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D E C I S I O N
of 3 November 1993

Case Number: T 0456/91 - 3.3.2

Application Number: 81305426.9

Publication Number: 0052510

IPC: A61K 9/50

Language of the proceedings: EN

Title of invention:

Microencapsulation of water-soluble polypeptides

Patentee:

Syntex (USA) Inc.

Opponent:

- 01) Debiopharm S.A.
- 02) Ipsen Biotech société au nom collectif
- 03) The Administrators of the Tulane Educational Fund
- 05) Deghenghi, Roman
- 08) Ferring Arzneimittel GmbH
- 09) Ares-Sereno N.V.
- 10) Stolle Research & Development Corporation

Headword:

Microencapsulation/SYNTEX

Relevant legal norms:

EPC Art. 54, 56, 83, 84, 87 to 89, 123(2) and (3)

Keyword:

"Amendments - extension of original disclosure (no)"
"Extension of protection (no)"
"Clarity (yes) - claims supported by description - broad claim not unclear"
"Sufficiency of disclosure (yes) - no undue burden to skilled person"

.../...

Keyword (cont'd):

"Priority right (yes) - no previous disclosure of claimed invention"

"Novelty (yes) - claimed invention not part of the state of the art"

"Inventive step (yes) - claimed solution not foreshadowed by state of the art"

Decisions cited:

T 0219/83, T 0238/88, T 0688/91, T 0292/85

Headnote/Catchword:

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Case Number: T 0456/91 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 3 November 1993

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Decision under appeal:

Interlocutory decision of the Opposition Division
of the European Patent Office dated 23 January
1991, posted on 28 March 1991 concerning
maintenance of European patent No. 0 052 510 in
amended form.

Composition of the Board:

Chairman: A.J. Nuss
Members: D. Holzner
S.C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 052 510 was granted to the Respondent on 27 August 1986 with 23 claims for ten Contracting States and 22 claims for Austria, in response to the European patent application No. 81 305 426.9, filed on 17 November 1981, claiming the priority of the earlier application US 207 864 of 18 November 1980. Claims 1 and 23 for the Contracting States other than Austria were worded as follows:

"1. A pharmaceutical composition designed for sustained release of an effective amount of drug over an extended period of time prepared in microcapsule form wherein the composition comprises:

at least one polypeptide which is a naturally occurring luteinizing 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 luteinizing hormone (LH) and follicular stimulating hormone (FSH);

optionally, at least one polymer hydrolysis modifying agent selected from organic acids, acid salts, neutral salts and basic salts; and

a biocompatible, biodegradable encapsulating polymer which is a polylactide polymer, polyacetal polymer, polyorthoester polymer or polyorthocarbonate polymer.

23. A process for preparing a composition of any one of the preceding claims comprising:

dispersing an aqueous solution containing the polypeptide, and optionally a polymer hydrolysis modifying agent, in a halogenated organic solvent containing said encapsulating polymer;

adding to the dispersion a coacervation agent; and collecting the microcapsules from this solution."

II. Notices of opposition were filed against the European patent by ten parties. Revocation of the patent was requested on the grounds of Articles 100(a), (b) and (c) EPC.

During the procedure before the Opposition Division the following documents, *inter alia*, were cited:

- (9) US-A-3 773 919
- (19) US-A-4 010 125
- (32) EP-A-0 021 234 of the Respondent itself published 07.01.81, filed 10.06.80 and claiming priority from *inter alia*
- (32A) US Application Serial Number 47661 of 11.06.79
- (51) Encyclopedia of Chemical Technology, Vol. 13/2 (1967), pages 436 to 456
- (53) US-A-4 010 196

III. The Respondent filed on 3 January 1991 a main request with amended independent claims, and also five auxiliary requests. This main request is the same as the main request before the Board. The amended Claim 1 of this main request for the Contracting States other than Austria was:

"A pharmaceutical composition designed for sustained release of an effective amount of drug over an extended period of time prepared in microcapsule form wherein the composition comprises:

at least one water soluble polypeptide which is a naturally occurring luteinizing 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 luteinizing hormone (LH) and follicular stimulating hormone (FSH);

optionally, at least one polymer hydrolysis modifying agent selected from organic acids, acid salts, neutral salts and basic salts; and

a biocompatible, biodegradable encapsulating polymer which is a poly(lactide-co-glycolide) copolymer; the lactide/glycolide molar ratio of the copolymer, its molecular weight, the capsule diameter, and the polymer hydrolysis modifying agent (if present), being such that the composition exhibits sustained release of an effective amount of the polypeptide over a period of at least one month."

The patent included an appropriately amended process claim for Austria.

(What is referred to in the patent in suit as a poly(lactide-co-glycolide) copolymer is synonymous with what in other documents is called PLGA.)

- IV. By a decision delivered orally on 23 January 1991, with written reasons posted on 28 March 1991, the Opposition Division maintained the patent in amended form as requested in the main request, holding that it was entitled to the priority of (32A) as claimed, that it was novel, that it was inventive over document (19) considered to be the closest prior art and that it fulfilled all the other requirements of the EPC.
- V. Notices of appeal were filed by six Opponents, namely Opponents 01 to 03, 05, 08 and 09, referred to hereinafter as Appellants 01 to 03, 05, 08 and 09. The arguments relating to the main request put forward by

the Appellants in writing and at the oral proceedings before the Board on 3 November 1993 were substantially as follows:

(a) Article 123 EPC

According to Appellant 02, the amended Claim 1 of main request did not satisfy Article 123(2) EPC because the restrictions introduced had been exemplified in the original description only for microcapsules containing Nafarelin, but not ones containing any other compound out of the huge number of polypeptides covered by the claim. Extrapolation from only one compound (Nafarelin) to the entirety of the water-soluble polypeptides now defined in paragraph 2 of Claim 1 involved adding subject-matter not originally disclosed.

Appellant 09 argued that there was no basis in the content of the application as filed for the time limit of "at least one month" introduced into Claim 1, because this had only been disclosed together with an upper time limit which had not been introduced into Claim 1.

Further the passage at page 6, lines 37 to 41 of the patent in suit was to be read as meaning that the presence of the hydrolysis modifying agent was essential if the release was to be over a minimum period of a month. Claim 1 by leaving the hydrolysis modifying agent as a merely optional feature added subject-matter not originally disclosed and extended the scope of the patent as granted thus contravening the provisions of Article 123(2) and 123(3) EPC.

(b) Article 84 EPC:

Appellant 09 was the only one to object that there was no clear teaching how the different parameters, namely the lactide/glycolide molar ratio of the copolymer, its molecular weight, the capsule diameter, and the polymer hydrolysis modifying agent (if present) must be varied to obtain a sustained release over a period of at least one month. The features had not been defined as precisely as was possible, and so did not satisfy the requirements stated in T 68/85 (OJ EPO 1987, 228).

(c) Article 83 EPC

Several Appellants objected on the basis that the water-soluble polypeptides according to the claimed invention comprised thousands of compounds, each of which could be expected to behave differently. For each such polypeptide the person skilled in the art had, at the cost of several hundred thousand dollars (as shown by documents submitted by Appellant 09), to carry out a large number of experiments which took a long time, at least one, sometimes several years, and to make a "new invention" himself before obtaining a pharmaceutical composition with the desired sustained release properties. Following T 14/83 (EPO OJ 1984, 105) one should be able reliably and quickly to obtain something that works. This was not the case here.

(d) Article 54 EPC

All the Appellants argued that Claim 1 lacked novelty over (32), which on page 41 in Example 8.B.2 disclosed a pharmaceutical composition comprising a LH-RH analogue in biodegradable microcapsules made of a 25/75

glycolide/lactide copolymer. Further as (32) specifically referred to (9) stating on page 12 lines 16-21 that "Another type of slow release depot formulation for injection would contain the compound or salt dispersed or encapsulated in a slow degrading, non-toxic, non-antigenic polymer such as a polylactic acid/polyglycolic acid polymer for example as described in U.S. 3,773,919", all Appellants argued that (32) and (9) should be considered as one document for the purpose of assessing novelty.

Appellant 01 provided experimental results, which, it was submitted, merely carried out the teaching of (32), and which resulted in something falling within Claim 1 of the main request. It was denied that unacceptably high doses of polypeptide were used.

It was submitted that the Opposition Division had adopted the wrong approach by looking only at the exact wording used in (32), rather than considering what the skilled person in the art would understand from (32) and (9) considered together as a whole. Not only the specific examples should be considered but the general teaching that could be derived from (9), column 2, lines 11 to 17. Example 8.B.2 of (32) had to be considered merely as a "recipe", and account had to be taken of the fact that the unprejudiced skilled person would increase the percentage of LH-RH analogue if he aimed at a release period of at least one month when applying such microcapsules.

(e) Article 56 EPC

(32) was not merely part of the state of the art under the provisions of Article 54(3) EPC, but also under the provisions of Article 54(1), and so (32) could be relied on to deprive Claim 1 of inventive step. Not

US application 207,864 of 18 November 1980 (the priority claimed) but US 47,661 (32A) of 11 June 1979, from which the Respondent claimed priority in (32) and whose text was substantially the same as that of (32), was the first application for the invention of Claim 1 for the purposes of Article 87(1) EPC. Accordingly everything, including (32), published before the 17 November 1981, the filing date of the patent in suit, was part of the state of the art in relation to Claim 1.

On this argument (32) was the closest state of the art, and Claim 1 of the main request clearly lacked inventive step over the combination of (32) and (9).

If, on the other hand, (32) could not be used for arguing lack of inventive step, it was submitted on behalf of all Appellants that document (19) should then be considered as the closest state of the art. This concerned LH-RH analogues and specifically referred to sustained release. Given the obvious desideratum of achieving a one month sustained release formulation for the LH-RH analogue of (19), the skilled person was in the position to combine the teachings of documents (19) and (9), particularly as (9) mentioned fertility drugs or hormones as possible applications, and would then inevitably come up with something falling within Claim 1.

(9) related to PLGA and contained a statement that depot injections with prolonged release values of drugs could be designed, by controlling molecular weight and composition, to undergo hydrolysis and to release drug from the depot at a desired rate (column 2, lines 6 to 17). There also appeared in it the statement "In general the higher the degree of polymerisation, that is the higher the molecular weight of the polylactide, the

slower is its rate of absorption, etc. in the body and the slower will be the rate of release of its associated drug" (column 8, lines 43 to 47).

According to Appellant 03, no prejudice or other deterrent prevented the skilled person from finding out whether or not the technical problem underlying the patent in suit could be solved by combining the teachings from (9) and (19). Further the inherent viscosity data given in Table II of the patent in suit (in hexafluoroisopropanol) showed that viscosities suggested in the patent in suit fell within the viscosity range disclosed in (9) (in benzene).

Even if (32) could not be relied on as state of the art when considering inventive step, (32) could be relied on by treating it as an expert opinion (German "gutachtlich") to show that the skilled person at its application date would have had (9) in mind as a solution to any sustained release problem.

Appellant 05 gave evidence in person at the oral proceedings to the effect that his company was the European licensee under the equivalent patents to (19) and that he was personally acquainted with the inventor of (19), Dr. A.V. Schally, who was a Nobel prize winner. Dr. Schally was perfectly aware of (9) but was prevented from using what it suggested because of the patent situation. Instead an alternative as disclosed in (53) was developed.

Appellant 05 also stated that when he wrote to one of the inventors of the patent in suit, congratulating her on work carried out, he was not referring to the subject-matter of Claim 1 of the main request, so that his letter was not an acknowledgement that the subject-matter of Claim 1 involved an inventive step.

A witness, Dr. Orsolini, gave evidence that the duration of the sustained release of LH-RH analogues could easily be made to exceed one month by heavy loading of the core of the microcapsule with the active ingredient. This could be done because the LH-RH analogues could safely be given in amounts greatly exceeding the minimum effective dose. Any invention made in the patent in suit must be considered limited to 1-2 % of core loading.

Appellant 08 submitted that starting from (19) the skilled man faced with the problem of obtaining one month sustained release would refer to an enclopedia such as (51), and also consider what more recently disclosed materials, particularly if they are essentially non-reactive and bio-degradable, could be used. This would lead him to (9) which would retain his interest because it referred to a controlled sustained release of the drug compound over a period of eight hours to two months or longer when administered parenterally thus providing an incentive to the skilled person to include document (9) in his evaluation of the combined teachings of (19) and (51). This led to the technical solution underlying the patent in suit. It was part of the general knowledge of the skilled person that varying the capsule diameter would modify the release time of a drug.

According to Appellant 09, the skilled person only had to adopt the teachings of Claims 1 and 3 of document (9) to specific parts of document (19) to make the subject-matter of the patent in suit clearly obvious over the combined teachings of (9) and (19), the more so as the patent in suit itself emphasised parallels to the basic technique set out in (9).

VI. The Respondent submitted substantially the following arguments:

- (a) The features introduced into amended Claim 1 restricted the claim compared to Claim 1 as granted which contained no requirement at all concerning a sustained release time period. The lower limit of one month introduced was fairly based on page 6, lines 37 to 41 of the text of the granted patent and the equivalent passage in the original application.
- (b) The functional wording used in the amended Claim 1 was not only clear, but also necessary to avoid undue limitation of the scope of protection.
- (c) A skilled person could without undue burden, follow the instructions given to make a pharmaceutical composition that exhibited sustained release of an effective amount of the polypeptide over a period of at least one month.
- (d) Even taking into account Example 8.B.2 of (32A) and the reference to (9), there was no direct and unambiguous disclosure in (32A) of LH-RH analogue/polylactide glycolide microcapsules having at least one month's sustained effective release, so Claim 1 of the main request was entitled to the priority of US serial No. 207,864, which was the first application for this subject-matter.
- (e) None of the test results by Appellant 01 were evidence that (32) showed the one-month sustained release. Further none of these experiments reproduced Example 8.B.2 of (32). The patent in suit was novel over (32) and no other documents had been relied on as destroying novelty.

- (f) The problem to be solved was to provide at least one month's sustained effective LH-RH analogue release. The patent in suit solved this.

The closest prior art was (19) in which the only statement concerning long-acting, slow-release preparations in connection with microencapsulation in a pharmaceutically acceptable coating material was made in the reference to document (51). The latter, however, covered an extremely general disclosure not confined to drugs.

Even if for some reason the skilled person had considered (19) and (9) together, the latter did not give sufficient information to suggest the microcapsules as being a solution to the problem for which there is a reasonable expectation of success.

Despite the fact that, prior to the present invention, LH-RH compounds, their action on prostatic cancer and endometriosis and document's (9) polylactide/glycolide formulations had been known for several years, no prolonged delivery formulation had been developed.

- (g) It was also submitted that despite the Respondent not yet having marketed the product, the Appellants were allegedly marketing with great success a product that allegedly infringed Claim 1 as now proposed. This was commercial success supporting the inventive merit of Claim 1. Further the inventiveness was also evidenced by the fact that an opponent, no longer part of the proceedings, had taken a licence, and that Appellant 05 had written to the inventor Dr. Sanders congratulating her on her work.

VII. The Appellants requested that the decision under appeal be set aside and that the European patent No. 0 052 510 be revoked.

No requests were filed on behalf of Appellant 10.

The Respondent requested as main request that the appeal be dismissed, and as auxiliary requests that the decision appealed against be set aside and that the patent be maintained on the basis of one of the auxiliary requests 1 to 5 submitted by letter of 29 September 1993.

Reasons for the Decision

1. The appeals are admissible.
2. *Amendments (Articles 123(2) and (3) EPC)*
 - 2.1 Claim 1 of the main request differs from that of the granted patent in as much as the following limitations have been introduced:
 - 2.1.1 Firstly the claimed "at least one polypeptide" is now limited to being "water-soluble". The amendment is supported by the disclosure on page 1, line 11, of the originally filed application.
 - 2.1.2 Secondly the biocompatible, biodegradable encapsulating polymer is now restricted to a "poly(lactide-co-glycolide) copolymer", which in the originally filed application has already been stated to be the most preferred polymer excipient (see page 13, lines 5 to 8 and lines 33 to 35; particularly page 14, lines 5 to 10).
 - 2.1.3 Thirdly Claim 1 is now restricted to "the lactide/glycolide molar ratio of the copolymer, its molecular weight, the capsule diameter, and the polymer hydrolysis modifying agent (if present), being such that the composition exhibits sustained release of an effective amount of the polypeptide over a period of at least one month". This limitation to "at least one month" finds a basis both in the originally filed application (see page 16, lines 28/29 and 32/33) and that of the patent as published (see page 6, lines 38 and 40/41), where the release time is stated to be one which may range from one month to three years, preferably about one month to 24 months. It is not of

significance for the purposes of Article 123(2) EPC that the one month limit was not stated to be an essential feature of the invention in the application as originally filed: it is sufficient that the lower limit was mentioned somewhere in the originally filed application.

- 2.2 The originally filed Claim 1 contained neither a lower limit nor an upper limit on the time period for effective release. The introduction of a lower limit on the time period is a restriction of the scope of the claim. No necessary connection between this lower limit and any of the specifically disclosed upper limits is mentioned in the application as originally filed, nor have the Appellants shown any reason why any reader might presume this to be the case. Accordingly the Board sees no objection to introducing the lower limit into Claim 1 without at the same time introducing an upper limit. The reference (see page 6, lines 38 to 41) in the description to upper limits remains unchanged.
- 2.3 There is also a basis in the originally filed application (see page 16, lines 28 to 32) for the variables relating to the encapsulating polymer being such as to provide the required release period. The qualifier "if present" for the polymer hydrolysis modifying agent has a basis in the application as originally filed which stated that the agent was optional (see page 10, lines 6 to 10).
- 2.4 Claim 20 specifying a molar ratio of about 50:50, has a basis in the originally filed Claims 6 and 7.
- 2.5 The set of claims for Austria has been modified in an equivalent way.

2.6 The main request thus complies with Article 123(2) and 123(3) EPC.

3. *Clarity and support (Article 84 EPC)*

3.1 According to the jurisprudence of the Boards of Appeal, the clarity of a claim is not diminished by the mere breadth of a term of art contained in it, if the meaning of such term is unambiguous for a person skilled in the art, either *per se* or in the light of the description (see T 238/88, OJ EPO 1992, 209 and T 688/91 of 21 April 1993 point 3.4 of the Reasons (not published in OJ EPO)). As in the present case it is clear from the claims when read in the light of the description (see page 2, line 39 to page 4, line 26) which peptides are suitable for the present invention, the present claims cannot be challenged under Article 84 EPC for the sole reason that an extremely large number of compounds can be used for carrying out the invention. Any arguments of the Appellants in connection with the large number of peptides covered by the present Claim 1 must therefore fail.

4. *Sufficiency (Article 83 EPC)*

4.1 The provision of Article 83 EPC that the disclosure of a patent must be sufficiently clear and complete for the invention to be carried out by a person skilled in the art, is, as has been stated by the Board of Appeal in Decision T 292/85, "Polypeptide expressions", (OJ EPO 1989, 275), satisfied "if at least one way is clearly indicated enabling the skilled person to carry out the invention". It is not necessary for the purpose of Articles 83 and 100(b) EPC that the disclosure of a patent be adequate to enable the skilled person to carry out **all** conceivable ways of operating the invention embraced by the claims. In view of the examples still

remaining in the description and the additional experimental data submitted by the Respondent (see submission of 30 August 1990, in particular page 18, last paragraph and page 19, Table 3) showing that following the instructions of the patent, compositions for two other peptides, Leuprolide and Buserelin, with at least one month's sustained release were made, the Board is satisfied that a *prima facie* case exists that the disclosure is sufficient to enable the skilled person without undue burden to carry out the invention as claimed.

- 4.2 The mere argument of the Appellants that because the Claim 1 covers an extremely large number of polypeptides, whereas the examples of the patent in suit all relate to a single polypeptide, Nafarelin, is not adequate to make out this ground of invalidity, in the absence of any evidence that there exists at least one polypeptide falling within the definition of Claim 1 for which a one month sustained release composition cannot be made following the teaching of the patent. Here the Appellants who are asserting this ground of invalidity have the burden of proof, and they have failed to discharge it (see T 219/83, OJ EPO 1986, 211).
- 4.3 Appellant 09 was the only one to submit evidence on the time it takes and the cost of arriving at a single sustained release formulation, and to argue that these were by themselves so great as to be evidence that the patent in suit contained insufficient instructions. However it is well known that developing and testing a marketable product in the medical field is commonly very expensive and time consuming even once the basic research has already been completed. Development of a product that is to achieve sustained release over one month, can be expected to be more expensive than average. In view of this the Board does not consider

that the time scale and costs quoted by Appellant 09 are so different from what could reasonably be expected, as to amount to evidence of the description of the patent being insufficient because an undue burden is imposed on anyone wishing to carry out the teaching of the patent in suit.

5. *Novelty (Article 54 EPC)*

5.1 Lack of novelty was only alleged in respect of (32), an earlier application by the Respondent with claims directed to particular polypeptides (including Nafarelin the polypeptide specifically referred to in the patent in suit) irrespective of whether they were used in a sustained release composition or not. (32) contained references to the desirability of the polypeptide being provided in a sustained release form. On page 41 in Example 8.B.2 there was disclosed a pharmaceutical composition comprising a LH-RH analogue in biodegradable microcapsules made of a 25/75 glycolide/lactide copolymer. Further (32) specifically referred to (9) stating on page 12, lines 16-21 that "Another type of slow release depot formulation for injection would contain the compound or salt dispersed or encapsulated in a slow degrading, non-toxic, non-antigenic polymer such as a polylactic acid/polyglycolic acid polymer for example as described in U.S. 3,773,919".

5.2 Example 8.B.2 did not specifically refer to the LH-RH analogue being Nafarelin, but as this was the preferred compound of (32) this seemed the natural interpretation. The Respondent provided evidence that if Example 8.B.2 was carried out using Nafarelin, the sustained release obtained was much less than one month. Appellant 01 provided evidence of some alleged attempts to repeat Example 8.B.2. The results did not show a sustained release for at least one month in all cases, and the

cases where at least one month release occurred the conditions of Example 8.B.2 had been departed from to such an extent that the Board does not consider that such results can be attributed to any normal way a skilled man might carry out 8.B.2. In particular, the only results showing an effective release time longer than one month, were obtained with either a drug loading very much higher than in Example 8.B.2 or a suspension different from the one disclosed in this example. The Board thus finds that Example 8.B.2 does not itself deprive Claim 1 of the main request of novelty.

- 5.3 (9) is concerned with sustained release compositions for pharmaceuticals using glycolide/lactide copolymers, but does not disclose any specific example of microencapsulation, though it refers to this possibility. The reference in (32) to (9) thus does not tell the skilled person to use anything in particular, but merely suggests this as a helpful publication for making further developments. What (32) and (9) taken in combination may suggest to the skilled person is something that might be taken account of when considering inventive step, but not when considering novelty. Novelty is interpreted narrowly by the Boards of Appeal, and when it is said that a document must be interpreted as it would be understood by the skilled person, this means only that what a skilled person would immediately understand without it being explicitly stated, can be read into a document. It does not mean that one can consider that for the purposes of novelty anything that reading a document may suggest to a skilled man has been actually disclosed.

6. *Priority (Article 87 EPC)*

6.1 The above finding that (32) does not destroy the novelty of Claim 1, necessarily implies that the subject-matter of Claim 1 is not disclosed in (32A), whose content can for this purpose be considered identical to that of (32). Thus (32A) cannot for the purposes of Article 87 EPC be considered as the first application for the same invention as now claimed.

6.2 Claim 1 is thus entitled to the priority claimed, which is earlier than the publication date of (32). Accordingly (32) is not prior art when it comes to considering inventive step under the provisions of Article 56 EPC.

7. *Inventive step (Article 56 EPC)*

7.1 For the purpose of considering inventive step the Board agrees with the Appellants that the closest state of the art is document (19), which discloses a decapeptide, now known as Triptorelin, having potent LH- and FSH-releasing hormone properties (see column 3, line 44 ff.) falling within the terms of Claim 1 of the main request.

7.2 (19) states that "when the decapeptide, preferably in the form of an acid addition salt, is employed in human medicine, it is administered systemically, either by intravenous, sub-cutaneous, or intramuscular injection, or by sublingual, nasal, or vaginal administration, in compositions in conjunction with a pharmaceutically acceptable vehicle or carrier" (see column 6, lines 38 to 45), and that "it is often desirable to administer the decapeptide continuously over prolonged periods of time in long-acting, slow-release, or depot dosage forms" (see column 7, lines 23 to 25) and that such dosage forms "may contain the decapeptide in the form of

a water-soluble salt together with a protective carrier which prevents rapid release" (see column 7, lines 29 to 31).

- 7.3 A different procedure of obtaining such dosage is referred to subsequently in column 7, lines 48 to 56 where it reads: "Long-acting, slow-release preparations of the decapeptide may also be obtained by microencapsulation in a pharmaceutically acceptable coating material, for example gelatine, polyvinyl alcohol or ethyl cellulose. Further examples of coating materials and of the processes used for microencapsulation are described by J.A. Herbig in "Encyclopedia of Chemical Technology", Vol. 13, 2nd Ed., Wiley, New York, 1967, pages 436-456". This latter is document (51) cited by the Appellants.

In this paragraph, microencapsulation is mentioned for the first and only time in document (19) and for details the skilled person is referred to (51) which provides a general overview of microencapsulation (see pages 436 to 450) in a great variety of technical fields (see pages 451 to 455), among which "Pharmaceuticals" takes a small place only (see pages 453, last paragraph to page 454, third paragraph).

- 7.4 In relation to this closest prior art, the Board considers that the problem to be solved can be stated as being to make available a pharmaceutical composition designed for sustained release of an effective amount of a water-soluble LH-RH polypeptide of the known type over a period of at least one month. This problem is to be solved by the pharmaceutical composition as defined in Claim 1 of the main request (see section III above).

- 7.5 Taking into account the results with the successful batches in Table II of the patent in suit (originally termed batches C, E, F) and the test results submitted by the Respondent (for details see under point 4.1 above) for additional compositions of effectively the same polymer system, giving at least one month's release as set out in present Claim 1, the Board considers that the above-stated problem has been plausibly solved by the pharmaceutical composition with the features required by Claim 1 of the main request.
- 7.6 Starting from (19) and set this problem the skilled person first turns to the suggestions made in (19) itself of long-acting, slow-release preparations based on gelatine, polyvinyl alcohol or ethyl cellulose as coating material, combined with the microencapsulation techniques given in (51). If this line is followed something other than what is covered by Claim 1 would be arrived at, as there is no suggestion that glycolide/lactide copolymer should be used for microencapsulation. There is no reason to believe that what is actually suggested would not be seriously contemplated by skilled persons.
- 7.7 The Board has no evidence that microencapsulation taken together with the biodegradable glycolide/lactide copolymers of (9) is a combination that the skilled person in the art at the priority date of the patent in suit would have seriously contemplated as a possibility. (9) itself is not referred to in (19), and while microencapsulation is mentioned as a possibility in (9) there are no specific examples of this. Further there exists a later document (53) referring to (9) and stating that the polymers of (9) presented several drawbacks as, *inter alia*, the formulation described in document (9) produced slow absorption in the body (see column 1, lines 19 to 27). (53) suggests what it

considers as better polymers than those of (9), namely a specific group of linear polyester salts with relatively low molecular weight which yet are hard, brittle and non-tacky solids (see Claim 1 and column 1, lines 19 to 68 of the description). Contrary to the Appellants' evaluation of the teaching of (9), this demonstrates how narrow the disclosure content of document (9) in substantiated form actually is.

- 7.8 The evidence by Appellant 05 that the Nobel Prize winning inventor of (19) at some unspecified date was aware of (9), but did not use it because of fears of possible patent infringement (quite apart from the fact that such hearsay evidence provided for the first time at the oral proceedings is a highly questionable form of evidence), allows no deductions to be made as to what the average skilled man would have known or considered at the priority date, nor does it explain why the possibility of using the polymer of (9) is not referred to in (19), even though (9) was published more than one and a half years before the filing date of (19).
- 7.9 The argument that the Respondent's own patent (32) can be used as an expert opinion (German "gutachtlich") to show that at its priority date (9) was well known fails because no such deduction follows inevitably. For all that appears, the Respondent may have been the only one to have taken this publication seriously. The clear prohibition contained in the second sentence of Article 56 EPC against the use of Article 54(3) EPC documents when considering inventive step, cannot be swept aside merely by the suggestion that a patent application might be relied on as an "expert opinion" as to the state of the art at its filing date.

7.10 Nevertheless even assuming that the skilled person would come across (9), it is by no means clear that this would have led him to make something falling within Claim 1. (9) related not only to PLGA but to copolymers with comonomers other than lactide or glycolide, such as other specific lactones or intermolecular cyclic esters of certain hydroxycarboxylic acids. The skilled person is thus faced with a document making numerous suggestions as to polymers of various chemical compositions and properties (see column 7, line 12 to column 9, line 10) which are applicable in the field of galenics (see column 1, line 61 to column 3, line 6). Even under the headline "preparation and administration of the formulation" a great variety of formulations result from the different procedures of coating (among which microencapsulation is mentioned), embedding and intimate mixing (see column 9, lines 12 to column 11, line 46). While it is true that the skilled person is told that "Drug compounds of the classes mentioned earlier may be coated, embedded, or intimately mixed in or with a matrix of one or a combination of different chain-length biodegradable polylactide polymers defined previously, to give a drug-polymer mixture which will provide a controlled sustained release of the drug compound over a period of 8 hours to 2 months or longer when administered parenterally" (see column 9, lines 65 to 72), and is taught different types of procedures (coating, embedding and intimate mixing) for this the preferred embodiments relate only to embedding. In the examples, without any exception, the polymer is melted at 225 to 250°C and a steroid drug is mixed into the melt. In two out of the nine examples given, it is disclosed that gross pellets of the product (80 mg or 100 mg) produced an oestrogenic response lasting for about one month (see Examples 5 and 6). From the entirety of the disclosure provided by document (9) in substantiated form, the skilled person does not get any

guidance whatsoever that just microencapsulation (see column 10, lines 39 to 57) might be successfully applicable in an attempt towards solving the technical problem underlying the patent in suit.

- 7.11 At the priority date of the patent in suit there was a multitude of possibilities, from the viewpoint of galenics, to formulate compositions for drug delivery over a prolonged period of time. However anything from 8 hours to two months was regarded as a prolonged period of time, and there was hardly any information as what should be chosen if a particular minimum release period was to be achieved for a particular drug.
- 7.12 It is not enough for the Appellants to show that by a judicious selection of one part of the teaching of one document, and another part of the teaching of another document the skilled man might have arrived at the invention claimed in Claim 1 of the main request. They must also show this selection is something the skilled person would have made with a reasonable expectation of success in achieving the release period of at least one month. Even taken together (19) and (9) neither suggest that microencapsulation together with PLGA will necessarily provide a solution, nor that this is at least as likely a way of achieving success as any other. The Appellants have failed to show any other reason why biodegradable PLGA and microencapsulation would be considered as the, or at least a, preferred route to successfully solving the problem at the priority date.
- 7.13 The Appellants have thus failed to show that the invention of Claim 1 of the main request lacks an inventive step. The other claims of the main request depend on Claim 1, so that they need not be separately considered. Accordingly, the main request is allowable.

7.14 In view of this finding, it is not necessary for the Board to consider the arguments relating to commercial success or to acknowledgements by third parties that there was an invention. Particularly in the medical field where inventions take a very long time to get on the market so that it is hard to assign precise causes for success or failure, such matters may generate a lot of paper, but provide little or no assistance on the issues actually to be decided.

Order

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

P. Martorana

A.J. Nuss