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D E C I S I O N
of 29 May 2001

Case Number: T 0091/98 - 3.3.4

Application Number: 88101795.8

Publication Number: 0306597

IPC: C07H 19/073

Language of the proceedings: EN

Title of invention:
Antiviral nucleosides

Patentee:
THE WELLCOME FOUNDATION LIMITED

Opponent:
Roche Diagnostics GmbH

Headword:
Antiviral nucleosides/WELLCOME

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - main, first, second and third auxiliary requests - no"
"Inventive step - fourth auxiliary request - yes"

Decisions cited:
G 0009/91, T 0750/94, T 0296/93

Catchword:
The date at which an information, put in a Lexis-Nexis data base, was publicly available not established to a degree of certainty established by the case law of the boards of appeal

(see T 750/94) (points 25 to 31).



Case Number: T 0091/98 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 29 May 2001

Appellant: THE WELLCOME FOUNDATION LIMITED
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Representative: Blakey, Alison Jane
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Respondent: Roche Diagnostics GmbH
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Representative: Ziebig, Marlene, Dr. Dipl.-Chem.
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 10 November 1997
revoking European patent No. 0 306 597 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
S. U. Hoffmann

Summary of Facts and Submissions

I. The appeal lies from the decision of the Opposition Division to revoke the European patent No. 0 306 597 with the title "Antiviral nucleosides" filed under the application No. 88 101 795.8 on 14 March 1986 as a divisional application of European patent No. 0 196 185. The granted patent comprised 40 claims for all Designated Contracting States except AT and 18 claims for the Contracting State AT. The patent in suit claims priorities from 16 March 1985 (GB 8506869), 9 May 1985 (GB 8511774), 17 September 1985 (US 776899), 27 September 1985 (GB 8523881) and 12 February 1986 (GB 8603450).

Granted claims 1 and 16 for all designated Contracting States except AT read as follows:

"1. A pharmaceutical formulation comprising a pharmaceutically acceptable derivative of 3'-azido-3'-deoxythymidine, and a pharmaceutically acceptable carrier therefor.

"16. Pharmaceutically acceptable derivatives of 3'-azido-3'-deoxythymidine which, upon administration to a human subject, are capable of providing (directly or indirectly) 3'-azido-3'-deoxythymidine, or an anti-retrovirally active metabolite or residue thereof, other than the following 5'-derivatives, namely the monophosphate, disodium monophosphate, 2-cyanoethyl monophosphate, monosodium 2-cyanoethyl monophosphate, 4-nitrophenyl monophosphate, triphosphate, p-toluene sulphonate, acetate, methanesulfonate and triphenylmethyl derivatives and where the 5'-C of 3'-azido-3'-deoxythymidine is linked to a further

nucleotide or nucleoside derivative."

Dependent claims 2 to 14 related to further features of the formulation of claim 1 and dependent claim 15 related to a process for the preparation of said formulations. Dependent claims 17 and 18 were directed to further features of the derivatives of claim 16. Claim 19 related to a process for the preparation of any of these compounds. Independent claims 20 to 28 related to pharmaceutically acceptable derivatives of 3'-azido-3'-deoxythymidine (hereafter called azidothymidine) for specific uses. Independent claim 29 was directed to pharmaceutically acceptable derivatives in specific forms. Independent claims 30 to 39 were directed to uses of said derivatives for the manufacture of a medicament. Claim 40 related to the use as in claims 30 to 39 wherein the active agent was in the form of a salt, ester or salt of an ester.

- II. The Board sent a communication under Article 11(2) of the Rules of Procedure of the Boards of Appeal, stating their preliminary non-binding opinion.
- III. In answer to the Board's communication, the Appellants (Patentees) filed three auxiliary claim requests.

Claim 1 of auxiliary request 1 read as follows:

"1. A pharmaceutical formulation comprising a pharmaceutically acceptable derivative of 3'-azido-3'-deoxythymidine, and a pharmaceutically acceptable carrier therefore which is other than water."

Claim 14 of auxiliary request 2 read as follows:

"14. Pharmaceutically acceptable derivatives of 3'-azido-3'-deoxythymidine which upon administration to a human subject are capable of providing (directly or indirectly) 3'-azido-3'-deoxythymidine, or an antiretrovirally active metabolite or residue thereof, which are esters selected from the group consisting of the 5'-diphosphate, 5'-(3-methylbutyrate), 5'-octanoate, 5'-palmitate, 5'-(3-chlorobenzoate), 5'-benzoate, 5'-hydrogen succinate and 5'-pivalate esters of 3'-azido-3'-deoxythymidine."

Claim 1 of auxiliary request 3 read as follows:

"1. A pharmaceutical formulation adapted for oral administration comprising a pharmaceutically acceptable derivative of 3'-azido-3'-deoxythymidine, and a pharmaceutically acceptable carrier therefore."

At oral proceedings the Appellants filed a fourth auxiliary request. Claim 1 of auxiliary request 4 read as follows:

"1. A pharmaceutical formulation comprising a pharmaceutically acceptable derivative of 3'-azido-3'-deoxythymidine, and a pharmaceutically acceptable carrier therefore, said formulation comprising a unit dose of between 5 and 1500mg of the active ingredient."

Dependent claims 2 to 12 related to further features of the pharmaceutical formulation of claim 1 and dependent claim 13 related to a process for the preparation of said formulations.

The corresponding claims 1 to 12 were filed for the designated Contracting State AT.

III. The following documents are mentioned in the present decision:

- (1): Glinski, R.P. et al., J.Org.Chem., Vol. 38, No. 25, pages 4299 to 4305, 1973,
- (7): Ostertag, W. et al., Proc.Nat.Acad.Sci.USA, Vol. 71, No. 12, pages 4980 to 4985, 1974,
- (8): print out of the Lexis Nexis data base filed by the espondents with their submissions dated 13 August 1996,
- (10): Robins, R.K., Pharmaceutical Res., Vol. 1, pages 11 to 18, 1984,
- (12): declaration of Connie Landis filed by the Respondents with their submissions dated 29 August 1997,
- (13): affidavit of Monica Kitts filed by the Respondents with their submissions dated 29 August 1997,
- (14): letter of Tobin Beck filed by the Respondents with their submissions dated 29 August 1997,
- (17): Ostertag, W. et al., Exp.Cell.Res., Vol. 116, pages 31 to 37, 1978,
- (22): Declaration of Martha St Clair filed by the Appellants with their submissions dated 21 May 1998.

IV. The arguments in writing and at oral proceedings by the

Respondents as far as they are relevant for this decision can be summarized as follows:

Main request

Article 56 EPC; claim 1

The closest prior art was document (7). At a time when anti-AIDS drugs were actively sought for, the teaching of this document would undoubtedly have come to the skilled person's attention. It was stated on page 4984 that the replication of a mouse retrovirus was inhibited by azidothymidine and that the compound was highly toxic to the virus but not to the cells. Document (7) would, thus, inevitably lead the skilled person to assess the effect of azidothymidine or its derivatives on the human retroviruses, which did not distinguish itself from the mouse retrovirus in any relevant manner. Even the teachings of document (7) that A-type particles were formed during differentiation of cells transformed by a mouse retrovirus would not detract the skilled person from trying azidothymidine as a drug, taking into account the immense pressure that there was at the time to try all compounds which appeared to have the potential of stopping retroviruses. The skilled person would have a reasonable expectation of success that azidothymidine or its derivatives could be used as a drug as it was toxic to the virus but not to the cells.

First auxiliary request

Article 56 EPC

The claims of this request were dependent claims in the requests before the opposition division and, therefore, the facts in the present case were in accordance with

those having been the findings of G 9/91 (OJ EPO 1993, 408). Claim 1 only differed from claim 1 of the main request which was not inventive in that the carrier compound within the claimed pharmaceutical formulation was other than water. It was a matter of routine for the skilled person to include in a pharmaceutical composition whichever carrier might be suited for the intended use.

Second auxiliary request

Article 56 EPC, claim 14

The claim related to **specific** derivatives of azidothymidine which were not characterized by any unit dose. Thus, it covered derivatives at a unit dose which would not result in the required effect of killing the virus without harming the cells. Such derivatives were not inventive. Furthermore, no surprising effect was attached to the structure of any of the claimed specific derivatives.

Third auxiliary request

Article 56 EPC, claim 1

It was a matter of common knowledge that pharmaceutical formulations to be taken orally had distinct advantages for the patients. As the claim covered very many derivatives of azidothymidine, it was to be expected that some of them would not be suited for oral administration. These at least did not involve inventive step.

Fourth auxiliary request

Article 56 EPC, claim 1

- Claim 1 enjoyed priority only from the filing date of the patent in suit (14 March 1986). The feature, which it contained, that the claimed formulations were to comprise a unit dose of between 5 and 1500 mg of the active substance did not impart inventive step over the teachings of document (8). This document was a printout of the Lexis-Nexis data base retrieved in paper form in 1996, disclosing the news dated 3 September 1985 that azidothymidine was an effective drug against AIDS virus. As the Lexis-Nexis data base was supplemented on a daily basis with incoming news, it must be accepted on the balance of probabilities that the news dated 3 September 1985 was available to the public at least on 4 September 1985. Evidence therefore had been provided in documents (12) to (14). Once it was known from document (8) that azidothymidine could be used as an antiretroviral drug, it required no inventive step to find the proper dosage for the drug.

- If document (8) was disregarded, there remained the declaration of Martha St Clair submitted by the Appellants on 23 May 1998 where it was stated that a meeting took place from 29 September to 2 October 1985 in Minneapolis, where azidothymidine was disclosed for the first time as an antiretroviral agent. At the filing date, the skilled person, thus, knew that the compound was effective at doses compatible with treatment and it required no inventive step to find which these doses were.

- Document (7) published before the priority date could also be seen as the closest prior art. Once its teaching was known that azidothymidine interfered with retroviral replication, it was obvious to determine the unit dose at which it would be suitable in a medical

treatment.

- V. The arguments by the Appellants in writing and during oral proceedings, insofar as they are relevant to the present decision are essentially as follows:

Main request

Article 56 EPC; claim 1

- In the course of the proceedings, the closest prior art was defined as document (7). Yet, this document was not concerned with finding an antiretroviral drug. It was a study on the effect of two chemical compounds, BrdUrd and azidothymidine on the induction of endogenous virus in cell cultures, ie when the virus was in a state different from the state it would be in the acute phase of a disease. Figure 1 showed that azidothymidine was toxic to the cells and, therefore, the inhibition of virus release which was also observed would be due to the fact that dead cells would not support viral replication. In view of these results, the skilled person would take the statement on page 4984 that azidothymidine inhibited virus replication as a mere speculation and not as a suggestion that azidothymidine and its derivatives should be used as a drug. This was all the more true because document (17) disclosed that the number of A-type particles (generally associated with cancer or with the suppression of immune systems) increased in the presence of azidothymidine.

Thus, the problem to be solved could not be formulated from document (7). In fact, there was no closest prior art, which emphasized the pioneering nature of the invention.

- Even if document (7) was taken into account, the skilled person would not have a reasonable expectation of success that azidothymidine could be used as a drug because of its toxicity to the cells.

First auxiliary request

Article 56 EPC, claim 1

- If the Board came to the conclusion that in accordance with decision G 9/91 (supra) the claims of this request which had not been opposed by the Respondents could nonetheless be examined for patentability, the case should be remitted to the first instance for further prosecution.

- If patentability was examined by the Board, then the subject-matter of claim 1 was to be found inventive over the teachings of document (7) in view of the fact that this document did not give the skilled person any incentive to prepare a pharmaceutical composition, let alone to prepare it with a carrier which would not be water.

Second auxiliary request

Article 56 EPC; claim 14

Claim 14 related to **specific** derivatives of 3'-azido-3'-deoxythymidine. If it was accepted that derivatives of this compound were inventive when used in the dose range where they inhibited viral replication but were not toxic to cells, then the specific derivatives were equally inventive, even if the dose range was not mentioned, because they would necessarily be used at the concentration where they would be effective ie at the "inventive" dose range.

Third auxiliary request

Article 56 EPC; claim 1

The inventive step of a pharmaceutical formulation adapted for oral administration lay in the fact that it remained active although administered in this way. It was advantageous for the patient to take the drug orally.

Fourth auxiliary request

Article 56 EPC; claim 1

- The claim related to the same pharmaceutical formulation as in claim 1 of the main request with the additional characteristics that a unit dose comprised between 5 and 1500 mg of the active ingredient. Document (8) cited by the Respondents as closest prior art must not be taken into account as the date of availability to the public of the information, it contained could not be ascertained. Document (8) was a print-out dating from 1996, of an entry in the Lexis-Nexis data base, of a "News wire" story itself dated 3 September 1985. That this entry was present in the data base in 1996 did not make evident when the information became state of the art.

- The affidavit, declaration and letter which the Respondents submitted as evidence that document (8) had been available on or shortly after the 3 September 1985 were deficient in many respects. In accordance with the case law of the Boards of Appeal (T 750/94, OJ EPO 1998, 32), when an issue of facts is examined and decided on the balance of probabilities, the more serious the issue, the more convincing the evidence to support it must be. In view of its content, document

(8) could be very relevant to inventive step and, therefore, the evidence as to its publication date had to be absolutely unambiguous.

- The Respondents' arguments relating to the Conference which took place from 29 September to 2 October 1985 should not be accepted in the proceedings as they were raised for the first time at oral proceedings although the declaration mentioning this conference was on file for three years.

- The closest prior art was document (7). Taking into account that the doses of azidothymidine used in document (7) were 10 fold higher than the claimed dose range, it was very surprising that azidothymidine was an efficient medicament at the claimed concentrations.

The subject-matter of claim 1 and all other claims which were dependent on claim 1 was inventive.

VI. The Appellants requested that the decision under appeal be set aside and that the patent be maintained as granted (main request) and auxiliarily, on the basis of the auxiliary requests 1 to 3 filed on 9 May 2001 or of auxiliary request 4 filed during oral proceedings.

The Respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Main request

Article 56 EPC; claim 1

2. The Appellants argued that, as there was no pharmaceutical formulations to treat diseases caused by retroviruses before that which they produced, there was no closest prior art to the claimed invention. The Board, although agreeing to the facts of the matter, does not consider that, in the given circumstances, they warrant the conclusion, the Appellants drew from them. Indeed, the etiologic agent causative of the diseases which the claimed formulation is intended to fight was identified as being retroviruses about three years before the first priority date of the patent in suit (see document (10), page 11, left-hand column for an historical perspective of the discovery of retroviruses as causative of diseases). As there is a practical impossibility for a pharmaceutical formulation against a given agent to be produced before this agent is identified, the fact that the claimed formulations were the first of the kind undoubtedly reflects the celerity with which the Appellants searched for a remedy against the diseases caused by the retroviruses. Yet, it is not a convincing proof of inventive step because, in such a situation, inventive step rather depends on the state of the art on retroviruses, which may or may not point out in an obvious manner to a way in which these viruses can be eliminated. In the Board's view, the ordinary skilled person would have looked in the literature for any known substances reported to have an effect on retroviruses because of the new and urgent need for a medicament against them. By doing so, he/she would have become aware of document (7) which is considered by the Board as the closest prior art.

3. Document (7) is a study of the effect of, in

particular, azidothymidine, on the release of a retrovirus from transformed mouse spleen cells. The data are shown in Figure 1 and analysed under the heading "Inhibition of viral replication by...azidothymidine", in the first paragraph on page 4981.

It is disclosed that in the presence of azidothymidine, the transforming activity of the virus is decreased to less than 5% of that obtained from virus released from untreated cells and that, at the same time, the growth rate of the mouse spleen cells is changed only minimally compared to that of uninfected cells. In the discussion of their results, the authors mention the inhibition of virus replication by azidothymidine, as well as the low toxicity of this compound for the cells but high toxicity for the virus. Finally, looking into the future which included treating diseases known to be caused by DNA viruses but, of course, did not include treating diseases caused by retroviruses, as these had not yet been discovered, they suggest that azidothymidine might favorably replace another compound, BrdUrd, in a medical treatment against diseases caused by said DNA viruses.

4. Starting from the closest prior art, the problem to be solved is to find a medical treatment against diseases caused by a human retrovirus.
5. The solution proposed is a pharmaceutical formulation comprising a pharmaceutically acceptable derivative of azidothymidine and a pharmaceutically acceptable carrier therefor.
6. The derivatives of azidothymidine were not argued to

present unexpected features compared to azidothymidine. They include such compound as the disodium salt of azidothymidine monophosphate (patent in suit, page 5, lines 9 to 16), the synthesis of which had already been achieved well before the first priority date (document (1), page 4300, right -hand column). Thus, in the assessment of the inventive step of the claimed subject-matter over document (7), no other features than that relating to azidothymidine per se need be taken into account.

7. In the Board's judgment, the skilled person aware from document (7) that azidothymidine had the property of inhibiting the replication of a mouse retrovirus and was little toxic to the mouse cells would find it obvious to test its activity or that of its derivatives on human retroviruses, because, as admitted by both parties, no differences were known to exist between retroviruses depending on their specific hosts (mouse or human). As the use of azidothymidine in a medical treatment is also envisaged in document (7), producing it or its derivatives in the form of a pharmaceutical formulation against diseases caused by human retroviruses would readily come to mind, said producing not being argued to require inventive step. It is, thus concluded that the subject-matter of claim 1 is derivable in an obvious manner from the teachings of document (7).

8. In this context, it should be pointed out that the approach to inventive step developed in genetic engineering cases, according to which inventive step is not denied on the sole basis that a project is obvious to try but in cases where there is a reasonable expectation of success that said project can be put

into practice (cf T 296/93, OJ EPO 1995,627) does not apply here. The rationale behind this approach is that one may easily conceive of inventions to be made by genetic engineering, yet realising them may cause problems in view of difficulties known or experienced when starting the project. Here, to find out whether derivatives of azidothymidine have an activity against human retroviruses while remaining non toxic to cells, it is enough to perform well-known, routinely carried-out in vitro tests of viral infectivity (such as in document (7)) so it is rather a "try and see" approach which applies.

9. The Appellants argued that document (7) would not be taken into account because the experiments which it disclosed were carried out on cells which were chronically infected whereas the retroviruses which caused human diseases had to be eliminated while the diseases were in the acute phase. This argument is not convincing because document (7) **explicitly** teaches that azidothymidine inhibits viral replication. Taking into account the urgency that there was at the time to find a drug against such diseases (patent specification page 1), any compound having shown potentialities at stopping the replication of retroviruses, irrespective of the conditions of their use, would be tested for its efficiency as a medicament.

10. The Appellants also argued that the skilled person would not think of using derivatives of azidothymidine as medicaments because Figure 1 of document (7) showed that azidothymidine was toxic to cells. Yet, the authors of document (7) interpreted their results otherwise (see point 3). They must have been convinced that azidothymidine was not so toxic to cells that it

could not be used as a medicament since they proposed such a use. There is no reason to doubt that the skilled person would have taken their conclusions at face value.

11. It was also pointed out that at the filing date azidothymidine had become known for having no appreciable activity against any DNA viruses. These viruses, however, are quite distinct from RNA viruses and, in the Board's judgment, the results obtained with them would not have been likely to alter the conclusion which the skilled person would draw from document (7) itself that azidothymidine has an effect on the latter.
12. Finally, the Appellants drew the Board's attention to document (17) which discloses that A-type particles are induced in the presence of azidothymidine during Friend's cell differentiation, implying that this would lead the skilled person away from using the compound as a drug. In document (17), it is stated on page 35 that the "intracisternal virus-like A-type particles might be precursors of the Friend virus or related to the Friend virus complex". The Board does not consider this statement as a possible deterrent from testing azidothymidine derivatives as medicaments.
13. The main request is rejected for lack of inventive step of claim 1.

First auxiliary request

Article 56 EPC; claim 1

14. Claim 1 of this request corresponds to granted claim 2. Granted claim 2 is dependent on granted claim 1 which fails for lack of inventive step (points 2 to 12,

above); it was not explicitly opposed by the Respondents. However, according to the Enlarged Board of Appeal decision G 9/91 (*supra*; point 11 of the decision), *"even if the opposition is explicitly directed only to the subject-matter of an independent claim of a European patent, subject-matters covered by claims which depend on such an independent claim may also be examined as to patentability, if the independent claim falls in opposition or appeal proceedings provided their validity is prima facie in doubt on the basis of already available information"*.

15. Claim 1 (granted dependent claim 2) differs from granted claim 1 by the feature that the carrier contained in the claimed pharmaceutical composition is other than water. No technical facts were presented nor have they been any submissions in the proceedings specifically in relation to using carriers other than water in the pharmaceutical preparation. Thus, the information available to assess the inventive step of claim 1 is the same as the one which led the Board to conclude that claim 1 of the main request failed for lack of inventive step. The patentability of claim 1 of this request is, thus, *prima facie* in doubt and said claim may be examined for patentability.

16. The Appellants suggested that in case the Board would come to this conclusion, the case should be remitted to the first instance to safeguard them the chance of having two instances considering the matter. In accordance with Article 111(1) EPC, the Board of Appeal may either exercise any power within the competence of the department which was responsible for the decision appealed or remit the case to that department for further prosecution. Remittal is, therefore, at the

Board's discretion. The present case being more than twelve years old, the Board decides for sake of expediency not to refer the case back to the first instance but to consider the matter of inventive step.

17. In view of the findings (points 2 to 12, above) that document (7) is detrimental to the inventive step of pharmaceutical formulations of azidothymidine derivatives in general, inventive step could only arise from the added feature that the carrier is other than water. Yet, it is a basic fact of pharmacology that each and every pharmaceutically active substance need to be formulated in a different way which depends on the mode of administration which is envisaged. If, for example, it is envisaged that the pharmaceutically active substance is to be administered as a solid such as tablets, then, of course, the carrier may be a solid carrier (povidone, gelatin and hydroxypropylmethylcellulose are mentioned in this respect on page 6, first paragraph of the patent in suit). No evidence was provided that obtaining azidothymidine derivatives in the form of a pharmaceutical formulation containing a carrier other than water was in any way difficult nor that the properties of said formulation were in any way surprising. Accordingly, the added feature (carrier other than water) does not impart inventive step to the rest of the claimed subject-matter (pharmaceutical formulations containing azidothymidine derivatives) which, as shown in points 2 to 12 above, is not inventive.

18. The first auxiliary request is rejected for lack of inventive step of claim 1.

Second auxiliary request

Article 56 EPC, claim 14

19. Claim 14 relates to specific ester derivatives of azidothymidine. No advantageous properties or surprising effect were demonstrated for any of them. The reasoning developed in points 2 to 12 above in relation to pharmaceutically acceptable derivatives of azidothymidine in general thus equally applies to the ester derivatives. The Appellants argued that, if using derivatives at a unit dose which inhibited viral replication but was not toxic to cells (such a unit dose being included in claim 1 of this request) was inventive, then the subject-matter of claim 14 was also inventive because the ester derivatives would de facto be administered at the "inventive" unit dose. However, as the feature argued to be inventive is not claimed in claim 14 here at issue, it cannot support any inventive step argument. Auxiliary request 2 is refused as claim 14 does not fulfill the requirements of Article 56 EPC.

Third auxiliary request

Article 56 EPC, claim 1

20. This claim differs from claim 1 of the main request in that the claimed pharmaceutical formulation is said to be adapted for oral administration. The Appellants argued that to be able to ingest the drug was a definite advantage for the patient compared to receiving it in any other form such as subcutaneously, intravenously, intradermally etc... In the Board's judgment, it is a matter of general common sense that oral administration is the least invasive means of taking up a drug and, thus, the feature as such cannot

impart inventive step to the subject-matter of claim 1. No evidence was provided that in case of azidothymidine derivatives, this mode of administration has unexpected advantageous properties. Thus, the added feature (adapted for oral administration) does not impart inventive step to the rest of the claimed subject-matter (pharmaceutical formulation of derivatives of azidothymidine) which was found not to be inventive (points 2 to 12, above). Accordingly, the third auxiliary request is rejected for lack of inventive step of claim 1.

Fourth auxiliary request

Article 123(2)(3) EPC; claim 1

21. A support is found in claim 12 of the application as filed for the pharmaceutical formulation comprising a unit dose of between 5 to 1500 mg of the active ingredient.
22. The scope of the claim is narrower than that of the corresponding granted claim 1 which relates to pharmaceutical formulations irrespective of their quantitative content.
23. The requirements of Article 123(2)(3) EPC are fulfilled.

Priority issue

24. In cases such as the present one, when multiple priorities are claimed, it is generally necessary to define the priority date of the subject-matter to be assessed for inventive step because only the documents pre-dating the priority date can be taken into

consideration. Here, however, of the three documents cited in respect of inventive step, document (7) was published in 1974 ie before the first priority date (16 March 1985), the date of publication of the information contained in document (8) cannot be established (see points 25 to 31 below) and the argument raised on the basis of document (22) may not be taken into account (see points 32 and 33, below). Accordingly, the priority date of the claimed invention has no bearing on the assessment of inventive step and need not be ascertained.

Article 56 EPC; claim 1

Document (8)

25. The Respondents challenged inventive step on the basis of, in particular, document (8). A prerequisite for the information contained therein to be taken into account for the assessment of inventive step is, of course, that its date of availability to the public be known. Document (8) is an entry of the Lexis-Nexis data base which, as accepted by both parties, was printed out in 1996, ie some ten years after the filing date of the patent in suit. The heading of this entry reads: "10th Story of Level 1 printed in Full format. Copyright 1985 U.P.I. September 3, 1985, Tuesday AM cycle".

26. The fact that document (8) was retrieved in paper form from the Lexis-Nexis data bank in 1996 implies, of course, that the information, it contains was entered in the data bank before the date of printout. Yet, it does not provide any evidence as to **when** this information was entered into the data bank ie as to when it was made available to the public. Neither can the date of availability be taken as the date mentioned

in the heading of the entry (3 September 1985) as this latter date cannot be equated to the distribution date of the information and need not even be right. How easily a document can be wrongly dated was shown during the appeal proceedings when the Appellants submitted a newspaper article dated by a hand-stamp 14 September **1985** although the Respondents provided evidence convincing the Board and the Appellants that this article was in fact published on 14 September **1986**.

27. The Respondents argued that, on the balance of probabilities, the information contained in document (8) must have been available to the public on or shortly after the 3 September 1985. In accordance with the case law of the Boards of Appeal (T 750/94, *supra*) *"when an issue of fact is being examined and decided by the EPO on the balance of probabilities, the more serious the issue the more convincing must the evidence be to support it."* Document (8) discloses the use of azidothymidine as an experimental drug capable of stopping the virus causing AIDS and being tested *inter alia* at the National Cancer Institute in Bethesda, Md. In the text are included citations of the director Dr Sam Broder and the spokesman Frank Mahaney of the National Cancer Institute about the positive results of experiments carried out with this drug. As this information could have a decisive impact on the Board's conclusions on inventive step, the submissions by the Respondents about the date at which this document was made available to the public must be supported by unequivocal evidence.
28. The Respondents filed a declaration of Connie Landis (document (12)), an affidavit of Monica Kitts (document (13)) and a letter of Tobin Beck (document (14)) to

support their position that document (8) must have been available to the public shortly after the 3 September 1985. Document (14) is from the managing Editor of United Press International (U.P.I.) who certifies "*that to the best of my knowledge, the Nexus copy of the UPI story dated Sep.3, 1985, is a true and accurate copy of the story UPI moved at that time*". In the Board's judgment, this statement does not amount to a clear and unequivocal statement that the information contained in document (8) was then available to the public because it is impossible to understand what kind of action the term "moved at that time" might involve. Furthermore, there is no indication why the managing director on August 27, 1997, the date of his letter, can exactly remember the story moved at that time ie twelve years before. He gives no explanations having special circumstances to remember that very article or having found a record of the article and the date of publication in the archives of UPI. The Board is convinced that the testimony in this letter is only influenced by the date written in document (8) and is not based on true recollection. Therefore, the expression in the said letter "to my best knowledge" is merely relative and cannot be considered as a factual argument.

29. Monica Kitts, the author of document (13) stated in her affidavit that "*from the printout of the data base, it is obvious to me that its content was distributed as a press-wire article to various newspapers in North Carolina and Tennessee on September 3, 1985*". She also recalls a conversation, she had in 1997 with the scientist cited in document (8) during which he mentioned having disclosed "*the use of AZT as a treatment for AIDS to the press in the mid 1980s*". Yet,

as the printout (ie document (8)) does not disclose that the information it contains was ever published in newspapers, the Board does not consider the earlier statement as bringing any level of certainty as to the date when this information was made available to the public. As for the latter statement, the reference to the mid 1980s is insufficient to prove that the disclosure took place before the filing date of the patent in suit (14 March 1986).

30. Document (12) stems from the actual product manager of the Lexis-Nexis data base who states that "*to the best of her knowledge*", document (8) "*was available in the LN's NEXIS service from and after September 4, 1985*". What kind of knowledge brought her to this conclusion is not supported by any facts. If the declaration was really made to the best of her knowledge, these facts should be mentioned. The Board cannot imagine that a document saved in a data bank is not recorded with the day of entry and this could not be verified at any time. It is also not stated whether she was employed by Lexis-Nexis in 1985 or has experience of the functioning of the data base in those days.

31. In view of these findings, the Board concludes that the date at which the information contained in document (8) was made available to the public cannot be unambiguously defined and, that, in consequence, this document cannot be taken into consideration to evaluate inventive step.

Document (22)

32. Document (22) is a declaration filed by the Appellants on 21 May 1998. In point 5 of said declaration, it is

disclosed that a scientific meeting took place in Minneapolis from 29 September to 2 October 1985. The declarant states: "*I attended the Minneapolis meeting and I was one of the ...scientists involved in making the presentation about our first results with zidovudine*. This presentation created considerable excitement both in the meeting itself and beyond...*"

(*The term zidovudine was linked to the term azidothymidine once azidothymidine had become a known antiretroviral drug; it was first listed in the 11th edition of the Merck index (1989), see declaration of J.Partridge, point 12, filed by the Appellants on 23 May 1998). For the first time at oral proceedings, the Respondents argued on the basis of this statement that the use of azidothymidine as a medicament was known to the skilled person as from the date of the meeting and, therefore, producing effective pharmaceutical formulations of it or its derivatives would be obvious.

33. The Board is not prepared to accept this argument into the proceedings because it has been submitted too late. Three years have passed from the moment the declaration containing the above mentioned statement was available to the Respondents. They, thus, had ample opportunity to make their objection known in good time for the Appellants to have a fair chance to comment on it.

Document (7)

34. As a consequence of the Board's finding with regard to documents (8) and (22), document (7) remains the only prior art document to be discussed. It discloses on page 4981, left-hand column, "Results", that azidothymidine is able to inhibit the replication of a

mouse retrovirus while being little toxic to mouse cells when used at a concentration of 250 μ M. It also suggests the use of azidothymidine in a medical treatment.

35. Starting from this closest prior art, the problem to be solved can be defined as producing a means to fight diseases caused by human retroviruses which would be effective against said virus while remaining non toxic to the host cells.
36. The solution provided is a pharmaceutical formulation comprising a pharmaceutically acceptable derivative of azidothymidine and a pharmaceutically acceptable carrier comprising a unit dose of between 5 and 1500 mg of active ingredient.
37. In points 2 to 13 above, it was established that the pharmaceutical formulations of azidothymidine derivatives in general were not inventive over the teachings of document (7). The question which remains to be decided is whether pharmaceutical formulations at the claimed unit dose would be.
38. In the patent in suit, page 5, lines 27 to 39, it is disclosed that the claimed unit doses are those which should be administered to achieve peak plasma concentrations, these being of about 1 to 75 μ M, ie some 3 fold to 250 fold lower than the concentration disclosed in document (7) as inhibiting the replication of the mouse retrovirus while being little toxic to mouse cells. In the Board's judgment, it is an unexpected as well as advantageous result that azidothymidine derivatives are effective against the human retroviruses at such low concentrations.

39. The Respondents argued that it only required routine work to find out which unit dose would be appropriate. This may well be, yet it does not affect inventive step, which, as was just mentioned, is not due to finding out the relevant dosis but to the fact that this dosis is substantially lower than that which had been found effective against the mouse retrovirus.
40. The fourth auxiliary request fulfills the requirements for patentability.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to maintain the patent on the basis of claims 1 to 13 for the Contracting States BE, CH, DE, FR, GB, IT, LI, LU, NL, SE and claims 1 to 12 for the Contracting state AT of auxiliary request 4 and description to be adapted thereto.

The Registrar:

The Chairwoman:

P. Cremona

U. Kinkeldey