A device for preparing a DNA product by means of Capillary Polymerase Chain Reaction

TECHNICAL FIELD

The present invention relates to a device for preparing a DNA product by means of Capillary Polymerase Chain Reaction; a manufacturing device for a pharmaceutical product; a manufacturing module for a pharmaceutical product; a method for preparing a DNA product by means of Capillary Polymerase Chain Reaction; the use of the device for preparing a DNA product by means of Polymerase Chain Reaction; and the use of the device for a production of a pharmaceutical product.

BACKGROUND OF THE INVENTION

Active pharmaceutical ingredients (APIs) in the form of biomolecules are used today largely in therapies of a variety of diseases. Such biomolecules are e.g. therapeutic antibodies, peptides and nucleic acids. Therapeutic nucleic acids including DNA molecules and RNA molecules.

RNA represents an emerging class of drugs. RNA-based therapeutics include mRNA molecules encoding antigens for use as vaccines. For the manufacturing of RNA, a DNA template is typically used in an RNA in vitro transcription reaction. Such a DNA template may be obtained by polymerase chain reaction (PCR). Accordingly, the production of DNA in the meaning of amplification of DNA by PCR is a critical step for the manufacturing of RNA as API.

Moreover, DNA as such may serve as API, for example DNA vaccines against Coronavirus are currently under clinical development. For the manufacturing of DNA in large amounts, i.e. for the amplification of DNA, a polymerase chain reaction (PCR) may be used.

Currently established manufacturing processes for APIs in the form of nucleic acids approved by regulatory authorities typically implement many separate manufacturing steps, all of which must comply with GMP-standards. Such steps are typically carried out in GMP-compliant rooms that are present in production plants and thus not portable. Furthermore, the rooms are typically set up for the production of a specific biomolecule and are thus not flexible but need to be rebuilt to a rather large extent if a different nucleic acids needs to be produced. In summary, the manufacturing of nucleic acids at API-grade requires a large degree of manual handling in a GMP-regulated, rather inflexible and fixed laboratory, executed by well-trained technical staff. In consequence, current established manufacturing processes are time consuming, cost intensive, and require a lot of laboratory space and laboratory equipment.

SUMMARY ~~OF THE INVENTION~~

As outlined above, there is the problem associated with common manufacturing processes for nucleic acids, in particular DNA and RNA, as APIs or intermediates during the production process of APIs that the processes are rather inflexible, not portable and typically require a large degree of manual handling of well-trained technical staff. Thus, there is a need for providing an improved device for preparing/amplifying in particular DNA and a corresponding manufacturing device comprising such a device, which is more flexible. The manufacturing device

should in particular provide the benefits to be operated under GMP-compliant conditions, to be portable and/or to be automated. Such a manufacturing device would reduce the time for manufacturing the API (e.g. DNA) or an intermediate (e.g. DNA that may serve as template for RNA production, wherein the RNA is the API) tremendously which is particularly important in the context of an outbreak of a virus (e.g. pandemic outbreak or local outbreak). Such a portable API / intermediate manufacturing device (comprising the device for preparing/amplifying in particular DNA, which may be referred to as "PCT reactor") could be easily shipped, installed and operated in pandemic hotspot regions around the globe and would therefore allow for a rapid production of a vaccine in said region. Therefore, it is of paramount importance that the manufacturing device of the invention is configured to produce nucleic acids APIs / intermediates under GMP-compliant conditions, and that a corresponding "PCR reactor" is configured to be operable in such a manufacturing device.

The above problem is solved by the subject-matter of the independent claims, wherein further embodiments thereof are provided in the dependent claims.

In **a first aspect**, the present ~~invention~~ disclosure is directed to a device for ~~preparing a~~ amplifying DNA ~~product~~ by ~~means of Capillary~~ Polymerase Chain Reaction (PCR). The "preparing a DNA product by means of Capillary PCR" may alternatively be referred to as "amplifying DNA by Capillary PCR" or "amplifying DNA by PCR". The device comprises a tube for guiding a PCR liquid, a first compartment, ~~and at least~~ a second compartment and a third compartment. The tube is wound ~~at least from~~ through the first compartment and from the first compartment to and through the second compartment, ~~and~~ from the second compartment (back) to and through the third compartment, and from the third compartment to the first compartment, wherein the tube wound from compartment to compartment forms a helical stack of tube windings and each tube winding represents one PCR cycle, wherein the tube comprises a PCR liquid inlet and a DNA product outlet. Typically, each tube winding represents one PCR cycle. The first compartment, ~~and~~ the second compartment and the third compartment each comprises means to adjust the temperature in the compartment to prepare the DNA product based on the PCR liquid, wherein the first compartment is configured to provide a temperature for denaturation, ~~and~~ the second compartment is configured to provide a temperature for annealing ~~and/or elongation~~, and the third compartment is configured to provide a temperature for elongation; wherein septum walls are arranged between the compartments to insulate the compartments from each other, wherein the septum walls comprise through holes for the tube to extend from one compartment to the next.

In preferred embodiments, the device for preparing a DNA product by means of Capillary Polymerase Chain Reaction (PCR) is not a microfluidics device or dimensioned to operate as a microfluidics device. In preferred embodiments, the device for preparing a DNA product by means of Capillary Polymerase Chain Reaction (PCR) is not dimensioned or configured to operate as an analytical PCR device. In preferred embodiments, the device for preparing a DNA product by means of Capillary Polymerase Chain Reaction (PCR) is dimensioned or configured to operate as an device for the preparative production of DNA (e.g. for the production of more than 1 mg DNA product, optionally even for the production of DNA in g-amounts, e.g. the production of 5 g DNA). If run in a continuous mode, the output is essentially unlimited such that e.g. a very large amount of DNA in g-amounts can be provided, in particular DNA serving as template DNA in a subsequent RNA in vitro transcription reaction when the overall aim is to produce RNA.

In an embodiment, the device is not constructed such that a recirculation of the PCR liquid inside the device and/or tube comprised in the device is possible but rather, as noted above, the tube is wound in a helical stack of tube windings, wherein the tube is at no position reconnected to a previous section of the tube (accordingly, the

PCR liquid enters the tube at the first end of the tube, stays inside the tube during all PCR cycles and leaves the tube at the second end with DNA product having been formed). In an embodiment, the device does not comprise a closed loop (which may e.g. be formed by the tube or by reaction tanks connected via the tube) for the PCR liquid. In an embodiment, the device does not comprise a closed loop for the PCR liquid connected to a valve, wherein the valve would allow the flow of the PCR liquid and the DNA product, respectively, into a separate tube exiting the device.

In **a second aspect**, the present ~~invention~~ disclosure is directed to a manufacturing device ~~for a pharmaceutical product~~ comprising ~~the~~ a device for ~~preparing a~~ amplifying DNA ~~product by means of Capillary Polymerase Chain Reaction of~~ according to the first aspect, further comprising a process chamber, a technical chamber and a control unit configured to control a gas flow through the process chamber as a gas shower.

In an embodiment, the manufacturing device for a pharmaceutical product comprises the device for preparing a DNA product by means of Capillary Polymerase Chain Reaction as described in the first aspect and at least one further functionality (e.g. additional chambers, additional units, a housing, etc.). In a preferred embodiment, the manufacturing device for a pharmaceutical product according to the second aspect comprises a process chamber, a technical chamber and the device for preparing a DNA product by means of Capillary Polymerase Chain Reaction as described in the first aspect.

Description of the manufacturing device and preferred embodiments thereof

The manufacturing device for a pharmaceutical product can generally be understood as a closed housing with different chambers for different purposes.

The process chamber is suitable and used for manufacturing the pharmaceutical product. The process chamber may also be referred to as “wet part” of the manufacturing device in a sense that essentially all wet processes during the production process take place in the process chamber. “Wet processes” means e.g. the provision of buffers and/or reactants and/or products to and from vessels or to and from chromatographic columns, the collection of waste fluid or waste gases, etc., as well as any connections of such buffers and/or reactions and/or products (e.g. connections in the form of flexible tubes). Such wet processes should ideally be separated from any technical media supply (in particular electric supply such as power cables) in order to render impossible or at least minimize accidents due to leakage of liquids in the process chamber and possible consequences thereof, in particular due to voltage. Should accidents due to leakage occur in the process chamber, safety is improved as there is the afore-mentioned separation, and it will only be required to clean the process chamber. The device according to the first aspect is located in the process chamber.

The technical chamber is suitable and used for providing technical support e.g. for housing apparatus, as e.g. a pump, a motor, a mixer, a processor or the like, which are not in direct contact with the process media. The technical chamber is typically suitable and used for providing (e.g. housing) technical media supply, which is in particular power supply, e.g. a power supply for an apparatus/unit that is located in the process chamber and that is in direct contact with the process media. The technical chamber may also be referred to as “dry part” of the manufacturing device in a sense that essentially no wet processes as defined above take place in the technical chamber. As noted above, this *inter alia* results in increased safety. One may refer to the technical chamber as being “not as clean” as the process chamber since the required level of cleanliness in the technical chamber is lower than in the process chamber. The technical media supply for the device according to the first aspect is located in the technical chamber.

The chambers may be separated by a separation element, which is plate-shaped, in particular plate-shaped when looking at the separation element from the process chamber. Thus, as will be outlined below, in order not to disturb the gas flow, the separation element may comprise at least one appendix with an opening towards the process chamber and an extension in the direction of the technical chamber, where apparatus may be housed that are in contact with the process media, in particular the device according to the first aspect.

In another, less preferred embodiment, vice versa, the appendix may also have an opening towards the technical chamber and an extension in the direction of the process chamber. In all cases, the appendix may be closable by a cover.

In an embodiment, the manufacturing device comprising the device for preparing a DNA product by means of Capillary Polymerase Chain Reaction further comprises a leakage sensor arranged in the appendix outside the device for preparing a DNA product. The leakage sensor may increase the safety of the device for preparing a DNA product. As noted above in the first aspect, the manufacturing device may also comprise the second part of a proximity sensor, wherein the first part is located at the device of the first aspect. Once the device has been installed properly in the manufacturing device, the two parts of the proximity sensor are connecting and preferably signaling that the installing was successful and/or preferably only then the device can successfully be started and operated. Accordingly, the proximity sensor comprising the two parts may also be active during operation and result in an alarm and/or stop of the operation once the two parts of the proximity sensor lost their connection.

In an embodiment, the pump unit for pumping the PCR liquid through a tube of the device for preparing a DNA product is arranged outside the device of the first aspect. It is preferred that the pumping unit is arranged in the process chamber of the manufacturing device for a pharmaceutical product. Alternatively, the pumping unit may be an external pumping unit. The external arrangement may save space within the manufacturing device and/or may allow a use of a powerful pumping unit. The pumping unit may be a pump.

In an embodiment, the manufacturing device comprising the device for preparing a DNA product by means of Capillary Polymerase Chain Reaction further comprises a coupling unit arranged at the casing of the manufacturing device for a pharmaceutical product and configured to couple the manufacturing device for a pharmaceutical product to another manufacturing device. The coupling unit may allow and ease a coupling of two or more manufacturing devices. A resulting manufacturing module is described herein in an example~~the third aspect~~.

The manufacturing device for a pharmaceutical product can be understood as a closed housing with a technical chamber and a process chamber. In an embodiment, the housing is sealed relative to the environment. In the same or another embodiment, the process chamber is sealed relative to the technical chamber. Throughout this application, the term “sealed” can be understood as compliant with at least IP64. IP codes are based on Degrees of protection provided by enclosures (IP Code) (IEC 60529:1989 + A1:1999 + A2:2013); German version EN 60529:1991 + A1:2000 + A2:2013 and/or ISO 20653:2013-02 Road vehicles - Degrees of protection (IP code) - Protection of electrical equipment against foreign objects, water and access. The term “sealed” can be understood as dust-tight and protection against splashing of water. “Dust-tight” can be understood as no ingress of dust and complete protection against contact. For testing, a vacuum is typically applied, test duration of up to 8 hours based on airflow, details can be found in above cited standards. “Protection against splashing of water” can be understood as water splashing against an enclosure from any direction shall have no harmful effect, utilizing either an oscillating fixture for 10 minutes or a spray nozzle with no shield for 5 minutes minimum, details can be found in above cited standards. A sealed housing or a sealed process chamber may have the benefit to be in particular clean, which means to have and to maintain low levels of particulates, such as dust, airborne organisms, or vaporized particles.

In an embodiment, the process chamber is a clean room and/or is configured to be at least a grade D room according to the above mentioned EU guidelines for good manufacturing practice for medicinal products, annex 1. Preferably, the process chamber is configured to be at least a grade C room. More preferably, the process

amplification of the specific DNA of interest, and this easy handling and adaption, respectively, may be referred to as “plug and play” system.

In an ~~third aspect~~example, the present invention is directed to a manufacturing module for a pharmaceutical product. The manufacturing module comprises at least two manufacturing devices including a device according to the second aspect. The at least two manufacturing devices are coupled with each other. The coupling may allow a mechanical coupling of the at least two manufacturing devices. The coupling may allow a fluid communication and coupling of the at least two manufacturing devices. The coupling may allow a data communication and coupling of the at least two manufacturing devices. The fluid communication includes in particular the transport of a pharmaceutical product from one device to another device, for example the transport of a DNA template after its purification and/or filtration in a first device from this first device to a second device, wherein the DNA template may then be used in an RNA generation unit comprised in the second device.

The manufacturing module may in particular be for the production of DNA template and then comprise a process media supply unit, a mixing unit, a device according to the first aspect (which may also be referred to as “DNA template generation unit”), an optional DNA modification unit, a purification unit and a filtration unit, wherein the units are preferably connected in the order as listed and the module is configured to produce template DNA. The amplification process (or “DNA template generation process”) is carried out using the device according to the first aspect.

The manufacturing module comprises a manufacturing device for a pharmaceutical product according to the second aspect and may further comprise at least one manufacturing device selected from the group consisting of a manufacturing device comprising a process media supply unit and a mixing unit, a manufacturing device comprising a purification unit, and a manufacturing device comprising a filtration unit.

In one embodiment, the manufacturing module comprises (i) a first manufacturing device comprising a process media supply unit and a mixing unit, (ii) a second manufacturing device according to the second aspect, (iii) a third manufacturing device comprising a purification unit and (iv) a fourth manufacturing device comprising a filtration unit, wherein the devices are preferably connected in the order as listed. Such a manufacturing module is configured to produce template DNA, preferably from DNA (optionally de-novo synthesized DNA) that is provided in the form of process media supply in the PCR liquid. In other words, such a manufacturing module is configured to produce from a small amount of DNA, which may be de-novo synthesized DNA and which may be produced by a preceding manufacturing module, a large amount of template DNA. This template DNA may optionally be modified by a DNA modification unit comprised in yet another manufacturing device.

This template DNA can in particular be used when producing RNA, preferably mRNA, by RNA in vitro transcription. Accordingly, either in a combined or in a separate manufacturing module, an RNA generation unit (for transcribing the obtained DNA into RNA) may be comprised in.

In one embodiment, the manufacturing module comprises a process media supply unit, a mixing unit, a de-novo DNA synthesis unit, a device according to the first aspect (which may be referred to as “DNA template generation unit”), optionally a DNA modification unit, a purification unit, a filtration unit, a formulation unit and an RNA generation unit, wherein the units are preferably arranged in the order of i) a process media supply unit, ii) a mixing unit, iii) a de-novo DNA synthesis unit, iv) a purification unit, v) a filtration unit, vi) a process media supply unit, vii) a mixing unit, viii) a device according to the first aspect, optionally in combination with a DNA modification

magnetic particles and that the bioreactor comprises a magnet for mixing the reaction solution including the DNA immobilized on magnetic particles.

In an embodiment, the purification unit comprises an HPLC unit, preferably a unit for performing RP-HPLC. Particularly preferred in that context is RP-HPLC using a method disclosed in WO2008/077592 preferably using a porous, non-alkylated poly(stryrene-divinylbenzene) reverse phase, wherein the reverse phase is formed by beads or occurs as a polymerized block (e.g. monolithic). Alternatively, or in addition, the purification unit may comprise an affinity chromatography unit, preferably an oligo dT purification unit for affinity purification of polyadenylated nucleic acid, in particular RNA, via oligo dT functionalized matrices or beads or columns (e.g. as described in WO2014152031A1). Alternatively, or in addition, the purification unit may comprise an anion exchange chromatography unit. Alternatively, or in addition, the purification unit may comprise a unit for nucleic acid precipitation and a unit for purifying said precipitated nucleic acid (e.g. using TFF or centrifugation or filtration). Alternatively, or in addition, the purification unit may comprise a unit for dsRNA removal e.g. a unit that involves RNase III treatment or a unit that involves a step of cellulose-based dsRNA purification. The purification unit may be used to purify in particular a nucleic acid, preferably the template DNA obtained in the de-novo DNA synthesis unit, the DNA obtained in the device according to the first aspect and/or the RNA obtained in the RNA generation unit. In preferred embodiments, the purification unit, in particular the purification unit for purifying RNA comprises an RP-HPLC unit and an oligo dT purification unit and, optionally, a unit for dsRNA removal.

In an embodiment, the filtration unit comprises a tangential-flow filtration unit. Particularly preferred in that context is tangential flow filtration as described in WO2016/193206, wherein TFF is used for diafiltration and/or concentration and/or purification of a nucleic acid. The filtration unit may be used to filter in particular a nucleic acid, preferably the template DNA or the RNA, after the purification unit. It can also be preferred that the filtration unit comprises a sterile filter, preferably a sterile filter with a size of 0.22 µm, in order to sterile-filter in particular a formulation comprising the RNA, in particular mRNA, more particularly LNP-formulated mRNA.

In a preferred embodiment, the fill-and-finish unit comprises a filling and/or dosing machine. The fill-and-finish unit is configured to fill a formulated pharmaceutical product, in particular formulated active pharmaceutical ingredient (in particular the formulated RNA, more particularly the LNP-formulated mRNA) into suitable vials, such as glass vials in an amount that corresponds to a single dose or multiple doses of the formulated active pharmaceutical ingredient. Typically the vials, such as the glass vials, are closed with caps (e.g. aluminium caps) under sterile conditions. In embodiments, the fill-and-finish unit comprises a freezing unit for freezing the obtained drug product to at least -20°C, preferably to at least -60°C or -80°C.

In **a ~~fourth~~ third aspect**, the present ~~invention~~ disclosure is directed to a method for ~~preparing~~ amplifying ~~a~~ DNA ~~product~~ by means of ~~Capillary~~ Polymerase Chain Reaction. The method ~~for preparing a DNA product~~ comprises the following steps, not necessarily in this order:

- providing a first compartment, a second compartment, a third compartment and a tube, wherein the tube is wound ~~at least~~ through the first compartment and from the first compartment to and through the second compartment, and from the second compartment to the third compartment, and from the third compartment to the first compartment, wherein the tube wound from compartment to compartment forms a helical stack of tube windings and wherein septum walls (14) are arranged between the compartments to insulate the compartments from each other, wherein the septum walls (14) comprise through holes for the tube (6) to extend from one compartment to the next,

- providing means to adjust a separate temperature in each compartment, and
- guiding a PCR liquid through the tube and thereby through the separate temperatures in each compartment to prepare the DNA product based on the PCR liquid.

The method according to the present invention for preparing a DNA product allows for a flexible adaption to different conditions, requirements and e.g. quantities of DNA. The present method allows for the preparation of large quantities of DNA (e.g. more than 2 mg per reaction, even up to g-amounts). Further, the preparation of a DNA product may be scalable. The present method for preparing a DNA product allows for a very fast preparation of a DNA product and thereby also a fast manufacturing of a pharmaceutical product. Also a change and adaption of the device for preparing a DNA product to a specific DNA product may be very fast. There may be no need for adjustment or calibration steps. There may be no or fewer need for cleaning steps. The turnover time for e.g. a vaccine manufacturing may be less than about a week.

In an embodiment, the temperature in the first compartment is configured for a denaturation step of the Polymerase Chain Reaction, the temperature in the second compartment is configured for an annealing step of the Polymerase Chain Reaction and optionally also for an elongation step of the Polymerase Chain Reaction.

In an embodiment, the temperature in the first compartment is in a range of about 85°C to about 105°C, preferably about 98°C. In an embodiment, the temperature in the second compartment is in a range of about 45°C to about 72°C, preferably about 60°C to about 72°C.

In an embodiment, the method comprises the provision of a third compartment. The tube is wound at least from the second compartment to the third compartment, and then back to the first compartment. The temperature in the third compartment is configured for an elongation step of the PCR, preferably in a range of about 65°C to about 75°C, preferably about 72°C.

In an embodiment, the method for preparing a DNA product is carried out under GMP-compliant conditions.

In an embodiment, the means to adjust a separate temperature in each compartment may be the provision of a separate thermal medium flow through each compartment by means of a thermal medium inlet and a thermal medium outlet in each compartment (to adjust a separate temperature in each compartment).

In another embodiment, the means to adjust a separate temperature in each compartment may be a heating unit (in particular a heating cartridge) and optionally a cooling unit (in particular a thermoelectric cooler) comprised in each compartment (optionally connected to a ventilator).

In **a fourth ~~fifth~~ aspect**, the present ~~invention~~ disclosure is directed to the use of the device for preparing a DNA product according to the first aspect ~~for preparing a DNA product~~ by means of ~~Capillary~~ Polymerase Chain Reaction~~,~~. **In a fifth aspect**, the present disclosure is directed to the use of the manufacturing device for a pharmaceutical product product according to the second aspect ~~for the production of a pharmaceutical product, and the use of the manufacturing module according to the third aspect for the production of a pharmaceutical product~~.

The pharmaceutical product may be formulated. The pharmaceutical product is preferably an active pharmaceutical ingredient in the form of a biomolecule or any precursor or any intermediate thereof, wherein the biomolecule is preferably a nucleic acid, more preferably DNA. The production is preferably GMP-compliant.

In an embodiment, the above uses are automated. This means the use or the operation of the device for preparing a DNA product by means of Capillary Polymerase Chain Reaction according to the first aspect, the

CLAIMS

1. A device (1) for ~~preparing~~ amplifying ~~a~~ DNA ~~product~~ by ~~means of Capillary~~ Polymerase Chain Reaction (PCR), comprising:
   - a tube (6) for guiding a PCR liquid,
   - a first compartment (7), ~~and~~
   - ~~at least~~ a second compartment (8), and
   - a third compartment (15),

   wherein the tube (6) is wound ~~at least~~ through the first compartment (7) and from the first compartment (7) to and through the second compartment (8), ~~and~~ from the second compartment (8) to and through the third compartment (15), and from the third compartment (15) to the first compartment (7), wherein the tube (6) wound from compartment to compartment forms a helical stack of tube windings and each tube winding represents one PCR cycle, wherein the tube (6) comprises a PCR liquid inlet (20) and a DNA product outlet (25), and

   wherein the first compartment (7), ~~and~~ the second compartment (8) and the third compartment (15) each comprises means to adjust the temperature in the compartment to prepare the DNA product based on the PCR liquid, wherein the first compartment (7) is configured to provide a temperature for denaturation, ~~and~~ the second compartment (8) is configured to provide a temperature for annealing and~~/or~~ the third compartment (15) is configured to provide a temperature for elongation;~~.~~

   wherein septum walls (14) are arranged between the compartments to insulate the compartments from each other, wherein the septum walls (14) comprise through holes for the tube (6) to extend from one compartment to the next.

~~2. The device (1) for preparing a DNA product according to claim 1, comprising~~
   ~~- a first compartment (7),~~
   ~~- a second compartment (8), and~~
   ~~- a third compartment (15),~~
   ~~wherein the tube (6) is wound from the first compartment (7) to the second compartment (8), from the second compartment (8) to the third compartment (15), and from the third compartment (15) to the first compartment (7),~~
   ~~wherein the first compartment (7), the second compartment (8) and the third compartment (15) each comprises means to adjust the temperature in the compartment to prepare the DNA product based on the PCR liquid, wherein the first compartment (7) is configured to provide a temperature for denaturation, the second compartment (8) is configured to provide a temperature for annealing and the third compartment (15) is configured to provide a temperature for elongation.~~

~~3. The device (1) for preparing a DNA product according to claim 2, wherein the tube (6) is wound through the first compartment (7) and from the first compartment (7) to and through the second compartment (8), from the second compartment (8) to and through the third compartment (15), and from the third compartment (15) to the first compartment (7).~~

~~4. The device (1) for preparing a DNA product according to any one of claims 1 to 3, wherein each tube winding represents one PCR cycle.~~

5. The device (1) for preparing a DNA product according to any one of claims 1 to 4, wherein the tube (6) comprises a PCR liquid inlet (20) and a DNA product outlet (25).

6.2. The device (1) for preparing amplifying a DNA product according to claim 51, wherein the PCR liquid inlet (20) is connectable to a pump unit for pumping the PCR liquid through the tube (6).

7. The device (1) for preparing a DNA product according to claim 5, wherein the DNA product outlet (25) is for a continuous preparation of the DNA product or wherein the DNA product outlet (25) is a closable DNA product outlet (25) for a discontinuous preparation of the DNA product.

8. The device (1) for preparing a DNA product according to any one of the preceding claims, wherein septum walls (14) are arranged between the compartments to insulate the compartments from each other.

9. The device (1) for preparing a DNA product according to claim 8, wherein the septum walls (14) comprise through holes for the tube (6) to extend from one compartment to the next.

10. The device (1) for preparing amplifying a DNA product according to any one of the preceding claims 1 or 2, wherein each compartment comprises a heating unit (31) and optionally a cooling unit (32, 33) as the means to adjust the temperature in each compartment; or .

11.3. The device (1) for preparing a DNA product according to any one of claims 1 to 9, wherein each compartment comprises a thermal medium inlet (12) and a thermal medium outlet (13) as the means to adjust the temperature in each compartment, namely to provide a separate thermal medium flow through the first compartment (7), the second compartment (8) and the optional third compartment (15) to adjust a separate temperature in the first compartment (7), the second compartment (8) and the optional third compartment (15).

12. The device (1) for preparing a DNA product according to claim 11, wherein the thermal medium inlet (12) and the thermal medium outlet (13) are arranged within each compartment to provide the thermal medium flow through the compartment essentially in a counter direction to a guiding direction of the PCR liquid in the tube (6).

13. The device (1) for preparing a DNA product according to claim 11 or 12, wherein the thermal medium inlet (12) is arranged at a lower position in each of the compartments and the thermal medium outlet (13) is arranged at an upper position in each of the compartments.

14.4. The device (1) for preparing aamplifying DNA product according to any one of the preceding claims, wherein the tube (6) extends within at least one and preferably in each of the compartments in a corrugated manner.

15. The device (1) for preparing a DNA product according to any one of the preceding claims, wherein a stacking direction of the helical stack of tube windings is different and preferably essentially perpendicular to a corrugation direction of the corrugated tube (6).

16.5. The device (1) for preparing amplifying a DNA product according to any one of the preceding claims, wherein each compartment forms a basin to be filled with a thermal medium or a thermal solid.

17.6. The device (1) for preparing a amplifying DNA product according to any one of the preceding claims, further comprising at least a stand (17) arranged in one of the compartments to provide a fixation point for the tube (6) and/or a deviation point for a corrugation of the tube (6).

18. The device (1) for preparing a DNA product according to claim 17, wherein the tube (6) extends partially or fully or more than once around an outer dimension of the stand (17).

19.7. The device (1) for preparing a amplifying DNA product according to claim 617 or 18, wherein the stand (17) is exchangeable and/or repositionable in the compartment.

20. The device (1) for preparing a DNA product according to claim 6, wherein the pump unit is arranged outside the compartments and preferably outside a shell (26) surrounding the compartments.

21. The device (1) for preparing a DNA product according to claim 6 or 20, wherein the pump unit is configured to provide a flow rate of the PCR liquid in a range of about 0.1 to about 10 mL/min, preferably about 0.2 to about 3 mL/min.

22. The device (1) for preparing a DNA product according to any one of the preceding claims, further comprising at least a sensor (21) arranged in at least one of compartments, wherein the sensor (21) is configured to detect a temperature, a flow rate or a leakage of the compartment.

23. The device (1) for preparing a amplifying DNA product according to any one of the preceding claims, wherein the tube (6) has a diameter in a range of about 0.5 mm to about 50 mm, preferably about 0.5 mm to about 1.5 mm, more preferably about 0.75 mm to about 1.25 mm; and/or.

24. The device (1) for preparing a DNA product according to any one of the preceding claims, wherein the tube (6) has a length between a tube inlet and a tube outlet in a range of about 10 m to about 200 m, preferably about 2550 m to about 50100 m; and/or.

25.8. The device (1) for preparing a DNA product according to any one of the preceding claims, wherein the tube (6) is dimensioned to contain PCR liquid in a range of about 10 mL to about 1500 mL, preferably about 20 mL to about 250 100 mL.

26.9. The device (1) for preparing aamplifying DNA product according to any one of the preceding claims, wherein the helical stack of tube windings comprises about 10 to about 50 windings, preferably about 15 to about 40.

27. The device (1) for preparing a DNA product according to any one of the preceding claims, wherein the device (1) for preparing a DNA product is configured to prepare about 1 mg and more of the DNA product per reaction, preferably in a range of about 1 to about 30 mg, more preferably in a range of about 15 to about 25 mg.

28. The device (1) for preparing a DNA product according to any one of the preceding claims, wherein the device (1) for preparing a DNA product is configured to prepare the DNA product in a range of about 50 µg to about 150 µg per mL PCR liquid, preferably about 75 µg to about 125 µg per mL PCR liquid.

29. A manufacturing device (10) for a pharmaceutical product comprising a device (1) for preparing a amplifying DNA product by means of Capillary Polymerase Chain Reaction according to any one of the preceding claims 1 to 9.

30.10. The manufacturing device (10) for a pharmaceutical product according to claim 29, further comprising a process chamber (2), and a technical chamber (3) and a control unit configured to control a gas flow through the process chamber (2) as a gas shower.

31. The manufacturing device (10) for a pharmaceutical product according to claim 30, further comprising a control unit configured to control a gas flow through the process chamber (2) as a gas shower.

32. The manufacturing device (10) for a pharmaceutical product according to claim 30 or 31, wherein at least the process chamber (2), preferably the manufacturing device (10), is operable according to the requirements of the EU guidelines for good manufacturing practice (GMP) for medicinal products, annex 1.

33.11. The manufacturing device (10) for a pharmaceutical product according to any one of claims 30 to 3210, further comprising a separation element (4) separating the process chamber (2) from the technical chamber (3), wherein the separation element (4) comprises an appendix (16) with an opening towards the process chamber (2) and protruding in the direction of the technical chamber (3), and wherein the device (1) for preparing amplifying a DNA product is insertable into the appendix (16).

34. The manufacturing device (10) for a pharmaceutical product according to claim 33, wherein a front face of the device (1) for preparing a DNA product ends essentially flush with the opening of the appendix (16) into the process chamber (2) when the device (1) for preparing a DNA product is inserted into the appendix (16).

35. The manufacturing device (10) for a pharmaceutical product according to any one of claims 29 to 34, wherein at least a handle (22) for handling the device (1) for preparing a DNA product in and/or out of the appendix (16) is positioned at the front face of the device (1) for preparing a DNA product.

36. The manufacturing device (10) for a pharmaceutical product according to any one of claims 29 to 35, wherein an intake for a PCR liquid (23) and/or an outfall for a DNA product (24) is/are positioned at the front face of the device (1) for preparing a DNA product.

37. The manufacturing device (10) for a pharmaceutical product according to any one of claims 29 to 36, wherein an intake for a thermal medium and/or an outfall for the thermal medium is/are positioned at a back plate of the device (1) for preparing a DNA product opposite to the front face of the device (1) for preparing a DNA product.

~~38. The manufacturing device (10) for a pharmaceutical product according to claim 37, further comprising a leakage sensor (21) arranged in the appendix (16) outside the device (1) for preparing a DNA product.~~

~~39. The manufacturing device (10) for a pharmaceutical product according to any one of claims 29 to 36, wherein a ventilator (34) and/or an air inlet (35) is/are positioned at a back plate of the device (1) for preparing a DNA product opposite to the front face of the device (1) for preparing a DNA product.~~

~~40. The manufacturing device (10) for a pharmaceutical product according to any one of claims 29 to 39, wherein the appendix (16) comprises exchange rails (27) to guide an exchange of the device (1) for preparing a DNA product with another device (1) for preparing a DNA product.~~

~~41. The manufacturing device (10) for a pharmaceutical product according to any one of claims 29 to 40, wherein a pump unit for pumping the PCR liquid through a tube (6) of the device (1) for preparing a DNA product is arranged outside the device (1) for preparing a DNA product, preferably wherein a pump unit for pumping the PCR liquid through a tube (6) of the device (1) for preparing a DNA product is arranged within the process chamber of the manufacturing device (10).~~

~~42. The manufacturing device (10) for a pharmaceutical product according to any one of claims 29 to 41, further comprising a coupling unit (18) arranged at the casing of the manufacturing device (10) for a pharmaceutical product and configured to couple the manufacturing device (10) for a pharmaceutical product to another manufacturing device (10).~~

~~43. A manufacturing module (100) for a pharmaceutical product, comprising a manufacturing device (10) for a pharmaceutical product according to any one of claims 29 to 42 and at least one manufacturing device selected from the group consisting of a manufacturing device (10) comprising a process media supply unit and a mixing unit, a manufacturing device (10) comprising a purification unit, and a manufacturing device (10) comprising a filtration unit.~~

~~44.~~12. A method for ~~preparing a~~ amplifying DNA ~~product~~ by means of ~~Capillary~~ Polymerase Chain Reaction (PCR), comprising:

- providing a first compartment (7), a second compartment (8), a third compartment (15) and a tube (6), wherein the tube (6) is wound ~~at least from~~ through the first compartment (7) and from the first compartment (7) to and through the second compartment (8) and from the second compartment (8) to and through the third compartment (15), and from the third compartment (15) to the first compartment (7), wherein the tube (6) wound from compartment to compartment forms a helical stack of tube windings and wherein septum walls (14) are arranged between the compartments to insulate the compartments from each other, wherein the septum walls (14) comprise through holes for the tube (6) to extend from one compartment to the next,
- providing means to adjust a separate temperature in each compartment, and
- guiding a PCR liquid through the tube (6) and thereby through the separate temperatures in each compartment to prepare the DNA product based on the PCR liquid.

~~45.~~13. The method according to claim ~~44~~12, wherein the temperature in the first compartment (7) is for denaturation, preferably in the range of about 85°C to about 105°C, preferably about 98°C; and/or~~.~~

~~46. The method according to claim 44 or 45,~~ wherein the temperature in the second compartment (8) is for annealing ~~and/or elongation~~, preferably in the range of about 45°C to about 72°C, preferably about 60°C to about 72°C; and/or wherein the temperature in the third compartment (15) is for elongation, preferably in the range of about 65°C to about 75°C, preferably about 72°C.

~~47. The method according to any one of claims 44 to 46, further comprising providing a third compartment (15), wherein the tube (6) is wound from the second compartment (8) to the third compartment (15) and from the third compartment (15) to the first compartment (7), and wherein the temperature in the third compartment (15) is for elongation, preferably in the range of about 65°C to about 75°C, preferably about 72°C.~~

~~48. The method according to any one of claims 44 to 47, wherein each compartment comprises a heating unit (31) and optionally a cooling unit (32, 33) as the means to adjust a separate temperature in each compartment.~~

~~49. The method according to any one of claims 44 to 47, wherein each compartment comprises a thermal medium inlet (12) and a thermal medium outlet (13) as the means to adjust a separate temperature in each compartment, namely to provide a separate thermal medium flow through the first compartment (7), the second compartment (8) and the optional third compartment (15) to adjust a separate temperature in the first compartment (7), the second compartment (8) and the optional third compartment (15).~~

~~50.~~14. Use of a device (1) according to any one of claims 1 to ~~28~~ 9 for preparing a DNA product by means of ~~Capillary~~ Polymerase Chain Reaction.

~~51.~~15. Use of a manufacturing device (10) according to ~~any one of~~ claim~~s 29 to 42~~10 or 11 ~~or of a manufacturing module (100) according to claim 43~~ for the production of a pharmaceutical product.