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Datasheet for the decision of 15 May 2013

Case Number: T 1919/11 - 3.3.02

Application Number: 03026211.7

Publication Number: 1398384

IPC: C12P 15/00

Language of the proceedings: EN

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

Applicant:
DFB Biotech, Inc.

Headword:
Production of taxanes/BIOTECH

Relevant legal provisions (EPC 1973):
EPC Art. 76(1)

Keyword:
"Added subject-matter (yes) - Multiple arbitrary selection of features"

Decisions cited:
T 1107/06

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1919/11 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 15 May 2013

Appellant: (Applicant)
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 4 April 2011 refusing European patent application No. 03026211.7 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
R. Cramer

Summary of Facts and Submissions

I. European patent application No. 03 026 211.7, filed as a divisional application in respect of the earlier (parent) application No. 97 926 731.7, the latter based on PCT/US1997/008907 and published as WO 1997/044476, was refused by a decision of the examining division on the basis of Article 97(2) EPC.

The wording of claim 1 of the set of claims of the main request as filed in the divisional application in suit is identical to original independent claim 9 of the parent application and reads:

"A method for producing taxanes in high yields in cell culture 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 or suspension cultures, and recovering one or more taxanes from said cells or said medium of said cell culture, or both,
wherein the one or more nutrient media contain silver at a concentration of 900µM or less in the form of a silver-containing compound, or a silver complex, or a silver ion, and at least one of the one or more nutrient media comprises an enhancement agent selected from:
a) jasmonic acid or an ester of jasmonic acid; and
b) an auxin-related growth regulator."

The decision of the opposition division was taken on the ground that the subject-matter of the main request was unclear in the sense of Article 84 EPC and lacked

novelty under Article 54 EPC and that the subject-matter of the auxiliary requests *inter alia* extended beyond the content of the earlier application as filed (Article 76(1) EPC 1973).

II. The appellant lodged an appeal against the decision of the examining division and filed grounds of appeal.

Claim 1 of its main request is derived from claim 9 as originally filed in the parent application and differs from this claim as shown below. It reads:

"A method for producing taxanes in high yields in cell culture of ~~a *Taxus* species~~ *Taxus chinensis* comprising: (a) cultivating in suspension culture, in ~~one or more~~ nutrient media under growth and product formation conditions cells of ~~a *Taxus* species~~ *Taxus chinensis* derived from callus or suspension cultures wherein production of taxanes is induced in the culture by changing the composition of the nutrient medium and wherein cells of said *Taxus chinensis* are cultivated by a fed-batch process, and
(b) recovering one or more taxanes from said cells or said medium of said cell culture, or both,
wherein the ~~one or more~~ nutrient media contain
(i) silver at a concentration of at least 1µM to less than 200µM in the form of a silver-containing compound, or a silver complex, or a silver ion, and
~~at least one of the one or more nutrient media comprises~~ (ii) an enhancement agent selected from:
a) jasmonic acid or an ester of jasmonic acid; and
b) an auxin~~-related growth regulator~~."

The text of claims 1 of auxiliary requests I and II is derived from the auxiliary request 4 before the examining division (added text with respect to claim 1 of this request marked):

"A method for producing taxanes
in high yields
in cell culture of *Taxus chinensis* comprising:
cultivating in suspension culture,
in one or more nutrient media
under growth and product formation conditions,
cells of *Taxus chinensis* derived from callus or suspension cultures,
and recovering one or more taxanes from said cells or said medium of said cell culture, or both,
wherein the one or more nutrient media contain silver at a concentration of at least 1µM to less than 200µM in the form of a silver-containing compound, or a silver complex, or a silver ion,
and at least one of the one or more nutrient media comprises an enhancement agent selected from:
a) jasmonic acid or an ester of jasmonic acid; and
b) an auxin,
wherein in product formation conditions fed-batch operation is used."

Claim 1 of auxiliary request III corresponds to claim 1 of the main request, with the passage "wherein the initial sugar level in the production medium is 2-20 times higher in the production phase than the growth phase," introduced after "a fed-batch process," before point (b) of the claim.

Claim 1 of auxiliary request IV reads (differences with respect to claim 1 of the main request marked):

"A method for producing taxanes in high yields in cell culture of *Taxus chinensis* comprising:
(a) cultivating in suspension culture, in nutrient media under growth and product formation conditions cells of *Taxus chinensis* derived from callus or suspension cultures wherein production of taxanes is induced in the culture by changing the composition of the nutrient medium from the composition of the medium during cell growth phase to the composition of the medium during taxane production phase and wherein cells of said *Taxus chinensis* are cultivated by a fed-batch process to sustain cells in production, the initial sugar level in the production medium being 2-20 times higher in the production phase than the growth phase, and
(b) recovering one or more taxanes from said cells or said medium of said cell culture, or both, wherein the nutrient media contain
(i) silver at a concentration of at least 1µM to less than 200µM in the form of a silver-containing compound, or a silver complex, or a silver ion, and
(ii) an enhancement agent selected from:
a) jasmonic acid or an ester of jasmonic acid; and
b) an auxin."

Claim 1 of auxiliary request V corresponds to claim 1 of the main request, with the passage "wherein a carbon dioxide concentration in the range of 0.3% to 15% (v/v in the gas phase that is in equilibrium with the culture medium) present," is inserted after "a fed-batch process," before point (b) of the claim.

In claim 1 of auxiliary request VI the insert reads "wherein oxygen is present in the range of 25% to 95% air saturation," and in claim 1 of auxiliary request VII there is a combination of the inserts of auxiliary requests III and V.

In claim 1 of auxiliary request VIII the text "wherein the volumetric productivity of taxanes is at least 15 mg/L/day averaged over the period of product formation conditions," is inserted before point (b) of the claim and in claim 1 of auxiliary request IX the corresponding text reads: "wherein the volumetric productivity of taxol is at least 10 mg/L/day computed for the period of taxol product formation conditions,".

III. Third-party observations were filed on 25 October 2012 and were commented on by the appellant with letter of 8 February 2013.

IV. Oral proceedings took place on 15 May 2013.

V. The appellant's arguments may be summarised as follows:

Throughout the whole description of the parent application as originally filed, *Taxus chinensis* provided for the best results with respect to the use of a *Taxus* species for producing taxanes; all the arguments and examples lead directly to the subject-matter of the current claims 1: the method of producing taxanes in cell cultures of *Taxus chinensis*.

The two sentences in the description of the earlier application regarding the possible concentration of

silver were to be understood as a listing of ranges, the one starting with something above zero concentration up to the upper limit and the other starting from the lower limit up to some reasonable concentration. In addition, the particular value of silver concentration in examples 15 and 17 fell within the range indicated in the claims 1.

Within the characterisations of "auxin-related growth regulators" set out in the description of the earlier application as originally filed as "including auxins, compounds with auxin-like activity, and auxin antagonists", "auxin" was the only term fulfilling the provisions of Article 84 EPC. It has therefore been selected to represent the b)-group of enhancement agents in claims 1.

The combination of the features *Taxus* species "*Taxus chinensis*", silver concentration of "at least 1µM to less than 200µM" and "auxin" as enhancement agent was represented in example 10 and the corresponding table 11.

Thus, the application as filed provided a direct and unambiguous basis for the claimed subject-matter.

VI. The appellant (applicant) requested that the decision under appeal be set aside and that a patent be granted according to the main request or alternatively according to one of the auxiliary requests I - IX, all filed with the grounds of appeal. More alternatively it requested that the case be remitted to the examining division for further prosecution.

Reasons for the Decision

1. The appeal is admissible.

2. *Main request; Article 76(1) EPC 1973*

2.1 The subject-matter of claim 1 of the main request relates to

a method for producing taxanes …

- in cell culture of ***Taxus chinensis*** comprising:
- (a) cultivating in suspension culture …
- (b) recovering one or more taxanes from said cells or said medium of said cell culture, or both, wherein the nutrient media contain
- (i) **silver at a concentration of at least 1 µM to less than 200 µM** in the form of a silver-containing compound, or a silver complex, or a silver ion, and
- (ii) an enhancement agent selected from:
  a) …; and
  b) an **auxin**.

Subject-matter marked bold characterises issues particularly discussed during the oral proceedings under Article 76(1) EPC 1973.

2.2 The question is whether these three features in the context of the whole subject-matter of claim 1 of the main request represent added subject-matter with respect to the parent application as originally filed.

2.2.1 The subject-matter of claim 1 of the main request relates to *Taxus chinensis* only.

In contrast, under the heading "Summary of the invention", on page 5, lines 13 to 18 of the description as originally filed for the parent application (synonymously used for "earlier application"; references relate to WO 1997/044476), it is set out that

"the inventors have discovered that taxol, baccatin III, and other taxol-like compounds, or taxanes, can be produced in very high yield from all known *Taxus* species, e.g., *brevifolia*, *canadensis*, *cuspidata*, *baccata*, *globosa*, *floridana*, *wallichiana*, *media* and *chinensis*. Further, by the methods of this invention it is possible to obtain taxol, baccatin III, and other taxanes in a much shorter time frame than previously reported."

This subject-matter is described in the text of the parent application as comprising "one embodiment" (see page 6, lines 4 to 29 relating to nutrient media containing an inhibitor of phenylpropanoid metabolism, see *ibid.*, line 9) and "another embodiment" (starting on page 7, lines 1 to 9 relating to claim 9 of the original parent application), the latter being selected as the subject-matter of the current divisional application (see point I above):

"In another embodiment, this invention provides a method for producing taxanes in high yields in cell culture of a *Taxus* species by cultivating cells of a *Taxus* species in suspension culture … the nutrient media containing silver … along with at least one enhancement agent …".

Page 8, lines 3 to 11, states:
"Preferably, cells cultured according to the method of this invention are cells of *Taxus* species, and the species may be *T. brevifolia, T. canadensis, T. chinensis, T. cuspidata, T. baccata, T. globosa, T. floridana, T. wallichiana*, or *T. media*. Preferably, the cells of a *Taxus* species used in the method of this invention are cells which produce taxol above background by ELISA in callus culture or suspension culture in medium that contains no enhancement agents. More preferably, the cells of a *Taxus* species used in the method of this invention are cells which produce taxanes in suspension culture at an average volumetric productivity of 10mg/L in a medium containing silver thiosulfate, methyl jasmonate and auxin."

In addition to this summarising text relating to a plurality of *Taxus* species, any particular mention of *Taxus chinensis* is followed by an endorsement that *Taxus chinensis* may be the best in many issues, but that the important subject-matter of the application equally is the teaching to use any member of the list of *Taxus* species for producing taxanes:

So, the text on page 5, lines 18 to line 23, reading "In particular, the inventors found that the species, *Taxus chinensis*, is capable of rapid growth and of producing extremely high levels of taxol, baccatin III, and taxanes within a short period of time. With the species *Taxus chinensis*, the inventors have been able to manipulate cells to yield taxol, baccatin III, and taxanes in amounts far in excess of the amounts

obtained from tissue cultures of the other *Taxus* species."
is followed by
"Particular modifications of culture conditions (i.e., media composition and operating modes) have been discovered to enhance the yield of various taxanes from cell culture of all species of *Taxus*." (see page 5, lines 24 to 26).

On page 5, line 30 to page 6, line 2,
"While the yield of taxanes from plant cell culture of *T. chinensis* is particularly enhanced by use of one or more of these conditions,"
is followed by
"yield of taxanes for all *Taxus* species has been found to benefit from use of these conditions." (see page 6, lines 2 to 3).

Finally, on page 10, lines 7 to 9,
"In particular, the inventors have identified the species *Taxus chinensis* as capable of producing significant quantities of taxol, baccatin III, and taxanes at high volumetric productivities."
is followed by the generalising text
"It has been found by the inventors that specific taxane content varies with plant species, and within plant species from tissue source and specific trees. Selecting a high yielding source and culture for taxane production is an important first step towards providing sufficient quantities of taxanes for therapeutic use." (see page 10, lines 10 to 13).

Consequently, some of the examples relate to different *Taxus* species and some use *Taxus chinensis* as a model

substance to show particular effects of the cultivation conditions.

On this basis, there is no direct and unambiguous disclosure that the subject-matter of the overall content of the application relates to nothing else than a method using *Taxus chinensis*.

2.2.2 The subject-matter of claim 1 of the main request relates to silver at a concentration of at least 1µM to less than 200µM.

Original claim 9 of the parent application contains the feature of silver content at a concentration of 900µM or less.

In the description, on page 22, lines 4 to 8, it is stated in two separate consecutive sentences that "When silver is incorporated in the medium, it will be added at a concentration of less than 900 µM, preferably less than 500 µM, and more preferably less than 200 µM." and
"When silver is incorporated in the medium, it will be added at a concentration of at least 10 nM, preferably 100 nM, more preferably 1 µM, and typically at 10 µM."

This present situation is not comparable with that in point 48 of T 1107/06 and dealt with in the settled jurisprudence of the boards of appeal, where - starting from a general and a preferred range - "a combination of the preferred disclosed narrower range and one of the part-ranges lying within the disclosed overall range on either side of the narrower range" is considered to be originally disclosed.

A general range, which means a lower limit which is unequivocally combined with an upper limit and a preferred disclosed narrower range - equally consisting of a lower limit which is unequivocally combined with an upper limit - are simply missing. Even a kind of parallel structure in indicating the upper and lower limits (less/at least, preferred or more preferred) implies no unequivocal correlation between a particular upper limit and a particular lower limit because there is no teaching that such an arrangement was intended.

Therefore, in the present case, one of the upper limits mentioned in the first sentence in the description of the parent application as originally filed (as cited above) and one of the lower limits mentioned in the second sentence are arbitrarily combined, which does not represent a direct and unambiguous disclosure.

2.2.3 The subject-matter of claim 1 of the main request relates to an enhancement agent selected from:
… and b) an auxin.

Since the auxin-related growth regulator mentioned in claim 9 of the parent application as originally filed as

"an enhancement agent selected from:
a) jasmonic acid or an ester of jasmonic acid; and
b) an auxin-related growth regulator"

is defined in the corresponding part of the description as including "auxins, compounds with auxin-like activity, and auxin antagonists" (see page 22, lines 9 to 11), the selection of auxin only under component b) is arbitrary.

2.2.4 Regarding the three particularly discussed features

- restriction to a method using ***Taxus chinensis*** together with the
- application of silver at a particular concentration of **at least 1µM to less than 200µM** and the
- restriction of auxin-related growth regulators to **auxin**,

the board comes to the conclusion that the skilled person was not in a position to derive in a direct and unambiguous way, from the parent application as originally filed, that these features were present in the particular combination now claimed. The selections are arbitrary and thus their present combination represents information not originally disclosed and, as such, added subject-matter.

3. *Auxiliary requests I to IX; Article 76(1) EPC 1973*

From the fact that the particularly discussed features in claim 1 of the main request (point 2.1 above) are equally present in claims 1 of auxiliary requests I to IX, with none of the additional features altering the argumentation under point 2.2 above, it follows that they too contain added subject-matter.

Consequently, the auxiliary requests are also not allowable under Article 76(1) EPC 1973.

4. Under these conditions, the further arguments of the appellant must also fail.

The statements that examples 15 and 17 contained silver in a concentration within the limits of current claims 1, and that in example 10 particular ingredients were used that represented an embodiment falling under the selections in these claims with regard to *Taxus* species, silver concentration and an auxin used as enhancement agent, simply show the normal correlation between the more general teaching of a claim and an example falling under this teaching. These statements do not justify by means of the mere existence of such examples the teaching of the claim in its full breadth with regard to added subject-matter.

With respect to the selection of auxin as enhancement agent, the statement that the description contained only one definition of this feature that met the provisions of a particular article of the EPC (namely "auxin" with respect to Article 84 EPC) cannot justify the assertion that the feature based on this definition complied with another article of the EPC (namely, in this case, Article 76(1) EPC).

Finally, the definition of upper limits of a concentration in one sentence and lower limits in a separate sentence, as in the current case, cannot be read as a list of ranges. Supposing the upper limits to represent ranges by virtually adding complementary lower limits infinitely close to zero or the lower limits by virtually adding complementary upper limits representing a "reasonable value" has no technically reasonable basis in the overall disclosure of the parent application as originally filed.

5. In these circumstances the appeal must be dismissed because the subject-matter of the divisional application in the form of the main request and auxiliary requests I to IX extends beyond the content of the earlier application as filed and thereby fails to meet the requirements of Article 76(1) EPC 1973.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald