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Datasheet for the decision of 4 June 2018

Case Number: T 1745/12 - 3.3.01

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Language of the proceedings: EN

Title of invention:
CONTROLLED RELEASES SYSTEM CONTAINING TEMOZOLOMIDE

Applicant:
Jiangsu Tasly Diyi Pharmaceutical Co., Ltd.

Headword:
Temozolomide/JIANGSU

Relevant legal provisions:
EPC Art. 56, 111(2)
RPBA Art. 13

Keyword:
Main request: inventive step - (no)
Late-filed auxiliary requests 1-8 - admitted (no) 9-12 - admitted (yes)
Remittal to the department of first instance - (yes)

Decisions cited:
T 0779/02

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Case Number: T 1745/12 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 4 June 2018

Appellant: (Applicant)	Jiangsu Tasly Diyi Pharmaceutical Co., Ltd. No. 168 Chaoyang Road Qingpu Industrial Park Huai'an, Jiangsu 223002 (CN)
Representative:	Goddar, Heinz J. Boehmert & Boehmert Anwaltspartnerschaft mbB Pettenkoferstrasse 22 80336 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 30 March 2012 refusing European patent application No. 03753238.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	M. Pregetter
	P. de Heij

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division refusing European patent application No. 03 753 238.9, published as EP-A-1 550 444.

II. The following documents, cited during the examination and appeal proceedings, are referred to below:

(1) WO99/11272

(2) Yung, Seminars in Oncology, 2001, 28(4), 43-46

(3) Leong et al., J Biomed.Mat.Res., 1985, 19, 941-955

(4) Rosen et al., Biomaterials, 1983, 4, 131-133

(5) Newlands et al., Br.J.Cancer, 1992, 65, 287-291

(6) US 4,888,176

(7) Krishnan Mahesh et al., Journal of Controlled Release, 2000, 69 , 273-281

(8) Berkland et al., Journal of Controlled Release, 2004, 94, 129-141

III. The decision under appeal was based on the main request, filed with letter of 20 May 2011, the sole request on file. The examining division found that claim 1 of the main request lacked an inventive step when starting from document (2) as closest prior art. The problem to be solved was identified as the provision of a formulation allowing prolonged release of temozolomide to the central nervous system. The use of a polyanhydride, especially a copolymer of 1,3-

bis(p-carboxyphenoxy)propane and sebacic acid, to provide a release system for temozolomide for prolonged, controlled release was considered to be obvious in view of documents (1), (3), (4) and (6). Documents (1) and (6) concerned implantable tablets/ drug delivery devices. Furthermore the choice of document (2) over document (5) as the closest prior art, the water solubility of various drugs and the loading of 3-10% temozolomide was discussed.

IV. With the statement setting out the grounds of appeal, the appellant (applicant) re-submitted the main request.

Claim 1 of the main request reads as follows:

"1. A controlled release system, comprising 3~10wt% of temozolomide and biodegradable poly(anhydride)s."

V. On 9 March 2018 the board issued a communication pursuant to Article 15(1) RPBA. The board indicated that claim 1 of the main request could be broadly construed. The issue of inventive step would be discussed along the line of argument of the contested decision.

VI. By letter dated 21 March 2018, the appellant re-filed the main request and submitted auxiliary requests 1 to 12.

The respective claim 1 of auxiliary requests 1 to 8 are product claims and contain various technical features further limiting the subject-matter of said claims. Said technical features relate to:

- restriction of the polyanhydride to a copolymer of

1,3-bis(p-carboxyphenox)propane (CPP) and sebacic acid (SA), with or without limitation to a weight ratio of CPP:SA of 20:80;

- restriction to implantable tablets;

- introduction of the definition that "the implantable tablet is capable of releasing the temozolomide in vivo during a period of time from 1 hour to 4 weeks";

- various combinations of said features.

Claim 1 of auxiliary request 9, which has two independent process claims, reads as follows:

"1. A process of preparing temozolomide controlled release implantable tablets, comprising 3-10 wt % of temozolomide and biodegradable poly(anhydride)s comprising:
a. Dissolving the poly(anhydride)s in a solvent to give a solution of poly(anhydride)s;
b. Dispersing temolozomide (sic) in or mixing temolozomide (sic) with said solution of poly(anhydride)s to produce a mixture of poly(anhydride)s and temolozomide (sic);
c. Spray-drying said mixture of poly(anhydride)s and temolozomide (sic) to obtain microspheres; and
d. Tabletting said microspheres to obtain implantable tablets".

VII. Oral proceedings were held on 4 June 2018.

VIII. The appellant's arguments, in so far as they are relevant to the present decision, may be summarised as follows:

Admission of auxiliary requests

The communication of the board had indicated that the claimed subject-matter might not be considered to be inventive over the entire scope claimed. As a reaction the auxiliary requests defined the scope of the claimed subject-matter in a narrower manner. The decision of the examining division had not addressed the breadth of the scope of claim 1.

Inventive step

The closest prior art was document (5), which discussed issues related to the administration of temozolomide, especially plasma concentration and half life of temozolomide (table II and figure 2), and thus represented the most promising starting point. Document (2) was an unreasonable starting point as it provided only indirect information on plasma concentration and the short half life of temozolomide. The appellant stressed in this context that only the awareness of the short half life of temozolomide made it necessary to look for a different form of administration.

Starting from document (2) as closest prior art, the objective technical problem solved by the subject-matter of claim 1 of the main request was the provision of an improved form of temozolomide administration to avoid unnecessary suffering by the patient.

The solution of claim 1 of the main request - a controlled-release system comprising temozolomide - was not obvious to the skilled person.

The abstract and other parts of document (2) taught away from using a controlled-release form for the administration of temozolomide. There, it was suggested to use higher concentrations of temozolomide or to combine temozolomide with other chemotherapeutic and biologic agents. The only alternatives to oral administration presented in document (2) was intratumoural and intrathecal administration which were not suitable to provide a solution for a controlled and prolonged release formulation of temozolomide.

Documents (3) and (4) were very old documents. The long period of time between their publication and the invention indicated that a prejudice against the preparation of controlled-release formulations of temozolomide using polyanhydrides existed (see T 779/02).

Document (1) related to different drugs with different chemical properties; the polarities of the drugs in particular were completely different. A person skilled in the art would thus not follow the teaching of document (1), which required that the drug co-dissolve with the carboxyphenoxypropane-sebacic acid anhydride, whereas the application under consideration required that the temozolomide not dissolve in the solvent used for dissolving the polyanhydride (application as filed, page 3, lines 1 to 4).

There was further evidence in the art that not all drugs were suitable to be released from a polyanhydride matrix. Document (6) taught that suitable drugs had to be able to be "homogeneously mixed" with the polyanhydride (column 4, line 17), but provided no clear teaching which compounds were suitable. Documents (7) and (8) provided evidence that many compounds were

not releasable from polyanhydrides. Document (7) explained that amines reacted with polyanhydrides. A skilled person would therefore not use temozolomide in a polyanhydride matrix, since temozolomide comprised several nitrogen atoms having free electron pairs.

The subject-matter of claim 1 of the main request thus involved an inventive step.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or, alternatively, on the basis of one of the auxiliary requests 1-12 as submitted with the letter dated 21 March 2018.

Reasons for the Decision

1. The appeal is admissible.

2. *Admission of auxiliary requests*

Together with the statement setting out the grounds of appeal the appellant re-submitted the main request as sole request. The auxiliary requests were filed only at a later stage of the appeal proceedings. According to the appellant, they were filed as a direct response to the communication pursuant to Article 15 RPBA. However, although these requests were presumably supposed to take into account certain statements made by the board, the accompanying letter neither explained the relation between the effected amendments and said statements, nor did it give any indication why these auxiliary requests would be allowable. In this respect the board notes that the decision of the examining division had addressed directly or indirectly all the technical features newly introduced into the claims of the

auxiliary requests.

2.1 *Auxiliary requests 1 to 8*

Due to the lack of explanation and the absence of substantiation regarding the technical significance of the features newly introduced into the claims of auxiliary requests 1 to 8, the board was left unaware of the appellant's reasons underlying the filing of these requests. Also, neither in its statement of grounds of appeal nor in the letter accompanying the submission of said requests has the appellant set out any reasons why the newly introduced features would lead to a reversal of the decision under appeal.

The board could only have speculated on the possibly complex reasons underlying the filing of these requests. Therefore, exercising its discretion provided by Article 13(1) RPBA, auxiliary requests 1 to 8 are not admitted into the proceedings.

2.2 *Auxiliary requests 9 to 12*

The situation is different for auxiliary requests 9 to 12. Auxiliary requests 9 to 12 do not contain independent product claims. They have been restricted to process claims. Since the reasoning of the decision under appeal does not extend to process claims, the appellant could not provide reasons and arguments in this respect.

Consequently, auxiliary requests 9 to 12 are admitted.

In this context, it should be noted that claim 2 of the eleventh auxiliary request - see appellant's comments on the eleventh and ninth auxiliary requests in its

letter of 21 March 2018 - contains an obvious error referring to the controlled-release system of claim 1 instead of the process of claim 1.

3. *Main request*

3.1 The application aims at the provision of a controlled-release drug system containing temozolomide (application as filed, first paragraph). Temozolomide is an anti-tumour drug, especially for use in the treatment of malignant melanoma, mycosis fungoides and advanced glioma (application as filed, second paragraph). Temozolomide is absorbed rapidly and has a short half-life time in plasma. Therefore, repeated administrations are required to keep the effective drug concentration in blood, linked to inconvenience and agony for the patients (application as filed, third paragraph).

3.2 Two documents, documents (2) and (5), have been discussed as potential closest prior-art documents.

Document (2) is an article entitled "Future Directions for Temozolomide Therapy" and discusses various aspects of therapies with temozolomide. In the abstract, ongoing clinical trials evaluating the efficacy and safety of temozolomide in, for example, glioma and other brain related conditions, melanoma and "other systemic tumors" are mentioned. Furthermore, information is provided that there are investigations on the dosing schedule, other routes of administration and treatment regimens relying on combination with other active agents. In the introductory part of document (2), reference is made to document (5) in the context of good oral bioavailability and the capability of temozolomide to cross the blood-brain barrier due to

its lipophilic properties (page 43, left column, paragraph 2, footnote 2). In a short dedicated chapter further routes of administration for temozolomide are discussed. Intratumoural and intrathecal temozolomide administration is mentioned (page 44, left column, paragraph 2). Document (2) thus discusses explicitly alternatives to the oral route of administration of temozolomide. A skilled person would consider every alternative presented in the context of aspects of therapies with temozolomide, including the information to non-oral routes of administration. The intratumoural and intrathecal administration is not further specified in document (2). These modes of administration aim at minimising systemic exposure and maximising local concentration of the active agent.

Document (5) reports on a phase I clinical trial of temozolomide. Determination of pharmacokinetic parameters, e.g. half life, was performed following oral or intravenous administration (e.g. figure 2). There is no discussion on general aspects of administration of temozolomide.

The board considers document (2) to be the more promising starting point since document (2) discusses possible changes to therapies based on temozolomide, whereas document (5) merely reports on a single study.

3.3 Claim 1 of the main request differs from the disclosure of document (2) in that the temozolomide is provided in a controlled-release form in a certain concentration range and the controlled-release form comprises a biodegradable polyanhydride.

3.4 The appellant has formulated the technical problem as follows:

"The objective technical problem is the provision of an improved form of administration of temozolomide which avoided unnecessary suffering of the patient."

The solution is the controlled-release form based on the biodegradable polyanhydride. The board considers that a controlled-release form, leading either to more constant drug levels or to less frequent administration provides advantages to a patient. Biodegradable polyanhydrides are well known for use as a matrix of controlled-release formulations. There is consequently no doubt that the problem is solved.

3.5 It remains to be determined whether the solution as defined by claim 1 of the main request is obvious.

3.5.1 There are several documents on file that describe the use of polyanhydrides. Especially carboxyphenoxyalkane-based polyanhydrides and in particular 1,3-bis(p-carboxyphenoxy)propane copolymerised with sebacic acid are used for controlled-release formulations. Of particular interest is document (1).

3.5.2 Document (1) deals with the treatment of intracranial tumours, i.e. brain tumours. Drug-loaded polymer wafers are implanted systemically or intracranially. The polymer matrix slowly erodes and thus releases the drug in a controlled way at a specific site within the body. The drug used in document (1) is an anticalcemic analog of vitamin D_3, the polymer used for the controlled-release system is a polyanhydride copolymer of 1,3-bis(p-carboxyphenoxy)propane and sebacic acid in a 20:80 molar ratio ("Summary of Invention", page 4). Document (1) suggests a drug loading ranging from 1 to

10% (page 21, lines 1 to 3).

3.5.3 A person skilled in the art starting from document (2) and thus aiming for improved ways for the administration of temozolomide, having intratumoural and intrathecal administration in mind, would consider the teaching of document (1), which relates to implantable wafers for the treatment of intracranial tumours. Applying the teaching of document (1) as discussed above, see point 3.5.2, to the disclosure of document (2) leads the skilled person directly to the subject-matter of claim 1 of the main request.

3.5.4 The subject-matter of claim 1 of the main request does not involve an inventive step.

3.6 *Further arguments*

3.6.1 The appellant has argued that the skilled person would not have chosen the system of document (1), since temozolomide has a completely different solubility pattern than the drugs employed in document (1). On the one hand, temozolomide is highly water soluble, whereas the drugs of document (1) are not. On the other hand and in contrast to the requirements according to the present application, where it is explicitly described that the drug is not soluble in the solvent used for preparation, document (1) teaches to completely co-dissolve the drug and the polyanhydride when preparing the implantable wafers.

The board cannot follow these arguments. The board notes first of all that claim 1 relates to a product claim not defining any process of its preparation. The skilled person would have been aware that the release of a drug from a biodegradable polyanhydride

matrix is dependent on the erosion of the matrix rather than on the solubility of the drug.

The following documents confirm this view of the board:

Document (3) is an article dedicated to the discussion of bioerodible polyanhydrides as drug carriers, including their release characteristics. The abstract explains that a close correlation of polymer degradation and drug release (at 10% loading) exists for poly[bis(p-carboxyphenoxy) alkane anhydrides]. The release mechanism is considered to be dominantly degradation-controlled. Document (3) provides further considerations of the release mechanism on page 953, first paragraph. There it is discussed that even though the (moderately) water soluble drugs of low molecular weight are susceptible to diffusional release from the system, the chosen polyanhydrides, i.e. the poly[bis(p-carboxyphenoxy) alkane anhydrides], function well as erosion-controlled systems.

Document (4), in line with the teaching of document (3), summarises in its abstract that studies show zero-order erosion kinetics and the release of the tested drug (cholic acid) at nearly the same constant rate as the erosion. The polyanhydride tested is poly[bis(p-carboxyphenoxy)methane]. 10.5 wt% of drug is incorporated into the polyanhydride (page 131, right column, paragraph 3).

Document (6) also relates to controlled-release systems based on bioerodible polyanhydrides. Exemplified are carboxyphenoxypropane-based polyanhydrides copolymerised with sebacic acid. In column 12, lines 37 to 66, the drugs to be used are discussed. The only selection criteria for the drug is its capability of

being intimately admixed with the polyanhydride and the subsequent formation into the desired shape without affecting the bioavailability of the drug. There is no restriction based on molecular weight or water solubility, as can be seen from lines 42 to 51: "The active substance [...]; it can be a macromolecule or a relatively low molecular weight molecule; and it can be soluble or insoluble in water". Anti-cancer drugs are disclosed in line 65. The examples of document (6) use a drug loading (for either colchicine or insulin) of 5 percent (examples X, XII, XIII).

Furthermore, the examining division has correctly summarised that polyanhydride systems have been used for several drugs having a broad range of solubilities in water (decision of the examining division, paragraph bridging pages 6 and 7).

Consequently, the skilled person would have considered a polyanhydride system also for drugs having a higher water solubility, such as temozolomide.

3.6.2 The board also does not accept that the disclosure of document (7) would discourage the skilled person from applying the teaching of document (1). Document (7) clearly refers to the reaction between amines and (poly)anhydrides leading to amides. The appellant has not shown that any of the amino groups present in temozolomide can readily form amides. Mere speculation about the nucleophilicity of amino atoms in heterocyclic ring systems are too remote to take away the skilled person's expectation of success, based on the successful use of polyanhydrides for the controlled release of several different drugs. Document (8) is post-published and thus not relevant in the present

case.

3.6.3 The board notes that documents (1) and (2) have publication dates that are within a couple of years of the priority date of the application under consideration. Decision T 779/02 is thus not relevant.

4. *Remittal*

The decision under appeal provides a detailed line of argument concerning the inventive step of the independent product claim. The process claims were however not addressed in the decision under appeal. In these circumstances the board finds it appropriate to exercise its power under Article 111(1) EPC and remit the case to the department of 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 department of first instance for further prosecution.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated