The invention relates to a cell sampling kit comprising a cell sampling device (7) and a container (100), wherein the cell sampling device (7) and the container (100) each comprise a threaded portion (101, 701) configured for attachment of the container (100) to the cell sampling device (7). The invention also relates to methods of cell sampling comprising the kit. The invention is particularly, but not exclusively, related to cell sampling kits in the field of biological or medical experimental, analytical or diagnostic assays and disease screening and monitoring.

Published:
— with international search report

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
CELL SAMPLING KIT

The invention relates to a cell sampling kit comprising a cell sampling device and a container and to methods of cell sampling comprising the kit.

The invention is particularly, but not exclusively, related to cell sampling kits in the field of biological or medical experimental, analytical or diagnostic assays and disease screening and monitoring.

According to one aspect of the invention, there is provided a container having first engagement means configured to be attached to a second container.

In one embodiment, the container additionally comprises second engagement means configured to attach a closure device to the container.

It will be appreciated that the second container may comprise any suitable container having corresponding features to enable the container of the invention to be attached to the second container.

In one embodiment, the first engagement means configured to be attached to a second container comprise a first threaded portion present on an inner surface of the container (e.g. an internal thread).

It will be appreciated that the design of the container of the invention should enable the container of the invention to be screwed to the second container. Thus, in one embodiment the cylindrical neck of the container is wider than the body of the container. This embodiment has the advantage that the body of the container may remain of a standard size for any given container and only the size of the cylindrical neck is widened to allow the cylindrical neck of the container of the invention to engage with a threaded portion on the cylindrical neck of a second container.
In one embodiment, the first engagement means configured to be attached to a second container comprise a compression or bayonet-type fitting which engages with corresponding features on the second container.

In one embodiment, the second container is a cell sampling device.

According to a second aspect of the invention, there is provided a kit comprising a cell sampling device and a container having first engagement means configured to be attached to the cell sampling device.

According to a third aspect of the invention, there is provided a kit comprising a cell sampling device and a container, wherein the cell sampling device and the container each comprise a complimentary threaded portion configured for attachment of the container to the cell sampling device.

This embodiment provides the advantage that the container may easily be attached to the cell sampling device and removed after use. Attachment may be effected simply by screwing the container of the invention onto the cell sampling device. Removal may likewise be effected by unscrewing the container from the cell sampling device.

It will be appreciated that references to "container" and "second container" include references to any container suitable for holding a substance (e.g. a solid or a liquid). In particular, the container may generally be suitable for conducting a reaction, assay, screen or other chemical, biochemical or medical experimental or analytical procedure. For example, the container may generally have an elongate body and/or may be transparent to enable analysis to be performed easily and rapidly.
The container typically includes a bottle, tube, flask or vial. The container may generally have a square, rectangular or cylindrical body for containing a substance. The container may also generally have a cylindrical neck for attachment of a closure device to the container. The container may also generally have a mouth or an opening into which a substance may be inserted into the container. The container may also generally have a flat, rounded or tapered base.

The container provides a modification to existing containers commonly available on the market, such as for example, Sterilin™ tubes (Barloworld Scientific Ltd., Beacon Road, Stone, Staffordshire, United Kingdom. ST15 OSA), Eppendorf™ tubes (Eppendorf AG, Barkhausenweg 1, 22339 Hamburg, Germany), Falcon™ tubes (BD, 1 Becton Drive, Franklin Lakes, NJ USA 07417), Duran™ bottles (Schott UK Ltd., Drummond Road, Astonfields Industrial Estate, Stafford, ST16 3EL, UK), Nunc™ containers (Nunc A/S, Kamstrupvej 90, Postbox 280, DK-4000, Roskilde), Corning™ bottles and containers (Corning Incorporated, Life Sciences, 45 Nagog Park, Acton, MA 01720) and the like.

The container may typically be fabricated from glass, Pyrex™ or a plastics material (e.g. polypropylene, polyethylene or polystyrene). In one embodiment, the container is constructed from a plastics material (e.g. polypropylene, polyethylene or polystyrene). This embodiment has the advantage of providing strength to the container, while being more likely to retain the contents when subjected to impacting stress (e.g. if the container is dropped or knocked during transport).

In one embodiment, the threaded portion is present on an inner surface of the container. During attachment, the threaded portion present on an inner surface of the container engages with the threaded portion on the cell
sampling device commonly found on the exterior surfaces of containers for usual engagement with a threaded cap or lid. The contents of the cell sampling device may therefore simply be transferred to the container without loss or leakage.

In a further embodiment, the threaded portion is present on an inner surface of the cylindrical neck of the container. Thus, in an embodiment wherein the container has a cylindrical body, the threaded portion may at least partially surround the circumference of an inner surface of the cylindrical neck of the container. In a further embodiment, the threaded portion entirely surrounds the circumference of an inner surface of the cylindrical neck of the container.

The embodiment wherein the threaded portion partially surrounds the inner surface circumference of the cylindrical neck provides the advantage that when transferring a sample into the container or when removing a sample from the container, the contents are channelled into and out of the container more effectively than when the threaded portion entirely surrounds the inner surface circumference of the cylindrical neck.

In one embodiment the container and/or cell sampling device comprise engagement means configured to attach a closure device thereto. In the embodiment wherein the closure device is a cap or lid having a threaded portion on an inner surface, the engagement means may typically comprise a second threaded portion on an outer surface of the container (i.e. the container will have a first threaded portion present on an inner surface (e.g. an internal thread for attachment to the cell sampling device) and a threaded portion present on an outer surface (e.g. an external thread for attachment to the container)). In this embodiment, the closure device may engage with a single threaded portion present on the outer surface of
the cell sampling device (e.g. an external thread for attachment to both the container and the closure device).

In one embodiment, the kit additionally comprises a closure device. In one embodiment, the closure device is a cap or lid having a threaded portion on an inner surface. In an alternative embodiment, the closure device is a snap-fit cap, lid, stopper or bung.

In one embodiment, the closure device is a snap-fit cap, lid, stopper or bung and the engagement means present on the container and/or cell sampling device comprise one or more protrusions configured to engage with the lid, stopper or bung in a snap-fit arrangement.

It will be appreciated that a threaded portion may be present on the inner and/or outer surfaces of the container and the inner and/or outer surfaces of the cell sampling device.

For example, in a first embodiment, a first threaded portion is present on the inner surface of the container (e.g. an internal thread) and a second threaded portion is present on the outer surface of the cell sampling device (e.g. an external thread). This first embodiment provides an arrangement wherein the container and cell sampling device may be attached to each other via the first and second threaded portions. In the first embodiment, a closure device for the container may be a stopper or bung or otherwise a cap or lid having a threaded portion on an outer surface (e.g. an external thread) for sealing the container having the internal thread. In the first embodiment, a closure device for the cell sampling device may be a cap or lid having a threaded portion on an inner surface (e.g. an internal thread) for sealing the cell sampling device having the external thread.
In a second embodiment, a first threaded portion is present on the inner surface of the container (e.g. an internal thread), a second threaded portion is present on the outer surface of the container (e.g. an external thread) and a third threaded portion is present on the outer surface of the cell sampling device (e.g. an external thread). For example, the container comprises both an internal and external threaded portion. This second embodiment provides an arrangement wherein the container and cell sampling device may be attached to each other via the first and third threaded portions. In the second embodiment, a closure device for the container and cell sampling device may be a cap or lid having a threaded portion on an inner surface (e.g. an internal thread) for sealing both the cell sampling device and container each of which have an external thread.

In a third embodiment, a first threaded portion is present on the outer surface of the container (e.g. an external thread) and a second threaded portion is present on the inner surface of the cell sampling device (e.g. an internal thread). This third embodiment provides an arrangement wherein the container and cell sampling device may be attached to each other via the first and second threaded portions. In the third embodiment, a closure device for the cell sampling device may be a stopper or bung or otherwise a cap or lid having a threaded portion on an outer surface (e.g. an external thread) for sealing the cell sampling device having the internal thread. In the third embodiment, a closure device for the container may be a cap or lid having a threaded portion on an inner surface (e.g. an internal thread) for sealing the container having the external thread.

For example, it will be appreciated that in the embodiments wherein the container and cell sampling device each comprise a single threaded portion, the single threaded portion may serve to engage both with the container or cell sampling device and a closure device.
In one embodiment, the container comprises a volume of liquid.

It will be appreciated that in the embodiment wherein the threaded portion partially surrounds the circumference of the cylindrical neck, a closure device with additional sealing means may be required to create an efficient seal without loss of material during transfer and storage.

In the embodiment wherein the threaded portion is present on the inner surface of the container, the threaded portion may have a reservoir attached thereto. In a further embodiment, the reservoir contains a liquid. In a yet further embodiment, the reservoir is a blister packet.

This embodiment provides the advantage that the action of screwing the container of the invention to the cell sampling device breaks the reservoir (e.g. blister packet) and therefore releases the contents into the cell sampling device. This embodiment, therefore enhances the process of suspending cells (or other collected solid substance or particulate material) present within the cell sampling device. For example, the cells will be suspended in the liquid and the entire contents can be transferred to the container of the invention without loss of material.

In a further embodiment, the liquid is a buffer such as an assay buffer, cell suspending buffer or cell lysis buffer, or a cell preserving solution. In a yet further embodiment, the liquid is a buffer, such as a cell suspending buffer.

In one embodiment, the buffer is a cell-lysis buffer which has the advantage of providing a key step prior to DNA extraction. In a further embodiment, the cell-lysis buffer may additionally comprise a proteolytic enzyme. This embodiment provides the advantage of being useful in nucleic acid purification. In an additional embodiment, the cell-lysis
buffer may additionally comprise immunomagnetic beads. This embodiment provides the advantage of allowing the efficient capture of nucleic acids. In an alternative embodiment, the buffer is a cell-preserving solution which has the advantage of allowing enhanced cytological, biochemical and immunohistochemical analyses on the resultant cell sample. In one embodiment, the cell-preserving solution is supplemented with one or more cell culture components (e.g. nutrients and antibiotics).

In one embodiment, the container comprises graduated marks or grooves. This embodiment provides the advantage of indicating the volume of the contents of the container to the user.

In one embodiment, the cell sampling device comprises a flexible membrane having a cell sampling surface.

In a further embodiment, the cell sampling device comprises an insertion member having a distal, insertion end, a proximal end and a closable interior cavity, a flexible membrane having an outer, cell sampling surface and an inner surface, wherein the membrane is sealingly attached to the distal, insertion end of the insertion member and held within the interior cavity, such that, in use, pressurisation of the interior cavity to at least a first elevated pressure causes the membrane to emit from the distal end of the insertion member to make contact with the cells and pressurisation of the interior cavity to a second reduced pressure causes the membrane to invert and return to the interior cavity of the insertion member.

In a further embodiment, the cell sampling device is a colorectal cell sampling device. In a yet further embodiment, the cell sampling device is a colorectal cell sampling device as defined in WO 2006/003447.
In one embodiment, the flexible membrane is expandable and is constructed from an elastic material. In a further embodiment, the flexible membrane is constructed from a nitrile, latex or rubber based substance.

In one embodiment, the closable interior cavity of the insertion member is closed.

In one embodiment, the cell sampling device further comprises means for pressurisation of the interior cavity, wherein the means are attached to the proximal end of the insertion member. In a further embodiment, the means for pressurisation of the interior cavity are attached to the cell sampling device via a valve (e.g. a self-sealing valve) present at the proximal end of the insertion member.

It will be appreciated that the means for pressurisation of the interior cavity may comprise any means suitable for applying a fluid (e.g. liquid or gas) to the flexible membrane. In one embodiment, the means for pressurisation of the interior cavity comprise a source of compressed air, a syringe or a pump (e.g. bulb).

In one embodiment, the means for pressurisation of the interior cavity comprise a source of compressed air which comprises a mechanical device capable of delivering a pre-defined quantity of a first elevated pressure and a second reduced pressure to the cell sampling device. This embodiment has the advantage of accurately regulating the pressure inside the insertion member and the mechanical device has the advantage of being re-used with an indefinite number of disposable colorectal cell sampling devices.
In a further embodiment, the means for pressurisation of the interior cavity comprise a syringe. The use of a syringe, allows for both simple operation, and for a fixed volume of air to be pumped into the flexible membrane (preferably at least a ten fold increase in the volume of air present in the flexible membrane). For example, in an embodiment of the invention where a 100ml syringe is attached at the proximal end of the insertion member, the plunger of said syringe could initially be set at the 70-90ml mark. A pre-defined quantity of a first elevated pressure could therefore be applied by pushing the plunger to its maximum extent (e.g. to the 0ml mark) which would fill the flexible membrane with an air volume of 70-90ml. A pre-defined quantity of a second reduced pressure could then subsequently be applied by pulling the plunger of the syringe back to its maximum extent (e.g. to the 100ml mark) which would draw the membrane into the interior cavity of the insertion member. In a preferred embodiment of the invention, the syringe would be supplied with one or more retention features (e.g. snap locations) to mark the plunger positions of the syringe at each stage during use (e.g. one position prior to insertion, one during insertion and one after withdrawal). The advantage of the means for pressurisation of the interior cavity being a syringe is that the colorectal cell sampling device may be adapted to fit onto commonly available and disposable laboratory and hospital equipment.

In one embodiment, the surface area of the outer, cell sampling surface of said flexible membrane is reproducibly controllable. This allows for a fixed surface area to be brought into contact with the mucosal surface being sampled, thereby providing a quantifiable collection of exfoliated cells which is correlated with the amount present on the surface of the colorectal mucosa. In a further embodiment, the surface area is controlled by the means for pressurisation of the interior cavity. This allows for a
fixed surface area to be brought into contact with the mucosal surface being sampled.

In one embodiment, the insertion member is adapted to engage with a rectal access tube. This embodiment has the advantage of allowing a rectal access tube and an obturator, such as an olive shaped obturator (a conjoined rectal access tube and obturator is commonly known as a proctoscope) to be inserted first to open the rectal cavity followed by withdrawal of the obturator prior to insertion of the sampling device of the invention. The sampling device could then remain held in position with the rectal access tube for whatever period of time was required to obtain a sample. The obturator would then be replaced once the sampling device is removed and the obturator and rectal access tube would be withdrawn together.

In one embodiment, the insertion member is configured to allow self-insertion. In such an embodiment, the insertion member is inserted together with a rectal access tube and therefore eliminates the need for an obturator (e.g. the insertion member has a rounded distal, insertion end).

This embodiment provides the advantage that the sampling device may be self-administered, for example, patients will be easily able to sample exfoliated cells from their rectal mucosa. In this embodiment, it is envisaged that the insertion member and rectal access tube are inserted and removed together and only separated upon removal.

In one embodiment, the flexible membrane forms a receptacle when held within the interior cavity of said insertion member, such that fluid from the container or other vessel may be added. This embodiment of the invention would allow for reagents to be added to the sampling device after a sample has been obtained without the need to transfer the sample
to a separate receptacle, thereby losing some of the material from the sample.

In one embodiment, the interior cavity of the insertion member is provided with adhesion means. This embodiment of the invention has the effect of drawing the flexible membrane towards the walls of the interior cavity of the insertion member once a sample has been obtained and application of the second reduced pressure has drawn the flexible membrane into the interior cavity of the insertion member. This feature has the advantage of providing a stable receptacle when filled with liquid.

In the embodiment wherein the cell sampling device comprises means for pressurisation of the interior cavity, said means are preferably detachable from the insertion member. This has the advantage of converting the sampling device into a compact assay vial which may be conveniently transported and stored with many other compact assay vials for subsequent screening reactions.

In one embodiment, the kit additionally comprises a rectal access tube and optionally an obturator.

The use of a rectal access tube provides both for more comfortable insertion of the sampling device, and prevents contact between the sampling device and any surface other than the mucosal surface to be sampled. The use of an obturator in addition to the rectal access tube, may ease the discomfort of inserting the rectal access tube.

In one embodiment, the kit may additionally comprise a lubricant, such as a lubricating jelly (e.g. K-Y jelly). This has the advantage of providing greater comfort during insertion of the obturator or cell sampling device of the invention.
In one embodiment, the obturator is disengaged from the rectal access tube after insertion of the conjoined obturator and rectal access tube into the rectal cavity.

It will be further appreciated by the person skilled in the art that any of the devices or kits previously described are suitable for sampling exfoliated epithelial tissue (e.g. colonocytes) from the surface of human colorectal mucosa.

In one embodiment, the threaded portion is present on an outer surface of the distal, insertion end of the cell sampling device.

According to a fourth aspect of the invention, there is provided a method of transferring the contents of a cell sampling device as defined herein to a container as defined herein, comprising the steps of:

(a) attachment of the container as defined herein containing a pre-measured amount of an appropriate buffer or liquid medium to the cell sampling device as defined herein by cooperation of their respective threaded portions;

(b) tilting the container and the cell sampling device to allow the contents of the cell sampling device to be transferred to the container; and

(c) removal of the container from the cell sampling device.

According to a fifth aspect of the invention, there is provided a method of transferring exfoliated cells from a colorectal mucosal surface of a human subject to a container, comprising the steps of:

(a) sampling the exfoliated cells in accordance with the procedures described in WO 2006/003447 Al;
(b) attachment of the container as defined herein containing a pre-measured amount of an appropriate buffer or liquid medium to the threaded portion of the cell sampling device as defined herein;
(c) agitation of the container and the cell sampling device to allow suspension of the exfoliated cells in the appropriate buffer or liquid medium;
(d) tilting the container and the cell sampling device to allow the suspended exfoliated cells to be transferred to the container;
(e) removal of the container from the cell sampling device; and
(f) optionally closing the container with a closure device.

In one embodiment, the sampling step (a) may typically comprise the following steps:
(i) inserting a rectal access tube and an obturator into the rectal cavity via the anal canal;
(ii) withdrawing the obturator from the rectal access tube;
(iii) inserting a colorectal cell sampling device as defined herein into the rectal cavity via the rectal access tube, without the flexible membrane of the sampling device making contact with any other body surface;
(iv) pressurising the interior cavity to at least a first elevated pressure so that the flexible membrane emits from the distal end of the sampling device;
(v) contacting the colorectal mucosal surface with the outer, cell sampling surface of said membrane;
(vi) obtaining a sample of exfoliated cells from the colorectal mucosal surface;
(vii) applying a second reduced pressure to the interior cavity so that the flexible membrane inverts and the sample present on the cell sampling surface of said membrane returns to the interior cavity of the cell sampling device;
(viii) withdrawing the cell sampling device from the rectal cavity via the rectal access tube, without the flexible membrane of the sampling device contacting any body surface;

(ix) replacing the obturator via the rectal access tube; and

(x) withdrawing the rectal access tube and obturator from the rectum via the anal canal.

The invention will now be described, by way of example only, with reference to the accompanying drawings in which

**Figure 1** shows a plan view of a container according to one embodiment of the invention; and

**Figure 2** schematically shows a method of transferring exfoliated cells from a colorectal mucosal surface of a human subject to a container according to the embodiment shown in **Figure 1**.

**Figure 3** schematically shows an alternative method of transferring exfoliated cells from a colorectal mucosal surface of a human subject to a container according to the embodiment shown in **Figure 1**.

Referring first to **Figure 1**, a container, shown generally as 100, has a generally cylindrical and hollow body 110, a rounded base 111 and a cylindrical neck 112 having a wider diameter than the body 110. The container 100 also comprises a first threaded portion 101 configured to be attached to a cell sampling device. In the embodiment shown in **Figure 1**, the first threaded portion 101 is present around the circumference of the inner surface of the cylindrical neck 112 of the container 100. The container 100 also comprises a second threaded portion 102 for attachment of a closure device to the container 100. In the embodiment
shown in Figure 1, the second threaded portion 102 is present around the circumference of the outer surface of the cylindrical neck 112 of the container 100. The closure device 105 will typically have a threaded portion 106 for attachment to the second threaded portion 102 of the container 100. In the embodiment shown in Figure 2G, the threaded portion 106 is shown to be present around the circumference of the inner surface of the closure device 105.

The kit of the invention may generally comprise the container 100 shown in Figure 1, the cell sampling device 7 shown in Figures 2A-2F and a closure device 105 shown in Figure 2G.

In use, exfoliated cells from a colorectal mucosal surface of a human subject may be sampled in accordance with the procedures described in WO 2006/003447 A1 and as shown in Figures 2A-2C.

For example, a first, elevated pressure is applied to the cell sampling device 7 (shown in Figure 2A as a syringe) which causes the flexible membrane 4 to inflate and emit from the distal end of the cell sampling device 7 (Figure 2B). The inflated flexible membrane 4 then makes contact with the colorectal mucosal surface of a human subject such that exfoliated cells 31 are transferred to the outer surface of the flexible membrane 4 (Figure 2B). A second reduced pressure is then applied to the cell sampling device 7 which causes the flexible membrane 4 to invert and return to the interior cavity of the cell sampling device 7 (Figure 2C).

Assay buffer or cell suspending buffer 103 from a vessel 104 is then introduced into the distal end of the cell sampling device 7 such that contact is made with the exfoliated cells 31 on the outer surface of the flexible membrane 4 (Figure 2D). The assay buffer or cell suspending buffer 103 and exfoliated cells 31 will therefore be contained within the
inverted flexible membrane 4. The container 100 is then screwed onto the threaded distal end of the cell sampling device 7 by way of engagement of the first threaded portion 101 present on the inner surface of the container 100 and a further threaded portion 701 present on the outer surface of the distal end of the cell sampling device 7 (Figure 2E). The container 100 and cell sampling device 7 are then agitated to ensure thorough suspension of the exfoliated cells 31 in the assay buffer or cell suspending buffer 103 and the container 100 and cell sampling device 7 are tilted to ensure that the contents 31 and 103 are transferred to the container 100 (Figure 2F).

The closure device 105 is then attached to the container 100 by way of engagement of the threaded portion 106 on the inner surface of the closure device 105 with the second threaded portion 102 on the outer surface of the container 100 (Figure 2G).

An alternative embodiment to the method described in Figure 2 is demonstrated by Figure 3. For example, in this embodiment, it is envisaged that the assay buffer or cell suspending buffer 103 will be contained as a pre-measured amount within the container 100 (as shown in Figure 3D). Such an arrangement will introduce the assay buffer or cell suspending buffer 103 from the container 100 to the cell sampling device 7 upon attachment and agitation shown in Figures 3E-3F. This embodiment therefore eliminates the need for the step performed in Figure 2D because suspension will occur simultaneously with the step performed in Figures 2E and 3E-3F.

In a yet further embodiment to the method described in Figure 3 it may be envisaged that a pre-measured amount of assay buffer or cell suspending buffer 103 will be present within a reservoir (e.g. blister packet) present on the first threaded portion 101 of the container 100. Such an arrangement will release the assay buffer or cell suspending buffer 103 from the reservoir (e.g. blister packet) upon screwing the container 100 to
the cell sampling device 7. As with the embodiment shown in Figure 3, this eliminates the need for the step performed in Figure 2D because suspension will occur simultaneously with the step performed in Figures 2E and 3E.

In further alternative embodiments, alternative means to pressurise the cell sampling device may be envisaged other than the use of a syringe 7. For example, compressed air may be administered to the cell sampling device either by a pump or an electronic or mechanical device.

In a yet further alternative embodiment, it is envisaged that the container 100 shown in Figure 1 may be modified to remove the second threaded portion 102 from the outer surface of the container (i.e. the container will have only a single threaded portion 101 on the inner surface of the container 100). In this alternative embodiment, it will be appreciated that the closure device 105 shown in Figure 2G will also be modified to be either a stopper or bung or otherwise a cap or lid having a threaded portion on an outer surface (e.g. an external thread) for sealing the container 100 having only an internal threaded portion 101.
CLAIMS

1. A cell sampling kit comprising a cell sampling device and a container, wherein the cell sampling device and the container each comprise a complimentary threaded portion configured for attachment of the container to the cell sampling device.

2. A kit as defined in claim 1, wherein the threaded portion is present on an inner surface of the container.

3. A kit as defined in claim 1 or claim 2, wherein the container and/or cell sampling device comprise engagement means configured to attach a closure device thereto.

4. A kit as defined in claim 3, wherein the closure device is a cap or lid having a threaded portion on an inner surface, and the engagement means comprise a second threaded portion on an outer surface of the container.

5. A kit as defined in any preceding claims, which additionally comprises a closure device.

6. A kit as defined in claim 5, wherein the container comprises a volume of buffer, such as cell suspending buffer.

7. A kit as defined in any preceding claims, wherein the threaded portion of the container has a reservoir attached thereto, such as a blister packet, containing a volume of buffer, such as cell suspending buffer.

8. A kit as defined in any preceding claims, wherein the container comprises graduated marks or grooves.
9. A kit as defined in any preceding claims, wherein the cell sampling device comprises a flexible membrane having a cell sampling surface.

10. A kit as defined in any preceding claims, wherein the cell sampling device comprises an insertion member having a distal, insertion end, a proximal end and a closable interior cavity, a flexible membrane having an outer, cell sampling surface and an inner surface, wherein the membrane is sealingly attached to the distal, insertion end of the insertion member and held within the interior cavity, such that, in use, pressurisation of the interior cavity to at least a first elevated pressure causes the membrane to emit from the distal end of the insertion member to make contact with the cells and pressurisation of the interior cavity to a second reduced pressure causes the membrane to invert and return to the interior cavity of the insertion member.

11. A kit as defined in claim 10, wherein the threaded portion is present on an outer surface of the distal, insertion end of the cell sampling device.

12. A kit as defined in any preceding claims, wherein the cell sampling device is a colorectal cell sampling device.

13. A kit as defined in claim 12, which additionally comprises a rectal access tube and optionally an obturator.

14. A method of transferring the contents of a cell sampling device as defined in any of claims 1 to 13 to a container as defined in any of claims 1 to 13, comprising the steps of:

(a) attachment of the container as defined in any of claims 1 to 13 containing a pre-measured amount of an appropriate buffer or
21

liquid medium to the cell sampling device as defined in any of claims 1 to 13 by cooperation of their respective threaded portions;

(b) tilting the container and the cell sampling device to allow the contents of the cell sampling device to be transferred to the container; and

(c) removal of the container from the cell sampling device.

15. A method of transferring exfoliated cells from a colorectal mucosal surface of a human subject to a container, comprising the steps of:

(a) sampling the exfoliated cells in accordance with the procedures described in WO 2006/003447 A1;

(b) attachment of the container as defined in any of claims 1 to 13 containing a pre-measured amount of an appropriate buffer or liquid medium to the threaded portion of the cell sampling device as defined in any of claims 1 to 13;

(c) agitation of the container and the cell sampling device to allow suspension of the exfoliated cells in the appropriate buffer or liquid medium;

(d) tilting the container and the cell sampling device to allow the suspended exfoliated cells to be transferred to the container;

(e) removal of the container from the cell sampling device; and

(f) optionally closing the container with a closure device.
INTERNATIONAL SEARCH REPORT

PCT/GB2007/000086

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61B10/00

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)

A61B

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P, X</td>
<td>WO 2006/003447 A (COLONIX LTD [GB]); LOKTIONOV ALEXANDRE [GB]; BANDALETOVA TATIANA [GB])</td>
<td>1-4, 7, 9-13</td>
</tr>
<tr>
<td></td>
<td>12 January 2006 (2006-01-12)</td>
<td></td>
</tr>
<tr>
<td>P, Y</td>
<td>page 24, line 27 - page 26, line 11; figures 2D, 3, 4</td>
<td>9, 10, 13</td>
</tr>
<tr>
<td></td>
<td>column 4 - paragraph 16; figure 1</td>
<td>9, 10, 13</td>
</tr>
<tr>
<td></td>
<td>column 2, lines 47-60 - column 4, line 17; figures 2, 3</td>
<td></td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

20 April 2007

Date of mailing of the international search report

09/05/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (31-70) 340-2040, Tx. 31 651 epo nl
Fax: (31-70) 340-3016

Authorized officer

Assion, Jean-Charles
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>column 5, line 31 - column 7; figure 1</td>
<td>9,10,13</td>
</tr>
<tr>
<td>X</td>
<td>WO 00/61010 A (QUEST DIAGNOSTICS INVESTMENTS [US]) 19 October 2000 (2000-10-19)</td>
<td>1-6,8,9,11,12,14,15</td>
</tr>
<tr>
<td></td>
<td>paragraphs [0001], [0017], [0023]; figures 1,2,6</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>EP 0 727 653 A2 (WAKO PURE CHEM IND LTD [JP]) 21 August 1996 (1996-08-21)</td>
<td>1-4,11,12,14,15</td>
</tr>
<tr>
<td></td>
<td>page 6, line 10; figure 1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>US 3 664 328 A (MOYLE HENRY DINWOODY JR ET AL) 23 May 1972 (1972-05-23)</td>
<td>9,10</td>
</tr>
<tr>
<td></td>
<td>figure 1</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>EP 0 004 318 A2 (BATTLE INSTITUT E V [DE]) 3 October 1979 (1979-10-03)</td>
<td>9,10</td>
</tr>
<tr>
<td></td>
<td>figures 1,2</td>
<td></td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2570714 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2004184966 A1</td>
</tr>
<tr>
<td>US 4353868 A</td>
<td>12-10-1982</td>
<td>NONE</td>
</tr>
<tr>
<td>US 5198365 A</td>
<td>30-03-1993</td>
<td>NONE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6063038 A</td>
</tr>
<tr>
<td>US 2005155440 A1</td>
<td>21-07-2005</td>
<td>NONE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69610569 T2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2151090 T3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 5882942 A</td>
</tr>
<tr>
<td>US 3664328 A</td>
<td>23-05-1972</td>
<td>NONE</td>
</tr>
<tr>
<td>EP 0004318 A2</td>
<td>03-10-1979</td>
<td>DE 2812709 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 55032576 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 4467816 A</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (patent family annex) (April 2005)