Qualification and Validation of a BFS-Installation including CIP/SIP

Presented by Christoph Bohn and Stefan Kiesel
Director Rommelag Pharma Service
Senior Manager Rommelag Pharma Service

Content -1-

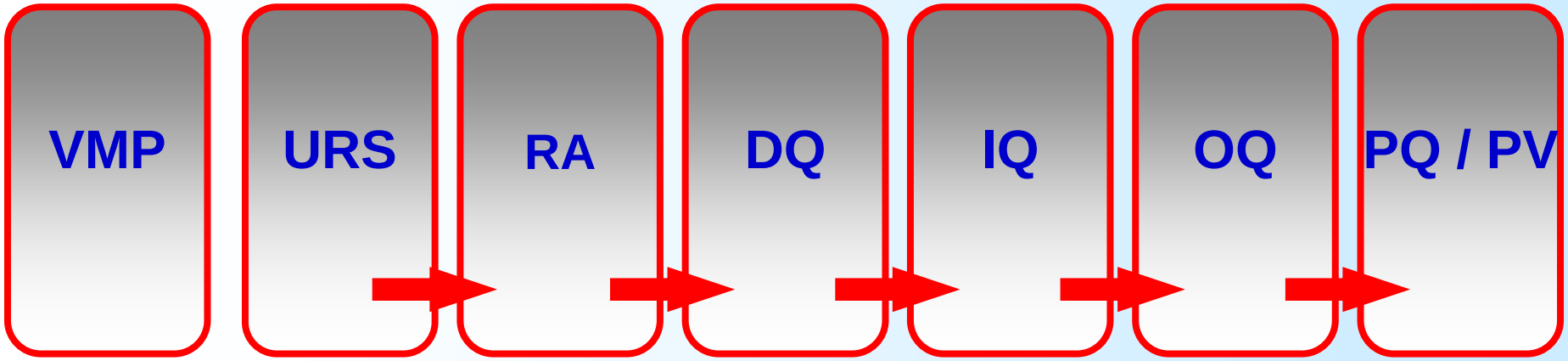
- Definition Qualification and Validation
- Chinese GMP Chapter 7 - Annex 1 BFS
  - Design Qualification
  - Installation Qualification
  - Operational Qualification
  - Performance Qualification, Process Validation
  - Validation Master Plan
  - Good Documentation Practise

Content - 2 -

- Specific Regulation for BFS
  - Cleaning-in-Place Validation
  - Sterilization-in-Place Validation
  - Background Clean-Room Environment

DEFINITIONS QUALIFICATION AND VALIDATION

Qualification steps



VMP = Validation Master Plan
URS = User Requirement Specification
RA = Risk Analysis
DQ = Design Qualification
IQ = Installation Qualification
OQ = Operational Qualification
PQ = Performance Qualification
PV = Process Validation

I. Definitions Qualification and Validation?

《药品生产质量管理规范（**2010**年修订）》

Good Manufacturing Practice (2010 revision)

- **Body part**
- 附录 **1, Annex 1**

Chinese GMP

Chapter 7 Qualification and Validation

Article 138: The **manufacturer** should identify what qualification or validation work **is needed**, to prove that the **critical attributes** of the operations **can be controlled** effectively. The **scope and extent** of qualification or validation should be **determined through risk assessment.**

Chinese GMP

Chapter 7 Qualification and Validation

Responsibilty of the Manufacturer

Critical attributs of the operation can be controlled effectively

Risk assessment to identify qualification and validation scope

THINK DEFINE ACT

International Operators Association

Qualification steps

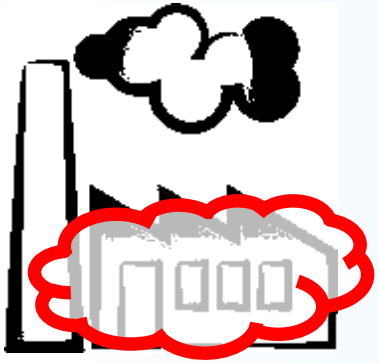
VMP → URS → RA → DQ → IQ → OQ → PQ / PV

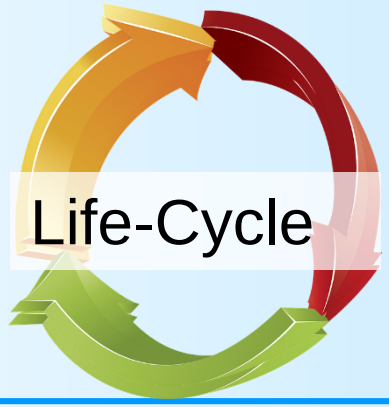
THINK DEFINE ACT

Chinese GMP

Chapter 7 Qualification and Validation

Article 139: The premises, facilities**, equipment** and testing instruments **should be qualified**. The validated manufacturing process, operation procedures and testing methods should be used for production, operation and testing, and **this validated state should be maintained.**



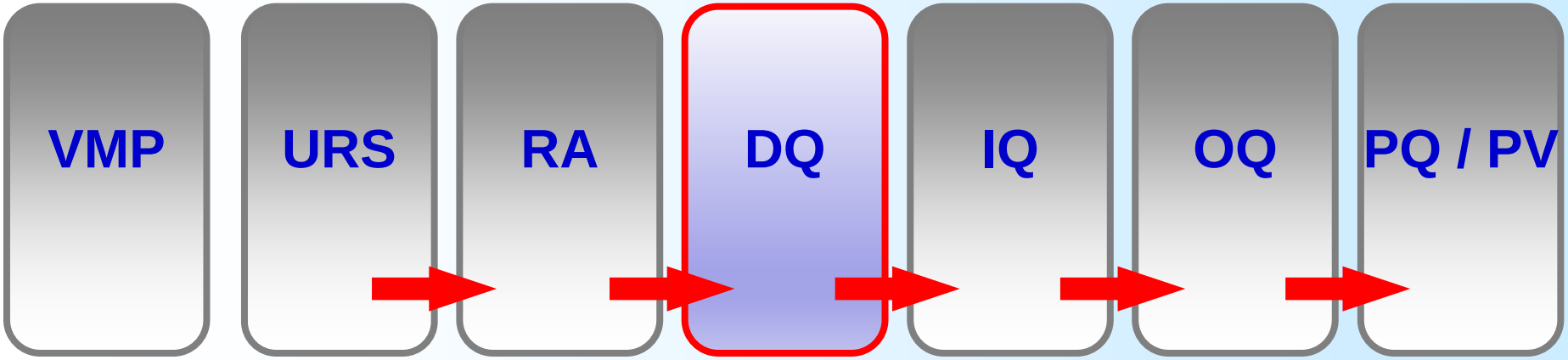


Chinese GMP

Chapter 7 Qualification and Validation

Article 140: **Documents and records should be established for qualification and validation as an evidence** for the following intended purposes:

Qualification step: Design Qualification

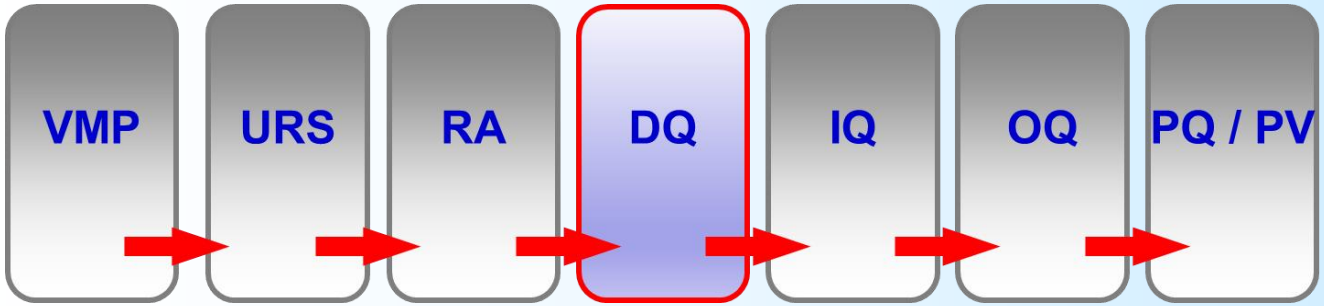


Article 140 1. **Design qualification is to verify that the design** of the premises, facilities and equipment is **suitable for the intended use** and in **compliance** with the provisions;

Qualification step: Design Qualification

⇨ Not only a document! – It is a qualification phase

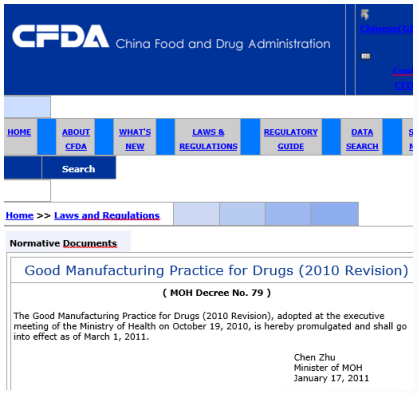
- Compliance of the design with GMP requirements has to be demonstrated
- Verification of the user requirements



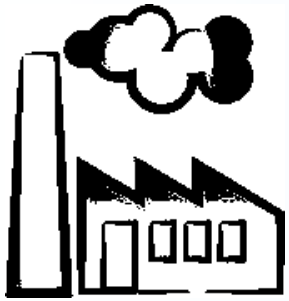
BFS IOA
BFS Training 2018 Kunming

International Operators Association

For Blow-Fill-Seal:



GMP Regulations

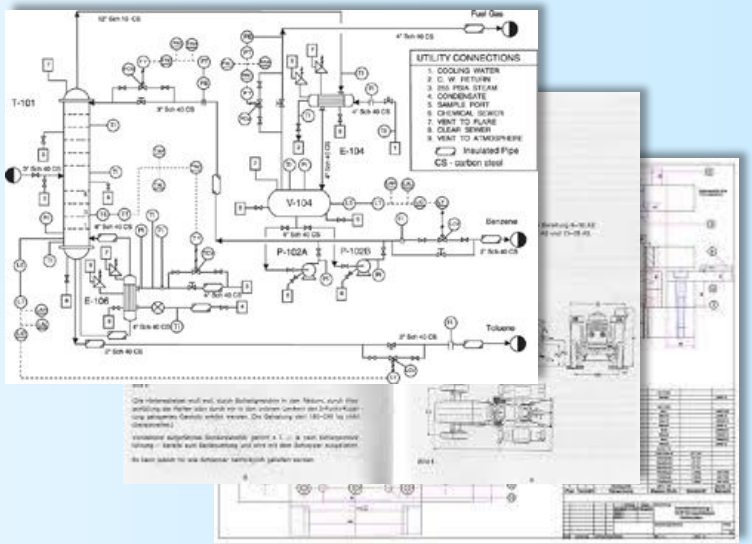


User Requirements

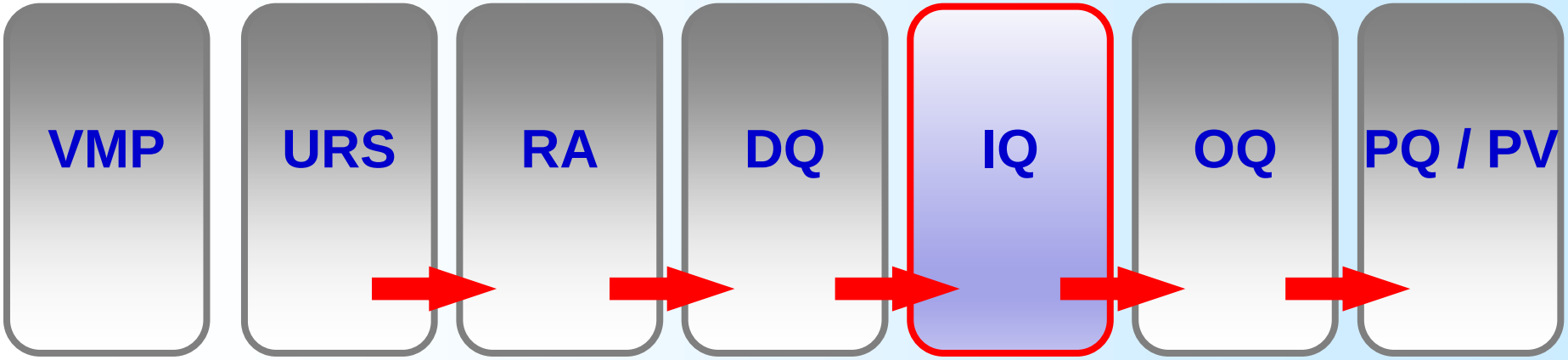
Design Qualification
Protocol => Report

DQ

Design Documents



Qualification step: Installation Qualification



Article 140 2. **Installation qualification** is to verify that the premises, facilities and equipment **have been built and installed** in accordance with their design specifications;

BFS IOA
BFS Training 2018 Kunming

International Operators Association

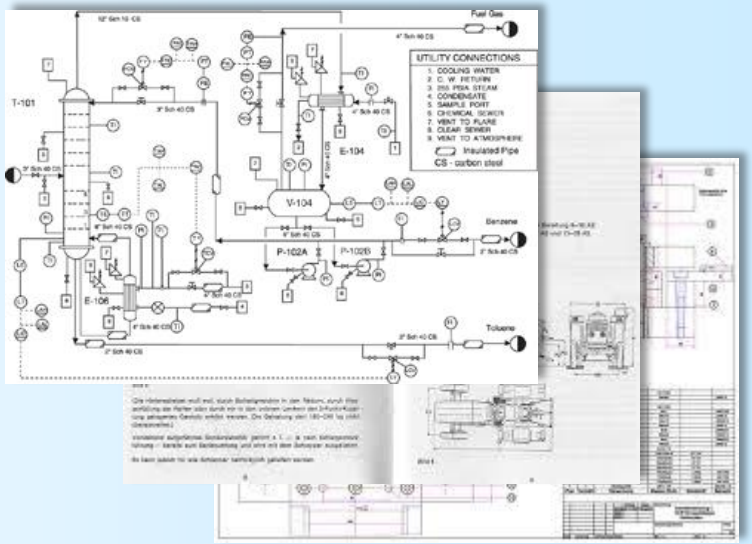
For Blow-Fill-Seal:

IQ

Installation Qualification
Protocol => Report

Equipment

Documents



International Operators Association

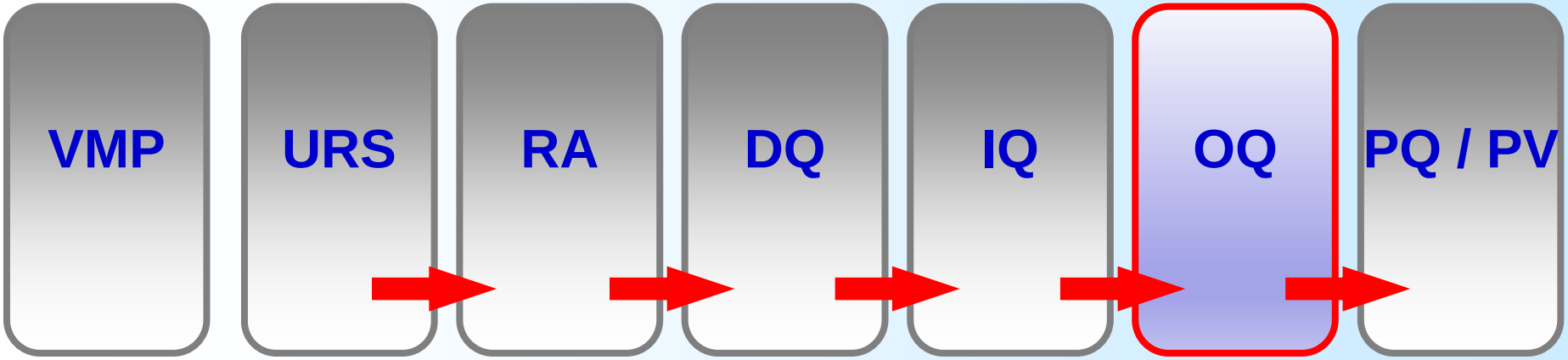
For Blow-Fill-Seal:

IQ

For example:

- ☑ Checking of the installation against P&I Diagramm
- ☑ Verification of slopes and Dead-legs in pipe work
- ☑ Verification of the surface roughness of the product-contacting components (measurement or certificate)
- ☑ Verification of the material specifications
- ☑ Verification of cleanability
- ☑ Check of the technical documentation for the components
- ☑ Verification of the calibration instructions / certificates for instrumentation
- ☑ …..

Qualification step: Operational Qualification



Article 140 3. **Operational qualification** is to verify that the premises, facilities and equipment **operate** in **accordance** with their **design specifications**;

For Blow-Fill-Seal:

Operational Qualification
Protocol => Report

OQ

Equipment in Operation

Specified Functions

For Blow-Fill-Seal:

OQ

For example:

- ☑ Functional check of the components:
  - ☑ Valves, measuring equipment, etc.
- ☑ Documentation of the process parameters
- ☑ Checking of the safety equipment
- ☑ Checking of the control system
- ☑ Checking of the process steps: CIP, SIP, Production
- ☑ …

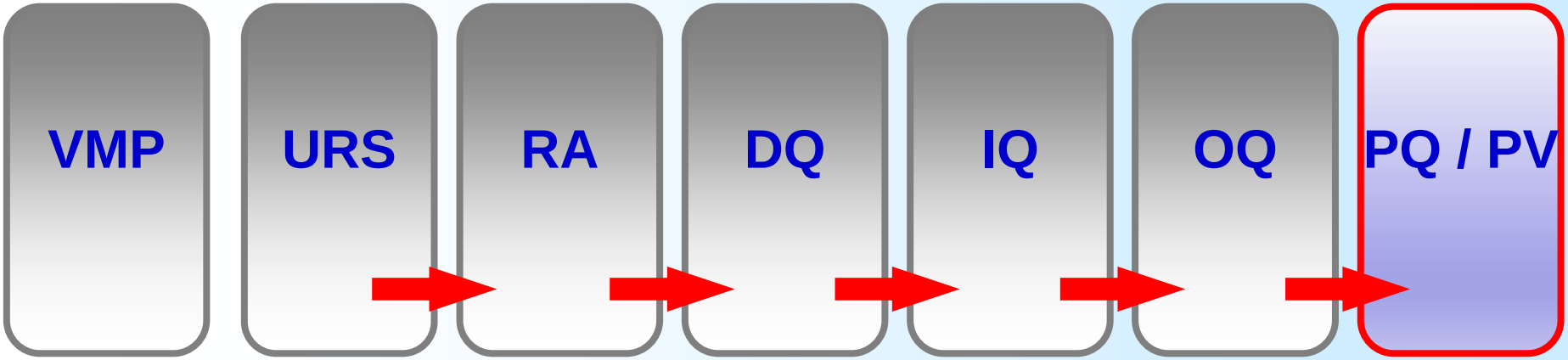
For Blow-Fill-Seal:

OQ

Process capability - for example:

- ☑ Wall thickness: establishing minimum and maximum parameters, correlation to empty unit weight etc.
- ☑ Container opening and container functionality (e.g. luer fit)
- ☑ Fill volume
- ☑ Handling of stoppages (e.g. whether a certain amount of product must be discarded upon re-start)
- ☑ …

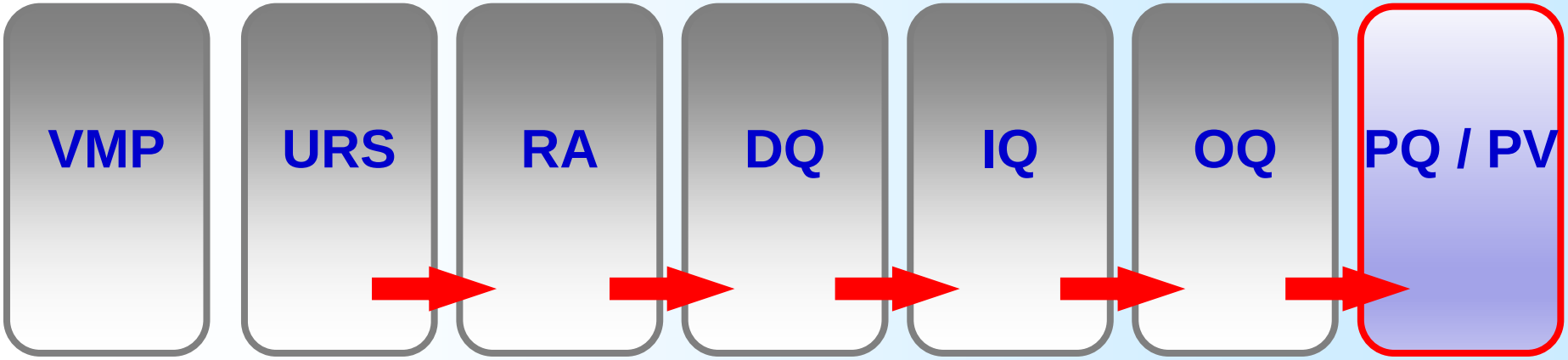
Qualification step: Performance Qualification / Process Validation



Article 140 4. Performance qualification is to **verify** that the premises, facilities and equipment, under **normal operating procedures and process conditions**, can **consistently meet performance specifications**;

5. Process validation is to verify that **a manufacturing process, operated** within established parameters, can **consistently produce products** that are suitable for their intended use and in accordance with the registration requirements.

Qualification step: Process Validation



Article 141: Before any new manufacturing formula or process is adopted, its suitability for routine **production should be validated**. The manufacturing process by using the defined starting materials and equipment, should **consistently produce products** suitable for their intended use and in accordance with the registration requirements.

For Blow-Fill-Seal:

Process over several steps

Performance Qualification
Protocol => Report
Process Valildation
Protocol => Report

PQ
PV

Specified Products

For Blow-Fill-Seal:

PQ

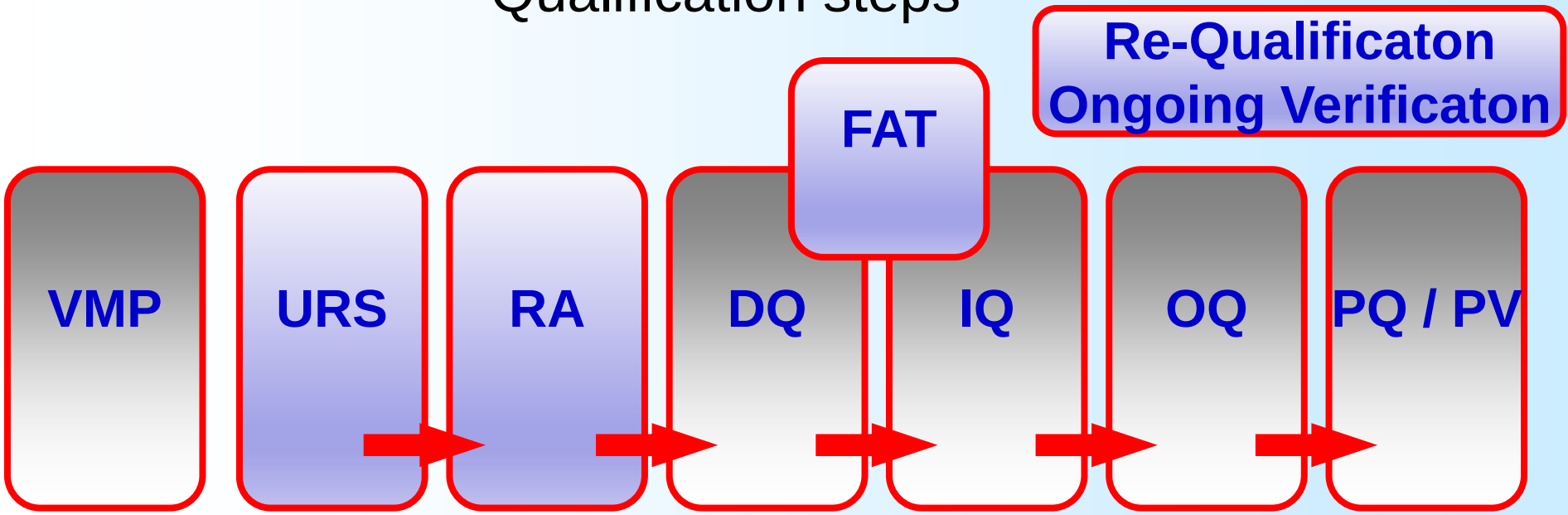
Process capability - for example:

- ☑ Wall thickness: establishing minimum and maximum parameters, correlation to empty unit weight etc.
- ☑ Container opening and container functionality (e.g. luer fit)
- ☑ Fill volume
- ☑ Handling of stoppages (e.g. whether a certain amount of product must be discarded upon re-start)
- ☑ …

International Operators Association

DIFFERENCES TO EUROPE GMP GUIDELINE ANNEX 15

Qualification steps



VMP = Validation Master Plan
URS = User Requirement Specification
RA = Risk Analysis
DQ = Design Qualification

IQ = Installation Qualification
OQ = Operational Qualification
PQ = Performance Qualification
PV = Process Validation
FAT = Factory Acceptance Test

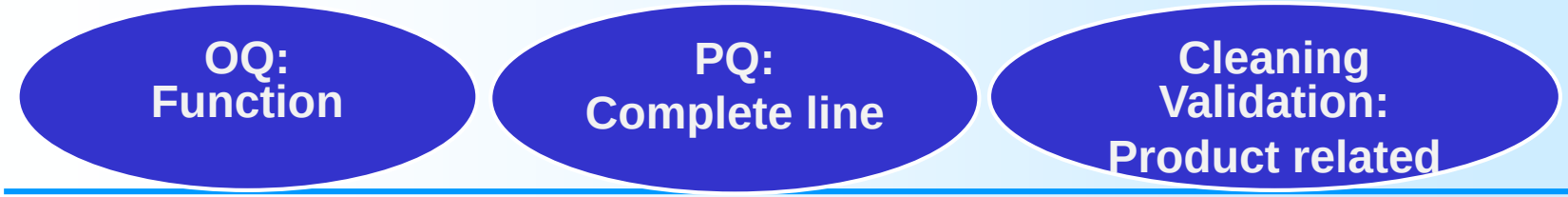
Chapter 7 Qualification and Validation

Article 142: Qualification or validation should be performed when there is **a change** in **major factors influencing the product quality**, including any change in starting materials, immediate packaging materials, production equipment and environment (or premises), manufacturing process or testing method, etc. Where necessary, the changes should be approved by drug regulatory departments.

Risk based

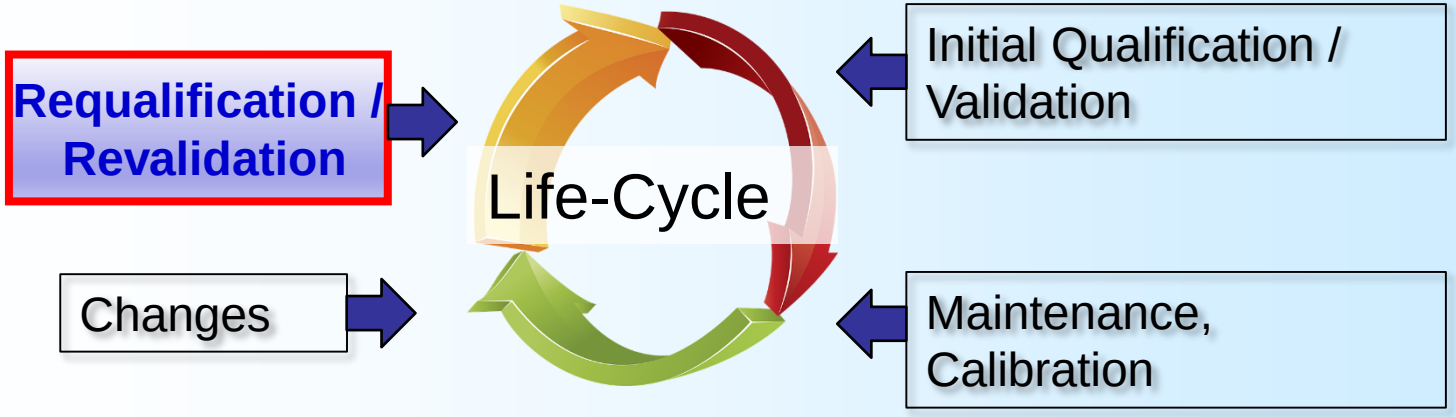
Chapter 7 Qualification and Validation

Article 143: **Cleaning validation** should be performed in order to confirm the effectiveness of a cleaning procedure, to effectively prevent contamination and cross-contamination. In cleaning validation, a comprehensive consideration should include factors such as the use of the equipment, the detergents and disinfectants used, the sampling methods and locations, the relevant recovery rate of sampling, the nature and limit of residues, and the sensitivity of the testing method for residues.



Chapter 7 Qualification and Validation

Article 144: Qualification and validation should **not be considered as a one time activity**. After initial qualification and validation, **requalification or revalidation** should be carried out according to the product quality review. Critical manufacturing processes and operation procedures should be revalidated at defined intervals to ensure the intended outcome.



Chapter 7 Qualification and Validation

Article 145: The manufacturer should make a **validation master plan** to document the key information of qualification and validation.

Article 146: Requirements should be defined in the validation master plan or other relevant documents to maintain **the consistent status** of premises, facilities, equipment, testing instruments, process, operation procedures and testing methods.

International Operators Association

Qualification steps

VMP → **URS** → **RA** → **DQ** → **IQ** → **OQ** → **PQ / PV**

THINK DEFINE ACT

QUALIFICATION STEPS
VALIDATION MASTER PLAN

VMP

- Validation strategy and philosophy of the company
- Responsibilities
- “Road map” for Qualification and Validation
- Bracketing Concepts
- Requalification, Revalidation Concept
- …

Chinese GMP

Chapter 7 Qualification and Validation

Article 147: The qualification or validation protocol should be prepared based on its object. The protocol should **be reviewed and approved. Responsibilities should be specified in the protocol.**

Protocol

Review and Approval

- ✔ Responsible Person(s)
- ✔ Quality Assurance

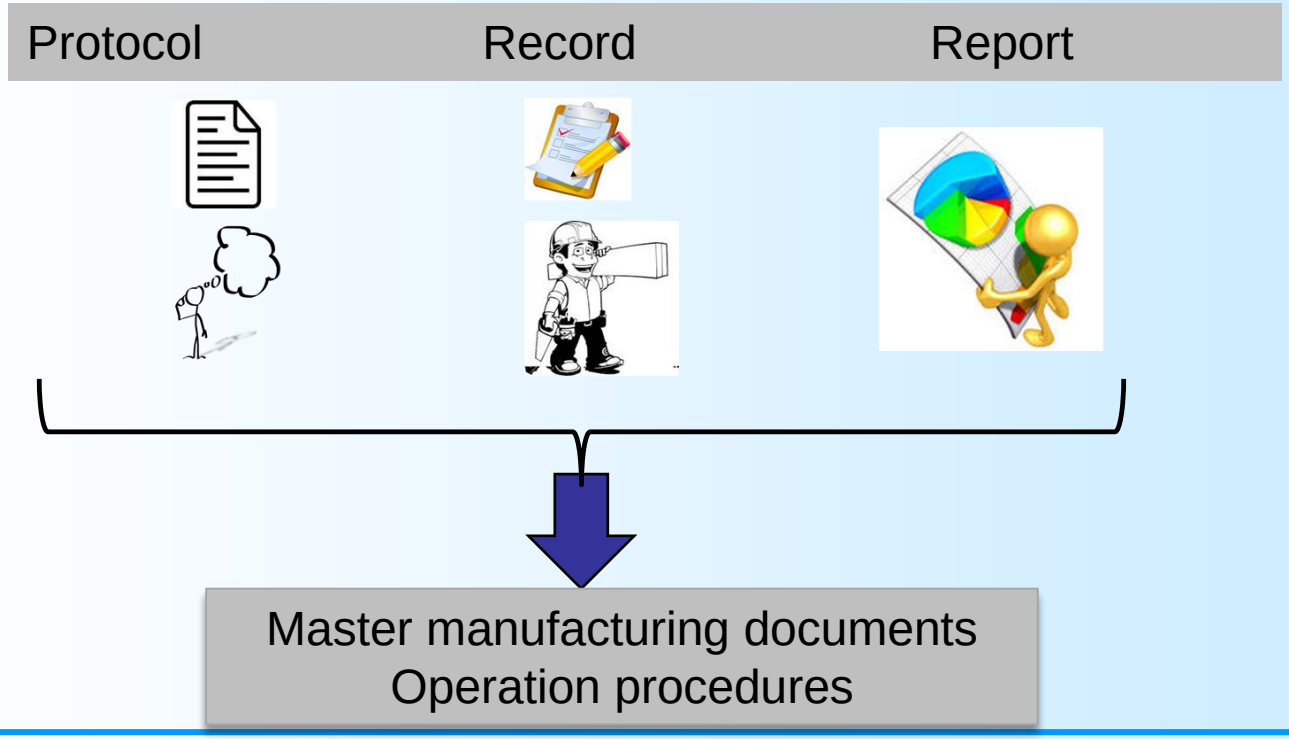
Chapter 7 Qualification and Validation

Article 148: Qualification or validation should be implemented in accordance with a **predefined and approved protocol**, and be **recorded**. Upon completion of qualification or validation, a **report** should be **prepared, reviewed and approved**. The qualification or validation result and conclusion (including comments and suggestions) should be recorded and archived.

Protocol	Record	Report
 	 	
Think / Define	Act	Prepare, Review, Approve

Chapter 7 Qualification and Validation

Article 149: Master manufacturing documents and operation procedures should be established according to the validation results.

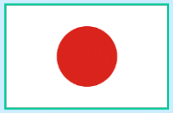


Specific Regulation for BFS Technology:

China:	**China GMP Annex 1 Chapter 16 BFS 2010**
World Wide:	WHO good manufacturing practices for sterile pharmaceutical products
	WHO Technical Report Series, No. 961, 2011 Annex 6, Chapter 9 BFS
Europe:	EU-GMP Guide Annex 1, Chapter 26-27, since 1996
USA:	FDA Guidance for Industry - Aseptic Processing 2004 Appendix 2: Blow-Fill-Seal Technology **USP <1116>** MICROBIOLOGICAL CONTROL AND MONITORING OF ASEPTIC PROCESSING ENVIRONMENTS
Japan:	Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing / 2005 / Chapter 20.2 BFS
……	







Specific Regulations for BFS technology

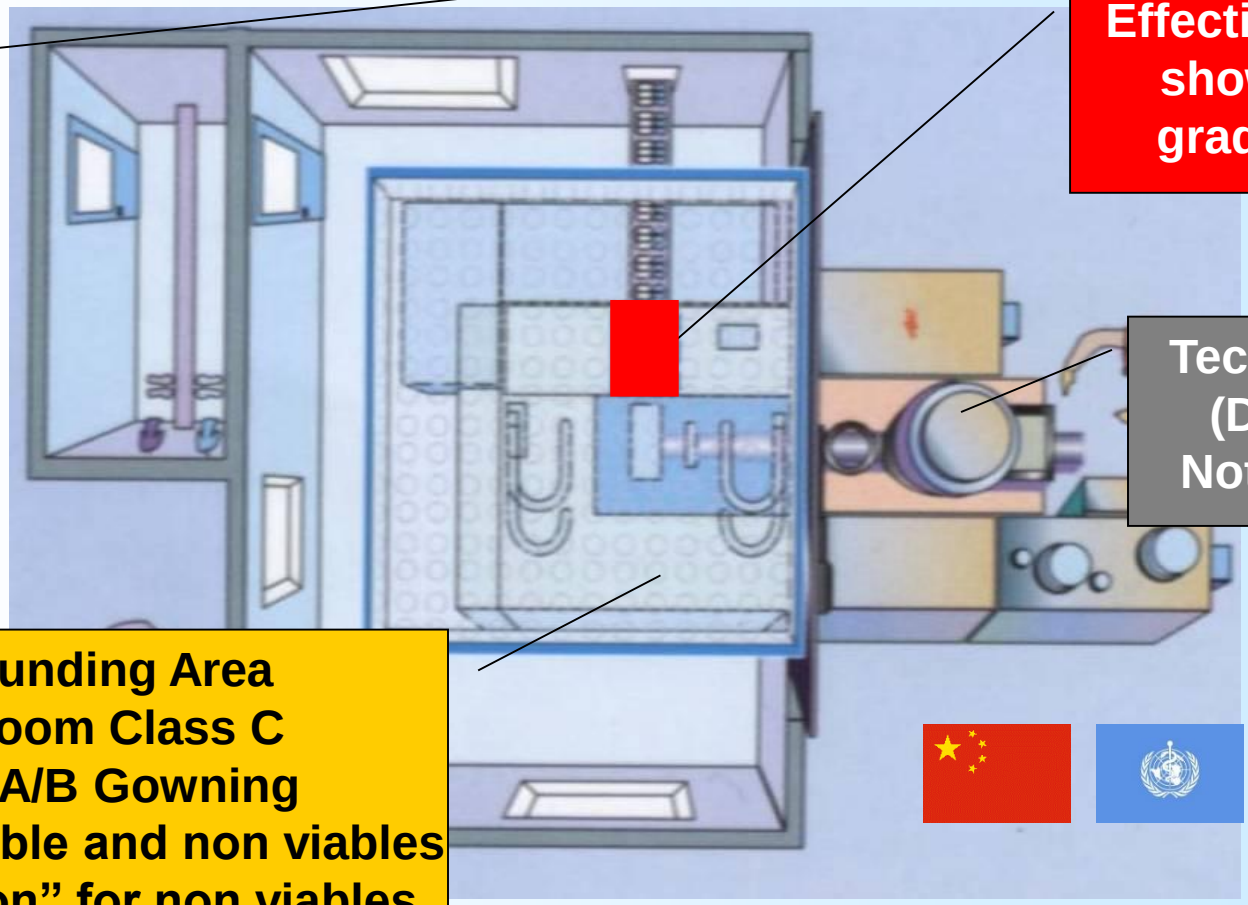
Chapter 5 Blow/fill/seal technology

Article 17 Blow/fill/seal equipment used for **aseptic production** which is fitted with an **effective grade A air shower** may be installed in at least a grade **C environment**, provided that **grade A/B clothing** is used. Under **at rest condition**, the suspended **particles and microorganism** should meet the standards. Under **in operation condition**, the **microorganism** should meet the standards. …

International Operators Association

BFS FOR ASEPTIC PRODUCTION - EXAMPLE

Secondary Packaging Not classified



Effective Air shower grade A

Technical Area (Dark Side) Not classified

- Surrounding Area Clean-Room Class C
- Class A/B Gowning
- “at Rest” viable and non viables
- “in operation” for non viables

Specific Regulations for BFS technology

Chapter 5 Blow/fill/seal technology

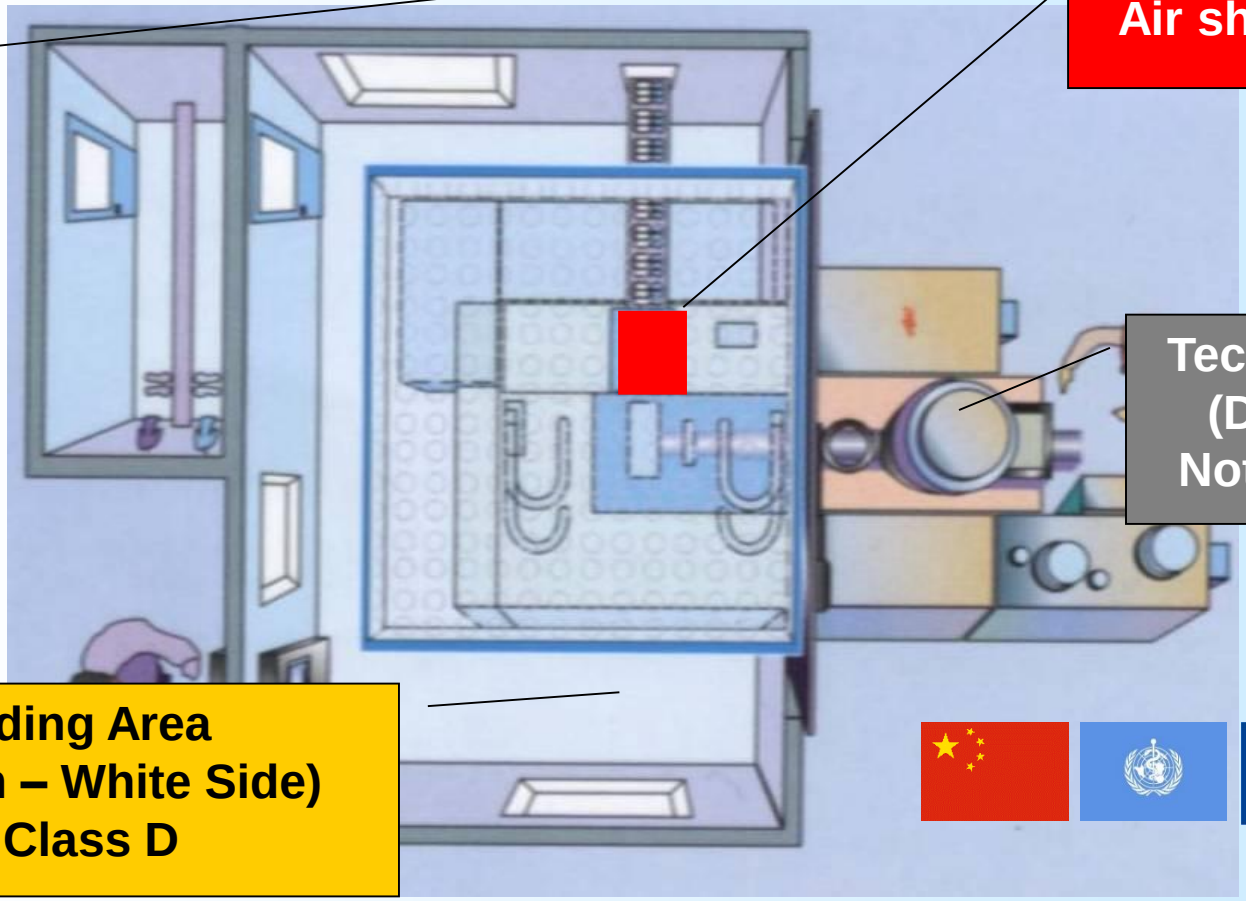
Article 17 …. Blow/fill/seal equipment used for the production of **products** which are **terminally sterilised** should be installed in at least a **grade D environment**.

International Operators Association

BFS FOR TERMINALLY STERILISED PRODUCTS - EXAMPLE

Secondary Packaging Not classified

Air shower



Technical Area (Dark Side) Not classified

Surrounding Area (Clean Room – White Side) Room Class D

Specific Regulations for BFS technology

Chapter 5 Blow/fill/seal technology

Article 18

Because of this special technology particular attention should be paid to, at least the following:

DQ IQ OQ PQ PV

- equipment design and qualification
- validation and reproducibility of cleaning-in-place and sterilisation-in-place

CIP / SIP Validation

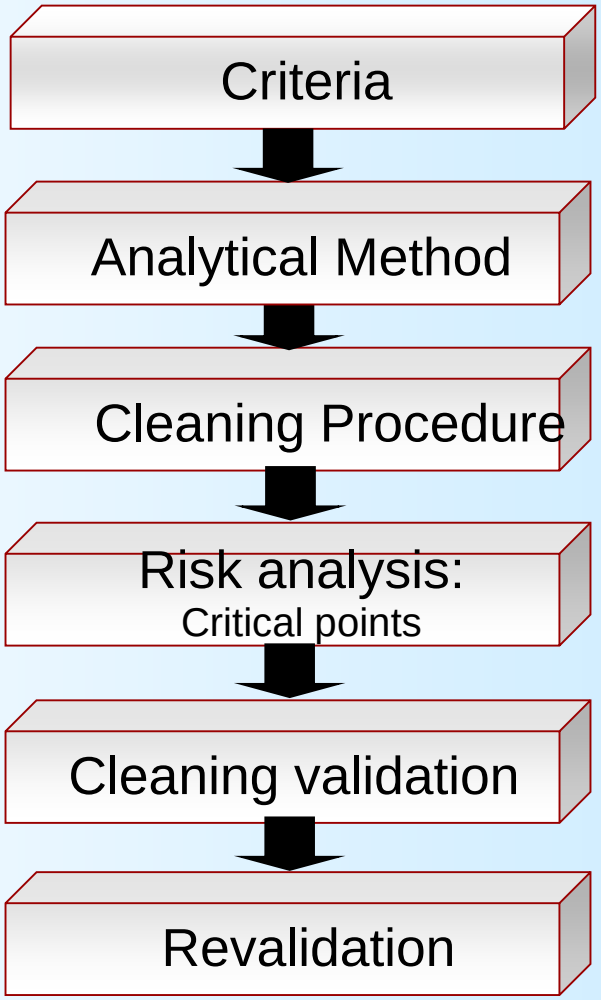
- background clean room environment in which the equipment is located

Qualification Clean Room

- operator training and gowning operations in the critical zone of the equipment including any aseptic assembly or set-up prior to the commencement of filling.

Media fill

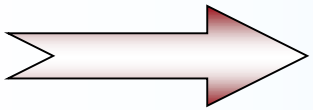
CIP Validation



CIP Validation

Sample Techniques

- **Swabs**
  - Physically removes samples
  - Technique needs some experience
- **Rinse Sampling**
  - Easy to sample, non-intrusive
  - Limited info about actual surface cleanliness

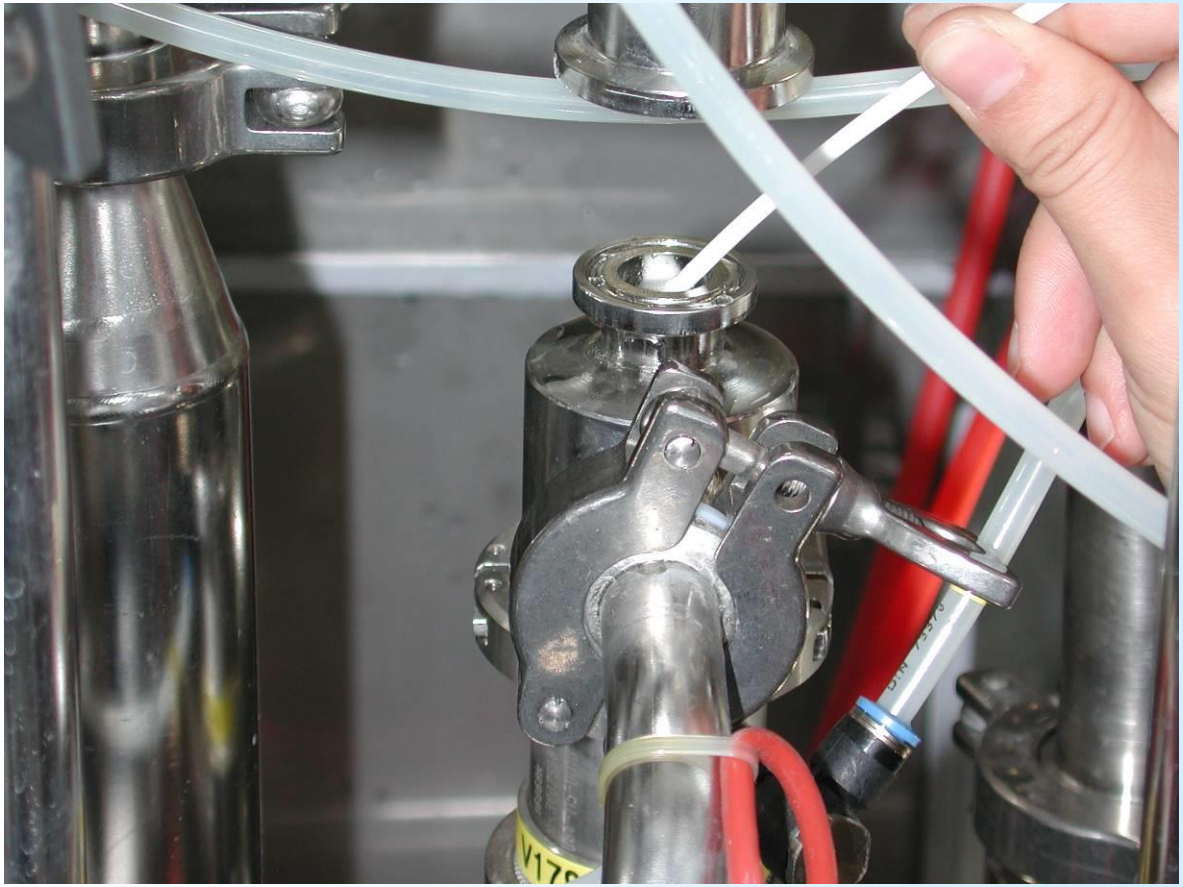


Combination of both techniques along with visual inspection is useful

CIP Validation

Swab sampling:

CIP Validation



CIP Validation

Cleaning procedure:

- Cleaning procedure with defined and reproducable cleaning steps
- Cleaning medium: water (hot or cold), steam, acid / caustic, detergents etc.
- Pressure, Flow, Time, Temperature

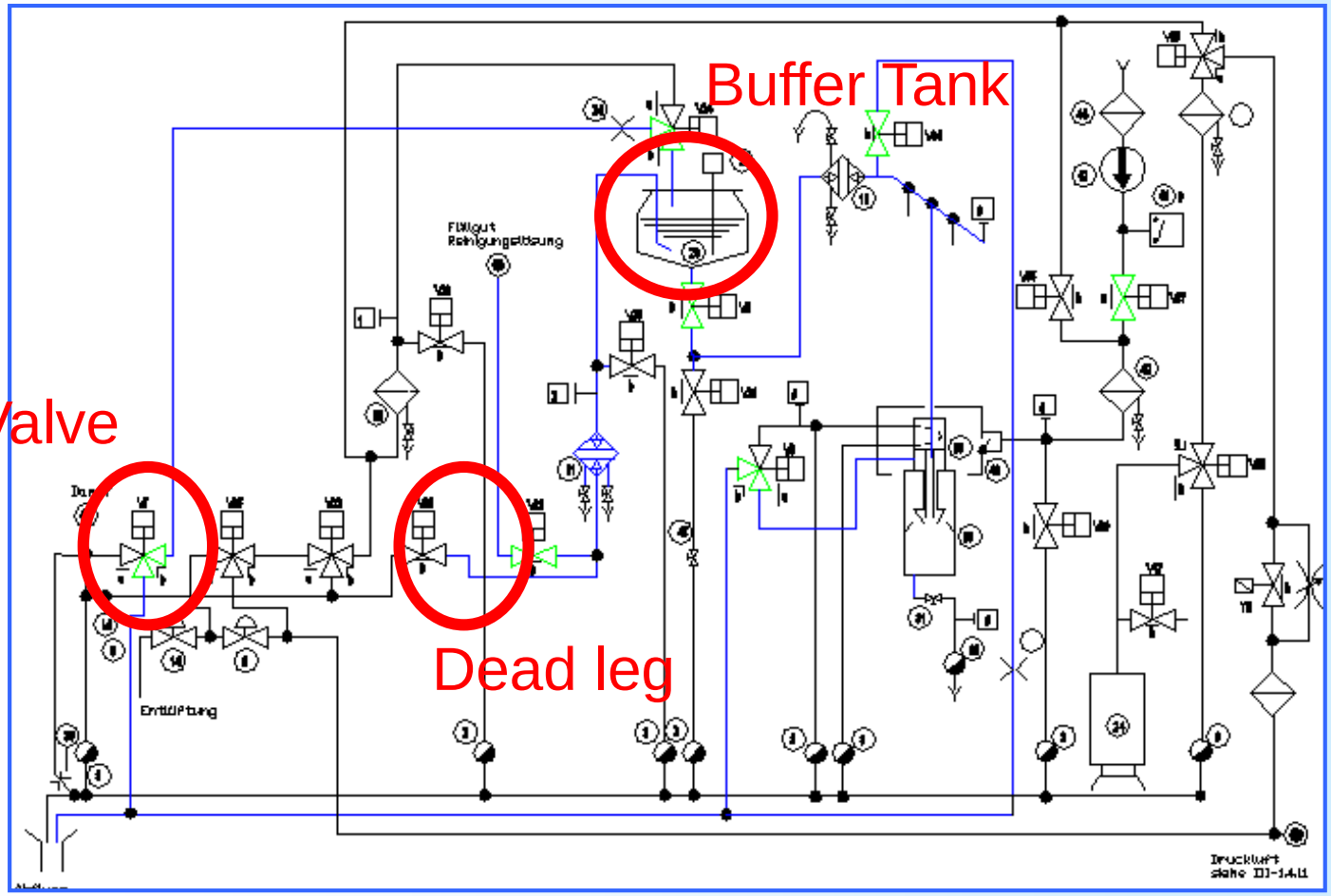
CIP Validation

Critical points to clean:

- Dead-Legs
- Diameterchanges of Pipes
- Valves
- Large Volumes, for example buffer tank
- Low flow rate of rinsing solution
- Edges and holes : stirrer, valves
- Sealings, gaskets

International Operators Association

CIP Validation – Critical Points - Example



CIP Validation

Cleaning validation runs:

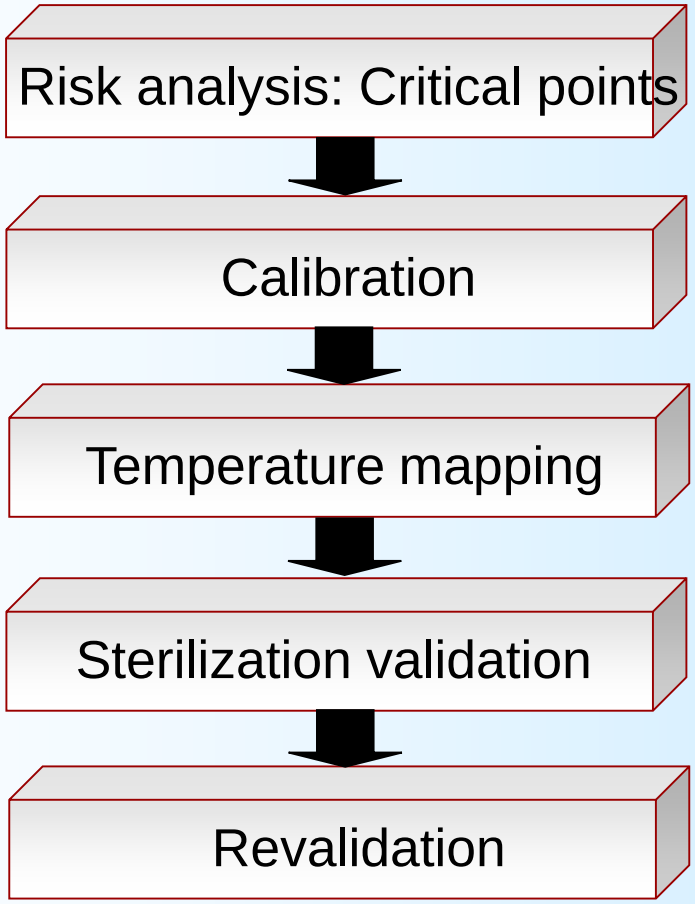
- Sampling incoming Water, Steam
- Positive samples
- Swab samples
- Rinse samples
- Documented cleaning procedure

CIP Validation

Cleaning validation:

- At least three successful cleaning validations for each product to show reproducibility
- Groups of products with similar chemical characteristics can be validated with the worst case product => Bracketing Concept

SIP Validation



SIP Validation

Criteria:

- SIP Validation to prove the microbial reduction of Bacillus stearothermophilus ATCC 7953
  Concentration germs: > 10^6
- D-value: > 1,0
- Standard cycle should demonstrate Overkill conditions: at least 12 log reduction
- Temperature: > 121,1 °C

SIP Validation

Saturated steam:

- Saturated steam
- Pressure: 2,5 bar ~ Temperature 121 °C
- Pressure: 3,0 bar ~ Temperature 135 °C
- Capacity of the steam generator
- Stability of the filter material

SIP Validation

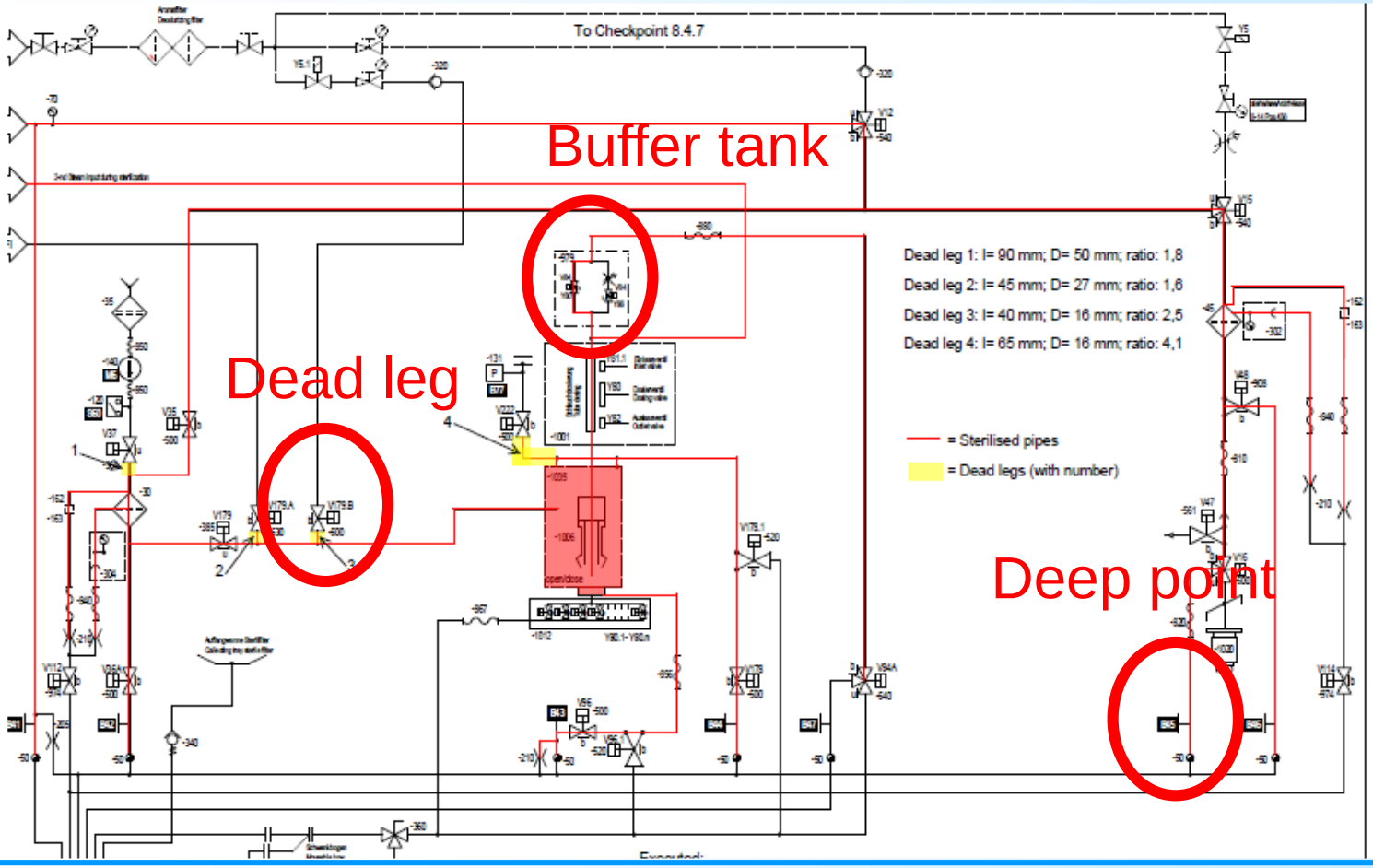
Risk analysis:

Critical points:

- Dead-legs
- Large volumes (Buffer tank)
- Change in diameter
- Deep points in pipe systems
- Heavy components (pumps, vessel)
- Parallel ways for steam

International Operators Association

SIP Validation – Critical Points - Example



SIP Validation

Critical Points:

SIP Validation

Temperature mapping:

- To find out the cold spots
- To verify position of stationary thermocouples
- To verify sterilization procedure

SIP Validation

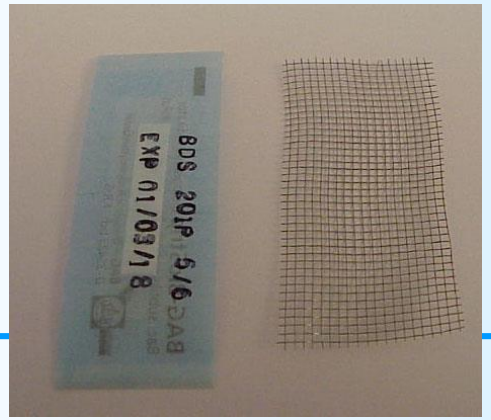
SIP-Validation:

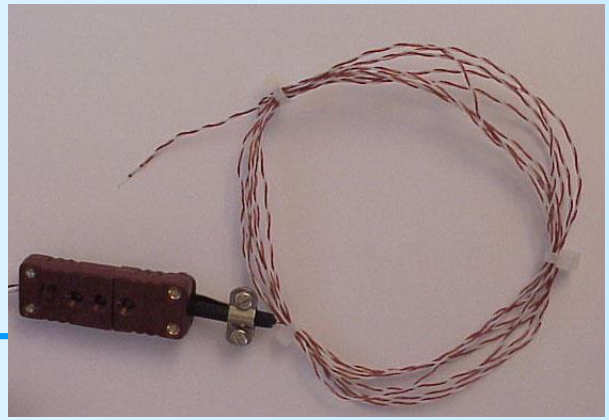
- For example 3 times half cycle with bio indicators
- Worst case cycle e.g. 15 min
- Full cycle = standard cycle e.g. 30 min

SIP Validation

SIP-Validation:

- Bio indicator stripes packed in paper for saturated steam
- > 10^6 germs of Bacillus stearothermophilus
- Verification of spore concentration
- Positive growth control for each validation
- Storage BI under controlled conditions





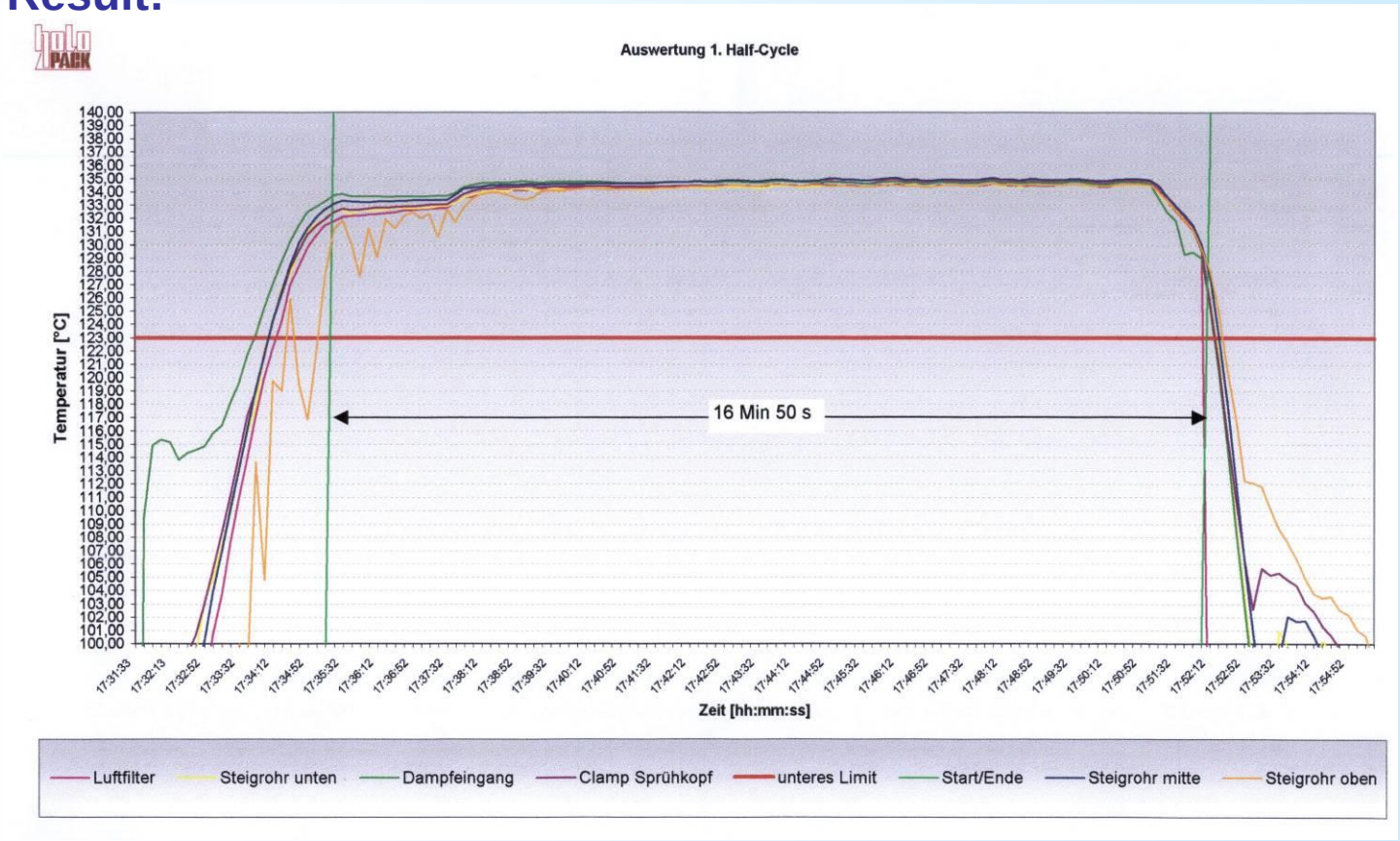
SIP Validation

Result:

- Three Worst case cycles with bio indicator
- One full cycle
- Coldest point, Minimum F_0-Value
- Slowest point to reach temperature
- Growth test negative

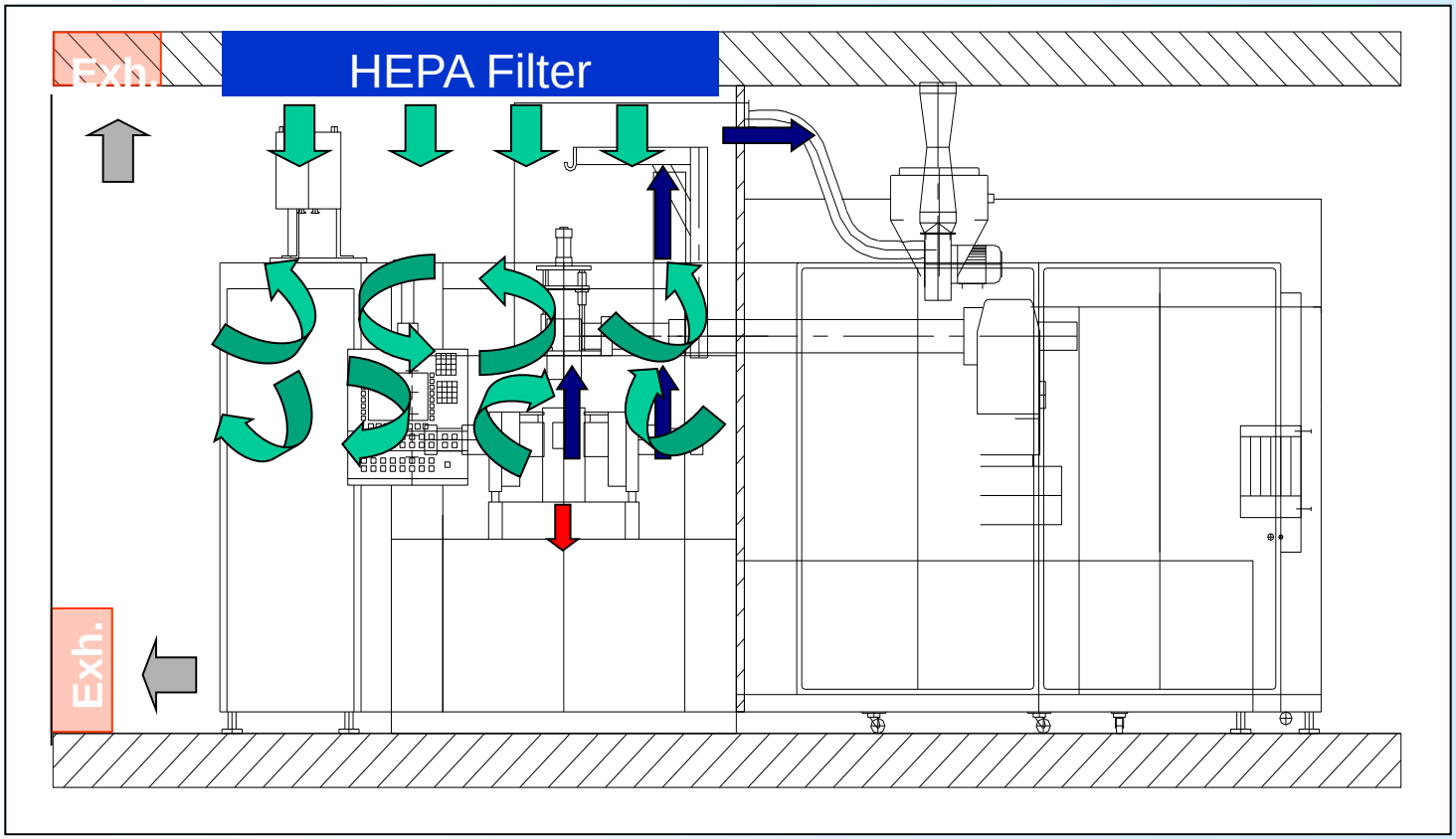
SIP Validation

Result:



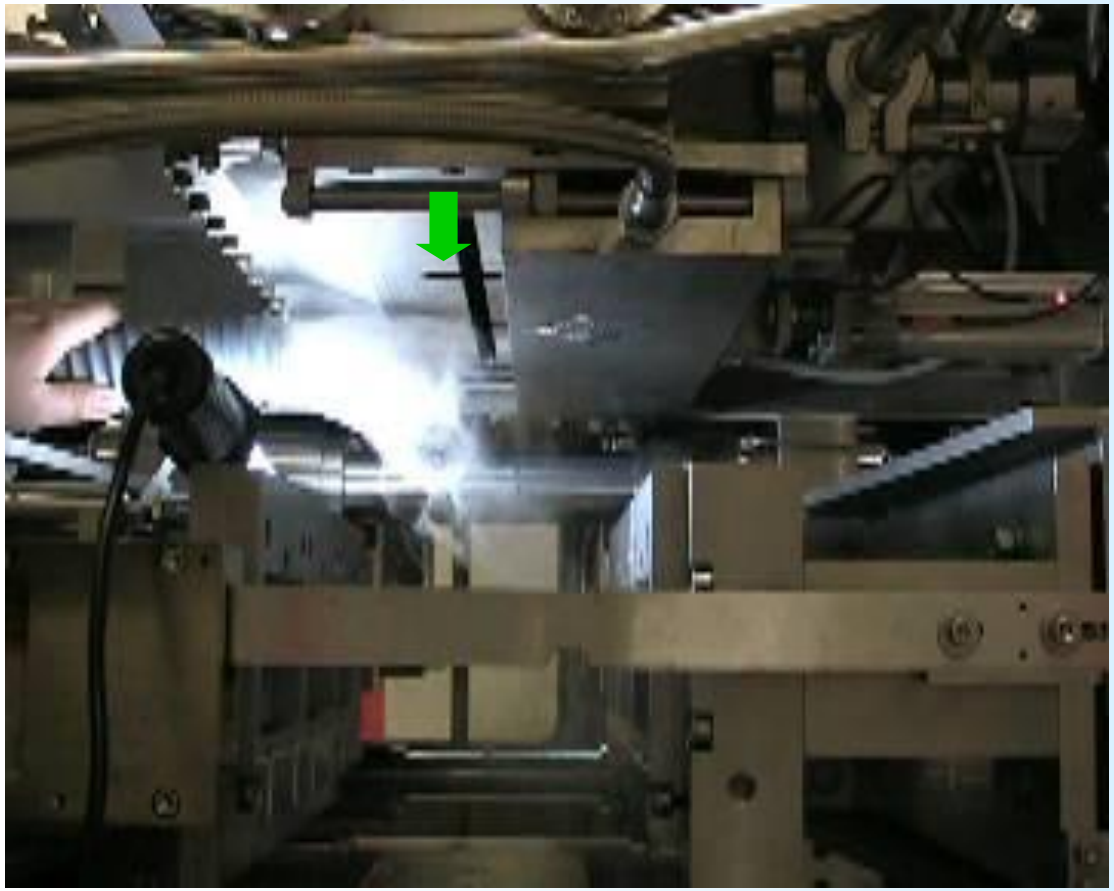
BACKGROUND CLEAN ROOM ENVIRONMENT

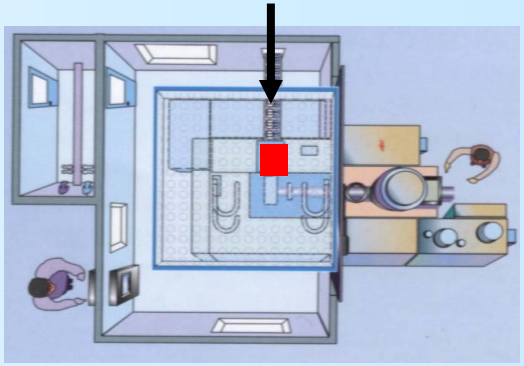
Air flow pattern example bottelpack 321:



BACKGROUND CLEAN ROOM ENVIRONMENT

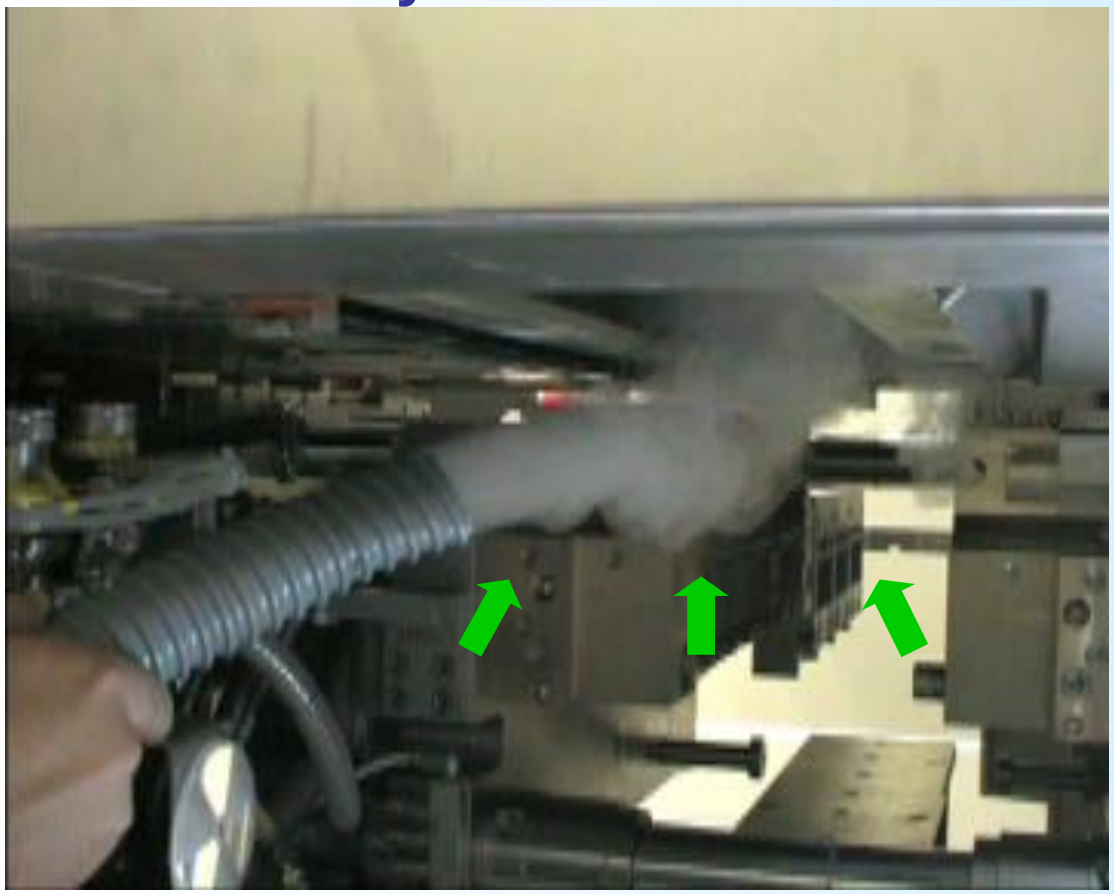
Air flow study ASR:

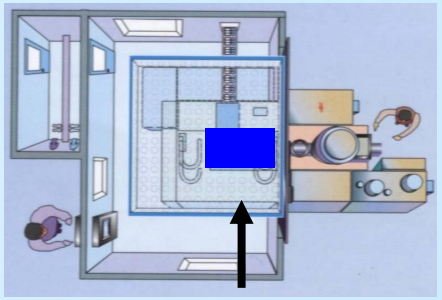




BACKGROUND CLEAN ROOM ENVIRONMENT

Air flow study exhaust:

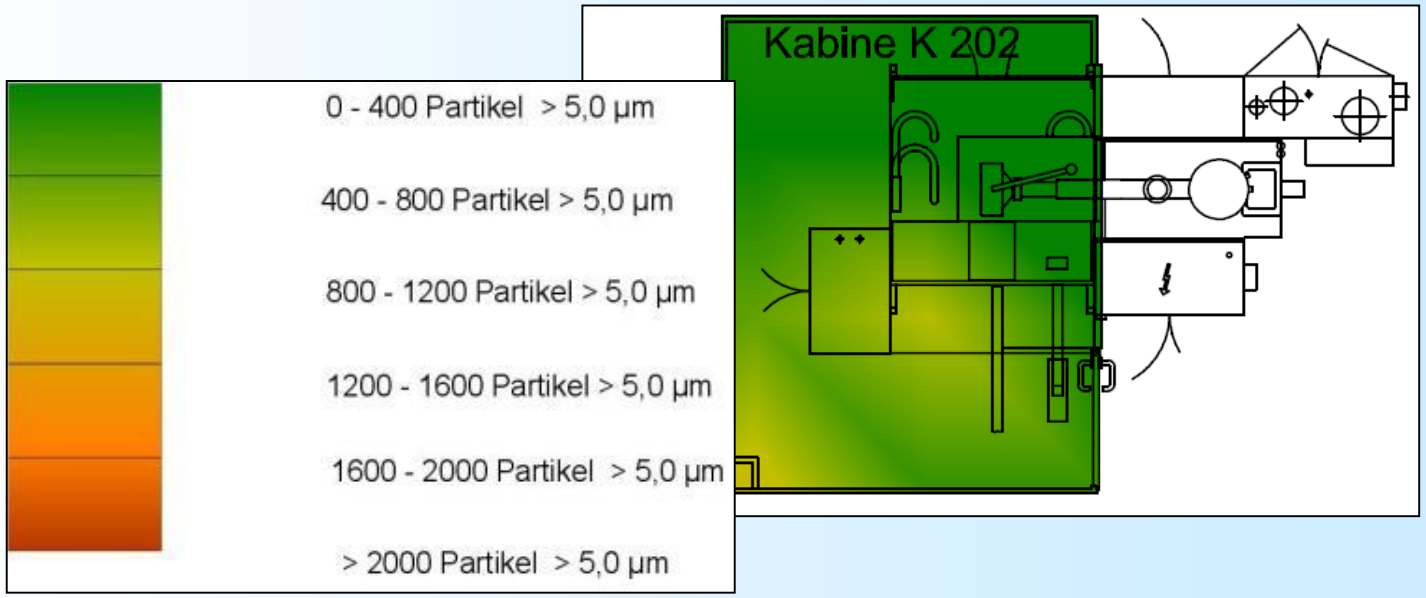




BACKGROUND CLEAN ROOM ENVIRONMENT

Particle mapping:

Evaluation:



SUMMARY: QUALIFICATION AND VALIDATION OF A BLOW-FILL-SEAL SYSTEM

- Specifications has to be defined in a URS and approved in Design Qualification
- Risked based approach: Qualification and Validation work have to cover critical attributes
- Because of the technology there are some specific points in qualification
- It is mandatory to have an experienced supplier as partner – Quality by design!
- Qualification and Validation should be used to have additional benefit: to optimize and have a safe, robust and effective process

Thank you for your attention!

Please feel free to ask

Christoph Bohn

Director Pharma Service

Senior Technical Consultant

Christoph.Bohn@rommelag.com

Stefan Kiesel

Senior Manager Pharma Service

Stefan.Kiesel @rommelag.com