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**Datasheet for the decision
of 24 November 2010**

Case Number: T 0927/06 - 3.3.02

Application Number: 93203295.6

Publication Number: 0600544

IPC: A61K 31/07

Language of the proceedings: EN

Title of invention:

Use of lycopene for reducing the activity of cells, especially of cancer cells, and pharmaceutical preparations

Patentee:

Lycored Natural Products Industries Ltd

Opponent:

DSM NUTRITIONAL PRODUCTS AG

Headword:

Use of lycopene/LYCORED NATURAL PRODUCTS INDUSTRIES

Relevant legal provisions:

EPC Art. 123(2), 123(3)
RPBA Art. 15

Relevant legal provisions (EPC 1973):

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Keyword:

"The main request and the first auxiliary request do not meet the requirements of Article 123 EPC"

Decisions cited:

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Catchword:

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Case Number: T 0927/06 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 24 November 2010

Appellant: Lycored Natural Products Industries Ltd
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 21 April 2006
revoking European patent No. 0600544 pursuant
to Article 102(1) EPC 1973.

Composition of the Board:

Chairman: U. Oswald
Members: M. C. Ortega Plaza
J. Van Moer

Summary of Facts and Submissions

I. European patent No. 0 600 544, which was filed as application number 93203295.6., was granted on the basis of ten claims.

Independent claims 1 and 8 as granted read as follows:

1. Use of lycopene for preparing a medicament for reducing the activity or inhibiting the growth of a cancer cell as measured by the MTT method by administering to a subject in need thereof, topically or by in situ injection or systemically, an activity-reducing or growth-inhibiting effective amount of lycopene, wherein the cancer cells the growth of which is to be inhibited are selected from among: mammary cancer, endometrial cancer, prostatic cancer, ovarian cancer, lung cancer small and non-small cell type, bladder cancer, pancreatic cancer, gastric cancer, hepatic cancer and cervical cancer cells.

8. A method for reducing the activity or inhibiting the growth of a cancer cell as measured by the MTT method comprising the step of administering *in vitro* to said cell an activity reducing or growth-inhibiting effective amount of lycopene, wherein said cancer cell is selected among: mammary cancer, endometrial cancer, prostatic cancer, ovarian cancer, lung cancer small and non-small cell type, bladder cancer, pancreatic cancer, gastric cancer, hepatic cancer and cervical cancer cells.

II. The following documents were cited *inter alia* during the proceedings:

(1) Lingen et al., Experimental Cell Research 16, 384-393 (1959)

(20) T. Mosman, Journal of Immunological Methods, 65, 55-63 (1983)

III. Opposition was filed and revocation of the patent in its entirety was requested pursuant to Article 100(a) EPC (lack of novelty and inventive step) and to Article 100(b) EPC for lack of sufficiency of disclosure.

- IV. The present appeal lies from a decision of the opposition division revoking the patent under Article 102(1) EPC 1973.
- V. The opposition division considered that claim 1 of the main request (patent as granted) lacked novelty vis-à-vis document (1). Moreover, the opposition division was of the opinion that the first and second auxiliary requests (in particular, claims 1 and 8) filed at the oral proceedings before the opposition division did not meet the requirements of Articles 123(2) EPC and 84 EPC. As regards the third auxiliary request, also filed at the oral proceedings before the opposition division, the opposition division considered that it met the requirements of Articles 123(2) and 84 EPC. Moreover, the opposition division was of the opinion that the subject-matter claimed in claim 1 of the third auxiliary request was novel, but that it did not meet the requirements of Article 56 EPC.
- VI. The patentee (appellant) filed an appeal against said decision. Moreover, it filed with the grounds of appeal a main request and a first auxiliary request.

Claim 1 of the main request reads as follows:

1. Use of lycopene for preparing a medicament for ~~reducing the activity or inhibiting the growth of a cancer cell as measured by the ³H~~thymidine incorporation and haemocitometer cell counting methods ~~the MTT method by administering to a subject in need thereof, topically or by in situ injection or systemically, an activity-reducing or growth-inhibiting effective amount of~~ lycopene, wherein the cancer cells the growth of which is to be inhibited are selected from among: mammary cancer, endometrial cancer, prostatic cancer, ovarian cancer, lung cancer small and non-small cell type, bladder cancer, pancreatic cancer, gastric cancer, hepatic cancer and cervical cancer cells.

Claim 1 of the first auxiliary request reads as follows:

1. Use of lycopene for preparing a medicament for inhibiting the proliferation growth of a cancer cell as measured by the [³H]thymidine incorporation and haemocitometer cell counting methods by administering to a subject in need thereof, topically or by in situ injection or systemically, a growth-inhibiting effective amount of lycopene, wherein the cancer cells the growth of which is to be inhibited are selected from among: mammary cancer, endometrial cancer, prostatic cancer, ovarian cancer, lung cancer small and non-small cell type, bladder cancer, pancreatic cancer, gastric cancer, hepatic cancer and cervical cancer cells.

- VII. The respondent (opponent) raised with its response to the grounds of appeal objections within the meaning of Articles 123(3) and 56 EPC in relation to the two sets of claims filed with the grounds of appeal.
- VIII. A board's communication within the meaning of Article 15(1) RPBA was sent to the parties, as an annex to the summons for oral proceedings, on 7 May 2010. In said communication the board expressed the preliminary opinion that claim 1 of the main request contravenes the requirements of Article 123(3) EPC owing to the replacement of the MTT method in claim 1. As regards the quantitative colorimetric assay for mammalian cell survival and proliferation the board cited document (20) under Article 114(1) EPC. Moreover, the board expressed the opinion that claims 1 and 8 of the first auxiliary request did not meet the requirements of Article 123(2) and (3) EPC. The board also informed the parties with said communication that the first auxiliary request "clean version" was not admissible.
- IX. The appellant did not file any substantive response to the board's communication sent as an annex to the summons for oral proceedings. With its letter of

2 November 2010 it only announced that it "will not be represented at the oral proceedings" before the board.

- X. The respondent did not file any substantive reply to the board's communication sent as an annex to the summons for oral proceedings.
- XI. Oral proceedings took place on 24 November 2010 in the absence of the appellant.
- XII. The appellant only filed substantive arguments with its grounds of appeal. The appellant's arguments, as far as relevant for the present decision, are as follows:

Claim 1 as granted covered two possible therapeutic applications of lycopene, one being the reduction of cancer cell activity and the other being the inhibition of cancer cell growth. Claim 1 of the main request covered one of these two therapeutic applications, namely the inhibition of cancer cell growth. Claim 1 as granted contained a mention to the MTT method. The scope of claim 1 of the main request was narrower since it had been limited to one of these two possible therapeutic applications. Thus, the requirements of Article 123(3) EPC were met.

Moreover, as stated on paragraph [0032] of the contested patent, the MTT method was used for estimating the mitochondrial activity of cells, i.e. the cancer activity. Since claim 1 of the main request did not cover the use of lycopene for reducing cancer cell activity, the mention of the MTT method in this claim was superfluous. Thus, the language "as measured by the MTT method" was no longer present in claim 1 of

the main request. On the other hand, as clearly stated on paragraph [0033] of the opposed patent, the cancer cell growth was measured by [³H]thymidine incorporation and haemocitometer cell count. Since claim 1 of the main request covered the use of lycopene for inhibiting cell growth, the mention of the [³H]thymidine incorporation and haemocitomer cell count was mentioned in said claim. Thus, the requirements of Article 123(2) EPC were also met.

Claim 1 of the first auxiliary request differed from claim 1 of the main request in the replacement of the language "for inhibiting the growth of a cancer cell..." with the language "for inhibiting the proliferation of a cancer cell...". The amendment was supported by paragraph [0032] of the patent in suit.

The appellant also argued that proliferation inhibition was the result of cancer cell growth inhibition. Thus, the requirements of Article 123(2) and (3) EPC were met by claim 1 of the first auxiliary request.

XIII. At the oral proceedings before the board the respondent did not add any comment to its written arguments.

The respondent's written arguments as far as relevant for the present decision can be summarised as follows:

The main request and the first auxiliary request filed with the grounds of appeal did not meet the requirements of Article 123(3) EPC.

The wording of claim 1 as granted specified the MTT method as the method for measurement of both the

reduction of the activity and the inhibition of growth of a cancer cell. The replacement of the method of measurement with another method implied a change in the scope of protection which lead to a different subject-matter ("*aliud*"), not covered by the granted claim.

Moreover, the concept of "cancer cell growth" was meant to concern both the rate of growth of a cancer cell and the growth of new cancer cells originated from cancer cells already existing. Claim 1 of the first auxiliary request related to something different ("*aliud*") from the subject-matter of claim 1 as granted.

XIV. The appellant (patentee) requested in written that the decision under appeal be set aside and the patent be maintained in amended form on the basis of the main request filed with the grounds of appeal, or, alternatively, on the basis of the first auxiliary request, also filed with the grounds of appeal.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. *Procedural matters*

1.1 *Admissibility*

1.1.1 The appeal is admissible.

1.1.2 The duly summoned appellant did not attend oral proceedings. The board was in a position to decide at the conclusion of the oral proceedings, since the case

was ready for decision (Article 15(5) and (6) RPBA) and the voluntary absence of the appellant was not a reason for delaying a decision (Article 15(3) RPBA).

- 1.1.3 The set of claims called "first auxiliary request (*clean version*)" does not correspond identically to the set of claims of the "first auxiliary request (*marked-up version*)", in particular, owing to the different wording of claim 8. There is no justification given in the grounds of appeal for having different independent claim's wording between two sets of claims numbered with identical ranking. The set of claims of the "first auxiliary request (*clean version*)" is not admitted into the proceedings since the appellant has not justified in any way the amendments undertaken in claim 8, which are manifestly unallowable under Article 123(2) and (3) and Article 84 EPC.

The parties were informed with the board's communication sent as annex to the summons about the reasons why the set of claims of the "first auxiliary request (*clean version*)" was not admissible. The appellant did not comment on those reasons.

1.2 *Main request*

A comparison of claim 1 of the main request with claim 1 as granted shows as a difference that the use concerning a medicament for "reducing the activity" of a cancer cell has been deleted. Moreover, the method for measuring cell growth of a cancer cell has been specified as "the [³H]thymidine incorporation and haemocytometer cell counting methods", whereas the reference to the MTT method has been deleted from the

claim. Therefore, it has to be investigated whether or not the so amended claim 1 extends the protection it confers beyond that of granted claim 1 (Article 123(3) EPC). In particular, it has to be assessed whether the scope claimed has been broadened in an unallowable way by replacement of the measurement method to determine cell growth.

As a first step, the wording of granted claim 1 has to be investigated. However, the claims have to be read in their **broadest technically meaningful sense**. The description cannot serve to restrict the meaning of broad claims which are technically meaningful.

Claim 1 as granted is a use claim in the Swiss-type form. The purpose of the medicament containing the lycopene is defined in the claim as follows: "a medicament for reducing the activity or inhibiting the growth of a cancer cell as measured by the MTT method".

The specification of the patent cannot be invoked for interpreting granted claim 1 in a restrictive way, since the claim does not pose problems of lack of clarity to the skilled reader. The claim clearly defines the MTT method as the measuring method for establishing both: the **reduction of the activity** and the **inhibition of the growth** of a cancer cell.

Already a decade before the filing date of the patent in suit T. Mosmann described as a rapid colorimetric assay, the first microculture tetrazolium assay (MTA) for monitoring **cell growth** and survival, which utilized MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl

tetrazolium bromide) (see page 62, under the heading "Discussion" of document (20)).

Therefore, the skilled reader understands that, in claim 1 as granted, the inhibition of the growth of a cancer cell is measured employing the MTT method.

The opposition division mentioned in its decision paragraph [0032] of the contested patent (page 6 of the opposition division's decision). In said paragraph, the MTT method is disclosed as the method for measuring cell activity in a spectrophotometric assay.

However, paragraph [0032] of the patent in suit clearly states that the MTT method is based on the cellular reduction of MTT to a blue formazan product by mitochondrial dehydrogenases of **viable cells**. Nothing in paragraph [0032] supports the opposition division's view that the MTT method is not at all appropriate for measuring the inhibition of the growth of a cancer cell.

Further inspection of the patent in suit shows the following statements in paragraph [0016]: "Lycopene has been found to be a potent inhibitor of mitochondrial activity. Cell activity is measured by the MTT method, which is based on the activity of mitochondrial dehydrogenases. Surprisingly, the **cell activity** is not a direct measure of **cancer cell growth**, and these two values **correlate well only at high lycopene concentrations**. In other words, cell activity, as measured by the activity of mitochondrial dehydrogenases, is not directly proportional to the reduction of cancer cells growth **at low lycopene contents**" (*emphasis added*).

Hence, the specification in the patent in suit does not support the view that the MTT method may not be used for determining inhibition of the growth of a cancer cell at high concentrations of lycopene.

Additionally, even if assuming that the [³H]thymidine incorporation and haemocitometer cell counting methods give more accurate results than the MTT method when measuring cell counting and the rate of cell proliferation, this piece of knowledge does not invalidate the meaning of a broad granted claim in relation to the MTT assay as the method of choice for determining cell growth.

Moreover, it has to be assumed in the light of the expressed above, that there are discrepancies to be expected between the results obtained from the different methods (in particular at low lycopene concentrations), which lead to different scopes of protection conferred by each claim 1 (claim 1 of the granted version and claim 1 of the main request). Therefore, the scope of claim 1 of the main request is not necessarily encompassed by the scope of the granted claim 1.

Consequently, the replacement in claim 1 of the MTT method, for determining the inhibition of cell growth in a cancer cell, with the [³H]thymidine incorporation and haemocitometer cell counting methods contravenes Article 123(3) EPC.

As already mentioned in facts and submissions, the appellant did not file any counterarguments to the board's findings.

Thus, the main request fails since claim 1 contravenes Article 123(3) EPC.

1.3 First auxiliary request

As regards claim 1 of the first auxiliary request, it has to be investigated whether or not the amendment which relates to the definition of the medicament "for inhibiting the proliferation of a cancer cell" (instead of "for inhibiting the growth of a cancer cell") meets the requirements of Article 123(2) and (3) EPC. In particular, since it cannot be seen that both terms "growth" and "proliferation" are interchangeable synonyms within the context of the claim.

The expression "the growth of a cancer cell" may imply the growth rate of a particular cancer cell (linked to the abnormal development of a cancer cell) or the growth by cell division (linked to the uncontrolled growth by division of cancer cells). Additionally, even if considering (see appellant's statement on top of page 15 of the grounds of appeal) that the inhibition of proliferation of a cancer cell may be seen as the result of the inhibition of the growth of a cancer cell, the board has doubts that inhibition of proliferation of a cancer cell is always caused by inhibition of the growth at the cellular level of a cancer cell. For instance, the inhibition of proliferation may be caused by interferences to cell adherence at the extra-cellular level, or by cell apoptosis (through

mechanisms not necessarily linked to the inhibition of the growth of a cancer cell). Therefore, the amended claim 1 of the first auxiliary request contravenes Article 123(3) EPC.

Additionally, an inspection of the description of the application as originally filed shows that there is support and disclosure for the inhibition of the growth of a cancer cell by lycopene, but not necessarily for the inhibition of the proliferation of a cancer cell by lycopene. The passage on page 11 of the application as filed (referred to by the appellant in relation to the granted version) relates to the general measurement procedures, and simply mentions how to estimate "the rate of cell proliferation". Furthermore, the examples appear to test and measure the effects of lycopene either on cell activity or on "cell growth". There is a mention to "proliferation" in example 5, but it refers to "(IGF-I)-induced proliferation".

Accordingly, claim 1 of the first auxiliary request does not meet the requirements of Article 123(2) EPC.

The appellant did not file any counterarguments to the board's findings.

Consequently, the first auxiliary request fails since it contravenes the requirements of Article 123 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

N. Maslin

U. Oswald