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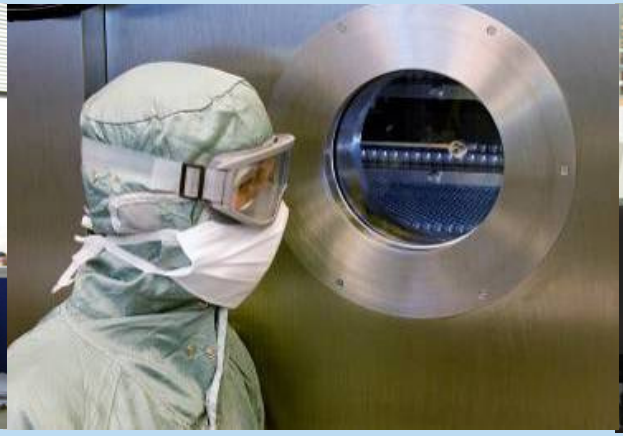
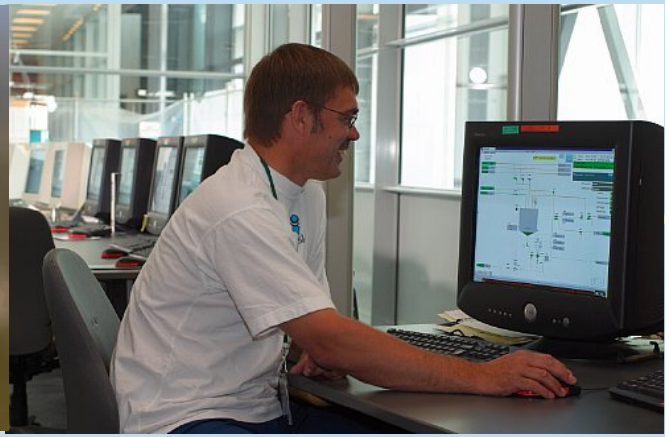
Autoclaves
Qualification & Validation

By Holger Fabritz

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Contents

- Types of autoclaves
- Regulatory Aspects
- GMP Risk Analysis
- URS / FDS
- Design Qualification
- Installation Qualification / Operational Qualification
- Performance Qualification / Process Validation
- Responsibilities
- Summary

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- Types of Autoclaves -

- **Steam Autoclaves**
- Sterilisation with
  - Steam / Air Mixture
  - Saturated Steam
  - with possible initial vacuum sequence(s)
- Cooling with
  - Air cooled down by heat exchanger
- **Hot Water Spray Autoclaves**
- Sterilisation with
  - Spraying of Water
  - (Flooding with water)
- Cooling with
  - Water cooled down by heat exchanger

- **Hot Air Sterilisers**

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- Types of Autoclaves -

Revolving Steam Autoclave
xxx chambers,

Large Steam Autoclave

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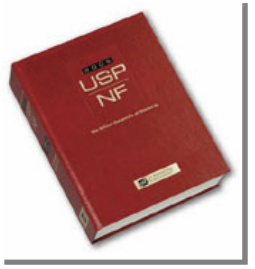
- Regulatory Aspects -

- **Ph. Eur. 6**
  - 5.1.1, Methods of Preparation of Sterile Products
  - 5.1.2, Biological Indicators of Sterilisation
  - 5.1.5, Application of the F0 Concept to Steam Sterilisation of Aqueous Preparations

- **USP 29**
  - <55> Biological Indicators - Resistance Performance Tests
  - <1035> Biological Indicators for Sterilisation
  - <1211> Sterilization and Sterility Assurance of Compendial Articles



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- Regulatory Aspects -

GMP-Regulations

- EU-GMP-Guideline Part 1, Annexes 1, 15 & 17
- Code of Federal Regulations (CFR) 21, Part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing of Holding of Drugs; General
- 21 CFR Part 211: Current Good Manufacturing Practice for finished Pharmaceuticals
- 21 CFR Part 11: Electronic Records; Electronic Signatures

FDA Guidance for Industry

- Sterile Drug Products Produced by Aseptic Processing
- Documentation for Sterilisation Process Validation

European Medicines Agency (EMEA)

- CPMP/QWP/054/98 Corr., Decision Trees for the Selection of Sterilisation Methods
- CPMP/QWP/3015/99, Note for Guidance on Parametric Release

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- Regulatory Aspects -

- **GAMP**
- The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems in Pharmaceutical Manufacture, Vol. 4
- **PDA Technical Reports**
- PDA Technical Report No. 1, Validation of Steam Sterilisation Cycles
- **HTM (Health Technical Memorandum)**
- 2010; Sterilisation; Part 3: Validation and verification; NHS Estates; Department of Health; UK
- **International, European and National Standards (ISO / EN / DIN) / Others**
- EN 285, Sterilisation, Steam Sterilisation, Large Sterilisers
- DIN 58950, Sterilisation , Steam Sterilisers for Pharmaceutical Products
- EN 554, Sterilisation of Medical Devices
- ...

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- GMP Risk Analysis -

GMP Risk Analysis at the beginning of the qualification activities:

- Definition of GMP-relevant issues to be considered in the design and further qualification steps:
  - GMP relevance of single components
    (e.g. heat exchanger, sterilisation chamber, valves)
  - Control System → computer validation, definition of the GMP-relevant instrumentation including requirements for accuracy and recording, GMP-relevant sensors (double measurement of critical parameters)
  - Utilities: quality of media → piping quality
  - Material specification incl. necessary certificates
  - Additional test devices
    (e.g. WIT-test possibility for aeration filter, incl. sensors)
  - Documentation including welding documentation, wiring check, software documentation etc.
- Possibility to have a traceability to the subsequent qualification steps
- → **Influence of Risk Analysis on Engineering activities (URS) & basis for DQ / IQ / OQ / ….**

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- GMP Risk Analysis -

1	2	3	4		5	6	7						
	Process step /	Possible failure	GMP Risk		Explanation	Tests / Measures	Traceability						
	Equipment		[Y/N]	[A/B/C]			D	IQ	OQ	PQ	CQ	NV	/ A
	Components with product contact	Inadequate material of steel surfaces	Y	A	Corrosion could deteriorate the product.	Steel: 316L min. certified by EN10204 2.2							
		Inadequate plastics or gaskets	Y	A	Material might not be inert against product.	Plastics/gaskets: Food graded materials certified acc. to CFR Title 21 §177.2600.							
		Wrong surface finishes	Y	A	Rough surface might lead to adherence of product or bad cleanability.	Surface finishing or surface roughness is defined and proven. Certificate of manufacturer is available.							
		Bad quality of weld seams (pipework)	Y	A	Weld seams of product or clean media pipes have another material and surface roughness than the tubes. Risk of porosities or material impurities.	Weld seams of stainless steel pipes should be welded under inert gas conditions and with appropriate welding material (TIG technique).							
					s. a.	As far as technically possible orbital welding should be applied.							
		Quality of weld seams is not traceable.	Y	B	When pipework is completed, the weld seams cannot be checked visibly any more.	Weld seams of pipework for product or clean media transfer should be visually checked by endoscope.							
					Required by ISPE publications	100% of handmade weld seams and an appropriate percentage of orbital weld seams have to be checked accordingly.							
					Requirement of good documentation practice.	Test report contains every weld seam with a single test.							

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- User Requirement Specification (URS) -

- To be issued by the User (Pharmaceutical Enterprise)
- Basis for GMP Risk Analysis and influenced by the results (e.g. documentation requirements, number of critical sensors)
- Reference to Pharmacopoeias, guidelines and standards to be used ($\rightarrow$ EMEA CPMP/QWP/054/98 Decision trees for the selection of sterilisation methods)
- Description of the sterilisation process (e.g. standard sterilisation, F0-sterilisation) on basis of the product properties
- Definition of all (as possible) relevant GMP-critical points (e.g. sterility of cooling media, coldest spots)
- Definition of the user needs for documentation and operation (e.g. batch documentation, operating instructions etc.)

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- User Requirement Specification (URS) -

- Completed by detailed technical specifications:
  - Volume of sterilisation chamber
  - Standards for electrical standards, wiring, valves,
  - Standards for materials to be used (stainless steel)including surface roughness (< 0,8 µm or higher values?)
  - Interfaces to existing systems
  - Drying / Air Filters (e.g. for stoppers for dry powder filling, clean room clothes)
- Definition of requirements for FAT / SAT

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- User Requirement Specification (URS) -

- Detail description of requirements for Computer Validation
  - Audit Trail
  - User Access
  - Backup / Recovery
  - Disaster Recovery
- Definition of requirements for qualification
  (in case that supplier should support qualification)

→ **Combined with commercial requirements as request for an offer to be submitted to different potential suppliers**

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- Functional Design Specification (FDS) -

- To be issued by the potential suppliers
- FDS should comprise detailed proposals for technical solutions for the URS requirements
- All requirements of the URS must be commented by the supplier (can be met or can't be met)
- In case of deviation from a requirement of the URS, an explanation and alternative proposals for technical solutions are necessary

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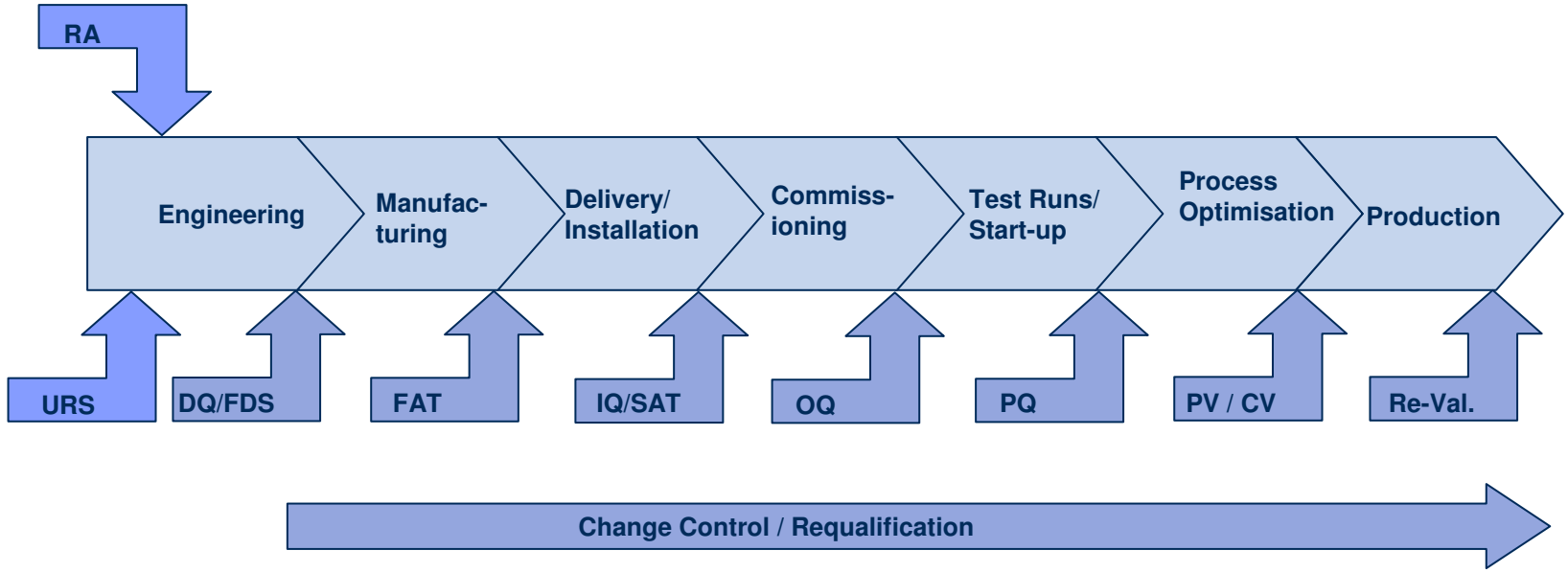
- Project Implementation -



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- Design Qualification (DQ) -

- is performed by documented comparison of URS and FDS, focussed on GMP- relevant topics
- all requirements set up be the URS (resulting from the risk analysis) should be met, traceability to risk analysis and URS should be given
- deviations from the requirements of the URS must be evaluated whether acceptable or not (→ GMP-requirements)
- Supplier Audits (quality system, software development) should be implemented in this phase
  Note: Implementation of supplier audit in Computer Validation strategy necessary

→ **Approval of DQ protocol and report respective approval of URS/FDS comparison by defined persons (VMP)**

→ **Start of project change control**

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- Summary of RA/URS/FDS/DQ -

Some practical experiences:

- Results of GMP Risk Analysis are often not considered in URS
  GMP Risk Analysis too detailed
  (discussion about construction of valves)
- Important company standards are not added to URS
  (Welding standards for pipes)
- FDS does not answer URS (standard documents by suppliers)
- Design Qualification finalised too late / after FAT
- Changes are performed but without change control
- .....

→ **Mistakes in early project stages lead to irritations/discussions/deviations during IQ/OQ/PQ**

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- Factory Acceptance Test (FAT) / Site Acceptance Test (SAT) -

FAT

- Qualification staff should join FAT
- Preliminary documentation should be available and should be checked during FAT (incl. IQ and OQ - protocols)
- First formal check of P&I-Diagram by qualification staff
- Definition of test program on basis of suppliers possibilities
- Structured FAT can substitute some IQ(OQ)-testing

SAT

- Basis for SAT should be mechanical completion of autoclave
- SAT should be performed as Pre-IQ / Pre-OQ / can substitute some IQ / OQ testing.

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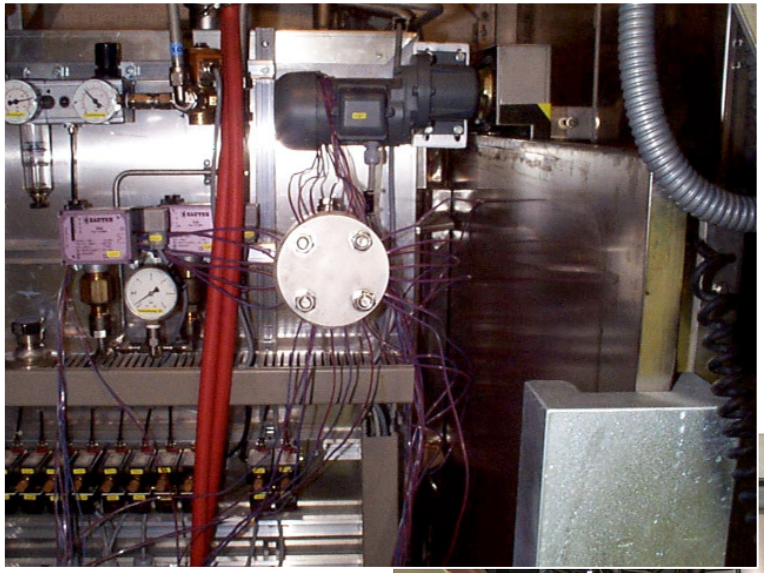
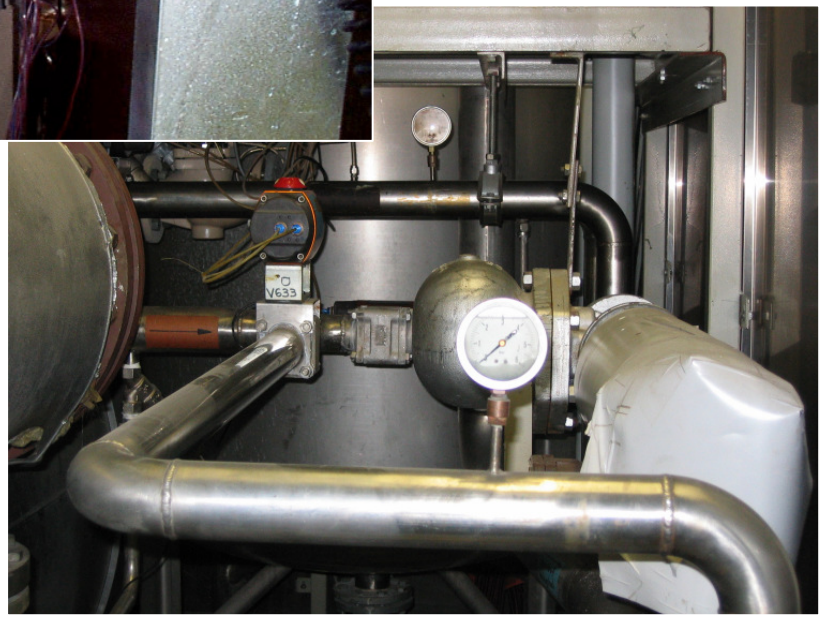
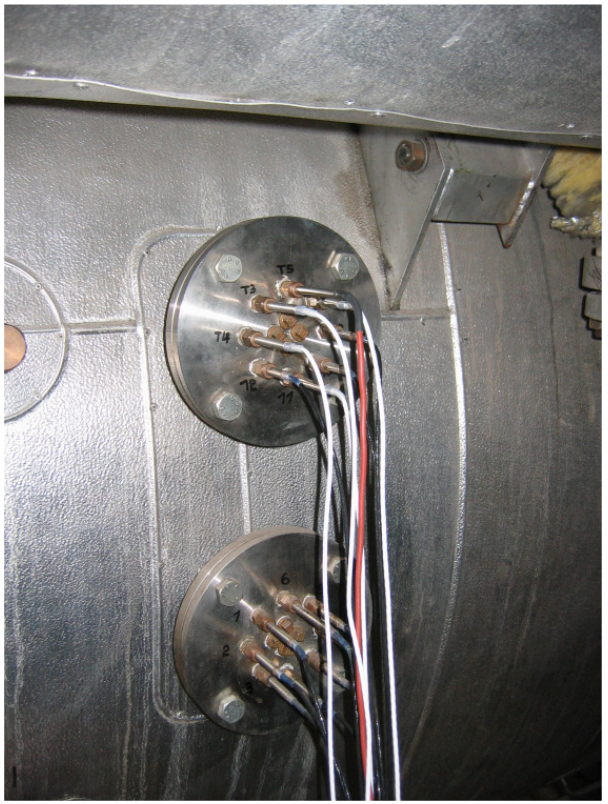
- Installation Qualification (IQ) -







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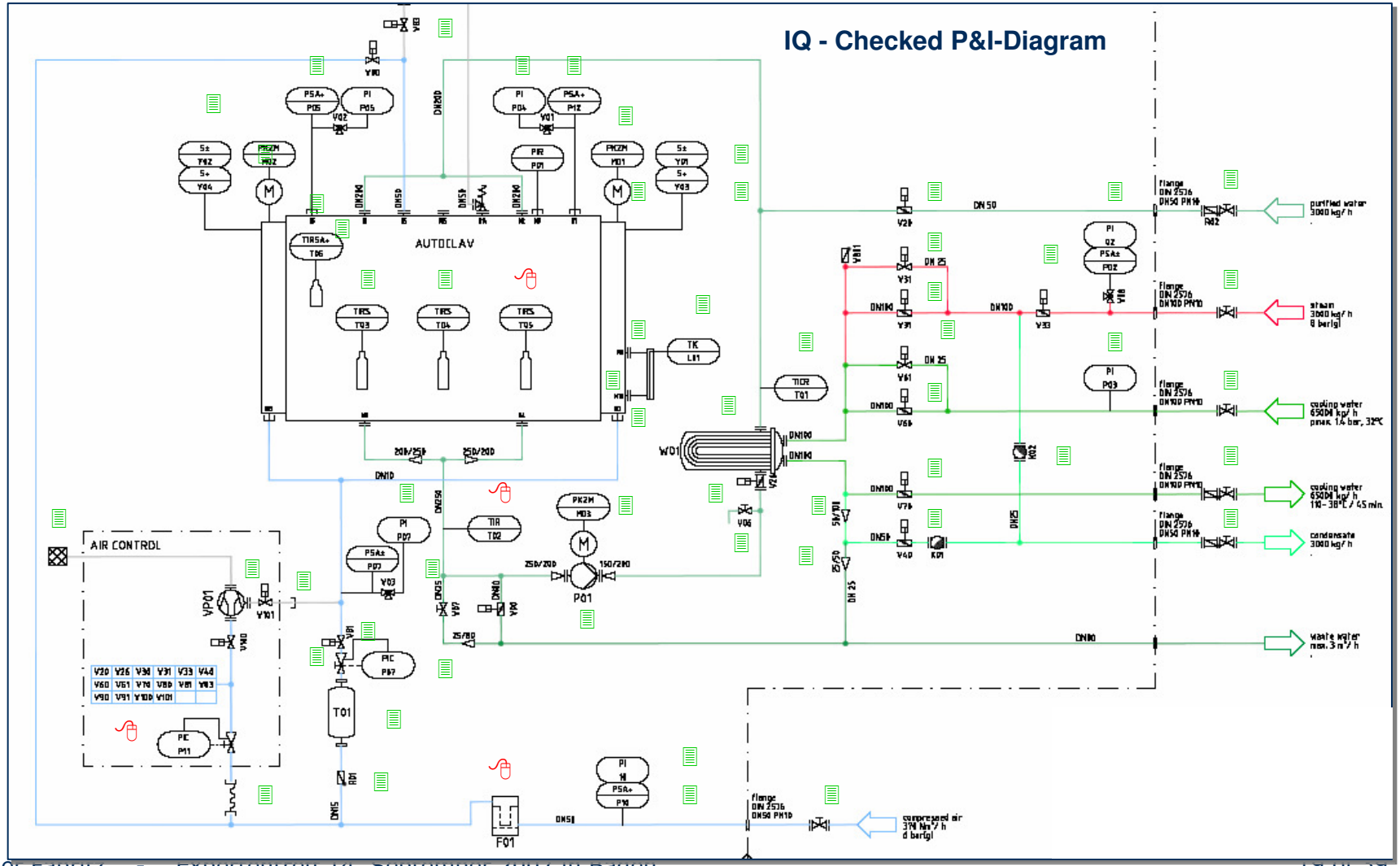
- Installation Qualification (IQ) -



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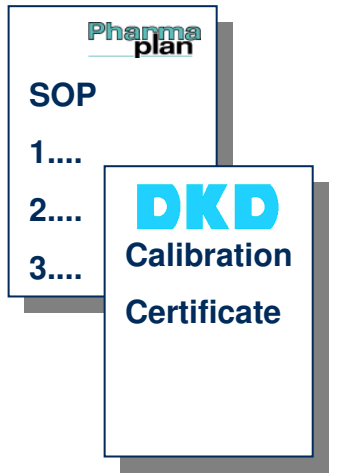
- Installation Qualification (IQ) -

...Further points to be checked

- Calibration of the different sensors
  - Three points for temperature/pressure
  - One point for timer or paper speed of the recorder
- Availability of relevant SOPs (operation, maintenance), at least as draft version
- Check of the supplier documentation
  - Completeness
  - Formal correctness
  - Correctness of content



Finalisation of IQ

- Deviations must be evaluated
- In case of GMP-critical deviations (e.g. wrong type of sensors), IQ not successful → remedy of deviation and repetition of IQ (Change Control)
- In case of non GMP-critical deviations, a pre-approval of the IQ is possible in order to start next qualification step

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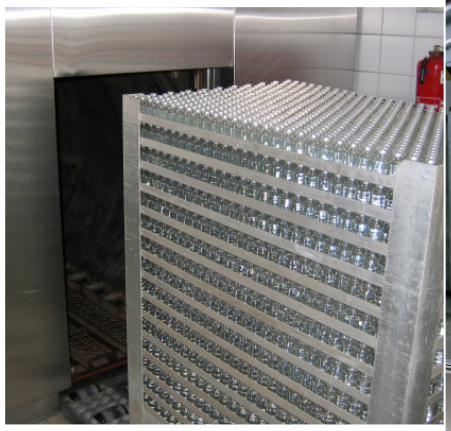
- Operational Qualification (IQ) -

Pre-requisites

- (Pre-)Approval of IQ
- Used measuring devices (e.g. Kaye system, data loggers) should be calibrated before performing measurement (and afterwards**)**

Function testing of all procedures & sequences

- Tightness and stability of piping after performing a sterilisation cycle (Visual checks!)
- Loading and unloading tests
- Interlocks of doors
- Check of programs
  - Fractionated pre-vacuum
  - Heating phase
  - Equilibration time
  - Sterilisation time
  - Drying and Cooling
  - Correct re-start after power failure



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- Operational Qualification (OQ) -

...Points to be checked

Check of alarms

- Temperature too high or too low
- Pressure too high or too low (pressure variations)
- Time limits of process steps
- Utility supply
- Cable break of sensors
- ...

Computer Validation related points

- User access and audit trail
- Data storage / Print Out
- Electromagnetic failure, radio frequency test
- ...

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- Operational Qualification (OQ) -

...Points to be checked

- **Check of steam quality (should be covered by qualification of clean steam system)**

Check of chamber tightness

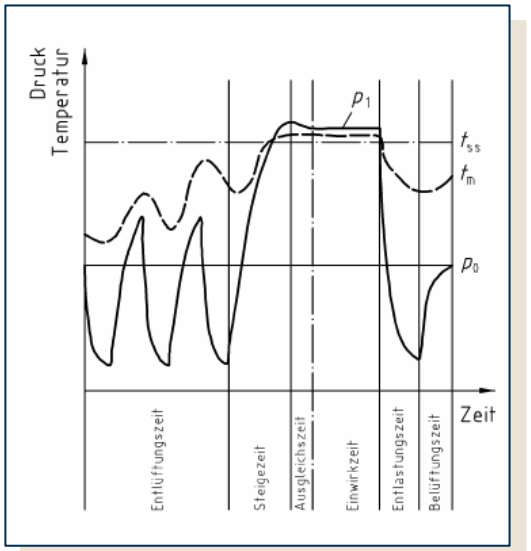
- Possible acceptance criteria: pressure drop ≤ 1,3 mbar / min
- Procedure: Evacuation of the chamber on a predefined pressure and closing of all valves. Measurement for 10 min

Bowie-Dick-Test for sterilisation cycles with saturated steam

- Use of test kids
- Colour change of indicator complete

Integrity of aeration filter

- Water Intrusion Test for hydrophobic filters



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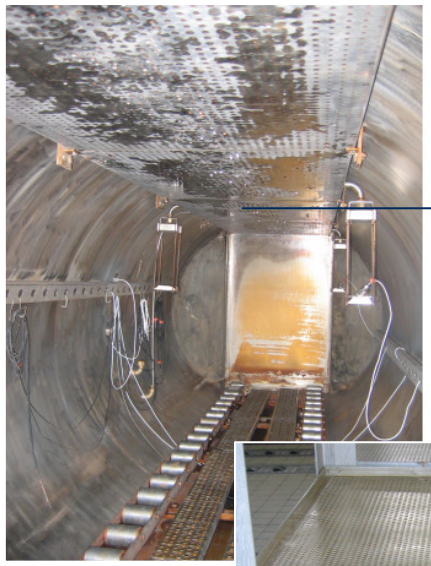
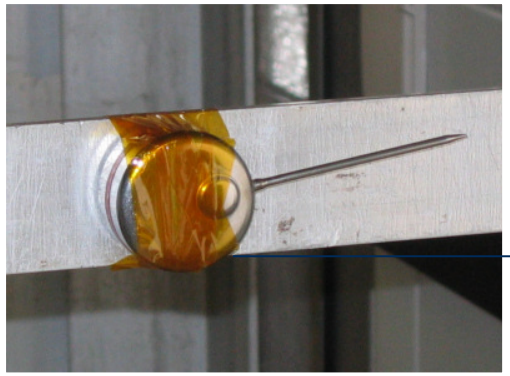
- Operational Qualification (OQ) -

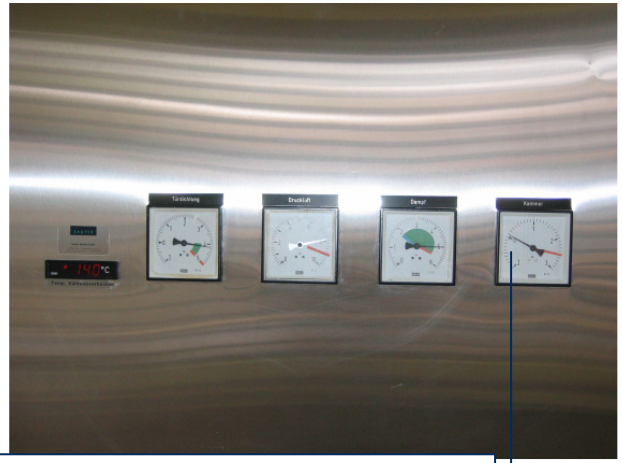


Measurement of Empty Chamber



Data Logger

Data Logger on Autoclave Tray



All operation parameters in specification

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- Operational Qualification (OQ) -

...Points to be checked:

Heat distribution check of the empty chamber (Identification of cold spots)

- Acceptance Criteria
  - Correct process incl. recording without alarms
  - Pre-defined maximum standard deviation not exceeded for validation sensors
  - Pre-defined maximum allowed deviation from the mean value for single validation sensors not exceeded for validation sensors
  - Pre-defined maximum allowed deviation from the mean value of the validation sensors for control and documentation sensors not exceeded

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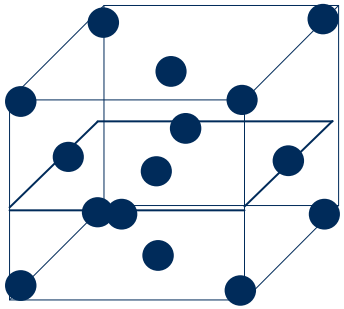
- Operational Qualification (OQ) -

...Points to be checked:
Heat distribution check of the empty chamber
(Identification of cold spots)

- Method
  - Repeated measurement of the empty chamber (e.g. 3 times)
  - Use of in minimum 10 to 12 sensors / m3 of chamber volume
  - One sensor should be near to the control sensor respect. near to the condensate drain
  - Documentation of the exact localisation of the used sensors



Autoclave Chamber with location of validation sensors

Finalisation of OQ

- Deviations must be evaluated
- In case of GMP-critical deviations (e.g. bugs in sterilisation cycles), OQ not successful → remedy of deviation and repetition of IQ (Change Control)
- In case of non GMP-critical deviations, a pre-approval of the OQ is possible in order to start next qualification step

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- Summary IQ / OQ -

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Some Experiences

- Surface roughness out of specified limits
- Valves incorrect mounted
- Documentation incomplete or wrong, e.g. material certificates not available
- Heat distribution out of specified range
- Failures during procedures (bugs in programming)
- ....

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- Performance Qualification (PQ)-
- Process Validation (PV) -

Definition as Performance Qualification or as Process Validation possible (in reality combination of both aspects)

- Focus of PQ on autoclave (heat penetration, reduction of viable germs on bio-indicators)
- Focus of PV on product quality (e.d. decomposition of active ingredient, increase of particulate contamination)

Test with product / material to be sterilised or with adequate placebo

Combination of heat penetration test controlled by external temperature sensors and bio-indicators

Detailed test plan including a risk based approach for planned procedure to be defined

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- PQ / PV -

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Bio-indicators:

Bio-indicators to be used defined in Pharmacopoeias

- Ph.Eur.6, 5.1.2
- USP 29 <1035>

Determination of population in independent laboratory of each batch

- viable spores > 10^5 - 10^7
- D-Value (> 1,5 min at +121 °C)

Independent determined number viable population should be taken for calculation of Sterility Assurance Level (SAL)

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- PQ / PV -

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Bio-indicators

- Incubation for ≥ 14 days between +55 and +60 °C
  (first results after 1 day possible)
- Parallel growth promotion test for each single sterilisation run
- Possible contamination of equipment should be considered and must be avoided by adequate measures (e.g. additional prolonged sterilisation run of empty autoclave after runs with bio-indicators)

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- PQ / PV -

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Procedure

- Pre-requisites and principle procedure of temperature mapping equivalent to temperature mapping of empty chamber
- Definition of the loading scheme(s) (SOP) to be validated
- Adequate and reasoned bracketing possible; validation of worst case loads
- Location of temperature sensor as near as possible to bio-indicators
- Location of temperature sensors inside product, if possible

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- PQ / PV -

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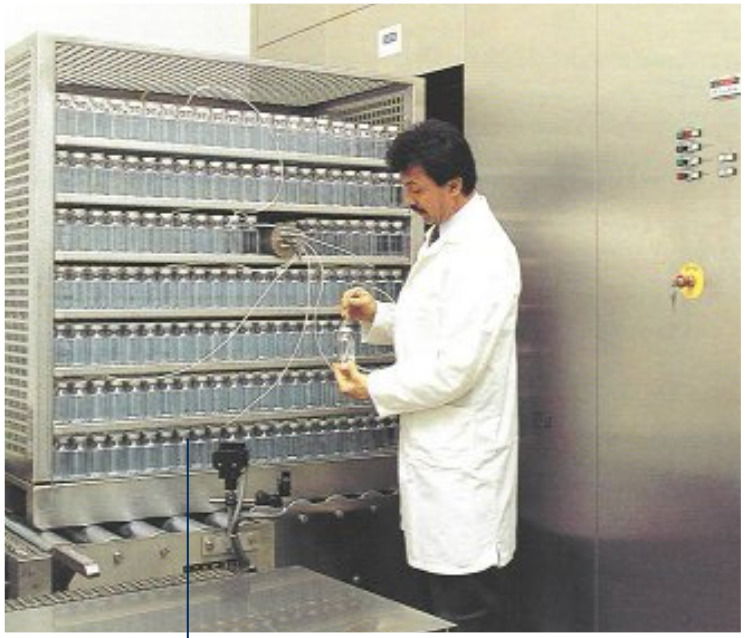
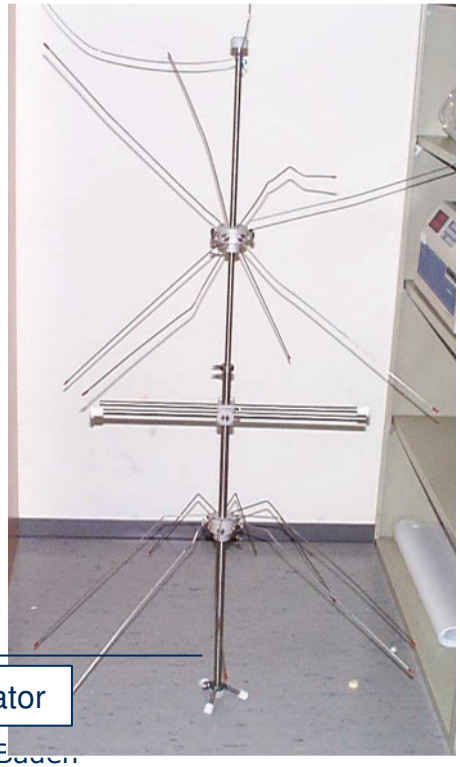
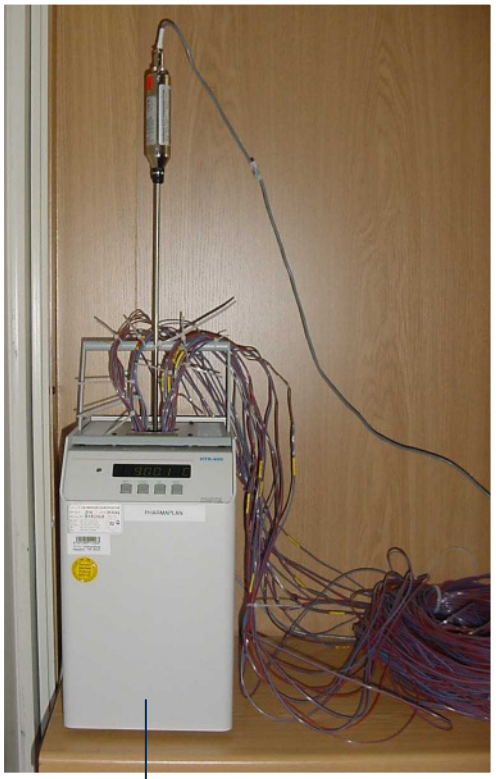


Placing of Validation Sensors in Autoclave Load



Sensor Holder for Kaye Validator



Kaye Validator

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- PQ / PV -

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Procedure:

Selection of cold spots on basic of experience and scientific approach (to be described in detail in the PQ/PV protocol):

- Small tubes
- Between primary and secondary packaging
- Contact areas of different materials

Consider maximum temperature and cycle time to determine maximum degradation

Repeat validation run 3 times

Re-Validation of sterilisation process (e.g. every 6 / 12 months)

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- PQ / PV -

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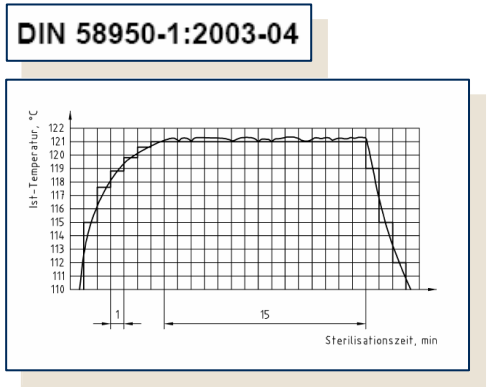

Acceptance Criteria:

Heat distribution

- Correct process incl. recording without alarms
- Predefined maximum standard deviation not exceeded for validation sensors
- Pre-defined maximum allowed deviation from the mean value for each single validation sensor is not exceeded

Microbiological evaluation

- Sterility Assurance Level (SAL) of 10^{-6} to be reached
- Growth of control bio-indicator (positive control)

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- PQ / PV -

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Acceptance Criteria:

Drying effectiveness, if applicable

- Evaluation of remaining humidity by adequate methods for critical material (e.g. rubber stoppers for powder filling lines) by
  - gravimetric methods (e.g. clothes, rubber stoppers)
  - analytical method (Karl-Fischer-titration)
- Optical control for metallic or plastic parts

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- PQ / PV -

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Validation of sterilisation process for parametric release, points to consider:

Guidelines

- EU-GMP-Guide Part 1, Annex 17
- CPMP/QWP/3015/99: Note for guidance on parametric release

- **Follow the requirements of the relevant guidelines**
- **Clear justification for the chosen approach**
- **Define the relevant physical parameters on basis of an risk analysis**
- **Definition of an overkill procedure under consideration of the bioburden**

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- Responsibilities -

The pharmaceutical manufacturer is responsible for the whole qualification on basis of VMP

GMP Risk Analysis should evaluate risks & define test measurements by team work betw. Autoclave manufacturer, engineering/qualification and pharmaceutical producer

Qualification work is usually performed by autoclave supplier / engineering. The approval of test protocols and test reports should be in the responsibility of pharmaceutical producer.

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- Summary -

- Define relevant requirements to be compliant with current GMP-requirements on basis of a **GMP Risk Analysis** during initial specification phase and verify them during Design Qualification
- Perform adequate IQ- and OQ-procedure incl. an adequate approach for Computer Validation. The traceability to GMP Risk Analysis should be considered.
- Define the strategy for PQ/PV with detailed justification and under consideration of the product properties (separate GMP risk assessment)
- Consider the relevant guidelines and recommendations especially for parametric release
- The final responsibility of qualification / validation is held by the pharmaceutical producer.

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- Summary -

→ **Sterilisation is a well known process with a lot of autoclave manufacturer experience.**

→ **Adequate qualification and validation shouldn't be a point of concern during inspections.**

→ **Rational approaches to reduce validation work is possible.**