Guideline for Validation of Packaging Processes according to ISO 11607-2

1 Scope

The standard series ISO 11607 stipulates validation of the packaging processes used for industry, health care facilities and wherever medical devices are packaged and sterilized (examples of health care facilities include hospitals, doctors' and dentists' surgeries).
The ISO 11607, Part 2 standard (Article 5.1.1) explicitly calls for validation of all packaging processes. The present Guideline deals with the following packaging processes:

- pouch, reel or bag sealing[2]
- sterilization sheets folding and wrapping
- filling and closing of reusable sterilization containers

Likewise, packaging processes not dealt with here must also be validated as per ISO 11607-2. Non-validable packaging processes are not acceptable in practice anymore (Self Seal pouches or taped paper bags).

2 Normative bases

The bases for drafting this Guideline include, inter alia, the following standards[3]:

- ISO 11607-1:2009
- ISO 11607-2:2006
- EN 868:2009, Part 2-10[4]
- ISO 11140-1:2009
- ISO 9001:2008
- ISO 13485:2010
- DIN 58953:2010, Part 1, 6, 7, 8, 9[5] (German Standard)

The standards stated in table 1 are of relevance for validation and should be made accessible to the user.

3 Prerequisites

The packaging materials used must be suited to and defined for the intended packaging and sterilization processes. Suitability shall be determined on the basis of the information provided by the manufacturer. This includes confirmation of conformity with the ISO 11607-1 standard and pertinent sections of the EN 868, Parts 2–10 standard series, in respect of:

- microbial impermeability
- compatibility with the sterilization process.

The number of process validations to be conducted can be elucidated and defined on the basis of Table 2 (see example Annex A.5, B.5 and C.5).
The number of combinations outlined in the table can be reduced by taking account of only the maximum material stress (worst-case scenario, while providing documentary proof to justify this).
Worst-case examples:

- Gusseted pouches and reels are more critical than flat pouches and reels.
- Steam sterilization at 134 °C/18 min is more critical than at 134 °C/5 min and 121 °C/20 min.

A further reduction can be achieved by a deliberate choice of packaging materials (e. g. see through pouch instead of paper bag).
Annex A.5, B.5 and C.5 show practical examples.

4 Validation of packaging processes

In principle, a documented process must be available for validation. This process comprises:

4.1 Drafting of a validation plan
4.2 Validation of packaging processes
4.2.1 Installation qualification (IQ)
4.2.2 Operational qualification (OQ)
4.2.3 Performance qualification (PQ)
4.3 Drafting of a validation report
4.4 Formal approval of validation
4.5 Process control and monitoring
4.6 Process changes and revalidation

4.1 Drafting of a validation plan

The validation plan should contain, at least, the following details:

Table 1: Standards of relevance for the validation

ISO 11607-1	Requirements for materials, sterile barrier systems and packaging systems
ISO 11607-2	Validation requirements

2 If the sealing processes were already validated in accordance with the «Guideline for validation of the sealing process as per ISO 11607-2 (Revision 1, status: July 2008)», there is no need to repeat initial validation.

3 The publication years of the pertinent standards are only given here.

4 EN 868, Part 1 has been replaced by the ISO 11607-1 standard.

5 German Standard DIN 58953, Parts 2–5 have been replaced by EN 868, Parts 2–5.

Table 2: Number of process validations to be conducted
The terms used for sterilization processes are based on the standard ISO 11140-1.

Sterile barrier system (SBS)	STEAM			FORM (Formaldehyde)	EO (Ethylene oxide)	VH2O2 (vaporized hydrogen-peroxyde; «Plasma»)
	134 °C/ 5 min	134 °C/ 18 min	121 °C/ 20 min			
Material A						
Material B						
Material C						
Material D						

– Competences
– Description of the packaging process
– Description of the materials /equipment
– Description of the sterilization processes
– Qualification steps (IQ, OQ and PQ)

The «Validation plan» checklists in Annex A.1, B.1 and C.1 can be used.

4.2 Conduct of validation

4.2.1 Installation qualification (IQ)

Definition: «Process of obtaining and documenting evidence that equipment has been provided and installed in accordance with the specification.»
That means that technical equipment (e. g. heat sealers) must have been properly installed and users trained.
In general, the packing processes involving sterilization sheets as well as reusable sterilization containers are purely manual processes, which is why proof of IQ is based on documentation of training of staff.
It is recommended that the corresponding checklists be used to conduct installation qualification (IQ). The «Installation qualification (IQ)» checklists in Annex A.2, B.2 and C.2 can be used for documentary purposes.

4.2.2 Operational qualification (OQ)

Definition: «Process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures.»
The «Operational qualification (OQ)» checklists in Annex A.3, B.3 and C.3 can be used for documentary purposes.
In principle, a distinction must be made here between automated and manual processes.

Automated processes
Here: pouch, reel or bag sealing.
The heat sealing process is defined on the basis of the following parameters:
– Sealing temperature,
– Contact pressure and
– Sealing time/speed (dwell).

The contact pressure and sealing speed or time (dwell) are generally set by the manufacturer of the heat sealer.
The optimum sealing temperature for the respective packaging material must be determined by the user. To that effect, the technical data sheet supplied by the manufacturer of the packaging material is needed. This must specify the sealing temperature (e. g.170 – 200 °C).
Sealing samples must be produced for the respective lower and upper limits.
The quality properties listed in ISO 11607-2, § 5.3.2 b must be assured:
– intact seal for a specified seal width
– no channels or open seals
– no punctures or tears
– no material delamination or separation

These quality properties must be verified and documented by means of suitable processes. The test methods in Table 3, for example, can be used as a guide.
Then the sealing temperature must be specified for routine operations. In general this is calculated from the mean value of the limit values (e. g. mean value from 170 °C and 200 °C is 185 °C).

Manual processes
Here: sterilization sheets' folding and wrapping; filling and closing of reusable sterilization containers[9].
First, the most critical packaging configuration must be determined (worst case).
Examples include:
– the heaviest and largest tray (container)
– large, unwieldy single instruments

Then these configurations must be packed according to the standard operating procedures.
When checking the sterile barrier systems produced all defined quality properties as well as the correct packing method set out in the standard operating procedure (see Annex B.6 and C.6) must be assured.
Pursuant to the ISO 11607-2, § 5.3.2 c standard the quality properties required for sterilization sheets and reusable sterilization containers are as follows:
– continuous closeness/integrity
– no punctures or tears (not applicable to reusable sterilization containers)
– no other visible damage or material irregularities[10].

The quality properties must be verified and documented by means of suitable processes or tests. For the combinations specified in the validation plan, 10 sterile barrier systems of the same material must be packed and their quality properties checked. To document the quality properties it is recommended that at least one photo is taken of each sample.

4.2.3 Performance qualification (PQ)

Definition: «Process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification.»
During performance qualification proof must be provided after sterilization that the process is under control and produces optimally sealed or closed sterile barrier systems.

Table 3: Test methods for verification of quality properties	
Test method	Suitable for verification of the following quality properties
Seal integrity test (e. g. «dye penetration test/InkTest» according to ISO 11607-1, Annex B[6])	– channels or open seals – punctures or tears
Seal integrity indicator[7] (e. g. Seal Check)	– intact seal for a specified seal width – channels or open seals – punctures or tears
Peel test according to EN 868, Annex E	– material delamination or separation
Visual inspection[8]	– intact seal for a specified seal width – punctures or tears

The «Performance qualification (PQ)» checklists in Annex A.4, B.4 and C.4 can be used for documentation purposes.
Here, too, a distinction must be made between automated and manual processes.

Automated processes

Verification is done by means of the seal strength test as per EN 868-5, Annex D[11]. The packaging must be sterilized before verification. The protocols/logs (batch documentation) related to the sterilization processes are part of validation.
For the defined combinations (see also Annex A.5) three empty pouches or reels of the same material must be sealed, clearly labelled (sealing device, serial number, sealing parameters) and then sterilized with the specified sterilization program (reels must be sealed at both ends). Each pouch must be added to a different sterilization load to take account of all the factors exerting an influence on the sterilization loads.
The test (as per EN 868-5, Annex D) is carried out as follows:

– Cuts measuring 15 mm in width are taken of the dried samples and at an angle of 90 ° to the seal seam. At least one sample of a produced seal seam must be taken from each packaging[12]. If only one sample of a seal seam is taken, the sample must be taken from around the centre.
– Simulation of the peeling process at a speed of 200 mm/min
– Recording of the seal seam strength[13]
– Evaluation and documentation of the results

The results of the seal strength test are confirmed in a report, containing at least the following information:

– Manufacturer and type of heat sealer
– Serial number of heat sealer
– Specification of the sealing parameters
– Identification of the verified product
– Maximum strength of seal of each sample measured in N/15 mm width
– Whether verification was done with the free end supported or not
– The frequency used (data per second of measurement)
– Test device (manufacturer, designation)/ last calibration
– Graphic display of resistance
– Date of test

Testing of the sealed and sterilized pouches can, for example, be carried out by an accredited test laboratory or by the device/material manufacturer.
The maximum strength must be entered into the table in Annex A.4. The maximum strength is the relevant value for assessment and, as per EN 868-5, must be greater than or equal to 1.5 N/15 mm width[14]. If the maximum tensile strength of one of the three tests is less than 1.5 N/15 mm width, PQ is deemed to have failed.
In addition the quality properties listed in ISO 11607-2, § 5.3.2 b must be assured:

– intact seal for a specified seal width
– no channels or open seals
– no punctures or tears
– no material delamination or separation

These quality properties must be verified and documented by means of suitable processes. The test methods in Table 3, for example, can be used as a guide.

Manual processes

For the test, sterilized packaging systems must be taken from the running processes. From three different cycles (batches) one sample must be taken in each case. The batch documentation (protocols) of the respective sterilization processes is part of validation.

6 The basis for this test method is ASTM F1929 2 «Standard test method for detecting seal leaks in porous medical packaging by dye penetration»

7 The seal integrity indicator must not under any circumstances be cut since it must always be guaranteed that the entire pinch roller of the sealing device is printed off. Furthermore, the seal indicator shall always be made of the same type of material as the porous part of the packaging (medical grade paper as per EN 868-3 or HDPE as per EN 868-9/10)

8 For visual inspection standardized test methods can be used (e. g. ISO 11607-1, Annex B [ASTM F1886])

9 The partial step «Filling of pouches and reels» is also a manual process and must be set out in a standard operating procedure. The heat sealing process itself is normally fully automated.

10 The ISO 11607-2 standard uses «No material delamination or separation» here.

11 Alternatively, the test method as per ASTM F88 can be used (validated and round robin approved test method).

12 EN 868-5:1999 specified five samples per seal seam. EN 868-5:2009 stipulates only one sample per seal seam. Additional samples may be needed if the length of a seal is more than 500 mm.

13 For further evaluation and documentation it is advisable to specify as a value the maximum (required as per EN 868-5 Annex D.3) and additionally the average tensile strength.

14 EN 868-5, § 4.5.1 «The minimum seal strength value for steam sterilization processes must be 1.5 N per 15 mm in health care facilities and 1.2 N per 15 mm in other sterilization processes in health care facilities». However, stipulation of a minimum value of 1.5 N/15 mm is recommended for all sterilization processes.

Assurance of the quality properties must be verified for each packaging system (sample).

Pursuant to standard ISO 11607-2, § 5.3.2 c the quality properties for sterilization sheets and reusable sterilization containers are as follows:

– continuous closeness/integrity
– no punctures or tears (not applicable to reusable sterilization containers)
– no other visible damage or material irregularities[15].

These quality properties must be verified and documented by means of suitable processes or tests. The sterile barrier systems or packaging systems are opened one step after the other, verified and documented (for photographic documentation see Annex B.8/C.7).

4.3 Drafting of a validation report

The validation procedures and results must be documented in a summary report. The checklists, protocols and any photographic documentation used serve as evidence and must be enclosed in an annex to the report.

The report must contain, at least, the following information:

Validation plan

– Evidence of implementation of the validation plan (IQ, OQ and PQ checklists completed as per Annex)
– Evaluation of the results
– Photographic documentation for manual packing processes
– Details and explanation of any deviations from validation plan
– Formal approval of validation
– Process control and monitoring
– Process changes and revalidation

4.4 Formal approval of validation

Validation, as documented and evaluated in the report, must be formally approved, and duly documented, by the competent person appointed by the operator. This can be recorded, for example, in a field provided to that effect in the validation plan. If all validation results are not accepted, this must be clearly documented, including assessment of any remaining risks.

4.5 Process control and monitoring

The routine tests that are established during the validation as being necessary must be documented (e. g.in the standard operating procedure). This is intended as a means of ensuring that changes in the packaging process are detected on time before they compromise the sterile barrier systems and the requirements are no longer met. These include, e. g.:

– Visual inspection[16]
– Peelability (e. g. peel test as per EN 868-5, Annex E «Method for determination of the peel characteristics of paper/plastic laminate products»)
– Seal integrity test (e. g. dye penetration test/ink test as per ISO 11607-1, Annex B[17])
– Seal integrity indicator[18] (e. g. Seal Check)
– Tensile strength of seal seam (e. g. determination of seal seam strength as per EN 868-5, Annex D «Method for determination of the seal seam strength of pouches and reels»
– Stepwise opening of packaging (in the case of sterilization sheets or reusable sterilization containers).

Intervals (e. g. daily, weekly, monthly, yearly) and acceptance values must be defined for the routine tests needed, including the action to be taken if a test result is not satisfactory. The routine test results must be documented. This procedure must be set out in the quality management system.

4.6 Process changes and revalidation

Processes must be revalidated:

– Unscheduled revalidation,
  • for example in the event of changes to materials, processes, including changes to equipment or occurring during sterilization (revalidation)
– Scheduled revalidation,
  • at regular intervals, i. e. in general after one year if no changes were made to materials, sealing process or sterilization (performance requalification).
  • provides evidence that the packaging process continues to be within the limits defined at the time of initial validation (IQ, OQ and PQ). That no changes were made to materials, processes or sterilization compared to the previous validation must be confirmed in the revalidation report. If changes are made to materials, processes or sterilization how such changes will affect the packaging process results must be elucidated. The results must be documented. Based on these, an individual revalidation plan must be drafted. Accordingly, in the event of material changes, for example, operational qualification (OQ) and performance qualification (PQ) must be partially or fully repeated, and if changes are made to the packaging process or to the equipment used installation qualification (IQ) must also be repeated. For revalidation it must be ensured that the documents used meet the current requirements. The checklists must be updated if necessary. An individual validation plan is required for each revalidation or performance requalification. The «Validation plan» checklists in Annex A.1, B.1 and C.1 can be used. ■

15 The ISO 11607-2 standard uses «No material delamination or separation» here.

16 For visual inspection standardized test methods can be used (e. g. ISO 11607-1, Annex B [ASTM F1886] for seal seams or EN 868-8 for reusable sterilization containers.

17 The basis for this test method is ASTM F1929 «Standard test method for detecting seal leaks in porous medical packaging by dye penetration».

18 The seal integrity indicator must not under any circumstances be cut since it must always be guaranteed that the entire pinch roller of the sealing device is printed off. Furthermore, the seal integrity indicator shall always be made of the same type of material as the porous part of the packaging (medical grade paper as per EN 868-3 or HDPE as per EN 868-9/10)