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D E C I S I O N
of 25 August 2005

Case Number: T 1219/03 - 3.3.04

Application Number: 93906156.0

Publication Number: 0672162

IPC: C12P 17/02

Language of the proceedings: EN

Title of invention:
Enhanced production of taxol and taxanes by cell cultures of taxus species

Patentee:
PHYTON, INC.

Opponent:
Samyang Genex Corpn.

Headword:
Production of taxol/PHYTON INC.

Relevant legal provisions:
EPC Art. 83, 84, 54, 56

Keyword:
"Main request: novelty (no)"
"Auxiliary request I: inventive step (no)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1219/03 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 25 August 2005

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 30 September 2003 concerning maintenance of European patent No. 0672162 in amended form.**

Composition of the Board:

Chair: U. Kinkeldey
Members: R. Gramaglia
G. Weiss

Summary of Facts and Submissions

I. European Patent No. 0 672 162 (application No. 93 906 156.0) was filed on 22 February 1993. The patent relates to the enhanced production of taxol and taxanes by cell cultures of Taxus species and was granted on the basis of 9 claims, of which claims 1 and 9 read as follows:

"1. A process for recovering taxol and other taxanes in high yields from cell cultures of a *Taxus* species comprising: cultivating in suspension culture, in one or more nutrient media under growth and product formation conditions, cells of a *Taxus* species derived from callus and/or suspension cultures and recovering said taxol and other taxanes from said cells and/or said medium of said cell culture, said conditions comprising one or more of: continuous or intermittent illumination with broadband or narrowband light; or nutrient media which are of altered medium composition for growth and production phases of the culture."

"9. A process as claimed in anyone of claims 1 to 8, wherein growth and product formation are achieved using one-stage or two-stage batch process, or a fed-batch process, or a semi-continuous process, or variations thereof."

Claims 2 to 8 related to specific embodiments of the process of claim 1.

II. Notice of opposition was filed by the opponent requesting the revocation of the European patent on the grounds of Articles 100(a), (b) and (c) EPC. By a

decision dated 30 September 2003 the opposition division maintained the patent on the basis of the claims of the Second Auxiliary Request then on file.

III. Appellant I (patentee) and appellant II (opponent) filed appeals against the decision of the opposition division.

IV. Appellant II submitted an Experimental Report (see Annex 3 to the submission dated 10 February 2004). In response thereto, Appellant I provided Declaration (D62) relating to further experiments.

V. With the submissions dated 25 July 2005, Appellant I provided an amended page 17 wherein "methyl jasmonate" had been deleted from Table III.

VI. Oral proceedings were held on 25 August 2005, during which appellant I filed a new main request and auxiliary request I. Claims 1 and 9 of the new main request read as follows:

"1. A process for recovering taxol and other taxanes in high yields from cell cultures of a *Taxus* species comprising: cultivating in suspension culture, in nutrient media under growth and product formation conditions, cells of a *Taxus* species derived from callus and/or suspension cultures and recovering said taxol and other taxanes from said cells and/or said medium of said cell culture, said conditions comprising nutrient media which are of altered medium composition for growth and production phases of the culture."

"9. A process as claimed in anyone of claims 1 to 8, wherein growth and product formation are achieved using two-stage batch process, or a fed-batch process, or a semi-continuous process, or variations thereof."

Claim 1 of auxiliary request I, which no longer comprised claim 9, read as follows:

"1. A process for recovering taxol and other taxanes in high yields from cell cultures of a *Taxus* species comprising: cultivating in suspension culture, in nutrient media under growth and product formation conditions, cells of *T. chinensis* derived from callus and/or suspension cultures and recovering said taxol and other taxanes from said cells and/or said medium of said cell culture, said conditions comprising nutrient media which are of altered medium composition for growth and production phases of the culture."

VII. The following documents are cited in the present decision:

(D1) WO-A-92/13961;

(D2) US-A-5,019,504;

(D3) Xu L.X. et al., Acta Pharmaceutica Sinica, Vol. 24, No. 7, pages 552-555 (1989);

(D9) Zhu W.H. et al., Chinese Medicine, Vol. 14, No. 9, pages 5-7 (1991);

(D10) Cheng K.D et al., Abstract from the Annual Meeting of Beijing Plant Physiology Society, August 1991;

(D40) Payne G.F. et al., in Plant Cell and Tissue Culture in Liquid Systems, Hanser Publications, John Wiley & Sons, Inc., New York, pages 51-70 (1992);

(D62) Declaration by Dr. Braden Roach dated 20 August 2004;

(D63) First Declaration ("Analysing Technical Submissions") by Dr. Venkatesh Srinivasan dated 20 August 2004;

(D64) Second Declaration ("Regarding Parameters") by Dr. Venkatesh Srinivasan dated 20 August 2004.

VIII. The submissions by appellant I (patentee), insofar as they are relevant to the present decision, can be summarized as follows:

Main request
Article 84 EPC

- There was no discrepancy between claim 9 and claim 1 because the cell growth and production phases were not necessarily separated.

- The expression "high yields" was already present in claim 1 as granted.

Novelty

- Document (D2) disclosed suspension culture of Taxus brevifolia cells to produce taxol and recovery of taxol from the culture. However, each culture disclosed in document (D2) used a single medium and none included any alteration of medium composition.

- According to Example 8 of document (D2), the fungal elicitor was added to the subculture at the beginning of the growth phase of the callus or cell suspension. Thus, document (D2) did not disclose a process for culturing cells of Taxus species in suspension culture and recovering taxol from the culture, wherein the culture medium composition was altered between growth and production phases, i.e., there was no separation of growth and production phases as defined by claim 1 at issue.

Auxiliary request I
Article 84 EPC

- The expression "high yields" was defined in paragraph [0010] of the patent in suit. The restriction of the claim to T. chinensis had not changed its meaning to the extent that this issue should be re-opened.

Article 83 EPC

- The Examples in the patent and the comparative tests described in Declaration (D62) showed that any strain of T. chinensis could be used to achieve the technical effect underlying claim 1.

Novelty

- None of the prior art documents, including document (D2), contained an explicit disclosure of a process according to claim 1 involving a cell culture of T. chinensis for the production of taxol. Document (D2) would rather dissuade since it was stated that T. brevifolia was preferred.

Inventive step

- The selection of T. chinensis, together with the separation of the growth phase from the production phase enabled cells to grow at high cell density with a productivity of taxol (expressed in mg taxol/l) 35- to 150-fold that reported in document (D2).

- The benefits provided by the present invention through separation of the growth phase from the production phase depended on the unsuspected fact that secondary metabolism in Taxus was not associated with biomass growth. Document (D2) confirmed that it was not obvious to the skilled person that taxol production was non-growth associated since the authors of document (D2) optimized growth and production in the same medium.

- Test Report (D62) showed that the production of taxol by T. chinensis in a two-batch process was at least five-fold that produced by various Taxus species under identical production conditions.

– The % DW taxol (DW = dry weight) calculation and the Experimental Report made or submitted by appellant II were not correct because (i) document (D2) did not provide any data about the cell biomass; (ii) the inoculum size and culture period were not the same; (iii) taxol production was non-growth associated and thus it did not increase uniformly with the increase of cell biomass; (iv) the ratio of fresh weight to dry weight depended on the specific cell culture conditions such as the medium and its osmotic pressure; (v) biomass was a function of the inherent capabilities of the cell, the medium composition, and the culture duration and (vi) the ratio of taxol to biomass also depended on whether the medium had been optimized for biomass growth or taxol production.

– The authors of document (D2) did not contemplate high density inoculum of the invention as being a strategy for promoting the high growth and productivity of taxol.

IX. The submissions by appellant II (opponent), insofar as they are relevant to the present decision, can be summarized as follows:

Main request
Article 84 EPC

– There was a discrepancy between claim 9, relating to a "one-stage" process, wherein the medium composition had to remain constant (see definition of the term "one-stage" given on page 8, paragraph

[62] of the patent in suit), and claim 1 relating to an "altered medium".

– Claim 1 lacked clarity owing to the presence of the relative term "high yields".

Novelty

– Document (D2) disclosed in Example 8 a process for culturing cells of Taxus species in suspension culture and recovering taxol from the culture, wherein use was made of differently composed growth and production media. Therefore claim 1 of the main request lacked novelty over the disclosure of document (D2).

– Claim 1 of the main request did not require separation of growth and production phases but merely that nutrient media had to be of altered medium composition for growth and production phases of the culture. Alteration of the medium composition could be achieved by simply adding a further component to the medium.

Auxiliary request I

Article 84 EPC

– Claim 1 of the auxiliary request lacked clarity owing to the presence therein of the relative term "high yields" in combination with the requirement that the species of Taxus being cultured had to be T. chinensis.

Article 83 EPC

– If the term "high yield" meant "yields higher than those of document (D2)", an objection under this Article arose since these "high yields" could not be obtained in using any culture media and any T. chinensis cell, but only with the non deposited T. chinensis cell line K-1.

Novelty

– Although the process for producing taxol by cell culture disclosed by document (D2) involved T. brevifolia, there was an implicit disclosure of the claimed process in column 2, lines 24-25 of document (D2), according to which any plant of the genus Taxus would produce taxol.

Inventive step

– At the priority date of the patent in suit, the use of altered media for growth and production phases was known from document (D2), which taught that a beneficial effect, i.e., increased taxol production could be achieved using altered media for growth and production phase, regardless of any mechanism underlying this technical effect. The use of T. chinensis for the production of taxol by cell culture was also known (see documents (D9) and (D10)). Thus the skilled person would replace T. brevifolia with T. chinensis.

– If the problem to be solved vis-à-vis the prior art was the production of taxanes at levels which were

"much higher" than those achieved in document (D2), the problem had not in fact been solved. This was because the opposed patent showed neither a higher % DW taxol value nor a higher specific productivity as compared with document (D2), since the alleged high yields observed in the opposed patent were not achieved by any inherent characteristics of T. chinensis. There could thus be no inventive step in the selection of T. chinensis cells.

- The yields of taxol expressed as the amount of taxol per unit volume (mg/l), as done in the patent in suit or in document (D2), did not constitute a meaningful basis on which to compare the intrinsic taxol productivities, the volumetric production being a function of both the inoculum size and the culture period. Instead, for a truly valid comparison, the inoculum size and culture period variables had to be removed from the equation by converting the volumetric production values to percentage content of taxol in a unit of dry weight values (i.e., % DW taxol = % of taxol per dry weight of cell biomass).

- Once the mg/l were transformed into % DW taxol, the taxol productivity in the process of document (D2) turned out to be 0.1 to 0.3%/DW, i.e., it was comparable to the results of Examples 9 of the patent in suit (0.18 and 0.065%/DW).

- Any higher yield achieved using T. chinensis in the Examples of the patent in suit was attributable to the specific media optimized for secondary metabolite production.

– Volumetric production values were not meaningful for comparing intrinsic taxol productivities of different taxus species (see document (D40)).

X. Appellant I (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 9 filed at the oral proceedings (main request) or alternatively, that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 8 filed at the oral proceedings (auxiliary request I).

XI. Appellant II (opponent) requested that the decision under appeal be set aside and that the European patent No. 0 672 162 be revoked.

Reasons for the Decision

Main request
Articles 84 and 123 EPC

1. Since the issue of compliance of the claims of this request with the requirements of Articles 84 and 123 EPC is not influential on the question of novelty, the board finds it expedient to deal with the key issue whether the claimed process is novel over that disclosed by document (D2).

Novelty

2. Claim 1 of the main request (see section VI supra) is directed to a process for recovering taxol from

cultures of a Taxus species comprising cultivating in suspension culture in nutrient media under growth and product formation conditions, cells of a Taxus species derived from callus and/or suspension cultures and recovering said taxol, said conditions comprising nutrient media which are of altered medium composition for growth and production phases of the culture.

3. Document (D2) discloses growing subcultures from suspension cells of Taxus brevifolia in the growth medium for a period of time of 2-4 weeks (see Examples 3 and 4) to produce taxol and recovery of taxol from the culture. Example 8 of document (D2) shows that the addition of a fungal agent, namely autoclaved mycelia or filter-sterilised culture filtrates from Cytospora abietis (an "elicitor" in the sense of the patent in suit; see page 7, lines 19, 21 and 26: "Elicitors"; "...which enhances productivity..." and "...filtrates from a selected group of fungi...") to growing cell cultures results in the induction of taxol production as measured by HPLC analysis. This expedient consisting in adding an elicitor to the growth medium during/after the growth phase is an alteration of the culture nutrient medium for growth and production phases, or stated otherwise, a use of "nutrient media which are of altered medium composition for growth and production phases" as required by claim 1 at issue.

4. Therefore, in the board's judgement, document (D2) discloses all the features/steps of the process of claim 1.

5. Relying on the passage in column 2, lines 49-52 of document (D2), appellant I maintains that the fungal

elicitor has to be added to the subculture at the beginning of the growth phase of the callus or cell suspension, so that this document fails to disclose any medium alteration or separation of growth and production phases as defined by claim 1 at issue.

6. However, in the board's view, the passage in column 2, lines 49-52 of document (D2) does not relate to elicitors, which are rather dealt with in column 3, lines 20-27. Moreover, the fungal elicitor is added after (or during) the 2-4 week growth phase referred to in Example 4 (c.f. the wording "...were **grown** as in Example 4" in column 6, lines 29-30; emphasis by the board) and the effect of this elicitor on the production of taxol could be detected 26 hr after its addition (see last sentence of Example 8). Example 12 of document (D2) confirms the view that the fungal elicitor is added after the growth phase has started. In fact, the medium to which the inoculum (20 µl cells) is added only consists of 45 ml of Gamborg's B5 and 5 ml of the growth hormone 2,4-D (see column 4, line 65 and column 7, lines 13-15), with **no** fungal elicitor. Example 12 of document (D2) goes on to state that "Cells were grown ..." and "Rapid production of taxol was achieved by addition of autoclaved Cytospora abietis mycelia homogenate at 2 ml per flask as done in Example 4" (see column 7, lines 15-19). In conclusion, all the above passages of document (D2) do not assist appellant I, arguing that the fungal elicitor exemplified in document (D2) had been incorporated into the growth medium before starting the growth phase of the callus or cell suspension.

7. Finally, claim 1 of the main request does not require any physical separation between the growth and production media but merely that the nutrient media have to be of "altered medium composition for growth and production phases of the culture". This claim interpretation finds support in paragraph [0043] of the patent in suit, wherein it is stated expressis verbis that "It is understood that growth can occur in a production medium, and that production can take place in a growth medium; and that both optimum growth and production can take place in a **single** nutrient medium." (emphasis by the board). Alteration of the medium composition can thus be achieved by simply adding an elicitor to the growth medium during/after the growth phase, as taught by Example 8 of document (D2).

8. Therefore claim 1 of the main request lacks novelty and this request is refused.

Auxiliary request I
Articles 84 and 83 EPC

9. The objections raised by appellant under these Articles hinge upon the expression "high yield" in claim 1, insofar as "high yield" means "higher than those of document (D2)" (see section IX supra). Since it does not matter for the issues of novelty and inventive step, how this term is interpreted, and in view of the conclusion arrived at by the board in the context of the inventive step (see points 24 and 31 infra), it is not necessary to deal with these issues further.

Novelty

10. Document (D2) discloses a process for producing taxol by cell culture of Taxus brevifolia in a suitable culture medium, with the produced taxol and other taxanes being recovered.

11. Document (D3) relates to a HPLC method for determining taxol in the extract from T. chinensis. Documents (D9) and (D10) deal with callus production from T. chinensis, without describing any isolation of taxol.

12. Therefore none of these prior art documents contains an explicit disclosure of a process according to claim 1 involving a cell culture of T. chinensis for the production of taxol, nor allows to implicitly derive said process. Hence the board concludes that the subject-matter defined in claim 1 of auxiliary request I is novel.

Inventive step
Problem to be solved and solution

13. According to paragraphs [0101] and [0102] of the patent in suit, the problem to be solved vis-à-vis the prior art is the production of taxanes at levels which are "much higher" than those achieved in document (D2). Appellant I argues that the selection of T. chinensis as a source of taxol, in combination with the specific growth and production medium conditions (two-stage culture process) enable cells to grow at high cell density with a productivity of taxol (expressed in mg taxol/l) 35- to 150-fold that of 1.0-3.0 mg/l reported in document (D2) (compare paragraph [0099] of

the patent in suit with column 6, line 21 of document (D2)).

14. A considerable portion of the parties' submissions relates to a heavy dispute about how taxol productivity should be expressed. Appellant II maintains that the yields of taxol expressed as the amount of taxol per unit volume (mg/l), as done in the patent in suit (see preceding point), do not constitute a meaningful basis on which to compare the intrinsic taxol productivities, the volumetric production being a function of both the inoculum size and the culture period, in the sense that if more cells are added when the cell culture is initiated, or if cell culturing is carried out for a longer period of time, volumetric production is higher. Instead, for a truly valid comparison, the inoculum size and culture period variables must be removed from the equation by converting the volumetric production values to percentage content of taxol in a unit of dry weight values (i.e., % DW taxol = % of taxol per dry weight of cell biomass), the relationship between % DW taxol and mg/l taxol being:

$$\% \text{ DW taxol} = (\text{mg/l taxol}) \times [\text{g/l DW})/1000] \times 100$$

In the view of appellant II, once the mg/l are transformed into % DW taxol according to the above formula, by entering data in the patent (see page 9, lines 42 and 43": "...cultures of T. brevifolia reached a cell density less than one gram dry weight per litre") and in document (D2) (see column 6, lines 19-20: "The concentration of taxol in the supernatant was in the range 1.0 - 3.0 mg/L"), the % DW taxol in the process of document (D2) turns out to be 0.1 to 0.3 %/DW, i.e.,

it is comparable to the results of Example 9 of the patent (0.18 and 0.065 %/DW). Appellant II also provides an Experimental Report (see Annex 3 to the submission dated 10 February 2004) showing, inter alia, that the yield of taxol strongly varies according to the nutrient medium.

15. Appellant I criticizes both the above % DW taxol calculation and the Experimental Report submitted by appellant II by highlighting the following facts:

- Document (D2) does not provide any data about the cell biomass (i.e. the cell density of the suspension).

- The essential point in any calculation and comparison of volumetric production is that the inoculum size and culture period must be the same (see point 3.1.10 of the submission by appellant I dated 27 August 2004).

- Expressing taxol productivity as % DW taxol does not remove the time variable since taxol production is non-growth associated and thus it does not increase uniformly with the increase of cell biomass. Therefore "...the % DW taxol is meaningless unless correlated with a particular culture period..." (see Declaration (D64), point 12).

- The ratio of fresh weight to dry weight depends on the specific cell culture conditions such as the medium and its osmotic pressure (see Declaration (D63), point 8).

– Biomass is a function of the inherent capabilities of the cell, the medium composition, and the culture duration (see Declaration (D64), point 7)

– The ratio of taxol to biomass is time dependent and also depends on whether the medium is optimized for biomass growth or taxol production" (see Declaration (D64), point 11).

16. As emerges from the above dispute, in the board's judgement, a number of essential parameters must be the same in order that any comparison between the taxol productivity by different cell lines be meaningful: the inoculum size, the culture period and the medium composition for both growth or production.

17. Appellant I maintains that the Examples in the patent in suit illustrate the production of taxanes at levels which are "much higher" than those achieved in document (D2) (see point 13 supra).

18. However, the board observes that there are differences in the inoculum size (cell density) between the techniques disclosed in document (D2) and those in the patent in suit (compare Examples 12 and 4 of document (D2) (20 µl ≈ 20 mg cells into 45 ml medium ≈ 0.444 g/l) and Example 3 of the patent (40-80 g/l). There are also differences in the culture periods (compare document (D2), column 5, line 22: a 2-4 week period and patent, Example 5: 20 days; Example 8: 7-8 days + 15 days).

19. As for the media, the modified Gamborg's medium of Example 4 of document (D2) differs from media B and C of Tables 5 and 9 of the patent in suit. These Tables

also show that specific media B and C are used only in connection with T. chinensis but not with the other T. species listed therein, which rely on media D, F, G and H. Further, it cannot be excluded that media B and C have been optimized for secondary metabolite production.

20. In conclusion, since the above critical parameters are not the same, any comparison between the taxol productivity achieved by the technique disclosed by document (D2) and that achieved by the process of claim 1 involving T. chinensis is not meaningful. There is thus no evidence before the board that the claimed subject-matter actually solves the problem emphasized under point 13 supra.

21. Appellant I provides Test Report (D62), Tables B and C of which purport to show that the production of taxol by T. chinensis in a two-batch process is at least five-fold that produced by various Taxus species under identical production conditions.

22. However, it is noted that the comparative tests according to document (D62) suffer from the same deficiencies pointed out above. In fact, the results reported in Table B of document (D62) are intimately linked to the specific production medium enhanced by addition of methyl jasmonate. Moreover, for any of the comparison batch listed in Table B, there is at least one difference in growth media, production media or inoculum sizes.

23. The experiments of Table C have been performed in the absence of methyl jasmonate, but only the 2nd and 8th

comparisons in the list appear to have been carried out in the same growth and production media, using the same inoculum sizes. However, these two valid comparisons merely show that the production of taxol by T. chinensis **in a two-batch process** in these **specific** media is higher than that of T. baccata and T. globosa under identical production conditions. Otherwise stated they are not relevant to the question emphasized under point 13 above whether the claimed process, which may also be a **one-batch process** (i.e., wherein the inducer is added to the growth medium: see point 7 supra) and which is not limited to specific growth and production media, achieves taxol levels which are "much higher" than those achieved in document (D2), relating to T. brevifolia.

24. On the evidence before the board, no conclusion can thus be drawn as to whether the claimed process is linked with the "universal" technical effect that taxol is produced at levels which are higher than those achieved in document (D2), i.e., that it solves the problem pointed out under point 13 supra.

25. The board also takes into consideration that the problem to be solved is the provision of an alternative process for producing taxol and it has to be decided whether or not this process recited in claim 1 follows from the prior art in an obvious manner.

26. At the priority date of the patent in suit, the use of altered media for growth and production phases was known from document (D2), which taught that a beneficial effect i.e., increased taxol production could be achieved using altered media for growth and

production phase, regardless of any mechanism underlying this technical effect. The use of T. chinensis for the production of taxol by cell culture was also known from documents (D9) or (D10). Therefore, in the board's judgement, the skilled person would have been motivated to replace T. brevifolia in the process of document (D2) with T. chinensis and arrive at the claimed subject-matter in an obvious manner.

27. Appellant I maintains that the authors of document (D2), being unaware of the fact that secondary metabolism in Taxus was not associated with biomass growth, optimized growth and production in the same medium. Hence, it was not obvious to the skilled person departing from document (D2) to arrive at the benefits provided by the present invention characterized by the separation of the growth phase from the production phase.

28. However, as already emphasized in point 7 supra, claim 1 at issue does not require any physical separation between the growth and production media but merely that the nutrient media have to be of "altered medium composition for growth and production phases of the culture". This interpretation is confirmed on page 6, lines 45-57 of the patent, wherein it is stated expressis verbis that "...it is understood that a single growth/production medium may be formulated for this culture". Therefore, claim 1 at issue also covers a process wherein the inducer is added to the growth medium. But this process is already taught by Example 8 of document (D2). The next step would be to replace T. brevifolia in the process of document (D2) with T. chinensis (see point 26 supra).

29. Appellant I further relies on the differences in the inoculum size (density) between the techniques disclosed in document (D2) and in the patent in suit (compare Examples 12 and 4 of document (D2): low density inoculum (20 µl ≈ 20 mg cells into 45 ml medium ≈ 0.444 g/l) and Example 3 of the patent: high density inoculum (40-80 g/l)), for arguing that the authors of document (D2) did not contemplate high density inoculum as being a strategy for promoting the high growth and productivity of taxol according to the patent in suit.

30. However, the above argument cannot serve to support inventive step, as long as claim 1 at issue does not contain a feature relating to high density inoculum.

31. In view of the above considerations, the board concludes that the subject-matter of claim 1 of auxiliary request I does not to involve an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: Chair:

P. Cremona U. Kinkeldey