, by virtue of Article 111(1) EPC, may exercise any power within the competence of the first instance, including the taking of new evidence.

In the present case, the new evidence is directly related to the grounds of opposition and to arguments developed by the appellants during the opposition phase. Under such circumstances, an important consideration for the admissibility of new evidence on appeal is whether it is filed so late that the other party is unable to conduct its own tests or prepare its own arguments thereon. This was obviously not the case here - the new evidence was produced at the very beginning of the appeal proceedings with the statements setting out the grounds of appeal. Accordingly, all the reports of experiments submitted by the parties are admissible.

3. *Main request*

3.1 Article 123 (2) and (3) EPC

No objection under Article 123(2) and (3) EPC has been maintained by the appellant in relation to the two sets of claims of the main request. The Board shares this opinion.

3.2 Article 83

The objection raised originally under Article 83 EPC by both appellants that not all the embodiments of the invention covered by claim 1 could be repeated, was abandoned by the remaining appellant during the oral proceedings.

Having considered the experiments reported in the patent specification, those subsequently produced by the appellants (Koll) and the counter-arguments and declarations submitted by the respondent, the Board is

satisfied that the invention is indeed disclosed in the description in a manner sufficiently clear and complete for all the claimed embodiments to be carried out by a skilled person.

3.3 Novelty

3.3.1 The active agent delivery system of claim 1 is characterised by:

- (a) polymeric matrix of a polylactide;
- (b) comprising not more than about 30 percent by weight of particles of denaturable macromolecular polypeptide and other optional water-soluble components;
- (c) the polypeptide having a molecular weight greater than 10,000;
- (d) the particles of polypeptide and other water-soluble components having diameters of 10 μm or less;
- (e) said particles being uniformly and discretely dispersed throughout the matrix;
- (f) and the polypeptide retaining at least about 50 percent of the biological activity which it possessed prior to manufacture of the matrix.

The system may be prepared following the two preferred methods disclosed in the patent. According to the methylene dichloride method (see example 2) an aqueous solution of eg beta-interferon, HSA and dextrose is

emulsified by vortexing into an organic solution of polylactic-polyglycolic acid in methylene dichloride (ie dichloromethane) to generate a W/O emulsion. This emulsion is immediately processed either by spraying it onto a polyethylene support to produce a film or by atomising it with a spray device in a counter-current or vortex of clean inert gas to prepare finely divided particles (example 8). In this latter case, the matrix acquires the form of a microsphere (microcapsule) containing a number of pockets or pores derived from the droplets of the aqueous internal phase of the emulsion including the polypeptide (interferon).

- 3.3.2 Most of the appellant's arguments alleging lack of novelty of the delivery system of claim 1 rely on document (8), and in particular on example 5. The Board agrees that this document is the most relevant prior art for the purpose of novelty.

The document describes delayed release microcapsules consisting of a polymeric biodegradable matrix such as polylactic acid or polyglycolic acid containing a water soluble drug, prepared by way of a double emulsification followed by evaporation. In the first stage, an aqueous solution of the drug and gelatin is emulsified in a polylactic organic solution (eg dichloromethane) to give a W/O emulsion, the internal aqueous phase being immediately subjected to gelation by cooling the emulsion. In the subsequent stage, the W/O first emulsion is then added to a further aqueous solution under stirring to form a W/O/W emulsion. This W/O/W emulsion is then subjected to desorption of the solvent in order to produce a solid polymeric matrix surrounding, in the form of microcapsules, the gelified droplets of the drug. After recovery from the external

aqueous phase by centrifugation or filtration, the microcapsules are warmed under reduced pressure to achieve a complete removal of the moisture still present. Actually each microcapsule results from a droplet of the first W/O emulsion and comprises one or more drug-containing pockets or pores resulting, upon evaporation, from the droplets of the internal aqueous phase of that first W/O emulsion.

According to example 5, which makes reference to example 1 as to the preparation process, the polypeptide is gamma interferon (2.2 billion units), the W/O emulsion is produced by sonication which results in a micro fine emulsion and the total retained activity of interferon is 25.000.000/dose per 50 doses, ie 1,250 billion units.

- 3.3.3 A number of features of the obtained microcapsules are explicitly disclosed in example 5, while other features are directly derivable from the preparation method reported in example 5 and in example 1, to which the former makes reference, and are therefore considered to be implicitly disclosed.

The use of polylactic acid as a matrix and the use of an active denaturable macromolecular polypeptide having a molecular weight greater than 10,000, ie gamma interferon, are undisputed.

- 3.3.4 The reported retained biological activity of the polypeptide is 1,25 billion units, which corresponds to the 57% of the activity which the polypeptide possessed prior to manufacture of the matrix. That the process of (8) is indeed delicate enough to preserve the biological activity of a denaturable macromolecular

polypeptide is also confirmed by example 10 where the retained activity of factor VIII is about 70% of the original activity. Thus in both cases the retained activity is more than the 50% as provided by claim 1 under consideration.

- 3.3.5 The amount of macromolecular polypeptide and other water soluble components can be calculated on the basis of the gamma-IFN specific activity supplied by the respondent itself. In her third sworn statement, L. Sander reported that the specific activity of gamma-IFN ranged from 7×10^6 to 3×10^7 units/mg. On the basis of these values, the amount of protein corresponding to 2,2 billion units of IFN ranges from about 73 to 314 mg. These results were discussed at the oral proceedings by the appellant without being disputed by the respondent. The Board therefore can only conclude that the above cited figures are reasonably correct.

As to the other water soluble component, ie the gelatin, example 5 refers to example 1 for the details of the process. There, 2.5 ml of 20% aqueous gelatin solution containing the active agent are added to 10 ml of 20% dichloromethane solution of the polylactic acid. The same amounts and percentages appear therefore to hold good for example 5, where the same 20% gelatin solution is added apparently in the same amount (2.5 ml to 10 ml) of 20% dichloromethane solution of polylactic acid. Accordingly the amount of gelatin used is about 500 mg. Since the amount of polylactic acid is about 2000 mg, ie 10 ml of a 20% solution, the percentage by weight of the water soluble components, ie IFN and gelatin, of the whole system is below the claimed 30%, namely in a range from 22% to 28% depending on the specific activity of the IFN.

3.3.6 A further feature of the claimed delivery system is the particle size of the water soluble components, which according to claim 1 under consideration, have a diameter of 10 Fm or less.

In this respect, the Board makes two observations. Firstly, it is plain that 10 Fm is not an exceptionally small size for particles or droplets. As is well known to those skilled in the art, and as any text-book in the specific field will confirm, the size of the internal phase particles of a normal emulsion is usually of the order of a few microns and, in the case of a microemulsion, the size are of the order of nanometres.

Second, it is important to emphasise that the active polypeptide and other water soluble components of the system are necessarily confined within the internal aqueous phase of the W/O emulsion which, according to both the present patent and document (8), is the starting point for the preparation of the delivery system . As explained by the appellant at the oral proceedings, in both cases, after desorption of the solvent and drying of the system the internal phase generates within the matrix pockets or pores filled with the polypeptide and the other water soluble components. Therefore the size of the droplets of the internal phase plays a decisive role in the determination of the size of the polypeptide particles.

In its turn, the size of the internal phase droplets depends, in part at least, on the technique used to produce the W/O emulsion. According to the methylene dichloride method described in the patent in suit, the emulsion is produced by vortexing, while according to

document (8), examples 5 and 1, the W/O emulsion is obtained by ultrasonication. As discussed by the respondent in writing and as recognised by Ms. Sander (the respondent's expert) at the oral proceedings, ultrasonication involves a higher stirring energy than vortexing, therefore results in a finer distribution and smaller particle size of the internal phase. This conclusion is also confirmed by the very wording of example 1 of (8) which defines the obtained emulsion as a "micro fine W/O emulsion" which must therefore be seen as a real "microemulsion". Under these circumstances, the Board is satisfied that in (8) the size of the internal phase droplets, and therefore the size of the pores resulting from these droplets after drying of the microcapsules, is already in itself much smaller than 10 Fm. Consequently, the particles of the active polypeptide contained in those pores cannot be larger than the limit of 10 Fm stated in claim 1 of the patent in suit.

It remains to clarify that the range of sizes of 2 Fm to 200 Fm cited in the general part of document (8), page 15, lines 23 to 27, and relied upon by the respondent in its submission, relates to the obtained microcapsules and not to the pores contained within those microcapsules. Therefore, that size range is completely immaterial for the definition of the size of the polypeptide particles contained in the matrix forming the microcapsules.

3.3.7 These polypeptide particles are according to claim 1 uniformly and discretely dispersed throughout the matrix.

The Board observes that, although these latter features

characterise the claimed delivery system in the solid form, no results of any analysis or tests carried out on the solid matrix are reported in the patent, nor were any such results produced during the proceedings, to show that these features were not simply presumed on the basis of the uniform and discrete distribution of the particles in the liquid suspension or emulsion (see example 4). If the uniform and discrete distribution of particles or droplets in the W/O emulsion is to be accepted as an indication that the same distribution will be found in the solid matrix, then the Board cannot find any reason to doubt that the W/O microemulsion of example 5 of (8) will also result after drying in a uniform and discrete distribution of polypeptide particles within the matrix forming the microcapsules. This is even more likely when one considers that the microemulsion of (8) is immediately cooled after sonication to cause gelation of the particles and to prevent any fusion of the droplets and formation of larger aggregates.

In conclusion, the Board considers that the skilled person carrying out the process described in example 5 of document (8) would inevitably obtain a product having all the features of the delivery system of claim 1. For this reason, the Board cannot share the opposition division's opinion that the claimed delivery system should be regarded as novel since document (8) does not individualise a composition having all the features cited in claim 1.

3.3.8 The respondent mainly focused its arguments on the biological activity retained by the microcapsules of (8), since, so it argued, the method therein described would have completely denatured a delicate

macromolecular polypeptide. For this reason it disputed the figures reported in example 5 and alleged that the document, though referring to the "biological activity", actually meant the take-up of the protein within the microcapsules. This conclusion was said to be justified by the fact that the document did not report any method for assessing the interferon activity.

The Board cannot share the respondent's opinion. In fact, document (8) contains many examples relating to different active substances. Some of these are synthetic substances or small synthetic polypeptides which are used in practical weight-dosages in amounts ranging from more than 100 mg up to 1 gr. In these cases the recovery of the active substances is calculated in terms of take-up of protein as shown by examples 1 and 2. In other examples, where the drug is a highly active biological polypeptide, the amount of substance used is defined in terms of units of biological activity and the yield of the process is also measured in term of recovered activity. This is the case of examples 5 and 10. Thus, in document (8) the integration of the drug into the microcapsules and the remaining activity is measured using deliberately two different parameters depending on the objectively different characteristics of the drugs. Under these circumstances, there is no reason to assume, as argued by the respondent, that when biological activity is expressly mentioned, as in example 5 and 10 of (8), what is actually meant is the take-up of the protein as in other examples. The fact that no method is described for assessing the activity of interferon or the activity of any other substance considered in (8), is not an indication that no method is available to the

skilled person but simply that the assessment of the activity is not a relevant aspect of the invention of (8) which is not directed or limited to the use of interferon, factor VIII, or any other specific drug, but to a novel releasing formulation in the form of microcapsules suitable for any type of drugs.

- 3.3.9 The respondent, referring to the photographs enclosed in the Ogawa report illustrating the internal structure of microcapsules according to (8), also questioned whether dispersion of the drug particles within the matrix of the prior document was the uniform and discrete. In doing so however, the respondent failed entirely to produce any corresponding evidence showing the real structure of the claimed compound and enabling any meaningful comparison with the closest prior art. In absence of such evidence, the Board can look no further than the considerations discussed above and conclude that the subject-matter of claim 1 of the main request lacks novelty.

4. *First auxiliary request*

Claim 1 according to the first auxiliary request differs from claim 1 of the main request only in that the matrix comprises not more than about 20 percent by weight of particles of the polypeptide and other water-soluble components.

As support for the amended text the respondent relied on the passage bridging page 20 and 21 of the filed application where compositions for polylactide matrix are disclosed, comprising a) 80 to 99.9999% polylactide; and b) 0.0001 to 20% biologically active macromolecular polypeptide and other optional water-

soluble components.

This passage, which is the only one to mention the figure "20%", describes preferred compositions in which the value 20% represents the upper limit of a defined range which is itself combined with a second defined range for the polylactide. To isolate the figure 20% from the context of this disclosure and elevate it to a limiting feature in claim 1 would in itself be questionable under Article 123(2) EPC. However, the limitation is not even to the exact figure "20%" but to the much vaguer "about 20%" which indisputably introduces a margin of variability which is definitely not disclosed in the cited passage or in any other part of the filed application. For these reasons, the first auxiliary request is not allowable since it contravenes the requirements of Article 123(2) EPC.

5. *Second auxiliary request*

5.1 Article 123(2)

In claim 1 of the second auxiliary request the expression "no more than about 20% by weight" is replaced by "not more than **10 percent by weight**".

As support for this amendment the respondent relied on the first passage of page 21 of the filed application. The passage reads "For very active polypeptides, the total amount of polypeptide and other water-soluble components may be as low as 10%, 5%, 2%, or less...".

Since amended claim 1 is not limited to "very active polypeptides" but covers any polypeptide meeting the claimed conditions, the allowability of the amendment

under Article 123(2) EPC was disputed by the appellant at the oral proceedings.

Although the Board considers compliance by the amended claim with the requirements of Article 123(2) EPC questionable, the issue need not be decided in view of the outcome of the decision.

5.2 Novelty

As calculated in relation to the novelty of the main request, the compositions according to example 5 or 10 of document (8) contain amounts of active polypeptide and other water-soluble components higher than 20% (example 5) or approaching 20% (example 10). Therefore document (8) is not prejudicial to the novelty of claim 1, now limited to an amount of 10% by weight.

The Board is also of the view that none of the other cited documents is relevant for purpose of novelty of the claimed subject-matter.

5.3 Inventive step

5.3.1 The appellant suggested document (8) as the closest prior art. The Board shares this opinion. In fact this document, and specifically example 5, relates to the preparation of prolonged release composition differing from the claimed subject-matter only in one point, namely, in the percentage by weight of the polypeptide and other water-soluble components being in claim 1 not more than 10%.

5.3.2 In order to support an inventive step of the claimed delivery system, the respondent sought to show an

advantage over the known systems. Accordingly, to define the technical problem underlying the invention as against document (8), it must be determined whether any such advantage actually exists.

Taking as its point of reference the delivery systems prepared according to the known heat-formation and extrusion method, as cited in the description of the patent in suit, page 2, lines 39, 40 and described in example 7, the respondent produced a large number of arguments to show that the preparation method according to the invention, being more delicate, preserved better the biological activity of the macromolecular polypeptide.

Although these arguments are correct in the context used by the respondent, the Board considers that, since the heat-formation method does not represent the closest prior art, any comparison with and advantage over compositions prepared according to that prior method (see example 7) are immaterial in assessing the existence of an inventive step.

As discussed in relation to the novelty of the main request, the preparation method described in (8) avoids any significant heating shock or other denaturing conditions and consequently enables the preparation of compositions having a retained polypeptide biological activity of more than 50% of the original activity as shown in examples 5 and 10 of that document. For this reason, no allegedly better preserving or stabilising effect on the polypeptide activity can be invoked when formulating the problem to be solved by the invention.

A further point raised by the respondent is the release

profile of the claimed delivery system. In the respondent's contention, the uniform and discrete dispersion of the active polypeptide within the matrix results in a linear, regular release of the active polypeptide during a long period of time, as shown in figure 1 of the patent. This property allegedly solves the drawback of an irregular multiphasic release profile generally associated with polylactide preparations.

Once again however, the respondent's arguments do not apply to the method of the closest prior art, document (8), which, as already seen above, enables the achievement of a uniform and discrete dispersion of the polypeptide within the matrix. Therefore, the Board does not see any objective reason to conclude that the release profile of the claimed delivery system is more uniform or more regular than that characterising the microcapsules of (8). On the other hand, any supposed advantage over the closest prior art could have been demonstrated by the respondent by way of experimental results. Absent any experimental support enabling a meaningful comparison with the closest prior art, no alleged advantage in relation to polypeptide release can be recognized by the Board.

5.3.3 Under these circumstances, the technical problem to be solved by the invention as against document (8) is that of providing an alternative delivery system for denaturable macromolecular polypeptides of molecular weight greater than 10,000.

5.3.4 The solution proposed by the patent in suit is that of decreasing the loading of the active polypeptide and other optional water soluble components within the

system, while maintaining a therapeutically meaningful activity. The solution is thus a delivery system comprising not more than 10 percent by weight of these components.

Having regard to the examples reported in the patent and to the results illustrated in figure 1, the Board is satisfied that the technical problem is plausibly solved.

- 5.3.5 The question then is whether the person skilled in the art, faced with the task of somehow improving the known delivery system, would have considered the polypeptide loading as a feasible means for achieving this goal.

A precondition for reducing the polypeptide loading in a composition which still needs to have a therapeutically meaningful activity is that a preparation method exists capable of preserving the biological activity during formulation. If in fact the only available method were one resulting in a substantial loss of biological activity, as would appear to be the case with the heat-extrusion method, then the skilled person would never envisage the possibility of reducing the starting amount of active agent. This is however not the case here, since the skilled person was aware from document (8) of the possibility of retaining a substantial amount of the original activity following a careful and sensitive procedure.

For this reason the Board considers there was no a *priori* technical bar to the skilled person decreasing the loading of the polypeptide in the composition.

5.3.6 The different factors contributing to the definition of drug release from biodegradable systems are discussed in document (22). Under the heading "Mechanisms of Drug Release", on page 29, the authors report that the rate and type of release can be controlled by modifying the nature and the biodegradable character of the polymeric matrix, by manipulating the surface area and the size of the microcapsules and by influencing the pathlength taken by the drug to reach the surface of the microcapsule by increasing or decreasing the core loading of the drug. In particular it is indicated that microcapsules with higher core loading release faster because the pathlength is shorter, which would lead the reader to conclude that lower core loading would release more slowly due to a longer pathlength.

Thus, the skilled person aware of the teaching of document (22) had only a limited number of factors to take into account when modifying the known delivery systems. He knew that, among these factors, the amount of drug in the matrix played an important role since by simply increasing or decreasing the loading he could influence the speed and accordingly the length of the release. Confirmation of the teaching in (22) would have been found in other prior art documents, as well as in the very closest prior art. In experimental example 1 and table 1 of (8) the duration of the action of several microcapsules is compared. All the formulations differ in the composition and molecular weight of the polylactide matrix but contain the same amount of active substance, ie 200 mg of TAP-144 (see example 1). Only microcapsules 039 and 0310 comprise respectively a half and 2.5 times the amount of the other formulations, while being identical to each other in all other respects. Table 1 shows that the former

microcapsule (039) containing the lower amount of active agent (100 mg) shows a much longer duration of action (60 days), while the latter containing the higher amount (500 mg) shows a duration of action of only less than 20 days.

Further confirmation would have been found by the skilled person in document (6). This document, which is prior art cited in the opposition proceedings and acknowledged in the patent in suit, emphasises even more clearly the influence of drug loading on the release of a controlled release insulin composition. Insulin is a denaturable polypeptide having a molecular weight of about 6000 and was within the scope of the invention as filed. The document teaches that "a higher insulin loading (weight insulin/weight polymer) while increasing the insulin release rate actually decreases the duration of action since it increases the porosity of the polymer matrix" (page 3, lines 21 to 25), while "a reduced loading would result in a less porous matrix, a lower insulin release rate, and thus a longer duration of action". (page 3, lines 30 to 32).

- 5.3.7 The Board therefore concludes that the skilled person, faced with the problem of providing an alternative delivery system to that of the closest prior art, would have considered among the few possible factors the amount of active polypeptide not only because suggested in itself among other factors but more importantly because he would have known that, by reducing the polypeptide loading in the composition, he could also guarantee the desired long duration of action.

For all these reasons, the Board considers that the subject-matter of claim 1 does not involve an inventive

step.

6. *Third auxiliary request*

- 6.1 Claim 1 according to the third auxiliary request (common to all the designated contracting states) is directed to a method for producing the active agent delivery system of claim 1 of the main request, **"said method comprising preparing a microsuspension of the polypeptide, and other optional water-soluble components, in the polylactide solution, and spray-casting or atomizing the microsuspension."** (emphasis added).

The Board wishes to stress that the expressions "spray-casting" or "atomizing" used in claim 1 are evidently used in the context of the invention to identify equivalent techniques which both imply as the first and essential step the "atomisation" of a liquid system, ie its separation into micro particles (see example 8). The atomised system is then either cast and dried on a solid support, which method is defined in the claim as spray-casting, or alternatively is dried in a counter-current of inert gas, thus in a spray-drying method, what is defined in the claim as atomizing. Therefore, although all the arguments which follow firstly apply to the latter technique (spray-drying or atomizing), they prove valid also for the former techniques since both share the same essential procedural steps.

The text of amended claim 1, now limited to a method claim, is based on the complete text of filed claim 1 for the contracting state Austria and on the passages on page 23, lines 15 to 22 and page 24, lines 9 to 18 of the filed application. On the other hand the

protection conferred by the method claim is limited vis-à-vis the protection conferred by the product-claim as granted. Therefore the claim complies with the requirements of Article 123(2) and (3) EPC.

6.2 Novelty

Novelty of the claimed method was challenged by the appellant on the basis of document (7), which is, in the Board's view, the only relevant prior art.

This document describes formulations of polylactide and drug which provide a sustained release of the drug over a controlled period of time. The document reports a certain number of general methods, known in 1973, all suitable for mixing an active agent with a polylactide matrix. The first method considered is spray draying. In this case a finely divided drug is suspended in a solvent system in which the drug is not soluble and which contains the dissolved polymer and then is atomized by spraying (column 10, lines 1 to 19). The relative proportion of the drug and polylactide polymer is said to vary over a wide range depending on the desired effect, although the ratios which have shown good results include 1 part of drug to from 4 to 20 parts of polylactide (column 9, lines 52 to 54).

The Board finds that the teaching in document (7) differs from the subject-matter of claim 1 in two respects. First, the document cites a very long list of possible drugs (see column 2, line 38 to column 7, line 11) among which trypsin is apparently the sole denaturable macromolecular polypeptide envisaged. As to the method, document (7) describes five general methods all equally suitable for integrating a drug into a

polymer matrix. Thus document (7) envisages a huge number of theoretically possible combinations of drug and method, without however disclosing the specific use of the spray-drying method for the preparation of a formulation specifically containing trypsin, ie the sole polypeptide meeting the condition stated in claim 1.

The second difference resides in the relative proportion of the drug to the polymer. For three of the five disclosed methods, namely pan or fluid bed-coating, micro-encapsulation and embedding, no ratio drug/poly lactide is explicitly given in the detailed description of the methods. The skilled reader would therefore understand that the general teaching of (7), specifically the preferred ratios cited in column 9, would apply to these methods. By contrast, with spray-drying and intimate mixing (which also implies a spray-drying step), the relative proportion of drug to polymer is explicitly disclosed and, in contrast to the aforementioned general and preferred teaching, this proportion is 50%:50%. Therefore document (7) indisputably teaches that for the spray-drying method, as for any method implying a spray-drying step, a drug/polymer ratio higher than that indicated in claim 1 of the patent in suit should be used. For these reasons, the Board considers that document (7) does not prejudice the novelty of claim 1.

Since no other cited document is more pertinent than document (7) as regard novelty of the claimed subject-matter, claim 1 is recognised as novel.

6.3 Inventive step

6.3.1 Since document (7) does not relate to controlled release formulations of denaturable macromolecular polypeptides, the Board does not share the appellant's opinion that it represents the closest prior art. On the contrary, the closest prior art can be identified as document (8) which, as already discussed, specifically describes in examples 5 and 10 prolonged release systems containing denaturable macromolecular polypeptides.

6.3.2 Since no advantage involved in the method of the present invention over that described in (8) has been actually shown, the technical problem to be solved by the present invention is that of providing an alternative method for preparing the delivery system under consideration, which method is capable of preserving at least 50% of the original biological activity and produces a delivery system which, as a result of having the claimed properties offers a regular drug-release profile as shown in figure 1 of the patent.

In order to solve that problem, the patent in suit proposes a method comprising the step of spray-casting or atomizing a microsuspension of the polypeptide, and other water-soluble components, in the polylactide solution.

Supported by the experimental results reported in the patent disclosure, specifically example 5 and figure 1, the Board finds that the underlying problem is plausibly solved.

6.3.3 As emphasised by the appellant, the skilled person faced with the problem to be solved would have found in

document (7) a number of possible alternative methods, including spray-drying.

6.3.4 This document discloses all the methods known and available in 1973 without expressing a preference among them. In fact, it does not enter into the merits of the specific properties of each method or their suitability to achieve a desired result, such as the preserving the drug activity or the type of drug release. For this reason alone, the very choice of the "spray-drying" technique from a number of apparently equivalent methods is *a priori* not necessarily obvious.

6.3.5 If nonetheless the skilled person had considered spray-drying as a possible alternative to the method disclosed in document (8), then he would have mainly relied on the passage in (7), column 10, lines 5 to 20 for the realisation of such a method.

Apart from an almost meaningless drug to polymer ratio of 1/99 to 99/1, this passage actually teaches that the suitable ratio by weight between these two components should be 1:1, which is much higher than the ratios dictated by claim 1 under consideration and even much higher than the ratios 1:4 to 1:20 reported as preferred in document (7), column 9, lines 52 to 54. This very high proportion of active agent would not be considered by the skilled reader as simply accidental as the same drug/polymer ratio of 1:1 is also disclosed in the "intimate mixing" method which also comprises a step of spray-drying (column 10, last paragraph). Hence, document (7) clearly suggests to the skilled person that when the method is based on a step of spraying either a suspension or a solution comprising a drug and a binding polymer, the proportion of the

active agent should purposely be kept very high; this in contrast to the preferred ratios taught for all the other methods disclosed in (7).

6.3.6 The document gives no explanation why such a high ratio should be used in spray-drying. However, it seems reasonable, in the Board's view, to envisage that the method is not one which would prevent a significant loss of drug activity; in which case the high amount of drug would either stabilise the activity or would guarantee the recovery of a therapeutically still meaningful level of activity in the final product.

6.3.7 This conclusion is not contradicted by the common general knowledge as illustrated by the "Spray Drying Handbook", K. Master, 1985, Chapter 16, pages 625 to 644, submitted by the appellant before the oral proceedings.

This document does not confirm, as the appellant contended, that spray-drying is *a priori* a suitable method for treating denaturable polypeptide. On the contrary, it underlines in different passages that all the parameters of the method will influence the properties of the final product, including retention of activity. For this reason, close attention to the operating conditions is required and advised. This applies specifically to denaturable proteins such as enzymes for which the control of drying temperatures are paramount. In this case, activity loss can be prevented by taking special measures as explained in paragraph 16.2. All these warnings as to the possibility of drug denaturing and measures to prevent it clearly indicate to the skilled person that the spray drying technique (which is indicated in the

patent in suit as atomizing) may indeed cause dramatic losses of biological activity.

- 6.3.8 Supported by this general knowledge, the skilled person faced with the problem to be solved would have had no apparent reason to select spray drying from among all the other known methods. If nevertheless he had opted for this technique, not only would he have found in the prior art no incentive to modify the ratio drug to polymer, or more generally the ratio of water soluble components to polymer, but he would even have been dissuaded from decreasing that ratio, as this modification of the operating conditions would have been expected to lead to a significant loss of biological activity.

Under these circumstances, the Board considers that the subject-matter of claim 1 is not obviously derivable from the closest prior art alone or in combination with any other prior documents.

Order

For these reasons it 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 the claims as in the third auxiliary request submitted on 23 September 2000 and a description to be adapted thereto.

The Registrar:

The Chairman:

A. Townend

U. Oswald