This checklist is intended for use in relation to aseptically manufactured / processed medical devices.

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| **Application ID (as it appears in the application form / change notification form)** |
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* *[X]* in this document: indicates a document to be named including page number - submitted for evidence. Grey guidance text may be replaced/deleted.
* In case of a Change Notification, please only fill in the applicable sections

# Short Product Description

*Note: Please replace grey italic text with respective information*

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| **Short description incl. picture of the device** - in case of changes, as far as relevant |
| Description of the device as far as relevant for aseptic manufacturing process (pictures for clearer understanding):  *To be added*  *Product Schematic and / or Photo of product, size, material, Intended Use / Intended Purpose according to IFU (inclusive total application duration, body contact, implantable, patient group), Packaging description, Picture*  Variants under assessment:  *To be added*  *Product variants (e.g. Same product in different SBS / Primary containers, Multiple products in same SBS)*  *Description of the Sterile Barrier System Specifications / Primary Packaging System / Container Closure System*  *Please describe the entire product presentation in terms of packaging system & layers (e.g. Plastic vial in pouch, Syringe in Double Blister)* |

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| **Manufacturing facility and Certification status of the applicable contract manufacturer** | |
| *Manufacturing site to be named* | *Please provide the applicable QMS Certificate 13485 or GMP license (including the full scope) of the used manufacturing site* |
| *CMO (Contract Manufacturing Organization) site to be named* | *Please provide the applicable QMS Certificate 13485 or GMP license (including the full scope) of the used CMO site, which is responsible and executing the aseptic processing / manufacturing.* |
| *Primary packaging manufacturer(s) to named* | *Please provide the applicable QMS certificate(s) 13485 or equivalent of the primary packaging supplier.*  *In case the primary container consists of different critical components (e.g. syringe barrel + syringe tip cap + rubber stopper + plunger rod) please provide the above requested information for each of the component manufacturer.*  *In case of Blow Fill Seal (BFS) equipment, please provide the above information for the supplier of the extrusion polymer.* |

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| **External laboratories if used for sterilization validation and certification status of the laboratory** | |
| *Name of the laboratory* | *Please name the test done by the laboratory (e.g. Microbiology BI testing, Sterility testing, Bioburden, Residuals). Please provide the applicable QMS Accreditation Certificate (e.g. ISO 17025 or GLP)* |
| *Name of the laboratory* | *Please name the test done by the laboratory (e.g. Microbiology BI testing, Sterility testing, Bioburden, Residuals). Please provide the applicable QMS Accreditation Certificate (e.g. ISO 17025 or GLP)* |
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*Note: In case 13485 certification was not issued by a Notified Body, further steps may need to be taken as part of the review process (e.g. Critical Supplier Audit, full review of method qualification, etc.)*

*Note: In case CCIT is executed in-line (=100% in-process control) to the production process please refer to section 4 and fill out the respective section. The table below addresses the validation aspect of the sterile barrier system (SBS) itself.*

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| **Container Closure Integrity Testing (CCIT) / Packaging Validation, according to EN ISO 11607** | |
| Which layers of the packaging presentation are claimed as a sterile barrier? | *Please describe which packaging layers are considered for the packaging integrity validation. E.g. only the syringe barrel & rubber closure system, or vial in double blister with each layer claimed as an individual sterile barrier.* |
| Is the packaging process validated? | yes, for each packaging layer the validation is documented in *[X,p.y]*   no *please justify:* |
| Which method is used to validate the primary container closure integrity? | Dye Ingress Test   Vacuum Decay Method   Microbial Ingress Test   Helium Mass Spectrometry   High Voltage Leak Detection   Laser-based headspace analysis using H2, He, CO2, O2, H2O |
| Transport Simulation performed and every claimed sterile barrier challenged for integrity? | yes documented in *[X,p.y]*   no *please justify:* |
| Shelf-Life / Stability study for every claimed sterile barrier was performed and challenged for package integrity? | yes documented in *[X,p.y]*   no *please justify:* |

# Risk assessment of the aseptic manufacturing process

*Note: All critical steps shall be identified and addressed in a risk assessment (e.g. manual handling steps, raw material control, monitoring of the aseptic core zone). Please provide respective evidence that this risk assessment was carried out and subsequently, which measures result from this risk assessment with respect to the execution of the manufacturing process.*

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| **Risk assessment according to ISO 14971 and/or ICH Q9** | |
| Starting materials covered? | yes documented in *[X,p.y]*   no *please justify:*  *Please provide the risk assessment covering all starting materials for the aseptically manufactured medical device, such as chemical raw materials & primary container materials. More detailed information on this is requested below.* |
| Process risk assessment covered? | yes documented in *[X,p.y]*   no *please justify:* |

# Manufacturing Environment & Zoning Concept

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| **Cleanroom Zoning according to ISO 14644 series / EN ISO 13408 / EudraLex Vol.4 Annex 1 (cGMP)** | |
| Cleanroom floor plan / layout provided? | yes documented in *[X,p.y]*   no *please justify:*  *Please also include in the cleanroom layout the positions of the air locks, environmental monitoring locations and material & personnel flows and equipment locations. For better readability it may be good to present this on different versions of the same floor plan.*  *Please clearly indicate the core aseptic processing area (APA)* |
| Room classifications available? | yes documented in *[X,p.y]*   no *please justify:*  *Please provide a document including the specifications and acceptance criteria for each of the rooms, e.g. particle classification for “in operation” and “at rest”, microbiological classification (grade A/B/C/D), air exchange rate, recovery time, differential pressure etc.* |
| Have there been outliers in the Environmental Monitoring (EM) for the core aseptic processing area (APA) / Grade A classified zone and which actions have been taken? | *Please provide an overview document of the particulate / microbiological excursion, which measures have been taken and have these measures been effective in subsequent production?* |

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| **Utilities / Media** | |
| Is Clean Steam used? | yes documented in *[X,p.y]*   no *please justify:*  *Please provide the following information*   * *How is steam generated?* * *Water quality / specifications for the steam generator* * *Specifications and acceptance criteria for the Clean Steam* * *Monitoring history of the critical specified parameters for the past two (2) years* * *What is the monitoring frequency for the Clean Steam and how was this frequency established?* |
| Is Compressed Air used? | yes documented in *[X,p.y]*   no *please justify:*  *Please provide the following information:*   * *Specifications and acceptance criteria for the compressed air* * *Where is the compressed air applied and is it in direct contact with the aseptically manufactured medical device? E.g. for cleaning of processing debris* * *What is the monitoring frequency for the Compressed Air and how was this frequency established?* |
| Is Inert gas used? | yes documented in *[X,p.y]*   no *please justify:*  *Please provide the following information:*   * *Supplier(s)?* * *How is incoming gas quality controlled?* * *Where is the inert gas applied and is it in direct contact with the aseptically manufactured medical device? E.g. nitrogen gas overlay* * *Is the Inert gas sterile filtered (1x, 2x, 3x) and where is the sterile filtration integrated?* * *What is the maintenance frequency of the sterile grade filters?* |
| Are all water qualities documented? | yes documented in *[X,p.y]*   no *please justify:*  *Please list all used water qualities and their respective specifications and acceptance criteria (e.g. WFI, Purified Water, Tab water), including their mode of use (e.g. formulation, source for Reverse Osmosis, cleaning etc.).*  *For each applicable water qualities please provide the following*   * *Monitoring history of the critical specified parameters for the past two (2) years for each water quality* * *What is the monitoring frequency for each Water Quality and how was this frequency established?* |

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| **Realization of Aseptic Core zone / Aseptic Processing Area (APA) / Grade A zone** | |
| Specify the type | Isolator system(s) used and documented in *[X,p.y]*   RABS (Restricted Area Barrier System) system used and documented in *[X,p.y]*   Transfer systems(s) used documented in *[X,p.y]* |
| For Isolator Systems(s) please specify | *Please tick the applicable box below:*   Filling Line Isolator   Cell Therapy Isolator   Containment Isolator   Sterility Test Isolator  *Operating Mode:*   Positive pressure   Negative Pressure   No pressure differential to surrounding zone. *Please provide justification*  Respective documented evidence can be found in [X, p.y] |
| For RABS System(s) please specify  (RABS = *R*estricted *A*ccess *B*arrier *S*ystem) | oRABS (open RABS)   cRABS (closed RABS)   Active RABS   Passive RABS |
| For Transfer systems (independent of the above cases), please specify the type and the applicable decontamination method | Transfer Air Lock (e.g. materials & tools) needed during the processing operation)   RTP Port (Alpha-Beta-Port)  *Type of decontamination agent used in Transfer Air Lock:*   H2O2 (Vaporized Hydrogen Peroxide)   NO2 (Nitric Oxide)   PAA (Peracetic Acid))   ClO2 (Chlorine Dioxide)   Other: *Please specify*  Documented evidence can be found in [X, p.y] |

# Aseptic manufacturing process and process controls

*Note: Please provide a full and concise description of the aseptic manufacturing process starting from the raw materials to final finished product. The key manufacturing steps shall be identified.*

*A* ***flow chart****, indicating the single key manufacturing steps would be beneficial for an easier understanding. The flow chart is provided in document [X, p.y]*

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| **Sterilization and Depyrogenation of (Primary) Containers, Closures, Equipment and Components** | |
| Raw materials (i.e. for formulation, upstream process) sterility controlled? | yes process (step) is documented in *[X,p.y]*   no *please justify:*  *Please provide information on how the raw materials are sterilized before introduction into the Aseptic Core Zone (Grade A)*   Moist Heat (Autoclave), Validation document provided [X, p.y]   Dry Heat, Validation document provided [X, p.y]   Ethylene Oxide (EO), Validation document provided [X, p.y]   Irradiation, Validation document provided [X, p.y]   Other: *Please specify* and provide validation documentation  [X, p.y] |
| Intermediate product (i.e. final formulation) sterility controlled? | yes process (step) is documented in *[X,p.y]*   no *please justify:*  *Please provide information on how the intermediate product is sterilized before introduction into the Aseptic Core Zone (Grade A)*   Moist Heat (Autoclave), Validation document provided [X, p.y]   Dry Heat, Validation document provided [X, p.y]   Ethylene Oxide (EO), Validation document provided [X, p.y]   Irradiation, Validation document provided [X, p.y]   Other: *Please specify* and provide validation documentation  [X, p.y] |
| Primary packaging / Primary container supply and sterility controlled? | yes process (step) is documented in *[X,p.y]*   no *please justify:*  *Please provide information on how the primary packaging is sterilized before introduction into the Aseptic Core Zone (Grade A)*   Moist Heat (Autoclave), Validation document provided [X, p.y]   Dry Heat, Validation document provided [X, p.y]   Ethylene Oxide (EO), Validation document provided [X, p.y]   Irradiation, Validation document provided [X, p.y]   Other: *Please specify* and provide validation documentation  [X, p.y] |
| Equipment & Component sterility controlled? | yes process (step) is documented in *[X,p.y]*   no *please justify:*  *Please provide information on how the equipment itself and the key equipment components (e.g. sterilizing grade filters, pipework, sorting bowl, filling tubes, etc.) are sterilized before introduction into the Aseptic Core Zone (Grade A)*   Moist Heat (Autoclave), Validation document provided [X, p.y]   Dry Heat, Validation document provided [X, p.y]   Ethylene Oxide (EO), Validation document provided [X, p.y]   Irradiation, Validation document provided [X, p.y]   Other: *Please specify the method (e.g. H2O2, PAA, etc.)* and provide validation documentation  [X, p.y], |

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| **Clean-In-Place (CIP), if applicable, according to EN ISO 13408-4** | |
| Clean-In-Place validation available? | yes documented in *[X,p.y]*   no *please justify:* |
| Which substances need to be cleaned by this process | *Please provide a full list of substances that are processed on the equipment (also including non-medical device substances like active pharmaceutical formulations) and need to be cleaned prior to the next filling campaign.*  *Are worst-case substances identified and used for the cleaning validation study?* |
| How is the cleaning cycle executed? | Fully automated   Semi-automated with manual intermediate steps   Fully manual |

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| **Sterilize-In-Place (SIP), if applicable, according to EN ISO 13408-5** | |
| Sterilize-In-Place validation available? | yes documented in *[X,p.y]*   no *please justify:* |
| Key sterilization parameters used | *Please describe the sterilization parameters that need to be achieved at the determined worst-case location (cold spot) and a rationale for identifying the worst-case location.* |
| Biological Indicator used? | *Please provide the CoA (Certificate of Analysis) for the used biological indicator, referencing e.g. the microorganism, D-Value, z-Value, population* |

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| **Sterilizing Filter / Vent Filter, if applicable, according to EN ISO 13408-2** | |
| Is sterile filtration used? | yes process (step) is documented in *[X,p.y]*   no *please justify:* |
| Sterilizing grade filter specification | *Please specify*  Documented evidence found in [X, p.y] |
| Filter validation / Filter suitability available? (*for both filters, incoming filter as well as vent filter*) | yes documented in *[X,p.y]*   no *please justify:*  *Please specify which tests have been performed as part of the filter validation and where the test data and results are documented*   Bacterial viability test [X, p.y]   Filter compatibility test [X, p.y]   Filter extractable & leachable profile / adsorption test [X, p.y]   Bacterial retention test [X, p.y]   Custom fluid wetting test / wet integrity test [X, p.y] |
| Is filter integrity testing performed and justified? | yes process (step) is documented in *[X,p.y]*   no *please justify:*   Bubble point Test   Diffusion Test   Pressure Hold Test   Pre-Use Post Sterilization Integrity Testing (PUPSIT)   Post-Use Integrity Testing, *Please justify if only post-use testing is used* |

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| **Lyophilization, if applicable, according to EN ISO 13408-3** | |
| Validation protocol and report available? | yes documented in *[X,p.y]*   no *please justify:* |
| Freeze drying method used | Manifold drying   Batch drying   Bulk drying |
| Lyophilizer sterilized? | Before each load, *if not please justify*  *Please specify the used sterilizing agent:*   H2O2   Moist Heat   NO2   ClO2  Sterilization validation is documented in [X, p.y] |

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| ***In-line* (=100%) Container Closure Integrity Testing** | |
| Is container closure integrity testing performed in-line? | yes process (step) is documented in *[X,p.y]*   no |
| Which method is used for in-line integrity testing | Visual inspection (e.g. camera imaging solution, hyperspectral imaging, etc.)   High-voltage leak detection (HVLD)   Laser headspace analysis   Other optical inspection methods (e.g. Terahertz wavelength) |
| How is ensured that leaks are adequately detected? | *Please provide CCIT validation, including the determination of minimum detectable leak whole size [X, p.y]* |
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# Production related Information

## Used aseptic manufacturing equipment

*Note: Please replace grey italic text with respective information. Please add additional lines if required. In case of changes fill in as applicable.*

*In case of multiple package presentations (e.g. 2R, 5R, 10R), please separate into individual lines and indicate the min/max speed for each presentation*

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| **Equipment including Identifier (e.g. int. ID/ serial number)** | **Site** | **Product container type**  **[e.g. fill volume in ml]** | **Min & Max processing speed [objects/min]** | **Fill pump type** | **All sensors / measurement devices (internal + external sensors, dataloggers for validation) are calibrated** |
| *Superfill 3000 Blow-Fill-Sealer* | *Inhouse or external source* | *Glass vial 10R* | *160-200 vials/min* | *e.g. Rotary piston pump, mass flow controller, peristaltic pump, time-pressure system* | Yes  No |
| *Megafill 3000 syringe nest filling machine* | *Inhouse or external source* | *Glass vial 2R* | *300-420 vials/min* | *e.g. Rotary piston pump, mass flow controller, peristaltic pump, time-pressure system* | Yes  No |

## Only applicable to *Change* of Clean Room Control / Validation

*Note: Please replace grey italic text with respective information. Please add additional lines if required. In case of changes fill in as applicable.*

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| Cleanroom | *Please identify the cleanroom(s) where the manufacturing takes place, including ISO classification* |
| Are action and alert levels/limits set appropriately for the subsequent product bioburden in cleanroom processes? | yes documented in *[X,p.y]*   no *please justify:*  Acceptance criteria for “in operation” condition:  Airborne particles [*size*]: particles/m3  Airborne microbiological contamination: cfu/m3 *(and/or settle plates)*  Surface microbiological contamination: cfu/ surface area  Product bioburden: cfu *(type – spores, fungi, anaerobe, bacteria) The bioburden shall be known to a degree to make decisions on resistance* |
| Monitoring points are defined for the above-mentioned measurements | yes documented in *[X,p.y]*   no *please justify* |
| Was IQ, OQ, PO of the cleanroom successfully established? | yes documented in *[X,p.y]*   no *please justify:* |
| Is all measuring equipment in a calibrated state? | yes documented in *[X,p.y]*   no *please justify:* |
| Are utilities and media monitored? | yes documented in *[X,p.y]*   no *please justify:*  *Please specify what media and related acceptance criteria are defined.*  *e.g. for water, compressed air…* |
| Are environmental parameters defined? | yes documented in *[X,p.y]*   no *please justify:*  Please specify - where applicable:  Temperature:  Humidity:  Pressure gradient/Pressure level at each room:  Air change rates: |

## Validation Development Data / Aseptic Process Simulation as per EN ISO 13408-1

*Note: Please replace grey italic text with respective information. In case of changes fill in as applicable.*

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| Full media fill validation available? | yes documented in *[X,p.y]*   no *please justify:* |
| Are all possible interventions considered during the process simulation (worst-case)? | yes documented in *[X,p.y]*   no *please justify:* |
| What is the routine batch size and number of samples used for process simulation? | *Please specify the routine batch size and relate to the number of samples used for the process simulation.* |

# Routine Release

*Note: Please replace grey italic text with respective information*

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| **Routine Processing and Release Criteria** | |
| Routine release | Routine release criteria and procedure are described in document [X, p.y] |
| End-process controls / final product specifications | *Please provide a full list of test and acceptance criteria executed on the final finished product to confirm conformity including sample sizes.* |
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| **Release by client:** | | | | |
|  |  |  |  |  |
| **Date** |  | Signature |  | Full Name |
|  |  |  |  |  |
|  |  |  |  | Name of Legal Manufacturer |

*Note as to the signature’s relevance: If this document is officially signed, the provided rationales and data herein can be officially used by the reviewer. Otherwise, only the referenced documents can be used as evidence.*