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# Datasheet for the decision of 16 June 2016

**Case Number:** T 1618/13 - 3.3.07

**Application Number:** 01986230.9

**Publication Number:** 1341557

**IPC:** A61K49/00

**Language of the proceedings:** EN

**Title of invention:**
NON-ISOTOPIC DETECTION OF OSTEOBLASTIC ACTIVITY IN VIVO USING MODIFIED BISPHOSPHONATES

**Applicant:**
Beth Israel Deaconess Medical Center

**Headword:**
NON-ISOTOPIC DETECTION OF OSTEOBLASTIC ACTIVITY IN VIVO USING MODIFIED BISPHOSPHONATES/Beth Israel Deaconess Medical Center

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

**Keyword:**
All request - Article 84 EPC (no)

**Decisions cited:**

**Catchword:**

Europäisches Patentamt
European Patent Office
Office européen des brevets

**Beschwerdekammern**
**Boards of Appeal**
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**Case Number: T 1618/13 - 3.3.07**

# D E C I S I O N
# of Technical Board of Appeal 3.3.07
# of 16 June 2016

| | |
|---|---|
| **Appellant:** (Applicant) | Beth Israel Deaconess Medical Center<br>330 Brookline Avenue<br>Boston, MA 02215 (US) |
| **Representative:** | Kirkham, Nicholas Andrew<br>Graham Watt & Co. LLP<br>St. Botolph's House<br>7-9 St. Botolph's Road<br>Sevenoaks, Kent TN13 3AJ (GB) |
| **Decision under appeal:** | **Decision of the Examining Division of the European Patent Office posted on 28 January 2013 refusing European patent application No. 01986230.9 pursuant to Article 97(2) EPC.** |

**Composition of the Board:**

| | |
|---|---|
| **Chairman** | J. Riolo |
| **Members:** | D. Boulois |
| | S. Fernández de Córdoba |

## Summary of Facts and Submissions

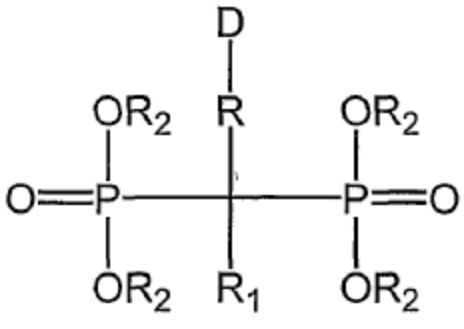
I. The appeal lies from the decision of the examining division to refuse European patent application n° 01 986 230.9.

II. The decision was based on 3 sets of claims as main request filed with letter of 15 October 2012 and as auxiliary requests 1 and 2 filed during the oral proceedings of 15 November 2012.

Claim 1 of the following requests read as follows, the difference with respect to the main request being indicated by **bold** (addition) or ~~strike through~~ (deletion)::

a) Main request

"1. A contrast agent represented in the general formula [I] or pharmaceutically acceptable salts thereof :




[I]

wherein
D represents a near-infrared fluorescent dye selected from the group consisting of a phthalocyanine dye, an indocyanine dye, a napthalocyanine dye, a metal complex dye, a triphenyl- or diphenylmethane dye, an azo dye, a quinone dye and a carbocyanine dye;

R represents a linking group that covalently links the dye (D) and bisphosphonate moiety;
$R_1$ represents H,-OH, or a halogen ; and
$R_2$ represents, independently for each occurrence, a free electron pair, hydrogen, or a pharmaceutically acceptable counterion.

b) Auxiliary request 1

The subject-matter of claim 1 has been restricted by a specification of the dye D as follows:
"D represents a **lower** near-infrared fluorescent dye selected from the group consisting of a phthalocyanine dye, an indocyanine dye, a napthalocyanine dye, a metal complex dye, a triphenyl- or diphenylmethane dye, an azo dye, a quinone dye and a carbocyanine dye, **that possess absorbance between 700 and 850 nm;**"

c) Auxiliary request 2

The subject-matter of claim 1 has been restricted by a further specification of absorbance measurement method as follows:
"D represents a **lower** near-infrared fluorescent dye selected from the group consisting of a phthalocyanine dye, an indocyanine dye, a napthalocyanine dye, a metal complex dye, a triphenyl- or diphenylmethane dye, an azo dye, a quinone dye and a carbocyanine dye, **that possess absorbance between 700 and 850 nm; if measured using a model DU-600 spectrophotometer (Beckman) using 1 µM of compound in 20 mM N-ethylmorpholine at pH 7.4 and 150 nM KCl (NK buffer);".**

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

D7: Nature Biotechnology, Vol. 19, p. 1148-1154, Dec. 2001, Zaheer et al
D11: Curr Cardiovasc. Imaging Rep, 2010, 3:12-17, Aikawa E.

IV. According to the decision under appeal, the feature characterizing the dye D was mentioned in the original description only as "compounds that possess absorbance at the lower NIR (700 to 850 nm)" (see page 12, lines 14-17). The omission of this feature changed the nature of the claimed dye and therefore the subject-matter of claim 1 of the main request did not meet the requirements of Article 123(2) EPC.

It was also not clear which compounds felt under the scope of the claims as the term "near infrared fluorescent dye" left the skilled reader in doubt as to the wavelength of the dyes which should be encompassed by the claims. There was indeed an uncertainty as to the NIR boundaries, as illustrated by some passages of the description of the application, wherein once it ranged from 700 to 900 nm (page 12, l. 4) in contrast to the range of "about 650 nm to 1000 nm" in another passage (page 12, lines 7-8). This uncertainty as to the NIR boundaries was supported by D7, defining the NIR window as ranging from 700 to 900 nm, or D11 referring to wavelengths of 650 to 900 nm.
The term "near infrared fluorescent dye" was furthermore unclear since it left the skilled reader in doubt as to the intensity of the fluorescence of the dye in respect to non-NIR wavelengths. It was not clear which of the following criteria had to be fulfilled in order to fall under the scope of the claims:
- presence of fluorescence and/or absorption in the NIR, or

- presence of intense fluorescence and/or absorption in the NIR, or
- presence of a regional fluorescence maximum and/or absorbance maximum in the NIR or
- presence of a global fluorescence maximum and/or absorption maximum in the NIR range.
The examining division concluded that the requirements of Article 84 EPC were not met by the main request.

The subject-matter of claim 1 of auxiliary request 1 had been amended with the specification that "D represents a lower near-infrared fluorescent dye" and "that possess absorbance between 700 and 850 nm". The claimed subject-matter was still unclear since the former term was still unclear and the latter term did not give sufficient information on the conditions used for measurement to decide if a compound emitted and/or absorbed within the lower NIR range. It was commonly known that absorption and fluorescence intensity of the dye moieties were dependent inter alia on the pH or solvent, dye concentration, cuvette selection, measuring device fluorescence quenching effects. In view of the fact that the claims were not restricted to dyes having their fluorescence and/or absorbance maximum within the NIR, the skilled person had to identify the detection limits for respective dyes, which depended largely on the chosen measurement method. The subject-matter of auxiliary request 1 lacked clarity in the sense of Article 84 EPC.

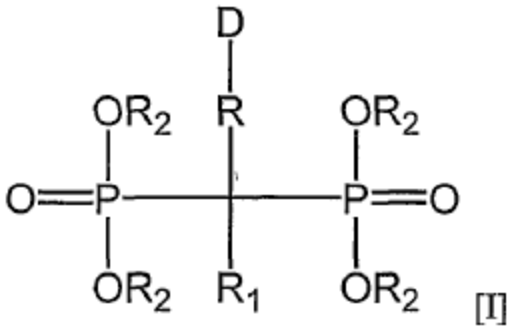
The subject-matter of claim 1 of auxiliary request 2 contained features relating to the measurement method taken from an example which infringed Article 123(2) EPC.

V. The applicant (appellant) filed an appeal against that decision. With the statement setting out the grounds of appeal, the appellant filed a new main request and 3 auxiliary requests. Additionally it requested that a further auxiliary request be considered, to each of the present requests where the claims were limited by the further feature "contrast agent for use in a method for in vivo imaging of tissue".

Claim 1 of the following requests read as follows, the difference with respect to the main request being indicated by **bold** (addition) or ~~strike through~~ (deletion):

a) Main request:

"1. A contrast agent represented in the general formula [I] or pharmaceutically acceptable salts thereof :




[I]

wherein
D represents a cyanine dye with absorption and emission in the near-infrared region;
R represents a linking group that covalently links the dye (D) and bisphosphonate moiety;
$R_1$ represents H,-OH, or a halogen ; and
$R_2$ represents, independently for each occurrence, a free electron pair, hydrogen, or a pharmaceutically acceptable counterion."

b) Auxiliary request 1

The subject-matter of claim 1 of auxiliary request 1 was further specified by the following feature:

"D represents a **lower** near-infrared fluorescent dye **selected from the group consisting of a phthalocyanine dye, an indocyanine dye, a napthalocyanine dye, a metal complex dye, a triphenyl- or diphenylmethane dye, an azo dye, a quinone dye and a carbocyanine dye, that possess absorbance between 700 and 850 nm;**"

c) Auxiliary request 2

The subject-matter of claim 1 of auxiliary request 2 was further specified by the following feature:

"D represents a **lower** near-infrared fluorescent dye **selected from the group consisting of a phthalocyanine dye, an indocyanine dye, a napthalocyanine dye, ~~a metal complex dye, a triphenyl- or diphenylmethane dye, an azo dye, a quinone dye and~~ a carbocyanine dye, that possess absorbance between 700 and 850 nm;**"

d) Auxiliary request 3

The subject-matter of claim 1 of auxiliary request 2 was further specified by the following feature:

"D represents a **lower** near-infrared fluorescent dye selected from the group consisting of a phthalocyanine dye, an indocyanine dye, a napthalocyanine dye, **~~a metal complex dye, a triphenyl- or diphenylmethane dye, an azo dye, a quinone dye and~~** a carbocyanine dye, **that possess absorbance between 700 and 850 nm if measured**

**using a model DU-600 spectrophotometer (Beckman) using 1 µM of compound in 20 mM N-ethylmorpholine at pH 7.4 and 150 nM KCl (NK buffer);".**

VI. With the communication sent in preparation for oral proceedings, the Board expressed its preliminary opinion that none of the requests met the requirements of Article 83 and 84 EPC.

VII. With a letter dated 9 June 2016, the appellant informed the Board that it will not be represented at the hearing.

VIII. Oral proceedings took place on 16 June 2016, in the absence of the appellant.

IX. The appellant's written arguments can be summarised as follows:

Main request

As to the question of clarity of the term "near infrared", it was a simple question as to whether a dye absorbed and emitted in the visible or infrared and the skilled person would not have had any difficulty in determining this fact for a particular contrast agent. Although the skilled person rarely defined the near-infrared range (NIR) as a precise numerical range of wave lengths, this did not mean that the skilled person had any doubt or difficulty in assessing whether or not a particular contrast agent absorbed or fluoresced in the visible or near-infrared. The use of the term "near-infrared" was wholly clear to the skilled person and this term was a common term of art that the skilled person frequently used and had no difficulty in assessing whether or not a particular dye was a NIR dye

even though the precise numerical limits were rarely used in the art.
As to the term "absorbance" and the intensity of the fluorescence referred to in claim 1, this referred to the absorbance maximum of the contrast agent. The skilled person used the terms "absorbance" and "absorbance maximum" interchangeably. The term "absorbance" should have been interpreted as clearly as "absorbance maximum".
The claimed structural definition of the contrast agent coupled to the specific family of dyes that formed the element D provided a definition that was clear to the skilled person.

Auxiliary requests 1-3

The comments made with respect of the main request were wholly applicable to the auxiliary requests.

Further auxiliary request

Claim 1 of this further request corresponds to each of the present requests with the following additional feature in bold, "contrast agent **for use in a method for in vivo imaging of tissue**". With this amendment, the skilled person would have been able to determine the absorbance maximum for a fluorochrome suitable for *in vivo* imaging, and whether the absorbance maximum of such a fluorochrome falls within the claimed range of 700 to 850 nm. The absorbance maximum would not have varied significantly when used as an in vivo imaging agent.

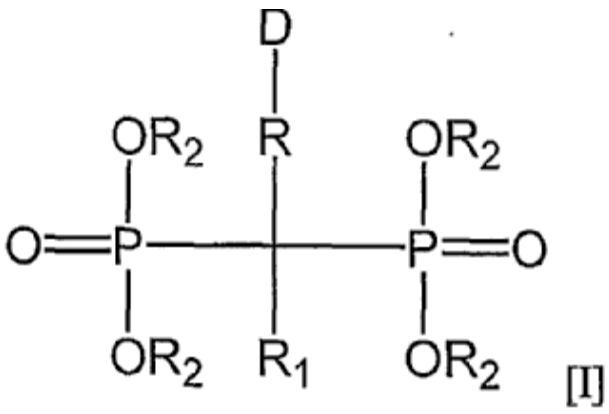
X. Requests

The appellant requested in writing that the decision under appeal be set aside and a patent be granted on the basis of the set of claims filed as main request or auxiliary requests 1-3 with letter of 7 June 2013 or a further auxiliary request to each of the present requests where the claims are limited by the feature "contrast agent for use in a method for in vivo imaging of tissue".

## Reasons for the Decision

1. Main request - Article 84 EPC

1.1 The subject-matter of claim 1 of the main request relates to a contrast agent represented by the general formula [I],




[I]

wherein R is a linking group and D a fluorescent moiety. The contrast agent of formula (I) intends to exhibit rapid and specific binding to hydroxyapatite in vivo, wherein the dye D allows the fluorescent detection of said hydroxyapatite.

Said dye moiety D and the technical result involved are thus key elements of the claimed invention, and the dye D constitutes an essential element of the contrast agent which is defined in claim 1 of the main request exclusively through the following functional term: "*D represents a cyanine dye with absorption and emission in the near-infrared region*".

1.2 The skilled person is however not in a position to determine if a particular chemical structure falls within the structure of formula (I) as regards the nature of said dye D, for the following reasons:
- The term "*near-infrared region*" (NIR) does not have a general recognized definition, and the skilled person does not know with certainty the boundaries of this range of wavelength. This is illustrated by some passages of the description of the application, wherein once it ranged from "700 to 900 nm" (page 12, l. 4) in contrast to the range of "about 650 nm to 1000 nm" in a following passage (page 12, lines 7-8). As mentioned by the examining division in its decision, this uncertainty as to the NIR boundaries was furthermore supported by several prior art documents, such as D7, defining the NIR window as ranging from 700 to 900 nm (see p.1148), or D11 referring to wavelengths of 650 to 900 nm (see p.12).
- The term "*absorption and emission*" remains vague, since it does not give any indication regarding the nature or the intensity of the absorption and the emission in the NIR wavelength range. It is indeed not clear from this term if it the claimed dye must have only a possible partial absorption and emission, or an intense or even maximal absorption or emission in said NIR range.

The skilled person is therefore left in doubt as to the subject-matter covered by the unclear and ambiguous feature "*D represents a cyanine dye with absorption and emission in the near-infrared region*" and is not in a position to identify clearly which dye D falls under this claimed feature.

1.3 Accordingly, the main request does not meet the requirements of Article 84 EPC.

2. Auxiliary request 1 - Article 84 EPC

2.1 Claim 1 of this request differs from claim 1 of the main request in that the definition of the dye D has been altered as follows in bold:
"*D represents a* ***lower*** *near-infrared fluorescent dye* ***selected from the group consisting of a phthalocyanine dye, an indocyanine dye, a napthalocyanine dye, a metal complex dye, a triphenyl- or diphenylmethane dye, an azo dye, a quinone dye and a carbocyanine dye, that possesses absorbance between 700 and 850 nm;***".

The modifications do not have any incidence on the lack of clarity, and even aggravate it for following reasons:
- the term "*lower near-infrared*" referring to the "*fluorescent dye*" is vague and unclear, not only with regard to its unknown boundaries, but also because it appears to be at least partially inconsistent with the further term present in claim 1, namely "*that possesses absorbance between 700 and 850 nm*", since it appears difficult to conceive that the emission, which is supposed to take place at a higher wavelength than the absorbance, might happen at a wavelength higher than 850 nm and still be considered to be in a "*lower near-infrared*" range.

- the term "*that possess absorbance between 700 and 850 nm*" does not help in the determination of the claimed dye, since it does not specify whether it relates to a low, partial, or secondary absorbance, an intense absorbance, or, as argued by the appellant to maximum absorbance.
- the chemical nature of the dye is not limited anymore to the cyanines, but extended to a great number of possibilities others than cyanine, which renders the identification of the claimed dye even more complex.

Thus, in view of the definition given to the dye moiety D, the skilled person is not able to determine if a particular chemical structure falls within the subject-matter of claim 1 or falls outside.

2.1.1 The Board could not follow the argument of the appellant that the terms absorbance and absorbance maximum related to the same technical concept and were interchangeable. It is indeed commonly known that absorbance measures the ability of a compound to absorb light wich passes therethrough, while maximum absorbance relates to a specific peak value of the absorbance. The concepts are thus not interchangeable.

The Board does not deny that in the spoken language the term "absorbance" might be used for defining in fact the "maximum absorbance", but it remains that both concepts are technically different, and that the wording used in a claim must be precise and not induce confusion.

2.1.2 The subject-matter of claim 1 of auxiliary request 1 is thus unclear and this request does not meet the requirements of Article 84 EPC.

3. Auxiliary request 2 - Article 84 EPC

The subject-matter of claim 1 of this request differs from claim 1 of auxiliary request 1 in that the definition of the dye D has been modified as follows in bold: "*D represents a lower near-infrared fluorescent dye selected from the group consisting of a phthalocyanine dye, an indocyanine dye, a napthalocyanine dye,* ***~~a metal complex dye, a triphenyl- or diphenylmethane dye, an azo dye, a quinone dye and~~*** *a carbocyanine dye, that possess absorbance between 700 and 850 nm;*".
In comparison to the subject-matter of claim 1 of auxiliary request 1, some categories of dyes have been deleted. This suppression cannot render the definition of the dye D clear. The arguments and the conclusions raised above for auxiliary request 1 apply thus *mutatis mutandis* to this request, which does not meet the requirements of Article 84 EPC.

4. Auxiliary request 3

The definition of the dye D in claim 1 of auxiliary request 3 differs from the definition given in claim 1 of auxiliary request 2 by the specification of the measurement method of the absorbance, namely as shown in bold:
"D represents a lower near-infrared fluorescent dye selected from the group consisting of a phthalocyanine dye, an indocyanine dye, a napthalocyanine dye, ~~a metal complex dye, a triphenyl- or diphenylmethane dye, an azo dye, a quinone dye and~~ a carbocyanine dye, **that possess absorbance between 700 and 850 nm if measured using a model DU-600 spectrophotometer (Beckman) using 1 µM of compound in 20 mM N-ethylmorpholine at pH 7.4 and 150 nM KCl (NK buffer);**".

The specification of the method of measurement of the absorbance cannot have any incidence on the definition of the dye D, since, as for the previous requests and for the same reasons, the skilled person is not able to determine if a particular chemical structure falls within the subject-matter of claim 1 or falls outside.

The subject-matter of claim 1 of auxiliary request 3 is unclear and this request does not meet the requirements of Article 84 EPC.

5. Further auxiliary request

This request was defined by the appellant as a request to each of the present request where the claims are limited to a "contrast agent **for use in a method for in vivo imaging of tissue**".

According to the appellant, with this amendment, the skilled person would be able to determine the absorbance maximum for a fluorochrome suitable for *in vivo* imaging, and whether the absorbance maximum of such a fluorochrome falls within the claimed range of 700 to 850 nm.

Although the definition of this further auxiliary request does not appear to be fully clear, the requirements of clarity will be examined for each previous requests amended in claim 1 by said feature "a contrast agent **for use in a method for in vivo imaging of tissue**".

5.1 Further auxiliary request to the main request

This amendment does not have any incidence as to the lack of clarity of the functional term "*D represents a cyanine dye with absorption and emission in the near-infrared region*" present in claim 1. The skilled person is still unable to determine if a particular chemical structure falls within the subject-matter of claim 1 for the same reasons already mentioned under point 1.1 above.

The Board could not follow the appellant's argument, since the question is not about to be able to determine the maximum absorbance, either *in vivo* or *in vivo*, but rather the possibility of determining which dye might possess an absorption and an emission in a wavelength region for which there are no precise boundaries. Moreover, the claim does not make any reference to a maximum absorbance or emission in the NIR region or in the range of 700 to 850 nm, but leaves open all the possibilities, namely whether it relates to possible partial absorption and emission, or an intense or a maximal absorption or emission in said NIR range.

Thus, this further auxiliary to the main request does not meet the requirements of Article 84 EPC for the same reasons than the main request.

5.2 Further auxiliary request to auxiliary request 1

As for the further auxiliary request to the main request discussed above, this amendment does not have any incidence as to the lack of clarity of the term present in claim 1 and defining the dye D, namely "D *represents a lower near-infrared fluorescent dye selected from the group consisting of a phthalocyanine dye, an indocyanine dye, a napthalocyanine dye, a metal complex dye, a triphenyl- or diphenylmethane dye, an*

*azo dye, a quinone dye and a carbocyanine dye, that possesses absorbance between 700 and 850 nm;*". The reason are the same as for auxiliary request 1 (see point 2.1). The fact that the contrast agent is used in an *in vivo* imaging method cannot render the functional definition of the dye clear.

As for the further main request and in response to the appellant's arguments, the question is not about to be able to determine the maximum absorbance, either *in vivo* or *in vivo*, but rather the possibility of determining which dye falls under the claimed definition.

The skilled person is unable to determine if a particular chemical structure falls within the subject-matter of claim 1 and the further auxiliary request to auxiliary request 1 does not meet the requirements of Article 84 EPC.

5.3 Further auxiliary request to auxiliary request 2

This amendment does not have any incidence as to the lack of clarity of the term present in claim 1 and defining the dye D for the same reasons as for auxiliary request 1 and auxiliary request 2.

The further auxiliary request 2 does not meet the requirements of Article 84 EPC.

5.4 Further auxiliary request to auxiliary request 3

This amendment does not have any incidence as to the lack of clarity of the term present in claim 1 and defining the dye D for the same reasons as for

auxiliary request 1, further auxiliary request 1 and auxiliary request 2.

The further auxiliary request 3 does not meet the requirements of Article 84 EPC.

## Order

## For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated