

Switching to other substrates comprising a smaller well bottom area would theoretically solve some problems such as combining the images. However, this has other drawbacks. The ratio between a planar surface of the well bottom to the non-planar edge region, in which shading and defocusing occur, would shift into the negative. The probability of a cell coming to rest at the edge would increase. The area at the well bottom or, above all, the volume of the well available to the cells for growing would be significantly smaller. Cells would grow worse and could not form sufficiently large populations. This would cause the entire work process to be more complex. Due to the small well volume, the medium would have to be exchanged or filled in order to supply the cells with nutrients for a sufficiently long period of time. The risk of cross-contamination or the probability of premature death of the population would increase.

Thus, the inventors have realized that a dispensing technology alone is not sufficient for the verification of a single cell in a fluid container such as a well of a microtiter plate. Furthermore, due to the above-described problems, imagers are also limited in their significance in this case. Ultimately, this may lead to the fact that the optimal population selected for the production cannot reliably be identified as monoclonal and, thus, has to be discarded. This leads to high economic risks and high costs.

Embodiments of the invention provide apparatuses and methods solving the above-described problems and enabling a reliable detection even of single cells or particles in a fluid container.

In Fig.1, an embodiment of an apparatus for detecting cells or particles is shown. The apparatus includes a fluid container 10. For example, the fluid container may be a well (cavity) of a microtiter plate comprising an array of corresponding wells. The fluid container may comprise a bottom and side walls limiting a volume of the fluid container and enabling the fluid container to be at least partially fillable with a fluid. In embodiments, the fluid container 10 consists of a transparent material. The fluid container 10 is at least partially filled with a fluid 12 such as a liquid. For example, the liquid may be a nutrient solution for a cell culture. In the following, reference is made to a liquid 12. The apparatus further comprises a dispenser 14 configured to dispense at least one cell or particle 16 into a defined sub-volume 18 of the liquid 12. The dispenser 14 may be a drop-on-demand dispenser configured to dispense a single drop, in which a cell or a particle is encapsulated, from a nozzle 20. The dispenser 14 is positioned or may be positioned

Claims

1. Apparatus for detecting cells or particles (16) in a liquid container (10), comprising:
 - 5 a liquid container (10) at least partially filled with a liquid (12);

a dispenser (14) configured to dispense a free-flying drop in which at least one cell (16) or at least one particle (16) is encapsulated into a defined sub-volume (18) of the liquid (12) with which the liquid container (10) is at least partially filled;

10 a detection apparatus (22, 32) configured to sense the at least one cell (16) or the at least one particle (16) in the defined sub-volume (18) of the liquid (12) with which the liquid container (10) is at least partially filled, and/or in one or several sub-volumes (18a-18d) underneath the defined sub-volume (18); and

15 a control configured to coordinate dispensing the cell or the particle by the dispenser and detecting by the detection apparatus in a timely manner to sense the at least one cell (16) or the at least one particle (16) when entering the liquid (12) with which the liquid container (10) is at least partially filled, or immediately

20 after entering the liquid (12) with which the liquid container (10) is at least partially filled no later than five seconds after entering the liquid,

wherein the detection apparatus (22, 32) comprises an image capturing apparatus (32) configured to focus on the defined sub-volume (18) and/or the one or several

25 sub-volumes (18a-18d) underneath the defined sub-volume (18) and to capture an image of the defined sub-volume (18) and/or the one or several sub-volumes (18a-18d) underneath the defined sub-volume (18)

wherein the dispenser (14) is configured to dispense the at least one cell (16) or the at least one particle (16) onto a surface of the liquid (12) and wherein the fluid

30 liquid container (10) is transparent and the image capturing apparatus (22, 32) is arranged underneath the fluid liquid container (10).

2. Apparatus according to claim 1, wherein the detection apparatus (22, 32) is configured to sense the at least one cell (16) or the at least one particle (16) no later than 1 second after entering the liquid (12).
- 5 3. Apparatus according to claim 1 or 2, wherein the defined sub-volume (18) comprises an area (A1) which is smaller than the area (A2) of an entry opening of the liquid container (10).
- 10 4. Apparatus according to any one of claims 1 to 3, wherein the detection apparatus (22, 32) is configured to, starting with a sub-volume (18d) in a greater depth, successively perform detections in several sub-volumes (18-18d) comprising a respectively decreasing depth, or, starting with a sub-volume (18) in a lesser depth, successively perform detections in several sub-volumes (18-18d) comprising a respectively increasing depth.
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5. Method for detecting cells or particles (16) in a liquid container (10), comprising:
20 dispensing (50, 60) a free-flying drop in which at least one cell (16) or at least one particle (16) is encapsulated into a defined sub-volume (18) of a liquid (12) with which a liquid container (10) is at least partially filled;
25 sensing the at least one cell (16) or the at least one particle (16) when entering the liquid (12) or immediately after entering the liquid (12) no later than five seconds after entering the liquid by performing (52, 62), in a time-coordinated manner with dispensing the at least one cell (16) or the at least one particle (16), a detection in the defined sub-volume (18) and/or in one or several sub-volumes (18a-18d) underneath the defined sub-volume (18),
30 wherein performing a detection comprises focusing an image capturing apparatus (32) on the defined sub-volume (18) and/or the one or several sub-volumes (18a-18d) underneath the defined sub-volume (18) and capturing an image of the defined sub-volume (18) and/or of the one or several sub-volumes (18a-18d) underneath the defined sub-volume (18)
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wherein the at least one cell (16) or the at least one particle (16) is dispensed onto a surface of the fluid liquid (12) and wherein the fluid liquid container (10) is transparent and the image capturing apparatus (22, 32) is arranged underneath the fluid liquid container (10).

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6. Method according to claim 5, wherein sensing the at least one cell (16) or the at least one particle occurs no later than 1 second after entering the liquid (12).

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7. Method according to claim 5 or 6, wherein the defined sub-volume (18) comprises an area (A1) which is smaller than the area (A2) of an entry opening of the liquid container (10).

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8. Method according to claim 5, wherein a detection of the at least one cell (16) or the at least one particle (16) is performed in the defined sub-volume (18) comprising a depth of less than 5mm from the upper surface of the liquid (12).

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9. Method according to any one of claims 5 to 8, wherein, starting with a sub-volume (18d) in a greater depth, detections are successively performed in several sub-volumes (18-18c) comprising a respectively decreasing depth, or, starting with a sub-volume in a lesser depth (18), detections are successively performed in several sub-volumes (18a-18d) comprising a respectively increasing depth.

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10. Method according to any one of claims 5 to 9, comprising positioning a dispenser (14), a detection apparatus (12) and each one of several liquid containers relative to each other in order to sense the at least one cell or the at least one particle when entering the liquid or immediately after entering the liquid of this liquid container no later than five seconds after entering the liquid.
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11. Method according to any one of claims 5 to 10, comprising using the liquid container (10) comprising a side wall with an edge, a contact angle of the liquid being adjusted with respect to the side wall such that the liquid (12) comprises a flat surface.
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