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**Datasheet for the decision  
of 11 December 2013**

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**Application Number:** 04805892.9

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**Language of the proceedings:** EN

**Title of invention:**  
NOVEL IMAGING AGENTS COMPRISING CASPASE-3 INHIBITORS

**Applicant:**  
GE Healthcare Limited

**Headword:**

**Relevant legal provisions:**  
EPC Art. 84

**Keyword:**  
Claims - clarity (no)

**Decisions cited:**

**Catchword:**



**Beschwerdekammern  
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Chambres de recours**

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Case Number: T 2017/09 - 3.3.07

**D E C I S I O N  
of Technical Board of Appeal 3.3.07  
of 11 December 2013**

**Appellant:** GE Healthcare Limited  
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Little Chalfont,  
Buckinghamshire HP7 9NA (GB)

**Representative:** Canning, Lewis R.  
GE Healthcare Limited  
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**Decision under appeal:** **Decision of the Examining Division of the  
European Patent Office posted on 26 May 2009  
refusing European patent application No.  
04805892.9 pursuant to Article 97(2) EPC.**

**Composition of the Board:**

**Chairman:** D. Semino  
**Members:** A. Usuelli  
M. Tardo-Dino

## Summary of Facts and Submissions

- I. The appeal of the applicant (appellant) lies from the decision of the examining division announced at the oral proceedings on 23 April 2009 refusing European patent application N° 04 805 892.9.
- II. Claim 1 of the application as filed read as follows:
- "1. An imaging agent which comprises a synthetic caspase-3 inhibitor labelled with an imaging moiety, wherein the caspase-3 inhibitor has a  $K_i$  for caspase-3 of less than 2000 nM, and wherein following administration of said labelled caspase-3 inhibitor to the mammalian body *in vivo*, the imaging moiety can be detected either externally in a non-invasive manner or *via* use of detectors designed for use *in vivo*".
- III. During the procedure before the first instance, new sets of claims were filed with letters of 11 May 2006, 16 November 2007 and 15 January 2008. Claim 1 of all these sets of claims was characterized *inter alia* by a feature requiring the caspase-3 inhibitor to have a  $K_i$  for caspase-3 of less than 500 nM.
- IV. In a communication dated 26 March 2008 and in the summons to oral proceedings sent on 12 November 2008, the examining division raised *inter alia* objections under Articles 83 and 84 EPC with regard to the feature concerning the inhibition constant  $K_i$ , arguing that its value was dependent from temperature and pH, and that the whole application did not provide any information as to the conditions of temperature and pH to be used in the assays for determining said constant.

V. With letter of 19 March 2009 the applicant submitted a new main request and seven auxiliary requests from which any reference to the constant  $K_i$  was deleted.

VI. The documents cited during the examination proceedings included the following:

D1: Nuclear medicine and Biology, 2001, volume 28(7), pages 793-798

D8: Biochemical Pharmacology, 1973, volume 22, pages 3099-3108

D9: Biochemie, VCH Verlagsgesellschaft mbH, 1992, page 331.

VII. The decision of the examining division was based on the sets of claims filed with letter of 19 March 2009. In the decision under appeal the examining division came to the conclusion that the subject-matter of the main request and of auxiliary requests 1 to 7 did not meet the requirements of Article 123(2) EPC, in view of the deletion of the requirement that the caspase-3 inhibitor must have a  $K_i$  below a given value. Furthermore, starting from D1 as closest prior art, the examining division held that the subject-matter of all requests did not comply with the requirements of Article 56 EPC.

VIII. The appellant lodged an appeal against that decision. With the statement setting out the grounds of appeal, the appellant submitted a new main request and three auxiliary requests.

The first part of claim 1 according to the main request read as follows:

"1. An imaging agent which comprises a synthetic caspase-3 inhibitor labelled with an imaging moiety, wherein following administration of said labelled caspase-3 inhibitor to the mammalian body *in vivo*, the imaging moiety is suitable for imaging using SPECT or PET and said imaging moiety is chosen from:

- (a) a radioactive metal ion;
- (b) a gamma-emitting radioactive halogen;
- (c) a positron-emitting radioactive non-metal;

wherein the synthetic caspase-3 inhibitors has a  $K_i$  for caspase-3 of less than 500 nM and comprises one or more of the caspase-3 inhibitors defined in (i) to (ix):..."

The remaining part of the claim comprised a definition of the caspase-3 inhibitors (i) to (ix) in terms of generic chemical formulae or chemical definitions of classes of compounds.

Claim 1 according to auxiliary requests 1 to 3 comprised a narrower definition of the imaging agent. The limiting feature requiring the caspase-3 inhibitors to have a  $K_i$  for caspase-3 of less than 500 nM was included in claim 1 of all requests.

- IX. Together with the statement of grounds the appellant submitted the following document:

D10: Caspase-3 Cellular Assay Kit PLUS - AK-703

- X. In a communication sent in preparation of oral proceedings, the Board raised *inter alia* its concerns with regard to the clarity of the claims in view of the feature requiring the caspase-3 inhibitors to have a inhibition constant  $K_i$  for caspase-3 of less than 500 nM. In particular, the Board pointed out that the application did not provide any information as to the

conditions at which the assays experiments for determining the inhibition constant were to be carried out. Furthermore, also D10 did not appear to provide the required experimental details for carrying out the assays. Since the value of the inhibition constant was a function of temperature and pH, the matter for which protection was sought was not clearly defined because it could vary depending on the conditions adopted for determining said constant.

- XI. With letter sent on 3 December 2013 the appellant informed the Board of its decision not to attend the oral proceedings.
- XII. Oral proceedings were held on 11 December 2013 in the absence of the appellant.
- XIII. The appellant's arguments can be summarized as follows:
  - a) Example 9 of the patent, provided the information for determining the inhibition constant  $K_i$ . In this example it was explained that a caspase-3 inhibitor assay could be carried out using commercially available kits, such as the kit produced by BIOMOL International. A person skilled in the art would find full experimental details of how to carry out the assay from the product instructions of the kit. D10, which was an example of such product instructions, suggested for instance carrying out the assays at a temperature of 37°C, i.e. the normal body temperature.
  - b) The practice of the European Patent Office was to grant patents containing the features  $K_i$  and nM. Thus, objecting the feature  $K_i$  would be at variance with the established practice.

- c) Insertion of full experimental details for determining the inhibition constant into the claims, would render the claims overly complicated, and thus against the requirements of Article 84 EPC.

XIV. The appellant requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of one of the requests on file (main request, auxiliary requests 1-3 as submitted with the statement of grounds of appeal).

### **Reasons for the Decision**

#### *Main Request*

1. *Article 123(2) EPC*

In its decision the examining division considered that the deletion of the feature concerning the inhibition constant  $K_i$  resulted in the introduction of subject-matter extending beyond the content of the application as filed. Since this feature has been reintroduced in claim 1 of all requests, the objection of the examining division has become obsolete. The Board has no other concerns with regard to the requirements of Article 123(2) EPC.

2. *Article 84 EPC*

Claim 1 relates to an imaging agent comprising a caspase-3 inhibitor, wherein said inhibitor is characterized by having an inhibition constant  $K_i$  for caspase-3 of less than 500nM.

2.1 Information concerning the determination of this constant are given in example 9 of the application where it is stated that the potency of the caspase-3 inhibitors was assessed using commercially available assay kits, such as Biomol of Biomol International (page 51, lines 24-26 of the application as filed). Example 9 contains also details concerning the content of a caspase-3 assay kit and an explanation of the biochemical principles underlying its functioning (page 51, line 26 to page 52, line 2). However, no indication is provided in the example as to any possible protocol to be followed for the use of the kits. In particular, no information is given as to the experimental conditions such as temperature and pH.

Except for example 9, there are no other parts of the application concerning the determination of the  $K_i$ .

2.2 D9 contains a short section explaining the meaning of the Michaelis constant ("Bedeutung der Michaelis-Konstanten ( $K_M$ )"). In this section it is affirmed that this constant is a function of temperature and pH (second paragraph of the section). The mathematical relationship between the constant of inhibition and the Michaelis constant is illustrated by equation (3) of D8 (see page 3100):

$$I_{50} = K_I(1+S/K_m) \quad (3)$$

Rearrangement of the above equation results in:

$$K_I = I_{50}/(1+S/K_m)$$



(wherein:  $K_I$  = inhibition constant,  $I_{50}$  = concentration of inhibitor producing 50% of inhibition,  $S$  = concentration of substrate,  $K_m$  = Michaelis constant).

Thus, from D8 and D9 it can be concluded that also the inhibition constant  $K_i$  depends on temperature and pH. This conclusion has never been disputed by the appellant.

- 2.3 This means that the assays for determining this constant can lead to different results if different experimental conditions are used. This implies also that whether an imaging agent comprising a caspase-3 inhibitor falls under claim 1 of the main request depends on the conditions of temperature and pH arbitrarily adopted for determining the inhibition constant of the caspase-3 inhibitor. Therefore, the boundaries of the claim are not clearly defined and the claim is not clear.
- 2.4 The appellant has argued that a skilled person would find all the relevant information for determining the inhibition constant  $K_i$  in the instructions of the kit assay. In order to support this position document D10 was submitted during the appeal procedure. The appellant's argument is however not convincing. As a preliminary remark with regard to D10, it is observed that this document does not relate to the same kit mentioned in example 9 of the application. Furthermore, D10 does not indicate that the experimental assays must necessarily be carried out at certain conditions. Quite to the contrary, the indication "Equilibrate the dilution to assay temperature, e.g. 37°C" (see section "To start the assay", point 3), implies that the temperature is a variable parameter of the experiments and 37°C represents only an example. This finding is

confirmed by the statement to be found under point 6 of the same section in which it is affirmed that "The assays illustrated in Figs. 1-5 were performed at 37°C. Similar data were obtained at 25°C, but rates of DEVD-pNA cleavage were 2/3 of those obtained with the same samples at 37°C." The latter statement is also an indication that the activity of the caspase-3 is markedly dependent on the temperature.

The Board made the appellant aware of the above considerations with regard to D10 in a communication sent in preparation to the oral proceedings. The appellant did not submit any argument to challenge the position expressed by the Board.

- 2.5 From the above the Board concludes that D10 does not indicate that the commercially available assay kits are to be used only under certain specific experimental conditions. Instead, this document suggests that certain parameters such as the temperature, can be set by the operator. Therefore the  $K_i$  values determined using these assay kits depend ultimately on the experimental conditions selected for the experiment.
- 2.6 The fact that some European patents have been granted with claims containing the parameter  $K_i$  and without any indication as to the conditions for determining this parameter, is a remark that does not invalidate the considerations made in the previous paragraphs. In any case, it is evident that that the granting of these claims cannot have any legal consequence on the present appeal.
- 2.7 Finally, the observation that inserting the experimental details for determining the inhibition constant into the claims would render them overly

complicated, it is of no relevance in present case, since these details are in any case not given in the application.

2.8 For these reasons, claim 1 of the main request is not clear and does not meet therefore the requirements of Article 84 EPC.

*Auxiliary requests 1 to 3*

3. As also claim 1 of auxiliary requests 1 to 3 includes the feature " $K_i$  for caspase-3 of less than 500 nM", the claim does not meet the requirements of Article 84 EPC for the same reasons as given for the main request.

**Order**

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

The appeal is dismissed.

The Registrar:

The Chairman:



G. Nachtigall

D. Semino

Decision electronically authenticated