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**Datasheet for the decision  
of 17 February 2012**

**Case Number:** T 1408/10 - 3.3.02  
**Application Number:** 06708536.5  
**Publication Number:** 1853277  
**IPC:** A61K 31/711, A61P 35/00  
**Language of the proceedings:** EN

**Title of invention:**

Defibrotide and/or oligodeoxyribonucleotides for treating  
angiogenesis-dependent tumors

**Applicant:**

Gentium S.p.A.

**Headword:**

Defibrotide and/or oligodeoxyribonucleotides/GENTIUM S.P.A.

**Relevant legal provisions:**

EPC Art. 123(2)

**Keyword:**

"All requests - allowability of amendments (no): no basis in  
the original application"

**Decisions cited:**

T 0054/82, T 0685/90, T 0907/90, T 0165/98, T 0068/99

**Catchword:**

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Case Number: T 1408/10 - 3.3.02

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.02  
of 17 February 2012

**Appellant:** Gentium S.p.A.  
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I-22079 Villa Guardia (Como) (IT)

**Representative:** Pistolessi, Roberto  
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**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 13 January 2010  
refusing European patent application  
No. 06708536.5 pursuant to Article 97(2) EPC.

**Composition of the Board:**

**Chairman:** U. Oswald  
**Members:** A. Lindner  
L. Bühler

## Summary of Facts and Submissions

- I. European patent application No. 06 708 536.5 was refused by a decision of the examining division pronounced on 19 November 2009 and dispatched on 13 January 2010 on the basis of Article 97(2) EPC on the ground that the subject-matter claimed in the main request and the auxiliary request contained subject-matter that extended beyond the content of the application as originally filed.

The examining division came to the conclusion that the feature "administered to a human on a daily basis" had no basis in the original application as the administration of defibrotide on a daily basis only referred to *in vitro* tests or animal models which could not be transferred to the treatment of humans.

- II. The applicant (appellant) lodged an appeal against this decision.
- III. In the annex to the summons to oral proceedings issued by the board pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), the board in its preliminary opinion concurred with the reasoning of the examining division in the decision under appeal.
- IV. IV. With a letter dated 11 January 2012, the appellant filed a main request and auxiliary requests I and II. The independent claims read as follows:

*(i) Main request*

"1. Defibrotide for use in the treatment of angiogenesis-dependent tumour, characterised in that it is administered to a human on a daily basis."

*(ii) Auxiliary request I*

"1. Defibrotide for use in the treatment of angiogenesis-dependent tumour, characterised in that it is administered on a daily basis."

*(iii) Auxiliary request II*

"1. Defibrotide for use in blocking angiogenesis of human microvascular endothelial cells, characterised in that it is administered on a daily basis."

- V. With a letter dated 9 February 2012, the appellant informed the board that he would not attend the oral proceedings.
- VI. Oral proceedings were held on 17 February 2012, in the absence of the duly summoned appellant, in accordance with Rule 115 EPC and Article 15(3) RPBA.
- VII. The appellant essentially argued as follows:

The only circumstance under which amendment was not allowable was if the overall change in the content of the application led to information that the skilled person could not unambiguously derive from the explicit and implicit disclosure of the original application. Furthermore, the following principles could be derived

from the established jurisprudence of the boards of appeal, in particular from decisions T 0054/82, T 0685/90, T 907/90, T 0165/98 and T 0068/99:

- the skilled person was the relevant addressee and he would consider the description in the light of the common general knowledge;
- different parts of the description could be read together and the relevant state of the art could be taken into account in making this assessment;
- both explicit and implicit disclosure had to be taken into account;
- the whole content of the application had to be taken into consideration, a purely literal interpretation was inappropriate;
- in the determination of the core features of the invention, the skilled person would first consider the examples together with the preferred embodiments of the description and the claims; in particular the combination of preferred embodiments should not result in added subject-matter even if the combination was not specifically mentioned in the original application.

The feature in question, i.e. the administration on a daily basis, was taken from an *in vitro* test. However, *in vitro* tests were common practice in clinical research in order to obtain preliminary results which could then be transferred to *in vivo* administration. Moreover, the Matrigel<sup>®</sup> tube formation assay, which said feature referred to, was the most widely used angiogenesis assay. Furthermore, some of the tests described on pages 5 and 6 of the original application were carried out by using human endothelial cells.

Finally, the administration to humans, which was disclosed in claim 9 as originally filed, constituted the most preferred embodiment of the invention. As a consequence, the feature "administered to a human on a daily basis" had a clear basis in the application as originally filed.

VIII. The appellant requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of the main request or the first or second auxiliary request submitted with letter of 12 January 2012.

### **Reasons for the decision**

1. Main request - Article 123(2) EPC

1.1 Basis for the feature "characterised in that it [defibrotide] is administered on a daily basis"

The appellant indicated page 5, lines 5-8 and 22, as the basis for the characterising feature of present claim 1. As was correctly pointed out in the decision under appeal, the passage on page 5, lines 5-8 relates to an *in vitro* test, i.e. the Matrigel<sup>®</sup> tube formation assay involving the administration of defibrotide to endothelial cells of the rat aorta.

The passage on page 5, line 22, which stresses the superiority of daily application, concerns an *in vitro* assay performed on the basis of microvascular endothelial cells vascularising through a layer of dermal fibroblasts.

*In vitro* assays constitute valuable tools in pharmacy for testing the usefulness of potential active agents for therapy but it goes without saying that the specific environment of an *in vitro* test cannot be compared to the situation in which said agents are administered to a mammal such as a human. In connection with the dosage regimen (daily administration), it is noted that *in vitro* assays do not encompass parameters such as resorption, pH changes within the gastrointestinal tract (if orally administered), distribution of the active agent within the human or animal body or its release profile from the galenic vehicle, which play a very important role for determining which quantities of the active agent have to be administered at which intervals for obtaining the desired pharmacological effect. In this context, it is noted that in general, a specific dosage regimen cannot be transferred even from one mode of administration to another: thus, an intravenous administration of an active agent once per day does not imply that the desired pharmacological effect is also obtained by daily administration of a tablet or a suppository. As a consequence, the fact that the daily administration of difenobrate was suitable in an *in vitro* assay does not allow the conclusion that the same dosage regimen would also work for the therapy of humans.

The appellant, making reference to the paragraph bridging pages 5 and 6, argued that the original application also referred to *in vivo* models. The board, however, notes that this paragraph is completely silent as regards the dosage regimen.

It follows therefrom that the dosage regimen applied for the *in vitro* assays on page 5 of the original application cannot be transferred to the treatment of mammals or humans. As a consequence, the requirements of Article 123(2) EPC are not met.

1.2 Additional arguments of the appellant

The appellant cited the following decisions in connection with the allowability of the amendments:

- 1.2.1 T 0054/82 of 16 May 1983 was cited in order to demonstrate the possibility to combine features from different parts of the application. This is not refuted by the board but does not apply to the present case where features from two separate entities (*in vitro* assay on the one hand and *in vivo* administration to humans or mammals on the other hand) involving different conditions and different environments have been combined.
- 1.2.2 T 0685/90 of 30 January 1992 was cited to show that the whole explicit and implicit disclosure of the original application has to be taken into consideration. Again, this is not contested by the board. However, the board notes that the new combination of features from two separate entities does not form part of the original explicit or implicit disclosure.
- 1.2.3 For the same reason, decisions T 0907/90 of 5 March 1992 and T 0165/98 of 6 March 2001 are not pertinent either. These decisions were cited in order to show that a purely literal interpretation of the original application is not appropriate. This finding has,



however, nothing to do with the subject-matter of claim 1 of the present main request involving a new combination of features from two different entities.

1.2.4 In view of the fact that the *in vitro* assay and the *in vivo* administration to humans or mammals cannot be combined, decision T 0068/99 of 12 June 2003 is not pertinent to the present case either. Referring to this decision, the appellant reasoned that the feature "human" was mentioned in dependent claim 9 of the original application and therefore constituted a preferred embodiment. As a consequence, it could be combined with the dosage regimen of the *in vitro* assay in the light of decision T 0068/99. The board wants to point out in this context that the feature "human" according to original claim 9 constitutes a preferred embodiment of the use according to original claim 1, which as a Swiss type claim concerns the use of a compound for the manufacture of a medicament for the treatment of the human or animal body. This preferred embodiment restricts the treatment of the human or animal body to the treatment of the human body but it is not in any way connected to the *in vitro* assay according to page 5 of the original application.

1.2.5 As a consequence, none of the decisions cited by the appellant in connection with the allowability of the amendments is pertinent to the present case.

## 2. Auxiliary request I

As compared to the main request, the characterising part of claim 1 was changed from "in that it is administered to a human on a daily basis" to "in that

it is administered on a daily basis". Deletion of "to a human" implies that difibrotide is no longer limited to the use in the treatment of angiogenesis-dependent tumour in humans but now also includes treatment of the animal body (see Article 54(5) EPC in combination with Article 53(c) EPC). The inclusion of the treatment of the animal body does, however, not change the reasoning according to point 1.2.

3. Auxiliary request II

As compared to claim 1 of auxiliary request I, claim 1 of auxiliary request II comprises a more specific definition of the disease to be treated. This amendment does not change the reasoning of points 1.2 and 2 above, which applies *mutatis mutandis* to the subject-matter of claim 1 of the auxiliary request II.

**Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairman

N. Maslin

U. Oswald