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Datasheet for the decision of 2 December 2009

Case Number: T 0601/05 - 3.3.04

Application Number: 94102560.3

Publication Number: 0614984

IPC: C12P 21/08

Language of the proceedings: EN

Title of invention:
Anti-TNF alpha human monoclonal antibodies

Patentee:
Bayer Corporation

Opponents:
Centocor, Inc.
Abbott Laboratories

Headword:
Anti-TNF alpha human monoclonal antibodies/BAYER III

Relevant legal provisions:
EPC Art. 54, 56, 57, 83, 84, 123(2)(3), 113(1), 114(2), 116

Keyword:
"Admission of late-filed documents - (partly)"
"Admission of late-filed auxiliary requests 1 to 3 - (no)"
"Main request - sufficiency of disclosure - (no)"
"Auxiliary request 4 - added matter, extension of scope (no); clarity and support (yes); sufficiency of disclosure, novelty, inventive step (yes)"
"Right to be heard violated by (i) non-admission of parts of documents and (ii) limitation of time to speak at oral proceedings (no)"

Decisions cited:
G 0001/03, T 0292/85, T 0260/85, T 0361/87, T 0431/96, T 0036/00, T 0792/00, T 0219/01, T 0609/02, T 0611/02, T 1936/07

Catchword:
see points 11 to 17, 21 to 44 and 121 to 126

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Case Number: T 0601/05 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 2 December 2009

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 16 February 2005 revoking European patent No. 0614984 pursuant to Article 102(1) 1973 EPC.**

Composition of the Board:

Chairman: M. Wieser
Members: G. Alt
R. Moufang

Summary of facts and submissions

I. The appeal was lodged by the patent proprietor (hereinafter "appellant") against the decision of the opposition division revoking European patent No. 0 614 984 pursuant to Article 102(1) EPC 1973.

II. In a first interlocutory decision, announced at the oral proceedings held on 18 October 2007 (in the following "Bayer I"), the board decided that the appeal was admissible, that the appellant's main and auxiliary request were admitted into the proceedings, and that claims 1 to 6 of the main request complied with the requirements or Articles 123(2) and (3), 84 and 54 EPC. In addition, the debate with regard to the issue of inventive step was closed.

III. In a second interlocutory decision given in writing on 24 April 2008 (in the following "Bayer II"), the board decided that the appellant's main request met the requirements of Article 56 EPC.

IV. Respondent I (opponent 1) filed a petition for review according to Article 112a(c) and (d) EPC. With the decision R 5/08 dated 5 February 2009 the Enlarged Board of Appeal rejected the petition as inadmissible.

V. By letter dated 18 March 2009, the parties were summoned for second oral proceedings to be held on 1 and 2 December 2009.

VI. By letter dated 1 October 2009, the appellant filed ten auxiliary requests, of which auxiliary request 7 corresponded to the auxiliary request already admitted

into the proceedings (see section II above). Furthermore, documents ID59 to ID72 were filed. By letter dated 24 November 2009 the appellant submitted documents ID82 to ID91.

VII. Respondent I filed declaration ID73 with annexes A to D and declaration ID74 with annex A by letter dated 3 October 2009, and documents ID94 to ID96 by letter dated 23 November 2009.

VIII. Respondent II (opponent 2) submitted declaration ID75 with annexes A to F and documents ID76 to ID80 by letter dated 13 October 2009, declaration ID81 by letter dated 30 October 2009 and document ID97 by letter dated 30 November 2009.

Oral proceedings

IX. At the beginning of the oral proceedings on 1 December 2009, the chairman of the board informed the parties that the oral proceedings were sound-recorded and that the recording was not public and served only to assist the board in writing its reasoned decision.

X. At the oral proceedings the appellant filed six auxiliary requests. Auxiliary requests 1 to 3 and 6 corresponded to auxiliary requests 2, 4, 6 and 9 of the set of auxiliary requests filed previously in writing. Auxiliary request 4 corresponded to the auxiliary request already admitted into the proceedings by the board (see section II above). Auxiliary request 5 was based on the already admitted auxiliary request 4, but wherein the expression "is capable of inhibiting" in claim 1 was replaced by the term "inhibits".

XI. After the board announced on the afternoon of the second day of the oral proceedings that the experimental data in documents ID73 to ID81 submitted by the respondents were not allowed into the proceedings, respondent II objected that excluding the experimental data infringed its right to be heard.

XII. On the evening of the second day of the oral proceedings at about 18.35 hrs after each of the parties had pleaded for about 30 minutes on the issue of the pharmaceutical effectiveness of the antibody B5, an issue arising in the context of sufficiency of disclosure with regard to claim 1 of auxiliary request 4, the chairman of the board announced that the board had no further questions on this issue and that the speaking time during a "final round" on this issue would be restricted to ten minutes for each party.

XIII. After deliberation the board announced at about 19.30 hrs its opinion on Article 83 EPC. At this point respondent I objected that its right to be heard had been violated due to the limitation of time to present its arguments.

XIV. Subsequently, the parties were heard on the issues of Article 57 EPC and the adaptation of the description. After the board gave its opinion on these issues, at about 20.10 hrs, respondent II also raised the objection that its right to be heard had been violated due to the limitation of time to present its arguments with respect to the issue of the pharmaceutical effectiveness of the antibody B5 (see section XII above).

XV. The parties' requests at the oral proceedings were as follows:

The **appellant** requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of claims 1 to 6 of the main request filed with letter dated 18 September 2007 or, in the alternative, on the basis of the first to sixth auxiliary requests submitted at the oral proceedings.

Claim 1 of the main request read:

"1. A pharmaceutical composition containing a human monoclonal antibody that binds to human tumor necrosis factor alpha."

Claim 1 of auxiliary request 1 read:

"1. A pharmaceutical composition containing a human monoclonal antibody that binds to human tumor necrosis factor alpha, wherein the antibody binds to tumor necrosis factor alpha on human cell surfaces."

Claim 1 of auxiliary request 2 read:

"1. A pharmaceutical composition containing a human monoclonal antibody that binds to human tumor necrosis factor alpha, wherein the antibody inhibits secretion of tumor necrosis factor."

Claim 1 of auxiliary request 3 read:

"1. A pharmaceutical composition containing a human monoclonal antibody that binds to human tumor necrosis factor alpha on human cell surfaces, and inhibits secretion of tumor necrosis factor."

Claims 1 to 4 of auxiliary request 4 read:

"1. A pharmaceutical composition containing a human monoclonal antibody that binds to human tumor necrosis factor alpha on human cell surfaces, and is capable of inhibiting LPS-induced human tumor necrosis factor alpha secretion by human monocyte cells.

2. The pharmaceutical composition of claim 1, wherein the antibody is an antibody of the IgM or IgG type.

3. The pharmaceutical composition of claim 1, wherein the antibody is suitable for intravenous administration.

4. The pharmaceutical composition of claim 1, wherein the antibody is expressed from the cell line deposited with the ATCC under designation CRL 11306."

Respondent I requested that the case be remitted to the department of first instance for further prosecution or, in the alternative, that the appeal be dismissed.

Respondent II requested that the appeal be dismissed.

XVI. At the end of the oral proceedings the board announced its decision.

XVII. The following documents are referred to in the present decision:

ID5: Journal of Immunological Methods, vol. 140, 1991, pages 37-43, Galloway, C.J. et al.

ID10: WO-A-92/11383

ID13: EP-A-0 585 705

ID19: Tibtech, vol.11, no. 2, 1993, pages 42-44, Harris, W.J. and Emery, S.

ID20: Science, vol. 252, 1991, pages 1657-1661, Waldmann, T. A.

ID32: The EMBO Journal, vol. 12, no. 2, 1993, pages 725-734, Griffiths, A.D. et al.

ID35: Declaration of Paolo Casali dated 1 May 2004

ID73: Declaration of Sander van Deventer dated 3 October 2009

ID74: Declaration of Fionula Brennan dated 3 October 2009

ID75: Declaration of Jochen Salfeld dated 3 October 2009

ID81: Declaration of Michael Neuberger dated 23 October 2009

ID97: Clinical Immunology, vol. 131, 2009, pages 308-316, Kaymakcalan, Z. et al.

XVIII. The following decisions are referred to in the present decision:

G 1/03 (OJ EPO 2004, 413)

T 292/85 (OJ EPO 1989, 275)

T 260/85 of 9 December 1987

T 361/87 of 15 June 1988

T 431/96 of 23 February 1999

T 36/00 of 2 October 2003

T 792/00 of 2 July 2002

T 219/01 of 15 December 2004

T 609/02 of 27 October 2004

T 611/02 of 9 November 2004

T 1936/07 of 13 October 2009

XIX. Unless it is a citation from a document, the term "human tumour necrosis factor alpha" is abbreviated as "TNF" throughout this decision.

Respondents I and II are referred to as "respondents" in this decision.

XX. The appellant's arguments, as far as they are relevant to the present decision, may be summarised as follows:

Remittal

In order to establish legal certainty as fast as possible the board should not remit the case to the department of first instance for consideration of Articles 83 and 57 EPC.

Admission of late-filed documents

Declaration ID75 contained inter alia voluminous experimental evidence. Due to the filing of document ID75 only seven weeks before the oral proceedings there had not been sufficient time to adequately react to this evidence. Therefore, this document should not be admitted into the proceedings even without reviewing its relevance.

Declaration ID81 should also not be admitted, since it commented on the results presented in declaration ID75.

The observations made in declarations ID73 and ID74 were not supported by experimental evidence and therefore amounted to pure allegations. Moreover, nothing was said that had not been said before. Consequently, these documents too should be excluded from the proceedings.

Main request

Article 83 EPC

The patent disclosed a method for the preparation of human monoclonal TNF-binding antibodies and disclosed a pharmaceutically useful effect for a composition containing these antibodies. Moreover, the patent provided an example of such an antibody which had the disclosed pharmaceutical effect. Hence the protection given by claim 1 was commensurate with the contribution that the patent made to the art.

Decisions T 292/85, T 361/87, T 431/96 and T 36/00 supported this view. In decisions T 292/85, T 361/87 and T 36/00 the boards adhered to the concept that a given subject-matter was sufficiently disclosed if the specification provided a teaching that enabled the skilled person to find suitable variants which had the same effect as the molecules that were exemplified in the specification. In decision T 431/96 the board ruled that the production of monoclonal antibodies by the hybridoma technique was routine.

Admission of auxiliary requests 1 to 3

It followed from the respondents' submissions that they considered the capability of binding with high affinity to TNF to be linked to the binding to soluble TNF. According to auxiliary requests 1 to 3 the antibodies in the composition had to bind to TNF on the cell surface and/or to inhibit secretion of TNF. Thus, the claims of these auxiliary requests took away the reason

for objecting to the main request. Hence, the requests should be admitted into the proceedings.

Auxiliary request 4

Article 84 EPC

Clarity

Claim 1 comprised the feature "is capable of inhibiting LPS-induced human tumour necrosis factor alpha secretion by human monocyte cells". This feature was based on a feature present in claim 11 as granted which read "which inhibits LPS-induced TNF alpha secretion by human monocyte-like cells". Since the discussion on Article 84 EPC could only arise with regard to amendments over granted claims, only the terms "capable of inhibiting" and "monocyte cells" were open for consideration of their compliance with the requirements of Article 84 EPC.

Both the expressions "monocyte cells" and "capable of inhibiting" were clear to the person skilled in the art.

Support

All claims of auxiliary request 4 were supported by the description.

Article 123(2) EPC

The subject-matter of all claims was clearly and unambiguously derivable from the application as filed.

Article 123(3) EPC

Claim 1 as granted related to "[a] composition comprising human monoclonal antibodies that bind to human tumor necrosis factor alpha". Present claim 1 related to "[a] pharmaceutical composition containing antibodies that bind to human tumor necrosis factor alpha" and which were further defined in the claim by the feature "capable of inhibiting LPS-induced human tumor necrosis factor alpha secretion by human monocyte cells". Therefore, the scope of present claim 1 was narrower than that of claim 1 as granted.

Article 83 EPC

The invention was to have shown that human monoclonal antibodies worked according to the mechanism stated in the claim, i.e. that they bound to TNF and were capable of inhibiting LPS-induced TNF secretion by human monocyte cells. Thus, all that mattered for the evaluation of the requirements of Article 83 EPC was that antibodies working according to this mechanism could be obtained on the basis of the disclosure in the patent. And this was so. Further properties such as the degree of affinity to soluble TNF were irrelevant for the question of sufficiency of disclosure.

The results in Table 10 were evidence of a pharmaceutical effect.

Articles 54, 56 and 57 EPC

No arguments were submitted in relation to Articles 54 and 56 EPC.

The patent clearly showed the pharmaceutical usefulness of the claimed compositions. Therefore, the requirements of Article 57 EPC were fulfilled.

XXI. The respondents' arguments, as far as they are relevant to the present decision, may be summarised as follows:

Remittal

The board should remit the case to the opposition division for consideration of Articles 83 and 57 EPC since the opposition division had not given a final decision on these issues.

Admission of late-filed documents

The experiments in declaration ID75 were basically a repetition of the assays described in the patent, but included more controls. They thus allowed a better evaluation of the results of the patent and were therefore highly relevant for the issue of the pharmaceutical usefulness of the specifically disclosed antibody of the patent under dispute, the antibody B5. Declarations ID73, ID74 and ID81 also contained highly relevant information. Therefore, these documents should be admitted into the proceedings.

The board's decision not to admit the experimental data in documents ID73 to ID75 and ID81 into the proceedings violated the requirements of Article 113(1) EPC.

Main request

Article 83 EPC

Claim 1 related to any human monoclonal antibody binding to any of the three known forms of TNF. Thus the claim covered also those antibodies binding to soluble TNF with high affinity.

With the hybridoma technology disclosed in the patent as the method for the production of human monoclonal antibodies, antibodies binding to soluble TNF with high affinity could not be obtained.

It was established case law (see for example decision T 792/00) that the disclosure in the patent, in combination with common general knowledge if necessary, had to enable the skilled person to carry out substantially all of the claimed embodiments. Since in the present case a considerable part of the claimed subject-matter could not be carried out, there was a lack of sufficiency of disclosure.

Admission of auxiliary requests 1 to 3

Claim 1 of none of these three auxiliary requests explicitly excluded high affinity antibodies binding to soluble TNF. Thus, none of the requests took account of the reasons for objecting to the main request for lack of sufficiency of disclosure. Therefore, none of the requests should be admitted into the proceedings.

Auxiliary request 4

Article 84 EPC

Clarity

The term "monocyte cells" as such was ambiguous because there were two types of monocyte cells: primary cells, i.e. those isolated from the body, and those coming from established monocytic cell lines. Moreover, due to this ambiguity it was unclear under which conditions the antibodies had to be "capable of inhibiting LPS-induced human tumor necrosis factor alpha secretion by human monocyte cells". Hence, the skilled person could not clearly establish whether or not a given TNF-binding antibody fell under the claim or not. Consequently, claim 1 lacked clarity.

The only assay available according to the patent to test the functional feature in claim 1, namely the capability "of inhibiting LPS-induced human tumor necrosis factor alpha secretion by human monocyte cells", could not discriminate whether or not a high-affinity, neutralizing anti-TNF antibody inhibited TNF activity by binding to TNF located on the cell surface or by binding to TNF in the supernatant, i.e. to soluble TNF. Other methods allowing discrimination were not part of the skilled person's knowledge at the priority date. Thus, the skilled person could not determine whether or not a high affinity, neutralizing anti-TNF antibody fell within the claim or not. Therefore, also for that reason the claim lacked clarity. If this objection was not accepted under

Article 84 EPC, it also arose under Article 83 EPC in view of decision T 611/02.

Support

The assay disclosed in the patent under dispute to determine the feature "is capable of inhibiting LPS-induced human tumor necrosis factor alpha secretion by human monocyte cells" was carried out with THP-1 cells which were however not of the monocytic type, but were in fact progenitors to monocytes. Therefore, claim 1 lacked support.

Article 123(2) EPC

It was an essential aspect of the invention that inhibition of secretion was mediated by binding of the antibody to TNF located on the cell surface. The feature of cell-surface binding was however absent from claim 1. According to decision T 260/85 it contravened the requirements of Article 123(2) EPC if a feature which the application as originally filed presented as an essential feature of the invention was absent from an independent claim.

Article 123(3) EPC

In contrast to the expression in claim 11 as granted "which inhibits LPS-induced TNF alpha secretion" the expression in present claim 1 "is capable of inhibiting LPS-induced human tumour necrosis factor alpha secretion" did not establish a mandatory requirement that the ability of inhibiting TNF secretion was indeed the one exploited for the pharmaceutical use. Hence,

since the pharmaceutical use could rely on any of the other possible properties of an antibody falling under the definition in claim 1, the scope of protection was extended vis-à-vis the claims as granted.

Article 83 EPC

Claim 1 covered compositions containing antibodies binding with high affinity to soluble TNF thereby neutralizing its activity. It was shown by document ID97 that this kind of antibody could also bind to cell-membrane TNF. Therefore, for the reasons given in respect of the main request, the disclosure in the patent did not enable this embodiment of claim 1.

The only assay disclosed in the patent for the determination of the feature in claim 1 "is capable of inhibiting LPS-induced tumour necrosis factor alpha secretion by human monocyte cells" did not allow to detect whether or not an antibody binding with high affinity to soluble TNF and neutralizing its activity actually inhibited the cytotoxicity of TNF in the assay via the binding to released, i.e. "soluble", TNF or via the binding to cell-bound TNF.

Antibodies binding with high affinity to soluble TNF and neutralizing its activity worked by neutralizing the cytotoxicity of soluble TNF and not by inhibiting the release of the cell-surface located form.

The only specifically disclosed antibody, the antibody B5, was not useful as a therapeutic agent for a plurality of reasons. Consequently, the patent did not provide evidence for a pharmaceutical use and therefore

contravened the requirements of Article 83 EPC in relation to a claim to a first medical use.

Since the board limited the time to present arguments with regard to the issue of the pharmaceutical usefulness of the antibody B5 in the context of Article 83 EPC, the requirements of Article 113(1) EPC were violated.

Articles 54, 56 and 57 EPC

No arguments were presented with regard to Articles 54 and 56 EPC.

The invention was not susceptible to industrial application because of the lack of evidence for a pharmaceutical usefulness and therefore the claims contravened the requirements of Article 57 EPC.

Reasons for the decision

Remittal

1. The respondents have requested remittal of the case to the opposition division for consideration of issues arising in the context of Articles 83 and 57 EPC, because these issues have not yet been finally considered by the department of first instance.

2. Article 111(1) EPC gives the boards of appeal the discretion either to "exercise any power within the competence of the department which was responsible for the decision appealed" or to "remit the case to that

department for further prosecution". It follows from this provision that a board is not obliged to remit a case for consideration to the first instance only because a final decision on an issue has not been taken during the first-instance proceedings.

3. When exercising the discretion given by Article 111(1) EPC the boards balance the interest in procedural economy and legal certainty about the scope of a patent with the entitlement of the parties to fair proceedings as enshrined by Articles 113(1) and 116 EPC.

4. The disputed patent was granted in the year 2001. Oppositions were filed in May 2002 and the appeal was filed in April 2005. First oral proceedings in appeal proceedings were held in October 2007. Since the case was not finally decided at these proceedings, further oral proceedings were to be held. The date proposed by the board was postponed twice on the respondents' request. Moreover, review proceedings pursuant to Article 112a EPC were initiated (see section IV above). As a consequence, a further date for oral proceedings, set by the board, was cancelled. Finally, the second oral proceedings were held on 1 and 2 December 2009. Seeing this chronology it is in the board's view high time that the parties and the public know what the final version of the patent in suit is before it eventually expires in March 2013.

5. Moreover, the board considers that keeping the case with it does not violate any parties' right to be heard, since extensive written submissions, in particular in respect of the issues arising under Article 83 EPC, are available from the opposition and appeal proceedings.

There was also ample time (see above point 4) for the parties and the board to consider these submissions and thus to prepare the case appropriately.

6. Hence, in accordance with Article 111(1) EPC the board has decided to deal with the case itself, thus avoiding the delay in reaching a final decision which would be entailed if the case was remitted.

Admission of late-filed documents

7. A considerable number of documents were submitted by the parties after the issuance of the second interlocutory decision in April 2008. The appellant filed documents ID59 to ID72 and ID82 to ID91 by letters dated 1 October 2009 and 24 November 2009. Documents ID73 and ID74, ID75 to ID80, ID81, ID94 to ID96 and ID97 were filed by the respondents by letters dated 3, 13 and 30 October 2009 and 23 and 30 November 2009.

8. These documents essentially relate to issues arising under Article 83 EPC, i.e. one of the two outstanding issues with regard to the main request after the first oral proceedings. Article 100(b) EPC had been put forward as one of the grounds for opposition in the present case. Thus, the board considers all of the documents filed after the issuance of the second interlocutory decision in April 2008 as not being filed in due time, i.e. as being "late-filed".

9. Pursuant to Article 114(2) EPC the non-admission of facts and evidence not filed in due time is at the board's discretion.

10. In this context the appellant refers to the documents submitted with the letters of 3, 13 and 30 October 2009. In particular, it requests the non-admission of declarations ID73, ID74, ID75 and ID81.

11. Declaration ID75 contains annexes A to E, showing a number of experiments and results, and sixteen pages of observations commenting, inter alia, on these experiments and results. The experiments disclosed in the annexes include the cDNA cloning of a heavy and light chain antibody gene as well as a J chain gene, the transient expression of these genes, the amino acid sequencing of proteins, comparisons and sequence alignments, PCR experiments, ELISA experiments, cell-surface binding experiments, LPS induction experiments, new recombinant cell lines and quantitative PCR mRNA assays.

12. The respondents submit that the experiments in declaration ID75 are basically only a repetition of the assays of the patent, but include more controls.

However, some of the experiments disclosed in declaration ID75 are definitely not part of the disclosure in the patent, for example the determination of the origin of the chains of the antibodies by PCR analysis.

13. The experiments in declaration ID75 are presented in an attempt to challenge the disclosure in the patent. Therefore, a proper reaction to these experiments by the appellant would entail at least their repetition

and, depending on the result, even the preparation of counter-experiments.

14. Declaration ID75 and thus also the annexed experimental part was filed only seven weeks before the oral proceedings which, given the wealth of information, is too short a time to give the appellant a proper opportunity to check the data for their validity.

15. In view of the foregoing, the board decides not to admit the experimental part of declaration ID75, i.e. annexes A to E, into the proceedings.

16. The remaining parts of declaration ID75, in particular those parts containing comments and information unrelated to the experimental evidence in the document, are admitted into the proceedings.

In the board's view, given the intensity with which the issue of sufficiency of disclosure has been dealt with throughout the whole proceedings, the time period between the filing of declaration ID75 and the oral proceedings (i.e. approximately 1 1/2 months) was sufficient for the appellant to review this material and deal appropriately with it.

Insofar as parts of declaration ID75 refer specifically to the experiments and results of annexes A to E, these statements will be regarded as not being supported by experimental evidence, since the supporting evidence is not admitted (see above point 15).

17. The approach to exclude parts of a document from the proceedings whilst admitting others is in the present

situation the fairest approach and also takes account of the case law of the boards of appeal applying a much stricter standard when the admission of late-filed experimental data is at stake (Case Law of the Boards of Appeal, 5th edition, 2006, VI.F.4, paragraph 5 to 8, and for example the recent decision T 1936/07, point 1.2).

18. The appellant objects also explicitly to the admission of documents ID73 and ID74 for the reason that the declarants' comments are only allegations unsupported by appropriate evidence.

The declarants of documents ID73 and ID74 comment on the disclosure in the patent from their scientific point of view. It is the very purpose of a declaration to provide observations on selected issues by a person who is not involved in the proceedings. Moreover, the format which declarations have to take is not prescribed in the EPC, i.e. in particular, that comments in declarations have to be supported by evidence. Thus, the appellant's argument is not a reason for the board not to admit documents ID73 and ID74.

19. Documents ID73 and ID74 essentially repeat and summarize arguments which have already been made in the proceedings. Consequently, these documents and also document ID81 are admitted into the proceedings for the same reason as document ID75 (see point 16 above). As far as document ID81 refers to the experiments in document ID75, the same applies as for document ID75 (see point 16, third paragraph).

20. No objection was raised by the parties against the admission into the proceedings of any of the other late-filed documents. The board too sees no reason not to admit these documents.

Main request

The only outstanding issues with regard to the main request are those arising pursuant to Articles 83 and 57 EPC.

Article 83 EPC

21. Claim 1 of the main request is directed to "[a] pharmaceutical composition comprising a human monoclonal antibody that binds to human tumor necrosis factor alpha".

22. Several disorders of the human body are associated with undesirably high levels of TNF, for example sepsis and inflammatory diseases such as rheumatoid arthritis (see for example the patent, paragraph [0005]; document ID5, first paragraph of the introduction).

TNF is known to exist in three forms, as "soluble" TNF and as two different forms located on the cell surface, one of them being a transmembrane form which is released from the membrane by proteolytic cleavage to become soluble TNF, the other being a receptor-bound molecule (see the patent, paragraphs [0002] and [0003]; document ID74, point 16).

Antibodies neutralizing the effects of TNF have been envisaged as pharmaceutical agents (see for example document ID10, page 22).

Monoclonal mouse antibodies to TNF were known at the priority date for pharmaceutical use (see for example document ID13). However, their use for treatment of human patients was problematic due to unwanted immune responses (see for example document ID19, page 42, second column, first full paragraph).

Thus, at the priority date of the disputed patent there was a desire for the production and use of human monoclonal antibodies having reduced immunogenicity for long-term therapy of TNF-related disorders (see for example document ID20, page 1657, second column, lines 9 to 19).

23. The strength of the binding between the binding site of an antibody and an epitope of an antigen is called the affinity of an antibody. The affinity of an antibody to a given antigen is a characteristic property of a particular antibody.

24. The uniform opinion at the priority date of the patent in dispute was that antibodies useful for treatment of TNF-related disorders should have a **high affinity** to **soluble** TNF and should be capable of **neutralizing** its activity (see for example document ID32, page 725, second column, second paragraph, lines 3 to 6).

25. Claim 1 of the main request indicates neither any affinity by which the antibodies bind to TNF nor the kind of TNF to which they bind. However, in the board's

view, since the affinity of a given antibody to a given antigen is a particular characteristic of that antibody (see point 23 above) and since TNF is known to occur in several forms (see point 22 above), the claim is to be interpreted as covering antibodies binding to any kind of TNF with any degree of affinity. The claim thus includes antibodies binding with high affinity to soluble TNF. Those antibodies were expected to be the therapeutically effective ones (see point 24 above).

26. It follows from the observations above that the essential issue to be considered with regard to claim 1 of the main request is whether or not the patent enables the production of human monoclonal antibodies binding with high affinity to soluble TNF and, consequently, whether or not the skilled person can practise the invention over the whole scope of the claim (see for example decision T 792/00, point 2 of the reasons).

27. The only method disclosed in the patent for the production of human monoclonal antibodies is the so-called hybridoma technique which is based on the Köhler-and-Milstein technique developed in the 1970s for the production of mouse monoclonal antibodies.

28. The human monoclonal antibodies are produced according to the patent as follows (paragraph [0036]): human antibody-producing peripheral blood mononuclear cells are transformed with Epstein-Barr-Virus, incubated in vitro with TNF and then selected for TNF antibody-producing cells. These cells are fused with mouse myeloma cells to give a monoclonal antibody-producing hybridoma cell line.

29. There is a large body of evidence before the board suggesting that the hybridoma technology is not suited to producing antibodies binding with high affinity to soluble TNF.

- The antibody B5 which has been produced according to the method of the patent and which is specifically characterized in the patent binds to soluble TNF with low affinity. It is stated in paragraph [0053] of the patent that:

  "B5Mab binds to soluble rhTNFα with detectable but low affinity."

- The patent further states in paragraph [0091] that :

  "The biological effects of TNFα, especially its ability to promote Ig secretion, may preclude the generation of a high affinity neutralizing human anti-TNFα autoantibody by the techniques used."

- Documents ID32 and ID35 indicate that high-affinity antibodies to TNF cannot be obtained with hybridoma technology (see points 10.6 to 10.8 of decision Bayer II).

- The signatory of declaration ID73 in points 40 to 46 comes to the conclusion that "using the information in the patent it would not be possible for the skilled man to make a neutralizing, high affinity anti-TNF-α antibody."

30. The explanation why the Köhler-and-Milstein hybridoma technology would not be suited to preparing high-affinity antibodies to TNF is convincing to the board. In normal healthy individuals the only high-affinity antibodies are antibodies against foreign (non-self) antigens. High-affinity, neutralizing antibodies against self-antigens would cause an autoimmune disease (see also point 43 of document ID73). Accordingly, human peripheral blood cells from a normal healthy individual cannot provide a route to high-affinity, neutralising antibodies to TNF (see also points 41 to 45 of document ID73).

31. Thus, in the light of the evidence summarized above, the board is convinced that the method disclosed in the patent, even if combined with common general knowledge relating to this method, does not enable the skilled person to produce antibodies binding with high affinity to soluble TNF.

32. The appellant argues that the disclosure of a method for preparing human monoclonal antibodies and one specific example of a human monoclonal antibody produced by the method is sufficient to illustrate to the skilled person how to carry out the invention which, in the appellant's view, are human monoclonal antibodies binding to TNF. In other words, it would not matter for the assessment of sufficiency of disclosure if high-affinity human monoclonal antibodies binding to TNF could not be made according to the method disclosed in the patent, because at least one example of a human monoclonal antibody binding to TNF and produced according to the method of the patent is disclosed in the patent.

33. Article 83 EPC stipulates that the patent shall disclose the invention in a manner sufficiently clear for it to be carried out by a person skilled in the art. However, the term "invention" in Article 83 EPC does not allude to what may be perceived as the invention from the contents of the specification or to what may be considered as the contribution to the art. Rather, it denotes the subject-matter of a particular claim (see for example decision T 792/00, point 2, first sentence). Thus, the assessment of the sufficiency of disclosure must be made in relation to the whole of the subject-matter of a claim - which is in the present case a pharmaceutical composition containing human monoclonal antibodies binding with any affinity to one of the known forms of TNF (see point 25 above).

34. The appellant relies on decision T 431/96.

Decision T 431/96 in the point referred to by the appellant (point 6) says that hybridoma technique is a routine technique and that all that is normally called for, if monoclonal antibodies are to be produced in that way, is perseverance. However, this is not true for the specific case of human monoclonal antibodies binding with high affinity to soluble TNF. The evidence cited above shows that in this case perseverance would not be sufficient to provide high-affinity human monoclonal antibodies against TNF.

35. The appellant furthermore relies on decisions T 292/85, T 361/87 and T 36/00.

36. In decision T 36/00 the board held that, if the subject-matter of a claim can be made to work in numerous ways, it is not required for the acknowledgement of sufficiency of disclosure that the claims be limited to exclude certain only hypothetically conceivable other embodiments which might also fall under the claims.

37. The underlying situation in decision T 292/85 was that a claim due to functional language related to "future" components, i.e. to subject-matter not available at the priority date. The board states in paragraph 3.1.5 of the decision:

"Consequently any non-availability at the priority date of some particular variants of functionally defined component features of the invention had no effect on the sufficiency of disclosure because suitable variants are known to the skilled person through the disclosure or common general knowledge which provide the same effect for the invention."

38. Decision T 361/87 relates to a similar situation. It was decided that the non-availability of some particularly effective strains in a class of micro-organisms is immaterial as long as other suitable strains are available to the skilled person.

39. In the board's view, these decisions are only comparable with the situation in the present case insofar as the claims extend to embodiments not available at the priority date.

40. However, as already emphasized by decision G 1/03 of the Enlarged Board of Appeal, if a claim comprises "non-working" embodiments this may have different consequences with regard to the fulfilment of the requirements of Article 83 EPC, depending on the circumstances (see point 2.5 of the reasons).

41. There may be situations where the specification contains sufficient information on the relevant criteria for finding appropriate alternatives ("variants") over the claimed range with reasonable effort. Under these circumstances the non-availability of certain variants encompassed by the claim at the priority date is considered immaterial for the sufficiency of disclosure.

42. However, in contrast to these situations, in the present case a whole class of compounds falling under the terms of claim 1 cannot be produced on the basis of the teaching in the patent. Moreover, this lack of availability concerns the very class for which a pharmaceutical use was obvious to the skilled person (see decision Bayer II) and the production of which was therefore particularly aimed at by the scientific community (see point 22 above).

43. Thus, none of the decisions relied on by the appellant fits the present situation and therefore none of them helps the appellant's case.

44. The board concludes that the disclosure in the disputed patent does not enable the skilled person to carry out the claimed invention over the whole scope of claim 1. Consequently, the main request does not fulfil the requirements of Article 83 EPC.

Admission of auxiliary requests 1 to 3

45. Auxiliary requests 1 to 3 were filed as auxiliary requests 2, 4 and 6 (in that order) two months before the oral proceedings and were rearranged to become auxiliary requests 1 to 3 at the oral proceedings in reaction to the board's decision on Article 83 EPC with respect to the main request.

46. According to Article 13(1) of the Rules of Procedure of the Boards of Appeal, "any amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at the Board's discretion."

Different criteria are looked at by the boards when deciding about the admission of late-filed material, such as the degree of lateness, the complexity of the issues raised by the amendments or whether or not they are caused by developments during the proceedings or whether or not they constitute a serious attempt to overcome objections (see Case Law of the Boards of Appeal, 5th edition 2006, VII.D.14.2).

47. On weighing these criteria in the light of the circumstances of the present case the board comes to the following conclusion.

48. As already noted in point 4 above, opposition proceedings in the present case started in May 2002 and were followed by appeal proceedings starting in April 2005. The present auxiliary requests 1 to 3 were only filed shortly before and rearranged only at the second oral proceedings held in December 2009. Moreover, they are placed before the auxiliary request already admitted at the first oral proceedings (see section II above). Thus, in particular when considering the history of the present case, it is a very late point in time during the proceedings at which the respondents are informed about the appellant's fall-back positions. Moreover, the amended claims are such that the board could not exclude that numerous new objections would be put forward against them. This could have led to an even further prolongation of the whole proceedings.

49. Thus, in view of the circumstances in the present case, the board decides not to admit auxiliary requests 1 to 3 into the proceedings.

Auxiliary request 4

50. Auxiliary request 4 is identical to the request already admitted by the board (see section II above). Therefore, its admission is not an issue.

Article 84 EPC

51. Article 84 EPC is not a ground of opposition. Therefore, the requirements of Article 84 EPC in relation to amended claims are assessed only insofar as modifications with regard to the claims as granted are concerned.

Clarity

52. Compared with the main request (which fulfils the requirements of Article 84 EPC, see point 5 of decision Bayer I), claim 1 of auxiliary request 4 includes the additional feature "is capable of inhibiting LPS-induced human tumour necrosis factor alpha secretion by human monocyte cells", a feature that is based on a feature present in claim 11 as granted.

Claim 11 as granted reads: "Use of the antibodies of claim 1 for the preparation of a pharmaceutical which inhibits LPS-induced TNF alpha secretion by human monocytelike cells."

Although claim 11 as granted is directed to a use, it relates de facto to the preparation of a "pharmaceutical", i.e. a pharmaceutical composition, which inhibits LPS-induced TNF alpha secretion by human monocytelike cells.

Present claim 1 is directed to "[a] pharmaceutical composition containing a human monoclonal antibody that binds to human necrosis factor alpha and is capable of inhibiting LPS-induced human tumour necrosis factor alpha secretion by human monocyte cells".

53. Thus, both claims define a pharmaceutical composition. In claim 1 it is defined per se, whereas in claim 11 it is defined as the result of a preparation-process. No new objection of lack of clarity arises when a feature defining a pharmaceutical composition in a claim to this composition is derived from the definition of the same pharmaceutical composition in a claim to a use of

compounds for the preparation of this pharmaceutical composition.

54. Had the feature in claim 1 been taken over word-for-word from granted claim 11, further objections under Article 84 EPC would not have arisen (see point 51 above). However, the definition of the pharmaceutical composition in claim 1 differs from that in granted claim 11 in that in present claim 1 the antibody in the composition is defined as being "**capable of inhibiting** LPS-induced human tumour necrosis factor alpha secretion" whereas according to claim 11 it "**inhibits** LPS-induced human tumour necrosis factor alpha secretion". Moreover, the secretion is from "**monocyte** cells" according to claim 1 and from "**monocytelike** cells" according to granted claim 11.

The further assessment of the requirement of Article 84 EPC is limited to these two differences (see point 51 above).

55. The term "monocyte cells" was well-known at the priority date of the patent. The skilled person would understand it to refer as well to primary monocytes, i.e. those isolated from the body, as to monocyte cells from an established cell line. No other meaning is given to the term in the patent.

Hence the skilled person would unambiguously understand the meaning of the term as such. It is also clear to the person skilled in the art what the secretion of TNF by monocyte cells means.

56. Insofar as the feature newly added to claim 1, i.e. the feature "is capable of inhibiting LPS-induced human tumour necrosis factor alpha secretion by human monocyte cells", alludes to the assay described in the patent for testing for the property of the human monoclonal antibody, the skilled person would have no doubt in the light of the well-known meaning of the term "monocyte cells" that this capability can be tested either with primary monocyte cells or with monocyte cells from a cell line. Thus, all antibodies giving a positive reaction when tested for inhibition of TNF-secretion with either of the two monocytic cell types fall under claim 1. Hence, no doubt as to the matter for which protection is sought arises.

57. Thus, the term "monocyte cells" in claim 1 does not lack clarity.

58. As to the term "capable of inhibiting", the skilled person would understand it to mean that the antibody according to claim 1 has to have the capacity of inhibiting LPS-induced TNF secretion by human monocyte cells.

59. By using the expression "capable of inhibiting" it is not excluded that the antibody thus-defined has additional properties. However, as far as the pharmaceutical application of the composition of claim 1 is concerned, the skilled person would construe the claim such that the capability of the composition to inhibit TNF secretion by human monocyte cells is the property on which the therapeutic use of the composition relies. This would be so, in the board's view, because it is the only property specifically

mentioned in the claim and disclosed in the specification of the patent in dispute (see also points 98 and 99 below). Thus, also in this respect the claims are not ambiguous.

60. The respondents submit that the assay disclosed in the patent for testing for the functional feature "capable of inhibiting LPS-induced human tumour necrosis factor alpha secretion by human monocyte cells" cannot discriminate whether or not a high-affinity, neutralizing anti-soluble TNF antibody inhibited TNF in the assay by binding to TNF on the cell surface or by binding to TNF in the supernatant. Therefore, since there is no way to determine whether a high-affinity, neutralizing anti-soluble TNF antibody falls under the claim, the matter for which protection is sought is not clear.

However, this argument is not related to a lack of clarity resulting from a modification of the claim when compared to the claims as granted. Rather it could be applied in the same way to claim 11 as granted. Therefore, the argument fails in the context of Article 84 EPC (see point 51 above). This issue can therefore only be dealt with in the context of Article 83 EPC (see point 88 below).

Support

61. The provision according to Article 84 EPC that the claims must be supported by the description is to ensure that the description and claims relate to the same invention.

62. The invention defined in claim 1 relates to a product, i.e. a pharmaceutical composition containing a human monoclonal antibody that binds to human TNF and is capable of inhibiting LPS-induced TNF secretion by human monocyte cells.

The description provides a method for preparing human monoclonal antibodies (paragraph [0036]). It is disclosed that antibodies of the IgG and IgM idiotype were prepared by the method (paragraph [0009]). The effect stated in the claim and an assay for determining it are disclosed (paragraphs [0088] and [0089]). The effect is presented as having functional significance (paragraphs [0088] and [0089]) and is therefore one on which a pharmaceutical application can be based.

Consequently, the disclosures in the description and in the claims, in particular in claim 2 with respect to IgG antibodies, are in harmony.

63. The effect stated in the claim is exemplified in the patent only for one specific antibody, the antibody B5. The skilled person would however not perceive that this is by way of limitation, but rather that it is by way of example. Since claims are almost always generalisations of specific examples, this does not give rise to an imbalance between the claims and description.

64. The respondents further argue that claim 1 lacks support because the test disclosed in the patent revealing the activity recited in claim 1 "is capable of inhibiting LPS-induced human tumour necrosis factor alpha secretion by human monocyte cells" has not been

performed with monocyte cells, but with THP-1 cells which are progenitors to monocyte cells.

65. The board is not convinced. THP-1 is denoted to be a human monocyte cell line at several instances in the patent, for example in paragraphs [0058], [0060], [0088] and in Tables 2 and 3, and the respondents have not submitted evidence for the submission that the THP-1 cell line is not a monocyte cell line.

66. The board does not agree with the respondents for a second reason. Even if it was assumed that the assay in the patent for the inhibition of the LPS-induced secretion of TNF had been carried out with non-monocyte cells and thus would not reflect the feature in claim 1, the disclosure of the assay with non-monocyte cells would already enable the skilled person to carry it out in an adapted manner with monocyte cells so as to match the feature of the claim, i.e. the skilled person would easily replace the THP-1 cells with "real" monocyte cells. Thus, even if the feature in claim 1 were not met by the specific disclosure in the patent, this would not have the consequence that the feature in the claim could not be implemented and therefore, also for this reason, there would be no lack of support.

67. Thus, the board concludes that the requirements of Article 84 EPC are fulfilled.

Article 123(2) EPC

68. A pharmaceutical composition containing a human monoclonal antibody that binds to TNF has a basis in claim 1 of the application as filed in combination with

the description as a whole (see decision Bayer I, points 3 to 3.4).

69. Antibodies characterized by the additional feature that they are "capable of inhibiting LPS-induced human tumour necrosis factor alpha secretion by human monocyte cells" are derivable from the application as a whole, in particular pages 35 and 36, for the reasons given in points 61 and 62 above, the contents of the application as filed and the patent being identical in this respect.

70. The respondents argue that claim 1 does not comply with the requirement of Article 123(2) EPC because the feature that secretion is inhibited by the binding of the antibody to TNF **on the cell surface**, which is a feature essential to the invention, is absent from claim 1.

71. It is known that TNF occurs in three forms, i.e. as a non-cell-surface-bound "soluble" form and as two different cell-surface-located forms, i.e. either as a transmembrane protein or as a form bound to its receptor. The transmembrane protein is released as soluble TNF by proteolytic cleavage (see also point 22 above).

72. In claim 1 reference is made to "inhibiting [...] human tumor necrosis factor alpha secretion by human monocyte cells". An antibody cannot have this property if it is bound to the soluble form of TNF. Thus, the only sensible interpretation of this feature in claim 1 is that the release of TNF from the membrane or its receptor (see paragraphs [0098] and [0100] of the

patent) is inhibited via binding of the antibody to TNF on the surface of the cell. As a consequence of this binding, the generation of soluble TNF is prevented. Hence, in the board's view, the target of the binding of the monoclonal antibody according to claim 1, i.e. cell-surface TNF, is an implicit feature of this claim. Thus, the literal absence from the claim of the feature that the inhibition of secretion of TNF occurs via binding to TNF on the cell surface does not add matter, since, on proper interpretation, the expression "inhibiting [...] human tumor necrosis factor alpha secretion by human monocyte cells" in claim 1 requires that the antibody binds to the cell-surface-located form of TNF.

73. Dependent claims 2 to 4 have a basis in claims 2, 4 and 7 as filed.

74. The requirements of Article 123(2) EPC are fulfilled.

Article 123(3) EPC

75. The extent of protection conferred by a European patent is determined by the content of all its claims. Thus, in order to asses whether or not the scope of protection is extended by an amendment, the protection conferred by the totality of the claims before the amendment is compared with the totality of the claims after amendment or more simply, the claims with the broadest protection are compared.

76. Among the claims as granted claim 1 is the claim with the broadest scope. It is directed to "[a] composition

comprising human monoclonal antibodies that bind to human tumour necrosis factor alpha".

The board has already stated in point 4 of decision Bayer I that this claim is to be interpreted as relating to compositions suited for any use.

77. The set of claims of the present auxiliary request, auxiliary request 4, consists of four claims, one independent and three claims dependent thereon (see section XV above). Claim 1, the claim with the broadest scope, relates to "[a] pharmaceutical composition containing a human monoclonal antibody that binds to human necrosis factor alpha and is capable of inhibiting LPS-induced human tumour necrosis factor alpha secretion by human monocyte cells."

Thus, this claim 1 is limited with regard to claim 1 as granted insofar as it is restricted to those compositions that are pharmaceutically useful and which moreover contain antibodies which are "capable of inhibiting LPS-induced human tumour necrosis factor alpha secretion by human monocyte cells".

78. The respondents maintain that claim 1 is in breach of Article 123(3) EPC. In contrast to claim 11 as granted, which requires that the antibody "inhibits", present claim 1 requires only that the antibody must be "**capable** of inhibiting". In the respondents' view, the latter definition does not establish the mandatory requirement that this capacity is the one used to achieve the pharmaceutical effect. Therefore, any other property of an antibody falling under the definition in present claim 1 could be exploited for treatment.

79. The board is not convinced of this argument for two reasons. Firstly, the board has concluded that the feature "capable of inhibiting" in the context of the claims characterizes the very effect relied on for therapeutic application (see point 59 above). Secondly, even if, for the sake of argument, it is assumed that there is a difference in meaning, the respondents' comparison is made between present claim 1 and claim 11 as granted, which latter claim is a claim to a use and therefore narrower than claim 1 as granted, which relates to a product. Hence, the basis for comparison is not correct.

80. Thus, the board concludes that the protection conferred by the amended claims of auxiliary request 4 is not extended vis-à-vis the claims as granted. The requirements of Article 123(3) EPC are fulfilled.

Article 83 EPC

81. The antibody contained in the composition according to claim 1 differs from the antibody of claim 1 of the main request in that it is additionally defined as being "capable of inhibiting LPS-induced human tumor necrosis factor alpha secretion by human monocyte cells".

82. The respondents argue that it could be seen from document ID97 that neutralizing antibodies binding to soluble TNF with high affinity also could have the capability of binding to cell-membrane located TNF. The respondents maintain that, consequently, claim 1 of auxiliary request 4 covers also these antibodies, i.e.

antibodies for which an enabling disclosure is lacking in the patent in suit (see points 21 to 43 above). Therefore, the respondents conclude that the disclosure in the patent with regard to claim 1 of auxiliary request 4 lacks sufficiency for the reasons given with regard to the main request.

83. Since this objection under Article 83 EPC is put forward by the respondents, it is for them to provide convincing evidence that an antibody binding with high affinity to soluble TNF and thereby neutralizing its activity is capable of inhibiting LPS-induced TNF secretion by human monocyte cells.

84. Document ID97, on which the respondents rely, discloses an assay wherein binding of high-affinity neutralizing anti-soluble TNF antibodies to membrane TNF on **transfected** cells is tested (see page 310, first column, last paragraph). This system involves the use of a cell line expressing a mutant form of human TNF that is non-cleavable by TACE (= TNF alpha converting enzyme, see document ID97, "Abbreviations"). Cleavage of TNF by TACE is the prerequisite for forming soluble, i.e. secreted, TNF (see ID74, point 16). Thus, since TNF cannot be released from the membrane, it is not possible with this assay of document ID97 to detect the secretion of TNF or the inhibition of it.

85. In a further assay disclosed in document ID97, high-affinity neutralizing anti-soluble TNF antibodies are tested for their binding to native membrane TNF on peripheral blood monocyte cells by incubating the cells with iodine-labelled TNF antibody (see page 310, second column, first full paragraph). The anti-TNF antibody

molecules bound per cell were determined. Thus, this assay too does not detect the secretion or non-secretion of TNF from the membrane.

86. The board furthermore notes that, in the context of a different objection under Article 83 EPC (see above section XVI and below point 87), the respondents have called into question the discriminatory power of the assay described in the patent for determining the capability of an antibody to inhibit TNF secretion. In particular they have argued that the assay fails to discriminate whether a high affinity neutralizing anti-soluble TNF antibody neutralizes TNF in the supernatant or inhibits the release of TNF from the membrane.

87. In the light of the evidence on file and the arguments made by the respondents as summarized in points 81 to 85 above, the board is not convinced that antibodies binding with high affinity to soluble TNF are capable of inhibiting LPS-induced TNF secretion by human monocyte cells. The board cannot therefore come to the conclusion that pharmaceutical compositions containing such antibodies are encompassed by claim 1. Thus, the respondents' argument fails.

88. As a further objection under Article 83 EPC the respondents maintain that the critical functional feature in claim 1, i.e. the capability of inhibiting LPS-induced TNF secretion by human monocyte cells, cannot be properly determined. In particular, they argue that the only assay available at the priority date and described in the patent for determining this feature is not suited to detecting whether a high-affinity soluble TNF-neutralizing antibody is capable

of inhibiting LPS-induced human TNF secretion by human monocyte cells. According to decision T 611/02 this would have the consequence that the invention is not disclosed in a manner sufficiently clear and complete for it to be carried out (see points 3 and 6 of the reasons).

89. However, the board considers that the patent provides a method suited to establishing whether or not a human monoclonal TNF-binding antibody produced by the technique described in the patent fulfils the functional requirement of claim 1 here at issue. The fact that the patent does not disclose a test system for determining whether or not other antibodies, which at the priority date of the patent were not at the skilled person's disposition, might also fulfil this requirement is not a basis for a successful objection under Article 83 EPC.

Evidence for pharmaceutical effect

90. The boards of appeal of the EPO consistently consider that, where a therapeutic application is claimed - be it in the form of a first or further medical use - this has the consequence under Article 83 EPC, that, unless this is already known to the skilled person at the priority date, the patent application or the patent must disclose the suitability of the product for the claimed therapeutic application (decision T 609/02, point 9 in relation to a claim to a second medical use; decision T 219/01, point 4, in relation to a first medical use).

91. For a sufficient disclosure of a therapeutic application it is required according to the case law that the patent provides some information in the form of, for example, experimental tests, to show that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se. Showing a pharmaceutical effect in vitro may be sufficient, if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application (decision T 609/02, point 9).

92. Claim 1 is directed to a pharmaceutical composition. Thus, the pharmaceutical effect of the composition is a feature of claim 1 and consequently the question of appropriate evidence for the pharmaceutical effect in the patent arises in the context of the evaluation of Article 83 EPC.

93. The patent discloses in paragraphs [0088] and [0089] and in the related Table 10 that the antibody B5 can inhibit secretion of membrane-bound TNF, thereby reducing the biologically active soluble form of TNF. For the board this evidence points to a potential use of the claimed composition as a pharmaceutical (see also decision Bayer II, points 5.3 to 5.9 and 7).

94. The respondents challenge this evidence in numerous ways. As to the standard of proof required to convince the board that the patent does not disclose the suitability of the claimed product for the claimed therapeutic application, the board adheres to the well-

established principle that serious doubts must be substantiated by verifiable facts.

95. The respondents doubt the reliability of the data obtained with the assay disclosed in paragraphs [0088] and [0089]. It is submitted that the experimental setup, in particular the lack of appropriate controls, was such that it is not demonstrated by the results that the inhibition of secretion is indeed generated by interaction of the antibody B5 with TNF. For example, one possible explanation of the data in Table 10 is that cell death was caused because the antibody itself was cytotoxic. Moreover it was possible that the antibody B5 affected secretion of other cytotoxic cytokines and not that of TNF. Finally, the diminished TNF-production could also be the result of LPS contamination.

96. Thus, in other words, the respondents' objection is that it is not certain that the effect seen in the assay of the patent is in fact due to interaction with TNF or that the antibody B5 is responsible for the effect.

However, in the board's view, the results of the experiments described in paragraphs [0088] and [0089] of the patent are prima facie evidence that the antibody B5 has an activity that is linked to the functional activity of TNF and therefore is potentially useful for therapeutic purposes (see above point 93). Moreover, there is at least one negative control, i.e. TNF secretion is determined in the absence of antibody B5. When the same experiment is made with concentrations of 5 to 40 µg/ml of antibody B5, the

detectable amount of TNF in the supernatant is reduced by up to 93%.

97. In order to convince the board, this prima facie evidence of an inhibitory activity of the antibody B5 could be rebutted by appropriate experimental data (see point 94 above). Since no such experimental data have been provided by the respondents in due time, no evidence in this respect is at the board's disposition. Thus, the respondents have not proven their allegation that it is uncertain that the inhibitory effect seen in the assay according to the patent is in fact due to interaction with TNF or that B5 is responsible for the effect. Therefore, these allegations are considered as theoretical assumptions and consequently this argument does not convince the board.

98. The respondents further argue that the induction of TNF by lipopolysaccharide (LPS) is an event that in vivo does not occur in the context of inflammatory disease, but only in the context of sepsis. Therefore, the assay disclosed in paragraphs [0088] and [0089] of the patent has to be seen as a model for the treatment of sepsis. The membrane-binding properties of an anti-TNF antibody would however not be useful in the successful treatment of sepsis because, once symptoms of sepsis are apparent in a patient, an excess of TNF is already circulating in the body. Thus, for the treatment of sepsis, removal of soluble TNF rather than inhibition of secretion of TNF from the membrane would be necessary. Therefore, the patent does not disclose any disease which could be treated on the basis of the effect revealed in Table 10 of the patent. Thus, the patent lacks evidence for therapeutic usefulness also for that reason.

99. The board does not follow this argument. Although it may not be as frequently used as phorbolmyristate acetate, LPS is one of the agents for the experimental induction of TNF. It is stated in the patent in paragraph [0065] that "LPS is a commonly used agent to induce TNFα secretion by human monocytes". Thus, its use in the assay disclosed in paragraphs [0088] and [0089] of the patent in dispute cannot be understood as a hint that the claimed composition is to be used for the treatment of sepsis only.

100. The respondents have put forward several reasons as to why the antibody B5, the only extensively characterized antibody of the patent, would not be considered as useful for a therapeutic application.

101. A first thing to note with regard to these objections is that generally examples are not a mandatory requirement in a patent. Also, the pharmaceutical usefulness of an agent may be prima facie evident in the light of common general knowledge. It is stated in decision T 609/02, point 9, second sentence: "As a consequence, under Article 83 EPC, **unless this is already known to the skilled person at the priority date**, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application". However, the board will assume in favour of the respondents that this is a case where an example is necessary to illustrate the claimed invention for the purposes of Article 83 EPC.

102. The main reasons submitted for the lack of a pharmaceutical usefulness of the antibody B5 are:

(a) B5 is not a "fully" human antibody;

(b) B5 lacks specific binding activity due to its low affinity to soluble TNF;

(c) B5 is an IgM antibody and could therefore not arrive at the place in the body where it is needed in the context of a TNF-related disorder;

(d) B5 is not mono-specific for TNF, but binds to antigens other than TNF or sticks unspecifically to the cell surface;

(e) B5 binds to unstimulated B and T cells, thus provoking unwanted immune reactions;

(f) B5 inhibits secretion of TNF insufficiently, thus leaving high concentrations of TNF in the patient;

(g) B5 inhibits TNF-secretion ineffectively, necessitating the application of high concentrations of it to the patient;

(h) B5 has a short half-life, thus requiring repeated applications;

(i) B5 does not bind to TNF at all.

103. In the board's view, these reasons for not acknowledging a pharmaceutical usefulness of the antibody B5 can be grouped into three main categories:

A) B5 is pharmaceutically ineffective;

B) B5 cannot be used as a pharmaceutical, since its target is not known;

C) B5 would have side-effects or pose difficulties in handling if it was used as a pharmaceutical.

Category A

104. The board is not convinced about the submission in this respect, in view of the experiments reported in sections [0088] and [0089] of the patent under dispute (see points 92 and 95 above). In short, these experiments provide prima facie evidence for a pharmaceutical usefulness of the antibody B5 that has not been challenged successfully by the respondents.

Category B

105. Failure to bind to TNF at all, with the consequence that no binding partner for the antibody B5 would be known, would certainly cast serious doubts on the therapeutic usefulness of the antibody B5. However, since verifiable evidence has not been submitted in due time and is therefore not at the board's disposition, this statement is an allegation and therefore does not convince the board. The board notes moreover that this argument is in direct contradiction with the argument that the antibody B5 binds in addition to TNF also to a further antigen (see point 102(d) above).

Category C

106. None of the arguments falling in this category has been substantiated by verifiable facts, i.e. it has not been determined whether any of the assumed effects in fact occur. Thus, also these arguments must be seen as unsupported assumptions and for that reason do not convince the board.

107. However, even if some or all of the alleged side-effects actually occurred, the board considers, firstly, that the occurrence of side-effects as such is not a reason for excluding the pharmaceutical use of a compound. Most, if not all, medicaments approved for a therapeutic use have side-effects.

108. Moreover, none of the effects is of such a quality as to prima facie preclude a pharmaceutical use of the B5 antibody. For example, even a highly toxic compound such as Botulinum toxin is an approved medicament for certain indications. Moreover, if a compound is the only one for treating a serious disease, it is likely that even the application of a high concentrations of that compound or its frequent application would be accepted.

109. In this context it is also noted that the balancing of the incidence and severity of side-effects of a particular compound in the treatment of a disease against its medical benefit is not an exercise which is carried out when patentability of this particular compound is at stake. Rather this is the task of national or international authorities granting market authorizations for pharmaceutical products. In the

framework of patent law when determining sufficiency of disclosure of a compound for medical use, it is sufficient to demonstrate that the compound has an activity in a suitable test system on the basis of which it may be considered as potentially useful for treatment (see points 90 and 91 above).

110. In summary, the board is not convinced by any of the respondents' arguments regarding the absence in the disclosure of the patent of the suitability of the composition according to claim 1 for a therapeutic application.

111. Thus, the board concludes that the requirements of Article 83 EPC are fulfilled.

Articles 54 and 56 EPC

112. The board found in decisions Bayer I and II that claim 1 of the main request, which is broader in scope than claim 1 of auxiliary request 4, fulfilled the requirements of Articles 54 and 56 EPC.

113. Novelty of the subject-matter of claims 1 to 4 of auxiliary request 4 was not called into question by the respondents anymore. The board too has no objection.

Thus, the subject-matter of claims 1 to 4 is considered as novel.

114. No arguments were presented anymore by the respondents against an inventive step of the subject-matter of the claims of auxiliary request 4.

The board observes that the subject-matter of claims 1 to 4 as far as it relates to low-affinity antibodies involves an inventive step for the reasons given in points 2 to 7, 10.9, first and second sentences, and 10.10 of decision Bayer II. In summary, at the priority date of the patent under dispute the pharmaceutical use of antibodies binding with low affinity to soluble TNF for the reason stated in the patent, i.e. because they are "capable of inhibiting LPS-induced human tumour necrosis factor alpha secretion by human monocyte cells", was not obvious.

In view of the reasons summarized in points 81 to 89 above there is in the context of auxiliary request 4 no need for the board to assess the requirement of inventive step for high-affinity antibodies to soluble TNF.

115. The requirements of Articles 54 and 56 EPC are fulfilled.

Article 57 EPC

116. The board has established in points 92 to 110 above that the patent discloses an effect which is exploitable for therapeutic use.

Therefore, the respondents' argument that the invention is not susceptible of industrial application is not tenable.

117. The requirements of Article 57 EPC are fulfilled.

Further matters

Article 113(1) EPC

118. Respondent II objects that its right to be heard has been violated by the non-admission of the experimental data contained in documents ID73 to ID81.

119. A party's right to be heard is limited by the provisions of Article 114(2) EPC allowing a board to disregard evidence not filed in due time.

The board arrived at the decision not to admit the experimental data contained in documents ID73 to ID81 by applying criteria established by the case law, in particular in relation to late-filed experimental evidence (see points 13 to 15, 17 above).

120. Thus, the board concludes that respondent II's right to be heard has not been violated by the non-admission of the experimental data contained in documents ID73 to ID81.

121. Both respondents object that their right to be heard has been violated by a limitation of the time to make their final submissions with regard to the pharmaceutical usefulness of the antibody B5 on the evening of the second day of the oral proceedings held on 1 and 2 December 2009 (see sections XI and XII above).

122. Article 116 EPC gives the parties a right to be heard at oral proceedings. However, the time to be heard at

oral proceedings is inevitably limited by the amount of time set by the board for oral proceedings.

123. In the present case, two days were foreseen for the oral hearing. This was communicated to the parties and not objected to by them. Knowing this time frame, it is in the board's view, on the one hand, the parties' attorneys' responsibility to structure their pleadings in such a way that the given time frame can be complied with.

124. On the other hand, it is the board's responsibility to conduct oral proceedings in such a way that the time frame is kept. For example, Article 15(6) of the Rules of Procedure of the Boards of Appeal states that the board shall ensure that each case is ready for decision at the end of oral proceedings, and their Article 15(4) states that the chairman presides over the oral proceedings. It follows from these provisions that the structuring of the oral proceedings is within the discretion of the board.

125. On the evening of the second day of the oral proceedings, in the context of the evaluation of the requirements of Article 83 EPC for auxiliary request 4, each party had altogether around thirty-five to forty minutes to plead in two consecutive rounds of presentation on the issue of whether or not the patent provided evidence for a pharmaceutical effect of the claimed pharmaceutical composition (see sections XI and XII above). Given that this was not a fresh issue, but had already been presented in detail in the written submissions, the board considers that this amount of time was as such sufficient for a skilled attorney to

properly present her or his arguments, even if they may be complex.

126. Thus, in the board's view, the limitation of the time to speak was a necessary procedural measure by which the respondents' right to be heard pursuant to Article 113(1) EPC in general and in particular its right to be heard at oral proceedings pursuant to Article 116 EPC had not been violated.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of the following documents:

   Claims: 1 to 4 of auxiliary request 4 filed at the oral proceedings.

   Description: page 3 filed at the oral proceedings; pages 4 to 18 of the patent specification.

   Figures: 1 to 12 of the patent specification.

The Registrar: The Chairman:

P. Cremona M. Wieser