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(71) Applicant *(for all designated States except US)*: FRESENIUS KABI AB [SE/SE]; S-112 87 Stockholm (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: HÖGSTRÖM, Peter [SE/SE]; Bolmensvägen 12, S-120 50 Årsta (SE).

(74) Agents: WILLQUIST, Bo et al.; Willquist & Partners Patentbyrå AB, S:t Larsgatan 23, S-582 24 Linköping (SE).

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(57) Abstract

The present invention relates to a reliable method of discarding containers storing an oxygen sensitive article which have defects in the oxygen barrier against the environment before sending them to the customers. The containers contain an oxygen sensitive article entirely enclosed in a sealing oxygen barrier forming, substantially airtight envelope together with an oxygen indicator. The method generally comprises the consecutive steps of sterilizing the containers, inspecting the oxygen indicators after said sterilization and discarding such containers in which the indicator has changed its characteristics in an identifiable manner.

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# Improvements related to containers

## Field of invention

The present invention relates to leak detection in containers for oxygen sensitive agents with an oxygen absorber which provides the manufacturer with effective means to discard defect containers immediately after their final sterilization.

## Background of the invention

The attempts of providing containers especially suitable for oxygen sensitive parenterally administerable fluids of flexible polymeric materials have been described in detail in the International Patent Application No. PCT/SE97/00590. Principally, these containers comprise a sealed inner, primary container made of a polymeric material which is filled with one or several agents in different chambers. The inner container is filled and sealed in a controlled atmosphere and thereafter enclosed in an outer airtight, flexible and transparent envelope together with an oxygen absorber capable of consuming both residual and penetrating oxygen and an oxygen indicator, whereupon the envelope is finally sealed and subjected to a final sterilization before it is ready to be delivered to the consumers. The outer envelope has a high resistance against penetrating oxygen, whereas the inner container is made of material admitting a certain oxygen transfer in order to allow dissolved residual oxygen of the stored parenteral agents to be consumed by the oxygen absorber. Suitable materials for the containers and oxygen absorbers are described in more detail in the mentioned PCT/SE97/00590. An especially suitable oxygen indicator which can be heat sterilized with maintained indicating capacity has been described in the Swedish Patent application No. 9602818-6.

The containers described in PCT/SE97/00590 have an unexpectedly advantageous storage capacity and admits notoriously problematic pharmaceutical agents such as lipid emulsions comprising a high amount of oxidation sensitive polyunsaturated fatty acids, to be stored with retained integrity and maintained physical properties for at least 12 months and preferably more at least 24 months,

while avoiding migration of undesired substances from the container material. The combination of container materials, the capacity of the deoxidizer and the carefully designed details of the container as well as its manufacturing and filling processes all contribute to the favorable storage results.

However, even if the containers according to PCT/SE97/00590 have a considerable degree of safety, there still exists a possibility that defect containers may reach the consumer, although they have been subjected to a careful visual integrity inspection based on standard oxygen indicating systems by controlling any change of indicator response. The reason is that oxygen leaking into the container through holes or other defects in the barrier of the outer envelope of such a container initially will be consumed by the oxygen absorber and will not have affected the indicator at an early inspection moment. Eventually, the oxygen absorber will be saturated with oxygen and cease to act as an oxygen scavenger and the indicator will be reached by a sufficient amount of oxygen to produce a detectable color change. For small defects in the outer envelope, this might occur a considerable time after their inspection at the manufacturing site when the container has arrived at the customer. Such defects typically arrives from inadvertent damages occurring during the manufacturing process, imperfections of the material of the envelope and in the transport and handling at hospitals.

It would therefore be highly desirable to be able to discard even such containers which have small defects, such as holes in the outer envelope, otherwise undetectable with visual or conventional product inspection, immediately after their final process step which preferably is the sterilization. Such an early removal of defect containers would lead to a higher product safety and a reduced waste of resources in all steps of the product handling and generally to a higher customer satisfaction.

An object of the present invention is to provide a selection method for discarding defect flexible containers storing oxygen sensitive pharmaceutical articles directly in connection to their production while being able to employ the same constituents of the container as normally intended (i.e. a substantially airtight envelope, oxygen indicator and optionally an oxygen absorber).

Another object of the present invention is to use the same oxygen indicator as intended to alert the user of an inappropriate oxygen exposure of the product during

long term storage to detect otherwise invisible defects in the oxygen barrier provided by the outer envelope of a container for storing an oxygen sensitive pharmaceutical article, already in connection to their manufacturing process.

## Description of the invention

The present invention is directed to a method of discarding such flexible containers storing an oxygen sensitive article which have defects in the oxygen barrier against the environment already in connection to the final manufacturing step. The containers are intended to comprise an oxygen sensitive article for long term storage and generally consist of an entirely sealed, oxygen barrier forming, substantially airtight, envelope which entirely encloses the article together with an oxygen indicator. In many applications it is preferred also to include an oxygen absorber or deoxidizer usually in the form of an oxygen scavenging composition enclosed in a sachet. The presence of an oxygen absorber is not mandatory to successfully perform the present invention, but many highly sensitive pharmaceutical liquids to be stored would in the absence of an oxygen absorber require laborious oxygen degassing process steps to be adequately protected. The article, the oxygen indicator and an optional oxygen absorber preferably are separate units, but it would be conceivable for the skilled to connect the indicator and/or the absorbent with the article in various manners.

The inventive method is principally characterized by the consecutive steps of sterilizing the containers, inspecting the oxygen indicators after the sterilization and discarding the containers in which the indicator has changed its characteristics in a predetermined identifiable manner.

In another aspect, the present invention is directed to the use of an oxygen indicator in the detection of defects in an oxygen barrier against the environment provided by a flexible transparent substantially airtight polymeric material in a container suitable for long term storage of an oxygen sensitive pharmaceutical article, entirely enclosed in a sealed outer oxygen barrier forming outer envelope together with an oxygen absorber. The indicator must thereby be capable of alerting the mentioned defects in connection with the final stage of the container manufacture.

It is a desire when obtaining an optimal product safety that the finally sealed containers storing the oxygen sensitive article is sterilized by heat or irradiation according to conventional methods as a final step of their manufacture before storage and/or delivery to the consumers. Preferably the sterilization is performed by means of high pressure steam, suitably at 121°C for about 15 minutes. The person skilled in packaging technology will be able to contemplate various different such heat sterilization methods whenever applicable due to variations in the agents to be stored and different container parameters. All conceivable variations in the heat sterilization process such as different temperatures, pressure and duration are intended to be covered by the present invention.

It is therefore obliged that the oxygen indicators utilized in the present invention are capable to withstand all such sterilization methods with maintained reliability of its detection capacity of oxygen.

According to the present invention, the inspection of the containers is performed after the sterilization process is finalized. If heat sterilizing the containers with steam, the inspection is performed after being brought out from the treatment station and cooled for a suitable time which optionally includes a period during which the container dries. The inspection is performed immediately after the sterilization which normally means from within a couple of minutes after terminating the sterilization, up to several days after the sterilization is finalized. It is an important advantage of the present invention that it admits a flexibility of the inspection time which provides the manufacturers of freedom to allocate resources due to variations in the production.

Furthermore, the inspection can be performed visually by readily trained persons or by automatic vision systems which scan the container for predetermined optic changes of the containers. Such systems may easily be conceived by the skilled person without undue development efforts and are not a part of the present invention.

It is also necessary that the present invention shall contribute to the detection of even minor defects in the oxygen barrier forming material in order to enable the removal of substantially all containers which potentially will contain damaged articles when arriving at the customer or after long term storage. For this reason defects generated by small holes or perforations of an average diameter size of about 20 μm in

the enveloping substantially airtight material are detectable according to the present invention.

The indicators employed in the present invention preferably change color in a visible and predetermined manner when subjected to a certain level of oxygen penetrating through the defective oxygen barrier of the container, in order to facilitate a manual inspection of the container through a transparent barrier forming material. However, it is of course conceivable and within the scope of the present invention to contemplate the change of other characteristics due to the penetrating oxygen than visual color which will enable an automatic inspection. It is also preferable that the sterilization method at least temporarily induces an increased reactivity with oxygen and most preferably the heat generated by heat sterilization, such as autoclavation induces an increase in the indicator reaction rate with oxygen. The reason is that the indicator shall be able to be sensitive enough for oxygen penetrating the container to undergo a change in color, also in the presence of an oxygen scavenging composition in the deoxidizer which competes for the oxygen molecules. A fast reaction with penetrating oxygen is also preferable to be able to inspect the containers immediately or a suitably short time after sterilization process is finished.

A further advantage of the present invention is that it readily enables the manufacturer to discard containers wherein the gas volume inadvertently have increased by a hole in the airtight material which may jeopardize that an effective sterilization is performed. For holes larger than about 50 μm, there is a considerable risk that a sufficient amount of air may enter the container that a significant increase in the gas volume inside the container is obtained. In such a case, there conventional inspection may lead to that defect containers are delivered to the customer. However, with the present invention, the indicator will respond already in connection with the sterilization, so the manufacturer can remove all such defect containers.

A suitable indicator comprises a composition which involves the oxidation of iron (II) to iron (III) with penetrating oxygen. It is preferable that the indicator comprises an agent affecting its reaction rate, suitably an organic acid and more suitably an organic acid having at least two carboxylic groups. Preferably, the organic acid has the general formula $HOOC-(CR_1R_2)_n-COOH$, wherein n=1-4, $R_1$ is hydrogen or hydroxyl radicals, and $R_2$ is hydrogen or carboxyl radicals. According to a preferred

embodiment, the organic acid is an alpha-hydroxy acid. Preferred iron(II) compounds of the indicator are a salt of iron selected from a group of salts consisting of iron(II)sulfates, iron(II)acetate, iron(II)nitrate, iron(II)chloride and iron(II)trifluoroacetate. Moreover, it is preferred that the indicator comprises an agent containing pyrogallol entities, suitably tannin of natural, synthetic or semi-synthetic origin.

According to a specifically preferred embodiment the indicator comprises iron(II)sulphate or iron(II)sulphate heptahydrate; tannin; and citric acid or citric acid 1-hydrate; optionally in combination with a suitable carrier agent. In such an indicator the relative amount of citric acid can be employed to affect its reaction rate. Generally a reduced amount of citric acid leads to a higher reaction rate, whereas increases in iron and tannin concentrations reduces the reaction rate. As indicators of this type can be sensitive to light, it may be suitable to keep the container product in darkness or in shelter from direct sunlight if the time period from sterilization to inspection is prolonged. These indicators are disclosed in more detailed in the International Patent Application PCT/SE97/01303 which hereby is incorporated as a reference.

The stored articles principally may be any type of oxygen sensitive article, such as pharmaceuticals, medical devices, food products, electronic articles. However, according to the present invention the articles preferably are pharmaceutical agents, intended for parenteral administration, in particular intravenous administration, stored in a primary inner container of polymeric material. Such agents can both in the form of fluids and in solid forms, e.g. a lyophilized composition. According to a preferred embodiment the stored article is an inner container made of polymeric material filled with at least one oxygen sensitive parenteral nutrient, such as lipid emulsions, amino acid solution and carbohydrate solutions. The inner container is made of flexible, transparent polymeric film material which is not completely airtight and admits oxygen transfer. This type of container is described in more detail in the International Patent Application PCT/SE97/00590 wherein especially advantageous containers are disclosed. Preferably, such material comprises polyolefins and particularly polypropylene homopolymers and copolymers. A suitable multilayered film material is disclosed in the European Patent 0 228 819 which besides a polypropylene-

polyethylene copolymer comprises a thermoplastic elastomer to provide the film with a desired flexibility.

The outer envelope, completely sealing the stored article from the environment preferably is made of a substantially airtight material admitting less oxygen transfer than about 0.5 ml per square meter, day and atmosphere, preferably less than 2 ml per square meter after heat sterilization, measured per day and at 25°C at 60% relative humidity.

To be suitable in the context of the present invention, the envelope materials must be sufficiently transparent so as to enable a simple reading of changed indicator. Such materials are composed of multilayered structures of several layers with complementary features. Preferably, such materials comprise a metal oxide layer, such as silicon or aluminum oxides and a layer with additional oxygen barrier forming capacity, such as (poly)ethylene vinyl alcohol (EVOH). Especially preferred materials for the envelope are further described in the mentioned PCT/SE97/00590.

The deoxidizer preferably comprises a solid oxygen scavenging composition containing iron and is of the type which increases its oxygen consumption when the relative humidity increases which rapidly occurs during a heat sterilization by means of high pressure steam. Suitable oxygen absorbers are disclosed in PCT/SE95/00684, DE 42 33 817 and in PCT/SE97/00590. Examples of commercially available oxygen absorbers which have been found suitable with the inventive method are Ageless®FX 50 to 400 from Mitsubishi.

The inventive method of discarding defect containers preferably is practiced with assembled containers each comprising a first inner container of polymeric material according to above, filled with one or several oxygen sensitive agents, an oxygen absorber and an oxygen indicator as separate units which are enclosed in an outer airtight envelope and finally sealed in a protected atmosphere which is depleted of environmental oxygen with conventional means. After the final sealing of the enclosing envelope the space between the envelope and the inner container will only contain low amounts of remaining oxygen. During the autoclavation with high pressure steam, moisture will penetrate the envelope and enter the space between the envelope and the inner container. At the same time, moisture will be forced out from

the inner container to the space with the oxygen absorber and the oxygen indicator. In a container with maintained integrity, the oxygen consumption of the oxygen absorber will be triggered by the moisture and the heat and start to scavenge remaining dissolved oxygen in the stored fluids of the inner container as well as the oxygen remaining in the space. For the case when the envelope contains defects in the oxygen barrier such as a hole or a crack, oxygen from the ambient air will enter the container during the steam sterilization. For big holes high amounts of oxygen will rush into the container and saturate the oxygen absorber and rapidly lead to a detectable change of the indicator. If the defects are smaller, there is a risk that the oxygen absorber for a considerable time will be able to consume the incoming oxygen to such an extent that the indicator not will change until a time after the product inspection. According to the inventive method, the indicator will be able increase its reactivity during the heat sterilization so a detectable change of the indicator occurs.

The following exemplifying part of the description is intended to illustrate how to perform a leak detection according to the present invention.

**Detailed description of the invention**

Example 1

*Manufacture of oxygen indicators*

Oxygen indicators to be used with the inventive method of discarding defect containers were made according to the following:

| Components | Composition (g/L) |
|---|---|
| tannic acid | 13 |
| iron(II)sulphate heptahydrate | 20 |
| citric acid monohydrate | 35 |
| water | up to 1 liter |

Water for injection (WFI) of 85 °C was filled in a 15 liter vessel. The water was stirred and nitrogen bubbled through a lance during approximately 2 hours. The citric acid-1-hydrate was weighed and added to the water. Stirring and nitrogen bubbling continued during 10 minutes. The tannic acid and the iron(II)sulphate-7-hydrate was then added in the same way. The indicator solution was filled, through a 0,22 µm Millipore filter, on glass flasks of 5 L. Filling of the indicator solution is performed in sachets made of Excel® film (38 mm). The film was converted from reels of 300-450 widths to a width of 38 mm. The reel of Excel film was placed on the carrier of a filling equipment. The Excel film was printed using a white hot-stamp foil. The film was double-folded and welded along the side and transversally. The glass flask with indicator solution was placed in a nitrogen-protected vessel above the filling station. The nitrogen overpressure was controlled during the filling process. Indicator solution flowed through a tube into the welded film and the transversal welding station welded a strip of indicators separated by welds of 6 mm. The volume of one indicator is approximately 1 ml. Strips of 50 indicators were packaged in airtight overwrap bags of the material disclosed in the Swedish Patent Application 9601348-7 together with Z-100 oxygen absorbers.

Example 2

*Manufacture of containers*

As a primary chamber-container a 2500 ml three chamber container having the dimension 420 x 310 mm, made of the material Excel® supplied from McGaw Inc. is used. The three chambers are divided from each other by welded heat seals which are rupturable by the user. The chambers were filled with liquid oxygen sensitive parenteral nutrients and sealed by permanently welded heat seals. The nutrient liquids are degassed with nitrogen gas before filling and the filling is performed in a controlled atmosphere zone with less than about 1% residual atmospheric oxygen. The primary container is then wrapped in outer airtight envelope made of the material R 1706 from Soplaril SA (multilayered film comprising the layers of polyethylene terephtalate-metal oxide/glue/polypropylene/(poly)ethylene

vinylalcohol/polypropylene) together with an oxygen absorber (Ageless FX200 PA from Mitsubishi) and an oxygen indicator made according to Example 1 (Oxalert® developed by Pharmacia & Upjohn AB). The oxygen indicator and the oxygen absorber are placed in the vicinity of the saddle-formed port system of the primary, inner container before permanently sealing the outer envelope.

Example 3

In a number of containers made according to Example 2 holes of a size between 20 and 30 μm were made in the airtight envelope close to the saddle-formed port of the inner container with a laser-drilling technique. Thereafter, containers with and without holes were subjected to heat sterilization with high pressure steam at 121°C for 20 minutes. Within one hour after the end of the heat sterilization, the containers were inspected for change of indicator color. The darkness of the indicator were visually measured at the inspection according to a scale from 1 to 5, where 1 was graded as fair (pale yellow), 2 as pale green, 3 as green, 4 as dark green and 5 as black.

Two different oxygen indicators were used, a standard type with components according to Example 1 and a modified type with a faster color change from a lower amount of included citric acid

| Oxygen indicator | Hole size (μm) | Indicator inspection |
|---|---|---|
| 1. standard | 0 | 1 to 1.5 |
| 2. standard | 30 | 2.5 to 3 |
| 3. modified | 20 | 3 to 5 |

1. 30 different containers were tested, of these 28 indicators graded with 1 in the color change scale and two indicators were graded with 1.5.

2. Two different containers were tested with indicator changed to 2.5 and 3, respectively.

3. Five different containers were tested with modified indicators with color change results graded 4, 4.5, 5, 3, 3 and 5.

These tests demonstrate that the indicators can perform suitably in leak detection tests after the autoclavation and enable that the producer can discard defect containers in connection with their manufacturing.

## Claims

1. Method of discarding such flexible containers storing an oxygen sensitive article which have defects in the oxygen barrier against the environment, wherein said containers comprise said oxygen sensitive article entirely enclosed in a sealing oxygen barrier forming, substantially airtight envelope together with an oxygen indicator characterized by the consecutive steps of:

(a) sterilizing said containers;

(b) inspecting the oxygen indicators after said sterilization; and

(c) discarding the containers in which the indicator has changed its characteristics in an identifiable and predetermined manner.

2. Method according to claim 1 characterized in that the oxygen sensitive article is an inner container made of polymeric material filled with at least one oxygen sensitive agent.

3. Method according to claims 1 or 2 characterized in that the sterilization induces an increased reactivity of the indicator with oxygen.

4. Method according to claim 3 characterized by sterilizing with high pressure steam.

5. Method according to claim 4 characterized by sterilizing with high pressure steam at 121°C for at least 15 minutes.

6. Method according to any of claims 1 to 5 characterized by admitting an inspection of the oxygen indicators from within minutes up to several days after the sterilization.

7. Method according to claim 6 characterized in that any defects in the oxygen barrier induces a color change in the indicator.

8. Method according to claims 6 or 7 characterized in that heat generated by the sterilization with high pressure steam induces an increased indicator reactivity with oxygen.

9. Method according to claim 7 or 8 characterized in that the color changing indicator reaction involves the oxidation iron (II) to iron (III).

10. Method according to any of claims 7 to 9 characterized in that the indicator comprises an agent affecting its reaction rate.

11. Method according to claim 10 characterized in that said agent is an organic acid.

12. Method according to claim 11 characterized in that the organic acid has at least two carboxylic groups.

13. Method according to claim 12 characterized in that the organic acid has the general formula HOOC-$(CR_1R_2)_n$-COOH, wherein n=1-4, $R_1$ is hydrogen or hydroxyl radicals, and $R_2$ is hydrogen or carboxyl radicals.

14. Method according to claim 13 characterized in that the organic acid is an alpha-hydroxy acid.

15. Method according to any of claims 9 to 14 characterized in that the indicator comprises a salt of iron selected from a group of salts consisting of iron(II)sulfates, iron(II)acetate, iron(II)nitrate, iron(II)chloride and iron(II)trifluoroacetate.

16. Method according to any of claims 8 to 15 characterized in that the indicator further comprises an agent containing pyrogallol entities.

17. Method according to claim 16 characterized in that the agent containing pyrogallol entities is tannin of natural, synthetic or semi-synthetic origin

18. Method according to claim 17 characterized in that the indicator comprises
(A) iron(II)sulphate or iron(II)sulphate heptahydrate;
(B) tannin; and
(C) citric acid or citric acid 1-hydrate; optionally in combination with a suitable carrier agent.

19. Method according to any previous claim characterized in that the container comprises an oxygen absorber.

20. Method according to claim 19 characterized in that the oxygen absorber contains iron.

21. Method according to claim 20 characterized in that the oxygen absorber increases its oxygen consumption when the relative humidity increases.

22. Method according to claim 21 characterized in that the oxygen absorber increases its oxygen consumption during heat sterilization.

23. A method according to claims 19 to 22 characterized in that the oxygen absorber is in the form of a sachet positioned in the space between the envelop and the oxygen sensitive article.

24. Method according to any previous claim capable of detecting leakages of oxygen into the container generated by defects constituted by a hole in the envelope having a size of less than about 50 μm.

25. Method according to any of claims 2 to 24 characterized in that the oxygen sensitive agent is parenterally administerable.

26. Method according to claim 25 characterized in that the oxygen sensitive agent is a parenterally administerable nutrient selected among lipid emulsions, amino acid solutions and carbohydrate solutions.

27. The use of an oxygen indicator to detect defects in the oxygen barrier against the environment as provided by a flexible transparent substantially airtight polymeric material in a container suitable for long term storage of an oxygen sensitive pharmaceutical article which is entirely enclosed in the sealed outer oxygen barrier forming outer envelope together with an oxygen absorber and said indicator characterized in that the indicator is capable of directly alerting the defects in connection with the final stage of the container manufacture.

28. The use according to claim 27 characterized in that the final stage of the container manufacture involves sterilization of the finally sealed container.

29. The use according to claim 28 characterized in that the sterilization involves high pressure steam.

30. The use according to claim 29 characterized in that the sterilization with high pressure steam heats the container to 121°C for at least 15 minutes.

31. The use according to any of claims 27 to 30 characterized in that the indicator is capable of detecting defects at least constituted by a hole in the envelope having a size about 20 μm.

32. The use according to any of claims 28 to 31 characterized in that the indicator reactivity with oxygen increases during the sterilization.

33. The use according to any of claims 29 to 32 characterized in that the indicator visibly changes color during the sterilization if the container has a defect in its oxygen barrier.

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00026

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: B65D 79/02, B65D 81/20, G01N 31/22, A61J 1/18
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: B65D, A61J, G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, MEDLINE, PACKAGING SCI AND TECH, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 9324820 A1 (VALTION TEKNILLINEN TUTKIMUSKESKUS), 9 December 1993 (09.12.93) -- | 1-33 |
| A | GB 2208287 A (ROUSSEL-UCLAF), 22 March 1989 (22.03.89) -- | 1-33 |
| P,X | WO 9803866 A1 (PHARMACIA & UPJOHN AB), 29 January 1998 (29.01.98) -- -------- | 1-33 |

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

02/03/99

International application No.
PCT/SE 99/00026

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9324820 A1 | 09/12/93 | AT 166152 T | 15/05/98 |
| | | AU 4073293 A | 30/12/93 |
| | | DE 69318564 D,T | 26/11/98 |
| | | EP 0666977 A,B | 16/08/95 |
| | | SE 0666977 T3 | |
| | | ES 2116448 T | 16/07/98 |
| | | FI 94802 B,C | 14/07/95 |
| | | FI 922570 A | 04/12/93 |
| GB 2208287 A | 22/03/89 | AT 25488 A | 15/05/91 |
| | | AT 393661 B | 25/11/91 |
| | | AU 600079 B | 02/08/90 |
| | | AU 1092288 A | 23/06/88 |
| | | BE 1004986 A | 16/03/93 |
| | | CH 674972 A | 15/08/90 |
| | | DE 3803772 A,C | 09/02/89 |
| | | DK 25888 A | 31/01/89 |
| | | DK 169380 B | 17/10/94 |
| | | FI 880236 A | 31/01/89 |
| | | FR 2618762 A,B | 03/02/89 |
| | | JP 1037375 A | 08/02/89 |
| | | LU 87111 A | 03/05/88 |
| | | NL 8800279 A | 02/05/88 |
| | | PT 86868 B | 30/09/93 |
| | | SE 8800204 A | 31/01/89 |
| WO 9803866 A1 | 29/01/98 | AU 3714697 A | 10/02/98 |
| | | SE 9602818 D | 00/00/00 |