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Datasheet for the decision of 4 February 2009

Case Number: T 0782/07 - 3.3.08

Application Number: 92306420.8

Publication Number: 0523949

IPC: C12N 15/13

Language of the proceedings: EN

Title of invention:
Production of antibodies

Patentee:
THE WELLCOME FOUNDATION LIMITED

Opponents:
Crucell Holland B.V.
MEDIMMUNE LIMITED
ABBOTT LABORATORIES

Headword:
Human Antibodies/WELLCOME

Relevant legal provisions:
EPC Art. 123(2), 87, 88, 89, 54, 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request - added subject-matter (no), novelty (no)"
"Auxiliary request I - admissibility (no)"
"Auxiliary request II - entitlement to priority (yes), novelty (yes), inventive step (no)"

Decisions cited:
T 0647/97, T 1212/97, T 0313/05, T 0516/06

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0782/07 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 4 February 2009

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 26 April 2007 concerning maintenance of European patent No. 0523949 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julià
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent No. 0 523 949, based on the European patent application No. 92 306 420.8 with the title "Production of antibodies", was granted with 14 claims. Three oppositions were filed on the grounds as set forth in Articles 100(a), (b) and (c) EPC. The opposition division found that that the patent in suit as amended according to a main request filed on 25 January 2007 fulfilled the requirements of the EPC.

II. The three opponents (appellants) filed notices of appeal, paid the appeal fees and submitted the statements setting out their grounds of appeal.

III. In a letter dated 13 March 2008, the patentee (respondent) replied to the appellants' grounds of appeal.

IV. Observations of a third party under Article 115 EPC 1973 were filed on 21 August 2008.

V. With the summons to oral proceedings, the board sent a communication dated 12 September 2008 pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), indicating its preliminary, non-binding opinion to the parties.

VI. In letters dated 30 December 2008 and 2 January 2009, opponents 02 and 03 (appellants II and III) replied, respectively, to the communication of the board. The respondent replied with a letter dated 5 January 2009 and filed auxiliary requests I and II. No reply was received from opponent 01 (appellant I).

VII. At the oral proceedings, that took place on 4 February 2009, the respondent filed new auxiliary requests I and II to replace all previous auxiliary requests.

VIII. Claims 1, 10, 11 and 12 of the respondent's **main request** (the request allowed by the opposition division) read as follows:

"1. A process for the production of a recombinant human antibody comprising:

(i) selecting a human lymphocyte-derived cell line that is capable of expressing a desired antibody;

(ii) isolating RNA from the cell line and separating mRNA from the other RNAs so isolated;

(iii) synthesising cDNA from the mRNA and inserting the cDNA into a cloning vector;

(iv) transforming a host cell with the vector containing the cDNA to obtain a library;

(v) screening the library for cDNA encoding the entire constant and variable regions of the antibody heavy and light chain genes;

(vi) inserting the cDNA encoding the entire constant and variable regions of the antibody heavy and light chains into an expression vector;

(vii) transfecting a host cell with the expression vector containing the cDNA; and

(viii) culturing the tranfected host cell and isolating the desired antibody."

"10. An expression vector suitable for transfecting of a host cell comprising cDNA encoding the entire

constant and variable regions of the human antibody heavy and light chains."

"11. A eukaryotic cell line transfected with cDNA for the expression of the entire constant and variable regions of the human antibody heavy and light chains."

"12. A process for the expression of cDNA encoding the entire constant and variable regions of the human antibody heavy and light chains, comprising transfecting a eukaryotic cell with a vector or vectors suitable for the expression of said cDNA."

Claims 2 to 8 related to particular embodiments of claim 1. Independent claim 9 was directed to a process for the production of a recombinant human antibody which, as first steps, comprised: i) micro-RNA preparation from approximately 1000 hybridoma cells producing human antibodies, ii) generation of a size-selected cDNA library, and iii) screening the library for cDNA encoding the entire constant and variable regions of the antibody heavy and light chains and isolating the same. Further steps (iv), (v) and (vi) of claim 9 read as steps (vi), (vii) and (viii) of claim 1.

IX. The **auxiliary request I** consisted of 12 claims. Claims 1 to 11 read as claims 1 to 11 of the main request except for the sentence "*obtainable by steps (i) to (vi) of claim 1 or steps (i) to (iv) of claim 9*" at the end of claims 10 and 11. Claim 12 read as claim 12 of the main request except for the fact that the vector or vectors were defined as being "*according to*

claim 10". The **auxiliary request II** consisted only of claims 1 to 9 of the main request.

X. The following documents are cited in this decision:

D1: V. Ebert, Diplomarbeit, Universität für Bodenkultur in Wien (AT), February 1991;

D2: F. Rüker et al., Annals N.Y. Acad. Sci., 27 December 1991, Vol. 646, pages 212 to 219;

D2A: Table of Contents of Annals N.Y. Acad. Sci., 27 December 1991, Vol. 646;

D2B: Declaration of Dr. F. Rüker dated 4 September 2008;

D9: S.D. Gillies et al., Bio/Technology, August 1989, Vol. 7, pages 799 to 804;

D10: WO 89/00999 (publication date: 9 February 1989);

D35: M.J. Page and M.A. Sydenham, Bio/Technology, January 1991, Vol. 9, pages 64 to 68.

XI. The arguments of the appellants relevant to the present decision may be summarized as follows:

Main request
Article 123(2) EPC
"cDNA encoding the entire constant and variable regions of the antibody heavy and light chain genes"

The application as filed related to the "rescue of entire heavy and light chain genes". An "entire gene"

comprised the sequences encoding the "entire heavy and light chains" and additional 5' and 3' untranslated sequences as well, such as endogenous leader sequences and polyA tails. The exchange of these untranslated sequences was not contemplated in the application as filed since it referred only to conventional cDNA cloning technology for rescuing the complete genes. However, the claims were not directed to "entire genes" but to cDNA and therefore, they included embodiments without these endogenous 5' and 3' sequences and containing only the entire coding sequences. These embodiments represented a subset of the originally disclosed "entire heavy and light chain genes" for which there was no basis in the application as filed.

The term "antibody" was defined in the application as including antibody fragments, such as F(ab) and $F(ab)_2$. Therefore, the wording "entire antibody heavy and light chain genes" included genes encoding antibody fragments. Although cDNAs encoding entire antibodies were embraced by the wording "cDNA encoding the antibody" and "cDNA sequences encoding the antibody heavy and light chain genes", these cDNAs were only a subset of the original subject-matter which embraced cDNAs encoding both entire antibodies and antibody fragments. There was no basis in the application to support a selection of this subset, not even implicitly. Nor was it possible to rely on disclosures relating to antibody functionality, since functional antibody fragments were contemplated in the application as filed. There was no evidence in the application as filed that the antibody function was dependent on the presence of the entire antibody heavy and light chains (loss of a few amino acids did not have to abolish this function). Moreover, contrary to

the claims of the application as filed, there was no requirement in the present claims for a correct assembly of the constant and variable regions so as to result in antibody heavy and light chains, let alone for expressing a functional antibody. The claims simply required the presence of an arbitrary cDNA which somehow encoded the entire constant and variable regions of the antibody heavy and light chains, nothing more. There was no support in the application as filed to equate a functional antibody with any protein comprising only these regions.

"an expression vector"

The application as filed did not disclose an expression vector as an aspect of the invention. The term "comprising" in claim 10 could be interpreted as referring to the host cell and not to the expression vector. In this case, the claim was not limited to an expression vector comprising a cDNA as defined in the claim but embraced any possible expression vector suitable for transfecting a host cell which already had a cDNA as defined in the claim or a group of vectors comprising those cDNAs. Since claim 10 lacked clarity, it had to be broadly interpreted. The more so in view of the fact that the application as filed did not disclose any single expression vector encoding both the light and heavy chain genes. Moreover, claims 10 to 12 referred only to structural features (subunits) of an antibody but without requiring them to be assembled in a functional antibody. The description of the application as filed could not be used to give a different meaning to a claim defined by features that had a clear technical meaning to a skilled person.

Article 54 EPC
Claims 10 to 12

These claims referred to a cDNA which, as a product, was not limited by any method of production. They could not be interpreted as relating only to naturally occurring or unmodified cDNA since cDNA could be obtained from several sources and thus, when compared to cDNA of the original germ line cell, many modifications could be included. These modifications could not be distinguished from other modifications introduced by, for instance, the method of document D10. This document disclosed several embodiments concerning chimeric antibodies, wherein the embodiment related to class switched human antibodies fell within the scope of the claims. These antibodies required a cDNA encoding the entire constant and variable regions of human antibody heavy and light chains. The fact that the cDNA was obtained by linking a cDNA encoding the constant region to a cDNA encoding the variable region - and thereby a few silent modifications could be introduced - was irrelevant, since the resulting cDNA had all the features required by the claims. Document D10 disclosed the expression of these cDNAs in mammalian host cells (with a single or two expression vectors), the secretion of functional antibodies and the use of oligo-dT as a primer for making the cDNA (by isolating a mRNA encoding the entire variable and constant regions without any modification). The patent in suit originally contemplated the modification of cDNA sequences encoding the entire constant and variable regions of human antibody heavy and light chains and, therefore, the mere deletion of this part

of the description was of no consequence for the claims, unless modifications were clearly excluded from the claims.

Auxiliary requests I and II
Admissibility

These requests were submitted at the oral proceedings and no reason was given for their late filing. The objection for lack of novelty over document D10 had already been raised before the opposition division and maintained in appeal proceedings. As for auxiliary request I, it comprised product claims (claims 10 and 11) defined in terms of product-by-process which raised a number of new objections under Articles 84 EPC and 123(2) EPC, such as, for instance, against the use of the terms "obtainable" and "or", and the fact that the said products were intermediate products of process claims having a different purpose than their production. There was no support in the application as filed for such product-by-process claims, which were also not directly derivable from a mere combination of previous claims. The admissibility of auxiliary request II was not contested.

Auxiliary request II
Article 123(2) EPC

The objections made to the main request applied, *mutatis mutandis*, to this auxiliary request.

Articles 87 to 89

The features "cDNA encoding the entire constant and variable regions of the antibody heavy and light chains genes" and "expression vector", contested under Article 123(2) EPC in the main request and which characterized also this request, were not disclosed in any of the priority documents. In particular, the term "entire" was not found in any of the priority documents P1 and P2 nor was the concept of rescuing an "entire" antibody gene (including the entire heavy and light chains) disclosed in them. The concept that only the rescue of an entire cDNA led to a functional antibody was not derivable from these documents which also failed to disclose a correlation between a functional antibody and the required structural elements (the "entire human antibody heavy and light chain genes"). The expressions "cDNA sequences encoding a functional antibody" and ″cDNA encoding the entire constant and variable regions of the human antibody heavy and light chains" were not equivalent. Thus, there was no entitlement to these priorities.

Furthermore, priority documents P1 and P2 did not refer to PCR prior art that was mentioned only in the priority document P3 and in the application as filed. This prior art changed the problem to be solved and thereby shifted the original invention in a different direction (cf. decision T 647/97 of 1 February 2001). The patent in suit was thus not entitled to the priority of documents P1 and P2. Nor was it the subject-matter of claim 9 which was only disclosed in the priority document P3.

Availability of document D2

The present case differed from those underlying decisions T 313/05 of 6 July 2006 and T 1212/97 of 14 May 2001. Document D2 did not originate from an oral disclosure but from a written presentation (poster) and therefore it had a defined content for which, as stated in document D2B, the author could be questioned. There was no evidence on file casting doubts on the availability or content of this poster, which was immediately published as evidenced by documents D2 and D2A. The time elapsed between the presentation of the poster and the publication of document D2 (18 months) was a normal delay for a peer-reviewed scientific journal. There was also evidence on file demonstrating that document D2 did not contain more information than the poster, since technical results known to the authors of document D2 (those of document D1) and available only after the presentation of the poster were not reported in document D2. In line with the criteria defined in the Guidelines for Examination in the EPO, C-IV, 6.1 and D-V, 3.3, and in the absence of any counter evidence, document D2 had to be considered as giving a true account of the earlier poster display, which was therefore part of the state of the art.

Article 54 EPC

Document D10 disclosed cDNA clones encoding the entire variable and constant regions of human antibody heavy and light chains, namely clones pGMH-15 and pK2-3 in Figures 4 and 6. Nothing prevented the skilled person from using these cDNA clones in a manner as disclosed in the patent in suit. Moreover, the term "comprising"

in the claimed method did not exclude the presence of additional steps between the specific steps mentioned in the claim, such as the preparation of cDNA modules from the isolated entire cDNA clones and their linkage to obtain combined variable and constant regions of heavy and light chains as disclosed in document D10.

Document D1 disclosed cDNAs encoding the entire constant and variable regions of a human antibody heavy and light chains. Steps (vi) to (viii) of the claimed method were explicitly disclosed in this document and, since a cDNA from a human lymphoma was used, it had to be derived from steps (ii), (iii) and (iv) as in the claimed method, which were thus implicitly disclosed. The more so given that these steps were conventional in the field.

Document D1 also disclosed expression vectors comprising these entire cDNAs, the transfection of host cells with these vectors and the production of fully functional antibodies. Thus, the document addressed the same problem as the patent in suit and provided the same solution. The teachings of document D1 were also enabling since the methods used therein were within routine capabilities of the skilled person using common general knowledge and they could be carried out using any available human antibody; they were not limited to the exemplified antibody 3D6.

Article 56 EPC

Document D35, the closest prior art, disclosed a method for producing the humanized monoclonal antibody Campath-1 which comprised all steps of claim 1. This

method was conventional in the art as shown by document D9 (cited in document D35) which explicitly disclosed steps (ii) and (iii) of claim 1. Documents D35 and D9 aimed at the same purpose as the patent in suit, namely the production of high amounts of recombinant human antibodies. Whereas document D9 used a mixture of cDNA and genomic DNA in lymphoid host cells, document D35 used only cDNA in CHO host cells, simplifying thereby the manipulation and expression in non-lymphoid cells. The sole difference between document D35 and the patent in suit was the type of cDNA used, i.e. the source from which the cDNA was isolated. Document D35 used a cDNA encoding a humanized antibody instead of a cDNA encoding a complete human antibody as in the patent in suit. The teachings of document D35 were not limited to Campath-1H but were general for the production of recombinant antibodies.

Starting from the closest prior art, the technical problem to be solved was the provision of alternative recombinant human antibodies and not the provision of an alternative antibody (with reduced immunogenicity) to the Campath-1H of document D35. Nor was the technical problem to provide an improved method for producing recombinant human antibodies since there was no requirement in the claims for any particular yield. The patent in suit failed to show higher levels of expression when compared to the art. Expected theoretical results had to be disregarded since they were not supported and could not therefore contribute to inventiveness.

The technical problem was known from document D35 and, in the light of the prior art on file which showed the

advantages of complete human antibodies, it was obvious for the skilled person to replace the humanized Campath-1H antibody of document D35 by a complete human antibody when looking for those alternatives. Indeed, the advantageous production of Campath-1H shown in document D35 would have prompted the skilled person to transfer the same method to any other established human monoclonal antibody. Sources from which cDNAs encoding complete human antibodies could be isolated without special technical difficulties were available to the skilled person and known in the art. Document D9 disclosed a human anti-tetanus antibody-secreting cell line ES12 and the derived hybridoma GF4/1.1 cells and document D1 described a hybridoma cell line (LC4) secreting a complete human monoclonal antibody (3D6) from which the cDNA had been isolated. There was nothing to prevent the skilled person producing the antibodies of documents D9 or D1 by using the advantageous method of document D35.

XII. The admissibility of the third party's observations under Article 115 EPC 1973 was contested by the respondent. These observations were directed against claims 10 to 12 of the main request and were based on document D10 and, in essential, overlapped with the arguments of the appellants.

XIII. The arguments of the respondent relevant to the present decision may be summarized as follows:

Main request

Article 123(2) EPC

"cDNA encoding the entire constant and variable regions of the antibody heavy and light chain genes"

The claims defined the cDNA by reference to the encoded protein. They were not directed to any polynucleotide but to a cDNA rescued from sequences encoding the entire heavy and light chain genes. However, they did not require the cDNA to be "entire" in the sense that it necessarily had to comprise the untranslated 5' or 3' sequences of the rescued genes. All introns and regulatory sequences of these genes were removed in the rescued cDNA which could thus comprise other non-coding sequences resulting from the manufacturing process.

Whereas antibody fragments were mentioned in a single passage of the application as filed, the rest of the application as filed was directed to entire antibodies as a distinct embodiment. Antibody fragments did not provide the full spectrum of functionalities of an entire antibody as those disclosed in the application as filed. Although the application did not expressly used the term "entire" in connection with an antibody or when describing the structure of a functional antibody, it was clearly derivable from the application as filed that an entire antibody consisted of the constant and variable regions of the heavy and light chains. These regions had also to be correctly assembled to produce a functional antibody, otherwise the resulting recombinant protein was not considered to be an antibody.

"an expression vector"

If there was any ambiguity in claim 10 as regards the term "comprising", the objection related to Article 84 EPC and not Article 123(2) EPC. The term was found in

granted claim 12 and no objection had ever been raised under Article 84 EPC. Appellants' interpretation was illogical and technically meaningless since the application showed "a vector suitable for insertion into a host cell for expression" to be an expression vector having a cDNA encoding the entire constant and variable regions of a human antibody heavy and light chains. The application also contemplated two vectors but there was no basis for a group of vectors.

Article 54 EPC
Claims 10 to 12

These claims required a cDNA sequence encoding the entire constant and variable regions of the human antibody heavy and light chains and excluded modifications in the original cDNA sequence. This was the key difference between the patent in suit and document D10. This document disclosed (cDNA or genomic DNA) gene region modules encoding the constant or the variable region of either the heavy or the light chain. Appropriate cDNA modules had to be linked and therefore, convenient restriction sites introduced into each of these cDNA modules for achieving the cDNA sequence of the claims. The methods used to isolate (using synthetic consensus primers) and to link these cDNA modules introduced modifications into the original cDNA sequence. Modifications in the boundary regions of the cDNA modules were inevitably introduced by these methods as shown in Figures 7, 20, 24 of document D10. Although silent mutations did not alter the amino acid sequence, they impacted the primary, secondary and tertiary structure of the generated mRNAs. In contrast, the cDNA of the patent in suit was obtained by rescuing

the entire gene and therefore, it did not contemplate any modification.

Document D10 disclosed several embodiments and class-switched human antibodies were only an embodiment mentioned in passing and not even exemplified. This embodiment represented a selection which required a combination of features picked up from other embodiments and which was made within a prior art emphasizing the difficulties found with human antibodies and referring to humanized antibodies as preferred alternative. The examples in document D10 described only murine variable regions joined to human constant regions by combination of mutagenesis, PCR and subcloning. Whereas a combination of cDNA modules was used for expression in prokaryotic or bacteria host cells, the expression in mammalian host cells used an advantageous combination of cDNA (variable region) and genomic DNA (constant region) modules.

Auxiliary requests I and II
Admissibility

These requests were submitted in direct answer to the board's findings as regards the lack of novelty of the main request over document D10. Auxiliary request I differed from the main request by a simple and clear amendment, namely the limitation of the products to those obtainable by the process of claims 1 or 9. This limitation was a mere combination of product and method claims present in the main request and it could not be a surprise to the appellants. Since these products were intermediate products obtained by these methods, the claims were accordingly drafted so as to have technical

sense. The amendment limited only subject-matter that was already present in the main request.

Auxiliary request II
Article 123(2) EPC

The arguments developed for the main request and the same conclusions applied to this auxiliary request.

Articles 87 to 89 EPC

The priority document P1 disclosed a cDNA encoding the entire constant and variable regions of the antibody heavy and light chains. Entire antibodies were a distinct embodiment of this document which referred to "cDNA encoding the antibody" and "cDNA encoding the antibody heavy and light chains" interchangeably and as having the same meaning. These antibodies were fully functional and comprised the entire constant and variable regions of the heavy and light chains. There was no indication that the term "antibody" included fragments and therefore, the sentence "cDNA encoding the antibody heavy and light chain genes" was to be interpreted as "a cDNA encoding the entire constant and variable regions of the antibody heavy and light chains". In the absence of any reference to fragments and since conventional recombinant cDNA cloning technology was used for rescuing these genes, the disclosed cDNAs were cDNAs encoding the entire constant and variable regions of the antibody heavy and light chains. It was not contested that claim 9 was entitled only to the third priority date. The additional references to PCR prior art in the priority document P3 and in the application as filed did not shift the

invention in a direction different from that already contemplated in priority documents P1 and P2.

Availability of document D2

The appellant's evidence failed to establish up to the hilt the content of the poster on which document D2 allegedly originated. A copy of the poster was not on file nor was any evidence showing that it was ever displayed let alone read and understood by a skilled reader. In the absence of this evidence, the declaration of the poster's author (document D2B) was irrelevant. The more so since it had been made 18 years after the alleged date of the poster presentation and, therefore, it was arguable whether the content of the poster could be remembered in detail. Document D2B did not state that the content of document D2 and that of the poster were identical but only that they were "in essential" the same. It failed, however, to define what was considered to be essential. Moreover, since document D1 contained less information than document D2, its content could not be used to demonstrate anything of the content of document D2.

Article 54 EPC

Although Figures 4 and 6 of document D10 depicted isolated cDNA clones encoding the entire constant and variable regions of a heavy and light chain, these were only cloning vectors not used for expression of these cDNAs. In fact, reference was immediately made to the corresponding cDNA modules encoding either the variable or the constant region as explained in the description of Figures 4 and 6. This was in line with the whole

disclosure of document D10, namely the advantageous use of cDNA modules. The gist of document D10 (use of cDNA modules) was completely different from that of the patent (use of entire cDNA). It was not correct to interpret the claims as directed to a method completely different from that disclosed in the patent in suit.

Document D1 referred to cDNA isolation from hybridoma cell line L4 and from other 5 clones without reference to their source or to the method used in this isolation. There was no reason to assume it to be as in the patent in suit, since many alternatives were available to the skilled person, such as use of mRNA without previous separation of cellular RNA. In the absence of any information regarding the method used for isolating the cDNA, document D1 did not anticipate the claimed method. Moreover, document D1 as a whole lacked sufficiency of disclosure and it did not allow the skilled person to repeat the experiments and to obtain the results described therein.

Article 56 EPC

Document D35 disclosed the production of the specific human monoclonal antibody Campath-1H in CHO host cells. This antibody had been humanized by grafting rat CDRs directly into genomic human heavy and light chain frameworks. There was no suggestion in document D35 to further humanize Campath-1H so as to obtain a complete human antibody. There was no information in the art as to how to achieve appropriate human sequences for replacing the rat CDR portions present in that antibody. Moreover, no incentive could be derived from document D35 to look for those human sequences since Campath-1H

had successfully been used to eliminate tumour cells in patients with non-Hodgkin lymphoma and no significant anti-globulin response was found in these patients.

The specific process steps of the method disclosed in document D35 could not be separated from the very specific purpose of this method, i.e. the production of Campath-1H. The references found in this document to the production of human recombinant antibodies in general did not go beyond the usual theoretical speculations in a scientific publication and they could not be taken as serious pointers with a sound technical basis. In line with the case law, the relevant question was not whether the skilled person could have looked for such antibodies but whether it would have had sound reasons to look for them. These reasons were missing in document D35 since it did not provide any pointer towards alternative complete human antibodies nor a hint at the claimed method. No technical problem could be formulated from document D35 without hindsight.

Hindsight was also required to combine document D35 with documents D9 or D1. Although document D9 referred to the rescue of cDNA encoding the entire heavy and light chains of a human antibody, it actually used a genomic fragment for expressing the heavy chain of this antibody. This was in line with other prior art on file that used genomic sequences in the belief that they contained some regulatory sequences needed for an efficient expression of recombinant human antibodies. The fact that genomic sequences were not needed in document D35 when expressing the specific Campath-1H antibody in CHO cells, did not remove the prejudice of the skilled person that these sequences were needed for

expressing a complete human antibody. In fact, document D1 also showed that the level of expression of the isolated clones (transfected with cDNA encoding the human monoclonal antibody 3D6) was below that of the original hybridoma cell line LC4. Thus, there was no motivation for the skilled person to combine the teachings of documents D35 and D1 nor could the claimed subject-matter be achieved by combining documents D35 and D9.

XIV. The appellants (opponents) requested that the decision under appeal be set aside and that the patent be revoked.

XV. The respondent (patentee) requested that the appeals to be dismissed or, in the alternative, that the patent be maintained on the basis of the auxiliary request I or auxiliary request II filed during the oral proceedings on 4 February 2009.

Reasons for the Decision

Main request

Article 123(2) EPC

"*cDNA encoding the entire constant and variable regions of the antibody heavy and light chain genes*" *and* "*expression vector*"

1. The application as filed refers to the invention as providing "*... a new process involving conventional recombinant cDNA cloning technology to facilitate the rescue of* ***complete*** *human, heavy and light chain antibody genes and their expression in eukaryotic cells using high level eukaryotic expression vectors ...*"

(cf. application as published, page 3, lines 54 to 57) (emphasis added by the board). Furthermore, it consistently refers to cDNA expression of the rescued entire heavy and light chain antibody genes which thus necessarily requires the presence of the coding sequences - including the entire constant and variable regions - of these genes. The examples, illustrating preferred embodiments of the invention, refer to the isolation of polyadenylated RNA comprising "***full length*** *L chain genes*" and "***full length*** *H chain inserts*" from which cDNA is synthesised and then cDNA libraries screened for "*human antibody heavy and light chain sequences*". Selected clones pH210H2 and pH210L2 contain, respectively, the cDNA of the human immunoglobulin heavy and light chains. The sequence of the respective (entire) variable regions is shown in Figures 2 and 3 and percentages of homology of the (entire) constant and variable regions of a cynomolgus light chain with other known antibodies are also reported (cf. page 14, Method 2, page 19, line 45 to page 20, line 16, and Tables 4 to 6). Although the application as filed refers to the definition of antibody as including also "*fragments such as F(ab), $F(ab)_2$ and FV*", it is explicitly stated that "*... the invention is* ***primarily*** *concerned with the rescue of* ***entire*** *antibody heavy and light chain genes ...*" (cf. page 8, lines 31 to 33) (emphasis added by the board).

2. The application as filed is not merely limited to the production of cDNA sequences encoding entire heavy and light chains but contemplates also the subcloning of these sequences into vectors suitable for insertion into a host cell for expression, wherein the construction of expression vectors is carried out in

accordance with procedures known in the art (cf. page 6, lines 30 to 33). It is further stated that "... *the heavy and light chain cDNA can be transfected in a single vector ... or co-transfected in two vectors...*" and "*... transfection of a host cell line with an expression vector includes within its meaning co-transfection of the host cell employing more than one vector ...*" (cf. page 6, lines 40 to 43). In the context of "*a process for the expression of cDNA encoding primate antibody heavy and light chains comprising transfecting a eukaryotic host cell with a vector or vectors suitable for the expression of said cDNA*", the use of regulatory elements - other than those of the genes from which the cDNA sequences are derived - is explicitly contemplated. In particular, reference is made to regulatory elements of viral origin and, as an example, to "*the use of the ß-actin promoter and cognate ß-actin polyadenylation signal*" (cf. page 7, lines 25 to 29 and 40 to 42).

3. The expression of cDNA sequences encoding the entire heavy and light chains in eukaryotic cells using high level expression vectors is carried out to produce functional antibodies (cf. page 3, lines 54 to 57). Antibodies are described in the application as being bifunctional molecules and these functions are known in the art to be associated with the structural regions of the antibodies, namely the variable and constant regions of the heavy and light chains (cf. page 2, lines 4 to 9). The importance of the "*functional pairing of genes (one for heavy chain and one for the light chain)*", even though mentioned in the context of the prior art (cf. page 3, lines 35 to 38), and the relevance of the "*expression of both chains in*

substantially equimolar proportions ... (for obtaining) *... optimum yields of functional antibody*" (cf. page 7, lines 47 to 48) are described in the application as filed. Standard methods for testing these functions are also disclosed (cf. page 5, lines 26 to 45) and references consistently made to functional antibodies (cf. *inter alia* page 7, lines 47 to 50). The claims as filed are directed to "*a vector suitable for transfection of a host cell comprising cDNA encoding primate antibody heavy and light chains*" (claim 12), "*a eukaryotic cell-line transfected with cDNA for the expression of primate antibody heavy and light chains*" (claim 13) and "*a process for the expression of cDNA encoding primate antibody heavy and light chains, comprising transfecting a eukaryotic host cell with a vector or vectors suitable for the expression of said cDNA*" (claim 14).

4. In view of the cited passages and in line with the established case law of the Boards of Appeal (cf. "Case Law of the Boards of Appeal of the EPO", 5th edition 2006, III.A.2, page 259), the board concludes that both contested features are directly and unambiguously derivable from the application as filed. Thus, the requirements of Article 123(2) EPC are fulfilled.

Article 54 EPC
Claims 10 to 12

5. Product claim 10 is directed to "*an expression vector suitable for transfecting of a host cell*" further comprising "*a cDNA encoding the entire constant and variable regions of the human antibody heavy and light chains*" (cf. point VIII *supra*). Neither the features of

the host cell nor those of the vector are specified. Product claim 11 and process claim 12 refer to an eukaryotic cell line transfected either with cDNA (claim 11) or else with a vector or vectors suitable for the expression of a cDNA (claim 12), the said cDNA being defined as in claim 10. Also in these claims the two terms "eukaryotic cell line" and "vector(s)" are kept general, no specific features being given. None of these claims contains any requirement regarding the efficiency, yield or level of cDNA expression (cf. point VIII *supra*).

6. Prior art document D10 discloses "*region gene modules*" encoding the constant or variable regions of the human antibody heavy chain (V_H, C_H) or light chain (V_L, C_L) (cf. *inter alia* page 24, point (2) and page 25, steps (1) to (3)). These modules are linked to construct the entire heavy or light chains and then expressed for producing these chains in selected hosts, including prokaryotic and eukaryotic host cells (cf. *inter alia* page 25, steps (4) and (5) and page 27, lines 7 to 9). Whereas the constant region gene is always derived from a human heavy or light chain gene, the variable region gene might be derived from non-human genes as well (cf. *inter alia* page 9, second and third paragraphs). However, document D10 explicitly contemplates the production of all human antibodies, namely class-switched antibodies (cf. page 2, last paragraph to page 3, second paragraph, page 12, fourth paragraph, page 40, first paragraph and last paragraph to page 41, first paragraph). No selection is needed to arrive at these class-switched antibodies since they are explicitly identified as a specific embodiment in the description.

7. Whilst the variable region gene module is always encoded by a cDNA, document D10 contemplates both cDNA and genomic DNA for the constant region (cf. *inter alia* page 9, second and third paragraphs). The advantages of using cDNA, such as ease and simplicity of manipulation, were known in the art and they are explicitly mentioned in document D10, particularly for expression in prokaryotic or in lower eukaryotic hosts, such as yeast (cf. page 12, second paragraph and page 28, last paragraph to page 29, second paragraph). Together with mammalian host cells, yeast and bacteria host cells are identified as preferred host cells (cf. page 31, last paragraph and page 34, last full paragraph). The use of cDNA encoding class-switched human antibodies when contemplating the production of these antibodies in the preferred lower eukaryotic or in bacteria host cells is thus directly derivable from document D10. Also the use of a single expression vector or of two expression vectors comprising such a cDNA is directly derivable from the document (cf. *inter alia* page 33, lines 3 to 16 and page 39, second to fourth paragraph).

8. As stated above, the construction of an entire heavy or light chain requires the linking of appropriate variable and constant region gene modules (cf. point 6 *supra*). This may be done by introducing suitable restriction sites by site-directed mutagenesis at a desired location near a boundary of these regions. The linkage is consistently characterized in document D10 as being "operational" which means "*in-frame joining of coding sequences to derive a continuously translatable gene sequence without alterations or interruptions of the triplet reading frame*" and resulting, as

exemplified, "*in the precise joining of a ... variable region segment ... to a ... constant region segment, each in the proper coding frame and with no alteration in amino acid sequence for either ... variable or ... constant region*" (cf. page 28, third paragraph and page 55, third paragraph). In line with these teachings, Figure 20 shows nucleotide changes introduced into the variable and constant (V/C) boundary resulting from mutagenesis to engineer restriction enzyme sites in this region and which are defined as "*silent changes*" (cf. page 18, third paragraph). Thus, the resulting chimeric cDNA encodes the entire constant and variable regions of the human antibody heavy and light chains, in particular when producing class-switched antibodies. Since the cDNA referred to in claims 10 to 12 is defined in general terms by the fact that it encodes the entire constant and variable regions of the human antibody heavy and light chains, no reference being made to any particular nucleotide sequence (cf. points VIII and 5 *supra*), it encompasses also cDNA sequences with "*silent changes*" which do not alter or modify the encoded amino acid sequences, such as those shown in document D10.

9. For these reasons, document D10 anticipates the subject-matter of claims 10 to 12, which thus does not fulfil the requirements of Article 54 EPC.

Auxiliary requests I and II

Admissibility

10. According to the RPBA, the statement of grounds of appeal shall contain a party's complete case (Article 12(2) RPBA). Any amendment to a party's case

after filing of the grounds of appeal may only be admitted at the board's discretion which shall be exercised in view of *inter alia* the complexity of the new subject matter submitted and the current state of the proceedings (Article 13(1) RPBA). It is acknowledged in the case law that the filing of a new request might give rise to new issues and therefore, the later its introduction into the proceedings, the greater the risk that it might be found inadmissible (cf. *inter alia* decision T 516/06 of 23 May 2007, points 2 to 5).

11. In the present case, the relevance of document D10 in relation to the product claims was already evident in the decision under appeal and, even though the opposition division decided that this document did not anticipate these claims (cf. point 5.1.3 of the decision under appeal), the objection for lack of novelty was maintained in the statements of grounds of appeal of the first and third opponents. In the board's communication sent to the parties with the summons to oral proceedings (cf. point V *supra*), the parties were informed that in the board's preliminary opinion, claims 10 to 12 were anticipated by document D10 (cf. point 17 of the board's communication). Thus, the importance of document D10 as regards the novelty of these claims should have been evident to the respondent from an early stage of the proceedings. In fact, in auxiliary requests I and II filed with the respondent's reply to the board's communication (cf. point VI *supra*), these claims were the sole claims amended, nevertheless none of them in terms of a product-by-process feature.

12. It is established case law of the Boards of Appeal that although claims defined in terms of processes for their preparation (product-by-process claims) are in principle admissible, they have to fulfil several conditions, such as *inter alia* that the claimed product cannot be described in any other way and that it must be patentable. In particular, novelty may be established if evidence is provided that the method of preparation provides distinct differences in the properties of the claimed product over those known from the prior art (cf. "Case Law", *supra*, II.B.6, page 211). In the present case, it seems to be arguable whether the processes of claims 1 and 9 might provide a cDNA that can be distinguished in a straightforward manner from other cDNAs containing "*silent mutations*", such as those described in document D10. Moreover, apart from the possible problems under Articles 84 and 123(2) EPC alleged by the appellants (cf. point XI *supra*), the presence of alternatives or different dependencies in these product-by-process claims might require an assessment of the patentability of each alternative over different prior art, since the priority rights of each dependency (on claims 1 or 9) may be different (cf. *infra*).

13. In view of the complexity of these issues and of the late stage at which the amendments were put forward, the board in exercising its discretion decided not to admit auxiliary request I into the proceedings. The admissibility of auxiliary request II was not contested by the appellants (cf. point XI *supra*) and the board does not see any reason not to admit it into the proceedings.

Auxiliary request II

Article 123(2) EPC

14. Appellants' objections and respondent's arguments under Article 123(2) EPC for auxiliary request II are identical to those submitted for the main request, since the two features objected in the main request are also present in this request (cf. points XI and XIII *supra*). In this respect, the same conclusions as in point 4 *supra* apply, and thus auxiliary request II is considered to fulfil the requirements of Article 123(2) EPC.

Articles 87 to 89 EPC

15. The priority document P1 (which is identical to the priority document P2 except for the presence in document P2 of a Figure 1 showing the karyotypic analysis of HT01 hybridoma cells) refers to the molecular structure of antibodies and to their bifunctional character as well as to the expression of functional antibodies which must comprise the variable region (to form the antigen binding site) and the constant region (to bind Fc receptors and to activate the complement system) of the antibody light and heavy chains (cf. *inter alia* page 1, second paragraph to page 2, second paragraph). Document P1 refers to the "*expression of both chains in substantially equimolar proportions* (for obtaining) *optimum yields of functional antibody*" and to the assemblage of the two chains within the host cell for secretion of a functional antibody into the culture media (cf. *inter alia* page 13, second paragraph and page 14, first paragraph).

16. This is in line with the examples of document P1 which show the isolation of clones pH210H2 and pH210L2 containing, respectively, inserts of the expected size "*for human immunoglobulin heavy chain cDNA*" and "*for human antibody light chain cDNA*" of the anti-hepatitis A virus monoclonal antibody D (cf. pages 23 to 26), wherein the "*expected size*" is that of the entire heavy and light chains and which thus includes their entire variable and constant regions. This is all the more so because document P1 does not define the term "*antibody*" as including antibody fragments and, therefore, the references to "*cDNA encoding the antibody*", "*cDNA which encodes the antibody heavy and light chain proteins*" and "*heavy and light chain cDNA*" (cf. *inter alia* page 10, second and fifth paragraphs, page 11, second paragraph, pages 13 and 14) must be interpreted as referring to entire cDNA sequences, i.e. to cDNA encoding the entire constant and variable regions of the human antibody heavy and light chains.

17. It has not been contested by the respondent that claim 9 can be entitled only to the third priority date (cf. point XI *supra*). The board also agrees therewith. The priority document P3 discloses a method for producing a recombinant human antibody which comprises as a first step a micro-RNA preparation from a few hybridoma cells (cf. page 11). The mention of new prior art in priority document P3 (cf. paragraph bridging pages 5 and 6) does not shift the invention when compared to priority documents P1 or P2. Neither the technical problem to be solved (production of functional recombinant human antibody) nor the essential feature of the solution proposed thereto

(cDNA encoding the entire human antibody heavy and light chain genes) differ in any of these documents. Document P3 provides only a further solution to a technical problem already identified in documents P1 and P2 and it does not shift the gist of the original invention.

18. It follows from the above that, except for claim 9 which is only entitled to third priority, all other claims of auxiliary request II are entitled to the first claimed priority.

Availability of document D2

19. According to the appellants, the content of document D2 (published in December 1991) is identical with that of a poster presented by Prof. Dr. F. Rüker (the first author of document D2) - and thereby made available to the public - at a conference held in Potosi, Missouri (USA) in June 1990, i.e. before the first claimed priority date. Neither the actual poster presented at this conference nor a copy thereof is on file. Documents D2A and D2B have been filed in support of appellants' allegations (cf. point XI *supra*).

20. Document D2A, the Index of the Volume in which document D2 was published 18 months after the date of the poster presentation, states that the published Volume "*is the result of a conference ... held on June 3-8, 1990*". In the board's view, it cannot be concluded from this statement that the published articles, in particular document D2, are a literal transcription of the posters presented at this conference. This statement does certainly not exclude a possible elaboration of the

original contents of the posters or at least the drafting of the published articles having in mind information that was not available at the date of drafting the posters but made available to the authors of the articles at a later date such as, for instance, at the date of the conference itself, i.e. information presented, discussed and exchanged at this conference.

21. Document D2B is a declaration of the first author of document D2 signed in 2008 for the purpose of the present proceedings. The time which has elapsed since the poster presentation is itself enough to cast doubt on the reliability of the author's recollection. Such doubt is reinforced by a detailed consideration of this evidence. Document D2B does not state that the contents of the poster and that of document D2 were identical, but that they were essentially the same ("*im Wesentlichen*", "*in allen wesentlichen Einzelheiten*"). It is thus acknowledged that document D2 was not a mere literal transcription of the poster presented at the conference held in June 1990. Indeed, it could not be otherwise since the literature references cited in document D2 show that it contains information that was not publicly available at the date of the poster presentation. In particular, within the context of identification of full-length clones of the heavy and light chains, document D2 refers to an article (reference 21) disclosing the sequences of these chains which was submitted in July 1990 and published only in August 1990 (cf. page 213, first full paragraph in document D2) - even though, admittedly, this information should be known to the authors of the poster since two of them contributed to the article. Moreover, the reasons for leaving out references to any

other information available to the authors of document D2 after the presentation of the poster cannot be derived from document D2 itself and might well be more than the mere intention to provide a literal transcription of the poster.

22. According to document D2B, the content of the poster was explained to and discussed with several colleagues at the conference held in June 1990. However, there is no evidence on file from these people to confirm the information conveyed by the poster or to describe those issues that required further discussion.

23. Thus, it cannot be concluded that the content of the poster presented at the conference held in June 1990 has been proved beyond any reasonable doubt or, as required by the case law for those cases where the revocation of a granted patent is at issue, up to the hilt (cf. decision T 313/05, *supra*, points 33 and 34 of the Reasons). Thus, the content of document D2 is not taken into account.

Article 54 EPC

24. Document D10 discloses "*region gene modules*" encoding the constant or variable regions of a human antibody heavy or light chains, the linkage of these modules to construct the entire heavy or light chains and their expression to produce functional human antibodies (cf. points 6 to 8 *supra*). Although Figures 4 and 6 show cDNA clones containing the entire variable and constant regions of the human IgG1 heavy chain (pGMH-15, Figure 4A) and IgK light chain (pK2-3, Figure 6A), none of these clones is used for expressing the entire

chains. On the contrary, in line with the teachings of this document, only the constant (CH_1, CH_2, CH_3) region of the IgG1 heavy chain is used to construct the heavy chain constant vector pGMH-6 of Figure 4B and only the constant (C_k) region of the IgK light chain is used to construct the light chain constant vector pING2001 of Figure 6B as described in Example I (cf. page 48 to 51, in particular page 49, first and second paragraphs and page 50, second full paragraph). Appropriate variable region modules of both chains must then be inserted in these heavy and light chain constant vectors to obtain the corresponding entire chains. There is no suggestion in document D10 to use the entire cDNA clones depicted in Figures 4 and 6 in a method as described in the patent in suit. As a matter of fact, in view of the described advantages of the "*region gene modules*", such a way of proceeding would be contrary to the teachings of document D10.

25. It would also be contrary to the teachings of the patent in suit to interpret the term "comprising" in the preamble of method claim 1 as allowing for the presence of additional process steps between steps (v) and (vi), for example - as proposed by the appellants - the additional steps of processing the "*cDNA encoding the entire constant and variable regions of the antibody heavy and light chain genes*" of step (v) into region gene modules to be linked anew for the production of the same or other "*cDNA encoding the entire constant and variable regions of the antibody heavy and light chain genes*" and to be then inserted into an expression vector (step vi). According to the teachings of the patent in suit (cf. points 1 to 3 *supra*), the term "***the*** *cDNA*" in steps (vi) and (vii) of

claim 1 (emphasis added by the board) can only be interpreted as referring directly to the cDNA of step (v) without further modification steps in between. Thus, the process of the claims at issue is different from that described in document D10.

26. Document D1 discloses pairs of expression vectors, namely pRCRSVLc and pRCRSVHc, pRCCMVLc and pRCCMVHc, pN12TELc and pN12TEHc, wherein one vector contains a cDNA encoding the light chain (Lc) of the human monoclonal antibody 3D6 and the other vector contains the cDNA encoding the heavy chain (Hc) of the same antibody 3D6. Both cDNAs contain thus the entire constant and variable regions of the corresponding chain and the cDNA sequences are under the control of a promoter (RSV, CMV and human metallothionein promoter IIA). These pairs of vectors are used to transfect CHO $DHFR^-$ host cells so as to obtain stable clones expressing the antibody 3D6 (cf. pages 20 to 21). Under the heading "*DNA preparation*", document D1 refers to the isolation of cDNA from 5 clones and from the hybridoma cell line LC4. However, immediately thereafter (cf. paragraph bridging pages 75 and 76), reference is made only to methods for isolating genomic DNA (methods I to IV) in which RNAse is used to digest cellular RNA (cf. pages 40 to 42). Contrary to the detailed disclosure of these methods, document D1 fails to disclose any protocol - and the specific steps performed - for selecting, isolating and synthesising cDNA sequences. There is no such protocol disclosed in document D1 under the heading "*Materials and Methods*" nor any evidence that a method according to claim 1 can directly and unambiguously be derived from this document.

27. The scarce information given on the human mouse hybridoma cell line LC4 from which, according to document D1, the cDNA of the human monoclonal antibody 3D6 was isolated (cf. pages 30 and 75), may also cast doubts on the public availability of this hybridoma as well as on the repeatability of the specific disclosure of document D1 even though, as argued by the appellants, the teachings of this document might not be limited to the specific antibody 3D6 exemplified therein. Nevertheless, in view of the deficiencies in document D1 pointed out above, there is no need to consider this matter in further detail.

28. The claimed subject-matter is thus considered to fulfil the requirements of Article 54 EPC.

Article 56 EPC

29. Document D35, which is considered to be the closest prior art, discloses high level expression of the humanized monoclonal antibody Campath-1H in CHO host cells. According to this document, "*the complementary determining regions from the rat Campath-1G monoclonal were originally grafted directly into genomic human heavy and light chain frameworks*" and, since cDNA clones were preferred for re-expressing these genes in CHO cells, "*two size selected cDNA λgt10 libraries were prepared from the recombinant myeloma cell line TF57 and used for the isolation of full length Campath-1H heavy and light chain cDNAs*" (cf. page 64, right-hand column, second full-paragraph and page 67, right-hand column, first full paragraph). These isolated full length cDNAs were used to construct light (pLD9,

Figure 1a) and heavy (pNH316, Figure 1b) chain expression vectors. Each of these expression vectors had a different selectable marker so that co-transfected $dhfr^-$ CHO host cells co-expressing both antibody chains exhibited a desired dual phenotype ($dhfr^+$/neomycin resistant). The co-transfected host cells were then subjected to rounds of amplification so as to elevate the Campath-1H antibody yield (selection/amplification procedure) (cf. page 65, left-hand column, first paragraph to page 66, left-hand column, first full paragraph). Furthermore, it is indicated that "*to derive correctly assembled recombinant antibodies it is important that the expression of the heavy and light chains is balanced*", i.e. an equimolar contribution of the expressed chains is required (cf. paragraph bridging pages 66 and 67).

30. Document D35 explicitly states that "*genomic immunoglobulin clones will likely contain additional regulatory elements within the introns that could adversely affect expression in non-lymphoid cells, such as CHO*" and that this problem is eliminated "*by isolating cDNA clones and manipulating them to contain minimal untranslated sequence*" which, as additional advantage, "*makes the constructs considerably easier to handle*" (cf. page 66, paragraph bridging left and right-hand columns). The document further refers to CHO cells as offering many advantages over other cell lines used for the expression of antibodies, such as the experience gained in their use for expression of several proteins of therapeutic value which has been approved by the regulatory authorities as an industrial process; they are thus well suited to scale-up and can be adapted to good growth conditions and productivity

under serum-free conditions. Therefore, document D35 concludes that the demonstration in this document "*of using engineered CHO cells to express and secrete high levels of clinically important recombinant antibodies, such as Campath-1H, should extend the utility of these cells for research and production purposes*" (cf. page 67, paragraph bridging left and right-hand columns).

31. The method of claim 1 differs from that described in document D35 in that it is directed to the production of a recombinant human antibody and not to a recombinant humanized antibody. Although both methods require a cDNA sequence encoding the entire constant and variable regions of an antibody heavy and light chain genes, in claim 1 the complete cDNA sequence is - only and exclusively - derived from a human antibody, whereas in document D35 the cDNA sequence is partly - even though in small part - derived from rat, namely the part of the cDNA sequence encoding the complementary determining regions (CDRs) of the rat Campath-1H antibody. Furthermore, the specific process steps (ii) and (iii) of claim 1 are not explicitly disclosed in document D35.

32. Starting from the closest prior art, the objective technical problem to be solved is the provision of alternative recombinant antibodies. The method of claim 1 insofar as directed to the production (and isolation) of recombinant human antibodies is the solution proposed for this technical problem. Although the patent in suit does not contain any example of the actual production and isolation of antibodies, the board is convinced by the prior art on file that no special difficulties would have been encountered by the

skilled person. The more so since no particular yield is required for the production of recombinant human antibodies in any of the claims under consideration (cf. point 35 *infra*).

33. The board cannot follow the respondent's argumentation that the references found in document D35 to the production of human recombinant antibodies in general are only theoretical speculations without technical basis (cf. point XIII *supra*). On the contrary, it is clear from the numerous advantages of the method disclosed in this document (cf. point 30 *supra*) that these references, including that to "*clinically important recombinant antibodies*" (cf. page 64, abstract and page 67, paragraph bridging left and right-hand column), would prompt the skilled person to use the advantageous method with non-lymphoid CHO host cells for production of other (clinically important) recombinant human antibodies. The teachings of document D35 are not limited to humanized Campath-1H antibody nor is there any indication in the document to further improve this Campath-1H antibody (i.e. increase its humanization). In the board's view, there is a strong pointer in document D35 towards the technical problem mentioned above as well as to the proposed solution. Indeed, document D35 refers to earlier studies on the expression of recombinant human antibodies using myeloma host cells and to the shortcomings of these studies, in particular a "*complex vector design, based around immunoglobulin gene regulatory elements ... and highly variable final expression levels*" (cf. page 64, paragraph bridging left and hand-right columns). Document D9 (reference 10 in document D35) is

explicitly cited within this context and thus no hindsight is required for combining these two documents.

34. Document D9 discloses the production of a human anti-tetanus toxoid monoclonal antibody (anti-TT) and reports, as a first step, the isolation and sequencing of the full-length heavy and light chain cDNAs from the mouse-human heterohybridoma cell line GF4/1.1, thereby disclosing the process steps (i) to (iii) of claim 1 (cf. page 799, last paragraph to page 800, left-hand column and page 803, left-hand column, first full paragraph). Expression vectors with these cDNAs are transfected into murine hybridoma Sp2/0 Ag14 host cells with a DHFR/MTX selection/amplification system (cf. page 800, right-hand column to page 801, left-hand column and page 803, left-hand column, third full paragraph to right-hand column, first paragraph). The advantageous effect of this system (used also in document D35), which allows for the selection of transfected cells with increased rates of antibody secretion, is suggested to be associated with the use of cDNA as opposed to genomic DNA (cf. page 802, paragraph bridging left and right columns), even though "*cDNA in its genomic configuration*" is reported to be used in the construction of the expression vectors when the "*cDNAs were modified for expression in mammalian cells*" (cf. page 800, right-hand column to page 801, left-hand column, first paragraph, Figure 2). These cDNAs modifications are, however, strongly discouraged when using non-lymphoid cells, such as the advantageous CHO cells of document D35 (cf. point 30 *supra*). The combination of documents D35 and D9 renders thus the claimed subject-matter obvious.

35. The board is also convinced that, when combining these two documents, a reasonable expectation of success arises. Firstly, both documents describe high levels of expression of recombinant human antibody (cf. title, abstract and page 67, left-hand column in document D35 and page 801, paragraph bridging left and right-hand column, page 802, left-hand column, second full paragraph and right-hand column, last paragraph in document D9). Secondly, there is no requirement in the method of claim 1 for any specific production yield or amount of recombinant human antibody to be produced (cf. point VIII *supra*), less ambitious goals being usually associated in the case law with higher expectations.

36. It follows from the above, that the requirements of Article 56 EPC are not fulfilled.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

K. Götz L. Galligani