The aim of this checklist is to summarize the provisions defined in the certified QM system that cover the manufacturing of certified medical devices for the processes of sterility assurance (sterilization) and packaging for terminally sterilized devices. This data will be assessed as part of quality management certification and surveillance. The summary will enable a directed and less iterative conformity assessment.

Of special interest are the requirements defined for triggering validation activities, the content of validation activities and their extent. The provisions shall assure that the QM system leads to the right conclusions for the processes, equipment and changes. The aim is to assure that substantial changes are identified and notified to the Notified body for further approval. Further guidance on reportable substantial changes is given at the end of this document.

In case of a complex documentation situation (e.g. multiple sterilization modalities in use) a separate checklist for each sterilization modality (EO, Irradiation, Moist heat …) may be beneficial or additional sections may be added in the document

[X] in this document: indicates a document to be referenced including page number. The respective document shall be part of the submitted documents for the assessment. Grey-colored guidance text provides additional explanatory information.

In case not all information to a specific requested item can be found within a single evidence document, please use specific document(s) and page(s) references, e.g. [Doc123, p. 3+4+8] for each individual bullet point.

# Quality management system in Relation to Packaging for Terminally Sterilized Devices:

Note: Please replace italic text with respective information.

|  |  |
| --- | --- |
| **Procedures relating to Packaging for Terminally Sterilized Devices** | |
| 1.1  QM provisions describing handling of equipment changes, relocations of packaging processes and if necessary, requirements when revalidation is performed (including handling of new packaging technologies):  EN ISO 11607-1, 9 EN ISO 11607-2, 5.7, MDR, Article 120 MDCG 2020-3, Chart E | The QM provisions are expected to address:   1. Contract packager   How is it assured:   * that appropriate validation (e.g. full / reduced) activities are triggered at the addition of a new contract packager/lines * Supplier control see item (e) below.   Evidence documented in *[X,p.y]*   1. Packaging equipment (machine, tool)  * How does the QM system assure qualification and validation including IQ, OQ and PQ for each internal (manufacturer owned) piece of equipment and process for each operating principle (fully automated, semi-automated, manual…)? * What is the statistical basis (i.e. appropriate sample sizes) for each validation activity and test and how are appropriate procedures applied? * For external equipment please refer to the sections on “new contract packager” and “supplier control”   Evidence documented in *[X,p.y]*   1. Relocation of equipment   How does IQ ensure that:   * all applicable media (e.g. electricity, air) are re-connected as in the original setup under consideration of potential mechanical impacts (e.g. vibration). * Machine operation and maintenance are kept the same. * How does the revalidation extent (OQ and PQ) for the equipment take into account:   + if equipment is disassembled / maintained   + moved assembled * In case of revalidation, how is the output for” equivalency” as described under the point “new sealing parameters” met?   Evidence documented in *[X,p.y]*   1. Supplier control   How is it assured:   * that appropriate certification and supplier control is established and continuously verified? * that external suppliers use qualified equipment and validated processes? * that appropriate quality agreements are in place how to handle changes in products, processes and responsibilities? * that these agreements assure the manufacturer possesses all relevant validation data from the supplier in his technical documentation?   Evidence documented in *[X,p.y]*   1. If applicable: Equipment equivalency:   How are the prerequisites/provisions for equivalence defined in the QM system?   * For a new candidate equipment of identical technology, as already in use, processing the identical material as the previously validated equipment, how is it assured:   + that (IQ), OQ, PQ for each individual candidate equipment is available and acceptance criteria are met?   + that candidate equipment is compared to the predicate equipment with defined requirements / acceptance criteria:   + the output of candidate equipment (e. g. seal strength at upper/nominal/lower limit) is within the validated window (e.g. seal strength ±%) of the predicate equipment   + packaging properties are maintained: seal width, peelability, seal integrity, absence of unacceptable material delamination * that a documented conclusion is present for the new equipment why the predicate design validation can be leveraged based on comparison * that in the case of no equivalency can be established, a full validation shall be triggered.   Evidence documented in *[X,p.y]*   1. New sealing parameters  * If applicable: Description how new process parameters or machines setting are evaluated to be equivalent with regards to the delivered output parameters at sealing (using adequate statistics, justified acceptable tolerance/variation in seal strength (and optional other parameters) in +-% from the fully validated process (of predicate equipment) * How are packaging properties maintained: seal width, peelability, seal integrity, absence of unacceptable material delamination   Evidence documented in *[X,p.y]*   1. New forming parameters  * In case of process parameters (setpoints) deviating from the predicate validated process - how is it assured that the output data such as essential dimensions meet the validated design?   Evidence documented in *[X,p.y]*   1. Are there any requirements for a time-based revalidation?  * What interval is set to regular revalidation of the packaging process?   Evidence documented in *[X,p.y]* |
| 1.2 QM provisions describing requirements on product adoption for new designs  MDR, Article 120  MDCG 2020-3, Chart E  EN ISO 11607-1, 9  EN ISO 11607-2, 5.7 | How do the QM system provisions address the impact of product changes on the packaging process as well as design? How do the QM system provisions define criteria that trigger an adequate partial or full revalidation?  How are the following aspects addressed:   1. New packaging material   In case of new packaging material, how is EN ISO 11607-1 compliance ensured in terms of the following:   * related physical data sheets meet a pre-defined specification: Critical parameters may be (but not limited to) minimum tensile strength, tear resistance, puncture resistance, air permeance, microbial barrier properties, thickness, chemical property and dimensions * suitability is adequate to not compromise biocompatibility of the packed product (e.g. cytotoxicity acc. ISO 10993-5 or USP).   Evidence documented in *[X,p.y]*   1. New packaging design  * How are changes in dimensions of the packaging design going through a risk assessment regarding potential impact on the validated predicate packaging design including usability? * How are changes in venting capability of packaging (e.g. label on breathable packaging portion), assessed regarding impact on sterilization? * How are changes in number of sterile barriers and protective packaging addressed by an assessment of the impact on sterilization, transport and usability? * How is it assured that completely new sterile barriers are fully validated (including performance testing and ageing)?   Evidence documented in *[X,p.y]*   1. New product design  * How are risks assessed regarding the potential impact on the validated predicate packaging process and design, if there are changes in dimensions of the product design (e.g. fitting of device in predicate packaging)? * How is it assured that a new process and design validation is triggered, in case of a new worst-case e.g product interacts with the packaging seal during sealing?   Evidence documented in *[X,p.y]*   1. Extension of shelf life  * In case of shelf-life extension, how is a new packaging stability study (accelerated and real time study) covering the claimed shelf life triggered?   Evidence documented in *[X,p.y]*   1. Packaging equivalence:  * How is a conclusion drawn on a comparison of the candidate product and the fully validated predicate product under consideration of:   + product aspects such as dimensions, geometry, weight, material, surface, sharp edges, chemical property equivalence determined by chemical method (e.g. IR spectroscopy)   + sterile Barrier System (SBS) aspects such as design, materials, dimensions, freedom of movement of product within SBS etc.   + protective packaging aspects such as components (shelf box, shipper box, etc), materials, number of SBS in shelf-box, number of shelf-boxes in shipper, etc.   + materials not meeting the predicate material specification (set point ± tolerance) result in a full process and design validation   Evidence documented in *[X,p.y]* |
| 1.3 QM provisions describing requirements to identify significant changes related to packaging to be notified to the Notified Body  MDR, Article 120  MDCG 2020-3, Chart E  EN ISO 11607-1, 9  EN ISO 11607-2, 5.7 | What provisions in the QM system are defined to ensure that packaging process changes as well as design changes are evaluated with regards to their significance?  Are actions defined if equivalency between predicate (equipment, process, packaging design and performance with impact on sterility) and candidate situation cannot be demonstrated?  Evidence documented in *[X,p.y]* |

# Quality management system in Relation to Sterilization

|  |  |
| --- | --- |
| **Quality Management provisions in relating to sterilization** | |
| 2.1  QM provisions describing handling of equipment changes or relocations of sterilization processes and if necessary, requirements when revalidation is performed (including handling of new sterilization technologies):  [EN ISO 13485, 7.5.6 + 7.5.7]  EN ISO 11135, 5.5, 6.3, 7.1.2 9.2, 9.3, 9.4, 9.5, 10, 12.3.1, 12.3, Annex A, Annex B  EN ISO 11737-2  EN ISO 11137-1: 5.1.2 6.2, 7.5 7.6, 8.2, 9.2, 9.3, 9.4.11, 12.2, 11.1, 12.3 12.4, 12.5 A.12.5.1 Tables A.1, A.2, A.3,  EN ISO 11137-2 4.4 6  EN ISO 11137-3 9.2 9.3  EN ISO 17665 6.1, 6.2, 8.1 8.10 8.11, 9.1.6, 9.1.7, 9.1.8, 9.2, 9.3 9.4 9.5, 10.3 12.2 EN 285 B.8.3.1.1  EN ISO 14937 6.2, 6.3 8.2 9.4 12.5.2 | For all sterilization modalities:   1. Contract steriliser   How is it assured:   * that a process validation (PQ) is triggered and that sterilizing agent residual levels are addressed (if applicable)? * if new sterilization lines (chambers, irradiators) are added at a contract sterilizer, these lines have to be added either by reduced or full PQ, depending on if equivalence data is available? * that IQ / OQ was done for the equipment in question? * for external equipment please refer to the section on “supplier control”   Evidence documented in *[X,p.y]*   1. Sterilization equipment:   What provisions are in place regarding the following topics:   * the QM system assures qualification and validation including IQ, OQ and PQ of each internal piece of equipment and process for each sterilization modality? * IQ: state of the art standards are used (e.g. EN 1422, EN 285)? * OQ: What are the minimum requirements for the operational qualification of the equipment?   + Is the number of sensors/dosimeters to be used defined? * PQ: How is it ensured that the cycle works within the defined process boundaries considering minimum and maximum load configurations. Are mixed loads possible/considered? * that the effect of the sterilization process on product safety and functionality is being assessed? * to ensure that BIs/PCDs are still appropriate for use in the new equipment? * for external equipment please refer to the section on “supplier control”   Evidence documented in *[X,p.y]*   1. Supplier control   How is it assured:   * that appropriate certification and supplier control is established? * that external suppliers use qualified equipment and validated processes? * that appropriate quality agreements are in place how to handle changes in products, processes and responsibilities? * that these agreements assure the manufacturer possesses all relevant validation data from the supplier in his technical documentation?   Evidence documented in *[X,p.y]*   1. If applicable: Equipment & process equivalency:   What provisions for acceptance of equivalency are defined for a new candidate equipment or process? How were the following aspects taken into account?   * (IQ), OQ, PQ for each individual candidate equipment * Strategy on how the candidate equipment is compared to the predicate equipment. * Process outputs shall be equal within pre-defined statistical limits (process capability in relation to delivered processes that are equivalent is adequately shown). * In the case equivalency cannot be concluded a full validation shall be triggered.   Evidence documented in *[X,p.y]*   1. New sterilization parameters   In relation to new cycle parameters for sterilization - How it is assured that:   * Operational parameters running outside established validated boundaries need an own validation * That product properties are maintained: Are functional product tests done to assure product conformity is maintained?   Evidence documented in *[X,p.y]*   1. Are there any requirements for a time-based revalidation?  * What interval is set to regular revalidation of the sterilization process? * What interval is set to reassure product families are still valid?   Evidence documented in *[X,p.y]* |
| 2.2 QM provisions describing actions triggered by new products, adoption for new designs to existing product families  EN ISO 11737-1,  A.7.2.1, A.5.1.2  EN ISO 11135 D.7.1.2 12.5  AAMI TIR 28  EN ISO 11137-2:  4.2.2, 4.2.1, 4.2.3, 4.2.4  EN ISO 11137-1:  7.5, 17665: 12.4, 12.5 | How do the QM system provisions address the impact of product changes on the sterilization process? How do the QM system provisions define criteria which trigger an adequate partial of full revalidation?  How are the following aspects taken into account:   1. New product design/manufacturing step  * How are risks assessed regarding potential impact on the validated predicate design related to changes in dimensions of the design or mass and material of the product? * How is the impact on sterilization assessed by changes in venting capability of the product? * How is it assured that in case of a new worst-case, new process and design validation is triggered? * How are resulting changes in manufacturing/material handled that lead to changes in bioburden levels, changed residues level and product functionality (related to sterilization)? * How is the impact of product changes on the validated load configuration verified?   Evidence documented in *[X,p.y]*   1. Product/process equivalence:   In this context, how are candidate products compared to existing (predicate) devices?   * Is e.g. AAMI TIR 28 / EN ISO11135 Annex D.7.1.2 adapted for EO processes? * How are key elements like bioburden, sterilizability, density and residuals based on diffusion barriers and pathways of the sterilant considered? * What provisions are in place if a new (potential) worst-case constellation is identified? What actions are performed as a consequence? * At what stage of the equivalency assessment is a sterilization specialist involved/approving the decision?   Evidence documented in *[X,p.y]* |
| 2.3 QM provisions to identify significant changes related to sterilization to be notified to the Notified Body  MDR, Article 120  MDCG 2020-3, Chart E  EN ISO 11135 12.4  EN ISO 11137-1 12.5  EN ISO 17665-1 12.5  EN ISO 14937 12.5 | What provisions in the QM system are defined to ensure that changes in sterilization affecting product conformity (e.g. residuals) are evaluated for their impact and a decision is drawn whether to inform the Notified Body?  *Impacts may be but are not limited to changes of:*   * *sterilization process (e.g. cycle specs)* * *manufacturing process (e.g. bioburden, Endotoxins)* * *design with impact on sterility (e.g. material compatibility, packaging, diffusion pathways)*   Evidence documented in *[X,p.y]*  How are the following aspects considered?   1. Change of load or packaging  * How are any changes in packaging or load composition evaluated regarding sterilization aspects? (e.g. density changes, changes of gas diffusion pathways, mass or volume etc.)   Evidence documented in *[X,p.y]*   1. Change on equipment  * What provisions are in place that assure that equipment changes, or major repairs will be assessed on their sterilization impact to potentially trigger revalidation or parts of the validation process?  1. Change of Bioburden controls/ specification / cleanliness  * How are changes in bioburden control steps (e.g. cleaning or disinfection) (bioburden quality or quantity) evaluated regarding their impact on SAL and residuals (e.g. endotoxins)? * How are limits for bioburden control established (history of bioburden, how is the relation to the acceptable count allowed going into sterilization)? * If alert/action limits are increased, how is it assured that the existing cycle still achieves the required SAL? * How are microbiological Out of Specification (OOS) results handled and followed up? (e.g. elevated bioburden, pyrogen results)   Evidence documented in *[X,p.y]* |

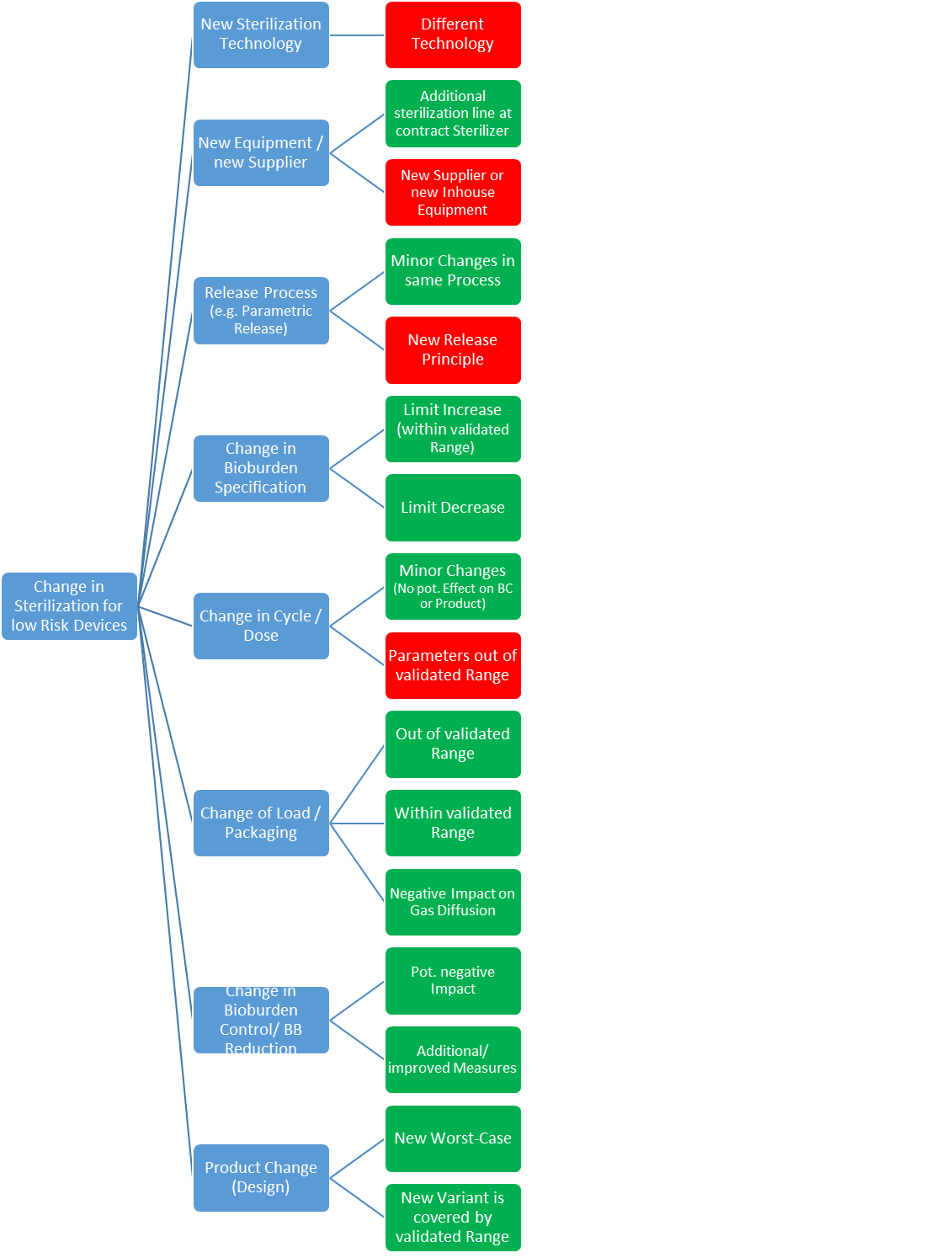
# Quality management system in Relation to Processing Instructions for Reusable DEviceS – if applicable

|  |  |
| --- | --- |
| **Procedures relating to reuse** | |
| 3.1  Provisions describing the interface to change management for processing instructions: | What decision rules on significance of device or IFU changes in relation to safe processing are defined?  Evidence documented in *[X,p.y]* |
| 3.2  Development procedure for reusable/initially to be processed devices related to the instructions for processing: | What provisions are defined in the QM system to handle the following aspects:   1. Development of new devices:   product adoption strategy including decision criteria for new validation  Evidence documented in *[X,p.y]*   1. The validation of instructions for use:   The respective procedure is expected to address reprocessing acceptance criteria (cleaning, disinfection, sterilization, biocompatibility and functionality), justified limits and test soil selection with scientific rationales based on the risk assessment (refer also to EN ISO 17664-1 5).  Evidence documented in *[X,p.y]*   1. If applicable: grouping strategy of product family:   Grouping strategy and worst-case product selection for cleaning, disinfection, sterilization, lifetime studies including biocompatibility and functional testing  Evidence documented in *[X,p.y]*   1. Risk management considering aspects of reuse and/or (initial) processing:   At least the relevant points according to EN ISO 17664-1, clause 5 are expected.  Evidence documented in *[X,p.y]*   1. National reprocessing requirements of EU member states:   Provisions for systematic search for and handling of national reprocessing requirements of EU member states, where the devices are placed on the market  Evidence documented in *[X,p.y]*   1. Requirements in relation to qualification of personnel regarding the assessment of reuse/biocompatibility data:   Trainings, CV related to EN ISO 17664-1 of involved decision maker of e.g. grouping of devices, instructions for reprocessing, product adoption, …  Evidence documented in *[X,p.y]* |
| 3.3  Provisions on Post Market Surveillance in relation to reuse/processing? | Evidence documented in *[X,p.y]* |

|  |  |  |  |
| --- | --- | --- | --- |
| **Regulatory release by client:** | ­­ |  |  |
|  | Date | Signature | Name |
|  |  |  |  |
|  |  |  |  |
|  |  |  | Name of Legal Manufacturer |

Informative Annex on significant changes to be reported to the Notified Body under MDR/IVDR and transition period under Article 120 MDR/ 110 IVDR

**Sterilization Class Is-IIb (with exceptions)**

****

Only under presumption that the QM system foresees the right risk analysis and/or validation work. Green becomes red if presumption is not met!

**Sterilization Class Is-IIb (with exceptions) Transition Period per Article 120 MDR and 110 IVDR**

Change in

Sterilization for

low

Risk

Devices

New Sterilization

Technology

Different

Technology

Transition to MDR/IVDR

required

New Equipment /

new Supplier

Additional

sterilization line at

contract Sterilizer

New Supplier or

new Inhouse

Equipment

Release Process

(e.g. Parametric

Release)

Minor Changes in

same Process

New Release

Principle

Change in

Bioburden

Specification

Limit Increase

(within

validated

Range)

Limit Decrease

Change in Cycle /

Dose

Minor Changes

(No pot. Effect on BC

or Product)

Parameters out of

validated Range

Change of Load /

Packaging

Out of validated

Range

Within validated

Range

Negative Impact on

Gas Diffusion

Change in

Bioburden

Control/ BB

Reduction

Pot. negative

Impact

Additional/

improved Measures

Product Change

(Design)

New Worst

-

Case

New Variant is

covered by

validated Range

Legend

No Change

n

otification required

Change

n

otification

required

Release under

§120

MDR/

§110

IVDR

transition period is

not possible

Only under presumption that the QM system foresees the right risk analysis and/or validation work. Green becomes red if presumption is not met!

**Sterilization Class IIb(i) & Class III**

Change in

Sterilization for

high

Risk

Devices

New Sterilization

Technology

Different

Technology

New Equipment /

new Supplier

Additional

sterilization line at

contract Sterilizer

New Supplier or

new inhouse

Equipment

Release Process

(e.g. Parametric

Release)

Minor Changes in

same Process

New Release

Method

Change in

Bioburden

Specification

Limit Increase

(within validated

Range)

Limit Decrease

Change in Cycle /

Dose

Minor Changes

(No pot. Effect on BC

or Product)

Parameters out of

validated Range

Change of Load /

Packaging

Out of validated

Range

Within validated

Range

Negative Impact on

Gas Diffusion

Change in

Bioburden

Control/

Reduction

Pot. negative

Impact

Additional/

improved Measures

Product Change

(Design)

New Worst

-

Case

New Variant is

covered by

validated Range

No Change

n

Change

n

required

Release under

§120

MDR/

§110

IVDR

not possible

Only under presumption that the QM system foresees the right risk analysis and/or validation work. Green becomes red if presumption is not met!

**Sterilization Class IIb(i) & Class III Transition Period per Article 120 MDR and 110 IVDR**

Change in

Sterilization for

high

Risk

Devices

New Sterilization

Technology

Different

Technology

Transition to MDR/IVDR required

New Equipment /

new Supplier

Additional

sterilization line at

contract Sterilizer

New Supplier or

new inhouse

Equipment

Release Process

(e.g. Parametric

Release)

Minor Changes in

same Process

New Release

Method

Change in

Bioburden

Specification

Limit Increase

(within validated

Range)

Limit Decrease

Change in Cycle /

Dose

Minor Changes

(No pot. Effect on BC

or Product)

Parameters out of

validated Range

Change of Load /

Packaging

Out of validated

Range

Within validated

Range

Negative Impact on

Gas Diffusion

Change in

Bioburden

Control/

Reduction

Pot. negative

Impact

Additional/

improved Measures

Product Change

(Design)

New Worst

-

Case

New Variant is

covered by

validated Range

Legend

No Change

n

otification required

Change

n

otification

required

Release under

§120

MDR/

§110

IVDR

transition period is

not possible

Only under presumption that the QM system foresees the right risk analysis and/or validation work. Green becomes red if presumption is not met!

**Packaging Class Is-IIb (with exceptions) Transition Period per Article 120 MDR and 110 IVDR**

|  |  |
| --- | --- |
| **Legend:** | 1. Old and new machine are manually guided sealers, or semi-automated sealers, or fully automated sealers, or…… respectively old and new machine use vacuum forming or pressure forming or negative forming (female) or positive forming (male), ..  2. e.g. heat sealing vs. ultrasonic sealing  3. Same thickness, material composition, .. – maybe different supplier, but consideration of biocompatibility needed!  4. Validated window is understood as validated process output (e.g. seal strength +/-10%)  5. Protocol needs to be approved by TÜV SÜD in course of the procedure review, otherwise Art. 120 is triggered and MDR/IVDR transition period is not possible!  6. Complete new packaging type (e.g. pouch => blister; breathable => non-breathable), new geometry (size, shape,..), lower number of sterile barriers (e.g. double pouch => single pouch), lower number of protective packaging, higher number of devices in a kit (for removal of devices in a kit, impact on transport validation shall be evaluated) |

**Packaging Class IIb(i) & Class III Transition Period per Article 120 MDR and 110 IVDR**

|  |  |
| --- | --- |
| **Legend:** | 1. Old and new machine are manually guided sealers, or semi-automated sealers, or fully automated sealers, or…… respectively old and new machine use vacuum forming or pressure forming or negative forming (female) or positive forming (male), ..  2. e.g. heat sealing vs. ultrasonic sealing  3. Same thickness, material composition, .. – maybe different supplier, but consideration of biocompatibility needed!  4. Validated window is understood as validated process output (e.g. seal strength +/-10%)  5. Complete new packaging type (e.g. pouch => blister; breathable => non-breathable), new geometry (size, shape,..), lower number of sterile barriers (e.g. double pouch => single pouch), lower number of - protective packaging, higher number of devices in a kit (for removal of devices in a kit, impact on transport validation shall be evaluated); |

**Packaging Class Is-IIb (with exceptions)**

Only under presumption that the QM system foresees the right risk analysis and/or validation work. Green becomes red if presumption is not met!

|  |  |
| --- | --- |
| **Legend:** | 1. Old and new machine are manually guided sealers, or semi-automated sealers, or fully automated sealers, or respectively old and new machine use vacuum forming or pressure forming or negative forming (female) or positive forming (male), ..  2. e.g. heat sealing vs. ultrasonic sealing  3. Same thickness, material composition, .. – maybe different supplier, but consideration of BC needed!  4. Validated window is understood as validated process output (e.g. seal strength +/-10%)  5. Protocol needs to be approved by TÜV SÜD in course of the procedure review, otherwise Art. 120 is triggered and MDR/IVDR transition period is not possible!  6. Complete new packaging type (e.g. pouch => blister; breathable => non-breathable), new geometry (size, shape,..), lower number of sterile barriers (e.g. double pouch => single pouch), lower number of protective packaging, higher number of devices in a kit (for removal of devices in a kit, impact on transport validation shall be evaluated) |

**Packaging Class IIb(i) & Class III**

Only under presumption that the QM system foresees the right risk analysis and/or validation work. Green becomes red if presumption is not met!

|  |  |
| --- | --- |
| **Legend:** | 1. Old and new machine are manually guided sealers, or semi-automated sealers, or fully automated sealers, or…… respectively old and new machine use vacuum forming or pressure forming or negative forming (female) or positive forming (male), ..  2. e.g. heat sealing vs. ultrasonic sealing  3. Same thickness, material composition, .. – maybe different supplier, but consideration of biocompatibility needed!  4. Validated window is understood as validated process output (e.g. seal strength +/-10%)  5. Complete new packaging type (e.g. pouch => blister; breathable => non-breathable), new geometry (size, shape,..), higher number of sterile barriers (e.g. single pouch => double pouch), lower number of sterile barriers (e.g. double pouch => single pouch), lower number of protective packaging, higher or lower number of devices in a kit |