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D E C I S I O N
of 7 November 2002

Case Number: T 0718/97 - 3.3.2

Application Number: 87304363.2

Publication Number: 0249347

IPC: A61K 21/485

Language of the proceedings: EN

Title of invention:

Controlled release dihydrocodeine composition

Patentee:

Euroceltique S.A.

Opponent:

Lannacher Heilmittel Ges.m.b.H.

Headword:

Dihydrocodeine Formulation/EUROCELTIQUE

Relevant legal provisions:

EPC Art. 52(1), 54, 56, 84, 123(2), (3)
EPC R. 29(6)

Keyword:

"Inventive step (no): claimed controlled - release dosage form comprising dihydrocodeine based on routine experimentation in view of the knowledge available in the state of the art"

Decisions cited:

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Catchword:

-



Case Number: T 0718/97 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 7 November 2002

Appellant: Euroceltique S.A.
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 6 May 1997 revoking
European patent No. 0 249 347 pursuant to
Article 102(1) EPC.

Composition of the Board:

Chairman: P. A. M. Lançon
Members: G. F. E. Rampold
S. U. Hoffmann

Summary of Facts and Submissions

I. The appellant is proprietor of European patent No. 0 249 347 which was granted with 10 claims on the basis of European patent application No. 87 304 363.2. Claim 1 for all designated Contracting States other than AT, ES and GR read as follows:

"A solid, controlled release, oral dosage form, the dosage comprising an analgesically effective amount of dihydrocodeine or a salt thereof in a controlled release matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C is between 25% and 60% (by wt) dihydrocodeine released after 1 hour, between 45% and 80% (by wt) dihydrocodeine released after 2 hours, between 60% and 90% (by wt) dihydrocodeine released after 3 hours and between 70% and 100% (by wt) dihydrocodeine released after 4 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of dihydrocodeine obtained in vivo occurs between 2 and 4 hours after administration of the dosage form."

Dependent claims 2 to 10 related to elaborations of the oral dosage form according to claim 1.

Claim 1 for the Contracting States AT, ES and GR was worded as follows:

"A process for the preparation of a solid, controlled release, oral dosage form characterised by incorporating an analgesically effective amount of dihydrocodeine or a salt thereof in a controlled

release matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C is between 25% and 60% (by wt) dihydrocodeine released after 1 hour, between 45% and 80% (by wt) dihydrocodeine released after 2 hours, between 60% and 90% (by wt) dihydrocodeine released after 3 hours and between 70% and 100% (by wt) dihydrocodeine released after 4 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of dihydrocodeine obtained in vivo occurs between 2 and 4 hours after administration of the dosage form."

II. The respondent filed notice of opposition requesting revocation in full of the European patent pursuant to Article 100(a) EPC on the grounds of lack of novelty and inventive step. Of the numerous documents cited during the first-instance opposition and subsequent appeal proceedings, the following remain relevant to the present decision:

(2): US-A-4 235 870

(4): DE-C-3 246 492

(8): F. J. Rowell et al, "Pharmacokinetics of Intravenous and Oral Dihydrocodeine and its Acid Metabolites", Eur. J. of Clin. Pharm. (25), 1983, pages 419 to 424.

III. The patent was revoked pursuant to Article 102(1) EPC by a decision of the opposition division posted on 6 May 1997. The stated ground for the revocation was lack of inventive step. The essence of the reasoning in the

opposition division's decision was as follows:

The problem to be solved was to provide a controlled-release pharmaceutical preparation containing dihydrocodeine which provided pain relief lasting for 12 hours, thereby allowing administration of the medicament on a twice-daily basis. According to the opposition division, citation (2) described a universally-applicable, slow-release pharmaceutical matrix material comprising a combination of a higher aliphatic alcohol, such as cetostearyl alcohol, and a hydrated hydroxy-alkyl cellulose, such as hydroxy ethylcellulose in a ratio of from 2:1 to 4:1. Inclusion of the combination of cetostearyl alcohol and hydroxyethylcellulose disclosed in (2) as the slow release matrix material in pharmaceutical preparations intended for oral administration resulted in a slow release of a therapeutically active compound during a predetermined period of time of from five to ten hours. Citation (2) taught that the period of sustained release did not depend on the particular active compound used, but arose from the properties of the matrix material itself. The cited document taught also that the duration of the releasing period could be controlled by varying the proportion of the slow-release matrix material present in the particular dosage form. In the opposition division's opinion, it was obvious for a skilled person, knowing the prior art of (2), to try to solve the problem by providing controlled-release dihydrocodeine compositions comprising a sufficient amount of the slow-release matrix material disclosed in (2) to afford a therapeutic level of dihydrocodeine during the desired 12 hour period.

IV. An appeal against the decision of the opposition division

was lodged by the proprietor (appellant). The statement of grounds of appeal was accompanied by Statutory Declarations by Kevin John Smith, Robert Kaiko and Timothy Hunt. In the Smith Declaration, reference was made, *inter alia*, to publication (8).

V. In a Board's communication dated 13 March 2002, the rapporteur questioned the coincidence of the results of certain experiments reported in the Smith Declaration with those disclosed in the patent in suit and expressed serious doubts as to the patentability of the claimed subject-matter in the patent in suit in view of the prior art disclosed in citations (2) and (4).

VI. In advance of the oral proceedings fixed for 7 November 2002, the appellant withdrew with its faxed letter of 30 October 2002 the existing claims and requested maintenance of the patent in amended form on the basis of a single claim reading as follows:

"A solid, controlled release, oral dosage form comprising tablets with the following composition:

	%
Dihydrocodeine tartrate	29.3
Anhydrous lactose	28.5
Hydroxyethyl cellulose	10.0
Cetostearyl alcohol	30.3
Talc	1.0
Magnesium stearate	1.0

the tablets being made by the procedure of Example 1."

VII. As a result of the Board's objections under Rule 29(6) EPC to the above-mentioned claim as raised early on during the oral proceedings, the appellant cancelled all previously-filed requests and presented, instead, a

new request comprising a single claim for all designated Contracting States other than AT, ES and GR and another single claim for the Contracting States AT, ES and GR. The current claim for the Contracting States except AT, ES and GR has been amended so as to replace the reference to the description at the end of claim 1 of the above request ("the tablets being made *by the procedure of Example 1*") with the following text from Example 1:

"..... the tablets being made *by the procedure of:* dihydrocodeine tartrate was wet granulated with anhydrous lactose and hydroxyethyl cellulose for 10 minutes and the granules were sieved through a 16 mesh screen; the granules were then dried in a Fluid Bed Dryer at 60°C; to the warmed dihydrocodeine containing granules was added molten cetostearyl alcohol and the whole was mixed thoroughly; the mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen; talc and magnesium stearate were then added and mixed with the granules, and the granules were then compressed into tablets."

The current claim for the Contracting States AT, ES and GR has been amended in a similar way.

VIII. The appellant's submissions presented in writing and during the hearing can be summarised as follows:

The problem addressed by the claimed invention was to provide a controlled-release oral dosage form of dihydrocodeine which afforded therapeutically active levels of dihydrocodeine in vivo over at least a twelve hour-period and could therefore be used on a twice-daily basis. Naively it might be assumed that for a

medicament to be effective over 12 hours, it was necessary to have release of the drug over 12 hours. This approach of the opposition division ignored the pharmacokinetic and pharmacodynamic factors and lacked a scientific basis. From the interpretation of the releasing rates in claim 1 it was evident that the release of dihydrocodeine was heavily weighted towards the initial part of the twelve-hour period for analgesia. These figures did not conform with the opposition division's finding that it was obvious to prolong the duration of sustained release beyond the 9 or 10 hours of citation (2).

As explained in the Smith Declaration, at the priority date of the patent in suit the aim would have been to prepare a formulation of dihydrocodeine, which met the releasing characteristics calculated in the said declaration. It would have been possible to make a preparation which had the calculated releasing rates which were widely available in 1986. The resultant preparation would give the 12-hourly pain control which was required but would not be in accordance with the claimed invention. It was surprising to find that an effective dihydrocodeine release composition had the upfront- release rates given in the contested patent, where most of the ingredient is released within the first 2 or so hours and all of the active ingredient could be released within 4 hours.

There was nothing in (2) which suggested that it was an appropriate starting point for a preparation which is intended to be taken at intervals of 12 hours. The disclosures in (2) specifically referred to by the opposition division in the impugned decision indicated that when a tablet contained 20% of matrix, the active

ingredient will be released in vitro over five hours but when the matrix was increased to 25% the release period was increased to 6 to 7 hours and at 30% concentration the release period was increased to 9 to 10 hours. On the contrary, the tablets of Example 1 of the patent in suit contained approximately 40% of the matrix and yet essentially all the active ingredient was released in about 6 hours. Consequently, there were many factors which influenced the design of a dihydrocodeine dosage form which can give effective pain relief over a period of 12 hours. The prior art, and in particular (2), did not point to the answer provided by the claimed invention.

IX. The main arguments submitted by the respondent in writing and at the hearing may be summarised as follows:

The calculations in the Smith Declaration were based on the incorrect assumption that dihydrocodeine released over 32 hours would remain in the body for 32 hours and have an effect over 32 hours. Starting from the comparison in Table 5 of the patent in suit the only adjustment required to make an uncontrolled-release dihydrocodeine preparation effective in pain relief over 12 hours, was a 2-hour shift in the plasma concentration of 31 ng/ml achieved after 10 hours when clinically testing an uncontrolled-release dihydrocodeine preparation.

Citation (2) disclosed the slow-release matrix material used for the controlled-release, oral dosage form containing dihydrocodeine claimed in the patent in suit and taught that both the nature of the active medicament and the dosage to be incorporated into this

matrix material were not critical to provide a controlled release of the medicament over the desired predetermined period of time. Citation (2) taught moreover that the time period during which the release of the medicament from the dosage form occurs could be controlled by the ratio of the amount of the matrix to the weight of the formulation. Since the appellant itself admitted that the claimed dosage forms were prepared by standard methods, the skilled person, reducing to practice the teaching of (2), would inevitably and without any inventive merit arrive at the claimed invention. No inventive step was therefore recognisable for the claimed subject-matter in the patent in suit.

- X. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the single request filed during the oral proceedings on 7 November 2002.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.
2. Although the appellant filed its current request for the first time during the hearing before the Board and thus at a very late stage of the proceedings, the Board decided to admit it largely because the respondent itself gave its consent that this late-filed request should be admitted and the Board and the respondent were clearly in a position to deal with it.

3. The claim as amended during the oral proceedings before the Board finds its support in originally-filed claim 1 in conjunction with Example 1 of the application as filed. In particular, the numerical values for the percentages of the individual constituents of the tablets specified in the current version of the claim (see paragraph VI above) have been calculated from the absolute amounts of these constituents contained in the tablets disclosed in Example 1 of the application as filed (see pages 7 to 8) and the patent as granted (see page 4). Tablets with the particular composition specified in the current claim and made according to the procedure set out in said claim have been shown in the application as filed to exhibit in vitro (see especially page 10, Table 1) and in vivo (see especially page 13, Table 5) release profiles as specified for the tablets in claim 1 of the application as filed. The claim according to the appellant's current request is thus adequately supported by the disclosure in the application as filed and complies in this formal respect with the requirements of Article 123(2) EPC.

Since the amendments introduced in the current claim amount to a restriction of the granted scope, Article 123(3) EPC is also satisfied.

4. The claim has been redrafted in the form of a product-by-process claim. The claimed oral dosage form is now defined in the claim partially by its composition (substance parameters) and partially by its method of manufacture (process parameters). According to the established jurisprudence of the Boards of appeal, claims for products defined in terms of processes for their preparation ("product-by-process" claims) are

from a formal point of view admissible only if there was no other information available in the application which could have enabled the applicant or patentee to define the product satisfactorily by reference to its composition, structure or some other testable parameter (see Case Law of the Boards of Appeal of the European Patent Office, 4th edition 2001, II.B.6.1, 6.3).

Since a comparison of Example 1 and Example 5 in the patent in suit appears to indicate that some properties of the claimed oral dosage form, such as the dissolution rate in vitro, may vary slightly depending on certain process parameters, such as the duration of the wet granulation period (see Table 1, column 3 **vs** Table 4), drafting of the claim as amended in the form of a product-by process claim appears justified and even necessary on the basis of the principles set forth above. The amended claim is therefore also acceptable under the terms of Article 84 EPC.

5. The claimed invention relates to a solid, controlled-release, oral dosage form containing dihydrocodeine tartrate for use in the treatment of moderate-to-severe pain. In the statement setting out the grounds of appeal, the appellant acknowledged that dihydrocodeine tartrate formulations for immediate release to relief pain for about four to six hours and to be taken about four times a day were available to physicians for the treatment of pain long before the priority date of the patent in suit. Dihydrocodeine tartrate (30 mg) normal-release tablets, which are disclosed in the patent specification (see page 7, line 29) and in citation (8) (see especially the paragraph bridging the left- and right-hand columns on page 419) by reference to their trade mark "DF 118", appear to be representative of

this state of the art. According to the disclosure of (8), "DF 118" has been widely used in the relief of mild-to-moderate pain for many years, including the relief of postoperative pain.

5.1 According to the appellant, dihydrocodeine had never been provided in a sustained release form despite the fact that, at the priority date, dihydrocodeine had been available for around 75 years and the technology of sustained-release compositions had been common general knowledge. Notwithstanding the appellant's above assertions, citation (4) discloses in general terms a process for the preparation of solid, controlled-release, oral dosage forms comprising the steps of

- (i) incorporating a therapeutically active amount of a medicament into a mixture of hydroxypropylmethylcellulose having a molecular weight of less than 50000 and ethylcellulose or sodium carboxymethylcellulose as the controlled-release matrix or carrier material, and
- (ii) compressing and forming the medicament/carrier mixture obtained from step (i) into solid single-dosage units for oral administration.

This citation provides an extensive list of a large number of medicaments which may be used for incorporation in the particular matrix or carrier material used in (4) (see page 5, line 21, to page 6, line 9) to form controlled-release dosage forms. Included in this list within a broad variety of different types of active medicaments are analgesics. The broad group of analgesics mentioned in (4) includes

as one example of this group **dihydrocodeine tartrate** (see page 5, lines 59 to 60).

5.2 Though it may be formally correct to regard citation (4) as the closest state of the art, since the former is the only piece of prior art available to the Board which mentions the possibility of providing a controlled-release, oral dosage form containing dihydrocodeine tartrate as the active ingredient, this citation does not, in the Board's judgment, provide in the present case a realistic starting point for the definition of the problem to be solved and, hence, an assessment of the inventive step. Indeed, the cited document merely refers in general terms to dihydrocodeine tartrate as one possible candidate, among hundreds of other suitable medicaments quoted in (4), for the preparation of a controlled-release dosage form, but does not give the skilled man any specific lead, clue or suggestion that would have led him to a controlled sustained-release formulation specifically containing dihydrocodeine tartrate as the active medicament, as defined in the present claim.

5.3 For the above reasons, the Board considers that in the present case known dihydrocodeine tartrate formulations for immediate release, for example, the commercially available normal-release dihydrocodeine tartrate tablets designated "DF 118" (see document (8)) are an appropriate and realistic starting point for discussing inventive step, largely because such tablets have actually been used at the priority date of the patent in suit for pain relief for four to six hours. The need to take analgesic medication at frequent intervals through the day and night means either that the patient has to be woken to take medication or pain emerges

prior to administering the next dose. Accordingly, the desirability of a controlled-release dihydrocodeine tartrate product, in addition to the available immediate-release products appears self-evident.

6. Thus, starting from the prior art referred to in points 5.1 and 5.3 above, the technical problem to be solved, in line with page 3, lines 50 to 51, and the appellant's submissions in the appeal statement and at the hearing, may be seen in providing a controlled sustained-release dihydrocodeine composition which affords effective analgesic levels of dihydrocodeine in vivo over a 12-hour period, thereby allowing administration of the medicament on a twice-daily basis.

The solution of the problem is the provision of the controlled-release, oral dosage form of dihydrocodeine tartrate defined more precisely in the current claim.

- 6.1 As pointed out by the Board in its communication dated 29 March 2002, the data of the clinical studies reported in Table 5 on page 7 of the patent in suit indicate that, 12 hours after the administration of the first dose of a controlled sustained-release dihydrocodeine preparation according to the present claim, the mean plasma concentration of dihydrocodeine in healthy volunteers amounts to 34 ng/ml. This figure is well below the minimum plasma concentration of 38 ng/ml considered in the Smith Declaration as the absolutely necessary minimum to provide pain relief over a 12-hour period. During the oral proceedings the appellant admitted that after the administration of the first dose of the claimed sustained-release dihydrocodeine formulation, administration of a

supplemental dose may be necessary to achieve effective pain relief lasting over a period of 12 hours. In the Board's view, there can be no doubt that doctors who are familiar with the claimed preparation would be aware of this need. However, the appellant explained to the satisfaction of the Board that the figure of 34 ng/ml shown in Table 5 is the concentration upon which plasma concentrations of dihydrocodeine would begin to accumulate when a second dose was taken. Plasma concentrations from the second, third, fourth and later doses of the preparation will always be higher than this value and a steady state will be achieved where even the minimum concentrations in any 12-hour interval are higher than that achieved from the first dose. According to the appellant, the purpose of developing a controlled-release dihydrocodeine preparation was to enable moderate-to-severe pain to be treated chronically dosing at 12-hourly periods.

6.2 On the basis of the appellant's plausible explanations set forth above and in the absence of any evidence to the contrary, the Board is satisfied that the problem posed has credibly been solved. Since this has not been disputed by the respondent, there is no need for further detailed substantiation of this matter.

7. Since none of the citations available to the Board from the proceedings before the EPO discloses a controlled-release dihydrocodeine composition comprising all the features of the single claim now on file, the claimed solution of the problem defined above is novel within the meaning of Article 54(1) EPC, and this finding has not been contested by the respondent. The Board accordingly sees no reason to depart from the opposition division's opinion on novelty expressed in

paragraph II of the decision under appeal.

8. However, the Board does not share the appellant's view that the proposed solution to the problem posed, namely providing tablets with the particular composition specified in the current claim, was not obvious in the light of the cited state of the art.

8.1 In this respect is observed that citation (2) discloses already the controlled release matrix material which has actually been used in the patent in suit for the preparation of the claimed tablets which afford therapeutic levels of dihydrocodeine in vivo over a 12 hour period. According to the claim in the patent in suit, the matrix material consists of

- *a combination of cetostearyl alcohol (30.3%) and hydroxyethylcellulose (10%)*
- *in a ratio of 3:1*
- *and is included in the tablets according to the claimed invention in an amount of about 40% by weight of said tablets. (see present claim). The tablets further contain as fillers and excipients:*
- *lactose (28.5%),*
- *talc (1%) and*
- *magnesium stearate (1%).*

The skilled person finds in citation (2) the teaching that

- the combination of *hydroxyethylcellulose and cetostearyl alcohol* (see, *inter alia*, claim 1, lines 43 and 46; Example 9, lines 18 and 27; column 4, lines 43 and 62)
- *in the preferred ratio of 3:1* (see column 3, lines 48 to 49; Example 9, line 32) and
- in an amount of *20% to 40% by weight* of the final pharmaceutical dosage form (see abstract; column 9, lines 31 to 39; column 10, lines 30 to 39)

is a particularly useful slow-release matrix material for the preparation of controlled release dosage forms (tablets, capsules) intended for oral administration of a broad variety of medicaments, to provide a slow release of the medicament over a predetermined period of from five to ten hours. According to Example 8 of (2) the known slow-release preparations are perfectly suitable for oral administration two or three times a day.

The tablets disclosed in (2) preferably contain as inert fillers or diluents (see column 5, lines 4 to 5; column 8, line 26; Example 2, lines 55 to 57):

- *lactose,*
- *talc* and
- *magnesium stearate.*

8.2 However, citation (2) discloses not only the slow release matrix material, inert fillers and excipients used for preparing the claimed sustained-release

dihydrocodeine preparation in the patent in suit, but contains the supplementary information that both the pharmacological nature of the active therapeutic ingredient and the dosage to be incorporated into the slow-release matrix are not critical to the achievement of sustained release of the medicament over the desired period of time. According to the disclosure of (2), any medicament requiring frequent repeated-dosage administration by the oral route to maintain a therapeutically-active blood level is particularly suitable for inclusion in the slow-release matrix disclosed in (2). The cited document draws the conclusion that the utility of the slow-release matrix described in (2) is not limited to one particular active ingredient, neither is the slow-release action achieved with only one class active therapeutic compounds, but arises from the properties of the particular slow-release matrix itself (see column 7, line 67, to column 8, line 21).

- 8.3 As regards the desired releasing period of the medicament, the cited document teaches that the slow-release matrix material disclosed in (2) permits an accurate prediction of the rate of release of a therapeutically-active compound per unit time from a unit dosage form (see column 3, lines 35 to 37). The predictability of the release rates over a predetermined period of time is based on the finding in (2) that the ratio of the amount of the slow-release matrix to the weight of the final dosage form (tablet, capsule) has a special effect in controlling the time period during which the release of the active ingredient from a unit dosage form will occur. A skilled person derives from the disclosure in (2) that by gradually increasing the

ratio of the slow-release matrix in the dosage form from 20 percent to 30 percent by weight or more the releasing period of the active medicament is gradually increased from about five hours to nine to ten hours (see column 4, lines 5 to 30; column 9, lines 31 to 38; column 10, lines 30 to 45).

8.4 In conclusion, on the basis of the teaching of citation (2) those skilled in the art could reasonably expect the problem posed to be solvable by using the slow release matrix material, fillers and excipients suggested in the cited document for preparing pharmaceutical dosage forms providing sustained controlled release of dihydrocodeine during a predetermined period of time. Having carefully studied the cited state of the art and the appellant's submissions in the proceedings, the Board cannot recognise a technical reason or at least a good argument which would possibly have prevented the skilled person from applying the technical teaching of (2) to the preparation of a controlled-release dosage form containing dihydrocodeine as the active ingredient which provides 12 hourly pain relief.

As admitted by the appellant itself in the course of the oral proceedings, the claimed tablets in the patent in suit are made according to a standard procedure. Citation (2) teaches clearly that the release rate of the active medicament from a unit dosage form according to (2) is controlled by the ratio of the amount of the release matrix to the total weight of the finished formulation and that the release rate of the active medicament can gradually be increased by gradually increasing this ratio. Thereafter, reduction of the teaching of (2) to practice by simply determining the

exact ratio of the known slow-release matrix required for preparing a controlled release dihydrocodeine composition which provides 12 hourly pain relief would be a matter of mere routine experimentation for the skilled practitioner armed with the knowledge of citation (2). The need to carry out suitable experiments in order to determine the correlation between the in vitro dissolution rates obtained and the desired plasma levels in vivo is unavoidable in the preparation of slow-release pharmaceutical compositions of any kind.

8.5 The principal line of argument relied on by the appellant in support of inventive step was that the aim of those skilled in the art, faced at the priority date with the solution of the technical problem posed, would have been to prepare a formulation of dihydrocodeine which met the releasing characteristics calculated in the Smith Declaration. However, this line of argument is not convincing. Since it is clear from the Board's observations in this decision that at the priority date an appropriate and fully satisfactory solution to the problem underlying the patent in suit was obviously derivable from the prior art in (2), those skilled in the art had no reason at all to try to solve the problem on the basis of the calculations in the Smith Declaration which are based on many assumptions the correct applicability of which is difficult to judge.

8.6 For the foregoing reasons, the claimed subject-matter in the patent in suit lacks an inventive step as required by Article 56 EPC. Therefore, neither the claim for the designated Contracting States other than AT, ES and GR nor that for the latter can be allowed to stand having regard to Article 52(1) EPC.

Order

For these reasons it is decided:

The appeal is dismissed.

The Registrar:

The Chairman:

A. Townend

P.A.M. Lançon