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D E C I S I O N
of 28 July 1994

Case Number: T 0296/93 - 3.3.4

Application Number: 85201908.2

Publication Number: 0182442

IPC: C12N 15/51

Language of the proceedings: EN

Title of invention:

Recombinant DNA molecules and their method of production

Patentee:

BIOGEN. INC.

Opponent:

- (01) INTERNATIONAL MUREX TECHNOLOGIES CORPORATION
(02) Institut Pasteur Etablissement public
(03) IMMUNO Aktiengesellschaft
(04) Hexal-Biotech GmbH

Intervener: Medeva PLC

Headword:

HBV antigen production/BIOGEN INC

Relevant legal norms:

EPC Art. 56, 87, 105(1)

Keyword:

"Admissibility of intervention of assumed infringer (no) - too late"

"Entitlement to priority (yes) - same invention"

"Citability of prior art document (no)"

"Novelty (yes)"

"Inventive step (yes)"

"Enlarged Board - referral (no)"

Decisions cited:

T 0301/87, T 0081/87, T 0073/88, T 0500/91, T 0886/91,
T 0292/85, T 0595/90, G 0004/91, G 0001/94, T 0381/87

Headnote

The applicable starting point for calculating the three month period for intervention under Article 105(1) EPC is always the date of the institution of the first court action. Where a court action for infringement was first brought by a patentee against an alleged infringer, Article 105(1) EPC first sentence applies, even though the latter later instituted a court action seeking a declaration of non-infringement under Article 105(1) EPC second sentence, with regard to the same patent.



Case Number: T 0296/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 28 July 1994

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Decision under appeal: Decision of the Opposition Division of the
European Patent Office dated 21 January 1993
revoking European patent No. 0 182 442 pursuant to
Article 102(1) EPC.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: L. Galligani
E. M. C. Holtz

Summary of Facts and Submissions

I. European patent No. 0 182 442 was granted for ten Contracting States with 26 claims and for Austria with 13 claims based on the European patent application No. 85 201 908.2 which was a divisional application of the European patent application No. 79 303 017.2 filed on 21 December 1979. The priority of three earlier GB applications was claimed, namely of 22 December 1978, 27 December 1978 and 1 November 1979 (hereinafter referred to as BI, BII and BIII, respectively).

II. Notices of opposition were filed against the European patent by four parties (hereinafter referred to as Opponents 1 to 4).

Revocation of the patent was requested on the grounds of Article 100(a) to (c) EPC. During the procedure before the Opposition Division, documents (1) to (54) were relied upon by the parties. Among them the following are of particular relevance for the purpose of this decision (the numbering used in the decision by the Opposition Division is adhered to):

- (1) Proc.Natl.Acad.Sci. USA, Vol. 74, No.4, 1977, pages 1530 to 1534;
- (3) C.R.Acad.Sc.Paris, Ser D, Vol.287, 18 December 1978, pages 1453 to 1456;
- (8) Proc.Natl.Acad.Sci.USA (1978), Vol.75, No.8, pages 3727 to 3731.
- (16) Ann.Rev.Microbiol., Vol.31, 1977, pages 357 to 377;
- (20) EP-A-0 020 251;
- (23) J.Virol., Vol.23, No.2, 1977, pages 368 to 376.

As for the documents quoted - for historical reasons - in this summary whose reference is not reported above, reference is made to the file.

The following abbreviations are used throughout the present decision:

HBV: Hepatitis B virus
HBsAg: Hepatitis B surface antigen
HBcAg: Hepatitis B core antigen
NCIB: National Collection of Industrial Bacteria

III. At the end of oral proceedings held on 28 October 1992 the Opposition Division announced its decision to revoke the European patent pursuant to Article 102(1) EPC, on the grounds of lack of inventive step over the prior art as of the date of filing of BI and lack of novelty and inventive step over the prior art as of the date of filing of BIII. The reasoned decision was dispatched on 21 January 1993.

Claim 1 in the version for all designated Contracting States except Austria (non-AT) was as follows:

"A recombinant DNA molecule characterized by a DNA sequence coding for a polypeptide or a fragment thereof displaying HBV antigen specificity, said DNA sequence being operatively linked to an expression control sequence in the recombinant DNA molecule and being expressed to produce a polypeptide displaying HBV antigen specificity when a suitable host cell transformed with said recombinant DNA molecule is cultured, the transformed host cell not producing any human serum proteins and any primate serum proteins other than the polypeptide displaying HBV antigen specificity."

Claims 2 to 7 concerned specific embodiments of the recombinant DNA molecule according to Claim 1, in particular Claims 3 and 5 related to HBcAg and Claims 4 and 6 to HBsAg.

Claims 8 to 26, which each referred back to one or more of the Claims 1 to 7, concerned transformed host cells, the polypeptide thereby produced, compositions for stimulating the production of antibodies to HBV, means and a method for detecting HBV infections in blood serum, and DNA sequences encoding HBV antigens.

The claims for Austria (AT) were formulated as corresponding process claims.

IV. The main reasons given in the decision for revoking the patent were as follows:

a) Claims 1 to 2 (non-AT) were entitled to the priority of BI.

Claims 3 to 7 (non-AT) were entitled to the priority of BIII.

As for the remaining claims they were entitled either to the BI or BIII priority date depending on the construction of their dependency.

b) None of the quoted documents affected the novelty of the claimed subject-matter which was entitled to the BI priority date.

As for the claims entitled to the BIII priority date, document (15) was considered to represent the state of the art because its contents extended over the contents of the BI priority document. Thus, there could not be protective effect under decision

T 301/87 (OJ EPO 1990, 335). Document (15) affected the novelty of Claim 3 (non-AT) under Article 54(1)(2) EPC.

The novelty of the claims 3 and 4 was affected under Article 54 (3)(4) EPC by document (20).

- c) The subject-matter of Claims 1 and 2 (non-AT) was obvious having regard to document (3) in combination with the general knowledge at the relevant priority date [see in particular document (8)].

The subject-matter of Claims 3 and 4 was obvious having regard to documents (4), (5) and (7).

The same arguments were applied by the Opposition Division *mutatis mutandis* for the set of claims for Austria.

- V. The Appellant (Patentee) lodged an appeal against the decision of the Opposition Division, and submitted its Statement of Grounds together with exhibits 1 to 9, including three auxiliary requests (exhibits 1 to 3).

- VI. The Respondents (Opponents 1 to 4 referred to hereinafter as Respondents I to IV, respectively) submitted a response to the appeal. Respondent IV submitted therewith attachments 1 to 8.

- VII. The Intervention by Medeva PLC:

- (a) Medeva PLC (hereinafter: Intervener) was served with a writ of summons on 1 July 1992 before a national court in the United Kingdom by which the Appellant requested the Intervener to cease alleged infringement of the European patent-in-suit.

- (b) On 30 September 1992, the Intervener filed a counterclaim against the Appellant, requesting from the court a declaration of non-infringement of said patent.
- (c) On 29 December 1992, i.e. after announcement of the Opposition Division's decision to revoke the present European patent (see section III, first paragraph, above), the Intervener filed a notice of intervention with the EPO.
- (d) The Formalities Officer of the Opposition Division issued a communication on 10 March 1993, indicating that the notice of intervention was admissible.
- (e) In a submission filed on 7 May 1993, the Appellant objected to the intervention, claiming that it was inadmissible because it had been filed more than three months after the Appellant had instituted United Kingdom infringement proceedings against the Intervener with regard to the same patent.
- (f) The Board of Appeal on 17 August 1993 issued its provisional opinion that the notice of intervention was inadmissible, having been filed out of time compared with the 1 July 1992 summons, given that the Intervener fell under the first of the two categories of time limits available under Article 105 EPC ("within three months of the date on which the infringement proceedings were instituted"). The time period for intervention, therefore, had expired on 1 October 1992.
- (g) In the ensuing proceedings, the Intervener argued essentially that it had instituted separate proceedings through their counterclaim. In its submissions, Article 105 EPC allowed for any third

party to intervene, who proves both that the patent proprietor has requested he cease the alleged infringement and that he has instituted proceedings for a court ruling that he is not infringing, two alternative means of intervention which were not mutually exclusive. As they had met the conditions of the second alternative, their intervention was admissible.

The Appellant responded that the argument by the Intervener would mean that the time limit would always be in the hands of the Intervener which would not be acceptable in procedural law.

VIII. By a letter dated 1 June 1994, Respondent IV and the Intervener filed an affirmation of Professor J.W.Almond.

By a letter received on 4 July 1994, the Appellant sent its observations to the replies of the Respondents together with exhibits 1 to 13, including a new main request and three amended auxiliary requests for the non-AT states (exhibits 2 to 5).

By a letter dated 12 July 1994, Respondent IV and the Intervener filed further observations together with attachments A to I.

By a letter received on 22 July 1994, Respondent II sent further observations together with annexes 1 to 3.

IX. Oral proceedings took place on 27 and 28 July 1994.

During oral proceedings, a new main request was filed in the two versions for non-AT States (Claims 1 to 23) and for AT (Claims 1 to 11). All auxiliary requests were withdrawn.

The said main request for non-AT States differed from the granted claims in that Claims 5 to 7 were deleted, the remaining claims renumbered and the claim dependencies changed correspondingly.

The set of claims for AT differed from the granted claims in that Claims 5 and 7 were deleted, the remaining claims renumbered and the claim dependencies changed correspondingly.

X. The Appellant argued essentially as follows:

a) The entitlement to priority

The disclosure of the BI priority document related to the production by recombinant DNA techniques of HBV antigens useful as a source of vaccine against HBV infection. This document provided the first demonstration of cloning and expression of fragments of the HBV genome with production of polypeptides displaying HBV antigen specificity and disclosed all the essential elements necessary for achieving this goal in respect of both the HBCAg and the HBsAg. The skilled person knew from the state of the art how to detect immunologically the core and surface antigen. The BI priority document taught the skilled person how to cleave appropriately HBV DNA with selected restriction enzymes (e.g. Kpn I, Bam HI) and insert the resulting fragments into a vector which could be used to transform a host microorganism so as to obtain production of polypeptides with HBV antigen specificity. The experimental approach which was disclosed was applicable to all HBV antigens. The overall technical information provided in the BI priority document was, therefore, sufficient to enable the skilled person to reduce the teaching to

practice across the claimed ambit. Evidence on file (see for example, the results reported in respect of the deposited strains; the witness statement of Professor K. Murray dated 6 September 1993 in the High Court of Justice, Chancery Division Patents Court, Biogen INC. vs. Medeva PLC - attachment 7 submitted by Respondent IV -, in particular item 94 and 95; document (41), in particular Figure 1 and Table 1) showed that by proceeding as taught in the application it was possible to produce polypeptides displaying both HBcAg or HBsAg antigen specificity. None of the Respondents had been able to show, for example, that the Bam HI fragment could not be used for HBsAg production. On the contrary, later patent applications by Institut Pasteur made use of a Bam HI fragment for preparing HBsAg.

Therefore, also in the light of decisions T 81/87 OJ EPO 1990, 250 and T 73/88 OJ EPO 1992, 557, the claimed matter was entitled to the BI priority date because all the essential elements of the claimed invention were disclosed in the BI priority document.

(b) The citability of document (3)

Document (3) was not prior art at the BI priority date because no oral presentation thereof was made at any public session of the Academy (see exhibit 8 submitted with the statements of grounds) and the published article was not sent out until 1 February 1979 (see exhibits 8 and 9, submitted with the statements of grounds);

The late evidence submitted by Respondent II concerning the "dépôt légal" [see section XI, b), below] did not contradict the evidence already on

file that document (3), in spite of the date printed thereupon, had not been made available to the public until after 1 February 1979.

(c) Inventive step

Document (16) best represented the state of knowledge on HBV before the present patent. This document did indeed provide information about the HBV genome, but indicated also a number of yet unanswered questions linked to the complex structure of the viral genome, such as, for example, whether the Dane particles were directly infectious, whether the complete viral genome could be contained in more than a single Dane particle, and whether the DNA from Dane particles was sufficient to specify the HBV-specific proteins.

Prior art document (1) had presented the results of an investigation at the level of the HBV specific polypeptides without providing information about the organisation of HBV.

Thus, the skilled person would have had to carry out some further research before deciding to try to express directly the HBV genome by recombinant DNA techniques. According to decision T 500/91 of 21 October 1992 (not published in the OJ of the EPO), the skilled person is normally not expected to solve a technical problem by performing scientific research in areas not yet explored.

As for the recombinant DNA technology, this was in its infancy in late 1978. In spite of at least five reports of successful expression of higher eukaryotic polypeptides in E.coli (see the affidavit of Dr Robert Old, exhibit 4 submitted by

the Appellant with the statements of grounds), a number of fundamental issues regarding the ability to clone, the transcription, translation, polypeptide instability, product toxicity, product activity, and the presence and relevance of introns, still constituted potential difficulties for the skilled person when attempting to express higher eukaryotic genomic DNA, in particular of eukaryotic viral DNA, for which no examples were available. Under these circumstances any prediction of success in recombinant HBV expression was impossible. Also document (8), heavily relied upon by the Respondents, would not have constituted for the skilled person a route which could provide any expectation of success in the expression of HBV polypeptides because its teaching was limited to the use of cDNA linked in frame to coding sequences at or near the 5' end without the presence of an upstream stop signal. This was supported also by the witness statement of Dr Villa-Komaroff (first author of the said publication) dated 5 September 1993 in the High Court of Justice, Chancery Division Patents Court, Biogen INC. vs. Medeva PLC (exhibit 10 filed on 4 July 1994).

XI. The Respondents argued essentially as follows.

a) The entitlement to priority

This question was linked by the Respondents to the issue of whether the BI priority document contained an enabling disclosure.

The Respondents maintained that entitlement to priority was not only a matter of finding formal support in the priority document (Respondent II, in particular, admitted that formal support for

Claim 1 could indeed be found in the BI priority document), but also a matter of finding therein all the elements necessary for the person skilled in the art to perform the claimed invention across its width. In their submissions, the technical contents of the BI priority document were scanty and barely sufficient to allow the skilled person to perform the invention only in a small corner of the area covered by Claim 1. The BI priority document merely taught the fragmentation of a HBV genome and the subsequent expression in E.coli of cloned fragments encoding an undefined product displaying an undefined antigen specificity. Nothing was said therein about the production of HBcAg or HBsAg. Nothing was said about the antigenicity (defined as ability to induce antibody production) of any product (cf. claim 2 at issue). Nothing was said about the starting material (origin of the HBV, its subtype, restriction enzyme analysis etc.) or about the type of assay used for activity determination. Thus, the BI priority document did not enable the preparation of any polypeptide displaying HBV antigen specificity other, possibly, than those produced by the specific host cells of deposits A and B for which the Board of Appeal in the parallel appeal case had recognized the entitlement to the BI priority date (see decision T 886/91 dated 16 June 1994, not published in the OJ of the EPO, concerning European patent No. 0 013 828, EP application 79 303 017.2; cf. Section I, above). The latter deposited host cells, however, did not provide enough support for broad claims which covered different distinct areas such as production of HBcAg and HBsAg (i.e. antigens which were in no way chemically related), and expression in bacteria, yeast and mammalian cells (i.e. hosts with quite different characteristics).

This was shown particularly by the embodiments relating to HBsAg production. There was clearly no enabling disclosure for these in the BI priority document as demonstrated by the Appellant's own admissions, e.g.:

- in the European patent specification (see statement on page 13, lines 57 to 59: "Such expression was not previously observed in suitable host cells transformed with recombinant DNA molecules that produced polypeptides displaying HBV antigen specificity or both HBV antigen specificity and HBV antigenicity");
- in document (41) (see statement on page 4511, right-hand column "Analysis of Expression of the HBsAg Gene": "Colonies of transformed cells were screened for HBsAg production by solid phase radioimmunoassay (8) but, as in previous experiments (2, 7), responses were weak and variable and results generally were inconclusive");
- in Nature, Vol. 304, 28 July 1983, page 297 (attachment G) (Article with title "Biogen's inside track": "Dr Murray explained last week that after experiments had shown that the gene could not be expressed in Escherichia coli,.....");
- in the statements by Prof. K. Murray during cross examination in the High Court of Justice, Chancery Division Patents Court, Biogen INC. vs. Medeva PLC [attachment B(1); see on page 4: "...they were not definitively positive..; on page 5: "...I would not need peer review to tell me that I needed to do further work on this to

say that we have definitively expressed the antigen."; on page 6: "Our results at that stage did not give us a definitive illustration of expression of surface antigen..."].

For the above reasons, not only Claims 3 and 4, for which the Opposition Division in its decision had correctly denied entitlement to the BI priority date, but also Claims 1 and 2 were not entitled to the said priority date. The latter claims embraced a wide area which also covered subject-matter such as, for example, the expression of HBsAg or expression of HBV antigens in yeast and mammalian cells, for which - as shown above - there was no enabling disclosure and which had not even been explored at the BI priority date. In this respect, the present case could not be compared with that of decision T 292/85 (OJ EPO 1989, 275) where no distinct areas were covered by the broad claims. Nor was the parallel drawn by the Appellant with the cases in decisions T 81/87 (loc.cit.) and T 73/88 (loc.cit.) of any relevance.

In relation to this issue, Respondent IV requested that the Board refer the following legal question to the Enlarged Board of Appeal under Article 112(1)(a) EPC: "Whether it is enough to entitle a claim to priority if the disclosure in the priority document only enables the person skilled in the art (without invention or an undue burden of experimentation) to perform the claim in one way or within a limited area; or whether if a claim embraces a wide area covering a number of distinct areas or classes,

it is necessary for the disclosure of the priority document to enable the skilled person to perform the claim across its width."

(b) The citability of document (3)

Respondent II, in particular, insisted that the evidence submitted by the Appellant was not sufficient to demonstrate that document (3), which carried the date of 18 December 1978, was not available to the public at the Académie des Sciences, a public institution, earlier than 1 February 1979, a date to which the testimonial letter of Mr Paul Germain, Permanent Secretary of the Institut de France, Académie des Sciences, made reference (see exhibit 8, submitted by the Appellant with the statements of grounds). Moreover, none of the letters from different technical libraries (see exhibit 9, submitted by the Appellant with the statements of grounds) provided information on the date on which document (3) had been received. Respondent II submitted evidence (inter alia the letter of A-M. Abecassis, Head of the Office "Dépôt Légal" at the French Ministry of the Interior) which, in its opinion, showed that the "dépôt légal" with the Ministry of the Interior of the issues of the Journal "C.R.Acad.Sc.Paris" published under the title of the year 1978 was indeed made in 1978.

c) Novelty

The issue of novelty, which was strictly linked to that of entitlement to priority, was raised exclusively in the written submissions by the Respondents, in particular in respect of Claims 3 and 4. The novelty of these claims was considered

to be affected under Article 54(1) and (2) EPC by document (15) and under Article 54(3) and (4) EPC by document (20).

d) Inventive step

Apart from document (3), documents (1), (16) and (23) were considered to best represent the state of the art on HBV prior to the patent-in-suit. It was submitted that the said documents had provided the skilled person with a good amount of knowledge on HBV:

- document (1) had disclosed the isolation of the two major component polypeptides of HBsAg and some important structural information thereon, such as amino acid composition and partial amino acid sequence. This document had also anticipated that fragments of the said polypeptides could have achieved the goal of a synthetic vaccine against HBV infection (see page 1533, right-hand column, last paragraph);
- document (16) had provided a general review on HBV illustrating the state of the art on HBCAg, HBsAg, on the structure of the Dane particles, including its DNA and on the mechanism of the endogenous DNA polymerase reaction;
- document (23) had identified the procedure for extracting DNA from Dane particles, the nature of the endogenous DNA polymerase reaction and a restriction map of the virus.

The above state of the art constituted for the skilled person an incentive to carry out cloning and expression studies on HBV. At least five

reports of successful expression of higher eukaryotic polypeptides in E.coli (see the affidavit of Dr. Robert Old, exhibit 4 submitted by the Appellant with the statements of grounds) had shown that certain obstacles to expression linked to transcription and translation could be overcome. Among them, the approach described in document (8) would have been regarded by the skilled person as particularly suitable for achieving the desired goal of expressing genomic HBV DNA, because it was presented as a general method for the expression of viral antigens (see in particular page 3730, right-hand column, paragraphs 2 and 3). The said method was not limited to cDNA, as submitted by the Appellant, although cDNA was referred to through much of the article. The reference to viral DNA (see page 3730, right-hand column, paragraphs 2 and 3) would have been read by a skilled person as indicating genomic DNA. In any case, the skilled person also had further strategies available for achieving expression of HBV antigens such as, for example, the cDNA route by preparing cDNA from the mRNA of Alexander cells [see document (22)] which were known to express viral antigens, or the route of first sequencing the cloned HBV genome and then expressing all or selected parts thereof, taking advantage of the N- and C- terminal amino acid sequence information of HBsAg provided by document (1).

Thus, the combined knowledge on HBV and on the expression of eukaryotic polypeptides would have encouraged the skilled person to produce polypeptides displaying HBV antigenicity by the genetic engineering route. A person of ordinary skill would have expected to achieve this by application of the known techniques without undue

difficulty. Based on the successful examples in the prior art, there was in late 1978 tremendous optimism in the field of recombinant DNA technology and this would have given an even higher expectation of success to the skilled person.

As for the alleged difficulties and prejudices of the skilled person referred to by Dr Old in his affidavit (see exhibit 4, submitted by the Appellant with the statements of grounds), these were unquestionably issues for the skilled person, but did not constitute a barrier which could have deterred him or her from trying a likely experimental approach. For example:

- the possible presence of introns would not have prevented the skilled person from trying expression, especially of small DNA fragments. Moreover, studies with SV40, the closest virus to HBV known in 1978, had shown the existence of a single intron in one gene out of five (see attachment 3 submitted by Respondent IV);
- genomic DNA was the obvious starting point for the skilled person as shown also by the fact that three teams (in addition to the Appellant) cloned **genomic** HBV DNA;
- the general method described in document (8) for the expression of eukaryotic polypeptides and viral antigens in E.coli was designed to ensure that the polypeptide was also transported to the periplasm. This would have minimised the questions of toxicity to the host cells or post translational modification;

- the question of proper folding of the polypeptide would also not have deterred a skilled person from attempting expression of genomic HBV DNA.

Therefore, the skilled person had no reason to suppose that expression of a viral antigen in E.coli would have been more difficult to achieve than that of any other non-prokaryotic polypeptide.

Respondent IV additionally submitted that the Appellant had been able to do the work disclosed in BI before others not because of any special technical merit or inventive step, but because of the looser restrictions on recombinant DNA work prevailing in the United Kingdom in 1978 and of the access to the special containment facilities. Moreover, in its submission, the fact that three other teams of workers embarked on this project demonstrated that the difficulties alleged by the Appellant could not have appeared as great as contended.

XII. The Appellant requests the decision under appeal be set aside and the European patent be maintained on the basis of the main request as filed at oral proceedings.

The Respondents request that the appeal be dismissed.

XIII. At the end of oral proceedings on 28 July 1994 the Board announced the decision reported in the order.

XIV. The Board received on 10 August 1994 a letter from Respondent II with further observations and a request for reconsideration of the case and on 17 August 1994 comments thereto from the Appellant.

Reasons for the Decision

1. *Admissibility and other procedural questions*

The appeal is admissible.

The submissions by Respondent II and by the Appellant on 10 August 1994 and 16 August 1994, respectively, are disregarded because they were filed after closing of the debate (in this respect see decision T 595/90 of 24 May 1993, to be published in the OJ of the EPO, in particular point 1 of the Reasons) and, what's more, after the announcement of the decision (see G 12/91, OJ EPO 1994, 285, points 2 and 3).

2. *Admissibility of intervention (Article 105 EPC)*

2.1 The Board firstly observes that the Opposition Division, through its announcement of the decision on 28 October 1992 to revoke the patent, had effectively severed itself from the case, and therefore could not take any decision on the intervention matter. Had no appeal been lodged against the decision to revoke, the intervention would have had no standing at all (see G 4/91, OJ EPO 1993, 707). This matter therefore must be dealt with by the Board. In G 1/94 of 11 May 1994 (to be published in the OJ of the EPO), the Enlarged Board of Appeal further established that an intervention at the appeal stage is admissible.

2.2 Article 105(1) EPC reads as follows:

"In the event of an opposition to a European patent being filed, any third party who proves that proceedings for infringement of the same patent have been instituted against him may, after the opposition period has ex-

pired, intervene in the opposition proceedings, if he gives notice of intervention within three months of the date on which the infringement proceedings were instituted. The same shall apply in respect of any third party who proves both that the proprietor of the patent has requested he cease alleged infringement of the patent and that he has instituted proceedings for a court ruling that he is not infringing the patent."

- 2.3 In the negotiations leading up to the adoption of the EPC, the question of intervention was raised in 1971 in Working Group I, who decided to propose the introduction of such an opportunity for third persons to enter into opposition proceedings, the object being to make it possible for an alleged infringer to avoid having to defend himself before a national court although central opposition proceedings were still pending before the EPO (BR/144/71, points 75 to 77).

In subsequent meetings to discuss further details, proposals were made to ensure that interventions would not lead to delays of the opposition proceedings (BR 168/72, BR 169/72, and BR 177/72). These time considerations led to a fixed period of three months after the institution of infringement proceedings before a national court.

In preparation for the Munich Diplomatic Conference in 1973, the Swiss delegation proposed a separate possibility to intervene, in the situation where no infringement action had been instituted by the Patentee, but he had requested - for example in an ordinary letter - a third party to stop infringing the patent and the third party had initiated proceedings for a court ruling that he was not infringing the patent (M/31, 28 May 1973). This proposal was adopted by the Conference

(M/PR/I, page 51), although one delegation questioned whether this further opportunity would not indeed cause delays in the opposition proceedings.

- 2.4 The Board cannot agree with the Intervener that the above cited **travaux préparatoires** indicate a right to choose at will which starting point for calculating the time period for intervention to invoke.

The second possibility of intervention was only introduced to make it possible at all for a third party to enter the centralised proceedings before the EPO, although no formal infringement action had been raised. The situation for this second category of Interveners is in fact identical to the first, with the very important difference that he otherwise could not avail himself of the centralised EPO proceedings. This was not considered justified in the case where a patentee chooses not to start a court action, thereby preempting the Intervener. The latter would then have to institute national proceedings himself, proceedings which could prove to be needless, i.e. if the patent were later to be revoked by the EPO.

- 2.5 The provision of the institution of court actions as starting dates for the calculation of the time periods for interventions guarantees an indisputable official date. As the Appellant rightly pointed out, it is not customary in procedural law that a party who wants to avail itself of a time limit also holds the means by which the starting point for its calculation can be controlled.

The principle behind Article 105 EPC is that, as soon as any court action has been brought, the sole available period for intervention starts running. Any other interpretation would open the possibility of abuse of

the intervention opportunity by the filing of national invalidity actions in order simply to trigger a new time limit under Article 105 EPC, regardless of earlier circumstances.

2.6 Consequently, the Board finds that the two alternatives offered under Article 105(1) EPC, first and second sentence respectively, are mutually exclusive for the same case of infringement. With regard to the same patent, an alleged infringer can only belong to one category, the decisive factor being which court action was the first to be instituted.

2.7 In the present case, therefore, the time period for intervention was triggered by the writ of summons of 1 July 1992. Not having been filed within three months of that date, the notice of intervention does not meet the requirements of Article 105(1), first sentence, EPC, and must therefore be rejected as inadmissible.

3. *Formal allowability of the amended claims
(Article 123(2) and (3) EPC)*

The deletion of Claims 5 to 7 (Claims 5 and 7 for AT) as well as the consequent renumbering and changes in dependencies of the remaining claims resulted neither in an extension of the protection nor in the generation of new subject-matter. Thus, there are no objections under Article 123(2) and (3) EPC to the amended claims.

4. *Entitlement to priority (Article 87 EPC)*

4.1 The right to priority is governed by Article 87, which requires that the European patent application and the application whose priority is claimed relate to the **same invention**. Thus, the main criterion in this respect is whether the claimed invention is disclosed in the

priority document as a matter of substance, i.e. with all its essential features. According to decision T 81/87 (loc.cit.) the disclosure of the essential elements "must be either express, or be directly and unambiguously implied by the text. Missing elements which are to be recognized as essential only later on are thus not part of the disclosure". This view was confirmed in a number of decisions of the Boards of Appeal (see, for example, T 301/87, loc.cit.).

4.2 The claimed subject-matter

Claim 1 (non-AT) at issue is essentially directed to a recombinant DNA molecule in which a DNA sequence coding for a polypeptide (or a fragment thereof) displaying HBV antigen specificity is operatively linked to an expression control sequence so as to be expressed in a suitable transformed host cell.

Claim 2 further specifies that the expressed polypeptide also displays HBV antigenicity.

Claims 3 and 4 specify that the said DNA sequence codes for a polypeptide (or fragment thereof) displaying the HBV antigen specificity of **HBcAg** and **HBsAg**, respectively.

Claims 5 to 23, which each refers back to one or more of the Claims 1 to 4, concern transformed host cells, the polypeptides thereby produced, compositions for stimulating the production of antibodies to HBV, means and a method for detecting HBV infections in blood serum, DNA sequences encoding HBV antigens.

4.3 The subject-matter of the BI priority document

The BI priority document relates to the transformation of host microorganisms with vectors containing HBV DNA, appropriately cleaved and inserted, so that they produce polypeptides with the specificity of HBV antigens (see page 3, lines 10 to 25). The intended purpose thereof is the provision of HBV antigen for vaccine studies and for use in the detection of the infection (see page 3, lines 2 to 5 and page 4, lines 12 to 16).

The said document teaches in general terms cleaving HBV DNA at only a single, or at most a few sites, with a restriction enzyme such as Kpn I, Bgl II, Bam HI, Ava I and Eco RI, inserting at least one of the resulting fragments into a vector such as a bacterial plasmid, transforming host microorganisms therewith, culturing the said transformed hosts and collecting the polypeptide from the culture (see page 4, line 3 to page 5, line 8).

In a specific worked example (see pages 5 to 9), HBV DNA is prepared from Dane particles and cleaved with Kpn I. The digestion products are inserted into the Pst site of pBR322. E.coli host cells are transformed with the resulting vectors, screened by colony hybridisation and tested for the production of HBV specific antigens by means of a radioimmunoassay with HBV antibodies. Cultures designated as deposit A are found to give a positive response both in the colony hybridisation and in the test for the viral antigen (see page 11). As established in the parallel case T 886/91 (loc.cit., see point 4.2 of the Reasons), this deposit corresponds to deposit A (NCIB 11548), which in the European patent specification is shown to produce a polypeptide with HBcAg antigen specificity.

In another worked example (see page 10), E.coli host cells transformed with vectors containing Bam HI fragments of HBV DNA designated as deposit B are also found to give a positive response both in the colony hybridisation and in the test for the viral antigen (see page 11). As established in the parallel case T 886/91 (loc.cit., see point 4.2 of the Reasons), this deposit corresponds to deposit B (NCIB 11549), which in the European patent specification is shown to produce a polypeptide with HBcAg antigen specificity.

Other examples of successful insertion of HBV DNA fragments into a plasmid, as measured by the positive signal in the colony hybridisation assay, are reported (see page 10, line 19 to page 11, line 14). However, no data with respect to viral antigen expression are reported in this case.

4.4 The essential elements of the disclosure in the BI priority document are:

- the cleavage of isolated HBV DNA with selected restriction enzymes;
- the insertion of the resulting fragments into a vector carrying selectable markers (drug resistance genes);
- the transformation of host cells with the resulting recombinant DNA molecule, their culture and selection on the basis of drug resistance;
- the screening of the transformants by colony hybridisation;
- detection and characterization of recombinants by means of immunological methods.

It is directly and unambiguously implied by the text that the expressed product could be a protein displaying the antigen specificity and antigenicity of one or more of the known HBV antigens, e.g. HBcAg and HBsAg, depending on the HBV DNA fragment used (see page 4, lines 17 to 20), and that detection and characterization should therefore be carried out by means of the corresponding specific antibodies (see inter alia page 9, lines 15 to 16). Such antibodies were admittedly available in the art at the BI priority date.

Compositions for stimulating the production of antibodies to HBV, means and methods for detecting HBV infections are also implied by the text of the BI priority document (see, for example, page 4 lines 12 to 16).

- 4.5 The fact that no actual demonstration of expression of either HBcAg or HBsAg is provided in the BI priority document is used by the Respondents as an argument to show that not all essential elements are disclosed therein.

In the Board's opinion, the lack of actual data on the production of a polypeptide with the antigen specificity and antigenicity of one or the other HBV antigen does not necessarily lead to the conclusion that essential elements of the claimed invention are missing in the disclosure of the BI priority document.

The worked examples in the BI priority document demonstrate that, by following the said experimental approach, expression in a recombinant DNA system of polypeptides displaying HBV antigen specificity can indeed be achieved. In this respect, it must also be kept in mind that expression of HBV antigen in general, **not** the efficiency of expression is at issue here.

None of the Respondents has succeeded in discharging the onus of proof by demonstrating that, by proceeding experimentally as indicated in the BI priority document, expression of proteins having the antigen specificity and antigenicity of either HBcAg or HBsAg cannot be achieved to some extent. The Respondents have been unable to point to one or more essential elements recognised as essential only later which are missing in the BI priority document. Their objections derive mainly from the lack of actual data on the polypeptides which are or can be expressed, **not** from any proven inadequacy of the disclosed experimental approach.

The evidence on file rather indicates that, by proceeding experimentally as taught in the BI priority document, expression of proteins having the antigen specificity and antigenicity of either HBcAg or HBsAg was achieved to some extent. The European patent specification confirms the validity of the approach and demonstrates inter alia that deposits A and B express polypeptides with the antigen specificity of HBcAg. The witness statement by Prof. K. Murray (attachment 7 submitted by Respondent IV) shows that some recombinant colonies gave positive signals in immunological assays also for surface antigen (see, for example, items 94 to 96). The cautious nature of Prof. K. Murray's statements in respect of the latter results [see, for example, attachment B(1); cf. Section XI a), above] are fully understandable when due account is taken of the complexity of the project and of the need to avoid a false interpretation of the results by carrying out further verifications. None of the Respondents, however, could successfully demonstrate that expression of polypeptides with HBsAg antigen specificity (even at a faint level) was impossible when following the teaching of the BI priority document. The criticism by the Respondents stems essentially from the fact that the

results referred to by Prof. Murray were preliminary and indicative. However, it must be remembered that what is at issue here is the expression of the desired polypeptides as such at any level (from faint to strong), **not** the improvement of any already known expression system.

4.6 In conclusion, the Board is not convinced by the Respondent's arguments that priority document BI is deficient in respect of relevant technical information necessary for reducing the claimed invention to practice by the person skilled in the art without undue burden (see points 4.4 and 4.5). If no essential elements (i.e. features) of the claimed invention can be said to have been recognised or added only later on in the sense that they are not part of the disclosure of the priority document, the claims under discussion and the priority document on which they are based must be regarded as relating to the **same invention** within the meaning of Article 87(1) EPC. Consequently, in line also with the existing EPO jurisprudence on this matter (see, for example, T 81/88, T 73/88 and T 301/87, loc.cit.), the said claims are considered to be entitled to the BI priority date.

4.7 As for the request put forward by Respondent IV to refer the legal question quoted above in section XI, item (a), last paragraph, to the Enlarged Board of Appeal, the present Board considers it unnecessary because it is already evident that, under the present EPO jurisprudence, the answer to the said question is that a broad claim must find adequate support for all its essential elements in the priority document (see point 4.1, above). However, this is a matter of substantive nature which must be decided in each particular case on its own merit.

In the present case, for the reasons given above, the Board has come to the conclusion that the claims at issue are entitled to the BI priority date.

5. *The citability of document (3)*

- 5.1 Document (3), published in the issue No.16, of Volume 287 of the "C.R.Acad.Sc. Paris", bears the date 18 December 1978. A footnote on page 1456 mentions "the meeting of 6 November 1978".

The Appellant submitted evidence aimed at showing that no oral presentation of the contents of the document (3) was made at any public session of the Academy of Sciences and that the published article was not sent out until 1 February 1979.

The Respondents agreed that the date of 6 November 1978 was in relation to the internal procedure of evaluation of the articles by the Reading Committee of the Academy which occurred under conditions of confidentiality. Thus, there is consensus on the fact that the said date is meaningless for the purpose of Article 54(2) EPC.

However, Respondent II insisted that document (3) must have been available at least at the Académie des Sciences, a public institution, on the date which it carried, i.e. on 18 December 1978. In its opinion, the testimonial letter of Mr Paul Germain, Permanent Secretary of the Institut de France, Académie des Sciences, did not exclude this (see exhibit 8).

Moreover, in its submission, none of the letters from different technical libraries (see exhibit 9) provided information on the date on which document (3) had been received. Respondent II submitted evidence which, in its opinion, showed that the "dépôt légal" with the Ministry

of the Interior of the issues of the Journal "C.R.Acad.Sc.Paris" published under the title of the year 1978 was made in 1978.

- 5.2 As stated in decision T 381/87 (OJ EPO 1990, 213), in relation to the question when a document was first made available to the public, the Board "must decide what happened having regard to the available evidence, on the balance of probability; i.e. it must decide what is 'more likely than not' to have happened" [see point 4.(4) of the Reasons].

In the present case, document (3) published by the "Institut de France - Académie des Sciences" carries the date of 18 December 1978. It being a public institution, the possibility cannot be discounted that a copy of it could have been made available to the public on the very same date e.g. in the public library of the said Academy. However, the Board observes that no declaration and/or affidavit to this effect has been submitted by the Respondents.

On the other hand, the Appellant submitted the quoted testimonial letter of Mr Paul Germain (see exhibit 8) stating that the date of 18 December was not the date on which the issue was received by the subscribers and the libraries and that only starting on 1 February 1979 was the said issue available to their readers. Furthermore, the Appellant submitted attestations from a number of different European libraries stating that the issue No.16, of Volume 287 of the "C.R.Acad.Sc. Paris" was received or registered on a date **after** 1 February 1979 (see exhibit 9).

The Respondents have not submitted any counter-attestation of other libraries showing that the issue No.16, of Volume 287 of the "C.R.Acad.Sc. Paris" was received or registered on a date **before** 1 February 1979, in particular on a date **before** 22 December 1978, which is the BI priority date, or that the document was otherwise available at this priority date.

The Board firstly notes that there is a gap in the chain of evidence as regards the period from 18 December 1978 to 1 February 1979. It is therefore not clear whether during this period third persons would have been in the position to take part of the document.

As for the late evidence submitted by Respondent II concerning the "dépôt légal" [see section XI, b), below], the Board considers that it has no bearing on this matter because it does not indicate a specific date (day of the month) on which the said "dépôt légal" was actually made.

The Board further notes the lack of express evidence from the Académie des Sciences that documents would have normally been available to the public as of the publication date printed thereon. On the contrary, there is evidence on file (see exhibit 8) indicating the opposite.

- 5.3 Having regard to the available evidence, noting in particular the evidence regarding the distribution to subscribers, the Board is satisfied that the contents of document (3) were not available to the public before or at the BI priority date.

Consequently, document (3) is not state of the art citable under Article 54(2) EPC against any subject matter which is entitled to the BI priority date.

6. *Novelty (Article 54 EPC)*

None of the cited documents made available to the public before the BI priority date discloses the claimed subject-matter which is, therefore, novel under Article 54(1)(2) EPC.

Document (20), a European patent application, claims a priority date later than the BI priority date. Thus, this document is not taken into consideration under Article 54(3) EPC.

7. *Inventive step (Article 56 EPC)*

7.1 Document (16) represents the closest prior art for the claims-at-issue. This document is a review on the information about HBV and Dane particles: the number of viral gene products, the size, structure and complexity of Dane particle DNA, the mechanism of the DNA polymerase reaction; the pattern of viral gene expression in infected cells. From the different pieces of information a working model for the structure of the HBV genome is proposed according to which Dane particles are viewed as defective, genetically heterogeneous hepatitis B virions which replicate by complementation in multiply infected cells (see Figure 2). The conclusion drawn at the end of the document is that "further research will be needed to confirm or refute the model" (see page 375).

Document (16) reports also the work disclosed in document (23) (see paragraph bridging pages 366 and 367; reference no.51) and, therefore, constitutes a more complete prior art document than the latter.

7.2 In the light of document (16) the technical problem to be solved can be seen in the provision of HBV DNA or fragments thereof in sufficient amounts for the elucidation of its structure and for the production of HBV antigens.

7.3 This problem is solved by providing the recombinant DNA molecules referred to in the present claims (see, for example, Claims 1 to 4). In view of the detailed information contained in the patent-in-suit on the preparation of polypeptides displaying HBV antigen specificity and antigenicity by use of the said recombinant DNA molecules, the Board is satisfied that the above-stated technical problem has been solved.

7.4.1 It is observed that, in spite of the good amount of knowledge which was available in the prior art in respect of HBV and its genome [see document (16)], the skilled person was still faced with a number of uncertainties such as, for example, :

- the actual size of the HBV genome [see document (16), page 358, third paragraph and page 371, item 2];
- the complex structure of the Dane particles in which the amount of DNA exceeded the amount of DNA in a single circular molecule, but was less than that in two such molecules [see document (16), page 372, item 4], indicating the structure of a circular DNA single stranded over approximately one third of its length (see therein Figure 1);
- whether or not the proteins containing HBV antigen reactivity were all specified by viral genes [see document (16), page 371, item 2];

- whether or not the total amount of unique nucleotide sequence in the DNA from Dane particles was sufficient to specify the HBV-specific proteins [see document (16), page 372, lines 2 to 5];
- whether or not Dane particles were directly infectious [see, for example, document (16), page 375, lines 2 to 5].

The observation of these uncertainties brought the authors of document (16) to the conclusion that further research into the structure of Dane particles and HBV genome was necessary. This *per se* demonstrates that at the BI priority date the skilled person would not have considered the cloning of the HBV genome, not to mention its expression in a host cell, to be readily achievable with a reasonable expectation of success. Before entering into the unexplored area of cloning and expression of HBV DNA, the average skilled person would have had to acquire further information about the Dane particles and HBV genome.

This is even more true, if due account is taken also of the additional uncertainties with regard to the technology available for expressing higher eukaryotic genomic DNA, which in late 1978 was still in its infancy. The Appellant and the Respondents essentially agree that there was a number of open issues in relation to cloning and expression, but disagree on the extent to which they would have conditioned the activity of the skilled person (compare affidavit of Dr Old with affirmation of Prof. Almond). In the Board's view, if the said general uncertainties are added to the particular ones in respect of HBV, it can only be concluded that the skilled person in late 1978 had no

reasonable perspectives of readily achieving expression of polypeptides displaying HBV antigen specificity and antigenicity by the genetic engineering route.

7.4.2 The parallel drawn by the Respondents with the studies on the virus SV40 (see attachment 3, submitted by Respondent IV) is misplaced because, firstly, the skilled person would not have seen a direct analogy between the two viruses [in this respect, see, for example, the statement on page 375, lines 10 to 12 in document (16)] and, secondly, no expression of fragments of SV40 genome had been reported.

7.4.3 Only with hindsight is it now possible to suggest a series of possible routes [for example, the experimental approach of document (8)] which could theoretically have lead the skilled person to the desired result. The facts in the present case rather indicate that, notwithstanding the available information, the studies of the primary structure of the HBV genome were quite precarious and that even predictions as to the possibility of cloning the genome were not possible; even less so as regards the possibility of achieving expression of fragments of the HBV genome.

7.4.4 Furthermore, the arguments put forward by Respondent IV based on the allegedly looser restrictions on recombinant DNA work in the United Kingdom and on the number of teams working in competition on the same project are immaterial to the issue of inventive step.

Neither the fact that a person (or a team) (here: the Appellant) was working under more favourable conditions nor that other persons (or teams) were concurrently performing research in the same area lessens the inventive step of any subject-matter claimed in a patent specification by the said first person (or team) in

relation to the said research work, if this subject-matter is not obvious to a person skilled in the art, having regard to the state of the art.

The fact that other persons (or teams) were also working on the same project might suggest that it was "obvious to try" or that it was "an interesting area to explore", but it does not necessarily imply that there was "a reasonable expectation of success". "A reasonable expectation of success", which should not be confused with the understandable "hope to succeed", implies the ability of the skilled person to reasonably predict, on the basis of the existing knowledge before the starting of a research project, a successful conclusion to the said project within acceptable time limits. The more unexplored a technical field of research is, the more difficult is the making of predictions about its successful conclusion and, consequently, the lower the expectation of success.

- 7.4.5 In the Board's view, the successful achievement of the expression of HBV genes in a recombinant DNA system, regardless of whether it was just a "lucky strike" or the result of "looking for the unexpected" or of a planned strategy, was a major breakthrough in HBV research which, for the reasons given above, no prior art document had anticipated or rendered obvious.
- 7.4.6 For these reasons, the Board concludes that the subject-matter of the main request involves an inventive step. Thus, the said main request (Claims 1 to 23 for non-AT States and Claims 1 to 11 for AT) is allowable.

Order

For these reasons it is decided that:

1. The intervention is rejected as inadmissible.
2. The decision under appeal is set aside.
3. The case is remitted to the first instance with the order to maintain the patent on the basis of Claims 1 to 23 (non-AT States) and Claims 1 to 11 (AT) as filed in the oral proceedings.
4. The request for referral of a question to the Enlarged Board of Appeal is refused.

The Registrar:

The Chairwoman:

L. McGarry

U. Kinkeldey

