

In-line sensors for process application, and method for putting the in-line sensors into operation

The invention relates to an in-line sensor for measuring measurement values of a measurand
5 representing an analyte content in a medium to be measured. The invention further relates to a method for manufacturing the in-line sensor and to a method for putting it into operation.

In order to determine the composition of measuring media – in particular, liquids, e.g., pure liquids,
liquid mixtures, emulsions, or suspensions – various analytical measuring devices are used in process
metrology and analysis metrology. An analytical measuring device generally comprises a sensor which
10 is designed to generate an electrical measurement signal dependent upon at least one analytical measurand, as well as an electronic evaluation device which, from the measurement signal, determines a measurement value representing the current value of the at least one analytical measurand in the medium to be measured. The analytical measurand can, for example, be a concentration or activity of an analyte or a parameter dependent upon a concentration or activity of at
15 least one analyte in the medium to be measured.

An analyte here means one or more substances contained in and, in particular, dissolved in the
medium to be measured, whose concentration in the medium to be measured is to be determined or
monitored by the sensor. The electronic evaluation device can be at least partially integrated into a
20 measuring transducer arranged directly at the measurement point, which transducer has a housing with display and input elements. At least one part of the electronic evaluation device may also be arranged together with the sensor in a common housing.

Such analytical measuring devices are used in a variety of fields, e.g., for monitoring and controlling
processes in pharmaceutical, chemical, biotechnical, or biochemical production, but also in processes
25 for water conditioning or sewage purification, and in environmental analysis. Insofar as an analytical measuring device is used in a process, the medium to be measured will typically be contained in a process vessel. Such a process vessel may, for example, be a pipeline of a process plant or a reaction vessel - for example, a bioreactor or a fermenter.

A bioreactor, often also called a fermenter, is a vessel in which certain microorganisms, cells or small
30 plants are cultivated under optimal conditions.

Sensors that are integrated into the wall of a process vessel for monitoring a measurand of a medium
to be measured contained in the process vessel are referred to as in-line sensors. An in-line sensor
detects the measurand directly in the medium to be measured to be monitored. With in-line sensors,
an extraction and pre-treatment of a sample from the process is therefore not necessary for
35 determining an analytical measurand. For the integration of a sensor into the process wall, diverse

adapters and fittings - in particular, immersion or retractable fittings - are known. An arrangement that comprises an in-line sensor integrated into the wall of a process vessel and, if applicable, a measuring circuit and an electronic evaluation device connected to the in-line sensor, but offset from this, is referred to as an in-line sensor arrangement. The in-line sensor may be fixed in the wall by means of a suitable adapter.

With processes that must be implemented under sterile or aseptic conditions - for example, as they occur in biotechnology, pharmaceuticals, or food technology - all parts of the process plant that come into contact with the process media - in particular, all process vessels and also the sensors integrated therein - are typically sterilized (for example, thermally, via heat) before the beginning of the process or between individual process steps. The heat sterilization may take place via dry heat (typically, with hot air between 160 °C and 180 °C as a sterilization medium) or via superheated steam as a sterilization medium under increased pressure, e.g., via autoclaving in a pressure vessel - what is known as an autoclave. For example, superheated steam sterilization methods are common in which temperatures of at least 120 °C or more may occur. If the heat sterilization is performed in an autoclave, the process-contacting parts of the process plant - possibly already connected to one another - are introduced into the autoclave and are sterilized there. The sterilized parts are subsequently removed from the autoclave again and placed in operation.

Alternatively, a process plant may be sterilized by means of what is known as an SIP method (SIP is the acronym for the English technical term, "sterilization in place"), in which the process vessel to be sterilized, including the in-line sensor integrated therein, is sterilized with superheated steam that is introduced into the process vessel over a predetermined time period. Therefore, in-line sensors must be able to withstand the conditions that occur in this case, such as high temperatures, humidity, and increased pressures, without loss of functionality.

In bioprocess metrology, e.g., for monitoring, controlling, and/or regulating biotechnology processes, sensors are also used that have immobilized biological recognition elements on the surface of the sensor element, e.g., those that – possibly as receptors – selectively and specifically bind to and/or react with the analyte. Biological recognition elements may be proteins such as enzymes or antibodies, DNA/RNA fragments, cell organelles, or whole cells and microorganisms. Such sensors are designated as biosensors.

After a typical, superheated, steam sterilization process, the receptors or biological recognition elements of such biosensors, in particular proteins, cell organelles, or microorganisms, are normally present with starkly reduced activity - most often, irreversibly denatured, i.e., their native three-dimensional structure (conformation) is destroyed. Such biosensors therefore, in principle, may not be used as in-line sensors in the wall of a process vessel and be sterilized with this by means of a typical SIP method, without taking further measures.

Many sensors with biological recognition elements, e.g., those that originate from mesophilic organisms which live in a temperature range of approximately 20-45 °C, may not be exposed to increased temperatures under SIP conditions, e.g., of 80 °C, in order to not lose their functionality.

Sterilizable biosensors based upon amperometric enzyme sensors are described in the literature. In
5 M. Phelps, Development of a regenerable glucose biosensor probe for bioprocess monitoring, master's thesis, University of British Columbia, 1993, an overview of the literature regarding such sensors is given. Strategies described therein for ensuring sterilization capability of such biosensors while maintaining their functionality include the introduction of the temperature-sensitive receptors arranged on a support - said support comprising, for example, a working electrode - only after the
10 sterilization process in a reaction chamber within a sensor housing which is sealed in relation to the process vessel by a membrane permeable to the respective analyte. The membrane in this instance represents the sterile barrier. The receptors may thereby be present immobilized on the subsequently introduced working electrode, or in a solution received into the reaction chamber. The sterile barrier may not be destroyed upon introduction of the receptors, which makes the handling of such in-line
15 sensors difficult.

In addition to the difficult handling, what is also disadvantageous with these in-line sensors known from the literature is that a fluctuating measurement performance of the biosensors is observed. One reason for this is that the quantity of the subsequently introduced receptors bound to a matrix is difficult to reproduce. The previously known in-line sensors that comprise biosensors are not practicable - in
20 particular, not with regard to applications for monitoring industrial processes.

In the field of single-use technology, which is increasingly used for bioprocesses, adapters or connectors have become known that allow the introduction of pre-sterilized sensors, e.g., by means of gamma radiation, into a pre-sterilized single-use bioreactor. However, these connectors are often not accepted or applicable for the use of large-volume process vessels in a conventional process
25 plant, which is sterilized, for example, by SIP sterilization methods.

The object of the invention is therefore to provide an in-line sensor and a method for its manufacture and for putting it into operation which overcomes the described disadvantages. The disadvantages of putting into operation an in-line sensors according to the prior art are, additionally, to be overcome. The in-line sensor should preferably also be universally usable in sterilizable process vessels, and
30 allow the safe aseptic introduction of a sensor element of the in-line sensor into a process vessel for measurement of the measurand in a medium contained in the process vessel. The in-line sensor should preferably be suitable for introducing a biosensor with biological recognition elements which do not withstand superheated steam sterilization into a process vessel to be sterilized at high temperatures.

This object is achieved by an in-line sensor according to the invention, by a sensor arrangement according to the invention containing the in-line sensor, and by a method according to the invention

for manufacturing an in-line sensor and for putting into operation an in-line sensor. Advantageous refinements are specified in the disclosed embodiments.

This sensor allows the aseptic introduction of heat-labile sensors into a process vessel that has previously been heat-sterilized, while maintaining the functionality of the sensors. This is made possible by using the in-line sensor described here and below, which, due to the design according to the invention, allows for simple putting into operation of the sensor system in the process vessel and the monitoring of manufacturing processes, preferably by means of biotechnology.

The invention relates to an in-line sensor (1) for measuring measurement values of a measurand representing an analyte content of a medium (6) to be measured, comprising an outer tube (2), an inner tube (3), a support (4) which is non-detachably connected to the inner tube (3), and at least one sensor element (5) which is non-detachably connected to the support (4), wherein the inner tube (3) and the support (4) which is non-detachably connected to the inner tube and contains the at least one sensor element (5) are movable unidirectionally relative to the outer tube (2) along the longitudinal axis (L) of the sensor (1) in the direction of the medium (6) to be measured from an irradiation position to a hot-steam-sterilization position and from the hot-steam-sterilization position to a measuring position, and can be locked in both the hot-steam-sterilization position and the measuring position, wherein

(i) the outer tube (2) has

- a substantially cylindrical cavity (7),

- at least one first connecting element (9) on an outer wall (8) at the end facing away from the medium,

- a third connecting element (11) on an inner wall (10),

and

- at least one sealing element (12), preferably a first (12) and at least one second sealing element (13) on the inner wall (10) at the medium-facing end;

(ii) the inner tube (3) has

- a fourth connecting element (14) on an outer wall (15) which is designed to engage in a third connecting element (11) on the inner wall of the outer tube (10) in the measuring position and

- on its end facing away from the medium,

is connected to a shell (17), wherein the inside of the shell (19) has at least one second connecting element (20) which is designed to allow one or more first connecting elements (9) to snap into the outer wall of the outer tube (8) in the hot-steam-sterilization position,

has an electronics housing (16) connected to the inner tube (3) in a gas- and liquid-tight manner, which is connected to the inner tube in a gas- and liquid-tight and detachable manner by means of a securing element (18), wherein the securing element (18) preferably consists of or comprises a terminal, removable, preferably screwable, transport lock (18), wherein

the transport lock (18) is designed in the installed state to prevent accidental and unintentional transfer of the inner tube from the hot-steam-sterilization position to the measuring position, and to allow movement after removal; wherein

the end of the inner tube released by the transport lock (18) has at least a third overhang (21) which is designed to prevent movement of the inner tube (3) and the associated support (4) containing the sensor element (5) beyond the measuring position,

(iii) the support (4) is non-detachably connected to the inner surface of the inner tube with a portion of its outer shell facing away from the medium, preferably with a medium-facing end portion; and

(iv) the at least one sensor element (5) is designed for receiving a value dependent on a measurand of a medium, wherein the sensor element is in gas contact with an interior of the sensor, the support (4) is positioned in the irradiation position in the cavity of the outer tube (7) in such a way that at least one gap (22) is arranged between the support (4) and the cavity of the outer tube (7), so that the interior of the sensor and the sensor element (5) arranged in the support (4) are in contact with the surroundings, preferably in gas contact,

the support (4) is positioned in the hot-steam-sterilization position in such a way that the medium-facing end portion of the support (4) seals the sensor interior and the sensor element (5) arranged in the support (4) in a gas-tight manner relative to the surroundings of the sensor, and

in the measuring position, the support (4) is positioned in such a way that the sensor element (5) is positioned so as to be in contact with the surroundings, preferably with the medium to be measured (6), following hot-steam-sterilization, wherein preferably the surroundings and the medium to be measured are sterilized.

The in-line sensor according to the invention, the sensor arrangement according to the invention, the manufacturing method, according to the invention, of the in-line sensor and the method according to the invention for putting into operation the in-line sensor have the advantage that a sterile sensor that can be installed in a process vessel is provided simply by a unidirectional movement of the inner tube along the longitudinal axis of the in-line sensor, which meets the high hygienic requirements in the food industry, biotechnology and/or the production of pharmaceuticals, for example biologics. The regions of the in-line sensor located inside the process vessel and in contact with the surroundings or the medium are designed to be hygienic.

After the sensor is installed in the process vessel, the surroundings are the interior of the process vessel.

In particular, the in-line sensor can be autoclaved, wherein the sensor activity is substantially, preferably not negatively, affected by heat and/or humidity. An arrangement according to the invention is therefore particularly easy to handle and thus particularly user-friendly.

In one embodiment, all elements of the in-line sensor that come into contact with the medium to be measured are made of materials suitable for sterilization by radiation. In all embodiments, these

materials are non-toxic to the biological organisms and/or media to be cultivated. The materials of the in-line sensor can also be sterilized using hot steam in the hot-steam-sterilization position.

In one embodiment, the components forming the outer surface of the housing preferably consist of one or more materials through which water vapor cannot diffuse or can only diffuse to a small extent.

5 Possible materials include glass, plastics material, or metal. Composite materials are also possible, which consist, for example, of a plastics material layer and a metal layer, or multi-layered plastics materials which consist of composite films. The inner tube is preferably made of a metal or a metal alloy.

10 In one embodiment, the individual components or parts of the sensor, which are non-detachably connected to each other, can be formed with a material bond, a positive connection, and/or a non-positive connection, alternatively in one piece, preferably as multi-component injection molded parts. The mobility of the inner tube (3) and of the support (4) which is non-detachably and positively connected to the inner tube and contains the at least one sensor element (5) relative to the outer tube (2) along the longitudinal axis (L) of the sensor (1) means that, on the one hand, a translational movement takes place along the axis of movement (L). In addition to the translational movement, a rotational movement can be performed, for example by mediating the movement via a thread or by locking the inner tube to the outer tube in the hot-steam-sterilization position and/or measuring position via at least one bayonet lock.

15 The movement along the longitudinal axis (L) of the in-line sensor can be performed either manually or via an actuator, which is, for example, pneumatically driven.

In an embodiment in which the movement is exclusively translational, the in-line sensor element has at least one, preferably two, anti-rotation devices (25) which prevent a rotational movement of the inner tube (3) relative to the outer tube (2) about the longitudinal axis (L) of the sensor.

The anti-rotation devices are those known according to the prior art.

25 The radiation in question is suitable for sterilization or disinfection. This includes UV radiation, X-rays, gamma radiation or particle radiation, in particular electron radiation. Preferably, the radiation is ionizing radiation, more preferably electron radiation or gamma radiation, and even more preferably gamma radiation.

30 In an advantageous embodiment, the gas volume in the interior of the sensor is largely composed of a protective gas, preferably one or more noble gases, wherein the protective gas consists of one or more noble gases, preferably argon. The gas volume in the interior of the sensor advantageously contains oxygen and/or nitrogen in a volume fraction of respectively less than 1 vol% - preferably, respectively less than 0.5 vol%, and, more preferably, respectively less than 0.1 vol%.

35 In the radiation sterilization position, the interior of the sensor comprises the entire cavity or hollow space of the sensor, which is enclosed by the outer shell of the sensor and accessible from the opening facing the medium. In the heat sterilization position, the interior of the sensor is the entire interior of

the sensor, which is sealed relative to the surroundings of the sensor with at least one sealing ring facing the medium.

5 In one embodiment, the at least second connecting element (20) is arranged on the shell (17) of the inner tube relative to the third connecting element (11) on the inner wall of the outer tube (10) closer to the end facing away from the medium along the longitudinal axis (L) of the in-line sensor.

In one embodiment, the at least first and the at least second connecting element are at least partially, preferably completely, complementary to each other.

In one embodiment, the at least third and the at least fourth connecting element are at least partially, preferably completely, complementary to each other.

10 In a preferred embodiment, the connecting elements, which are at least partially complementary to each other, consist of a notch or at least one groove and at least one overhang which is at least partially complementary to it.

15 In one embodiment, the notches or grooves at their end facing away from the medium include a stepped shoulder that prevents movement of the inner tube in the opposite direction to the measuring position.

20 In one embodiment, the in-line sensor has in each case as connecting elements at least two first - and/or two - grooves as second and/or fourth connecting elements, and also at least two first overhangs and/or two second overhangs as third and/or fourth connecting elements. Additionally, the in-line sensor has at least two third overhangs. The first and second grooves, as well as the first, second and third overhangs, are either the same or different, preferably identical in design. In a further embodiment, the connecting elements each have at least one groove and at least one overhang, ensuring that a snapping or engagement with the at least partially complementary connecting elements takes place by virtue of the fact that the first connecting elements snap or engage with the second connecting elements and the third connecting elements snap or engage with the fourth connecting elements.

25 In one embodiment of the in-line sensor, the at least one, preferably the first and optionally the second sealing element, in the heat sterilization position, preferably the hot-steam-sterilization position, seals at least a portion of the support which faces the medium and which comprises the at least one sensor element, and also the sensor interior and the at least one sensor element contained therein, in a liquid- and gas-tight manner from the surroundings of the in-line sensor.

30 In one embodiment, the first and second sealing elements can be part of a one-piece component, which is preferably designed as a multi-component injection molded part. In an alternative embodiment, the first and at least the second sealing element can be present separately. In a preferred embodiment, the sealing elements are O-rings.

The sensor interior is the space enclosed by the outer tube, the inner tube, and the electronics housing. The parts of the sensor interior that are not on the medium side of at least one sealing element can be sealed gas-tightly and liquid-tightly from the surroundings by transferring the sensor from the radiation sterilization position to the hot-steam-sterilization position. This step is performed before the sensor is removed from the at least one radiation-sterilized packaging.

In the hot-steam-sterilization position, the first sealing element is pressed by the support 5, thereby sealing the radiation-sterilized sensor interior from the surroundings in a liquid- and gas-tight manner. In the measuring position, the at least one, preferably the first 12 and the at least second sealing element 13 are pressed by the support 5, wherein at least one part of the sensor interior arranged on the non-medium side of the at least one sealing element is sealed liquid-tightly and gas-tightly from the surroundings, preferably the sterilized surroundings, or the medium, preferably the sterilized medium.

In a preferred embodiment, the sealing elements are O-rings.

In one embodiment, the support is designed as a circular cylinder, preferably as a vertical circular cylinder, the surface of which, preferably on the outer peripheral surface, comprises at least one recess and optionally a cavity in which the at least one sensor element is arranged, wherein preferably the recess is not encompassed by the portion of the support which faces the medium.

The portion of the support which faces the medium comprises the part of the support which is located on the medium side of the recess. The at least first sealing element on the outer tube is pressed onto the medium-side portion of the support by the support in the hot-steam-sterilization position. In the measuring position, the portion which is not on the medium side of the recess is pressed by at least one sealing element, preferably the first and at least the second sealing element.

In one embodiment, the outer tube has an opening on the medium side, which is designed to bring at least one medium-facing end portion of the support and the at least one sensor element arranged in the support into contact with the surroundings, preferably with the medium to be measured, in the measuring position, after heat sterilization, for example autoclaving, wherein preferably the surroundings, and more preferably the medium to be measured, are sterilized.

The heat sterilization may take place via dry heat (typically, with hot air between 160 °C and 180 °C as a sterilization medium) or via superheated steam as a sterilization medium under increased pressure, e.g., via autoclaving in a pressure vessel - an autoclave. For example, superheated steam sterilization methods are common in which temperatures of at least 120 °C or more may occur. If heat sterilization is carried out in an autoclave, the process-contacting parts of the process plant, possibly already connected to each other, are placed in the autoclave, sterilized there, then removed from the autoclave and put back into operation. Alternatively, a process plant may be sterilized by means of what is known as an SIP method (SIP is the acronym for the English technical term, "sterilization in

place”), in which the process vessel to be sterilized, including the in-line sensor integrated therein, is sterilized with superheated steam that is introduced into the process vessel over a predetermined time period. Therefore, in-line sensors must be able to withstand the conditions that occur in this case, such as high temperatures and increased pressures, without loss of functionality.

- 5 In one embodiment, the sensor interior of the in-line sensor contains a desiccant, wherein in particular the desiccant consists of or contains a hydrophilic material, wherein the desiccant preferably consists of or contains a zeolite, glass or ceramic, and more preferably aluminum oxide and/or titanium oxide and/or silicon oxide.

- 10 In all embodiments, the inner tube contains at least one ventilation opening, preferably multiple ventilation openings, to establish gas contact between the sensor element and the desiccant located in the inner tube. The openings can be designed, for example, as holes, slots or gaps, wherein the openings are designed in such a way that the desiccant located in the inner tube remains in the inner tube. Gas contact occurs in both the irradiation position and the hot-steam-sterilization position.

- 15 In one embodiment, the in-line sensor has, in addition to the at least one sensor element, a humidity sensor which is designed to detect a measurand representing a relative humidity prevailing within the chamber.

- 20 Additionally or alternatively, the in-line sensor has a temperature sensor designed to capture measurement values representing the temperature of the sensor interior. In a preferred embodiment, the temperature sensor is arranged in the inner tube of the in-line sensor. For example, the temperature sensor is a Pt100 sensor. In one embodiment, the temperature sensor is arranged in the support, preferably in the area of the recess of the support.

- 25 In one embodiment, the inner tube of the in-line sensor is designed such that the relative humidity prevailing within the housing does not exceed a value of 77% - preferably, of 23%, more preferably, of 3%, and, even more preferably, of 1% - given an external heat sterilization of the housing at a temperature of 110 °C over a time period of 15 min.

- 30 The housing of the in-line sensor can comprise a wall or outer surface of the housing formed from one or more components of the sensor that are in contact with the surroundings, which tightly encloses the sensor interior and forms a barrier against the diffusion of water vapor into the interior of the sensor in the hot-steam-sterilization position. A mean water vapor permeability of the wall, i.e., a mean value of the water vapor permeability of the components forming the wall, advantageously amounts to, at a temperature of 110 °C, a pressure difference of less than 5 bar prevailing between the chamber and the surroundings of the housing wall, and a difference in the relative humidities prevailing in the chamber and in the surroundings of the wall of more than 67%, less than 420 g/(m²d) - preferably, less than 125 g/(m²d), more preferably, less than 15 g/(m²d), and, even more preferably, less than 6 g/(m²d).
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During hot-steam sterilization by means of SIP, the surfaces located inside the process vessel that are not sealed in a gas- and liquid-tight manner from the surroundings are sterilized.

5 In one embodiment, the inner tube is designed in such a manner that, upon heat sterilization, the at least one sensor element is, at least temporarily, thermally decoupled such that, during the action of a medium, with a temperature of 110 °C, on at least one partial region of the outer surface of the housing over a time period of 15 min, the temperature of the sensor element, starting from an initial temperature of the sensor element of 25 °C at the beginning of this time period, increases by less than 55 °C - preferably, by less than 35 °C, and, more preferably, by less than 10 °C.

10 Alternatively or additionally, the in-line sensor may comprise means for active and/or passive cooling of the sensor element, whereby the quantity of heat transferred per time unit between outer surface of the housing and sensor element is at least partially dissipated by the sensor element so that the temperature change in the sensor element is avoided or slowed. For example, these means may comprise a gas cooling system, a cooling system with cooling fluid, a thermoelectric converter, for example a Peltier cooling system, cooling fins, or a different heat sink.

15 A cooling system with cooling fluid and/or cooling gas can advantageously be designed as a fluid-flowable channel structure in a housing wall of the in-line sensor.

In order to improve the thermal decoupling, it is advantageous if the housing or at least one or more components forming the housing are made of a thermally insulating plastics material having a thermal conductivity of $\leq 0.5 \text{ W m}^{-1} \text{ K}^{-1}$ - in particular, are made of PEEK.

20 A cooling system with gas can, for example, involve a space filled with a thermal insulator, such as air.

When put into operation, the in-line sensor may advantageously be cooled before the heat sterilization - preferably, to 8 °C or below 8 °C, more preferably to 4 °C or below 4 °C. In one embodiment, the cooling proceeds to below 0°C. During the heat sterilization, the temperature curve of the at least one sensor element may be monitored via at least one temperature probe/sensor of the in-line sensor.

25 In one embodiment, the transport lock of the in-line sensor in the installed state prevents accidental or unintentional movement from the heat sterilization position, preferably hot-steam-sterilization position, to the measuring position. Once the transport lock is removed, the movement is released. In one embodiment, the transport lock comprises a predetermined breaking point which irreversibly destroys the transport lock when it is removed. In one embodiment, the transport lock is designed as a first anti-rotation device.

30 In one embodiment, the in-line sensor has at least one further, preferably two further, anti-rotation devices which are not designed as transport locks and which prevent a rotational movement of the inner tube relative to the outer tube about the longitudinal axis (L) of the sensor.

In one embodiment, the outer tube comprises a connection, preferably a thread, in particular a PG13.5 thread for installation in a fitting, pipeline, process vessel, in particular bioprocess vessel, preferably fermenter.

5 The integration of the in-line sensor arrangement into the wall of the process vessel may take place by means of a fitting or a process connection that is connected tightly - in particular, fluid-tightly, i.e., gas-tightly and/or liquid-tightly - to the in-line sensor arrangement. The connection is thereby, preferably, such that the process vessel is sealed fluid-tightly against the surroundings of the process vessel. This is preferably produced by means of one or more hygienic sealing elements that are designed such that their surfaces in contact with the inside of the process vessel can be sterilized by
10 means of an SIP process. For example, this sealing element may be a suitable hygienic molded seal, as they are fundamentally known from the prior art for fittings and retractable assemblies for use in hygienic applications.

Process vessels include, for example, single-use process vessels designed for individual applications (often made of plastics materials) or classic, reusable containers, often made of glass or stainless
15 steel. The process vessel can also be designed as a bioreactor or fermenter on a small or large scale. The sensor is used, for example, in process automation technology or biotechnological/biological manufacturing methods, in particular in the production of biopharmaceuticals or in the life science sector as well as the food and beverage industry.

In a preferred embodiment, the in-line sensor is designed as a one-way sensor or single-use sensor.

20 In one embodiment, the sensor comprises one or more electrodes, wherein the electrode contacting lines run within the in-line sensor, preferably inside the inner tube of the in-line sensor.

In one embodiment, the in-line sensor has an amperometric or potentiometric reference system. This can be electrically connected to the in-line sensor in the form of an in-line sensor arrangement and can be located outside the in-line sensor. Alternatively, the reference system can be comprised by the
25 in-line sensor, for example, by placing the reference system in the sensor interior, such as inside the inner tube.

In one embodiment, the in-line sensor is an optical sensor, preferably an optical glucose sensor.

The invention further relates to a sensor arrangement comprising the sensor according to the invention
30 or an embodiment thereof, wherein the in-line sensor has an electronics housing at the end facing away from the medium, to which the measuring circuit used for acquiring measurement values can be electrically connected, wherein the measuring circuit is designed to be electrically connected to a higher-level evaluation or control unit, which receives and further processes the measurement signals output by the measuring circuit.

35 In a preferred embodiment, the measuring circuit is arranged outside the in-line sensor.

In the event that the sensor is designed as an amperometric sensor, the measuring circuit serves to apply a voltage between at least two electrodes of the sensor and to detect the current that thereby flows, and to output this or an electrical signal derived from this as a measurement signal. The in-line sensor may comprise an evaluation circuit which is designed to determine, from the electrical signals output by the measuring circuit, measurement values of the measurand in the unit of the measurand, and to output via an interface to a higher-level unit or via an indicator device - for example, a display. The electronic evaluation device can be at least partially integrated into a measuring transducer arranged directly at the measurement point, which transducer has a housing with display and input elements. At least one part of the electronic evaluation device may also be arranged together with the sensor in a common housing.

In one embodiment, the at least one sensor element of the in-line sensor according to the invention is a biosensor element, wherein the biosensor element comprises at least one biological recognition element for the analyte, wherein the biological recognition element is preferably a protein, preferably an enzyme.

The biological recognition element is preferably embedded in a polymer matrix.

In one embodiment, the at least one sensor element of the in-line sensor according to the invention is an enzyme-based sensor element, preferably a lactate oxidase, glutamate oxidase, glutaminase or glucose oxidase, more preferably a sensor element comprising glucose oxidase.

In its function as a biocatalyst, the glucose oxidase enzyme converts the analyte glucose to gluconic acid and hydrogen peroxide. This process consumes oxygen. The increase in hydrogen peroxide concentration or the decrease in oxygen concentration is recorded amperometrically, depending on the choice of electrolysis potential.

The invention also relates to a method for manufacturing a sensor according to any of the preceding claims, comprising the steps of:

(i) positioning the inner tube inside the outer tube in the first irradiation position,

(ii) installing the transport lock

(iii) gas-tightly packaging the sensor within at least one radiation-sterilizable flexible packaging, preferably within at least one radiation-sterilizable bag, wherein steps (i) to (iii)

are carried out under a protective gas atmosphere.

In a preferred embodiment, the sensor is packaged in two sterilizable flexible packagings, preferably two sterilizable bags. The packaging is suitable for radiation sterilization, preferably gamma sterilization. The first, inner packaging is preferably optically transparent, and further preferably made

of a film with higher barrier properties for oxygen and water vapor compared to conventional polyethylene films. The second, outer packaging is preferably optically opaque, and further preferably made of metal composite foil, preferably aluminum composite foil.

5 The invention also relates to a method for putting into operation an in-line sensor according to the invention or an embodiment thereof, comprising the steps of:

(i) positioning the inner tube inside the outer tube in the first irradiation position,

(ii) installing the transport lock

(iii) gas-tightly packaging the sensor

10 within at least one radiation-sterilizable flexible packaging, preferably within at least one radiation-sterilizable bag, wherein steps (i) to (iii) are carried out under a protective gas atmosphere.

(iv) sterilizing the sensor enclosed in at least one flexible packaging containing the sensor element by means of sterilizing radiation

15 (v) transferring the sensor from the irradiation position to a hot-steam-sterilization position in the radiation-sterilized at least one packaging, preferably a bag, under a protective gas atmosphere, by moving the inner tube (3) along the longitudinal axis of the sensor (1) in the direction of the medium (6) to be measured, wherein the interior of the sensor containing the sensor element (5) is enclosed in the gamma-sterilized protective gas atmosphere.

(vi) unpacking the sensor from the at least one radiation-sterilized packaging, preferably a bag

(vii) mounting the sensor on a process vessel

20 (viii) heat-sterilizing the sensor, preferably by hot steam, wherein sterilization is preferably carried out by autoclaving or on-site sterilization,

(ix) removing the transport lock (19) after completion of the heat sterilization

(x) moving the inner tube (3) into the measuring position and bringing the sensor element (5) into contact with the medium to be measured, preferably bringing it into contact aseptically, and

25 (xi) connecting the electronics housing to an evaluation and/or control unit.

In one embodiment, the inner tube is filled with a desiccant before step (i).

In the figures:

Fig. 1 is a side view of the in-line sensor according to the invention in the irradiation position.

Fig. 2 is a side view of the in-line sensor according to the invention in the hot-steam-sterilization position.

Fig. 3 is a side view of the in-line sensor according to the invention in the measuring position.

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Fig. 1 shows an in-line sensor 1 which substantially comprises an inner tube 3 and an outer tube 2. The inner tube 3 is axially movable within the outer tube 2 along the longitudinal axis of the in-line sensor. The anti-rotation devices 25 prevent a rotational movement of the inner tube relative to the outer tube around the longitudinal axis of the sensor. The inner tube 3 is non-detachably, preferably positively, connected by its end facing the medium to an end of the support 4 facing away from the medium, wherein the support comprises the sensor element 5. The sensor element 5 is arranged in a recess 23 of the support. In the irradiation position, the inner tube, the associated support and the sensor element 5 encompassed by the support are located not on the medium side of the first and second sealing elements 12 and 13. This creates a gap 22 between the support 4 and the outer tube 2 as well as between the inner tube 3 and outer tube 2, which allows the interior of the sensor to be filled with a protective gas, for example argon gas, and sterilized by radiation in the irradiation position. The inner tube is also gas-tight, preferably non-detachable, and more preferably positively connected at the end facing away from the medium to an electronics housing 16. The outer side of the inner tube is connected at the end facing away from the medium to a shell 17 and to a detachably connected securing element or transport lock 18. The securing element is preferably designed as a transport lock, wherein the securing element comprises an anti-rotation device, for example a thread. A third sealing element 26 is arranged between the transport lock and the electronics housing, this sealing element preferably being designed as an O-ring. The sensor has a part on the side of the medium / contacting the medium, and also a non-medium-contacting part. At the end region of the part on the side facing away from the medium, the outer tube 2 comprises a thread 24, for example a PG 13.5 thread 24, for installing the in-line sensor 1 in a fitting, a process vessel, pipeline or a fermenter. If the thread 24 is designed as an external thread, the fitting has a corresponding internal thread. The part on the medium side or contacting the medium has a length similar to that of common sensors used in process automation, i.e., approximately 120 mm, 225 mm or 360 mm. The in-line sensor is packaged in at least one, preferably two, flexible and radiation-sterilizable packagings and sterilized by means of radiation suitable for disinfection or sterilization, wherein the radiation is UV, X-ray, gamma radiation or electron radiation.

Fig. 2 shows an in-line sensor 1 in the hot-steam-sterilization position. The support 4 is enclosed on the medium side by the first sealing element 12, for example a sealing ring, wherein the interior of the sensor, which is located on the non-medium side of the sealing ring, is sealed gas-tightly from the surroundings. The transition to the heat sterilization position, preferably the hot-steam-sterilization position, is facilitated on the side facing away from the medium via the first connecting elements 9, which are positively attached to the outer wall 8 of the outer tube 2 and the second connecting elements 20, which are positively attached to the inside of the shell 17. After being transferred to the

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heat sterilization position, preferably the hot-steam-sterilization position, the sensor is removed from the at least one radiation-sterilized packaging and the connection 24, preferably a thread, is installed in the vessel to be sterilized. The connection 24 is preferably installed with a non-positive connection on the outer wall 8 of the outer tube 2. In the hot-steam-sterilization position, the sensor element is
5 insulated against the hot steam sterilized vessel in a gas- and liquid-tight manner.

Fig. 3 shows an in-line sensor 1 in the measuring position. The sensor is moved into the measuring position after heat sterilization, preferably hot-steam-sterilization. In order to allow the inner tube to be moved axially further towards the medium 6 to be measured relative to the outer tube, the securing
10 element, preferably the transport lock 18, is removed. Locking along the longitudinal axis of the sensor is achieved through the interaction of the third and fourth connecting elements.

All the embodiments of the in-line sensor and of the method described above can be combined with each other in each case, provided that this is technically possible.
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Reference signs are not to be understood as a limitation of the scope of the subject matter protected by the claims. They serve only the purpose of making the claims easier to understand.

List of reference signs

- (1) in-line sensor
- (2) outer tube
- (3) inner tube
- (4) support
- (5) sensor element
- (6) medium to be measured
- (7) cavity of the outer tube
- (8) outer wall of the outer tube
- (9) first connecting element or first connecting elements
- (10) inner wall of the outer tube
- (11) third connecting element or third connecting elements
- (12) first sealing element
- (13) second sealing element
- (14) fourth connecting element or fourth connecting elements
- (15) outer wall of the inner tube
- (16) electronics housing
- (17) shell
- (18) securing element, transport lock
- (19) inner side of the shell
- (20) second connecting element or second connecting elements
- (21) third overhang or third overhangs
- (22) gap
- (23) recess
- (24) connection, thread
- (25) anti-rotation device or anti-rotation devices of the inner tube
- (26) third sealing element
- (27) ventilation opening

Claims

1. An in-line sensor (1) for measuring measurement values of a measurand representing an analyte content of a medium (6) to be measured, comprising:
- 5 an outer tube (2), an inner tube (3), a support (4) which is non-detachably connected to the inner tube (3), and at least one sensor element (5) which is non-detachably connected to the support (4), wherein the inner tube (3) and the support (4) which is non-detachably connected to the inner tube and contains the at least one sensor element (5) are movable unidirectionally relative to the outer tube (2) along the longitudinal axis (L) of the sensor (1) in the direction of the medium (6) to be measured from an irradiation position to a hot-steam-sterilization position and from the hot-steam-sterilization position to a measuring position, and can be locked in both the hot-steam-sterilization position and the measuring position, wherein
- 10 (i) the outer tube (2) has
- a substantially cylindrical cavity (7),
 - 15 - at least one first connecting element (9) on an outer wall (8) at the end facing away from the medium,
 - a third connecting element (11) on an inner wall (10),
- and
- at least one, preferably a first (12) and at least one second sealing element (13) on the inner
 - 20 wall (10) at the medium-facing end;
- (ii) the inner tube (3) has
- a fourth connecting element (14) on an outer wall (15) which is designed to engage in a third connecting element (11) on the inner wall of the outer tube (10) in the measuring position
 - 25 - and
 - on its end facing away from the medium,
- is connected to a shell (17), wherein the inside of the shell (19) has at least one second connecting element (20) which is designed to allow one or more first connecting elements (9) to snap into the outer wall of the outer tube (8) in the hot-steam-sterilization position,
- has an electronics housing (16) connected to the inner tube (3) in a gas-, liquid-tight manner,
- 30 which is connected to a securing element (18) in a gas- and liquid-tight and detachable manner, wherein the securing element (18) preferably consists of or comprises a terminal, removable, preferably screwable, transport lock (18), wherein
- the transport lock (18) is designed in the installed state to prevent accidental and unintentional transfer of the inner tube from the hot-steam-sterilization position to the measuring position,
- 35 and to allow movement after removal; wherein
- the end of the inner tube released by the transport lock (18) has at least a third overhang (21) which is designed to prevent movement of the inner tube (3) and the associated support (4) containing the sensor element (5) beyond the measuring position,

(iii) the support (4) is non-detachably connected to the inner surface of the inner tube with a portion of its outer shell facing away from the medium, preferably with a medium-facing end portion; and

(iv) the at least one sensor element (5) is designed for receiving a value dependent on a measurand of a medium, wherein the sensor element is in gas contact with an interior of the sensor, the support (4) is positioned in the irradiation position in the cavity of the outer tube (7) in such a way that at least one gap (22) is arranged between the support (4) and the cavity of the outer tube (7), so that the interior of the sensor and the sensor element (5) arranged in the support (4) are in contact with the surroundings, preferably in gas contact,

in the hot-steam-sterilization position, the support (4) is positioned in such a way that the medium-facing end portion of the support (4) gas-tightly seals the sensor interior and the sensor element (5) located in the support (4) with respect to the surroundings of the sensor, and

in the measuring position, the support (4) is positioned in such a way that the sensor element (5) is positioned so as to be in contact with the surroundings, preferably with the medium to be measured (6), following hot-steam-sterilization, wherein preferably the surroundings and the medium to be measured are sterilized.

2. The in-line sensor (1) according to claim 1, wherein the at least second connecting element (21) is arranged on the shell (17) relative to the third connecting element (11) on the inner wall of the outer tube (10) closer to the end facing away from the medium along the longitudinal axis (L) of the in-line sensor.

3. The in-line sensor (1) according to claim 1 or 2, wherein the at least first (9) and the at least second connecting element (21) and the third (11) and the at least fourth (14) connecting element are at least partially, preferably completely, complementary to each other.

4. The in-line sensor (1) according to any of the preceding claims, wherein a first, second, third or fourth connecting element, on the end facing away from the medium, comprises a stepped shoulder that prevents movement of the inner tube in the opposite direction to the measuring position.

5. The in-line sensor (1) according to any of the preceding claims, wherein the first (12) and optionally the second sealing element (13) in the hot-steam-sterilization position surrounds at least a portion of the support (4) which faces the medium and which encloses the at least one sensor element (5) in a liquid- and gas-tight manner, and seals the sensor interior and the at least one sensor element (5) contained therein in a liquid- and gas-tight manner from the surroundings of the in-line sensor (1).

6. The in-line sensor (1) according to any of the preceding claims, wherein the support (5) is designed as a circular cylinder, preferably as a vertical circular cylinder, and on the surface, preferably on the outer peripheral surface, comprises at least one recess (24) and optionally a cavity in which the at

least one sensor element is arranged, wherein preferably the recess (24) is not encompassed by the portion of the support (5) which faces the medium.

7. The in-line sensor (1) according to any of the preceding claims, wherein the outer tube (2) has an opening on the medium side which is designed to bring at least one medium-facing end portion of the support (5) and the at least one sensor element (5) arranged in the support into contact with the surroundings, preferably with the medium to be measured in the measuring position, after hot-steam-sterilization, wherein preferably the surroundings, preferably the medium to be measured, is sterilized.

8. The in-line sensor (1) according to any of the preceding claims, wherein the sensor interior contains a desiccant, wherein in particular the desiccant consists of or contains a hydrophilic material, wherein the desiccant preferably consists of or contains a zeolite, glass or ceramic, and more preferably aluminum oxide and/or titanium oxide and/or silicon oxide.

9. The in-line sensor (1) according to any of the preceding claims, wherein the sensor comprises, in addition to the at least one sensor element, a temperature sensor which is configured to measure measurement values representing the temperature of the sensor interior, and which is preferably arranged in the inner tube.

10. The in-line sensor (1) according to claim 9, wherein the inner tube is designed such that the relative humidity prevailing within the housing does not exceed a value of 77% - preferably, of 23%, more preferably, of 3%, and, even more preferably, of 1% - given an external heat sterilization of the housing at a temperature of 110 °C over a time period of 15 min.

11. The in-line sensor (1) according to any of the preceding claims, wherein the outer tube (2) comprises a connection (24), preferably a thread (24), in particular a PG13.5 thread for installation in a fitting, pipeline, process vessel, in particular bioprocess vessel, preferably fermenter.

12. The in-line sensor (1) according to any of the preceding claims, wherein the in-line sensor element has at least one, preferably two anti-rotation devices (25) which prevent a rotational movement of the inner tube (3) relative to the outer tube (2) about the longitudinal axis (L) of the sensor.

13. The in-line sensor (1) according to any of the preceding claims, wherein the sensor has an amperometric or potentiometric reference system.

14. The in-line sensor (1) according to any of the preceding claims, wherein the at least one sensor element is a biosensor element, wherein the biosensor element comprises at least one biological recognition element for the analyte, wherein the biological recognition element is preferably a protein, preferably an enzyme.

15. The in-line sensor (1) according to claim 15, wherein the sensor element is an enzyme-based sensor element, preferably a lactate oxidase, glutamate oxidase, glutaminase or glucose oxidase, more preferably a glucose oxidase-comprising sensor element.

16. The in-line sensor arrangement (1) comprising an in-line sensor according to any of the preceding claims, wherein the in-line sensor arrangement has an electronics housing at the end facing away from the medium, to which the measuring circuit used for acquiring measurement values can be electrically connected, wherein the measuring circuit is designed to be electrically connected to a higher-level evaluation or control unit, which receives and further processes the measurement signals output by the measuring circuit.

17. The in-line sensor arrangement according to claim 16, wherein the measuring circuit is preferably arranged outside the sensor.

18. A method for manufacturing a sensor (1) according to any of the preceding claims, comprising the steps of:

(i) positioning the inner tube (3) inside the outer tube in the first irradiation position,

(ii) installing the transport lock (18)

(iii) gas-tightly packaging the sensor (1) within at least one radiation-sterilizable flexible packaging, preferably within at least one radiation-sterilizable bag, wherein steps (i) to (iii)

are carried out under a protective gas atmosphere.

19. The method according to claim 18, wherein before step (i) the inner tube is filled with a desiccant.

20. The method for putting into operation an in-line sensor (1) according to any of claims 1 to 16, and comprising the steps, following the method steps of claim 18 or 19, of:

(iv) sterilizing the sensor enclosed in flexible packaging containing the sensor element by means of sterilizing radiation

(v) transferring the sensor from the irradiation position to a hot-steam-sterilization position in a sterilized packaging, under a protective gas atmosphere, by moving the inner tube (3) along the longitudinal axis of the sensor (1) in the direction of the medium (6) to be measured, wherein the interior of the sensor containing the sensor element (5) is enclosed in the sterilized protective gas atmosphere.

(vi) unpacking the sensor from the sterilized bag

(vii) mounting the sensor on a process vessel

(viii) heat-sterilizing the sensor, preferably by hot steam, wherein sterilization is preferably carried out by autoclaving or on-site sterilization,

(ix) removing the transport lock (19) after completion of the heat sterilization

(x) moving the inner tube (3) into the measuring position and bringing the sensor element (5) into
5 contact with the medium to be measured, preferably bringing it into contact aseptically, and

(xi) connecting the electronics housing to an evaluation and/or control unit.