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D E C I S I O N
of 20 March 2003

Case Number: T 1074/97 - 3.3.1

Application Number: 91200118.7

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IPC: C07D 498/18

Language of the proceedings: EN

Title of invention:
Prodrugs of rapamycin

Applicant:
THE UNIVERSITY OF KANSAS

Opponent:
-

Headword:
Rapamycin prodrugs/KANSAS UNIVERSITY

Relevant legal provisions:
EPC Art. 76(1), 111(1)

Keyword:
"Main request: divisional application - extension beyond the content of the parent application as filed (yes) - deletion of a technical feature"
"Auxiliary request: unallowable extension (no) - remittal to the first instance"

Decisions cited:
T 0012/81, T 0150/82, T 0194/84, T 0331/87, T 0552/91

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1074/97 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 20 March 2003

Appellant: THE UNIVERSITY OF KANSAS
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Decision under appeal: Decision of the Examining Division of the European Patent Office posted 21 March 1997 refusing European patent application No. 91 200 118.7 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: A. J. Nuss
Members: J. M. Jonk
S. C. Perryman

Summary of Facts and Submissions

I. This appeal lies from the decision of the Examining Division refusing the European divisional patent application No. 91 200 118.7, published under number 0 429 436, and relating to prodrugs of rapamycin.

II. The Examining Division refused the present divisional patent application on the ground that the subject-matter of the claims of the main request then on file extended beyond the content of the parent application No. 86 309 449.6 (published under number 0 227 355) as filed (Article 76(1) EPC).

It held in particular that claim 1 of the set of claims of the main request for the designated Contracting States BE, CH, DE, FR, IT, LI, LU, NL and SE was related to any mono-aminoacylated rapamycin product, whereas the parent application as filed only related to rapamycin products mono-substituted at position 28 and di-substituted at the positions 28 and 43.

In this context, it considered that the decision T 552/91 referred to by the appellant was not applicable, since the parent application as filed clearly intended to claim the 28-mono-substituted derivative.

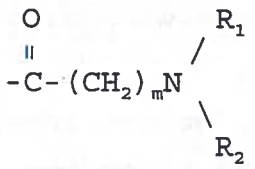
Moreover, the Examining Division considered that the claims of the auxiliary request then on file would be allowable under Article 76(1) EPC, but that it was not appropriate to examine their patentability since the appellant was not prepared to limit the claims of the main request accordingly.

III. Oral proceedings before the Board were held on 20 March 2003.

IV. The appellant defended the patentability of the subject-matter of the present divisional application on the basis of the sets of claims submitted during the oral proceedings before the Board as main request and on 6 August 1997 as the third auxiliary request. During the oral proceedings before the Board he withdrew the first auxiliary request and the second auxiliary request.

Claim 1 of the present main request read as follows:

"A water-soluble prodrug of rapamycin, said prodrug being a pharmaceutically acceptable salt of a mono-substituted derivative of rapamycin obtainable by acylation of rapamycin with an acylating agent containing a substituent having the configuration



wherein m is an integer from 1 to 3, and R_1 and R_2 are each hydrogen or an alkyl radical having from one to three carbon atoms or wherein R_1 and R_2 together with the nitrogen atom to which they are attached to form a saturated heterocyclic ring having four to five carbon atoms, separating the product by chromatography and if required acidifying to give a pharmaceutically acceptable salt thereof."

The claims of the present third auxiliary request substantially corresponded to those of the auxiliary request considered by the Examining Division.

V. The appellant disputed that the claimed subject-matter did not meet the requirements of Article 76(1) EPC. In this context, he essentially argued as follows:

Having regard to the specification of the parent application as filed indicating

(i) that the object of the claimed invention was to provide water soluble products,

(ii) that the water soluble products of the invention **comprised** mono-substituted derivatives at position 28 and di-substituted derivatives at positions 28 and 43 of the rapamycin structure, and

(iii) that the mono-substituted derivatives **included** those having the aminoacyl substituent at the 28 position of the rapamycin structure,

it would be clear to the skilled person that the disclosure of the claimed invention was not restricted to said mono- and disubstituted derivatives.

In view of the disclosure of the disubstituted derivatives at the positions 28 and 43 of the rapamycin structure, and having regard to the similar chemical environment of said positions the skilled person would immediately understand that the 43-mono-substituted isomer would inevitably form part of the reaction product of the acylation process as defined in claim 1 of the present main request. In support, the appellant submitted on 6 August 1997 a declaration of Mr Asselin and a test-report.

The allowability of the claims would also be consistent with the jurisprudence of the Boards of Appeal, in particular in view of T 12/81 (disclosure of a product as the inevitable result of a process), T 552/91 (definition of a product by its preparation method instead of a structural formula), and two decisions concerning the allowability of divisional applications under Article 76(1) EPC, namely, T 194/84 (novelty-test) and T 331/87 (essential-test).

VI. The appellant requested that the decision under appeal be set aside and the case be remitted to the Examining Division for further prosecution on the basis of the claims of the main request as submitted on 20 March 2003 or on the basis of the claims of the third auxiliary request as submitted on 6 August 1997.

VII. At the conclusion of the oral proceedings the Board's decision was pronounced.

Reasons for the Decision

1. The appeal is admissible.

2. *Main request*

2.1 Compliance with Article 123(2) EPC

2.1.1 In the Board's judgment, the subject-matter of present claim 1 is supported by the divisional application as filed and, therefore, meets the requirements of Article 123(2) EPC. Having regard to the Board's findings with respect to this request, the provision of details for this judgment is not considered to be necessary.

2.2 Compliance with Article 76(1) EPC

2.2.1 European divisional applications may only be filed in respect of subject-matter which does not extend beyond the content of the parent application as filed (Article 76(1) EPC, second sentence). According to the established jurisprudence of the Boards of Appeal this means that the subject-matter of a divisional application has to be directly and unambiguously derivable from, and consistent with, the parent application as filed.

2.2.2 In the present case, claim 1 of the divisional application in suit relates to water-soluble mono-substituted derivatives of rapamycin defined in terms of a process of preparation (i.e. a "product-by-process" claim) **without indicating the position(s) of the substituent in the rapamycin structure**, whereas claim 1 of the parent application as filed for the designated Contracting States BE, CH, DE, FR, IT, LI, LU, NL and SE concerned a water-soluble derivative of rapamycin **which is a mono-substituted derivative at position 28 or disubstituted derivative at positions 28 and 43 of rapamycin** with the substituent having the configuration as defined in the present claim 1 of the divisional application in suit.

2.2.3 The question to be answered is therefore whether the skilled person would directly and unambiguously derive from the application as filed that the invention as disclosed in the parent application as filed is not restricted to mono-substituted derivatives having the aminoacyl substituent at the 28 position of the rapamycin structure as originally claimed in the parent application, but also includes mono-substituted derivatives having the aminoacyl substituent at the possible 43 or 15 position.

2.2.4 The statements in the parent application as filed referred to by the appellant and indicating (i) that the invention relates to water soluble prodrugs of rapamycin and in particular to certain acylamino derivatives (page 2, lines 1 to 4 and lines 19 to 23), and (ii) that the object of the disclosed invention was the provision of water soluble prodrugs suitable for preparing injectable solutions (page 2, lines 15 to 18) indeed do not indicate any relevance of the 28 position of the aminoacyl group in the rapamycin structure. However, the first statement generally specifies the technical field to which the invention relates in accordance with Rule 27(1)(a) EPC, whereas the second statement defines the object of the invention in the light of the prior art, as far as known to the applicant. Thus, in view of the nature of these two statements, the skilled person would immediately understand that they do not specify the essential features of the invention. In fact, the specific disclosure of the invention in the parent application as filed starts on page 2, last paragraph. Consequently, these statements do not provide any support for the appellant's submission that the removal from the claims of the non-essential feature that the mono-substituent is at the 28 position would not violate Article 76(1) EPC.

2.2.5 It is true that further statements in the specification of the parent application as filed referred to by the appellant (see point V above under (ii) and (iii)) disclosing the invention more specifically (see page 2, last paragraph to page 4, line 13), as well as the structural formula of rapamycin on page 3 indicating the relevant positions 28 and 43, might suggest that the mono-substituted derivatives are not restricted to the 28-substituted derivatives.

2.2.6 However, from the originally filed parent application as a whole, in particular the claims and the statement in the specification indicating that the invention provides a process for preparing water-soluble rapamycin derivatives mono-substituted at the 28-position or disubstituted at the positions 28 and 43 (see the paragraph bridging pages 4 and 5 of the application as filed), it can only be derived by the skilled person that said position 28 with respect to the mono-substituted rapamycin derivatives is essential.

2.2.7 Moreover, the parent application as filed does not provide any pointer, let alone a direct and unambiguous disclosure, indicating that the aminoacylation of rapamycin and the separation of the product by chromatography as indicated in present claim 1 would give a mixture of mono-substituted derivatives or a mono-substituted derivative having the aminoacyl substituent at another position than the 28-position. It is true that it follows from the preparation of the 28,43-di-substituted derivatives that the 43-position could be substituted by an aminoacyl group. However, having regard to the complexity of the molecular structure of rapamycin, and in view of the different structural environments of the OH-groups at the 28, 43 and 15 positions, in the Board's judgment, it cannot unambiguously be predicted which position or positions in preparing mono-substituted rapamycin derivatives would be aminoacylated. In any case, it can be derived from the Examples 1 to 4 of the parent application as filed that the aminoacylation and separation by chromatography as indicated therein only give the 28-mono-substituted product. In this respect,

the Board observes that the declaration by Mr Asselin and the test-report submitted on 6 August 1997 are not relevant for assessing the allowability of present claim 1 under Article 76(1) EPC, since they do not form part of the parent application as filed.

2.2.8 The appellant's submission that present claim 1 would be allowable in view of T 12/81 and the fact that the aminoacylation of rapamycin inevitably produces rapamycin which is mono-substituted at the 43-position as supported by said test-report cannot be accepted, since said test-report does not represent a true reproduction of the examples of the application as filed. In fact, as indicated in the preceding paragraph, the examples concerning the preparation of mono-substituted derivatives only show the forming of a rapamycin derivative substituted at the position 28.

2.2.9 The decision T 552/91 referred to by the appellant concerns a particular case relating to chemical substances originally defined by an incorrect chemical structural formula, in which indeed a product-by-process claim was considered to be compatible with Article 123(2) EPC. However, the allowability of a product-by-process claim always depends upon the specific details of a case, so that already in view of the fact that the circumstances of the present case and those of said decision are not comparable, this decision is considered to be not relevant. Moreover, the Board observes that according to the established jurisprudence of the Boards of Appeal the form for a claim to a patentable product as such defined in terms of a process of manufacture (i.e. "product-by-process claims") should be reserved for cases where the product cannot be satisfactorily defined by reference to its composition, structure or other testable parameters (see T 150/82, OJ EPO 1984, 309). Therefore, having regard to this jurisprudence, present claim 1 of the

divisional application in suit rather does not seem to define the matter for which protection is sought in terms of the technical features of the invention as required under Rule 29(1) EPC.

2.2.10 With respect to the decision T 331/87 referred to by the appellant, in which criteria are indicated allowing the deletion from an independent claim of a non-essential feature, the Board observes that it is clearly stated in this decision that the determining factor allowing such a deletion is the original disclosure of the application as filed (see point 3 of the Reasons). Therefore, this decision is in line with the established jurisprudence of the Boards of Appeal followed by this Board in assessing the allowability of present claim 1 under Article 76(1) EPC (see also points 2.2.1 and 2.2.2 above).

2.2.11 The decision T 194/84 (OJ EPO 1990, 59) referred to by the appellant actually confirms, that the test for additional subject-matter corresponds to the test for novelty only in so far as both require assessment of whether or not information is directly and unambiguously derivable from that previously presented in the originally filed application.

2.2.12 Thus, having regard to the above considerations, the Board concludes that the skilled person would not directly and unambiguously derive from the parent application as filed that the invention is not restricted to mono-substituted derivatives having the aminoacyl substituent at the 28 position of the rapamycin structure, and that the jurisprudence referred to by the appellant does not jeopardize this point of view.

2.2.13 Therefore, present claim 1 does not meet the requirements of Article 76(1) EPC and, consequently, the appellant's main request is not allowable and must be rejected.

3. *Auxiliary request*

3.1 Remittal to the first instance

3.1.1 The claims of the present third auxiliary request substantially correspond to those of the auxiliary request solely considered by the Examining Division to be allowable under Article 76(1) EPC, i.e. without further examination with respect to their patentability under the EPC.

3.1.2 Therefore, the application in suit in the present form still needs further examination in order to establish whether it meets the other requirements of the EPC. In these circumstances, the Board finds it appropriate to make use of the Board's power under Article 111(1) EPC and to remit the case to the first instance for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division for further prosecution on the basis of the claims of the third auxiliary request as submitted on 6 August 1997.

The Registrar: The Chairman:

N. Maslin A. Nuss