

**Internal distribution code:**

- (A) [ - ] Publication in OJ
- (B) [ - ] To Chairmen and Members
- (C) [ - ] To Chairmen
- (D) [ X ] No distribution

**Datasheet for the decision  
of 2 July 2024**

**Case Number:** T 0460/22 - 3.3.02

**Application Number:** 16726531.3

**Publication Number:** 3303307

**IPC:** C07D257/02, C07C229/16,  
A61K49/10

**Language of the proceedings:** EN

**Title of invention:**

NEW GADOLINIUM CHELATE COMPOUNDS FOR USE IN MAGNETIC RESONANCE  
IMAGING

**Patent Proprietor:**

Bayer Pharma Aktiengesellschaft

**Opponent:**

De Simone & Partners

**Headword:**

BAYER / GADOLINIUM CHELATE COMPOUNDS / MRI CONTRAST AGENTS

**Relevant legal provisions:**

EPC Art. 108, 56  
EPC R. 99(2)  
RPBA 2020 Art. 12(3), 13(2)

**Keyword:**

Admissibility of appeal (yes)

Amendment after summons - exceptional circumstances (no) - new  
evidence admitted (no)

Inventive step - main request (yes)

**Decisions cited:**

**Catchword:**



**Beschwerdekammern**  
**Boards of Appeal**  
**Chambres de recours**

Boards of Appeal of the  
European Patent Office  
Richard-Reitzner-Allee 8  
85540 Haar  
GERMANY  
Tel. +49 (0)89 2399-0  
Fax +49 (0)89 2399-4465

Case Number: T 0460/22 - 3.3.02

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.02**  
**of 2 July 2024**

**Appellant:**

(Opponent)

De Simone & Partners  
Via Vincenzo Bellini 20  
00198 Roma (IT)

**Respondent:**

(Patent Proprietor)

Bayer Pharma Aktiengesellschaft  
Müllerstraße 178  
13353 Berlin (DE)

**Representative:**

König Szynka Tilmann von Renesse  
Patentanwälte Partnerschaft mbB Düsseldorf  
Mönchenwerther Straße 11  
40545 Düsseldorf (DE)

**Decision under appeal:**

**Decision of the Opposition Division of the  
European Patent Office posted on  
20 December 2021 rejecting the opposition filed  
against European patent No. 3303307 pursuant to  
Article 101(2) EPC.**

**Composition of the Board:**

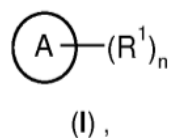
**Chairman** M. O. Müller  
**Members:** M. Maremonti  
M. Blasi

## Summary of Facts and Submissions

I. The appeal by the opponent ("appellant") lies from the decision of the opposition division to reject the opposition against European patent No. 3 303 307 ("the patent").

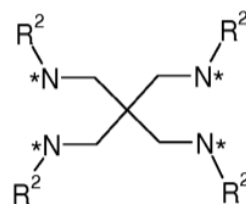
II. Claim 1 as granted reads as follows:

1. A compound of general formula (I),

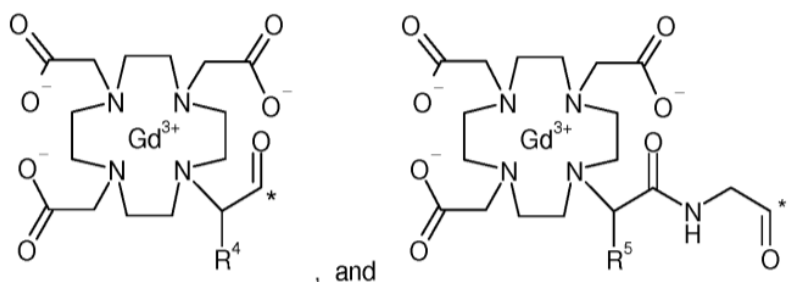


in which :

$\textcircled{\text{A}}$  represents a



group,  
 in which group \* indicates the point of attachment of said group with R<sup>1</sup> ;  
 R<sup>1</sup> represents a group R<sup>3</sup> ;  
 n represents an integer of 4 ;  
 R<sup>2</sup> represents a hydrogen atom ;  
 R<sup>3</sup> represents a group selected from :



in which groups \* indicates the point of attachment of said group with the rest of the molecule ;  
 R<sup>4</sup> represents a hydrogen atom ;  
 R<sup>5</sup> represents a hydrogen atom or a methyl group ;

or a stereoisomer, a tautomer, a hydrate, or a solvate thereof, or a mixture of same.

III. The opposition was filed invoking the grounds under Article 100(a) to (c) EPC. Reference was made *inter alia* to the following documents:

D2: WO 97/32862

D13: Di Gregorio *et al.*, "Gd loading by hypotonic swelling: an efficient and safe route for cellular labeling", *Contrast Media Mol. Imaging*, 2013, 8, pages 475 to 486

D14: WO 2012/059576 A1

D26: Swiss Federal Institute of Technology Lausanne, NMRD measurements - final report

D26a: Annex to D26

D28: Caravan, "*Strategies for increasing the sensitivity of gadolinium based MRI contrast agents*", Chem. Soc. Rev., 2006, 35, pages 512 to 523

D29: Declaration by Dr. M. Berger and Dr. T. Frenzel, Bayer AG, Berlin, Germany, dated 2 July 2021

IV. The opposition division came to, *inter alia*, the following conclusion:

- None of the grounds for opposition invoked by the opponent prejudiced maintenance of the patent as granted.
- In particular, the subject-matter of the granted claims involved an inventive step in view of D2 taken as the closest prior art.

V. In its appeal submissions, the appellant argued that the subject-matter of claims 13 to 15 as granted extended beyond the content of the application as filed. Moreover, the subject-matter of claim 7 as granted was insufficiently disclosed and the subject-matter of claim 11 as granted was not patentable in view of Article 53(c) EPC. The subject-matter of granted claim 1 further lacked novelty over the application from which priority had been claimed in the patent. Finally, the appellant submitted that the subject-matter of the claims as granted also lacked inventive step in view of D2 taken as the closest prior art. The appellant corroborated its arguments by filing the following new items of evidence (denoted D30 to D33 by the appellant; new numeration introduced by the board):

A030: Miéville *et al.*, "*Synthesis, complexation and NMR relaxation properties of Gd<sup>3+</sup> complexes of*

*Mes(DO3A)<sub>3</sub>*", Dalton Transactions, 40, 2011, pages 4260 to 4267

A031: Livramento *et al.*, "A benzene-core trinuclear  $Gd^{III}$  complex: towards the optimization of relaxivity for MRI contrast agent applications at high magnetic field", Dalton Transactions, 2008, pages 1195 to 1202

A032: Zhang *et al.*, "Multilocus Binding Increases the Relaxivity of Protein-Bound MRI Contrast Agents", *Angewandte Chemie Int. Ed.*, 44, 2005, pages 6766 to 6769

A033: Fischer G., "Chemical aspects of peptide bond isomerisation", *Chemical Society Rev.*, 29, 2000, pages 119 to 127

- VI. The patent proprietor ("respondent") contested the admissibility of the appeal. It also contested the admittance of items of evidence A030 to A033. Moreover, it rebutted the appellant's arguments maintaining that none of the grounds for opposition invoked by the appellant prejudiced maintenance of the patent as granted.
- VII. The parties were summoned to oral proceedings as per their requests. In preparation for the oral proceedings, the board issued a communication under Article 15(1) RPBA. In that communication, the board expressed, *inter alia*, the preliminary opinion that the subject-matter of the claims as granted involved an inventive step in view of D2 taken as the closest prior art.
- VIII. By letter dated 7 May 2024, the appellant replied to the board's communication and corroborated its submissions by filing the following new items of

evidence (denoted D34 and D35 by the appellant; new numeration introduced by the board):

A034: Affidavit of Prof. Caravan dated 26 February 2024

A035: Curriculum vitae of Prof. Caravan dated  
26 February 2024

- IX. By a subsequent letter, the respondent contested the admittance of A034 and A035 and the related submissions.
- X. By letter dated 20 June 2024, the appellant maintained its submissions based on A034/A035. However, it withdrew its objections under Articles 123(2), 53(c), 83 and 54 EPC.
- XI. Oral proceedings before the board were held by videoconference on 2 July 2024 in the presence of both parties. During the oral proceedings, the respondent withdrew its request that A030 to A033 not be admitted.
- XII. Final requests relevant to the decision
- The appellant requested that the appealed decision be set aside and that the patent be revoked in its entirety. It further requested that documents A030 to A035 be admitted into the proceedings.
- The respondent requested that the appeal be rejected as inadmissible. Alternatively, it requested that the appeal be dismissed and that the patent be maintained as granted, meaning that rejection of the opposition be confirmed. The respondent further requested that A034 and A035 and all submissions based thereon not be admitted.
- XIII. As regards the parties' submissions that are relevant to the decision, reference is made to the reasons for the decision set out below.



## **Reasons for the Decision**

Admissibility of the appeal - Article 108 and Rule 99(2) EPC and Article 12(3) RPBA

1. The respondent challenged the admissibility of the appeal.
2. At the oral proceedings, the board decided that the appeal was admissible. However, since the final decision was that the appeal had to be dismissed (see below), it is considered unnecessary to provide the reasoning on the appeal's admissibility in the present decision.

Items of evidence A034 and A035 and submissions based thereon - admittance into the proceedings - Article 13(2) RPBA

3. The appellant filed items of evidence A034 and A035 by its letter dated 7 May 2024, and in that letter made submissions based on those documents. That letter was filed after the board had issued a communication under Article 15(1) RPBA in preparation for the oral proceedings. The respondent requested that A034 and A035, and all related submissions, not be admitted into the proceedings.
  - 3.1 The appellant argued that the filing of A034 and A035 and all related submissions did not constitute an amendment to its appeal case within the meaning of Article 13(2) RPBA. A034 had merely been submitted to refine the objection based on document D2 in combination with D28. A034 was an affidavit by the author of D28, Prof. Caravan, who confirmed the appellant's arguments on the obviousness of the solution defined in claim 1 as granted. A035 confirmed that Prof. Caravan was an expert in the technical field of the patent. No new arguments had been filed either

in these documents or with the letter accompanying them, so the admittance of A034, A035 and related submissions did not lead to a surprising development in the proceedings and was not detrimental to procedural economy. Moreover, A034, A035 and related submissions had been filed two months prior to the oral proceedings, thus giving the respondent and the board sufficient time to consider them. That sufficient time was available was confirmed by the fact that the respondent could comment and respond to the content of A034, A035 and related submissions prior to the oral proceedings. The appellant thus concluded that A034 and A035 and related submissions should have been admitted into the proceedings.

- 3.2 Under Article 13(2) RPBA as in force since 1 January 2024, any amendment to a party's appeal case made after notification of a communication under Article 15(1) RPBA shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.
- 3.3 A034 is an affidavit made by the author of D28, Prof. Caravan, in which he not only agrees with the analysis of D28 made by the appellant (see last line on page 4 of A034) but also makes various assertions (see pages 5 and 6 of A034) based on citations from several documents that are not part of these proceedings and were not filed. A035 is the curriculum vitae of Prof. Caravan. In the letter with which A034 and A035 were filed, the appellant made further submissions based on these assertions in A034 to reinforce its objection of lack of inventive step.
- 3.4 Since A034, A035 and related submissions contain new assertions based on citations from new items of evidence, the board concurs with the respondent that

the filing of A034, A035 and related submissions does represent an amendment to the appellant's case made after notification of a communication under Article 15(1) RPBA, and, as such, is subject to the above provisions of Article 13(2) RPBA.

3.5 The appellant could not name any exceptional circumstance which might have justified the filing of A034, A035 and related submissions at a late stage of the proceedings. The board could not identify any such exceptional circumstance either. In fact, at point [0016] on page 2 of the letter dated 7 May 2024 accompanying the filing of A034 and A035, the appellant stated that "*[f]aced with the difficulty of convincing the present Bord [sic] of Appeal, the Appellant finally decided to contact Prof. Caravan to ask for confirmation of his understanding of D28 alone and in conjunction with D2*". However, the fact that the board was not convinced by previous submissions is not an exceptional circumstance that could justify the filing of additional items of evidence A034 and A035 in the case at hand.

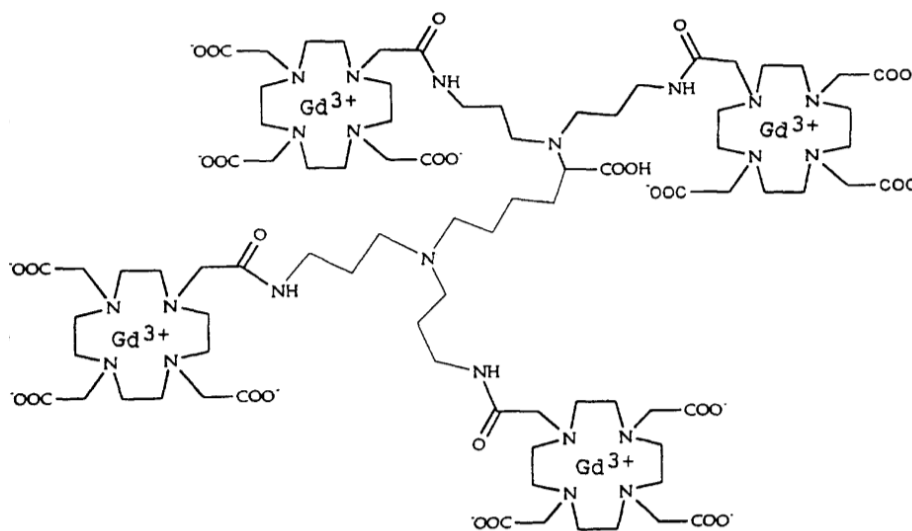
3.6 For these reasons, pursuant to Article 13(2) RPBA the board decided not to admit A034 and A035 and all related submissions into the proceedings.

Main request - patent as granted - claim 1 - ground for opposition under Article 100(a) EPC - inventive step under Article 56 EPC

4. Closest prior art

4.1 In accordance with the appealed decision (page 9, point 4.4), both parties indicated document D2, especially the compound disclosed in example 6, as the closest prior art for the subject-matter of claim 1 as granted.

4.2 D2 discloses (page 1, lines 1 to 7; page 3, lines 3 to 8; page 6, lines 11 to 14) gadolinium chelate compounds having increased relaxivity to be used especially as contrast agents for magnetic resonance imaging (MRI). In its example 6 (pages 40 and 41), document D2 discloses the preparation of the following compound (gadolinium complex of  $N^\alpha, N^\alpha, N^\epsilon, N^\epsilon$ -tetrakis-[4-aza-5-oxo-6-(1,4,7,10-tetraazacyclododecyl-4,7,10-triacetate)hexyl]-L-lysine):

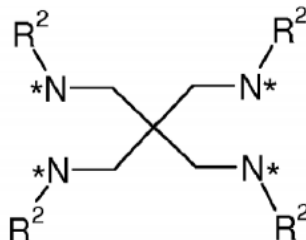


As stated by the respondent (reply to the statement of grounds of appeal, footnote on page 57) and not disputed by the appellant, the compound of example 6 of D2 has a molecular weight of about 2538 g/mol, which is comparable with the molecular weight of the compounds defined in claim 1 as granted. According to D2 (page 41, line 27 in combination with page 34, lines 14 to 16), the compound of example 6 has a relaxivity of  $8.35 \text{ s}^{-1}\text{mM}^{-1}$  measured at a field strength of 0.5 T.

5. Distinguishing features

It was common ground that the subject-matter of claim 1 as granted (point II above) differs from the disclosure

in example 6 of D2 in the moiety A bound to the gadolinium complexes, A having the structure:



with R<sup>2</sup> being a hydrogen atom.

6. Objective technical problem

6.1 The respondent referred to the experimental results reported in tables 1 and 2 of the patent (pages 102 and 103) as well as in experimental report D26/D26a. These results demonstrated that the claimed compounds had higher relaxivities compared with reference compounds. Moreover, the respondent referred to experimental report D29, where the compound of example 6 of D2 has been synthesised and tested for its relaxivity. The respondent argued that the results in D29 demonstrated that the claimed compounds showed higher relaxivities as compared with the compound of example 6 of D2. In view of these results, the respondent formulated the objective technical problem as being the provision of gadolinium contrast agents with higher relaxivity.

6.2 At the oral proceedings, the appellant no longer contested that the claimed compounds had a higher relaxivity as compared with the compound of example 6 of D2. However, in line with the appealed decision (page 9, bottom), the appellant argued that the fact that the claimed compounds and the compound of example 6 of D2 had a comparable molecular weight had to be taken into account in formulating the technical problem. Therefore the objective technical problem

should be to provide gadolinium contrast agents with comparable molecular weight and higher relaxivity.

6.3 In reaching the present decision, for the sake of argument only and in the appellant's favour, the board adopted this formulation of the objective technical problem as proposed by the appellant.

7. Obviousness of the claimed solution

7.1 The appellant referred to document D28, which is directed to strategies for increasing the relaxivity of gadolinium-based MRI contrast agents. Two approaches were mentioned in D28 (page 513, left-hand column), namely

- optimisation of the molecular parameters, and
- linking of multiple gadolinium complexes together.

7.1.1 The appellant argued that in view of the posed technical problem the skilled person would not have considered the second approach, since adding further gadolinium complexes to the compound of example 6 of D2 would have led to a huge increase in the molecular weight.

7.1.2 Thus, according to the appellant, the skilled person would have followed the first of the above-mentioned approaches. In this respect, D28 explained that relaxivity was particularly dependent on the electronic properties of the gadolinium, water exchange, rotational diffusion, i.e. rotational motion, first and second coordination sphere hydration and the ion to water proton distance. The appellant argued that, of these properties, only the rotational motion was different between the compound of example 6 of D2 and the claimed compounds. This was because the electronic properties of the gadolinium, the water exchange, the first and second coordination sphere hydration and the

ion to water proton distance were fully linked to the chemical structure of the selected gadolinium chelates, which were identical between the claimed compounds and the compound of example 6 of D2. Therefore, contrary to the opposition division's view, the skilled person would have faced a one-way street, with the rotational motion being the only factor that would have had to be varied to increase relaxivity. This was further confirmed in D28, which disclosed that the mobility depended on molecular size and rigidity, and that the rotational dynamics of the final molecule were critical. Moreover, rotational motion was identified in the conclusion of D28 (page 523) as the most important parameter influencing relaxivity. D28 reported that slowing down rotation resulted in an increase in relaxivity at a field strength of 1.5 T, see page 519, left-hand column.

- 7.1.3 D28 further identified in figure 2 dendrimer structures as molecular constructs able to increase relaxivity. Starting from the dendrimer structure of the compound of example 6 of D2, the skilled person would not have changed this structure, but rather acted on the molecule's core.
- 7.1.4 This notion about the importance of rotational motion was further confirmed by A030, A031 and A032. The appellant submitted that the rotational motion was dependent on the molecular structure and notably the structure of the dendrimer's core. The modification of the core would thus have been the key point considered by the skilled person in order to solve the posed technical problem.
- 7.1.5 The appellant submitted that in view of D28, A030, A031 and A032 the skilled person would have slowed down the rotational motion of the compound of example 6 of D2 when aiming to increase relaxivity. To do this, they

would have decreased the molecular size of the core of the compound of example 6 of D2, so preventing internal motion of each chelate. Shortening the core of the compound of example 6 of D2 to the maximum would have led to the compound of example 10 of the patent falling under claim 1 as granted. The feasibility of such a shortened core would have been confirmed to the skilled person by both documents D13 and D14, disclosing MRI contrast agents having this molecule's core.

7.1.6 The appellant further argued that, when arriving at the compound of example 10, the compounds of examples 3 and 11 of the patent would also have been arrived at by the skilled person in an obvious way. It referred to document A033 disclosing that a peptide bond, i.e. an amide bond, conferred rigidity on a molecule bearing it. Therefore the presence of four amide bonds in the compounds of examples 3 and 11 as compared with corresponding bonds in the compound of example 10 would have conferred even more rigidity and thus further increased the relaxivity. The appellant thus concluded that the subject-matter of claim 1 as granted lacked inventive step. The same also applied to all the remaining claims as granted.

7.2 The board finds the appellant's arguments unconvincing for the following reasons.

7.2.1 Document D28 (title, abstract) is indeed directed to strategies for increasing the relaxivity of MRI contrast agents by *inter alia* optimising the molecular parameters (page 513, left-hand column).

7.2.2 As regards this approach, D28 makes it clear (page 513, right-hand column) that since relaxivity is dependent on molecular motion, and since the mobility will be dependent on molecular size, rigidity, and possible protein binding, relaxivity has to be optimised on a



case-by-case basis. As submitted by the respondent, D28 identifies several interrelated factors affecting relaxivity, *inter alia* water exchange, rotational motion, first and second coordination sphere hydration, and the ion to water proton distance (page 513, left-hand column and conclusion on page 523). Hence rotational motion, the parameter exclusively relied on by the appellant, is only one of many relevant factors available to the skilled person following this approach disclosed in D28.

- 7.2.3 The board concurs with the respondent that, when obviousness is assessed, this has to be done without taking the knowledge of the claimed invention into account. Only in this way is a hindsight line of argument avoided. Therefore the appellant's argument that the skilled person would not have considered any of the further factors mentioned in D28 which are linked to the chemical structure of the gadolinium chelates since they were identical between the claimed compounds and the compound of example 6 of D2 cannot be accepted because it presupposes knowledge of the claimed compounds.
- 7.2.4 On the contrary, when starting from the compound of example 6 of D2, the skilled person, following the teaching of D28, might have acted on the gadolinium chelates or the core when aiming to increase relaxivity. Contrary to the appellant's view, no one-way street pointing to the rotational motion as the sole parameter to be varied to increase relaxivity would have been available to the skilled person when considering D28. Nor would only a change of the core of the molecule have been considered. In this respect, as pointed out by the respondent, D2 itself, on pages 10 to 12, discloses that chelates different from those of the compound of example 6 may also be used.

- 7.2.5 Even accepting that the skilled person would have chosen to act on the molecule's core, D28 depicts in figures 2 and 3 some examples of molecular constructs able to increase relaxivity. None of the constructs show a structure of the core similar to that defined in the claims as granted. Rather, aromatic structures are suggested at the molecule's core in particular for slowing rotational motion. A non-aromatic molecule's core in the form of a tetraamine structure with one single nitrogen atom of the core linked by amide bonds to one gadolinium chelate as defined in claim 1 as granted is neither mentioned nor suggested in D28, let alone with the aim of increasing relaxivity.
- 7.2.6 The same considerations as for D28 also apply to documents A030 to A032 (at oral proceedings the respondent withdrew its request for these documents not to be admitted, and consequently they were taken into account by the board). In fact, as pointed out by the respondent, these documents, while disclosing that relaxivity might be increased by slowing down the rotational motion of the molecule (A030: page 4260, left-hand column, bottom; A031: page 1195, right-hand column, middle; A032: page 6766, right-hand column, lines 7 to 12 and page 6767, left-hand column, lines 19 to 22), neither propose nor suggest a molecule's core in the form of a tetraamine structure with one single nitrogen atom of the core linked by an amide bond to one gadolinium chelate as defined in claim 1 as granted. On the contrary, aromatic structures as in D28 (A030: page 4260, right-hand column, bottom and schemes 1 to 3 on pages 4261 and 4262; A031: scheme 2 on page 1197 and "*Rotational dynamics*" on page 1199) or structures with protein linkages (A032: figures 1 and 2 on page 6767) are suggested.

- 7.2.7 As regards A033, this document (page 119, right-hand column) concerns the structural features of peptide bond conformation in oligopeptides and proteins. A033 does not concern MRI contrast agents, let alone their relaxivity. This document is thus not relevant to the assessment of inventive step of the claimed subject-matter.
- 7.2.8 In view of the above, none of D28 and A030 to A033 would have prompted the skilled person, faced with the posed objective technical problem, to modify the structure of the compound of example 6 of D2 so to arrive at the compounds defined in claim 1 as granted.
- 7.2.9 The mere fact that MRI contrast agents having a tetraamine core are shown in documents D13 (scheme 1 on page 476) and D14 (page 28, compound of formula (II)) cannot change this conclusion by the board. In fact, none of D28 or A030 to A033 refer to D13 and D14. Moreover, neither D13 nor D14 link the presence of the tetraamine core to improved relaxivity.
- 7.3 Therefore the board concludes that the subject-matter of claim 1 as granted involves an inventive step within the meaning of Article 56 EPC. The same conclusion applies *mutatis mutandis* to the subject-matter of claims 2 to 15 as granted, referring back to claim 1.
8. For these reasons, the ground for opposition under Article 100(a) EPC in combination with Article 56 EPC does not prejudice maintenance of the patent as granted.

#### Conclusion

9. The appellant withdrew all other objections raised on appeal in relation to the patent as granted.

10. Therefore the respondent's request that the appeal be dismissed, with the consequence that the patent is maintained as granted, is allowable.

## Order

### For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



U. Bultmann

M. O. Müller

Decision electronically authenticated