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D E C I S I O N
of 16 June 1997

Case Number: T 1024/96 - 3.3.2

Application Number: 91310143.2

Publication Number: 0484186

IPC: A61K 31/44

Language of the proceedings: EN

Title of invention:
Formulations and their use in the treatment of neurological diseases

Applicant:
Elan Corporation PLC

Opponent:
-

Headword:
Oral preparation/ELAN CORPORATION

Relevant legal provisions:
EPC Art. 84

Keyword:
"Clarity - Functional features (yes)"

Decisions cited:
T 0068/85, T 0954/92, T 0142/94

Catchword:
-

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Case Number: T 1024/96 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 16 June 1997

Appellant: Elan Corporation PLC
Monksland Industrial Estate
Athlone
County Westmeath (IE)

Representative: Ryan, Anne Mary
c/o Anne Ryan & Co
60 Nothumberland Road
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Dublin 4 (IE)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 1 July 1996 refusing European patent application No. 91 310 143.2 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: C. Germinario
J. A. Stephens-Ofner

Summary of Facts and Submissions

I. European patent application No. 91310143.2, published under No. 0 484 186, was refused by the examining division. The decision was taken on the basis of a set of claims 1 to 24 filed on 12 February 1996.

II. Claims 1 reads as follows:

"1. A pharmaceutical formulation comprising a mono- or di-aminopyridine for oral administration on a once-or twice-daily basis, said formulation including said mono- or di-aminopyridine active agent in a polymer carrier effective to permit release of said mono- or di-aminopyridine at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period and at a rate sufficient to achieve therapeutically effective blood levels over a period of 12-24 hours following oral administration, said rate being measured *in vitro* as a dissolution rate of said formulation, which when measured in a type II dissolution apparatus according to U.S Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following:

a) no more than 50% of the total mono- or di-aminopyridine is released after 1 hours of measurement in said apparatus;

b) no more than 75% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus; and

c) 100% of the mono- or di-aminopyridine is released no earlier than after 8 hours of measurement in said apparatus."

III. The examining division rejected the application under Article 97(1) EPC on the grounds that claim 1 did not comply with the requirements of Article 84 EPC together with Rule 29(1) EPC.

The examining division maintained that claim 1 did not contain any technical feature characterising the structural composition of the claimed formulation and therefore did not indicate how the desired effect could be achieved.

It also held that the claim contained an almost literal repetition of the underlying technical problem and that the dissolution profile defined in the claim merely represented a method of testing whether a given formulation showed the desired properties so that did not permit the components or structures required to achieve the said effect to be determined

IV. The appellants lodged an appeal against this decision, filing an auxiliary request and requesting oral proceedings as a precautionary measure.

The appellants' arguments can be summarised as follows. Claim 1 cites several technical features, which are either structural or functional. According to decision T 68/85 (OJ EPO 1987, 228) a functional characterisation is permitted when a structural definition would unduly limit the scope of protection and when the functional result can be directly and positively verified by tests or procedures specified in the description.

The *in vitro* release profile and the *in vivo* adsorption properties defined in the claim do in fact represent a functional result which can be directly and positively measured according to known procedures.

The appellants also relied on decision T 954/92, in which it was accepted that a controlled release composition could be characterised *inter alia* by way of its *in vitro* dissolution rate profile, as in the present case.

V. The appellants requested maintenance of the patent in the form filed with their letter dated 9 February 1996 (received by the EPO on 12 February 1996), as their main request, or in the form of the auxiliary request enclosed in the statement setting out the grounds of appeal. They also requested oral proceedings, should refusal of the main request be envisaged.

Reasons for the Decision

1. The appeal is admissible.

2. Article 84 EPC and Rule 29(1) EPC.

In order to assess whether a claim meets the requirements of Article 84 EPC, the matter for which protection is sought needs to be properly identified in order to recognise which features are essential for the definition of the invention, and which are not. The former must be defined in the claim, whereas the latter, although not prejudicial to the clarity of the claim, are likely to unduly limit the protection conferred and therefore are not necessary for the definition of the claimed subject matter.

The present application relates to formulations for the controlled and delayed administration of a mono- or di-aminopyridine active agent in the treatment of neurological diseases. These formulations are suitable for once- or twice-daily administration.

According to the statement of the prior art, as discussed in the description of the patent application, satisfactory formulations for controlled/delayed administration of this type of mono- or di-aminopyridine have not been previously described. It follows that the subject-matter for which protection is sought and which is to be defined in the independent claim is represented by the aforementioned formulations in the most general meaning of the term, as opposed to the rapid-release preparations suitable for administration in multiple daily doses described in the prior art.

3. The formulation of claim 1 is characterised by means of the following features which are in part structural and in part functional:

(a) it includes a mono- or di-aminopyridine active agent,

(b) in a polymer carrier,

(c) [which is] effective to permit release of the said mono- or di-aminopyridine at a rate allowing controlled absorption thereof over, on the average, not less than a 12-hour period and at a rate sufficient to achieve therapeutically effective blood levels over a period of 12-24 hours following oral administration (this feature could be qualified as the *in vivo* profile),

(d) [the formulation] displays a defined *in vitro* dissolution rate as measured in a type II dissolution apparatus according to US Pharmacopoeia XXII in water at 50 r.p.m, the distinct values thereof being given (*in vitro* profile).

4. Features (a) and (b) are structural technical characteristics of the composition. They are supported by the description which cites the 4-aminopyridines and 3,4 di-aminopyridines and discloses a large number of suitable and available polymers. Therefore these features do not give rise to any doubt as to the clarity of the claim.

5. Features (c) and (d) define the *in vivo* properties and the *in vitro* dissolution profile of the claimed formulation. The examining division held that these functional characteristics did not include any technical teaching for the skilled person.

5.1 The parameters characterising a controlled/delayed administration, ie the dissolution rate, the absorption rate and the plasma level of the medicament in the active form, are not absolute properties valid for any delayed formulation but, on the contrary, they necessarily depend on factors, which are specific for a defined medicament, treatment and disease. These factors have to be seriously evaluated and defined before a delayed/controlled formulation can be successfully devised. In fact, formulations may be produced, which, though delayed, do not necessarily bring about the desired technical effect and for this reason would be unsuitable in practice for the intended therapeutical purpose. The *in vitro* dissolution rate also offers a preliminary criterion, well accepted in the specialised circle, for assessing and defining the delayed effect. In fact, a satisfactory correlation between the plasma level and the dissolution characteristics is normally observed.

For these reasons, the *in vitro* and *in vivo* profile of the claimed formulation are recognised as technical features which, in the board's judgment, not only contribute to the definition of the subject-matter for

which protection is sought, but also represent the very core of the invention. For this reason the board cannot share the examining division's finding that claim 1 does not contain any technical features.

5.2 The question now arises whether the functional language adopted should be allowed in the present case. A functional characterisation is normally accepted and in line with previous decisions (see T 68/85, OJ EPO 1987, 228 and T 954/92 of 28 May 1993, not published in OJ EPO) when the claimed subject matter cannot be otherwise defined without unduly restricting the protection sought and if this feature provides instructions which are sufficiently clear for the skilled person to reduce them to practice without undue experimentation. It is inherent in this latter requirement that an analytical method must be available to allow direct and positive evaluation of the functional results.

As already set out above, and without prejudice to the following substantive examination as to novelty and inventiveness, the present patent application covers mono- or di-aminopyridine formulations in the most general terms exhibiting the claimed *in vivo* and *in vitro* properties. It is immediately evident to the board that the claimed functional characteristics can be matched by a multiplicity of structurally different formulations obtained by combining in the correct amounts the different polymers and additional components thoroughly disclosed in the description and available to the skilled person. Therefore, in the board's judgement, any structural characterisation of the claimed formulation, as suggested by the examining

division, would undoubtedly and unjustifiably limit the scope of the claim to a specific and practical embodiment of the invention.

As to the second condition set out in T 68/85, the board notes that mono- or di-aminopyridines were, on the priority date of the application, well known medicaments for the treatment of neurological diseases. The therapeutically effective blood level and the suitable analytical methods to check such a blood level are disclosed, for example by D. R. A. Uges et al. in Pharm. Acta Helv., vol. 57, No. 4, 1982, 122-8 (document (2)) and in the numerous pieces of literature referred to in the said article.

The *in vitro* dissolution profile also represents a known and well accepted method for evaluating the *in vivo* behaviour of a given formulation. Methods, apparatus and means for determining and evaluating the results of a dissolution test are available from the US Pharmacopoeia XXII as explicitly indicated in the claim.

Therefore, the board's judgment is that functional language is clearly allowable in the present case and that no further characterisation, disclosed in the description or in any dependent claims is necessary for the definition of the claimed subject matter. This conclusion is consistent with the previous decisions T 954/92 (28 May 1993, not published in OJ EPO) and T 142/94 (16 January 1997, not published in OJ EPO), where similar characterisations of delayed/controlled release formulations have already been accepted by the competent board.

6. In its decision, the examining division also expressed the opinion that the first part of claim 1 comprised nothing but the almost literal paraphrasing of the underlying technical problem to be solved and that the cited functional characterisation did not permit the component or the structure required to obtain the claimed effect to be determined.

In the board's judgment, once the *in vitro* dissolution and the *in vivo* absorption criteria to be satisfied have been set forth, the additional contribution requested from the skilled person in manufacturing the formulation is merely that of carrying out the appropriate adjustments of the ingredients as well as the necessary measurements by relying on the exhaustive disclosure of components and procedures taught in the specification. Moreover, as it is emphasised in the description, all the necessary components are commercially available and all the necessary procedures are well known *per se*. Therefore, no undue experimentation or inventive merit is required of the skilled person.

On the other hand, the board makes it clear that, as long as the closest prior art is not identified, no underlying technical problem can be identified either. Therefore, the technical problem indicated by the examining division should be regarded, at present, simply as a theoretical or provisional problem. In any case, the board is not of the opinion that claim 1 attempts to characterise the claimed subject matter merely by paraphrasing the said problem. The examining division's view is in fact founded on an incorrect definition of said problem, which, as worded in the decision under appeal, already includes many potential elements of the solution, such as dissolution rate, adsorption time and blood level of the medicament - technical features which, as already seen, can

distinguish the proposed solution from other delayed formulations that may be unsuitable for achieving the desired therapeutic effect.

7. Other aspects under Article 84 EPC.

During the proceedings, the examining division also objected to the expressions: "on the average, not less than a 12 hour period" and "therapeutically effective blood level" cited in the text of claim 1.

The release of active agent from the polymer carrier, which must be such as to permit a controlled adsorption over, **on the average**, not less than a 12 hour period, does not simply depend on the easily controlled structural features of the formulation but is obviously influenced by the composition of the physiological liquid phase in which said formulation dissolves. Since this phase has no constant composition but changes in time and from subject to subject, it is reasonable to expect that the adsorption period varies around an average value. The extent of this variation is immaterial to the clarity of the claim since the expression "on the average" implies in itself that the release/adsorption test necessary to check whether or not a formulation is comprised in the scope of the claim is to be performed more than once in order to assess whether said formulation exhibits, on the average, the adsorption time cited in the claim. Therefore, the expression is regarded as clear.

The same applies to the expression "therapeutically effective blood level". As already seen above, mono- or di-aminopyridines were already well known medicaments on the priority date of the application, as disclosed eg in (2). Therefore the skilled person would, without any difficulty, have found the blood concentration of the medicament effective for developing the desired

therapeutic activity. Indeed, under the same circumstances, the same or an equivalent expression was accepted without objection in decisions T 142/94 (supra) and T 954/92 (supra).

On the basis of the reasons discussed above, the board holds that claim 1 of the main request meets the requirements of Article 84 EPC.

Since the substantive examination as to the novelty and the inventive step of the claimed subject-matter was based on the incorrect premise, now reversed by the board, that the obtained results (features c and d) were not limiting or characterising features of the invention, the case is remitted to the department of first instance for the further prosecution of the substantive examination.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution on the basis of the main request.

The Registrar: The Chairman:

P. Martorana P. A. M. Lançon