SIMVal

Hot or Not?

The Importance of Temperature Mapping and Validation

https://simval.dk/knowledge-hub

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Agenda and Objectives

- Introduction
- Why Temperature Validation Matters
- Guidelines and Best Practice
- C&Q Lifecycle
- Case study 1: Cold storage
  - Temperature Mapping
  - Reporting → From Mapping to Monitoring
- Case Study 2: Sterilization

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Who is SIMVal?

- Engineering company specialized in validation, engineering, and temperature calibration for the life-science and pharmaceutical industry
- Proven track record of various engineering and validation projects
- Growing company
- On track to DANAK accreditation and ISO 17025 with ongoing laboratory expansion for full-package solutions
  - Project supported by Biosolutions Zealand II

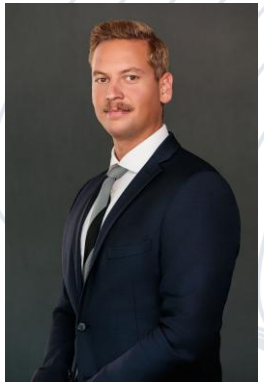
Meet the Team

Mads Skjærbæk

Flow and Thermodynamics in GxP Environments

Johan Bjørn Ildor

C&Q and Compliance Requirements



Daniel Tykgaard Madsen

C&Q and Compliance Requirements

Kristian Mikkonen Leth

SAP Specialist

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Project Manager

Nicolai Grøn

Student Assistant

Mads Skjaerbaek

Flow and Thermodynamics in GxP Enviroments

Mads Skjærbæk

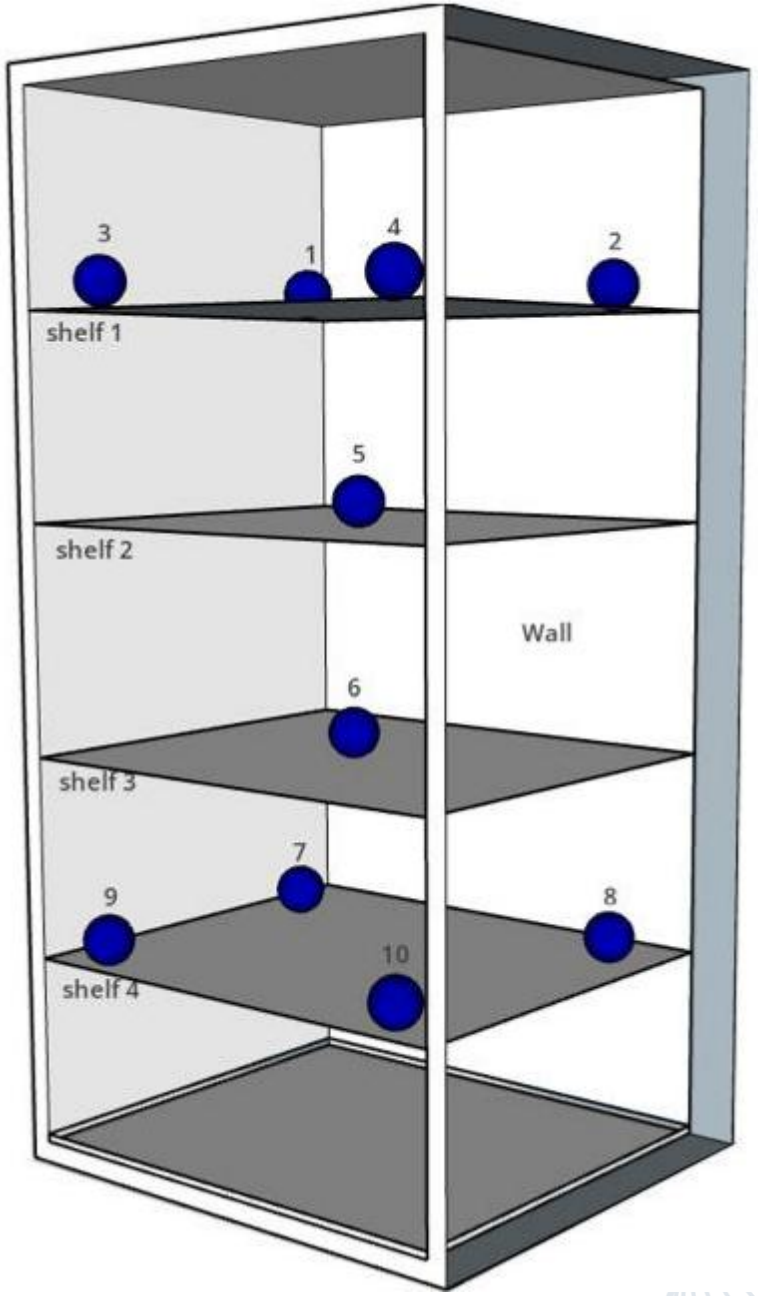
Flow and Thermodynamics in GxP Environments

- Co-founder and owner SIMVal
- Mechanical Engineer from Technical University of Denmark and University of Florida
- Specializing in flow and thermodynamics
- 6 years of experience working with validations in GxP environments

Areas of Expertise

- Project Management
- End-to-end Validation Services
- Commissioning and Qualification
- HVAC and Cleanroom Services
- Quality Assurance and Compliance
- Engineering and Energy Optimization

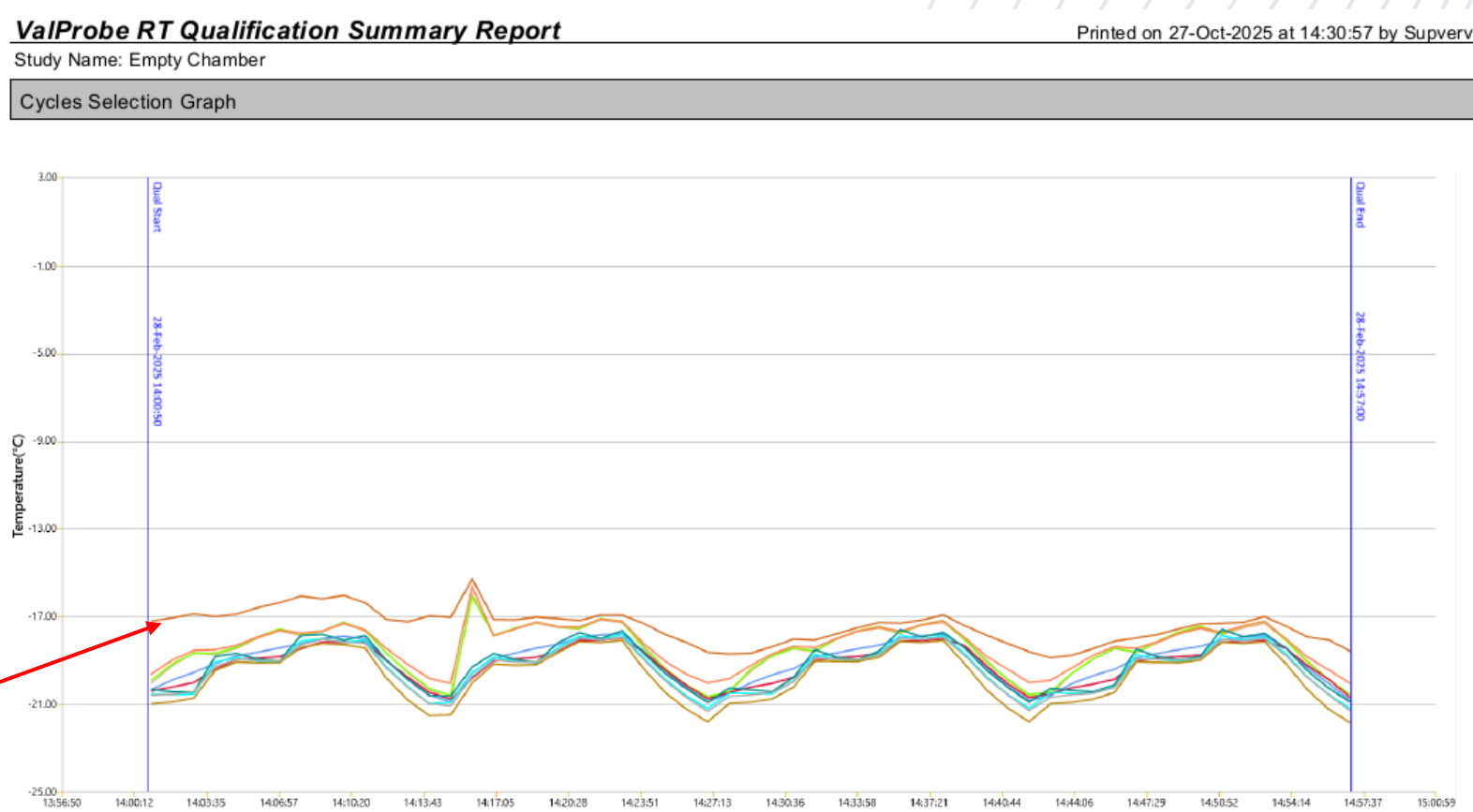
Temperature Case



Temperature Case

Temperature Data (°C)					
				Qual	
Sensor Label	S/N	Min	Max	Avg	Max-Min
Pos1	MJT1-A	-20.75	-15.95	-18.54	4.80
Pos2	MJU2-A	-20.63	-16.08	-18.50	4.55
Pos3	MKH3-A	-18.85	-15.26	-17.42	3.59
Pos4	MKJ0-A	-20.03	-15.61	-18.34	4.42
Pos5	MKJ3-A	-20.87	-17.76	-19.07	3.11
Pos6	MKK3-A	-20.75	-17.95	-19.21	2.80
Pos7	MLK5-A	-21.17	-17.80	-19.35	3.37
Pos8	NHC4-A	-20.89	-17.56	-19.16	3.33
Pos9	NHK0-A	-21.82	-18.06	-19.68	3.76
Pos10	NHM3-A	-21.30	-17.92	-19.41	3.38

Pos 3



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Validation – Why even bother?

Protect patients

Prove systems are fit for purpose

Control risk

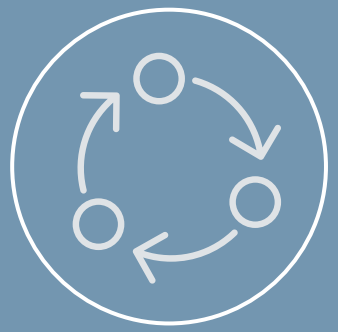
Show critical controls/CAs work as intended

Meet regulations

Documented science- and risk-based evidence

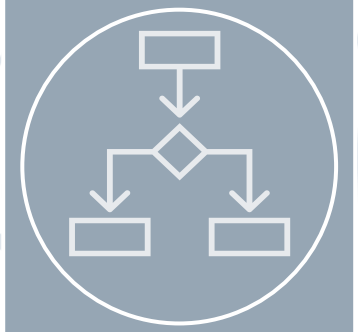
Justify monitoring

Worst-case points, alarm limits, SOPs



Lifecycle control

Change control, periodic review, continual improvement



Process control

Documents how we handle deviations from the intended

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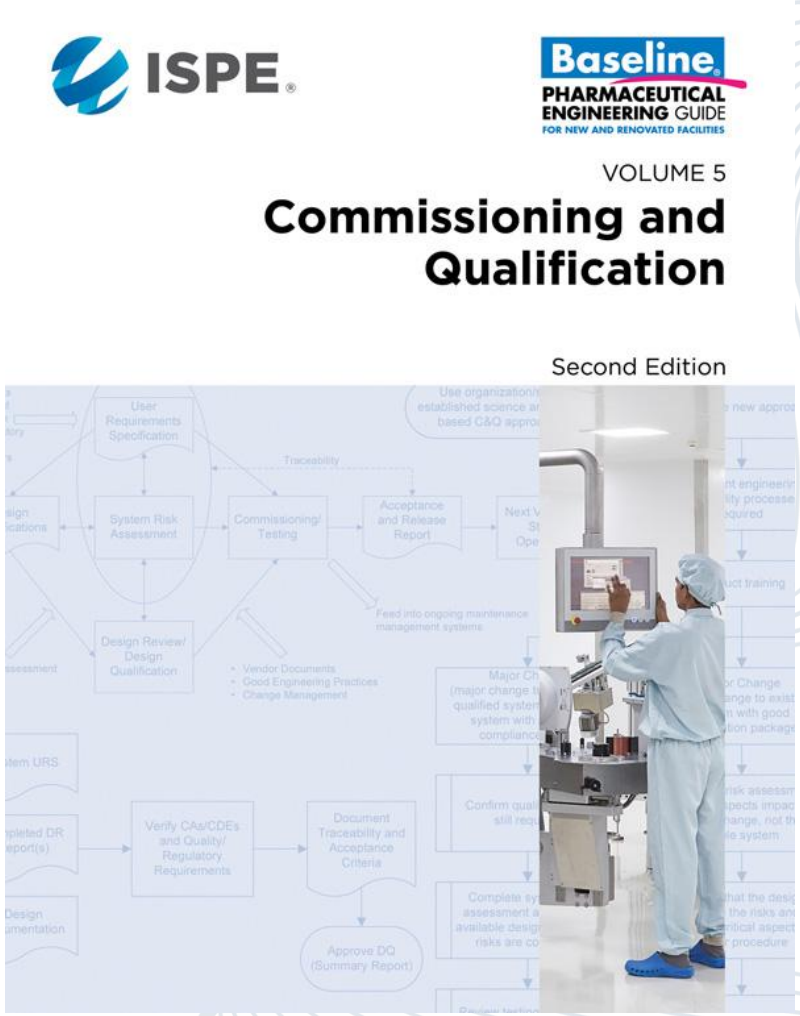
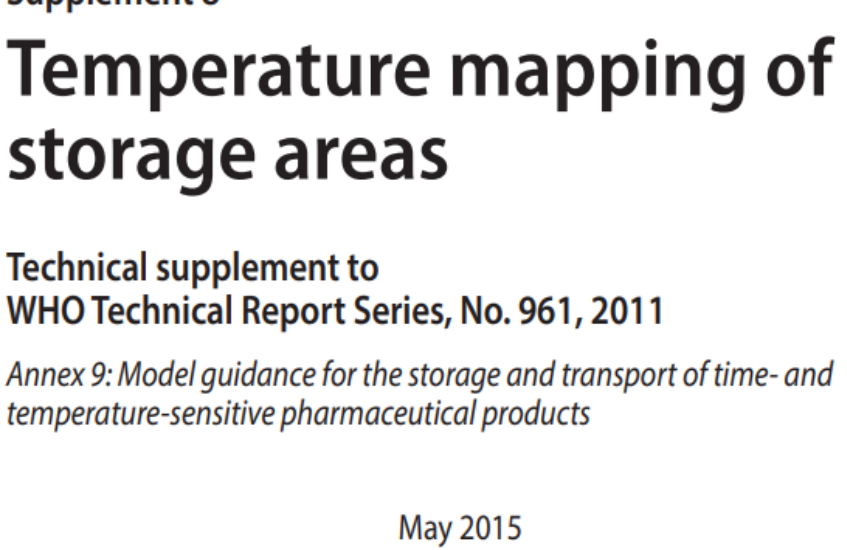
ISPE Baseline Guide 5

- Uncertainty about compliance requirements drives up costs and discourages innovation - hurting public health
- The Guide promotes a compliant, integrated science- and risk-based approach to make C&Q efficient and cost-effective
- It aligns with key guidances: EU GMP Annex 15 (Oct 2015), FDA Process Validation (Jan 2011), and ICH Q9 QRM (Nov 2005)
- This revision aims to simplify and improve C&Q by consolidating the “best of the best” into one document.



WHO Technical Report Series, No. 961, 2011 Annex 9

"A temperature-mapping exercise is required for any space allocated for the storage and handling of products with a specified labelled storage temperature. This includes freezer rooms, cold rooms, temperature-controlled storage areas, quarantine areas and receiving and loading bays. It may also include laboratories."


Supplement 8

Temperature mapping of storage areas

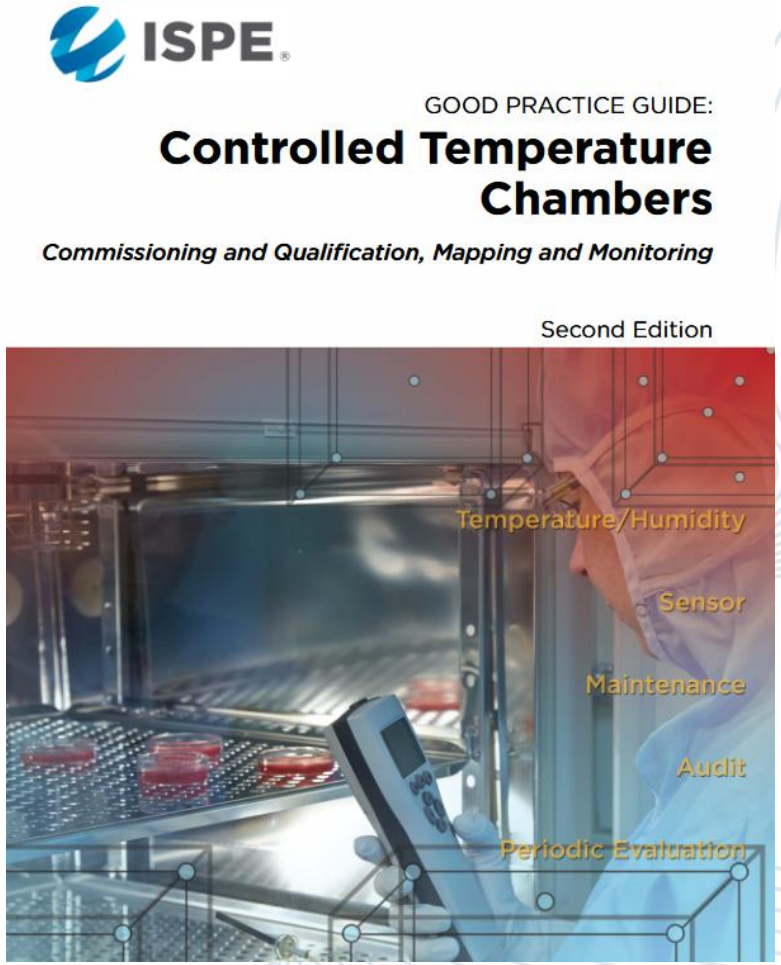
Technical supplement to
WHO Technical Report Series, No. 961, 2011

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

ISPE Good Practice Guide: Controlled Temperature Chambers

- Guides how to map CTCs based on the increased complexity for distribution of medicine
- Aligns with guidances of the ISPE Baseline Guide: Volume 5 – Commissoning and Qaulification
- Covers full life cycle of CTCs from C&Q ⟶ Monitoring ⟶ Periodic Maintanence



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SRV C&Q Principles

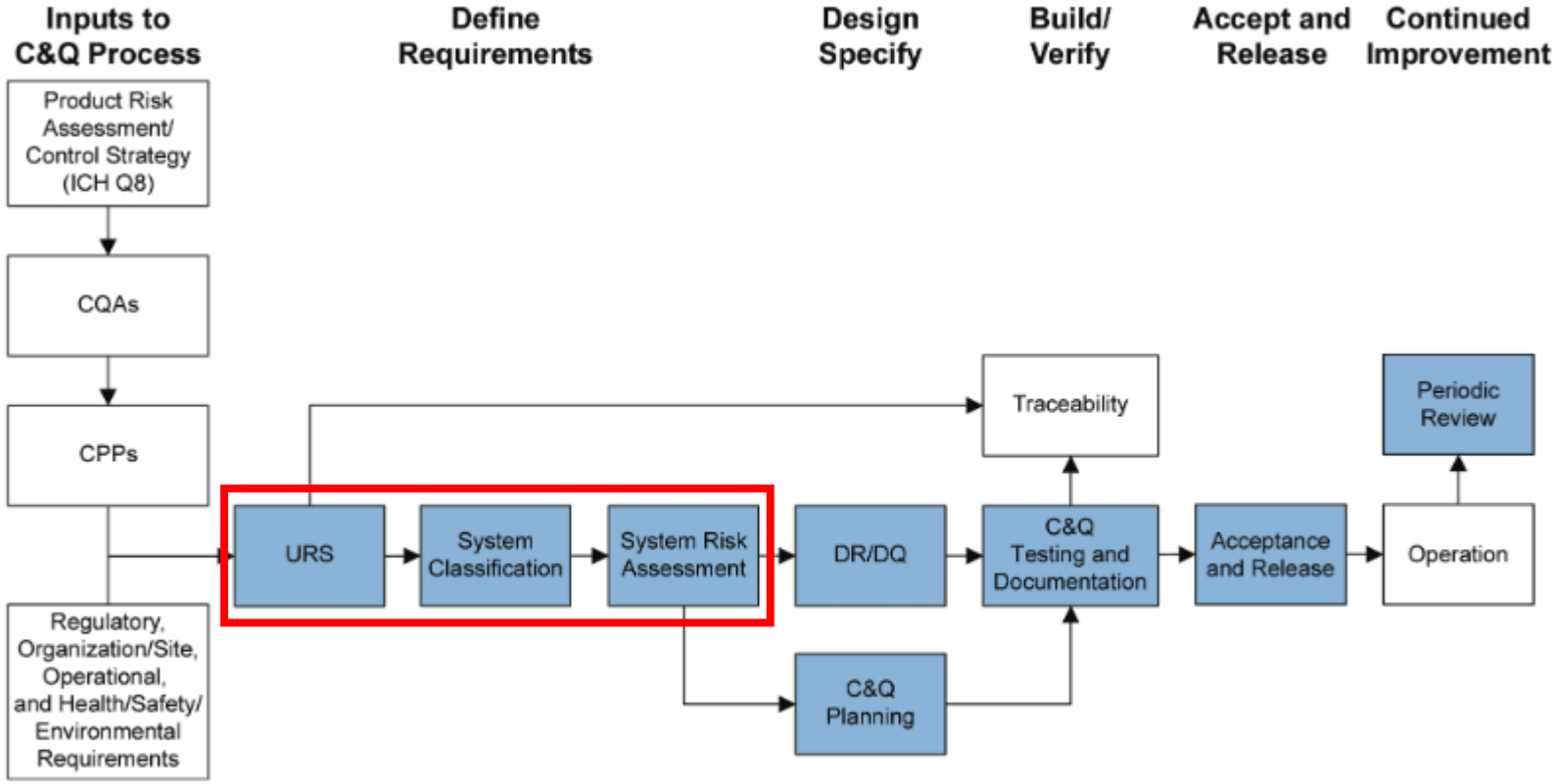
Science- & risk-based

Effort follows patient/product risk

- Focus on CA's/CDE's: Verify the controls that truly matter
- **Leverage commissioning/supplier tests: Avoid duplicate testing**
- URS-linked acceptance & traceability: Decide "what good looks like" up front
- Quality oversight where it matters: Direct-impact systems, SME rationale, deviations handled scientifically
- Lifecycle control: Evidence flows into monitoring, change control, and periodic review

BG5 Process Overview

Figure 1.1: Science and Risk-Based C&Q Process Map



Note for Figure 1.1: Shaded boxes indicate the major blocks within the process maps that are addressed by chapters in this Guide.

URS and SRA

Figure 2.1: Relational Diagram for C&Q Activities and Documents – User Requirements Specification

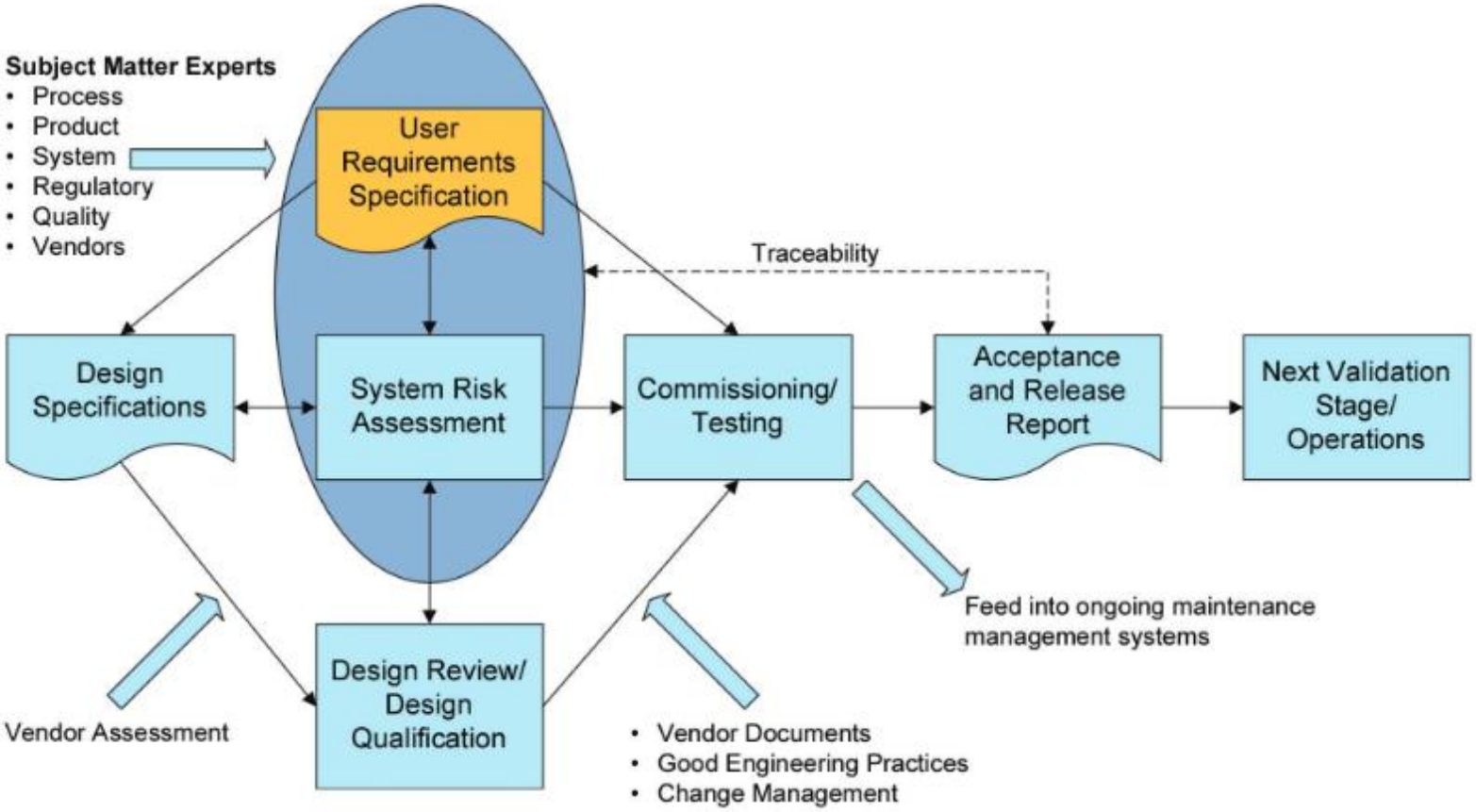
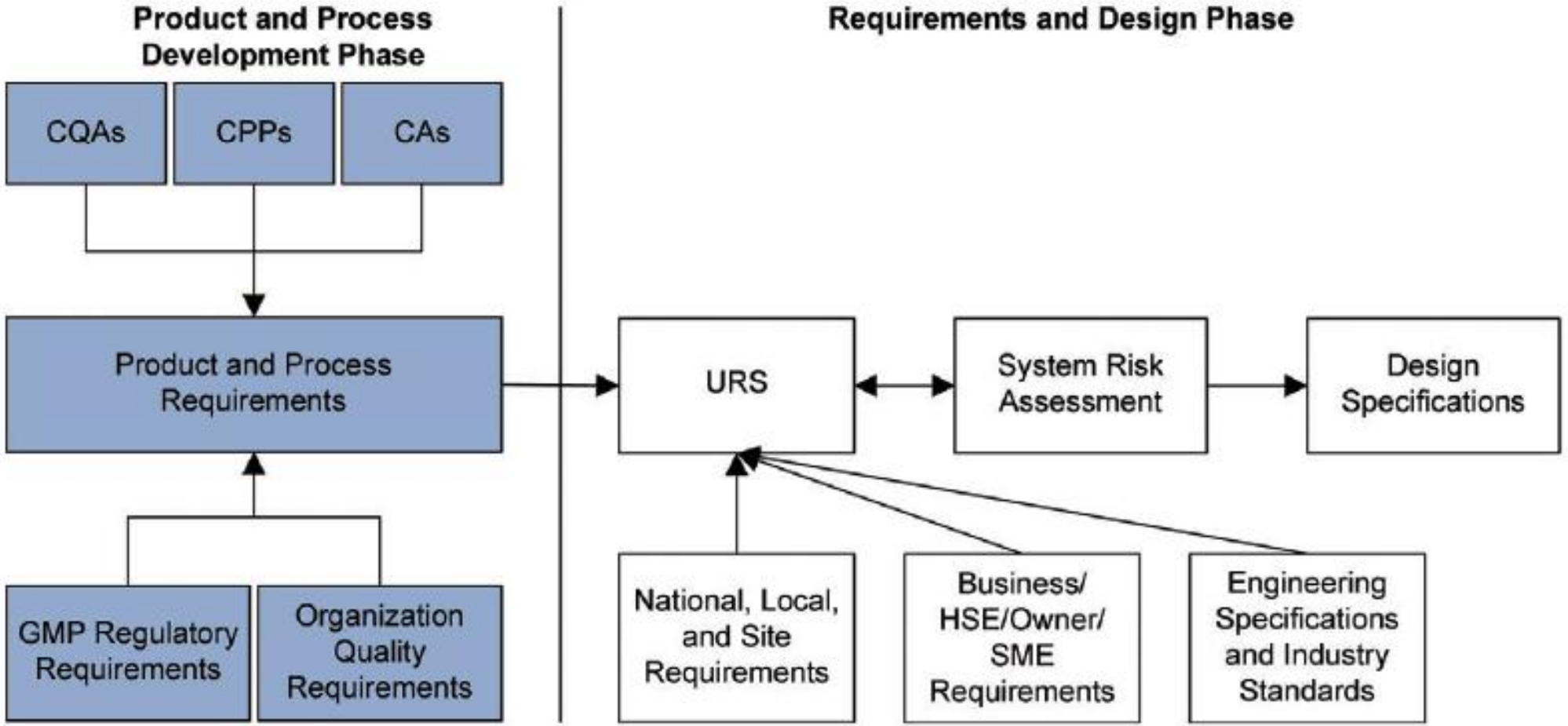


Figure 2.2: Data Sources Used to Develop the User Requirements Specification



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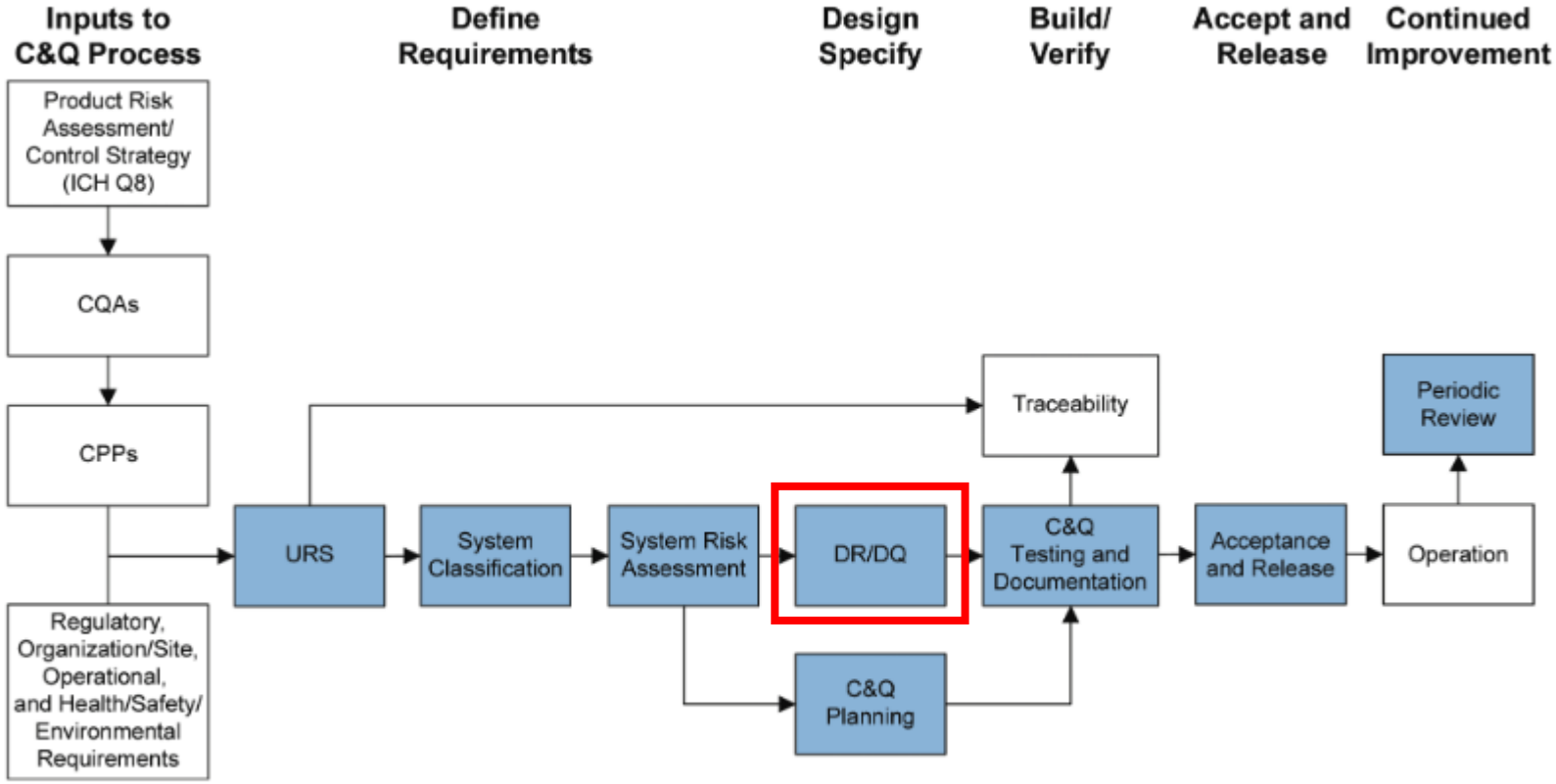

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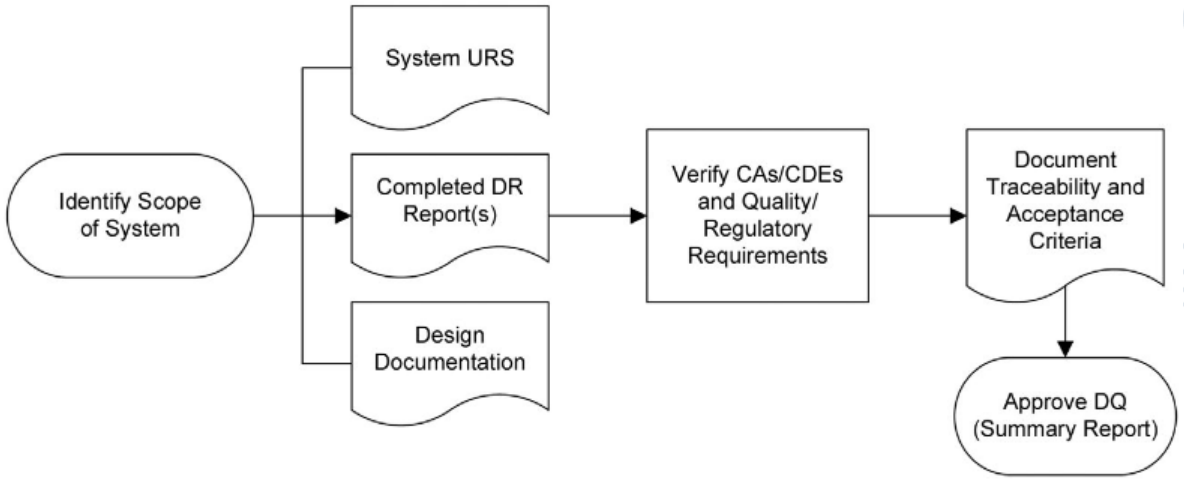
DR/DQ

- Integrated DR→DQ; risk-based & for direct-impact systems
- Cross-functional review (incl. Quality): align design to URS, define CAs/CDEs; leverage credible vendor/commissioning evidence
- DQ proves risk control: acceptance criteria + traceability to CQAs/CPPs. Quality approval required
- Outputs & timing: CA/CDE specs + trace matrix → final DQ report (suitability for use); DR throughout design, DQ after final DR (can be combined for small projects)

Figure 5.2: Design Qualification Process Flow



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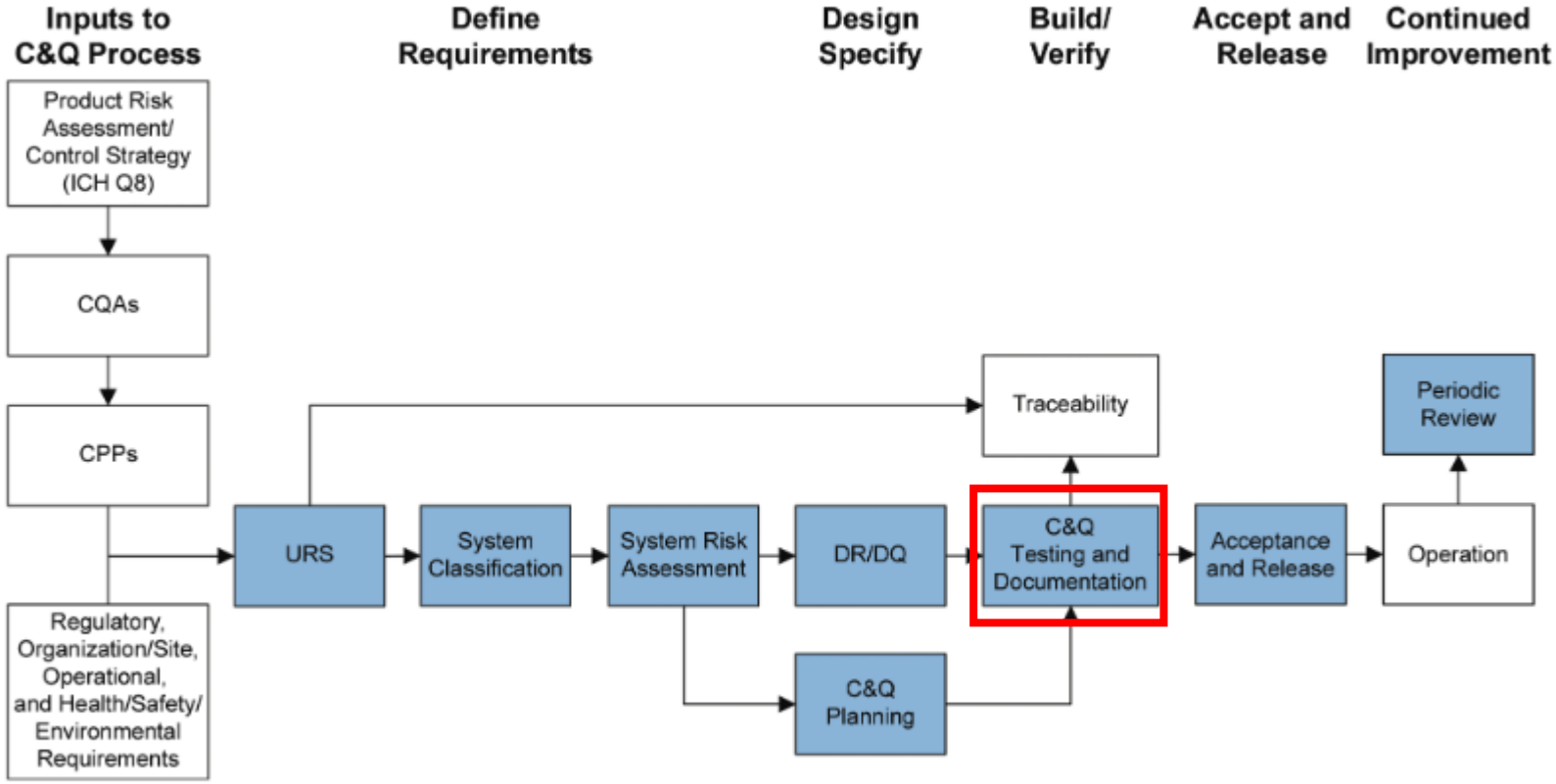

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Smart Testing & Vendor Docs

- Science- & risk-based testing: aim tests at CAs/CDEs - not box-ticking
- Leverage FAT/SAT/commissioning: reuse supplier tests in RTM after suitability assessment (scope, acceptance, calibration, traceability, independence)
- Avoid duplicate testing
- Define acceptance up front: URS/SRA-linked criteria; pre-approved protocols; protect data integrity (raw data, audit trails)
- Traceabililty: URS ⟶ CAs/CDEs ⟶ IV/OV/PV testing ⟶ RTM

BG5 Process Overview

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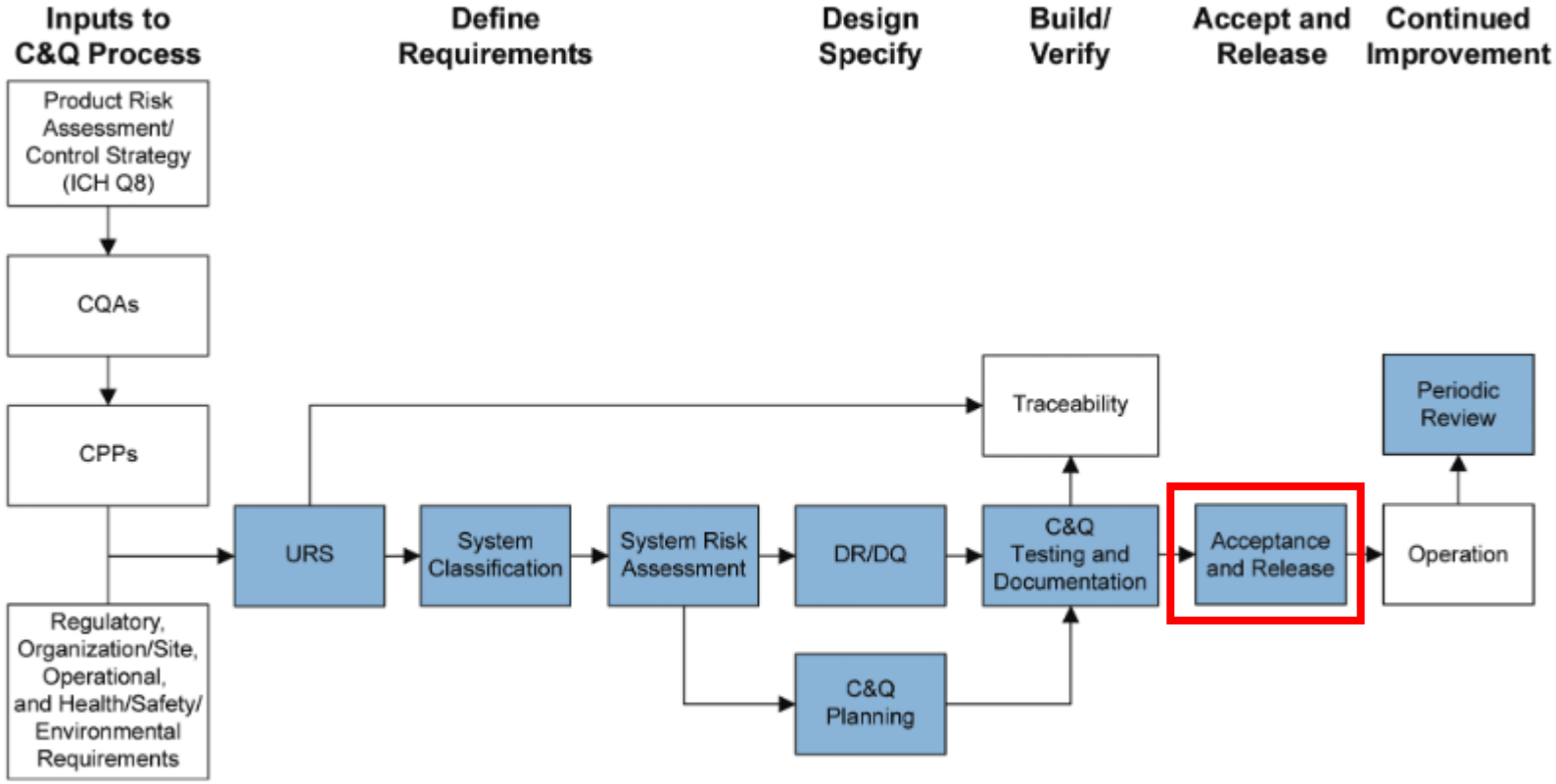

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System Acceptance and Release

- Testing results should be reviewed
- Unexpected results should be investigated
- Discrepancies to the testing plan should be addressed
- Engineering changes should be closed
- Discrepancies should be addressed through Engineering Change Management and/or adjusted and retested

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Types of Controlled Temperature Chambers

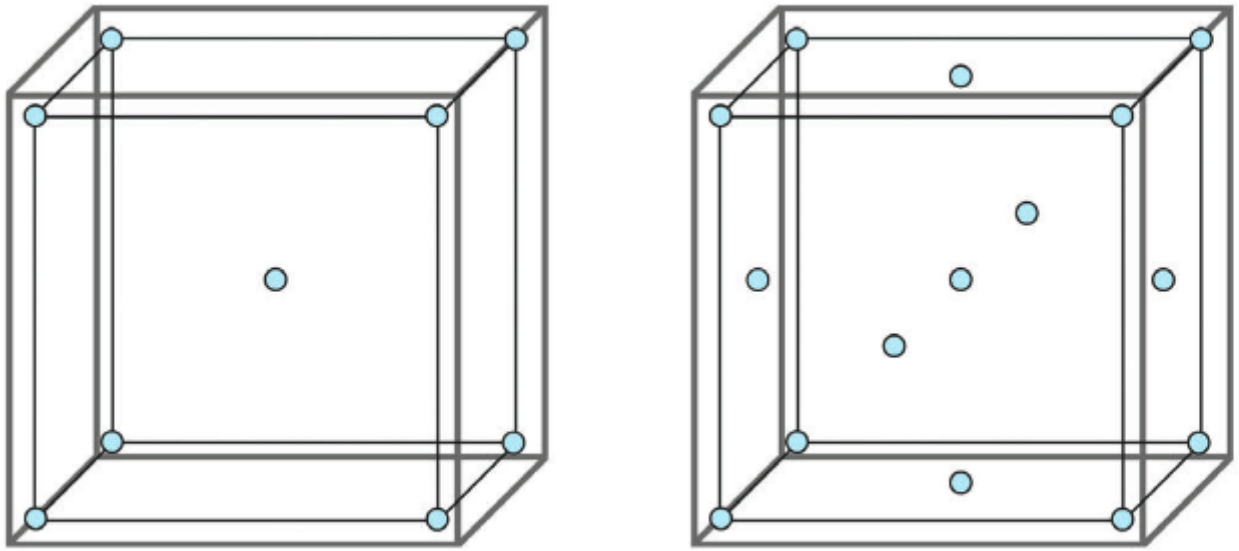
- Refrigerators
- Freezers
- ULT Freezers
- Liquid Nitrogen Freezers
- Cold Rooms
- Stability Chambers
- Incubators
- Heated Chambers
- Warehouses

Logger Strategy

- Select an appropriate number of loggers with an appropriate accuracy

<2 m^3 >2 m^3

Figure 5.3: Example Sensor Locations



Note: The inner box represents the working area (where product is stored), the circles represent the sensor locations.

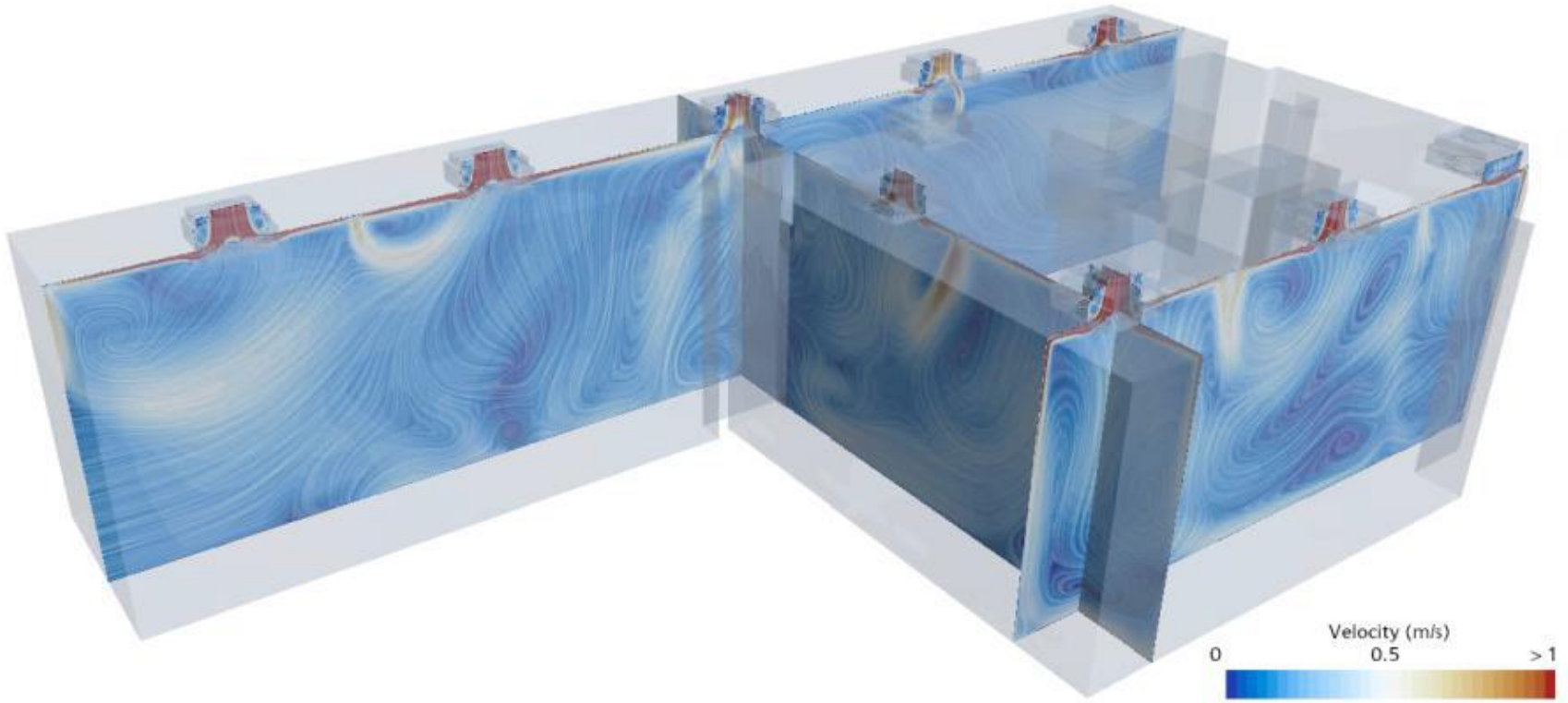
Mapping Strategy

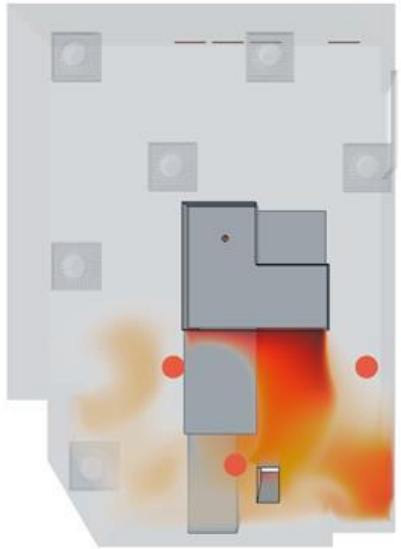
- External weather fluctuations (Summer and winter mapping)
- Load – minimum and maximum load
- Science and **Risk** Strategy:

"There are some strategies that require a sensor every 3 meters (12 feet). This Guide suggests that the **location** and **number** of sensors to be used **should be established based on a scientific rationale**: if there is no reason for the temperature to change then there is no reason for an additional sensor. For example, a long wall with equal conditions on the inside and outside will be the same temperature along its length, so there is no value adding multiple sensors"

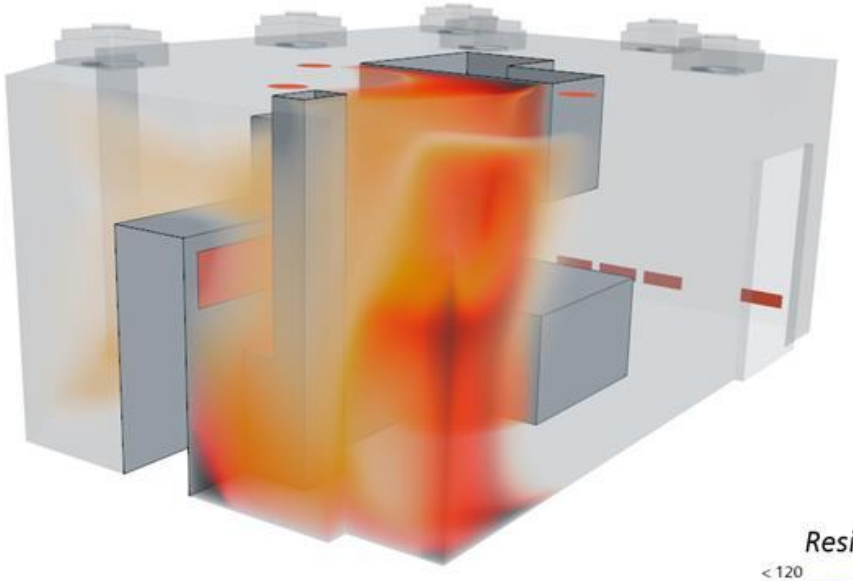
– ISPE Good Practice Guide: Controlled Temperature Chambers

Leverage of Flow Simulations






Residence Time [s]
< 120
170
> 220

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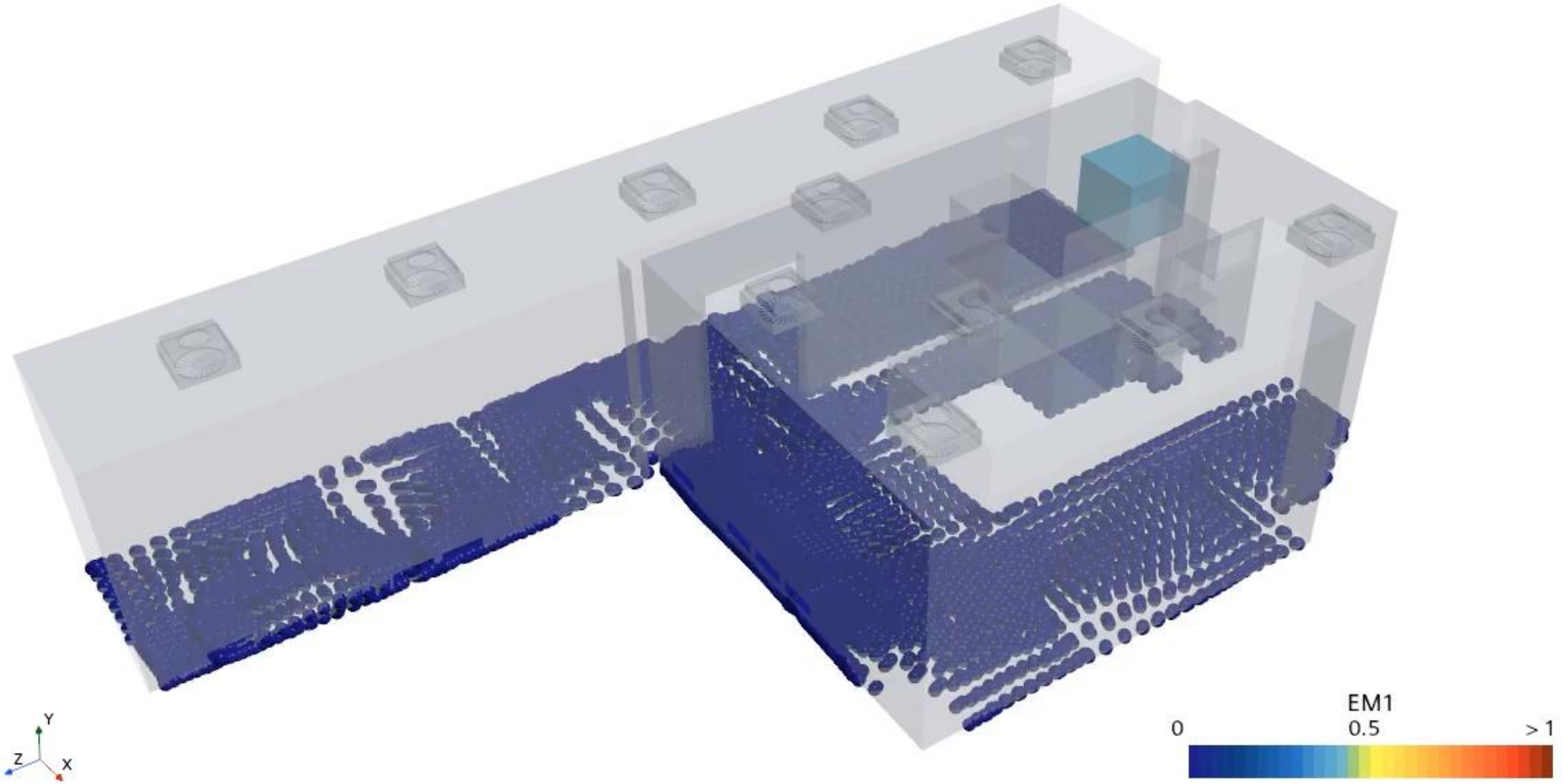

Solution Time 1 (s)

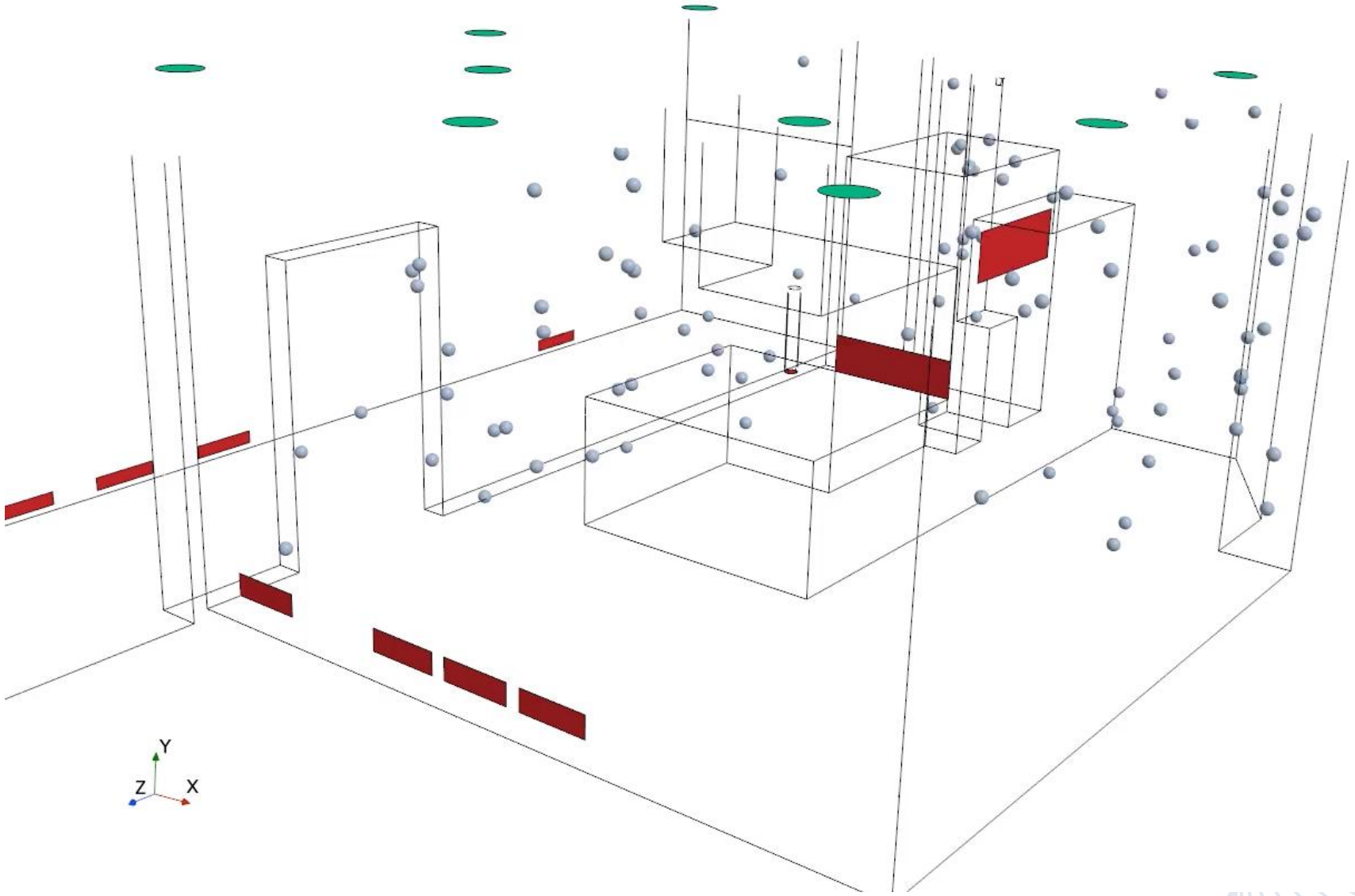
Y
Z
X

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Table 5.2: Recommended Placement of Mapping Sensors

Location	Rationale
Adjacent to temperature sensor used for control of the chamber	Provides data that can be used to assess the mapping data compared to the temperature the system controller records
Storage rack corners including geometric center of rack	Provides data for the extreme storage locations on the rack
Storage locations adjacent to ingresses/ egresses (door)	A potential area for temperature extremes
Storage locations near air supply and return outlets	A potential area for temperature extremes
Storage locations opposite or under evaporators	To monitor potential location for lowest temperatures, and the impact of defrost where applicable
Storage locations near air distributors (i.e., fans, blowers, etc.)	A potential area for temperature extremes
Shelving	A potential area for temperature extremes if the shelving has the potential to create dead air pockets leading to temperature deviations.
Storage locations adjacent to physical or structural obstructions, and in CTC corners	A potential area for temperature extremes if there are pockets of dead air
Bottom and top of any potential stored product	Mapping the height of component storage ensures that the worst-case locations are identified.
Storage locations adjacent to lights	Ensures that the light does not create warm spots when turned on that may impact component temperature

Monitoring Strategy

- For storage < 2 m^3 one sensor is usually sufficient based on a **uniformity criteria**
- For larger rooms at least a sensor in hot and cold spot is needed
- Dampening strategy might be deployed:
  - Alarm delays
  - Simulated product

Calibration Strategy

- Low Calibration Point must be below lowest operating point
- Check Point must be at operating point
- High Calibration Point must be at ambient to document excursions correctly
- Quality related alarms must be tested periodically; ISPE and WHO suggest every second year

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Useful Guides

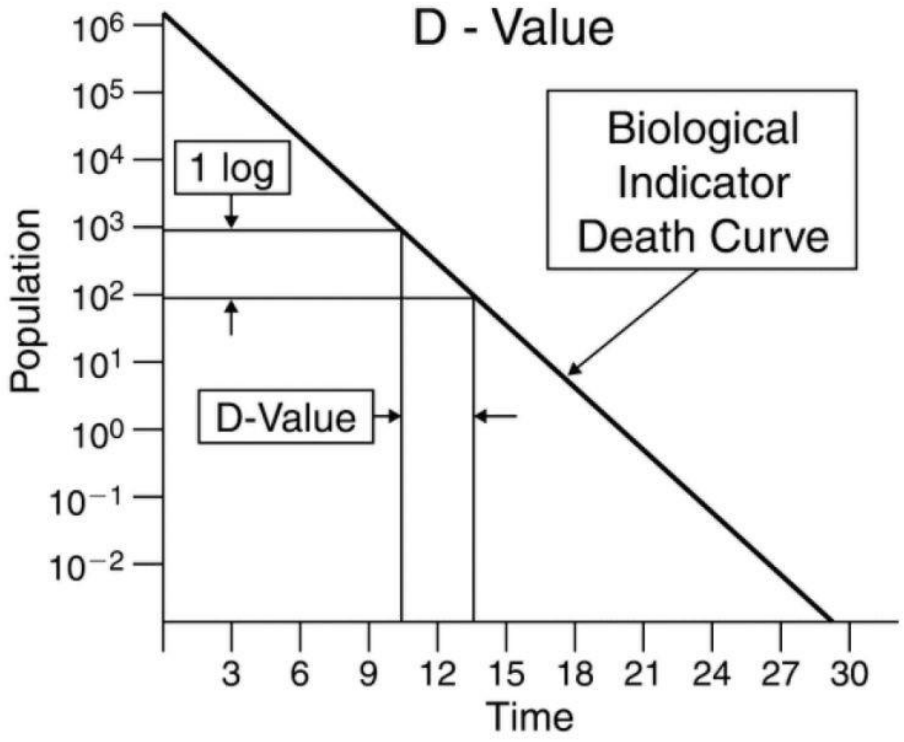
- ISO/EN 17665 - Sterilization of health care products - Moist Heat (Parts 1 and 2)
- ISO/EN 11135 - Sterilization of health care products - Ethylene Oxide (Parts 1 and 2)
- ISO/EN 11137 - Sterilization of health care products - Radiation (Parts 1,2 and 3)
- “Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and ongoing Control. PDA Technical Report No. 1 Revised 200

What is sterile

- Free from microorganisms: In practice no such absolute statement regarding absence of microorganisms can be proven
- Sterile Assurance Level (SAL): Defined as the probability of 1 in a million of a container being contaminated (10-6)
- Organisms are killed in an exponential fashion
- Focus on moist heat and dry heat

D-value

- D-value - Time (or dose) required to reduce the population of organisms by 1 log (or 90%)



F0 and Z-value

- The Z value measures how the D value changes as the temperature changes. It tells you how sensitive the microbes are to temperature changes during the sterilization process.
- The F0 value measures the total amount of sterilization that has occurred. It accounts for both the temperature and the time of the sterilization process. A higher F0 value means more thorough sterilization.

$$F_0 = \Delta t \times 10^{(T - 121/Z)}$$

Where,
T= Temperature for Sterilization
Δt = 60 Sec. = 1min.
Z = 10°C

Validation

- The minimum Fo required by a sterilzation process is related to the resistance of the bioburden (D-value)

$$F_0 = D_{121}(LogA - LogB)$$

where:

- "D121" is equal to the time at 121°C to reduce the population of the most resistant organism in each product container by 90% (or 1 log)
- "A" is the number of microoganisms per container
- "B" is the maximum acceptable probability of survival (Sterility Assurance Level , 10-6)

Biological Indicators

- Device consisting of a known number of microorganisms, of a known resistance to a particular sterilization process in or on a carrier and enclosed in a protective package
- Most common: Geobacillus Stearothermophilus D-value =1 – 2.8

Recap of Hot or Not: The Importance of Temperature Validation

Importance of Temperature Validation	Protects product quality & patient safety; enables compliance via a science- & risk-based approach (ISPE BG5 aligned with EU GMP Annex 15 / FDA PV / ICH Q9).
SRV Principles	Process overview: URS & risk assessment → design review & DQ → smart testing leveraging FAT/SAT/commissioning → traceable reporting → system acceptance & release.
Storage Mapping Essentials	Classify CTCs (refrigerators, freezers/ULT, LN_2, cold rooms, incubators, stability & heated chambers, warehouses); right logger count/accuracy; seasonal & load scenarios; hot/cold spots; use CFD where helpful.
Monitoring & Calibration	Monitoring strategy (dampening, alarm delays, simulated product); calibration points (low/check/high) and periodic quality-related alarm tests.
Guidelines	WHO TRS (Technical report series) no. 961 Annex 9 requires mapping for storage areas ISPE Good Practice: Controlled Temperature Chambers
Sterilization Basics	SAL 10^{-6}, D-value, z-value, F_0; verify with biological indicators (e.g., Geobacillus stearothermophilus); key standards ISO 17665/11135/11137; PDA TR 1.
SIMVal Overview	Specialized in validation, C&Q, HVAC/cleanrooms & calibration; proven project cases; on track for ISO 17025/DANAK accreditation.

Q&A

We thank you for your participation and attention!

We invite you to follow SIMVal's continued journey on LinkedIn where we give you a view of how we strive to be the preferred engineering and validation partner in the Nordics!

This presentation can be found free of charge on SIMVal's Knowledge Hub: www.simval.dk/knowledge-hub or by scanning the QR code.