Case Number : T 130/90 - 3.3.2

Decision of 8 October 1991
correcting errors in the Decision
of the Technical Board of Appeal 3.3.2
of 28 February 1991

Appellant : (Opponent 01)	Hybritech Incorporated 11095 Torreyana Road San Diego, California 92121 US
Representative :	Hudson, Christopher Mark Erl Wood Manor Windlesham Surrey GU20 6PH GB
Respondent : (Proprietor of the patent)	The Board of Regents, the University of Texas System 201 West 7th Street Austin, Texas 78701 US
Representative :	Burford, Anthony Frederick W.H. Beck, Greener & Co. 7 Stone Buildings Lincoln's Inn London WC2A 3SZ GB
Other Party : (Opponent 02)	AKZO Pharma B.V. Wethouder van Eschstraat 1 Postbus 20 NL-5340 BH OSS
Representative :	Douma, Anno Dominicus Postbus 20 NL-5340 BH OSS
Decision under appeal :	**Interlocutory decision of the Opposition Division of the European Patent Office dated 13 December 1989 concerning maintenance of European patent No. 0 068 763 in amended form.**

Composition of the Board :

Chairman : P. Lançon
Members : U. Kinkeldey
C. Holtz

In application of Rule 89 ECP the decision given on 28 April 1991 is corrected as follows:

- page 16, line 17:
  replace "information" by "conformation"

- page 17, line 21:
  replace "4.2" by "3.3"

The Registrar:

P. Martorana

The Chairman:

P. Lançon

BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Publication in the Official Journal ~~Yes~~ / No

File Number: T 130/90 - 3.3.2

Application No.: 82 303 197.6

Publication No.: 0 068 763

Title of invention: Recombinant monoclonal antibodies

Classification: C12P 1/00

D E C I S I O N
of 28 February 1991

Proprietor of the patent: The Board of Regents, the University of Texas System

Opponent: 01) Hybritech Incorporated
02) AKZO Pharma B.V.

Headword: Recombinant monoclonal antibody/UNIVERSITY OF TEXAS SYSTEM

EPC Articles 54 and 56

Keyword: "Novelty (yes), after amendment - product produced by cultivation of a trioma - or quadroma cell" - "Inventive step (yes)" - "Auxiliary requests by the Appellant and by the Respondent correspond in substance"

Headnote

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 130/90 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 28 February 1991

Appellant : (Opponent 01)
Hybritech Incorporated
11095 Torreyana Road
San Diego, California 92121
US

Representative :
Hudson, Christopher Mark
Erl Wood Manor
Windlesham
Surrey GU20 6PH
GB

Respondent : (Proprietor of the patent)
The Board of Regents, the University of Texas System
201 West 7th Street
Austin, Texas 78701
US

Representative :
Burford, Anthony Frederick
W.H. Beck, Greener & Co.
7 Stone Buildings
Lincoln's Inn
London WC2A 3SZ
GB

Other Party : (Opponent 02)
AKZO Pharma B.V.
Wethouder van Eschstraat 1
Postbus 20
NL-5340 BH OSS

Representative :
Douma, Anno Dominicus
Postbus 20
NL-5340 BH OSS

Decision under appeal :
Interlocutory decision of the Opposition Division of the European Patent Office dated 13 December 1989 concerning maintenance of European patent No. 0 068 763 in amended form.

Composition of the Board :

Chairman : P. Lançon
Members : U. Kinkeldey
C. Holtz

Summary of Facts and Submissions

I. European patent application No. 82 303 197.6 was granted as European patent No. 68763 with twenty-one claims.

II. Notices of opposition against the European patent were filed by two parties. Revocation of the patent was requested on the grounds of Articles 100(a), (b) and (c) EPC. During the procedure before the Opposition Division about thirty documents were filed by the parties, out of which the following remained relevant in the appeal proceedings:

(5) R. Luedtke et al., Biochemistry, 1980, Vol. 19, pages 1182-1192.

The Respondents submitted during oral proceedings before the Opposition Division a set of new claims. Claims 1, 5, 6 and 13 read as follows:

"1. A method for producing a monoclonal antibody comprising incubating a hybrid cell in culture or in the peritoneal cavity of a mouse, and separating soluble protein from the culture supernatant or ascites fluid, respectively, characterized in that the hybrid cell is a trioma or quadroma cell formed by the somatic cell fusion of (a) a hybridoma cell derived by somatic fusion of a myeloma cell and a lymphocyte and producing an antibody having specific binding affinity for a desired antigenic determinant and (b), in the case of a trioma cell, a lymphocyte producing an antibody having specific binding affinity for a different desired antigenic determinant or, in the case of a quadroma cell, a hybridoma cell derived by somatic fusion of a myeloma

cell and a lymphocyte and producing an antibody having specific binding affinity for a different desired antigenic determinant, said trioma or quadroma cell producing an antibody having binding affinity for said two different desired antigenic determinants, and the antibody produced is a recombinant monoclonal antibody (i.e. has specific binding affinity for two different desired antigenic determinants).

5. A quadroma cell formed by the somatic cell fusion of (a) a hybridoma cell formed by the somatic fusion of a myeloma cell and a lymphocyte and producing an antibody having specific binding affinity for a desired antigenic determinant and (b) a hybridoma cell derived by somatic fusion of a myeloma cell and a lymphocyte and producing an antibody having specific binding affinity for a different desired antigenic determinant, said quadroma cell producing an antibody having specific binding affinity for the said two desired antigenic determinants.

6. A trioma cell formed by the somatic cell fusion of (a) a hybridoma cell derived by somatic fusion of a myeloma cell and a lymphocyte and producing an antibody having specific binding affinity for a desired antigenic determinant and (b) a lymphocyte producing an antibody having specific binding affinity to a different antigenic determinant, said trioma cell producing an antibody having specific binding affinity for the said two desired antigenic determinants.

13. An antibody comprising intact immunological chains and containing $F(ab')_2$ and Fc portions characterised in that each Fab' portion has specific binding

affinity for a respective different desired antigenic determinant, whereby the antibody has dual specificity and is obtainable by cultivation of the quadroma cell of Claim 5 and/or the trioma cell of Claim 6."

III. The Opposition Division maintained the patent on the basis of these claims.

(a) According to the Opposition Division's opinion, the requirements of Articles 83 and 123 EPC were met.

(b) None of the documents submitted by the parties described a method or quadroma cells or trioma cells as claimed and so far novelty of the respective independent claims was accepted (Article 54 EPC).

As far as the antibodies claimed in Claim 13 were concerned, those documents which already described antibodies having two different specificities were not novelty destroying because the antibodies prepared according to these documents underwent harsh chemical conditions and thus no native structures of the antibodies could be expected as a result of these methods. The antibodies of Claim 13 thus differed from those described in the prior art.

(c) All independent claims also involved an inventive step (Article 56 EPC). When regarding document (5) as the closest prior art, the underlying technical problem of the patent in suit was "to provide intact monoclonal antibodies having dual specificity by a process involving cells formed by somatic cell fusion". This solution was not obvious. Some of the prior art documents submitted by the parties would have even taught the skilled man away from the method

of the formation of trioma and quadroma cells, secreting the antibodies having dual specificity.

IV. Appellants (01) lodged an appeal against the decision and submitted a statement of grounds.

Oral proceedings took place on 28 February 1991.

(a) During the appeal proceedings they filed several documents to provide evidence that the antibodies produced by the method described in the closest prior art document (5) were indistinguishable from those claimed in the patent in suit. These documents were:

- Two Declarations by Professor Nisonoff
- Declaration by Dr. Walker
- Two Declarations by Dr. Johnstone

(b) The Appellants argued essentially as follows:

(ba) The Opposition Division was wrong to allow the amendments which contravened Article 123 EPC.

(bb) As to Claim 13, relating to the monoclonal antibodies as such, it was submitted that these antibodies were not novel compared to those described in prior art document (5) merely because of the wording of the claim "... obtainable by cultivation of the quadroma cell of Claim 5 or the trioma cell of Claim 6". The Opposition Division apparently was convinced that the step of chemically recombining antibody half-molecules as described in the prior art document (5) would have denatured or modified the antibody to give a product which was not native, assuming that in an **in vitro** process side reactions were likely to occur. This position failed to

consider the question of the extent of such side reactions or the amount of native antibodies that might still result from the chemical reaction despite side reactions taking place. Under the conditions of document (5), in which no modifying reagents were employed, the native antibody would have been produced. This view was supported by the filed declarations.

(bc) Furthermore, even if the amended antibody claims were said to be novel, they were nevertheless obvious. Antibodies having dual specificity were an obvious desideratum and antibodies having this function had been produced chemically.

(c) During oral proceedings an auxiliary request was filed containing an amended Claim 13.

V. The Respondents filed during the oral proceedings two sets of new claims as a main request and an auxiliary request respectively.

(a) In the set of claims according to the main request, Claim 5 was amended such that the word "formed" was replaced by the word "derived" and Claim 13 reads as follows:

"13. An antibody comprising intact immunological chains and containing $F(ab')_2$ and Fc portions, each Fab' portion having specific binding affinity for a respective different desired antigenic determinant, whereby the antibody has dual specificity and said antibody is derived from monoclonal source(s)."

In the set of claims according to the auxiliary request, Claim 5 was amended the same way as Claim 5 according to the main request and Claim 13 reads as follows:

"13. A recombinant monoclonal antibody produced by cultivation of a quadroma cell of Claim 5 and/or a trioma cell of Claim 6 and comprising intact immunological chains and containing $F(ab')_2$ and Fc portions, each F(ab') portion having specific binding affinity for a respective different desired antigenic determinant, whereby the antibody has dual specificity."

(b) The Respondents argued essentially as follows and supported their submission by the following documents:

- Two Declarations by Dr. van Regenmortel
- Declaration by Dr. Bazin
- Declaration by Dr. Strosberg
- Declaration by Dr. Reading.

(ba) The amendment of "antigene" to "antigenic determinant" in Claims 13 of both requests was made in order to clarify the scope of the relevant claims. There was a clear and unequivocal basis for this amendment in the sentence of lines 12/16 of column 10 of the description of the granted patent.

(bb) As to the question of novelty of the antibodies claimed in Claim 13, it was apparent that the process reported in document (5) resulted in significant irreversible denaturation. It

appeared that the authors of all declarations submitted by the Appellants had overlooked the fact that the procedure of document (5) involved treating the peptide in a solution of pH 2.5 for 60 minutes. These conditions could not be estimated as "mild conditions".

It was further particularly important to note that in document (5) polyclonal antibodies, derived from antiserum obtained from immunized rabbits, were used. Thus, the hybrid "antibody" product according to document (5) was a mixture of so many different antibody molecules that it would not have been possible to have separated or characterised any individual antibody molecule. Thus, even if, according to document (5), there were hybrid antibodies produced identical with one obtained by biological means, the presence of that antibody was de minimis and it could not be isolated or identified and accordingly document (5) would not constitute an enabling disclosure of an antibody of that kind.

(bc) During oral proceedings these arguments and evidence were further emphasised by the molecular structure of an antibody, having a multiplicity of cysteins, which provided the sulphur group, necessary for the formation of disulphide bridges. These were essential for any re-assembling of the molecule after a denaturation. With regard to the multiplicity of the possibilities of non-native re-assembling of the covalent binding between sulphur groups, it was not at all likely that, under the conditions described in document (5), a recoverable

renaturation of the antibodies took place.

Further, Professor Reading, the inventor of the patent in suit, mentioned at oral proceedings literature disclosing that it was likely that the method of document (5) caused irreversible denaturation of the treated antibodies.

VI. The Appellants requested that the decision under appeal be set aside and that Claims 13 to 21 be disallowed entirely (main request); alternatively that the patent be maintained with amended Claim 13 as submitted by the Appellant during the oral proceedings (auxiliary request).

The Respondents requested that the appeal be dismissed and that the patent be maintained on the basis of Claims 1 to 21 as submitted during oral proceedings (main request); alternatively, Claims 1 to 21 as submitted during the oral proceedings (auxiliary request).

The auxiliary requests of both parties correspond in substance.

Reasons for the Decision

1. The appeal is admissible.

2 **Amendments (Article 123(2) and (3) EPC)**

2.1 Claim 5 of the main request and the auxiliary request are made clearer in that the quadroma cell of Claim 5 is formed by the somatic cell fusion of a hybridoma cell derived by the somatic fusion of a myeloma cell etc. The use of the word "derived" instead of the word "formed" is

acceptable because this word is also used in the same claim in an analogous way such that "... (b) a hybridoma cell derived by somatic fusion of a myeloma cell and a lymphocyte and producing an antibody ..."; and it is further clear for the man skilled in the art that the hybridoma cell used for the fusion with the result of a quadroma cell is a derivative of a fusion as mentioned in the claim. It is further clear for the skilled man that the whole disclosure of the patent in suit does not relate to one single fusion product being the first achieved but rather relates to cell fusion products derived from preceding fusions. Thus, this amendment does not contravene the requirements of Article 123(2) EPC.

2.2 The Board, further, cannot see any violation of the requirements of Article 123(3) EPC, because in the present context the meaning of the word "formed" has the same scope of protection as the word "derived".

2.3 As far as Claim 13 of the main request is concerned it has to be examined whether the new wording "said antibody is derived from monoclonal source(s)" provides new matter or broadens the scope of the claims. It is clear from the description and the claims as originally filed that the described triomas and quadromas produce "monoclonal" antibodies. The wording now used in Claim 13 is thus implicitly contained in the original disclosure. This amendment is, therefore, allowable according to Article 123(2) EPC.

2.4 Claim 13 according to the auxiliary request is amended such that "a recombinant monoclonal antibody, produced by cultivation of a quadroma cell of Claim 5 and/or a trioma cell of Claim 6" is claimed.

The specification of the patent in suit as a whole relates to "monoclonal" antibodies, i.e. antibodies produced by a cloned hybridoma. The term "recombinant" monoclonal antibody is explained in detail on column 3, lines 20 to 62. The production of the recombinant monoclonal antibodies by cultivation of a quadroma cell or trioma cell was originally disclosed by the claims to which the new feature refers back and further in the description as a whole. There are, therefore, no objections to the allowability of Claim 13 according to Article 123(2) EPC.

2.5 The new features in Claims 13 of both requests are, further, not such that the scope of protection was broadened because the more precise identification of the antibody in both cases is actually a limitation of the claim. Therefore, the requirements of Article 123(3) EPC were met as well.

3. Product-by-process claims

3.1 Claim 13 of the main request can be understood as a product-by-process claim as far as the wording "derived from monoclonal sources" defines starting products for a process which results in the claimed antibodies.

3.2 Claim 13 of the auxiliary request is worded as a product-by-process claim whereby the product is inter alia defined by its process of preparation. The definition of this way is two-fold in the new claim as firstly the term "monoclonal" implicates the process how the antibody is prepared. According to the definition in the art, a "monoclonal" antibody is an antibody produced by a hybridoma. The second reference to the process is the mentioning of the production of the recombinant monoclonal antibody by "cultivation of a quadroma cell of Claim 5 and/or a trioma cell of Claim 6".

3.3 There is an established case law of the Boards of Appeal (T 150/82, OJ EPO 1984, 309; T 251/85 of 19 May 1987; T 248/85, OJ EPO 1986, 261) accepting the form of product by process claims under circumstances defined there but also establishing that products defined by their processes have to fulfill the requirements of patentability like novelty and inventive step. According to this case law the conditions to define a certain product by its process are that there are no other parameters available for a further definition of the product. This is also the case here, where the reason for defining the product by its process is the limitation of the products over the prior art. The Board is of the opinion that also this situation justifies the form of a product-by-process claim. If it turns out that the only way of limiting a claim over the prior art, according to the merits of each case, is the definition of the product by its process it would be unjustified to leave the inventor without protection only because the product cannot be defined otherwise. The product-by-process claim is, therefore, so far, according to the requirements of Article 84 EPC, allowable.

4. Novelty (Article 54 EPC)

Main request

4.1 The Appellants do not contest novelty of Claims 1 to 12 and there is no reason for the Board to further examine this question of its own motion.

4.2 It is, however, an issue whether or not Claim 13 is novel with regard to the disclosure of document (5). Whether or not the definition of the antibodies of the patent in suit by its process renders these antibodies novel was the subject-matter of all affidavits mentioned above in

paragraphs IV(a) and V(c) and the pleadings during oral proceedings.

4.3 Document (5) relates to experiments which should answer the question of the shape of antibodies, in particular the distance of separation between the adjacent sites of an antibody. For this purpose, fluorescence energy transfer experiments by steady-state and nanosecond monophoton techniques were carried out with a covalently-linked hybrid rabbit IgG antibody containing one antilactose site and one anti-Dns (5-(Dimethylamino)-1-naphthalenesulfonyl) site. The hybrid antibody was prepared from antilactose and anti-Dns antibody by reduction, disassociation into half-molecules in acid and random re-association with re-formation of the single disulphide bond between the heavy chains.

4.4 Document (5) reports that there is incomplete reoxidation of the inter-heavy-chain disulphides. In particular, it is stated at line 19/20 of column 2, page 1183 of document (5) that "80% reoxidation of the inter-heavy-chain disulphides were achieved". Thus, even if the acid treatment does not interfere with the structure of the antibody chains as such, the hybrid "antibody" obtained by the process of document (5) is a chemically re-associated hybrid antibody. In connection with document (5) it is important to note that the authors were concerned with the use of fluorescence energy transfer to study the proximity of antibody binding sites.

4.5 In detail the following process steps were carried out:

Rabbits were injected with immunogenes against which the immune system of the rabbits was expected to produce the respective antibodies. The anti-serum used consisted of a pool of four bleedings from the rabbits. By conventional

processes the desired antibodies were recovered. The two different groups of antibodies were subsequently treated such that the four chains of an antibody, namely two heavy and two light chains were separated. To this end, the solution was flushed with N_2 for a minimum of 30 minutes prior to reduction and then treated with 2-mercaptoethanol at a final concentration of 20 mM for 60 minutes at room temperature. After adjustment of the pH to 2.5 with 1.2 N HCl, the reduced protein solution was stirred for 60 minutes. It was then dialysed over night to allow for the re-formation of inter-chain disulphides. A solution of that kind contains hybrid antibodies of the type of anti-Dns/anti-Dns, antilactose/antilactose and anti-Dns/antilactose. Hybrid antibodies of the type anti-Dns/anti-Dns can be removed by use of a respective affinity column. The following process selects for populations of antilactose/antilactose and anti-Dns/antilactose hybrid antibodies with the result of a heterogeneous rabbit anti-Dns antibody preparation.

4.6 In the preparation of the described hybrid antibodies the authors of document (5) sought to re-associate the rabbit antibody into a configuration similar to the native molecule. The molar ratio of rabbit antilactose to anti-Dns antibody was 70:30, resulting in the following theoretical combinations: 9% anti-Dns/anti-Dns, 49% antilactose/antilactose and 42% anti-Dns/antilactose. The result of reoxidation to a covalent antibody form was that 79 to 80% of the total protein was in the covalent form. The reason for incomplete reoxidation of rabbit antibodies during the preparation of the covalent hybrid was said to be unclear. One reason could be that some sub-groups inefficiently reoxidise inter-heavy-chain disulphide bonds and/or certain hybrid combinations of rabbit antibody sub-groups would be incompatible for inter-heavy chain reoxidation. A further possibility arose

as the result of the generation of other oxidation products (i.e. R-SOH, $R-SO_3H$). Fractionation with an antilactose-specific immune adsorbent yielded population in which each IgG molecule contained no more than one anti-Dns site per antibody.

4.7 When comparing this population of antibodies with the antibodies claimed in Claim 13 a difference was said by the Respondents to be established by the wording of Claim 13 "... said antibody is derived from monoclonal source(s)". In view of the teaching of document (5), the Board cannot accept this allegation. Indeed, the real teaching of document (5) is directed to the chemical process of preparation of bispecific antibodies, starting from monospecific antibodies and independently of the monoclonal or polyclonal quality of these monospecific starting antibodies. The Board takes the view that both starting materials are explicitely or implicitely, but in any case unambiguously disclosed in combination with the process described in document (5), and also that the product of this process is unambiguously disclosed. Applied to monoclonal antibodies, this process results in a product which is "derived from monoclonal source". Thus, this derived product is encompassed by the definition of claim 13. Therefore, as far as this product is concerned, no distinction is established by the new wording of the claim.

4.8 Furthermore, at the oral proceedings, all parties agreed that the product according to document (5) is in fact a mixture of hybrids which contains bispecific antibodies, which could, according to the teaching of document (5) be isolated and identified as far as their feature of bispecificity was concerned. This feature does not allow an extrapolation to further features of an antibody molecule produced by a living cell (see paragraph 4.11

circumstances, in the view of the Board, and contrary to the submissions of the Respondents the question of the amount of the respective antibodies in the mixture cannot play any significant role so far as the skilled man was able to isolate the relevant bispecific and in so far intact antibodies. No evidence to the contrary has been submitted.

4.9 Since Claim 13 is for these reasons not novel over the antibodies described in document (5), the main request is not allowable.

Auxiliary Requests

4.10 There is agreement among all parties and the experts who provided declarations that by cultivation of triomas or quadromas, being further developments of hybridomas, a population of antibodies can be produced in which the individual antibodies are identical to each other and are in a native form because they are produced within the cell in a physiological environment. This process makes use of the constructive "machinery" of a living cell including numerous complex enzymatic reactions which make sure that any non-covalent and covalent bindings within the antibody molecule and any folding of the antibody resulting in a certain stereochemical three-dimensional shape and thus causing the native function occurs in a correct way. In particular, as far as the immunoglobulin heavy chains are concerned, during their synthesis on the ribosome, they become co-translationally associated with a chaparonin, the heavy chain binding protein (BiP) and enter the endoplasmatic reticulum. During the in vivo folding of the immunoglobulin, various isomerase enzymes catalyse slow steps of protein folding which ensures that correctly folded, native molecules are obtained. It is thus clear that the biosynthesis, assembly and transport of

antibodies in the cell is a precisely regulated process which explains its high efficiency in producing 100% functionally active molecules. This is in marked contrast to the artificial and drastic chemical dissociation of firstly naturally produced antibodies and a re-association of the molecule under conditions which do not lead to 100% active molecules. Rather, it is undeniable that the conditions used in document (5), i.e. an acidification with 1.2 N HCl to bring the pH to 2.5 for one hour, will, to a significant degree, unfold the individual peptide chains and it is, therefore, not realistic to see the procedure of document (5) as a simple separation of two half antibody molecules, that would have remained completely native and folded, followed by reassociation of two intact halves into a native hybrid molecule. The light and heavy chains in the half molecules could not have retained their native, original information during the disassociation which means that in the subsequent reassociation steps some misfolding, mispairing of disulphides, oxidation or detamination of some sensitive amino acid residues must have occurred.

4.11 The Board takes the position that the Appellants were not able to provide the convincing evidence that the antibodies described in document (5) were the same antibodies as those produced in a living cell. At oral proceedings there seemed to be agreement among the parties that the product according to document (5) was in fact a mixture of hybrids which may or may not contain intact native bispecific antibodies. In any case there is no disclosure in document (5) whatsoever as to how to distinguish between fully reassociated and in no way chemically altered, i.e. "native", molecules and those which may be bispecific but otherwise artificial. On the basis of the submissions and evidence on file and the common general knowledge, the Board, therefore, believes

that the definition of the claimed antibodies by their effective process of preparation, namely the cultivation of a quadroma cell and/or a trioma cell distinguishes these antibodies from those which can be recognised by a skilled man from the teaching of document (5).

4.12 Consequently, so far as it is not possible to distinguish the antibodies of the patent in suit over the prior art antibodies of document (5) otherwise than by limiting them to the product directly obtained by the specific process of their preparation, such a feature is accepted as a distinguishing parameter for the purpose of novelty. This view is apparently also accepted by the ~~Appellants~~ whose auxiliary request clearly shows that in the present case they accept a significant difference of the meaning of the two expressions "produced by" and "obtainable by", for the purpose of defining the antibodies of the patent in suit compared to those described in document (5).

The very specific circumstances of the present case, which differ from those having been the basis of the decisions of the Boards of Appeal as mentioned above under paragraph ~~4.2~~ 3.3, which entered into the Guidelines for substantive examination (C-III, 4.7b), make the expression "produced by" necessary. The respective part in the Guidelines states that: "A product is not rendered novel merely by the fact that it is produced by means of a new process". In the present case, however, as reasoned above, it is the process which renders the product novel.

Thus, the Board accepts the wording of Claim 13 of the auxiliary requests of both parties as satisfying the novelty requirements of Article 54(2) EPC.

4.13 Claims 14 to 21 are directly or indirectly dependent on Claim 13 and thus there are no novelty objections to these claims.

5. **Inventive step (Article 56 EPC)**

5.1 The Appellants did not contest the presence of an inventive step of the method Claims 1 to 12 and the Board has no reason to raise this issue of its own motion.

5.2 As stated above, claims which are formed as product-by-process claims have to fulfill the requirements of an inventive step also. As far as this issue in relation to Claim 13 is concerned, the Board considers the analysis of the prior art documents as stated in the decision of the Opposition Division as proper and also comes to the conclusion that, taking document (5) as the closest state of the art, the underlying technical problem was to be seen to provide a homogeneous population of native monoclonal antibodies having dual specificity. The problem has been solved by the monoclonal antibodies of Claim 13.

5.3 The disclosure of the patent in suit leaves no doubt that antibodies having the claimed characteristics can be achieved.

5.4 Taking into account the disadvantages and problems discussed in detail above, relating to chemically synthesized antibodies, and the fact that none of the other prior art documents submitted during the procedure comes closer than document (5) and provides no pointer, and the known difficulties even to produce known hybridomas, it was not obvious to provide the art with monoclonal antibodies having dual specificity with all its advantages, for example in the field of diagnosis and therapy, which are reliable in their natural and thus physiological functional condition by the process of forming triomas or quadroma. An inventive step is thus acknowledged.

5.5 Since Claim 13 is considered to be inventive, Claims 14 to 21, which are directly or indirectly dependent on Claim 13, fulfill the requirements of an inventive step equally.

5.6 The patent must be maintained on the basis of the auxiliary request of the Respondents. This request corresponds to the auxiliary request of the Appellants, whose main request (revocation of the patent) has to be rejected.

Order

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of Claims 1 to 21 of the auxiliary request submitted by the Respondents during the oral proceedings.

The Registrar: The Chairman:

P. Martorana P. Lançon