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D E C I S I O N
of 16 June 1994

Case Number: T 0886/91 - 3.3.2

Application Number: 79303017.2

Publication Number: 0013828

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:
Recombinant DNA, hosts transformed with it and polypeptides produced by the hosts; processes for their preparation; detection processes using the polypeptides; compositions and means containing the polypeptides; DNA sequences.

Patentee:
BIOGEN, INC.

Opponent:
01 - Abbott Laboratories
02 - Takeda Chemical Industries, Ltd
03 - Warcoin, Jacques Cabinet REGIMBEAU
04 - SmithKline Beecham Corporation
05 - Institut Pasteur Etablissement public
Intervener: Medeva PLC

Headword:
Hepatitis B virus/ BIOGEN INC.

Relevant legal norms:
EPC Art. 105, 87, 88, 83, 57, 54, 56
EPC R. 28

Keyword:
"Admissibility of intervention of assumed infringer during appeal (yes)"
"Entitlement to priority"
"Sufficiency of disclosure (yes)"
"Industrial applicability (yes)"
"Citability of document published between the second and third priority dates against subject-matter entitled to the third priority or filing date (yes)"
"Novelty (yes)"
"Inventive step-main request (no)"
"Inventive step-first auxiliary request (yes)"

Decisions cited:
T 0010/82, T 0301/87, T 0073/88, T 0441/91, G 0001/94, T 0500/91, T 0223/92, T 0013/84, T 0158/91, T 0014/83

Catchword:
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Case Number: T 0886/91 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 16 June 1994

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office dated 3 September 1991 concerning maintenance of European patent No. 0 013 828 in amended form.**

Composition of the Board:

Chairperson: U. M. Kinkeldey
Members: L. Galligani
E. M. C. Holtz
A. J. Nuss
G. Davies

Summary of Facts and Submissions

I. European patent No. 13 828 was granted for nine Contracting States with 8 claims and for Austria with 8 claims based on European patent application 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 five parties (hereinafter referred to as Opponents 1 to 5).

Revocation of the patent was requested on the grounds of Article 100(a) to (c) EPC. During the procedure before the Opposition Division, fifty-seven documents [(1) to (57)] 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) Nature, Vol. 279, 3 May 1979, pages 43 to 47;
(2) Nature, Vol. 280, 30 August 1979, pages 815 to 819;
(3) Nature, Vol. 281, 25 October 1979, pages 646 to 650;
(4) C.R.Acad.Sc.Paris, Ser D, Vol.287, 18 December 1978, pages 1453 to 1456;
(6) Nucl.Acid Res., Vol. 7, no.2, 25 September 1979, pages 335 to 346;
(7) Nature, Vol. 282, 6 December 1979, pages 575 to 579;
(8) Ann.Rev.Microbiol., Vol.31, 1977, pages 357 to 377;
(9) Proc.Natl.Acad.Sci. USA, Vol. 74, No.4, 1977, pages 1530 to 1534;
(12) Proc.Natl.Acad.Sci. USA, Vol. 72, No.11, 1975, pages 4597 to 4601;

(13) J.Virol., Vol.23, No.2, 1977, pages 368 to 376;
(15) Proc.Natl.Acad.Sci. USA, Vol. 78, No.7, 1981, pages 4510 to 4514;
(25) Proc.Natl.Acad.Sci. USA, Vol. 74, No.2, 1977, pages 560 to 564.

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. The Opposition Division, which included also a legally qualified examiner, announced at the end of oral proceedings held on 17 October 1990 the decision to maintain the patent in amended form on the basis of the set of claims filed at oral proceedings in the two versions for all designated Contracting States except Austria (non-AT States) (Claims 1 to 12) and Austria (Claims 1 to 16). The reasoned interlocutory decision within the meaning of Article 106(3) EPC was dispatched on 3 September 1991.

The opposition by Opponent 3 was considered inadmissible under Rule 55(a) and (d) EPC with reference to decision T 10/82 (OJ EPO 1983, 407) on the ground that the representative had not provided sufficient evidence that he was acting exclusively on his own behalf and not on behalf of a client.

Claim 1 of the set for non-AT States was as follows (the two specific DNA sequences recited therein are not reported here; for further details in this respect reference is made to the file):

"The use of a DNA sequence coding for a polypeptide displaying HBV antigenicity, said DNA sequence being selected from DNA sequences of the formulae:

(a) (first DNA sequence) and fragments thereof which encode polypeptides displaying HBV antigenicity;
(b) (second DNA sequence) and fragments thereof which encode polypeptides displaying HBV antigenicity; and
(c) DNA sequences which are degenerate as a result of the genetic code to any of the foregoing DNA sequences and which encode polypeptides displaying HBV antigenicity for the production of polypeptides displaying HBV antigenicity."

Claims 2 and 3, 4 and 5, 11 and 12 referred, respectively, to specific, deposited recombinant DNA molecules, to the corresponding transformed hosts and to the corresponding process for producing a polypeptide.

Claim 6 was directed to a polypeptide and fragments thereof displaying antigenicity of an HBV surface antigen.

Claims 8 and 10 referred, respectively, to a composition for stimulating the production of antibodies containing the said polypeptide and to means for detecting HBV infections in blood serum.

Claims 7 and 9 were directed, respectively, to a composition for stimulating the production of antibodies containing a polypeptide displaying HBV core antigenicity coded by a specified DNA sequence and to the corresponding means for detecting HBV infections in blood serum.

The claims for Austria were formulated as corresponding process claims.

IV. The main reasons given in the decision for maintaining the patent on the basis of the above claims were as follows:

a) The change in category (from product to use) of Claim 1 (non-AT) did not violate Article 123(3) EPC because the extent of protection was not enlarged. Furthermore, the introduction in Claim 6 of the feature "the polypeptide is free of any human and primate serum proteins" found support on original page 4, lines 4 to 35. Thus, also the requirements of Article 123(2) EPC were met.

b) Claims 2, 4 and 11 (Claims 7 and 13 for AT) were entitled to the priority of BI.

Claims 1, 6 to 10 (Claims 1 to 6, 9 to 12, 15 to 16 for AT) were entitled to the priority of BIII.

Claims 3, 5 and 12 (Claims 8 and 14 for AT) were entitled to the filing date of the European patent application.

c) The depositions of the transformed cells with NCIB were considered valid (Rule 28 EPC). Moreover, there was sufficient information in the application for the skilled person to put into practice the claimed invention. Thus, the requirements of Article 83 EPC were considered to be met.

d) None of the quoted documents affected the novelty of the claimed subject-matter.

In particular, document (1) was considered to be the publication of the contents of the first priority document and as such it was not considered state of the art in the light of decision T 301/87 (OJ EPO 1990, 335).

However, even if considered state of the art, it would not have affected novelty as no enabling disclosure of plasmids pHBV-66, pHBV-100 and pHBV-139 was found therein.

e) The matter of Claims 2, 4, 11 was not considered to be the obvious result of any genetic engineering experimental route suggested or derivable from the prior art, in particular from document (4).

The subject matter of Claims 1, 6 to 10 was not rendered obvious by any of the documents (1), (2), (3), (4), (6) neither alone nor in combination.

The subject-matter of Claims 3, 5, 12 was inventive also over document (7).

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

V. The Appellants (Opponents 1 and 5 referred to hereinafter as Appellants I and V, respectively) filed in due time an appeal against the decision of the Opposition Division with the payment of the fee, and submitted the statements of grounds.

Appellant V submitted a new citation, namely:

(58) Nature, Vol. 279, 24 May 1979, pages 346 to 348.

VI. The Respondent (Patentee) submitted a response to the appeals together with Exhibits 1 to 8 arguing on the basis of the claims as maintained (see above section III).

VII. On 30 September 1992, Medeva Plc (hereinafter: Intervener) filed a notice of intervention under Article 105 EPC and transmitted therewith copy of the Writ of Summons issued by Biogen, Inc. against Medeva Plc dated 1 July 1992. The Intervener relied in its argumentation inter alia on a new citation, namely:

(59) Proc.Natl.Acad.Sci.USA (1978), No.8, Vol.75, No.8, pages 3727 to 3731.

On 26 April 1993, the Board issued a communication pursuant to Article 110(2) EPC whereby the intervention was held provisionally admissible and Medeva Plc was considered as a party of right under Article 107 EPC.

In the letter dated 29 July 1993, the Respondent stated that it did not oppose the admissibility of Medeva's intervention.

VIII. With letter dated 6 December 1993, the Respondent filed a response to Medeva Plc's notice of intervention.

With letter dated 11 May 1994, the Intervener filed observations on the Respondent's response together with attachments 1 to 11, the affidavit of Dr Peter J. Cozens and the affirmation of Professor J. W. Almond.

With letter dated 25 May 1994, Appellant V submitted further observations.

With letter dated 8 June 1994, the Intervener submitted a table providing a comparison between the amino acid sequence of Claim 6 and those of documents (2) and (6).

IX. Oral proceedings took place on 15 and 16 June 1994.

During oral proceedings, two auxiliary requests were filed by the Respondent in the two versions for the non-AT States and for Austria.

The first auxiliary request (non-AT) consisted of Claims 2 to 5, 11 and 12 (renumbered 1 to 6) from the set of claims as maintained by the Opposition Division (main request non-AT).

The second auxiliary request (non-AT) consisted of Claims 2, 4, 11 (renumbered 1 to 3) from the said main request.

The corresponding sets of claims for AT consisted only of Claims 11 and 12 (first auxiliary request: Claims 1 to 2) and Claim 11 (second auxiliary request: Claim 1) from the main request non-AT.

X. The Appellants and the Intervener argued essentially as follows.

(a) The entitlement to priority

Appellant I submitted that Claim 1(b) was not entitled to the priority of BIII because in the latter document expression of the recited DNA sequence was not achieved. The mere identification of a sequence could not serve as a basis for a claim related to its actual expression in a transformed host cell. For the same reasons,

Claims 6, 8 to 10 were not entitled to the said priority because the subject polypeptide was not produced.

The Intervener submitted that the subject-matter of Claims 2, 4 and 11 was not entitled to the priority of BI because, as shown by the witness statement of Professor K. Murray dated 6 September 1993 in the High Court of Justice, Chancery Division Patents Court, between Biogen, Inc. and Medeva Plc. (attachment 4), the initial deposits A to F at Porton Down were informal deposits each comprising a large number of different clones (see e.g. item 94 of the said statement) which were no longer available. When deposits A to F were made with NCIB a short time before the filing date of the European patent application only one clone for each deposit was selected (see item 100 of the said statement). As a selection took place, the backdating of the deposits to priority BI was not justified.

(b) The citability of document (1)

The Appellants and the Intervener maintained that document (1) was prior art citable against the subject-matter which enjoyed a later effective date. This was because the said document contained a considerable amount of additional, more specific information when compared with the general, non-specific disclosure of the BI priority document.

(c) Novelty

According to Appellant V, Claims 1, 6 to 10 lacked novelty because the reported sequences did not substantially differ from those disclosed in documents (2), (3) and (6). In its opinion, when

the particular nature of the field was taken into account, small differences were of no relevance since nothing is exactly identical in nature. Moreover, no special technical effect was shown to be linked to the reported differences.

Furthermore, the novelty of Claims 1, 7 and 9 was affected by document (1), which disclosed DNA fragments from the genome of HBV with adyw serotype and their expression in a recombinant system to produce a polypeptide having HBcAg antigenicity.

The Intervener additionally observed that the subject-matter of Claim 1 was anticipated by the contents of documents (2), (3) and (6), in particular in view of the fact that the sequences disclosed in the latter contained identical sequence stretches and the said claim was not limited to partial sequences encoding protein fragments bearing a distinct antigenic determinant.

(d) Inventive step

In respect of Claims 2, 4, and 11, it was argued that, in view of the extensive knowledge of HBV in the prior art [see in particular documents (8), (9) and (13)] and of the demonstration in document (4) that the full genome of the HBV could be cloned in E.coli, there was no inventive merit in the proposal of recombinant molecules including an HBV DNA fragment of undetermined sequence and encoding a product displaying an undefined HBV antigenicity. Such recombinant DNA molecules could have been easily obtained by applying known techniques, e.g. those described in document (59).

The Intervener additionally submitted that the Respondent 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 its 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 Respondent could not have appeared as great as contended.

In respect of Claims 1, 6 to 10, it was argued that they lacked an inventive step having regard to the disclosure of document (1) in combination with that of either document (2), (3) or (6). Document (1) had shown the construction of recombinant DNA molecules containing fragments of HBV DNA of subtype adyw capable of expressing in E.coli a polypeptide with HBcAg antigenicity. Documents (2), (3) and (6) had disclosed the identification and characterisation of DNA sequences encoding surface and core antigens of HBV of either ady or adw subtypes. The combined teachings of these documents would have induced a person of ordinary skill in the art to try to identify, characterise and express DNA fragments encoding surface and core antigens of the HBV subtype adyw. This merely implied the use of known techniques [see, for example, document (25)]. Even assuming that any of the alleged prejudices and/or difficulties existed (possible presence of intervening sequences, instability or degradation of the expressed product etc.), these had been removed by the disclosure of (1). Furthermore, no unexpected effects nor surprising properties had been shown to be linked

to the specific subtype or to the sequence differences in comparison with the prior art. The relevance of the adyw serotype indication was also disputed.

As for Claims 3, 5 and 12 their subject-matter was not inventive having regard to the already-quoted prior art and to the additional teaching of document (7), which provided exact guidance as to the achievement of expression of any structurally different HBV-related gene. The latter document demonstrated also that the production of a polypeptide with surface antigenicity was actually feasible in E.coli cells.

(e) Industrial applicability (Article 57 EPC)

Appellant V maintained that Claims 2, 4 and 11 did not satisfy the industrial applicability requirement of Article 57 EPC because there was no useful indication as to the nature of the "HBV antigenicity" referred to therein.

(f) Sufficiency of disclosure

Appellant V maintained that Claims 2, 4 and 11 did not meet the requirements of Article 83 EPC because the priority documents BI and BII did not meet the basic conditions for a sufficient disclosure. In respect of Claims 3, 5, 12, Appellant V stated that the patent specification contained an insufficient description of the feature "VA+".

According to the Intervener, the patent specification did not enable the expression in E.coli of HBsAg in an immunogenic form.

The above arguments were held true in respect of the claims of the first and second auxiliary requests (see section IX above).

XI. In reply to the above arguments the Respondent argued essentially as follows.

a) The entitlement to priority

According to Article 88(2) EPC multiple priorities could be claimed for any one claim. Claim 1 was entitled both to the priority of BI (due to the feature of the expression of a DNA sequence encoding polypeptide displaying HBV antigenicity) and to that of BIII (due to the feature of the specific DNA sequences).

Claims 3, 5 and 12 were entitled to the priority of BIII because the latter disclosed all the information necessary for the construction of the subject recombinant DNA molecules.

As for the recombinant DNA molecules of Claims 2, 4 and 11, these were entitled to the priority of BI because they were disclosed in the said document. The first deposits were made with the Culture Collection of the Microbiological Research Establishment at Porton Down because under the then applicable regulations none of the microorganisms could be removed from the category IV facility until their plasmid DNA had been shown not to contain a complete HBV genome. The availability to the public at the publication date of the patent application was admittedly ensured by the deposits with NCIB. These could be traced back to the

distinguished, separate entities having identical features deposited at Porton Down at the earlier priority date.

b) The citability of document (1)

Document (1), published between the priority dates of BII and BIII, described no more than what was disclosed in priority documents BI and/or BII. Although priority documents BI and BII were drafted in more general terms, according to the UK standard at that time, their technical content was essentially identical with that of the publication (1): both dealt with the same problem, disclosed the same experimental procedures and demonstrated expression of the same polypeptide displaying HBV antigenicity (in this respect reference was also made to decision T 73/88, OJ EPO 1992, 557). Apart from the scientific interpretation of the results, document (1) contained nothing beyond the content of BI (or BII) which could be relevant for Claims 1, 6 to 10. Thus, in accordance with decision T 301/87 (loc.cit.), document (1) was not citable.

In this respect, the Respondent proposed that the Board should refer the following legal question of its own motion to the Enlarged Board of Appeal under Article 112(1)(a) EPC: "Can a publication be cited against a claim of a European patent application for which two priorities of different dates have been claimed under Article 88(2), second sentence, EPC, if said publication occurred between the two priority dates, insofar as the technical contents of said publication are identical to those of the first priority document?"

c) Novelty

The claims entitled to the BI priority date were novel over (4), (8), (9) and (13). These documents disclosed neither the specific recombinant DNA molecules nor the specific, transformed host cells which contained them.

The claims entitled to the BIII priority date were novel over (2), (3), and (6). These documents disclosed neither identical DNA sequences nor identical HBV surface antigen amino acid sequences. None of the said documents disclosed expression of any polypeptide displaying HBV antigenicity. Nor could the fragments of the DNA sequence of Claim 1(b) which encoded polypeptides displaying HBV surface antigenicity be derived directly and unmistakenly by a person skilled in the art from any of the said documents.

As for the matter of Claim 1(a), this differed from the disclosure in document (1) in that an essential element was given, namely the specific DNA sequence.

d) Inventive step

The subject-matter of the claims entitled to the BI priority date could not be derived in an obvious manner from the teaching of document (4), which described the insertion of linearized HBV-DNA into a bacteriophage vector and the subsequent replication thereof, but provided no guidance as to how to express the cloned DNA. Also when document (4) was viewed together with documents (8), (9), (12) and (13) there was no impact on the inventive step of the said claims.

During oral proceedings, the Respondent submitted that document (4), in spite of the date printed thereon, was not prior art with respect to the claims entitled to the BI priority date because evidence showed that it was not made available to the public before the BI priority date. The Respondent had not previously put forward this evidence.

The subject-matter of the claims which were entitled to the BIII priority date was inventive vis-à-vis documents (2), (3), (6), which all failed to reveal expression of any polypeptide. Even if the said document had succeeded in expressing an HBV surface antigen, that polypeptide would have had different epitope characteristics from the claimed one. Moreover, the intron prejudice existed at the date of the invention [see documents (2), page 816, (3) page 648 and (6) page 344]. Even if document (1) was taken into consideration [see, however, item (b) above], the unique DNA sequences recited in the said claims and the specific valuable end products derivable from their use in a recombinant DNA system were not enabled thereby and, in any case, could not be predicted therefrom.

As for the claims entitled to the filing date of the European patent application, their subject-matter was inventive over reference (7), which neither identified nor suggested any point within the HBV genomic DNA sequence from which the specific inserts were taken. In respect of this document, the Appellant pointed out that it constituted the publication of the contents of the BIII priority application and thus, in accordance with decision T 301/87 (loc.cit.), was not citable [see also item (b), above].

e) Sufficiency of disclosure

The patent provided a general method for the recombinant production of polypeptides displaying HBV antigenicity and all the means therefor, including the specific deposited recombinant DNA molecules. Expression of HBsAg in E.coli was achieved by the Patentee as confirmed also later by document (15) and further by other groups at Institut Pasteur and University of California.

XII. The Appellants and the Intervener requested that the decision under appeal be set aside and the European patent be revoked.

The Respondent requested that the appeals be dismissed, the intervention be rejected and the patent be maintained on the basis of the main request or, alternatively, of the first or second auxiliary request in the two versions for non-AT States and for AT.

Reasons for the Decision

1. The appeals are admissible.

2. The initial finding by the present Board that the intervention of Medeva Plc was admissible under Article 105 EPC (see section VII, second paragraph) has been confirmed by the decision of the Enlarged Board of Appeal G 1/94 dated 11 May 1994 (to be published in the OJ EPO) insofar as the latter Board found that an intervention raised at the appeal stage is admissible. The present Board finds the intervention by Medeva Plc admissible also with regard to the further conditions laid down by Article 105 EPC concerning time limits and a written notice of intervention.

In said decision the Enlarged Board of Appeal further found that an intervention may be based on any ground for opposition under Article 100 EPC and that, if a fresh ground is raised by the Intervener, the case should normally be remitted to the first instance for further prosecution (see point 13 of the Reasons). In the present case, the intervention by Medeva Plc was essentially based on the same grounds, arguments and documents put forward by the Appellants. Thus, a remittal of the case to the first instance on the ground that an intervention was filed is not necessary.

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

The extent of protection conferred by the amended claims of the main request or by the claims of the two auxiliary requests is either unchanged or narrower when compared with that conferred by the granted claims. Thus, the requirements of Article 123(3) EPC are met.

With respect to the requirements of Article 123(2) EPC, it is observed that, although the expression "being free of any human and any primate serum proteins" used to qualify the polypeptide in Claims 6 to 10 (non-AT) of the main request is not explicitly mentioned in the application documents as originally filed, it is unambiguously derivable from their context (see in particular page 4, lines 4 to 35). Thus, also the requirements of Article 123(2) EPC are met.

4. *Entitlement to priority (Articles 87 and 88 EPC)*

4.1 The right to priority is governed by Article 87 EPC, which requires that the European patent application and the application whose priority is claimed relate to the **same invention**. Article 88(3) EPC further specifies

that, if one or more priorities are claimed in respect of a European patent application, the right of priority shall cover only those elements of the application which are included in the application(s) whose priority is (are) claimed.

4.2 Claims 2, 4 and 11 (non-AT) of the main request, as well as Claims 1, 3 and 5 (non-AT) of the first auxiliary request and Claims 1 to 3 (non-AT) of the second auxiliary request, relate to two specific recombinant DNA molecules, which have been deposited in the form of transformed E.coli cells containing them (deposit A: NCIB 11548 and deposit B: NCIB 11549) on 20 December 1979 (i.e. before the date of filing of the European patent application) with a recognised depositary institution, namely NCIB (cf. OJ EPO 1/1980, page 4; see Rule 28(1) and (9) EPC). The NCIB deposits were duly made available to the public from the date of publication of the patent application [see Rule 28(3) EPC].

According to attachment 4, items 94 and 95 [see section X, item (a), above], the corresponding deposits A and B referred to in the BI priority document, which - due to the strict regulations in force at that time (see attachment 4, item 93) - were deposited a short time before the BI priority date with the Culture Collection at Porton Down (in 1978 this was not among the six depositary institutions recognised for the purpose of Rule 28 EPC) consisted each of a number of distinct exemplary colonies picked onto array plates from the same transformation exercise. The said deposits had the features recited on page 11 of the BI priority document.

According to attachment 4, item 100, when deposits A and B with NCIB were made for the purpose of the European patent application, one colony from each original array

plate deposit was transferred. The NCIB deposits A and B had the features stated on page 23, lines 9 to 12 of the original application document which are **the same** as those of the corresponding deposits A and B of BI priority document.

The Intervener questions the identity of the deposits A and B of the two documents and, thus, the entitlement of the NCIB deposits A and B to the BI priority on the basis of the fact that a selection took place at the time of the transfer.

The evidence available shows that, having at its disposal for each of the initial deposits A and B a number of substantially equivalent exemplary colonies obtained from the same transformation exercise (**same** starting materials, **same** protocols, **same** experimental conditions), the Respondent simply transferred one exemplary colony from each of the original deposits A and B to the NCIB collection. This was not a selection which implied a motivated preferential choice, but merely the choice of **one representative** from a group of **alternative exemplary colonies**. As deposit A (NCIB 11548) and deposit B (NCIB 11549) can be traced back and identified with those of BI priority application, they represent subject-matter in respect of the **same invention** as that disclosed in this priority document, which means that under the provisions of Articles 87 and 88 EPC the quoted claims are entitled to the corresponding priority date.

The fact that the Intervener, as stated at the oral proceedings, could no longer compare the initial deposits at Porton Down with the later NCIB deposits in order to provide evidence about their identity or non-identity because the initial deposits were no longer

available, cannot reverse the burden of proof and thus cannot be held against the Respondent.

4.3 In respect of Claims 1(b), 6 and 8 to 10 of the main request, Appellant I maintains that they should not be entitled to the BIII priority date because no actual expression data are provided in BIII for HBsAg.

The Board observes that the BIII priority document provides the complete DNA sequence of the cloned HBV DNA, identifies therein the actual portions which encode HBcAg and HBsAg and provides the corresponding amino acid sequences. Furthermore, BIII proposes some cleavages and construction schemes for expression vectors which are stated to result in the production of a polypeptide that exhibits antigen specificity in the radioimmunoassay for HBsAg (see page 7, line 17 to page 10, line 7). Therefore, notwithstanding the absence of a worked example, it cannot be denied that the person skilled in the art has been given comprehensive information about how to carry out the invention, i.e. how to proceed in order to achieve expression. Thus, in the absence of evidence to the contrary, there is no reason to believe that priority document BIII is deficient in respect of some relevant technical information necessary for reducing the claimed invention to practice by the person skilled in the art. 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 in 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, the said claims are considered to be entitled to the BIII priority date.

4.4 The Respondent maintained that the "general" part of Claim 1, i.e. "The use of a DNA sequence coding for a polypeptide displaying HVB antigenicity...for the production of polypeptides displaying HVB antigenicity" was to be considered as an "element" within the meaning of Article 88(3) EPC of the "same invention", namely the expression of HBV antigenic proteins, as disclosed in priority document BI. Consequently, in its submission, Claim 1 under the provisions of Articles 87(1) and 88(2) and (3) EPC was entitled to both the BI and BIII priority dates.

The said general part of Claim 1 defines the framework of the **actual invention**. In this sense it is not an "element", i.e. an essential feature, of the claimed invention within the meaning of Article 88(3) EPC. Although it is true that it is the subject-matter of the claim as a whole which embodies the claimed invention (see in this respect decision T 13/84, OJ EPO 1986, 253, in particular point 15 of the Reasons), the essential features of the invention defined in present Claim 1 reside in the two **selected** embodiments, one being specifically related to sequence (a) and the other specifically to sequence (b). As there is no support for these two coding sequences either in the BI or in the BII priority document, the "same invention" must be regarded to have been disclosed for the first time in the BIII priority document. Thus, in accordance with Articles 87(1) and 88(3) EPC, Claim 1 is entitled only to the BIII priority date.

4.5 According to the Respondent, Claims 3, 5 and 12 (non-AT) of the main request (and, consequently Claims 2, 4 and 6 of the first auxiliary request) should be entitled to the priority of BIII because the latter discloses all the information necessary for the construction of the subject recombinant DNA molecules.

The Board observes that, although the BIII priority document provides general information about the construction of expression vectors, there is **no support** for the detailed, specific information in respect of the unique recombinant DNA molecules now referred to in the quoted claims. Such specific information together with the deposit accession number of the corresponding transformed cells is provided only subsequently in the European patent specification (see page 13, lines 54 to 56; see also page 36 of the European patent application). Thus, in the absence of any basis in the BIII priority document for the specific subject-matter of the quoted claims, these are not entitled to the BIII priority date, but to the filing date of the European patent application.

4.6 For the above reasons, the Board confirms the allocation of the priorities as made in the decision under appeal.

5. *Sufficiency of disclosure (Article 83 EPC)*

5.1 The Intervener maintains that the teachings of the patent specification are not sufficient to enable the expression in E.coli of HBsAg in a form (including a proper three dimensional structure) which permits it to display HBV antigenicity, i.e. immunogenicity. In its submission, this has not yet been achieved.

Appellant V considers, in particular in relation to Claims 3, 5 and 12, that the patent specification contains an insufficient description of the feature "VA+".

5.1.1 As stated in decision T 158/91 dated 30 July 1991 (not published in the OJ of the EPO), an examination as to sufficiency of a disclosure depends on the correlation of the facts of the case to general parameters such as,

for example, the character of the technical field and the average amount of effort necessary to put into practice a written disclosure in that field, the common general knowledge at the time when the disclosure was made and the amount of technical detail disclosed (see point 2.3 of the Reasons).

5.1.2 As for the amount of technical detail disclosed, the Board observes that the present specification provides the complete DNA sequence of the portions of the HBV genome (serotype adyw) which encode the surface and the core antigens (see granted Claim 1 - non-AT). The amino acid sequences of the latter are also disclosed (see granted Claim 8 - non-AT). The construction of recombinant DNA molecules which lead to the expression in a transformed host of polypeptides displaying HBV antigenicity is set forth (see pages 7 to 13 of the granted patent).

Transformed host strains containing the said recombinant DNA molecules and producing polypeptides displaying HBV antigenicity ("VA+") have been duly deposited in accordance with the provisions of Rule 28 EPC (see page 10, lines 10 to 22 and page 13, lines 50 to 56).

HBV antigenicity is measured in the specification on the basis of a positive response in a radioimmunoassay (HBcAg and HBsAg) and/or of the ability to induce in vivo antibodies which are reactive in immunodiffusion assays (HBcAg). It is well known that the ability to react specifically in a radioimmunoassay does not necessarily imply immunogenicity which is not an inherent property of a molecule but depends on the system and conditions employed for producing immunity.

The reported positive response of the polypeptides expressed in E.coli in the respective radioimmunoassays

for HBcAg and HBsAg showed that they displayed indeed HBV antigen specificity. The serological activity in vivo of the HBcAg-like polypeptide expressed in E.coli showed that it displayed indeed HBV antigenicity. It was thus demonstrated by the specification that the synthesis of HBV polypeptides in a recombinant DNA system was indeed feasible. This was the immediate objective of the disclosure and the correlation of the facts of the case with general parameters shows that it was achievable to a reasonable extent. To judge the sufficiency of disclosure on the basis of a further objective to be achieved, i.e. immunogenicity, - as demanded by the Intervener - would not be justified.

5.1.3 As for the amount of general knowledge at the time of the disclosure, the Board observes that, although at the priority/filing date of the present patent specification the recombinant DNA technology was still in its infancy, the Appellants have submitted nothing which would show that the common general knowledge in combination with the technical guidance of the specification would not have allowed the putting into practice of the claimed invention by a person skilled in the art.

5.2 Appellant V maintains that Claims 2, 4 and 11 do not meet the requirements of Article 83 EPC because the priority documents BI and BII do not meet the basic conditions for a sufficient disclosure for the reason that the only information provided in the BI and BII priority documents is the deposition number, nothing being said about the antigen specificity of any product.

5.2.1 Once it is established under Articles 87 and 88 EPC that a particular claimed subject-matter is entitled to a given priority date because it is the same invention as sufficiently disclosed in the corresponding priority document (see point 4.2 above), the examination as to

the sufficiency of disclosure of the invention thus claimed is to be carried out on the basis of the contents of the European patent specification as a whole, i.e. the claims, the description and the drawings or figures, if present (see, for example, T 14/83, OJ EPO 1984, 105).

In the present case, as already stated in point 4.2, above, deposits A (NCIB 11548) and B (NCIB 11549) are entitled to the priority date of BI. Since the Appellants have not shown that the **European patent specification** does not disclose the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, the Board is satisfied that - in the absence of evidence to the contrary - there is sufficient disclosure in the patent-in-suit not only in respect of the recombinant DNA molecules contained in the strains duly deposited according to Rule 28 EPC, but also in respect of some of their properties such as HBV antigenicity (see page 10, lines 10 to 32).

5.3 In view of the foregoing, the Board concludes that the requirements of Article 83 EPC are met.

6. *Industrial applicability (Article 57 EPC)*

Appellant V objects to Claims 2, 4 and 11 (non-AT) under Article 57 EPC because it finds no useful indication as to the nature of the "HBV antigenicity" referred to therein.

As used in the context of the present patent specification, the expression "HBV antigenicity" in relation to the polypeptides produced by a cultured transformed host refers both to their ability to react specifically in a radioimmunoassay with antibodies

against HBcAg or HBsAg (antigen specificity) and/or to their ability to induce in vivo antibodies which are reactive in immunodiffusion assays (see point 5.1.2 above). The statements on page 8, line 61 to page 9, line 41 of the patent-in-suit (see also the originally filed application from page 19 line 10 to page 21 line 16) indicate that both activities have an application in the pharmaceutical/diagnostic fields. Thus, in the Board's view, the objection raised under Article 57 EPC by Appellant V is unfounded.

7. *The citability of document (1)*

7.1 In the opinion of the Respondent, the technical content of document (1) is essentially identical with that of the BI (or BII) priority document. In this respect, the Respondent makes reference also to the criteria used for allocating priority (see, for example, decision T 73/88, loc.cit.). The Respondent submits that, in accordance with decision T 301/87 (loc.cit), document (1) should not be considered state of the art for the subject-matter entitled to a subsequent priority date.

7.2 In decision T 301/87 (loc.cit.), the Board - in an obiter dictum - expressed the view that the subsequent publication of the content of the priority application was not to be considered state of the art against the European application (see points 7.5 to 7.8). The facts in the case at issue there indicated that the subsequent publication was no more than effectively a true disclosure of the first priority document (see point 7.9). In the same decision, the Board indicated also that "if such publication goes beyond the content of a previously filed application and includes subject-matters not covered by the disclosure of that application, such disclosure may in principle be cited against any claim in the (final) European patent

application relying on a priority date subsequent to the publication date" (see point 7.8).

In decision T 441/91 dated 18 August 1992 (not published in the OJ EPO), the Board decided that the publication of the technical content of the priority document in the priority interval was to be considered state of the art under Article 54(2) EPC for the European patent application which, in the specific case, was not entitled to the claimed priority (see point 3.2).

This point of law is now pending before the Enlarged Board of Appeal (Ref. No. G 3/93; see OJ EPO 1993, 477).

7.3 In the present case, although some of the **general** information contained in BI (or BII) is also part of the said publication (1), the latter contains a considerable amount of **specific** and **essential** technical information which is not derivable from BI (or BII). For example, document (1) provides information about the donor source and the HBV serotype (adyw), it provides a specific restriction enzyme analysis, it relates to specific plasmids (see Table 1) which are not disclosed in the BI priority document, it provides experimental protocols which are more detailed than those provided in the BI priority document and which moreover partly differ therefrom, it provides data as to the nature of the expressed product(s), it reports results from radioimmunoassays and provides information about the specific antisera used and it indicates that 'introns' are probably absent (see, in particular, pages 45 to 47). All these pieces of information and data are not provided in the BI priority document.

Therefore, the Board does not agree with the Respondent's view that the technical contents of the BI (or BII) priority application are essentially identical

with those of document (1) and that the only difference is the scientific interpretation of the results given in document (1). The Board is rather of the opinion that document (1) is **far more than effectively a true disclosure** of the BI (or BII) priority document. As shown above, the BI (or BII) priority application and publication (1) show considerable differences in the substance of their disclosure so that they are to be viewed as documents having different technical contents. The fact that the two documents have in common the **general** teaching of the fragmentation of HBV DNA and the construction of vectors to be used for the preparation of products displaying HBV antigenicity does not render them essentially identical or equivalent.

In this situation, the application of the criteria used in examining the validity of a priority as suggested by the Respondent with particular reference to decision T 73/88 (loc.cit.) is not of much help, because it would lead to the same conclusion that the two documents in question have differing technical contents.

7.4 The Opposition Division discarded document (1) because it considered the disclosure of the plasmids of Table 1 as not enabling. However, in the Board's view, non-enablement of the said plasmids alone would not be sufficient to render the entire technical teaching of document (1) non-enabling for the reason that the said plasmids are merely an example of recombinant DNA molecules which can be prepared by applying the detailed protocols that are given. The said protocols provide sufficient information to enable the preparation of alternative recombinant DNA molecules displaying the same properties.

7.5 The Board, therefore, concludes that document (1) is state of the art citable against any claimed subject-

matter which is entitled to a priority date subsequent to its publication date.

Under these circumstances, the Board does not consider it necessary to refer to the Enlarged Board of Appeal the legal question formulated by the Respondent [see section XI, item (b), second paragraph] because it is not relevant to the present case where the technical contents of the two documents (priority application and publication) are different. In fact, even if the Board in evaluating inventive step were to exclude the part of the disclosure of document (1) which is in common with the BI priority document (see above point 7.3, second paragraph, last sentence) as proposed by the Respondent, this would not have a decisive effect on the outcome of the examination in view of the relevance of the additional, specific technical information provided in document (1) (see point 7.3, first paragraph, above).

For the same reasons, it is also not necessary in the present case to await the pending decision of the Enlarged Board of Appeal on this point of law (see point 7.2 above, last paragraph).

8. *The main request: Claims 1, 6 to 10 (non-AT)*

8.1 Novelty (Article 54 EPC)

8.1.1 Claims 1, 7 to 10 relate to specific DNA sequences, to fragments thereof and to DNA sequences which are degenerate as a result of the genetic code to any of the previous sequences, which encode a polypeptide with HBV antigenicity. Claim 6 as well as Claim 10 relate to a specific amino acid sequence or fragments thereof displaying antigenicity of HBsAg.

8.1.2 Prior art documents (2), (3) and (6), which were relied upon by the Appellants and the Intervener, all relate to the cloning and structural analysis of HBV DNA of either adw or ady subtypes. Document (3) reports the complete primary structure of the viral genome and identifies eight open reading frame regions, in particular the region which contains the HBsAg gene. Both documents (2) and (6) disclose the location of the HBsAg gene in the genome, its nucleotide sequence and the deduced amino acid sequence of the encoded antigen.

None of the said documents discloses sequences or fragments thereof identical with those recited in the claims at issue.

The argument propounded by Appellant V that, in view of the particular nature of the field, small differences in a sequence are not sufficient to confer novelty cannot be accepted by the Board as it is well known that even a change in one amino acid can dramatically change the properties of a protein molecule.

The argument put forward by the Intervener that novelty of the claims under consideration should be affected because a comparison of the known sequences with the claimed sequences shows that they contain identical stretches is, in the Board's opinion, merely theoretical because none of the cited documents discloses or suggests any discrete fragment of the reported sequences as an identifiable entity which could be used for a comparison.

8.1.3 On the other hand, document (1), which reports the cloning and expression of DNA fragments of HBV subtype adyw and which represents the closest prior art here, does not report any definite sequence data which can be said to affect the novelty of the claims at issue. In

fact, although the nucleotide sequences referred to in the latter are likely to be contained in the said fragments, they are not identified and characterised in their exact primary structure and thus they are not made available in the sense of Article 54(2) EPC.

8.1.4 For the above reasons, the subject-matter of the claims at issue is novel.

8.2 Inventive step (Article 56 EPC)

8.2.1 As already stated, document (1) represents the closest prior art for the claims at issue. This document reports the construction of cloning and expression vectors containing DNA fragments of HBV genome subtype adyw. Cells transformed with the said vectors are reported to produce antigenic material that reacts specifically with antisera to HBV antigens, in particular HBcAg (positive reaction) and also HBsAg (faint positive reaction).

8.2.2 In the light of document (1), the technical problem to be solved can be seen in the exact identification and characterisation of DNA sequences of HBV genome subtype adyw encoding HBcAg and HBsAg within the known discrete DNA fragments in view of their use in a recombinant DNA system for the production of HBV antigens and of compositions containing the latter.

8.2.3 This problem is solved by providing the specific DNA sequences encoding HBcAg and HBsAg referred to in the present claims, (see, for example, Claim 1). In view of the detailed information contained in the patent-in-suit on the preparation of polypeptides displaying HBV antigenicity by use of the said sequences (see also point 5.1.2, above), the Board is satisfied that the above-stated technical problem has been solved by the said specific DNA sequences.

8.2.4 The relevant question in respect of inventive step is whether it was necessary for the skilled person to apply inventive skill in order to arrive at the claimed solution.

When coping with the underlying technical problem, the skilled person would have considered the contents of prior art documents which dealt with the characterisation of the primary structure of HBV genomes of other serotypes or with the characterisation of the HBV antigens.

At the BIII priority date, which is the relevant time limit for the claims at issue (see above point 4.3), a good amount of knowledge was available in the prior art in respect of HBV and its genome [see, for example, documents (2) to (4), (6), (8) to (9), (12) to (13)]. In particular documents (2), (3) and (6) had already provided extensive DNA and amino acid sequence information on HBV of other subtypes. Document (1) had disclosed discrete DNA fragments of HBV genome subtype adyw which comprised the DNA sequences encoding HBcAg and HBsAg and had shown expression thereof in a recombinant DNA system.

In the light of all the information available, it would have readily occurred to the skilled person to try to complete the work described in document (1) by identifying and characterising the primary structure of the DNA sequences encoding HBsAg and HBcAg within the said fragments of the genome of HBV subtype adyw and to express them in a recombinant DNA system such as, for example, that described in document (1) so as to produce antigenically active products. This would have involved nothing out of the ordinary for a skilled person in the field of molecular biology at that time as all the necessary methods and means (e.g. antisera specific for

HBcAg and HBsAg) as well as techniques for the location and DNA sequence analysis were known in the art [see e.g. (25)]. The skilled person merely needed to proceed experimentally as done by previous authors in documents (2), (3) or (6), knowing from document (1) that the expression of antigenically active products was to some extent feasible in a recombinant DNA system. In this respect, it must be kept in mind that expression of HBV antigen in general, **not** the efficiency of expression is at issue here.

Document (1) had also removed the alleged prejudices as to the presence of intervening sequences and/or to the degradation of the expressed products (see page 47, left column, "Conclusions and further implications"). For these reasons, the skilled person would have performed the experimental work with a reasonable expectation of success.

Moreover, being aware of the heterogeneity of the HBV genome and of the different subtypes, the skilled person would have expected with good reason to find differences between the newly isolated nucleotide and amino acid sequences of the adyw subtype and those of the prior art.

This situation cannot be compared with one where production of a partially known protein in a recombinant DNA system was achieved and considered inventive on the basis of the fact that in the specific circumstances of the case there was no realistic expectation of success (see e.g. T 500/91 of 21 October 1992, not published in the OJ of the EPO and T 223/92 of 20 July 1993, not published in the OJ of the EPO). In the present case, document (1) had already disclosed the cloning and expression of the HBV genome subtype adyw. The identification and characterisation of the now claimed

specific sequences of the **same genome** involved for the skilled person nothing more than the carrying out of experimental work by routine means within the framework of the normal practice of filling gaps in knowledge by application of the existing knowledge. In the Board's view, no inventive skill was required by the skilled person therefor.

8.2.5 The Board, therefore, concludes that it would have been obvious for the skilled person to try to identify and characterise the DNA sequences of HBV subtype adyw encoding HBcAg and HBsAg and that he or she would have readily done so with a reasonable expectation of success thereby arriving in a straightforward manner at the subject-matter of present claims 1, 6 to 10. Thus, the said claims lack an inventive step and the main request is not allowable.

9. *The first auxiliary request*

Claim 1 (non-AT) reads as follows:

"A recombinant DNA molecule selected from the recombinant DNA molecules contained in the transformed E.coli HB strains identified by accession numbers 11548 and 11549."

Claim 2 (non-AT) reads as follows:

" A recombinant DNA molecule selected from the recombinant DNA molecules contained in the transformed E.coli HB strains identified by accession numbers 11558, 11559 and 11560."

9.1 Novelty (Article 54 EPC)

All claims of this request relate to specific recombinant DNA molecules duly deposited in the form of transformed E.coli cells according to Rule 28 EPC (see points 4.2 and 5.1.2, second paragraph, above).

None of the prior art documents quoted during the proceedings discloses the same specific recombinant DNA molecules or construction schemes which inevitably lead thereto. Thus, the subject-matter of this request is novel.

9.2 Inventive step (Article 56 EPC)

9.2.1 Claims 1, 3, 5 (non-AT) and Claim 1 (AT)

As already stated above (see point 4.2), these claims are entitled to the priority date of BI.

The Appellants and the Intervener deny an inventive step to these claims in the light of the combination of document (4) with the common general knowledge of HBV, in particular documents (8), (9) and (13), and of gene expression, in particular document (59).

The Respondent maintains that document (4) is not prior art with respect to these claims [see section XI, item (d), second paragraph].

At oral proceedings, the question whether the date printed on document (4) was in fact the date on which the said document was made generally available to the public within the meaning of Article 54(2) EPC raised by the Respondent's late submissions was not examined because - as shown below - the Board found that the

outcome of the examination with regard to inventive step was the same regardless of the answer to the said question.

If the assumption is made that document (4) was state of the art at the BI priority date, it represents indeed the closest prior art. This document discloses the cleavage of DNA of HBV with a restriction enzyme, notably EcoRI, the insertion of the linearized genome into a lambda phage derivative and its cloning in E.coli. The aim of the studies disclosed in document (4) is to arrive at the production of HBV polypeptides in a recombinant DNA system for vaccine preparation. However, neither expression data nor information nor hints on how expression could be achieved are provided therein.

In view of document (4), the underlying technical problem is to be seen in the preparation of HBV polypeptides by expression of the HBV genome in a recombinant DNA system.

The solution consists in the specific, deposited recombinant DNA constructs of the claims at issue which indeed have shown to express polypeptides with HBV antigenicity in E.coli (see pages 12 and 13 of the patent specification).

The person skilled in the art confronted with the said technical problem needed to consider carefully, in addition to the prior art related to HBV, also the state of knowledge in respect of expression of foreign genes, in particular of viral genes, in recombinant DNA systems.

As for HBV, some knowledge was available concerning the Dane particles and their constituents (inter alia HBsAg, HBcAg, circular DNA and DNA polymerase activity) [see

documents (8), (9) and (13)]. However, there was some uncertainty on whether the Dane particles might be the complete virus and whether the HBV polypeptides were all specified by viral genes. Moreover, little or no information was available on the physical structure and on the genomic chart of the genome [see for review document (8)].

As for the state of the art in respect of the expression of foreign genes in recombinant DNA systems, admittedly at the BI priority date recombinant DNA technology was still in its infancy. There were some reports of successful expression of eukaryotic proteins in E.coli expression systems [see, for example, document (59)], but no reports whatsoever of expression of any eukaryotic viral antigen. Moreover, there were some uncertainties in respect of expression of eukaryotic genes in a prokaryotic host linked especially to the presence of introns and to the instability or degradation of the expressed products. The Appellants and the Respondent essentially agree on the above estimation of the state of the art, but disagree on the extent to which the person skilled in the art would have been conditioned by the said uncertainties in his or her activity (cf. affidavit of Dr Old and affirmation of Prof. Almond).

In the Board's view, the person skilled in the art would not have arrived readily at the specific constructs of the claims at issue for the reason that nothing in the available prior art would have readily suggested cleaving the HBV genome subtype adyw with two specific restriction enzymes, namely Kpn I or Bam HI, selected from the large number which was already known at that time so as to obtain the specific fragments used in the construction of the claimed recombinant DNA molecules. As a matter of fact, only with hindsight is it now

possible to follow the specific route leading to the construction of the two successful recombinant DNA molecules of the claims at issue. Nothing in document (4) or in any other document would have suggested to the skilled person precisely this construction route.

Moreover, even in the light of document (4), the stated uncertainties both in respect of the HBV and of the expression of eukaryotic genes in prokaryotic hosts would not have allowed the skilled person in 1978 to make any reasonable prediction about the possibility of achieving expression of HBV genome fragments in a prokaryotic host. This would be even less so, if document (4) is not taken into consideration.

Consequently, an inventive step is to be recognised for the said claims.

9.2.2 Claims 2, 4, 6 (non-AT) and Claim 2 (AT)

As already stated above (see point 4.5) these claims are entitled to the filing date of the European patent application.

The Appellants and the Intervener deny an inventive step to these claims, in particular on the basis of document (7), which was published between the BIII priority date and the filing date.

The Respondent points out that document (7) corresponds to the publication of the contents of the BIII priority publication and thus, in accordance with decision T 301/87 (loc.cit.), should not be citable.

At oral proceedings, the question whether document (7) was citable or not in the light of decision T 301/87 (loc.cit.) was not examined because - as shown below -

the Board found that the outcome of the examination with regard to inventive step was the same regardless of the answer to the said question.

If document (7) is taken into account, it represents indeed the closest prior art. This document, while disclosing in particular the expression in E.coli of HBcAg, localizes and elucidates the DNA sequence encoding HBsAg within the HBV subtype adyw genome and reports in general terms that in some experiments with recombinant plasmids some clones have given positive reactions in a radioimmunoassay for HBsAg (see page 578, right-hand column). Neither a specific description of the latter plasmids nor of the route for their construction is provided in document (7).

In view of document (7), the underlying technical problem is to be seen in the provision of alternative expression vectors for HBsAg.

The solution consists in the specific, deposited recombinant DNA constructs of the claims at issue which indeed are stated in the specification to express in E.coli polypeptides with HBV antigenicity (see page 13 of the patent specification, in particular lines 54 to 56). The said constructs are obtained by insertion of specific restriction fragments excised from plasmid pHBV114 either into pBR322 (NCIB 11559 and NCIB 11560) or into pUR2 (NCIB 11558).

Both document (7) and document (1) make reference to recombinant plasmids producing in transformed cells a positive reaction in a radioimmunoassay for HBsAg [see document (1), page 46, right-hand column and document (7), page 578, right-hand column]. However, these two documents do not give any specific structural information in respect of the said plasmids. Document

(7) reports the nucleotide sequence of HBV DNA (subtype adyw) and shows therein the beginning of the sequence encoding HBsAg. This document also discloses inter alia plasmid pHBV114 for which the left endpoint (-80) and right endpoint (ca. 2270) of the HBV DNA insert are reported.

In the Board's view, although on the basis of the above information the skilled person would have been in a position to readily construct expression vectors for HBsAg such as those generally reported in documents (7) and (1), he or she would not have arrived readily at the specific constructs of the claimed recombinant DNA molecules because neither document (7), nor document (1), nor any other document gave any hint as to the specific route to be followed therefor. Only with hindsight, i.e. knowing the structure of the final products, can such a specific route now be traced. Nothing in the said documents would have readily directed the skilled person to the excision precisely of restriction fragments Hha I or Ava I or Taq from plasmid pHBV114. These were among the multitudes of possibilities for the skilled person as the HBV DNA insert had several restriction endonuclease targets. On the other hand, the Appellants have been unable to show why the skilled person would have readily selected the restriction fragments in question when trying to develop alternative expression vectors for HBsAg.

Furthermore, in evaluating the inventive step of the subject specific constructs, account should be taken of the fact that, apart from the stated general references to recombinant plasmids producing in transformed cells a positive reaction in a radioimmunoassay for HBsAg in documents (1) and (7), no other comparable, specific construct was known in the art which had already resulted in the successful expression of a product

displaying HBsAg antigenicity. Thus, in tracing out a construction scheme for expression vectors for HBsAg, the skilled person did not have the possibility of starting from already-known construction schemes which could have made easier the finding of alternative ones.

For these reasons, the Boards concludes that the subject-matter of the claims at issue involves an inventive step.

Consequently, the first auxiliary request is allowable.

10. *The second auxiliary request*

In view of the above conclusion in respect of the first auxiliary request, a discussion of the second auxiliary request is superfluous.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the claims of the first auxiliary request (non-AT and AT), as submitted in the oral proceedings, and a description to be adapted thereto.

The Registrar: The Chairwoman:

P. Martorana U. Kinkeldey