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Letter of confirmation of a Fax transmission

22 December 2008

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To
European Patent Office
Directorate General 2
Erhardtstrasse 27

D-80 298 M u n i c h

EP 1 684 775 B1	**Pelargonium**
Proprietor of the patent:	Schwabe GmbH & Co KG, 76 227 Karlsruhe (DE)
Title:	Use of extracts from Pelargonium species
Application number:	04790852.0
Date of application:	26.10.2004
Priority	29.10.2003 DE 10350338
Publication of the grant:	26.03.2008 Patent Bulletin 2008/13

O P P O S I T I O N

In the name and on behalf of

1) **Mariam Salim Mayet, 3A, 4th Avenue, Melville, Johannesburg, South Africa, 2109** and
2) **Nkqayi Funeka, Private Bag 1310, Llokhwe, Masakhane, Alice, Eastern Cape, South Africa, 5700,** and
3) **Bern declaration (association), Postfach, CH-8026 Zurich, Switzerland**

objection is raised against the abovementioned patent pursuant to Art. 99 EPC and the following petition made:

1. To revoke the patent EP 1 684 775 "Use of extracts from Pelargonium species" in its entirety (all 6 patent claims).
2. Alternatively: To schedule a hearing in case the opposition division should intend to dismiss the objection or maintain the patent in a modified form.

The objection is raised pursuant to Art. 100, viz. Art. 100 a, b) and c) EPC. We enclose the EPO Form 1010 for payment of the opposition fee in the amount of EUR 670.00. This amount was paid into the account of the European Patent Organisation at the Union Bank of Switzerland UBS AG in Zurich on 17.12.08. It is also requested that a possibly owing shortfall be charged to our current account: Dolder & Partner, Account no. 281 101 05 at the EPO Munich.

G r o u n d s

1. Art. 53 (a) EPC ("ordre public")

1.1 A violation of "ordre public" or morality may, among other, be given if there were serious violations of ethics when the teaching in accordance with the invention was first obtained (see Moufang GRUR Int. 1993, 439 – 450, for instance). With inventions based on traditional knowledge, the two criteria of *previous informed consent (PIC)* and *benefit sharing* must be examined, as stipulated in Art. 8-j, 15, 16 of the Convention on Biological Diversity (CBD). The country of origin of the Pelargonium roots, South Africa, as well as most of the EPO member states, is/are signatories of the CBD. The regulations of the CBD with respect to access to traditional knowledge are *self-executing* under South African law and therefore do not require national legislation to be legally effective.

The patent applicant is obligated to prove compliance with the applicable stipulations when initially obtaining the inventive teaching if, based on the description of the invention, there are indications of an ethically sensitive situation. Such a situation may be assumed if traditional knowledge from a bio-diverse country is a *critical* prerequisite to the success of the inventive step, i.e. vital to the technical success in terms of the conditional theory. Switzerland, an EPO member state, has for instance included in the application procedure a corresponding formal burden of proof on the patent applicant in its revised patent law dated 30.6.2007:

> Art. 49-a PatG (neu) *[Patent Act (new)]*
> With inventions relating to genetic resources or traditional knowledge, the patent application must include information on the source: (….)
> b. of the traditional knowledge of indigenous or local communities about genetic resources, (….)

1.2 It is overlooked at times, however, that the holders of traditional knowledge must first be informed and give their consent and that this process also includes *commercial realisation of profits* through patents. But, especially in this respect, there are *significant and substantial reservations* in this case, whether the patent applicant complied with the above regulations and fulfilled the relevant obligations with respect to the patent in-suit.

1.3 Apart from *previous informed consent* it must be assumed that the holders of the traditional knowledge are entitled to regular financial benefits from the proceeds of patents, if the latter could only be obtained because of source material or traditional knowledge which they provided. Art. 8-j and 15 CBD with reference to the utilisation of indigenous traditional knowledge form the basis and point of reference for such *benefit sharing*.

In this case, the subject matter of the patent in-suit is based primarily on the fortunate circumstance that the traditional knowledge the South African communities have on the medical treatment with Pelargonium extracts of the human immunodeficiency disease AIDS, was available and a favourable starting position for the work of the proprietor of the patent.

1.4 Based on these deliberations, it is necessary to verify that Art. 8-j, 15, 16 CBD are complied with in the application procedure and verified by documentation (or other forms of evidence) and that the *previous informed consent* must explicitly include permission for *commercial exploitation of the traditional knowledge by means of patents* and a corresponding *benefit sharing agreement* with the indigenous communities entitled thereto.

In this case, the proprietor of the patent has to date not presented any relevant proof. As long as the proprietor of the patent has not submitted corresponding proof of compliance with the CBD, it may be assumed that the patent in-suit is in conflict with Art. 53 a) EPC.

2. Prior art

The opposing arguments refer to the following documents attached to this submission and which are supplementary to documents D1 to D6 cited in the notification by the International Searching Authority PCT dated 11.10.2005 and notification by the EPO examining division dated 26.2.2007. Numbering in the PCT notification is continued:

D7 Laidler et al., South African Journal of Science, 25 (1928), 433-447, Page 443 in particular;
D8 M. Heger, V.V. Bereznoy, Nicht-streptokokkenbedingte Tonsillopharyngitis bei Kindern, in: V. Schulz et al. (publ.), Phytopharmaka VII, Research and clinical application, Darmstadt 2002: Steinkopff, Pages 13 to 25;
D9 Arznei-Telegramm (Berlin) 2006, No. 10, Page 93: Article Umckaloabo – Indikationen zusammengestrichen;
D10 Arznei-Telegramm (Berlin) 2008, No. 10, Pages 105/106: Article Umckaloabo bei akuter Bronchitis: Nutzen belegt ?

A1 Affidavit Mnyamezeli N x a k a l a
A2 Affidavit Elizabeth N k q a y i
A3 Affidavit Zamile N g e t h u
A4 Affidavit Yaziwe G i d i
A5 Affidavit Notsomi B e v i l e

A6 Affidavit K h u l u n g u

The Opponents reserve the right to request all or some of the authors of the cited documents and/or affidavits to be summoned as *witnesses* in the alternatively requested hearing.

3. The patent claims: Unlawful extension Art. 123 (2) EPC

3.1 After restriction in the proceedings for grant, the patent in-suit includes another six patent claims: The independent Claim 1 represents a *Swiss Type Claim* and comprises the prophylactic and/or therapeutic treatment of 4 indications in total, namely

- disease-related behavioural changes,
- chronic fatigue syndrome,
- post viral fatigue syndrome,
- stress-induced chronic illnesses

These four different pathological conditions are bundled under the umbrella term *"Sickness behaviour"* in the description terminology of the patent in-suit (Sections 2, 5 to 9).

Claims 2 to 6 all reference Claim 1 and comprise more detailed embodiments of the subject matter of Patent claim 1.

3.2 The originally filed and the current form of Claim 1 differ as follows:

> Original text of Claim 1:
> Use of extracts *from Pelargonium species* or parts of the plants for prophylaxis or treatment ….
>
> Current text of Claim 1 in B1:
> Use of extracts *from Pelargonium species selected from P.sidoides and P.reniforme* or parts of the plants *to produce a medicinal product* for prophylaxis or treatment ….

Claim 1 was therefore only rephrased to a Swiss Type Claim during the examination procedure, in consideration of Art. 53-c (or formerly 52 (4)). For this reason, the interim phase of *"Production of a medicinal product"* is not explicitly described anywhere in the original documentation: The term "medicinal product" does not appear anywhere in Sections 17 to 20 of the current B1.

3.3 According to T770/90, a claim that is too broad and not supported in the original description is not a suitable "reservoir" for changes:

The transition from the *Pelargonium species* (original documentation) to the two individual species *P. sidoides* and *P. reniforme* introduces the transition of a genus comprising ***220 to 280 individual Pelargonium types*** to a group of only two species. The original claim *was therefore undoubtedly too broad* and was not supported in the original description: Nowhere in the original documentation is there a reference, or even experimental proof, that other Pelargonium species (than *P. sidoides* or *P. reniforme*) could also be used to produce the claimed medicinal product: refer e.g. Sections 10 and 13 (at the end). The introductory Section 1 of B1 is therefore also *currently* still too broad and should be restricted accordingly.

In the description, the proprietor of the patent persistently points out that *"Sickness behaviour"* is a clinical condition, independent of other pathological conditions and autonomous (Sections 2 to 9 of B1). He distances himself from **D5** and **D6** by stating that these documents gave no indication that a positive development of the behavioural changes or "Sickness behaviour" could also result ***without*** improvement of the respiratory symptoms, by administering Umckaloabo. He states that **D5** and **D6** did not document an independent positive effect on the symptoms of "Sickness behaviour" (Section 15) either.

In the current text of B1, Claim 1 also includes circumstances in which, more or less fortuitously, clinical pictures such as respiratory symptoms etc. etc. associated with or causing the "Sickness behaviour" are also treated or influenced prophylactically. These are, however, facts in **D5** and **D6** that are prejudicial to novelty. It should therefore at least be made clear, in a corresponding *Disclaimer*, that Claim 1 refers *exclusively* to therapy for the *independent* and *isolated* "Sickness behaviour", as an autonomous illness, and that the therapy for "Sickness behaviour" in association with other clinical pictures is excluded from the teaching of the patent in-suit.

4. Art. 54 EPC (Novelty)

4.1 Claim 1 is therefore devoid of novelty with respect to A1 to A6.

All affidavits A1 to A6 by practitioners of the South African traditional medicines describe the successful treatment, prior to the date of filing the patent in-suit, of *"Sickness behaviour"* with Pelargonium extracts in the region of the Alice Community (and other regions) in South Africa. The therapeutic successes were achieved both with "Sickness behaviour" as an *independent* clinical picture *(behavioural changes)* and with "Sickness behaviour" in combination with other clinical pictures. Examples:

A1, no. 7.2,
A2, nos. 8, 10,
A3, no. 8,
A4, no. 7,
A5, no. 7, and
A6, no. 6.

This prior art was *common medical knowledge* since time immemorial in the relevant regions in South Africa. Consequently, Claim 1 is devoid of novelty with respect to A1 to A6.

It is surprising that the Examining Division has not explored the South African traditional medicines in more detail, despite *explicit* reference to the prior art of this traditional medicine in Section 10 of the patent in-suit.

4.2 Claims 2 and 3 are devoid of novelty with respect to A1 to A6.

All the affidavits A1 to A6 by practitioners of South African traditional medicines describe the treatment of "Sickness behaviour" in the region of the Alice Community (and in other regions) in South Africa with aqueous ethanolic extracts from the roots of the two Pelargonium species:

Examples: A1 no. 6 , 9 and especially 10; A2, No. 4, 12 and 13; A3 no. 4 and 12; A4, no. 4 and 11; A5 no. 4 and 11; A6, no. 4 and 10.

Consequently, Claims 2 and 3 are also devoid of novelty with respect to A1 to A6.

5. Art. 56 EPC (Inventive step)

The purpose of the invention in the contested patent follows from the description (Section 9) of the urgent need for effective treatment methods, without side effects, for behavioural changes due to illness, i.e. of "Sickness behaviour". This purpose is achieved by use of extracts from *Pelargonium sidoides* and/or *reniforme* to produce a medicinal product for the treatment of "Sickness behaviour" (Section 16).

The description (Section 0015), the notices of the PCT Searching Authority dated 11.10.2005 and of the EPO Examining Division dated 26.2.2007 consider **D5** and **D6** as closest prior art. These documents disclose the use of Pelargonium extracts for the treatment of acute bronchitis in children and examine the efficacy and tolerance of these extracts under such treatment. These documents disclose that administration of Umckaloabo resulted in a positive development of the behavioural changes, i.e. "Sickness behaviour" and *additionally in an improvement in the respiratory symptoms*. But improvement of Sickness behaviour *without* simultaneous improvement of the respiratory symptoms was disclosed neither in **D5** nor in **D6** (as per Section 15 of the patent in-suit).

5.1 Claim 1 lacks inventive level based on **D5/D6** combined with **D7** (Page 443)

Based on **D5** and **D6**, the problem to be solved may be seen as finding an *additional* therapeutic or prophylactic application of Pelargonium extracts for treating "Sickness behaviour" *independently* and *isolated* from the treatment of respiratory (or other) symptoms, apart from the treatment of "Sickness behaviour" in combination with respiratory symptoms (e.g. bronchitis).

D7 (Laidler et al.) disclose (Page 443) that extracts *("boiled in milk")* of the South African Pelargonium species *Pelargonium anceps* are used successfully in traditional medicines of the Cape region and in Namaqualand for the treatment of *"weaknesses"*. This is another way of describing the illness condition which may, by present terminology, broadly correspond with the aforementioned "Sickness behaviour":

"The Afrikander names it rooi wortle or rooi storrm. It is used for anaemias and weaknesses and repeated doses are given during fevers. The Boer uses it boiled or "set op brandywijn".

Based on this information in **D7**, the use of Pelargonium extracts for the treatment of "Sickness behaviour", *independent* of and *isolated* from the treatment of respiratory (or other) symptoms, is directly pointed out to the average skilled person. Based on this teaching in **D7**, **D5** and **D6** suggest the use of the extracts from *P. sidoides* and/or *P. reniforme* for the prophylaxis and/or therapy of "Sickness behaviour".

If **D5** and **D6** successfully treat "Sickness behaviour" in combination with respiratory symptoms and if it is known from **D7**, on the other hand, that "Sickness behaviour" can be successfully treated with Pelargonium extracts as an independent syndrome – the average skilled person readily deduces from this that the independent "Sickness Behaviour" can in all probability be treated with *P. sidoides* and/or *P. reniforme*: If the therapy of "Sickness behaviour" in combination with other symptoms is successful in accordance with **D5** and **D6**, it is **foreseeable**, based on the teaching of **D7**, that it will also be successful with "Sickness behaviour" *isolated from other illness symptoms*.

Consequently, Claim 1 lacks inventive level with respect to **D5/D6** in combination with **D7**.

5.2 Claim 1 lacks inventive level based on **D5/D6** in combination with **D8** (Pages 15 and 21, Fig. 6).

Based on **D5** and **D6**, the objective problem may be seen as finding an additional therapeutic application of Pelargonium extracts for treating "Sickness behaviour" *independently* and *isolated* from the treatment of respiratory (or other) symptoms, apart from the treatment of "Sickness behaviour" combined with respiratory symptoms (e.g. bronchitis).

To evaluate the effect of a therapy using an extract from Pelargonium sidoides (EPs 7630), **D8 (Heger and Bereznoy)** on Page 15, Fig. 1 and Page 21, Fig. 6, use an Item 1 that is autonomous and independent of all other test criteria:

"I have had enough of all this."

This evaluation criterion could to a great extent measure the existence and intensity of "Sickness behaviour". The changes in this Item 1 on day 6 of the treatment are shown in Fig. 6 of **D8**, demonstrating a remarkable *independence or autonomy* with respect to the development of other testing criteria, illustrated in Fig. 4 and Fig. 5, for instance (Pages 20 and 21).

Based on this information in **D8**, the use of Pelargonium extracts for the treatment of "Sickness behaviour", *independent* of and *isolated* from the treatment of respiratory symptoms, is pointed out directly to the average practitioner. Under these circumstances, **D5** and **D6** suggest that "Sickness behaviour" should not be treated only in combination with respiratory (or other) symptoms (bronchitis, tonsillopharyngitis), but also as an independent illness: The effect on this clinical picture could then be easily measured against the independent Item 1. If the therapy for "Sickness behaviour" combined with other symptoms is successful according to **D5** and **D6**, it is **foreseeable**, based on the teaching of **D8** and especially on the independent Item 1 applied there, that success is also likely with a therapy using Pelargonium extracts for "Sickness behaviour" *isolated* from other illnesses.

Consequently, Claim 1 lacks inventive level with respect to **D5/D6** combined with **D8.**

5.3 Claim 1 lacks inventive level based on **D5/D6** in combination with one or more affidavits **A1 to A6**.

Based on **D5** and **D6**, the problem to be solved once again comprises finding another therapeutic application of Pelargonium extracts for treating "Sickness behaviour" *independently* and *isolated* from the treatment of respiratory (or other) illness symptoms, apart from the treatment of "Sickness behaviour" in combination with respiratory symptoms (e.g. bronchitis).

All the submitted affidavits from South African traditional medicine **A1 to A6** disclose the effect of a successful therapy for fatigue conditions by the use of an extract from Pelargonium sidoides or reniforme: It may therefore be assumed that, within the framework of South African traditional medicine, the therapy for independent "Sickness behaviour" has been successfully applied from time immemorial.

Based on this information in **A1 to A6**, the use of Pelargonium extracts for the treatment of "Sickness behaviour", *independent* of the treatment of respiratory (or other) illnesses, is pointed out directly to the average skilled person. Based on the information in **A1 to A6**, **D5** and **D6** suggest that not only should "Sickness behaviour" in combination with respiratory symptoms (bronchitis, tonsillopharyngitis) be treated, but also "Sickness behaviour" as an independent illness. If the therapy with Pelargonium extracts of "Sickness behaviour" combined with other illnesses is successful according to **D5** and **D6**, it is **foreseeable**, based on the teaching of **A1 to A6**, that it should also be successful when applied to "Sickness behaviour" *independent of other illnesses*.

Consequently, Claim 1 lacks inventive level with respect to **D5/D6** in combination with **A1 to A6**.

6. Art. 83 EPC (Sufficient disclosure)

Jurisprudence of the Boards of Appeal with respect to Art. 83 puts on record that the description must make it possible to realise the subject matter of the invention over the entire scope and without undue experimentation (refer e.g. T 409/91, T 435/91 and T 19/90). In this case, this is not complied with on several counts.

6.1 Across the entire scope

On the one hand, the description of the specifications of the patent in-suit is not complete: It is not proven in this description that *all* the indications listed in the claim can be successfully treated by prophylaxis or therapy with Pelargonium extracts. It is not clear whether four distinct symptom groups or one umbrella-term of "Sickness Behaviour" are referred to:

- disease-related behavioural changes,
- chronic fatigue syndrome,
- post viral fatigue syndrome,
- stress-induced chronic illnesses.

It may be expected that *by no means all* imaginable "disease-related behavioural changes" or all imaginable "stress-induced chronic illnesses" can be successfully treated but, at best, some of the examples of disease-related behavioural changes described in Claim 4. The description provides, for instance, *no evidence* of successful therapy of behavioural changes associated with injuries, traumas, tumorous illnesses, reactions to inflammations or auto-immune diseases: Claims 1 and 4 therefore appear as pure speculation on the effective date of filing, intended to provide the proprietor of the patent with a scope of protection which his alleged invention does not deserve, based on the disclosed experiments.

The concept of "disease-related behavioural changes" furthermore contradicts the arguments in Sections 15 and 16 of the patent in-suit, where the teaching of the patent is separated from the treatment of "Sickness behaviour" in combination with other symptoms of illness: Does the teaching of the patent in-suit only comprise the treatment of autonomous "Sickness behaviour" or also of "Sickness behaviour" combined with or caused by other clinical pictures?

There is certainly no evidence of a successful prophylaxis using the teaching of the patent in-suit: Even if individual therapeutic successes are said to be proven (which is contested), this would by no means prove that the teaching of the patent in-suit is effective for *prophylaxis* of the illness conditions in question.

Claims 1 and 4 are therefore shown as largely speculative under the criterion of the *entire scope*, since the realisation across the *entire scope* does not appear to be assured - neither at the decisive point of the date of filing nor to the present moment.

6.2 *Undue experimentation*

The information on the tests of the pharmacological effectiveness of Pelargonium extracts for the unclear indications (Sections 20 to 22), as disclosed in the description of the contested patent, is still well within the pre-clinical phase and lacks virtually all details about successful treatment of "Sickness behaviour" in humans: required dose, required period of treatment, preferred and excluded forms of administering, undesirable side effects and contra-indications etc. etc.

It is unacceptable that a few highly primitive preliminary observations on a few mice in a light-dark box are "sold" as adequate and serious proof of clinical efficacy of Pelargonium extracts for the prophylaxis and therapy of "Sickness behaviour" in humans.

It is disputed that such observations on mice in a light-dark box are even *relevant* to the assessment of the efficacy of Pelargonium extracts for the treatment of "Sickness behaviour" (in mice!). And even less should such experiments be simply extrapolated to include the clinical treatment of "Sickness behaviour" in humans.

Furthermore, the statistical methods applied by the proprietor of the patent are not even correct: Contrary to the explanations in Section 22, line 44, Page 4 of the patent in-suit, no *dose-dependent* effect of the Pelargonium extracts was in fact proven.

All these errors and imperfections in the submitted data show that a successful prophylaxis and/or therapy of "Sickness behaviour" in humans (if it should ever be possible!) would require an enormous number of additional tests and scientific evidence *(undue burden of experimentation).* The teaching of the patent in-suit on the decisive date of filing thus appears largely speculative and consequently does not meet the requirements of Art. 83.

6.3 Lacking reproducibility

The teaching of the patent in-suit also violates Art. 83, since clinical efficacy of Pelargonium extracts for the prophylaxis or therapy of "Sickness behaviour" in humans was not proven, neither on the decisive date of filing or priority, nor to this day, rendering the teaching of the patent in-suit irreproducible:

D9 dated October 2006 discloses that, in the autumn of 2006, the indications for the UMCKALOABO Pelargonium plant extract of the proprietor of the patent were massively reduced by the German Pharmaceutical Institute in the course of an approval procedure for new indications, with the result that the only remaining indication is acute bronchitis.

D10, dated October 2008, expands on this information and reaches the succinct conclusion, among other, due to the questionable statistical methods used in the various clinical tests (so-called adaptive design of the investigation) that *no clinical use whatsoever* of Umckaloabo has been proven to this day.

Motion to take evidence, document edition:
Submitted by the proprietor of the patent;
alternatively:
Submitted by the Federal Institute for Drugs and Medical Devices,
Kurt-Georg-Kiesinger-Allee 3,
D-53176 B o n n :

All the files of the proprietor of the patent on the registration and approval procedure for new indications of the UMCKALOABO medicine;

Consequently, Claims 1 to 6 lack sufficient disclosure and are contrary to the requirements pursuant to Art. 83 EPC.

7. Summary

On the basis of the expounded arguments, it is hereby respectfully requested that the patent should be revoked in its entirety.

Yours sincerely

(signed F.D.)

Prof.Dr. F. Dolder

Annexures:
- Powers of attorney (3)
- Form 1010 with UBS AG Zurich bank receipt
- Form 2300
- Documents D 7 to D10
- Affidavits A1 to A6

All annexures via DHL courier service