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Datasheet for the decision of 17 September 2013

Case Number: T 0475/10 - 3.3.01

Application Number: 98942181.3

Publication Number: 1006802

IPC: A01N65/00, A61K35/78, G01N33/94

Language of the proceedings: EN

Title of invention:
CHEMICAL AND PHARMACOLOGICAL STANDARDIZATION OF HERBAL EXTRACTS

Applicant:
fx Life Sciences AG

Headword:
Standardised plant extraction/fx LIFE SCIENCES

Relevant legal provisions:
EPC Art. 56, 123(2)

Keyword:
"Main request, first and second auxiliary requests: added subject-matter (yes) - amended features not unambiguously disclosed in connection with the claimed process" "Third and fourth auxiliary requests: inventive step (no)"

Decisions cited:

Catchword:

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Case Number: T 0475/10 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 17 September 2013

Appellant: (Applicant)	fx Life Sciences AG Grafenaustrasse 11 6300 Zug (CH)
Representative:	Böhm, Brigitte Weickmann & Weickmann Patentanwälte Postfach 860 820 81635 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 15 May 2009 refusing European patent application No. 98942181.3 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman: A. K. Lindner
Members: C. M. Radke
L. Bühler

Summary of Facts and Submissions

I. European patent application no. 98 942 181.3 was published as WO-A-99/09 837.

II. It deals with a method for obtaining a standardised process for the extraction of pharmaceutically active components from a plant and with a method of standardising the pharmacologically active components in such an extract.

III. Claims 1 and 8 as originally filed read as follows:

"1. A method of obtaining a reproducible extraction process for use as a standard process for extracting a pharmacologically active mixture of chemical components from a plant, the method comprising:

(a) extracting a plurality of pharmacologically active mixtures of chemical components from a plant in a plurality of different extraction processes, to produce a plurality of extracts;

(b) obtaining a biological fingerprint of the pharmacological activity of each extract from step (a) by conducting at least two *in vitro* and at least two *in vivo* pharmacological tests on each extract, wherein each of the tests is known to correlate with effective treatment of a medical condition in a patient;

(c) choosing the one of the plurality of extracts which displays the best pharmacological activity in step (b);

(d) repeating, at least once, the extraction process used to produce the chosen extract of step (c), to produce at least one test extract;

(e) (1) obtaining chemical fingerprints of the chosen

extract and the at least one test extract by distinguishing the identity and amount, relative to each other, of the chemical components in the pharmacologically active mixture of each extract, and

(2) repeating said obtaining step (b) using the at least one test extract; and

(f) comparing the chemical fingerprints and the biological fingerprints of the chosen extract and the at least one test extract, wherein

when the chemical components of the at least one test extract are present in an amount which is at most 10% more or less than the amount of the same chemical component of the chosen extract, and

when each pharmacological test result of the at least one test extract is at most 10% more or less than the corresponding pharmacological test result of the chosen extract,

then the extraction process used to produce the chosen extract is selected as the standard process for extracting the pharmacologically active mixture of chemical components from the plant."

"8. A method of obtaining a pharmacologically active mixture of chemical components having a reproducibly high pharmacological activity derived from a plant source comprising,

(a) conducting a plurality of different extraction processes on a plurality of samples from the same plant source to produce a plurality of plant extracts;

(b) conducting at least two *in vitro* and at least two *in vivo* pharmacological tests known to correlate with effective treatment of a medical condition in a patient on each plant extract;

(c) selecting the plant extract displaying the highest

pharmacological activity in step (b);

(d) repeating the extraction process used to produce the selected extract of step (c) to produce a test extract;

(e) obtaining chemical fingerprints providing at least one of qualitative and quantitative information regarding chemical components of both the selected extract and the test extract;

(f) repeating the tests of step (b) on the test extract;

(g) comparing the chemical fingerprints and the biological activity of the selected extract and the test extract, such that

when the chemical component(s) of the test extract are present in an amount which differs no more than about + or - 10% that of the corresponding pharmacological test activity of the selected extract, then that extraction process used to produce the selected extract is chosen as the standard process for extracting the pharmacologically active mixture of chemical components having a reproducibly high pharmacological activity."

IV. The appeal of the patent applicant is directed against the decision of the examining division to refuse the application.

V. The documents cited during the examination procedure include the following:

(D1) US-A-5 565 200.

VI. In particular, the examining division decided

- that the subject-matter of the claims of the main request then on file was not inventive in view of document (D1);

- that the subject-matter of the claims of the third auxiliary request contravened Article 123(2) EPC;

and did not admit the claims of the first, second and fourth auxiliary requests into the proceedings.

VII. The appellant enclosed amended claims with its statement setting out the grounds of appeal.

VIII. In the communication annexed to the summons to oral proceedings, the board gave reasons for its preliminary opinion that

- the claims then on file did not meet the requirements of Article 123(2) and Rule 43(2) EPC, and
- that their subject-matter was not based on an inventive step starting from document (D1) as the closest prior art in view of the following document introduced by the board:

(D7) Good manufacturing practices for Active ingredient manufacturers, European Federation of Pharmaceutical Industries and Associations, April 1996, pages 1-54.

IX. In reply to this communication, the appellant presented counterarguments and filed amended claims. During the oral proceedings before the board, the appellant stated that these claims replaced those submitted with the statement setting out the grounds of appeal and filed two additional auxiliary requests.

X. The present claim are

- claims 1-16 of the main request,
- claims 1-14 of the first auxiliary request,
- claims 1-8 of the second auxiliary request,

all filed with letter dated 30 August 2013, as well as
- claims 1-14 of the third auxiliary request and
- claims 1-7 of the fourth auxiliary request,
both submitted during the oral proceedings before the board.

a) Claim 1 of the main request reads as follows:

"1. A method of obtaining a standardized extraction process for extracting a pharmacologically active mixture of chemical components from a plant, the method comprising:

(a) extracting a plurality of pharmacologically active mixtures of chemical components from the plant in a plurality of different extraction processes, to produce a plurality of extracts;

(b) obtaining a pharmacological fingerprint of the pharmacological activity of each extract of the plurality of extracts from step (a) by conducting *in vitro* and/or *in vivo* pharmacological tests on each extract, wherein each of the tests is known to correlate with effective treatment of a medical condition in a patient;

(c) selecting the one of the plurality of extracts which displays the best pharmacological activity in step (b) to provide a selected extract;

(d) repeating the extraction process used to produce the selected extract of step (c), to produce one or more test extracts;

(e)

(1) obtaining chemical fingerprints of the selected extract and the one or more test extracts from step (d) by distinguishing the

identity and amounts, relative to each other, of the chemical components in the pharmacologically active mixture of each of the selected extract and the one or more test extracts, and

(2) repeating said obtaining step (b) using the one or more test extracts from step (d) to provide pharmacological fingerprints for the one or more test extracts; and

(f) comparing the chemical fingerprints and the pharmacological fingerprints of the selected extract and the one or more test extracts, wherein

when the chemical components of the one or more test extracts are present in an amount which differs no more than about + or - 10% from that of the same chemical components of the selected extract, and

when the results from each pharmacological test on the one or more test extracts differ no more than about + or - 10% from the results from the corresponding pharmacological test on the selected extract,

then the extraction process used to produce the selected extract is selected as the standardized extraction process for extracting the pharmacologically active mixture of chemical components from the plant."

b) Claim 1 of the first auxiliary request differs from claim 1 of the main request only in that ",the plant being ginseng plant" has been inserted at the end of the definition of step (a).

c) Claim 1 of the second auxiliary request differs from claim 1 of the main request only in that the

following has been inserted at the end of the claim:

"wherein either (i) the plant is a ginseng plant and the pharmacological activity comprises stimulation of the immune system, antidepressant activity, antihypertensive activity or neuroprotective activity, or (ii) the plant is a *Panax quinquefolius* plant and the pharmacological activity comprises alleviating memory loss".

d) Claim 1 of the third auxiliary request and claim 1 of the fourth auxiliary request are identical. They differ from claim 1 of the main request only in that
- in the definition of step (b) "by conducting *in vitro* and/or *in vivo* pharmacological tests on each extract" has been replaced by "by conducting at least two *in vitro* and at least two *in vivo* pharmacological tests on each extract" and that
- after the definition of step (f) the word "about" has been deleted in both expressions "about + or - 10%".

XI. During the oral proceedings before the board, the appellant submitted the following additional documents:

(D8) H. Terlau et al., Das medizinische Potential von Naturstoffen, Der Gynäkologe, vol. 33(1) (2000), pages 6-7

(D9) Sheet with the title "Standard drug development using a single pharmacological activity test"

(D10) Sheet with the title "Method of obtaining a

standardized extraction process according to the present application".

XII. The arguments of the appellant as far as relevant for this decision may be summarised as follows:

(a) The claims have been amended for reasons of clarity.

Support for the terms "*in vitro* and/or *in vivo* pharmacological tests" and "about + or - 10%" in claim 1 of the main request could be found on page 5, lines 7-8, page 4, lines 15-21 and page 13, lines 22-23, respectively.

(b) The appellant argued that document (D1) dealt with a different problem. It did not compare the extraction protocols in order to select the extract with the highest pharmacological activity.

Table 3 of document (D1) showed activity data for different versions of just two extracts (n-T4GEN and ISCADOR). The extraction method of example 2 using double distilled water did not differ much from that of example 1 (yielding n-T4GEN), where the water was not distilled. No comment was made on example 3, where the same plant was extracted with acetone.

Document (D1) started with a single extract and used a single biological assay.

Multiple pharmacological tests were, however, vital as different compounds might contribute to the desired effect, be it that they showed a synergetic effect (as shown in tables 2 and 3 of

the present application) or that one compound lowered the toxicity of the other (as mentioned in document (D8)). Furthermore, unknown compounds might contribute to the pharmacological effect. The multiple assays might respond to different components of the extracts (as illustrated on sheets (D9) and (D10)).

The present claims required that a chemical fingerprint was taken from the extracts, whereas only lectins, viscotoxins and alkaloids were determined in document (D1).

The problem solved in view of document (D1) was to provide a standard extraction process yielding optimal pharmacological results.

(c) Document (D7) did not hint at the solution of this problem as it merely indicated that the quality attribute of the active ingredient that is to be validated includes activity. It did not teach or suggest obtaining a chemical or a pharmacological fingerprint of an active ingredient.

XIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or, alternatively, of the first or second auxiliary request, all filed with letter dated 30 August 2013, or, alternatively, on the basis of the third or fourth auxiliary request submitted during oral proceedings before the board on 17 September 2013.

XIV. At the end of the oral proceedings, the chairman announced the decision of the board.

Reasons for the Decision

1. The appeal is admissible.

2. Article 123(2) EPC

2.1 Main request

2.1.1 Claim 1 of this request relates to a "method of obtaining a standardized extraction process". It corresponds to claim 1 as originally filed (relating to a "method of obtaining a reproducible extraction process for use as a standard process", from which it differs *inter alia*, in that

- in step (b) the words "conducting **at least two** *in vitro* and **at least two** *in vivo* pharmacological tests on each extract" were replaced by "conducting *in vitro* and/or *in vivo* pharmacological tests on each extract";
- "at most 10% more or less" on page 33, lines 24+27 has been replaced by "**about** + or - 10 %".

As a basis for the first amendment, the appellant referred to page 5, lines 7-10, and as a basis for the second one to page 4, lines 15-21 of the application as filed.

2.1.2 These parts of the application as filed do indeed disclose these two features. This is, however, not sufficient unless said features are disclosed in combination with the process of original claim 1. This is necessary because the application as filed covers not only

- the "method of obtaining a reproducible extraction process for use as a standard process" of original claim 1, but also
- the methods of original claims 2 and 8 relating to the preparation of a mixture having a reproducibly high pharmacological activity derived from a plant.

The process of original claim 1 differs from the process of original claims 2 and 8 *inter alia* in that

- claim 1 teaches in **step (a)** the preparation of a plurality of extracts "from a plant" whereas claim 2 and 8 require that these extracts are made "from the same plant source";

- claim 1 requires the selection of the extract displaying the "best" pharmacological activity in **step (c)**, whereas claims 2 and 8 require that the one with the "highest" activity is selected;

- claim 1 requires that the amount of the chemical components and the pharmacological test result of the test extract "is at most 10% more or less" than those of the selected extract, whereas in claims 2 and 8 the tolerated differences are "no more than about + or - 10%".

(See point III above as far as the wording of originalclaims 1 and 8 is concerned).

2.1.3 Hence, the features of original claim 1 differ from those of original claims 2 and 8.

Due to the number of differences the board does not share the appellant's view that any reference to a

method in the application as filed referred to both types of method. Rather, it is evident that it was intended that the two types of method comprise different process steps. As a consequence of this, a disclosure in the application as filed not clearly referring to the process of claim 1 may not be considered as an unambiguous disclosure of subject-matter intended to pertain to that claim.

Hence, it is necessary to assess in what context the sentences on page 4, lines 15-21, and page 5, lines 7-10 - which the appellant cited as a basis for the amendments - are disclosed in the application as filed.

The starting point is the sentence on page 3, lines 19-21, which reads as follows:

"The present invention provides both a method of obtaining standardized biological compositions having high pharmaceutical activity and to a method of obtaining standardized processing procedures."

Hence it clearly refers to both types of method, one for obtaining a standardised composition and one for determining standard process conditions.

The first sentence of the next paragraph reads as follows:

"The methods of the present invention used for standardization of a biologically or pharmacologically active mixture ..."

Thus it only refers to the first type of method, namely the methods of original claims 2 and 8. This is in line with the reference to "the highest pharmacological

activity on page 4, line 23, which is a feature of step (b) of original claims 2 and 8, but not of original claim 1.

The appellant referred to lines 20-21 of said paragraph, which read as follows: "... then the process used to produce the selected product is chosen as the standard process ...". At a first glance these lines seem to refer to the process of claim 1. On the other hand, they could also refer to the methods of claims 2 and 8, the last line of which reads as follows: ", then that extraction process used to produce the selected extract is chosen as the standard process for ...", though this is in contradiction with the first three lines of both claims 2 and 8. Nor do the remaining parts of the three paragraphs from page 4, line 1, to page 5, line 14, specify clearly that features disclosed therein are meant to refer to the method of original claim 1.

Accordingly, the sentences on page 4, lines 15-21, and page 5, lines 7-10 - which the appellant cited as a basis for the amendments - do not clearly and unambiguously refer to the method of original claim 1.

Hence, these sentences cannot serve as a basis for the amendments mentioned above.

Moreover, amended claim 1 provides the person skilled in the art with information different from that of original claim 1 and the application as filed as a whole, as it no longer requires **at least two** *in vitro* and **at least two** *in vivo* pharmacological tests on each extract and as it permits differences in activity of more than 10 % in the extracts. The appellant considered that it was generally preferred to conduct

"at least two *in vitro* and at least two *in vivo*" tests. As is apparent from the preceding conclusions, the application as originally filed does not support this argument.

Consequently, amended claim 1 contravenes the requirements of Article 123(2) EPC.

2.1.4 The board can only decide on a request as a whole. Hence, the main request was refused.

2.2 First and Second Auxiliary Requests

As can be seen under points X (b) and (c) above, claim 1 of each of these requests differs from claim 1 of the main request only in that additional features have been added. Hence, these auxiliary requests still contain the amendments objected to under point 2.1 above. Therefore, the conclusion drawn under point 2.1.3 that claim 1 contravenes the requirements of Article 123(2) EPC also applies to claim 1 of the first and second auxiliary requests.

Hence, the first and second auxiliary requests were also refused.

2.3 Third and Fourth Auxiliary Requests

Claim 1 of these requests is identical. It differs from claim 1 of the main request in that the amendments mentioned under point 2.1.1 above have been reversed. As a consequence of this, claim 1 of these auxiliary requests is properly based on claim 1 as originally filed. In view of the outcome of this decision it is not necessary to give detailed reasons why this is so or to assess whether or not the remaining claims of

these requests meet the requirements of Article 123(2) EPC.

3. Inventive Step

3.1 The closest prior art

3.1.1 The appellant did not contest the finding of the examining division that document (D1) is to be considered as the closest prior art.

This document relates to the extraction of Korean mistletoe (see the abstract). The problem addressed was to find a method "for the manufacture of a standard preparation and uniform quality control" (see column 3, lines 42-46).

Several extracts were produced, e.g. in example 1 by extracting with water (see column 12, lines 45-47), in example 2 with double distilled water (see column 17, lines 49-52) and in example 3 with cold acetone (see column 18, lines 44-47). The different activity values given for the n-T4GEN extract samples 2, 5, 6 and 8 to 10 in table 3 (see column 10, lines 16-34) also imply that these samples were prepared under different processing conditions. For each of the extracts in examples 1 and 2, the chemical fingerprint was determined by fractionating the samples (see column 12, lines 63-66, column 18, lines 1-18 and table 6 in columns 17-18) and the biological fingerprint with respect to the L1210 leukaemia system (see Tables 4 to 6).

3.1.2 The problem addressed in the present application is to "standardize processing conditions in order to

obtain ... standardized herbal compositions" (see page 3, lines 7-10).

This problem is closely related to the one addressed in document (D1), where it is stated that "[i]f the protein levels fall within the limits required in accordance with the present invention, then the extract is identified as pharmaceutical grade" (see column 18, lines 3-6).

3.1.3 For these reasons the board is satisfied that document (D1) represents the closest prior art.

3.2 In view of the disclosure cited under point 3.1.1. above, the board does not share the appellant's opinion that document (D1) taught starting from a single extract and that it did not compare the extraction protocols.

Therefore, the disclosure of document (D1) differs the process of claim 1 only in that (D1) does not teach

(1) repeating the extraction to yield at least one test extract, and selecting the method as a standard process if the chemical and pharmacological fingerprints of the test extract(s) differ(s) no more than + or - 10 % from that of the selected extract;

(2) conducting at least two *in vitro* and at least two *in vivo* pharmacological tests in present step (b); and

(3) selecting the extract having the **best** pharmacological activity in step (c) but only requires that said activity be above a certain value.

3.3 The problem to be solved

The appellant defined the problem to be solved in view of document (D1) as to provide a standard extraction process yielding optimal pharmacological results. The board consents to this definition. In view of the examples in the present application the board is satisfied that this problem is solved by means of the process of claim 1, in particular by means of the features (1), (2) and (3) mentioned under point 3.2 above.

3.4 Obviousness of the solution

3.4.1 Feature (1) mentioned under point 3.2 above

A very common set of rules for standardising processing conditions in pharmacy is that of the Good Manufacturing Practices (D7).

Document (D7) defines a batch as a "defined quantity of material produced in a process or series of processes so that it is expected to be **homogeneous within specified limits**" (see page 8, und the heading "Batch (or lot)"; emphasis added by the board).

This requires the manufacturer to set certain limits within which certain parameters of the product may vary and to validate that the products meet these requirements.

"During early development such validation will normally consist of a more intense in-process and final product control" (see page 27, the second sentence under the heading "Principle").

According to chapter 10.4.1 on page 28,

"10.4.1.1 Prospective validation is establishing documented evidence that a system does what it purports to do **prior to the commercial distribution** of a new A.I. or an A.I. made by a new or modified process.

10.4.1.2 The number of batches to be run will depend on the process and the number of critical parameters but **in general three successful sequential runs at production scale** under the defined process conditions should be made."

(Emphasis added by the board; A.I. stands for active ingredient)

Therefore, it was obvious to the person skilled in the art in charge of solving the problem mentioned under point 3.3 above to modify the process disclosed in document (D1) by

- setting up certain limits within which the chemical components and the pharmcological activities may vary (e.g. within +/- 10 %);
- considering the process as a standard only if the chemical compositions and the pharmacological activities of extracts produced in three sequential extractions are within these limits.

In doing so, the person skilled in the art would have ended up with a process involving feature (1) mentioned under point 3.2 above.

3.4.2 Feature (2) mentioned under point 3.2 above

This feature requires conducting at least two *in vitro* and at least two *in vivo* pharmacological tests in present step (b).

According to document (D1), the "method for measuring inhibitory action is set forth in numerous scientific articles including the references mentioned previously. It is preferred that the inhibitory action be measured *in vitro* with respect to leukemia L1210 cells. This procedure is preferred because L1210 cells are readily available, they are easily maintained by well-known culturing procedures and provide consistently reproducible results" (see column 9, lines 6-13).

Hence, there is no indication in this document that at least two *in vitro* and at least two *in vivo* pharmacological tests are excluded. Moreover, document (D1) mentions that

"[t]he extracts which are identified as meeting the composition requirements are then used in treatment programs for treating diseases such as AIDS and cancer. The extracts are not only useful in treating AIDS, but they may be used to treat any individual with a suppressed immune system" (see column 9, lines 47-52).

First of all, this hints at *in vivo* tests in respect of at least two different diseases, i.e. at least two *in vivo* tests. Secondly, this renders the use of a more specific *in vitro* test in respect of AIDS in addition to the test with leukaemia cells obvious.

Therefore, document (D1) renders feature (2) mentioned under point 3.2 above obvious.

The argument of the appellant that multiple pharmacological tests were vital as they could be sensitive to the different compounds contributing to the desired effect is speculative. The fact that multiple tests are made does not ensure that these tests are sensitive to different compounds contributing to the desired effect.

3.4.3 Feature (3) mentioned under point 3.2 above

This feature requires selecting the extract having the **best** pharmacological activity in step (c).

Firstly, document (D1) teaches selecting an extract, the pharmacological activity of which is above a certain value. This does not exclude selecting the one having the "best" activity. Secondly, the best activity is a desideratum. An extract exhibiting the best activity is thus an obvious selection.

3.4.4 The appellant has not argued that any **combination** of features (1), (2) and 3 gives rise to an unexpected result.

3.5 For these reasons, it was obvious to the person skilled in the art to modify the process disclosed in document (D1) by the features (1), (2) and (3) mentioned above, and thus to end up with the method of claim 1.

3.6 Therefore, the subject-matter of claim 1 of the third and fourth auxiliary requests is not based on an inventive step. Hence, these requests were also refused.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. K. Lindner

Decision electronically authenticated