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D E C I S I O N
of 8 June 1994

Case Number: T 0051/93 - 3.3.4

Application Number: 87106858.1

Publication Number: 0290644

IPC: A61K 37/38

Language of the proceedings: EN

Title of invention:

Subcutaneous administration of human chorionic gonadotrophin

Applicant:

Serono Pharmazeutische Präparate GmbH

Opponent:

-

Headword

HCG/SERONO

Relevant legal norms:

EPC Art. 54, 56

Keyword:

"Second medical use - way of administration"

"Novelty of auxiliary request (yes)"

"Inventive step (yes) - benefit contrary to prior art expectation"

Decisions cited:

G 0005/83, T 0119/82, T 0019/86, T 0290/86

Catchword:

A different mode of administration for a pharmaceutical can render a medical use claim drafted according to decision G 5/83 novel.



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Boards of Appeal

Chambres de recours

Case Number: T 0051/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 8 June 1994

Appellant: Serono Pharmazeutische Präparate GmbH
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Representative: Kraus, Walter, Dr.
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Decision under appeal: Decision of the Examining Division of the European
Patent Office dated 10 September 1992, refusing
European patent application No. 87 106 858.1
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
S. C. Perryman

Summary of Facts and Submissions

- I. The appeal is against the Examining Division's decision to refuse the European patent application No. 87 106 858.1, filed on 12 May 1987, published under No. 0 290 644, and relating to the use of human chorionic gonadotrophin (HCG) for the manufacture of a medicament for subcutaneous administration.

- II. The reasons given for refusal were that the subject matter of the single Claim 1 for DE, GB, FR, IT, NL, SE, LI CH, BE, and LU, and the Claims 1 and 2 for AT, ES, and GR, lacked novelty and inventive step over document

(1) FR-M-2 608

More particularly, in the Examining Division's view, document (1) implicitly disclosed the subcutaneous administration of HCG for treating male sexual disorders. The Examining Division came to this conclusion by relying on a passage of document (1) which stated that the depot HCG-Zn++ complexes disclosed therein, used for treating male sexual disorders, could be administered either intramuscularly or subcutaneously, together with the disclosure in document (1) of a series of in vivo tests, wherein use of a depot HCG-Zn++ complex was compared to the use of HCG alone, and the slow release effect of the former composition emerged.

In connection with inventive step, the Examining Division held that the subcutaneous administration of HCG was an obvious alternative to intramuscular administration.

III. The appeal was lodged and the fees paid on 6 October 1992 with a request that the decision be reversed and that a patent be granted on the basis of the claims rejected by the Examining Division. On 17 December 1992, the Appellant filed a Statement of Grounds.

IV. The Board of Appeal in a communication of 4 May 1994 expressed doubts about the possibility of the claims being entitled to the benefit of Article 54(5) EPC, as the claims were not formulated in the way approved for a second medical use claim in decision G 5/83 (OJ EPO 1985, 64) of the Enlarged Board of Appeal. The Appellant's attention was also drawn to

(4) Remington's Pharmaceutical Sciences 1980, page 894

disclosing the intramuscular administration of **non depot** HCG for the treatment of cryptorchidism in boys. In reply the Appellant filed new claims.

V. Oral proceedings were held on 8 June 1994, during which the Appellant abandoned the previous claims and submitted documents (C) and (D) being respectively a new main request and a new auxiliary request.

The single claim of the main request for the contracting states DE, GB, FR, IT, NL, SE, LI CH, BE, and LU, reads:

"Use of HCG for the manufacture of a non-depot medicament for use in the treatment by subcutaneous administration of infertility or male sexual disorders."

The two claims of the main request for the contracting states AT, ES, and GR read:

"1. A process for the manufacture of a non-depot medicament for use in the treatment by subcutaneous administration of infertility or male sexual disorders comprising mixing HCG with a carrier and/or diluent.

2. Use of HCG for the manufacture of a non-depot medicament for use in the treatment by subcutaneous administration of infertility or male sexual disorders."

The single claim of the auxiliary request corresponds to the single claim for the contracting states DE, GB, FR, IT, NL, SE, LI CH, BE, and LU set out above.

VI. In support of his requests, the Appellant argued essentially as follows:

(a) It was agreed that document (4) represented the closest prior art, since unlike document (1), it dealt with **non-depot** HCG. Document (1) was concerned with intramuscular administration of HCG, and did not enable a person skilled in the art to practice the subcutaneous administration according to the invention, without undue experimentation and without knowing the pharmacokinetics and the biological effect of the subcutaneous administration of HCG. As was known to anybody skilled in the art, the resorption of a subcutaneous administration drug was slower than for the case of an one injected intramuscularly, because subcutaneous tissues, unlike muscular tissues, were poorly vascularized and moreover comprised a lipid layer. Therefore, the man skilled

in the art was fully aware that a higher dose of HCG would have been needed for subcutaneous administration, in order to achieve blood levels comparable to those achieved with intramuscular administration. However, a higher HCG dose, besides being more expensive, was expected to induce skin erythema and/or allergic reactions. Having regard to the above, the skilled person would not have considered subcutaneous administration as an alternative to intramuscular administration. Only the unexpected finding underlying the present invention, namely that contrary to expectation, a subcutaneous HCG dose achieved biological effects that were the equivalent of those achieved by intramuscular administration of the same amount of HCG, led to the realization that an effective subcutaneous dose of HCG could be administered without inducing skin erythema or allergic reactions.

- (b) In support of the process Claim 1 in the set of claims for the contracting states AT, ES and GR, the appellant drew attention to case law relating to what are called analogy processes, and argued that the concepts underlying this case law should be applied in the present case to acknowledge the novelty of this process claim.

VII. At the end of the oral proceedings the appellant requested that the decision under appeal be set aside and as

main request that a patent be granted on the basis of the single claim for the contracting states DE, GB, FR, IT, NL, SE, LI CH, BE, and LU, and the two claims for

the contracting states AT, ES and GR forming document (C) submitted during the oral proceedings on 8 June 1994, and a description to be adapted, and as

auxiliary request that a patent be granted on the basis of the single claim for all designated contracting states forming document (D) submitted at the oral proceedings on 8 June 1994 and a description to be adapted.

Reasons for the Decision

1. The appeal is admissible.
2. *Main request*
 - 2.1 Amendments - Article 123(2) EPC
 - 2.1.1 In the application as filed there appears on page 2, lines 6 and 7 the statement "HCG has been clinically used ... for the treatment of female and male infertility ... exclusively by intramuscular (i.m) injection" and on lines 12 and 13 "It has now been found that HCG can be efficaciously administered by subcutaneous injection." This provides a basis for the rephrasing appearing in the claims now put forward, including the introduction of the term "infertility", as it is apparent that infertility was always contemplated as one of the sexual disorders to be treated according to the present invention by subcutaneous administration.
 - 2.1.2 The subject matter of document (1) is not limited to HCG-Zn++ complexes as the only possible depot formulations, but also contemplates other depot formulations (see page 2, right hand column, first

sentence of second paragraph) to the effect that other known pharmaceutical aids endowed with depot effect may be added. Accordingly the use of the term "non-depot" is an appropriate and allowable restriction on the claims put forward to exclude the subject matter of document (1) therefrom by way of disclaimer.

2.2 *Novelty*

2.2.1 Document (4) discloses vials for injection containing HCG and diluent, which vials will of necessity have been obtained by mixing HCG with a carrier or diluent. That the process of mixing HCG with a carrier and/or diluent is the same irrespective of whether the intended use is for subcutaneous administration or intramuscular administration, is confirmed by the application text itself, where the same formulation of the medication is used in the comparative test of subcutaneous administration with intramuscular administration. Thus document (4) anticipates the process Claim 1 put forward in the set of claims for AT, ES and GR, as the novelty of the intended use of the product can only be taken into account as a technical feature limiting the claim where the claim takes the form of a use claim as approved of in decision G 5/83 (loc. cit.).

2.2.2 The use claim as approved in decision G 5/83 (loc. cit.) emphasizes that the intended use is a technical feature to be taken into account in assessing novelty, and which limits the claim. Normally, however, in a claim to a "Process for making X for use Y comprising the steps of..." the process claim is interpreted as covering the particular process of making X irrespective of whether that X is to be used for use Y or not. Thus, in such a process claim the wording "for use Y" is intended not as a distinguishing technical feature but merely as an illustration of what X can be used for. Consequently the

Board considers that in the process Claim 1 for AT, GR and ES the words "for use in the treatment by subcutaneous administration ..." are to be treated in accordance with common practice for process claims as merely illustrative and not as a restrictive technical feature capable of establishing novelty. That in the use claim the wording "for use in the treatment by subcutaneous administration ..." is to be treated in accordance with decision G 5/83 (loc. cit.) as a technical feature capable of conferring novelty on the claim, whereas this wording is not so treated in a process claim, is established practice, and serves the useful function that it gives applicants, where the process is novel, the opportunity of claiming protection for the process as such irrespective of intended uses of the product, and where the process is not novel, it gives applicants the opportunity of claiming the use of the product in the manufacture of a medicament for a novel medical treatment.

- 2.2.3 In the set of claims for AT, ES and GR, the use Claim 2 can best be categorized as a restricted form of the process Claim 1, the restriction being necessary to achieve novelty. No principles in the case law (see for example Paterson, The European Patent System, 9-59 and decision T 119/82, OJ EPO 1884, 217) on claims allowable for analogy processes, where an existing process is merely minimally adapted to make a new and inventive product, appear to the Board to provide any argument for treating process Claim 1 as novel. In analogy processes the process was *per se* novel, and it was a question of whether inventive step could be recognized for the process on the basis of the product being inventive - here the process is not *per se* novel.

2.2.4 For the purpose of assessing novelty in European Patent Office proceedings, the interpretation to be given to a claim must be the same irrespective of the contracting states for which the claim is put forward. That the contracting states AT, ES and GR have, for a time, laws restricting claimable subject matter, cannot, where the prior art is the same for all designated states, lead to a claim being interpreted as novel and allowable for these states if it is not also novel and allowable for all other contracting states. Thus the fact that process Claim 1 is put forward only for AT, ES and GR does not assist the Appellant.

2.3 Accordingly the main request is not allowable.

3. *Auxiliary request*

3.1 Novelty

3.1.1 The treatment of disease, cryptorchidism in boys, disclosed in document (4) is a treatment of infertility or male sexual disorders using HCG by way of intramuscular injection. The claim is not restricted to the medicament being manufactured in any particular concentration, dosage or formulation. Thus the only difference between the invention as claimed and the disclosure of document (4) is that the claim is directed to an intended method of subcutaneous administration. The claim is drafted in the form approved in decision G 5/83 (loc. cit) for claims where the novelty is solely that of the intended therapeutic use, so the only question is whether a difference in the mode of administration of a medicament can be treated as a new therapeutic use.

3.1.2 In decision T 19/86 (OJ EPO 1989, 25) it was considered that a medical treatment is incomplete if the subject is not identified, and thus a new medical use should be recognized not only where the disease involved is different but also where the target group (in that case pigs) was new. In decision T 290/86 (OJ EPO 1992, 414) it was considered that there was a further medical indication compared to a prior document if it is based upon a different technical effect which is both new and inventive over the disclosure of the prior document. In accordance with the line adopted in these cases, the Board finds it sufficient for acknowledging novelty of the therapeutic treatment of the present claim as a whole, if only one of the features of the treatment, namely the mode of administration, is novel. The mode of administration may be a critical factor in a medical treatment, and no reason can be seen for any **a priori** bar to relying on this difference when distinguishing over the prior art. Rather patentability must be treated as depending only on whether this modification is in fact novel and inventive. Thus novelty over document (4) can be acknowledged.

3.1.3 Document (1) is directed to the use of depot HCG compositions, which are suggested for use by intramuscular or subcutaneous injection. The only examples given however relate to administration by intramuscular injection. It is also mentioned that a comparison was performed with non-depot HCG administration, but the method of administration is not stated. This document contains no clear and unambiguous disclosure of administering non-depot HCG subcutaneously. The Board cannot agree with the Examination Division's view that the comparative tests must have involved both the intramuscular and the subcutaneous injection of non-depot HCG. The document does not say this, and any speculations the

reader would be led to make should appropriately be dealt with when considering inventive step, and not when considering novelty.

3.2 Inventive step

3.2.1 The most appropriate starting point for a problem/solution analysis appears to the Board to be document (4), a standard pharmaceutical text book which describes the intramuscular injection of HCG. In relation to this starting point the problem to be solved can be defined as providing an improved mode of administration that avoids the known drawbacks of intramuscular administration. These are that it cannot be used for self administration but rather requires a visit to a doctor or hospital, thus causing problems of patient compliance, the possibility of nerve lesions and the high risk of abscesses. The solution as claimed is subcutaneous administration and the Board is satisfied that this solution solves the problem.

3.2.2 Although with the benefit of hindsight the solution might appear simple, the Appellant has submitted that those in the art thought that subcutaneous administration was to be avoided. As the resorption of a subcutaneously administered drug was slower than for the case of one injected intramuscularly, because subcutaneous tissues, unlike muscular tissues, were poorly vascularized and moreover comprised a lipid layer, it was thought that for an effective subcutaneous dose a much larger quantity of HCG would be required than for the intramuscular route, and that this larger dose would cause skin irritations making it unacceptable to the patient. The fact that for several decades only the intramuscular route had been mentioned in textbooks, whereas for other hormones both the intramuscular and the subcutaneous routes were practised (see for example

the cited page of document (4), which refers to the subcutaneous administration of corticotrophin) makes the existence of such a prejudice plausible. The inventors showed, that contrary to this expectation, the subcutaneous route was practicable because although a dose administered subcutaneously in contrast to intramuscularly produced lower HCG blood levels, the desired therapeutic effect on testosterone/LH/FSH levels was substantially the same as when the dose was administered intramuscularly, despite the lower HCG blood levels. This unexpected and advantageous effect is clearly shown in Tables 1-4 of the application. An inventive step can thus be acknowledged over the prior art as represented by document (4).

- 3.2.3 Given an expectation that subcutaneous administration of non-depot HCG is not practicable, document (1) contains nothing to make the claimed invention obvious. In view of the examples relating only to intramuscular injection, a reader would naturally assume that the comparative test with non-depot HCG used intramuscular injection, which was the only standard method practised in the art. It must be doubtful if a reader would be persuaded that depot HCG was suitable for subcutaneous injection, in the absence of any pharmacokinetic information on this mode of administration, or any statement that the degree of skin irritation caused was acceptable. But even if the reader derived from document (1) an indication that the particular depot HCG described was suitable for subcutaneous injection, the document contains nothing to change the view that non-depot HCG was unsuitable for subcutaneous administration. That depot-HCG did not cause undesirable skin irritation, would not allow any conclusions to be drawn about non-depot HCG. Document (1) had been published for some twenty four years by the time of the present application, and on the evidence available has

not led to any form of subcutaneous administration of HCG. So the combination of documents (1) and (4) does not render the claimed subject matter obvious.

- 3.3 For the above reasons the auxiliary request relates to something novel and inventive over the art considered, and is thus allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to grant a patent on the basis of the auxiliary request (Document D) submitted at the oral proceedings on 8 June 1994 and a description to be adapted.

The Registrar:



L. McGarry

The Chairwoman:



U. M. Kinkeldey

