
PHARMACEUTICAL
CONSULTANCY
SERVICES
VALIDATION
QUALIFICATION
Jaap Koster

AGENDA

- Introduction Validation & Qualification
- Pre-requisites
- Process Validation (PV)
- Analytical Methods Validation (AMV)
- Shipping Validation / Supply Chain
- Re-validation / evaluation

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INTRODUCTION
VALIDATION & QUALIFICATION

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REGULATIONS

- Annex 15 of Eudralex Volume 4
  - New annex in effect 1st of October 2015.
  - LIFE CYCLE APPROACH
- EMA Process Validation Guideline Finished Products (27 Feb 2014)
- Guidance to Process Validation (FDA, January 2011)
- WHO guideline on non-sterile Process Validation QAS/13.527 (draft, Jan 2013)
- ICH - Q 2, 8, 9, 10 & 11

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OTHER SOURCES

- PIC/S
- GAMP5
- ASTM-2500 (uses the term Verificati…,
- PDA / ISPE
- …

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VALIDATION (INCL. QUALIFICATION)

What is Validation / Qualification

Refer to the descriptions in the guidelines, but in general:

The documented evidence of the verification that a pharmaceutical:

- Process (production, cleaning, shipping,….)
- Machine
- Testing-method
- Procedure
- Etc.

Meets the (pre-determined) requirements including knowledge development.

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VALIDATION (INCL. QUALIFICATION)

- Requirements can be found in the guidelines.
- By knowledge development during (product/process) development or project phases.
- Multidisciplinary input is required for an hollistic approach

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TYPES OF VALIDATION

- Process validation
  - Aseptisc processes
  - Biotech processes
- Cleaning
- Analytical Methods
- Holding Times: store (of semi-finished products, buffers etc.)
- Pharmaceutical Gasses
- Automated Systems
- Shipping
- …….

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TYPES OF QUALIFICATION

- Paradigm:
  - URS
  - FAT/SAT
  - DQ/IQ/OQ/PQ (US-FDA; Qualification of Facilities/PPQ)
- Equipment
- Air treatment
- Utilitities
- Vendors
- Personnel
  - For Example: Visual Inspection; Aseptic Production

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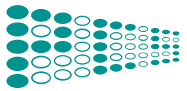

COMPLEX

- TYPES of Validations/Qualifications
- TYPES of PROCESSES/STUDIES

- Protocols
- Risk Assessments
- Test Scripts
- Reports

- Raw Data

- (project) Validation Master Plan

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VALIDATION MASTER PLAN (VMP)

- A VMP should/could contain the following elements:
  - Validation/qualification and re-validation/re-qualification guidelines, including “Risk Assessment”
  - Annual Validation Plan:
    - Plant(s)
    - Utilities
    - Systems
    - Equipment
    - Processes, including cleaning
  - Project Validation Plan
  - Organization and responsibilities
  - Documentation norms for validation

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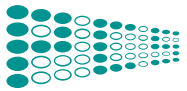

QUALIFICATION PREPARATION/EXECUTION

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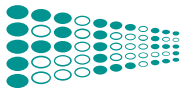
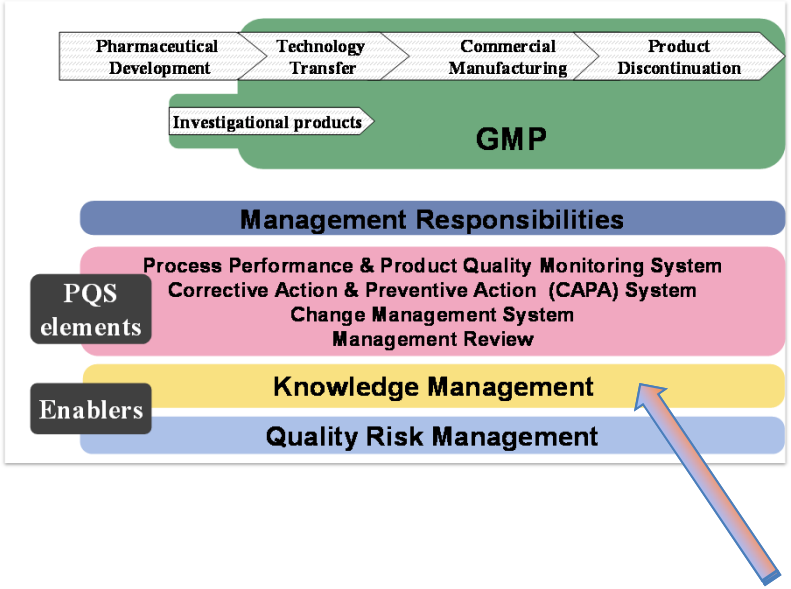


KNOWLEDGE

- Posessing knowledge of what is to be validated/re-validated is a pre-requisite.

- We have to know/control “the case”, and not just the validation procedures by itself.

  An common pitfall of many validation studies.



- Knowledge can originate from R&D-work, peers/communities, risk assessments, guidelines, education, SME’s, professional literature, VENDROS,….

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EXAMPLE TRAJECTORY

New Autoclave for penetrable loads

Activities:

- Gather a group of SME's
- Determine loads
- Create a URS
- Vendor Selection
- DQ (Design Qualification)
- FAT / SAT

  Factory Acceptance Testing / Site Acceptance Testing

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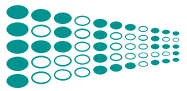

EXAMPLE TRAJECTORY

New Autoclave for penetrable loads

Activities:

- IQ (Installation Qualification)
- OQ (Operational Qualification)
- Cycle / Load Development
- WCL / WCS Determinatie

  Worst Case Locations / Worst Case Situations
- PQ (Performance Qualification)

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POINTS TO CONSIDER

New Autoclave for penetrable loads

Important Characteristics:

- Only saturated steam creates (at t=15 min and T =121°C (249,8 F)) a log-reduction of 10^6 micro-organisms

  SAL (Sterility Assurance Level)

- Air >> 1 hour at the same temperature (e.g. 120min 160°C (320 F))
- Initial-Situation when start autoclaving = only air…..
- This Implies: removing the air and replacing it with steam (saturated, "all" air is gone).
- Air and steam cannot be mixed, steam is heavier than air.

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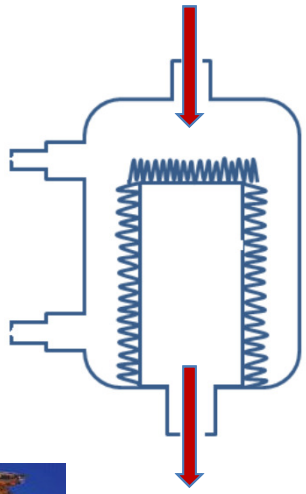
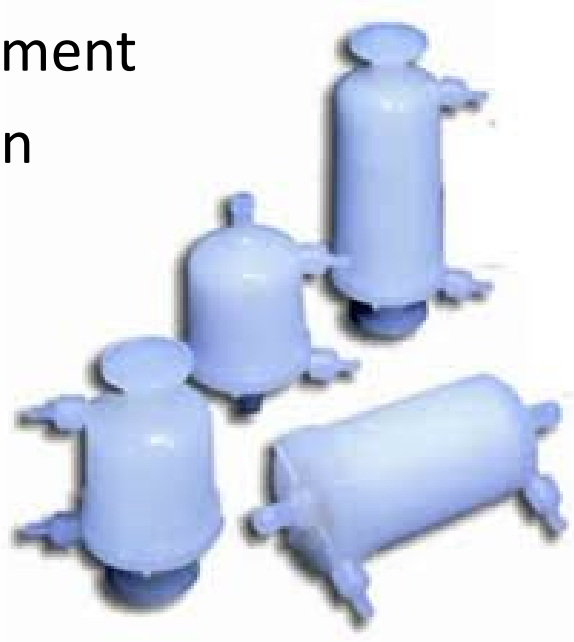
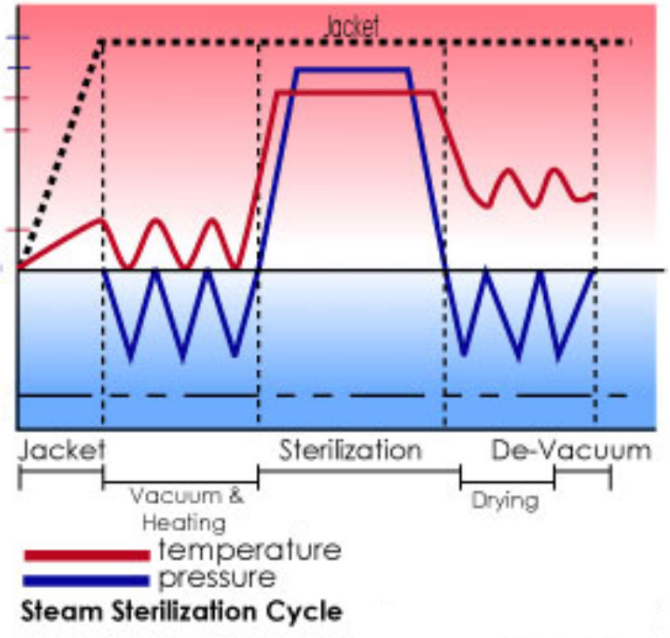
POINTS TO CONSIDER

Load/Cycle development

WCL/WCS discussion







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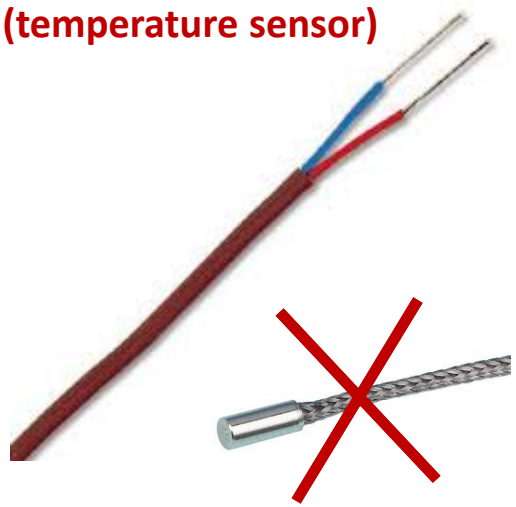
POINTS TO CONSIDER

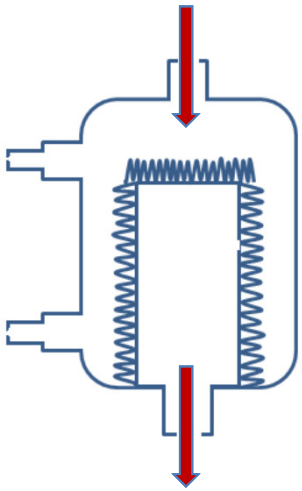
Load/Cycle development

WCL/WCS discussion

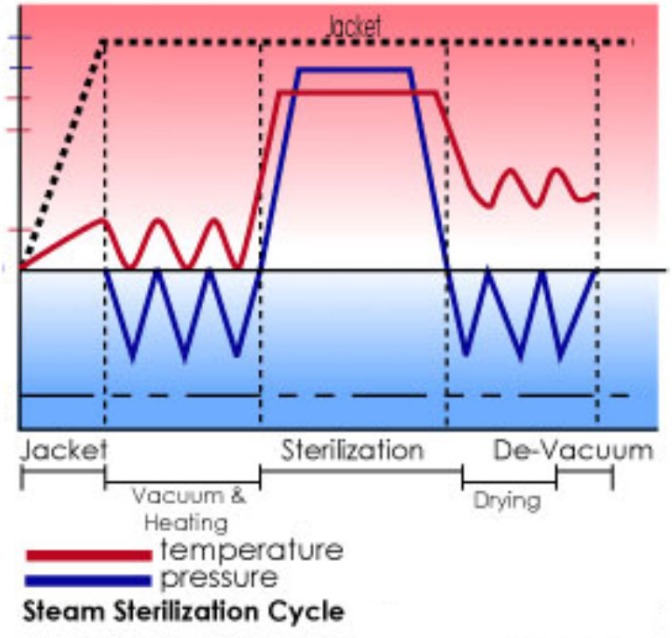
Thermocouple (temperature sensor)



RTD's/Pt-100
(too "slow" and too thick)



Liquid Flow (in process)



Steam Sterilization Cycle

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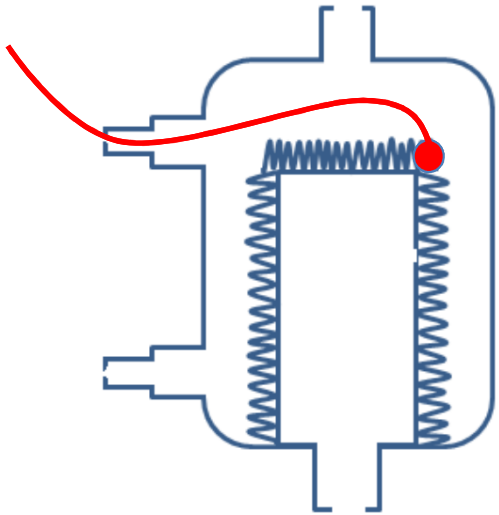
POINTS TO CONSIDER



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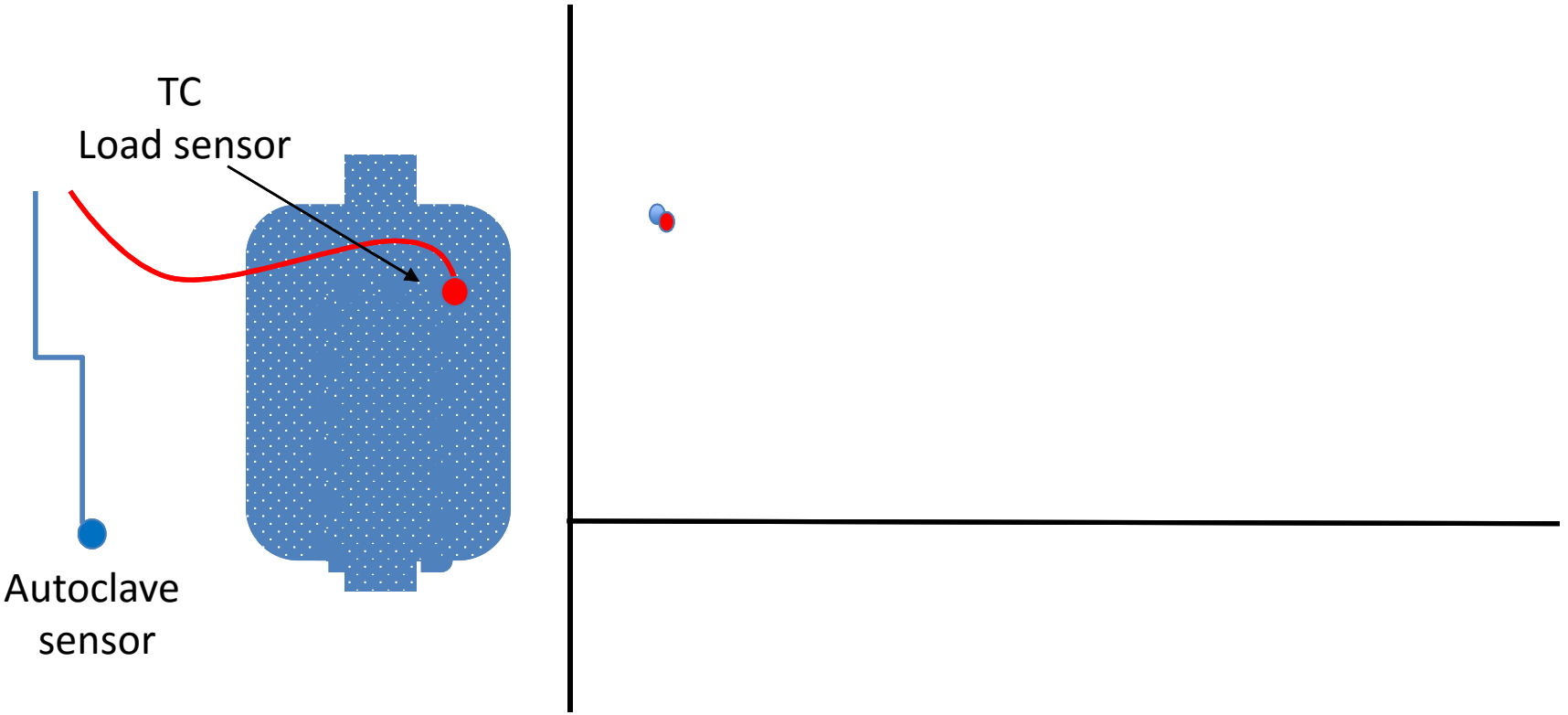

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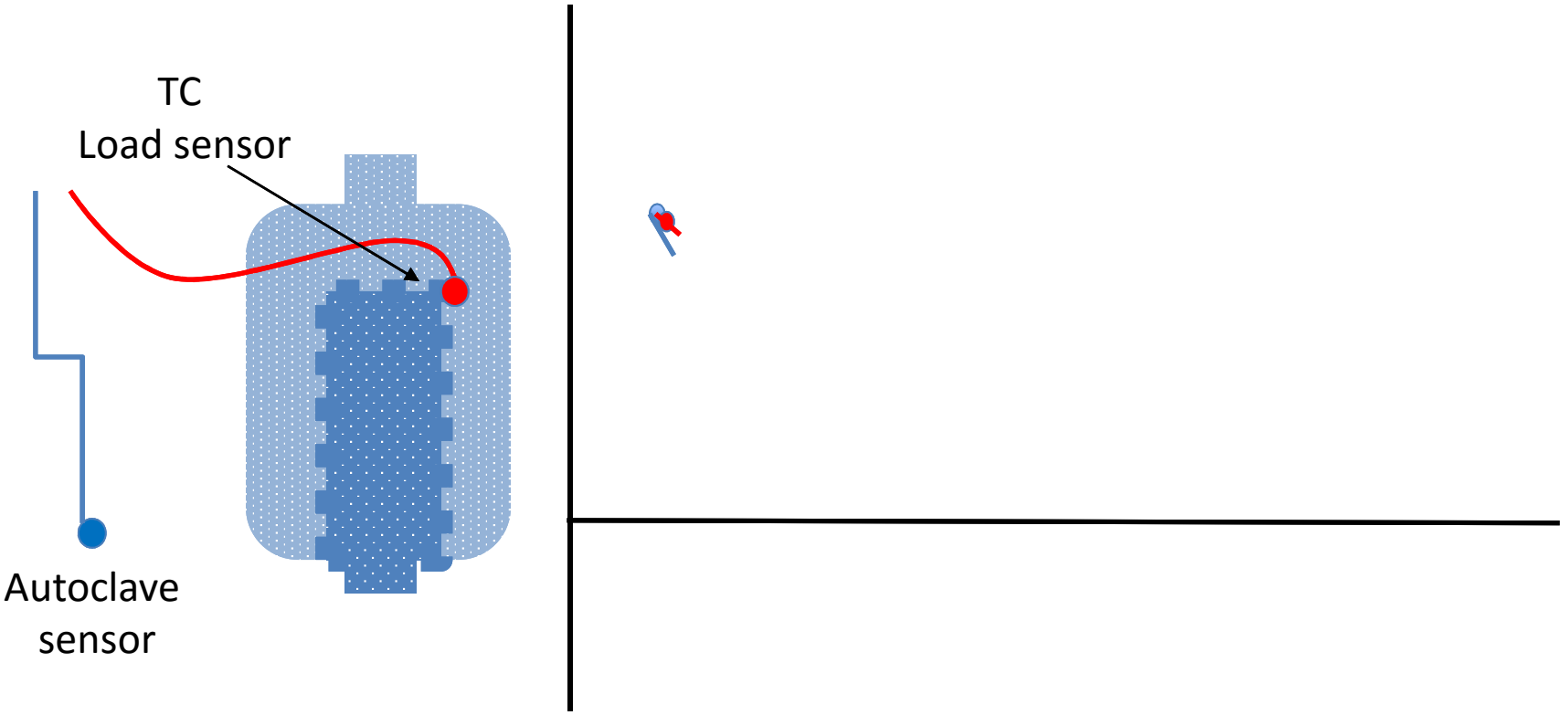

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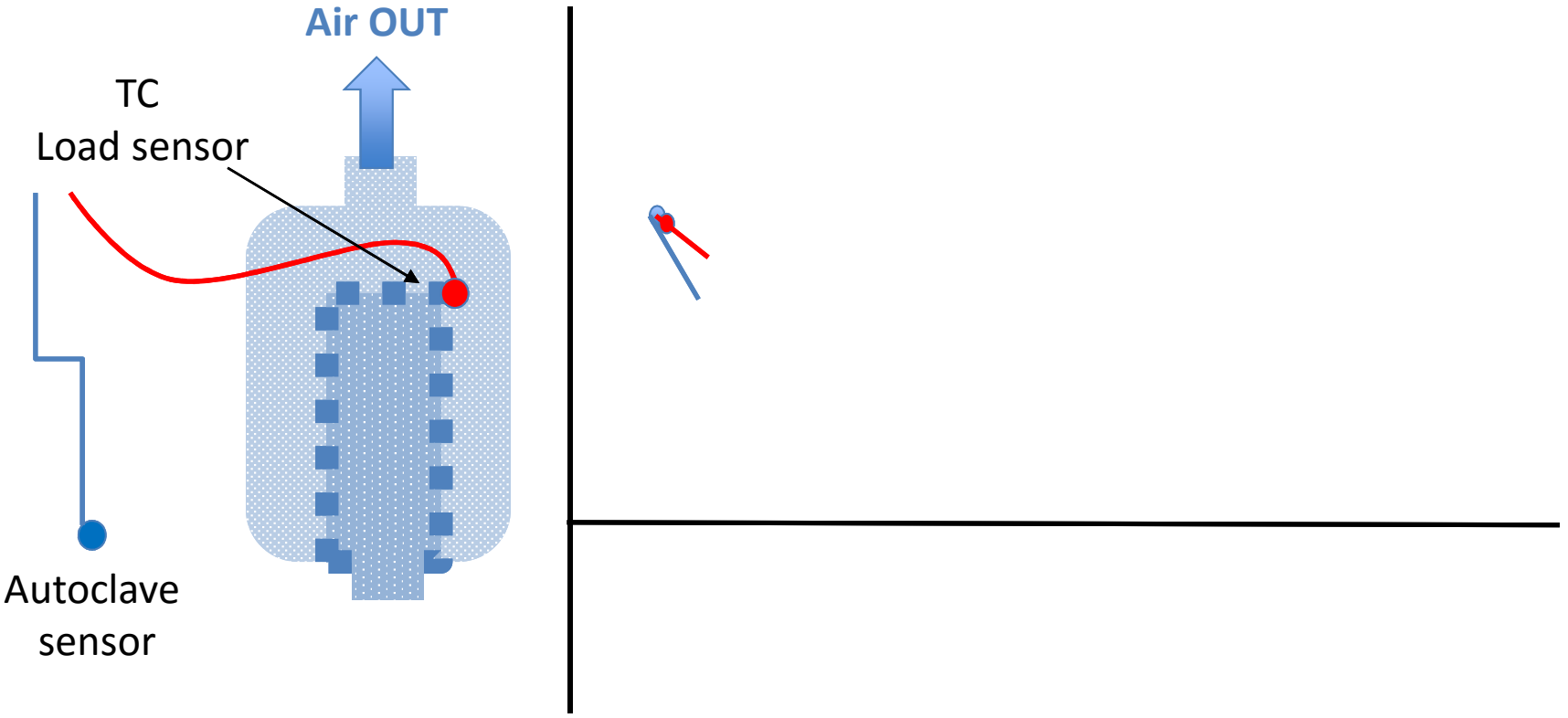

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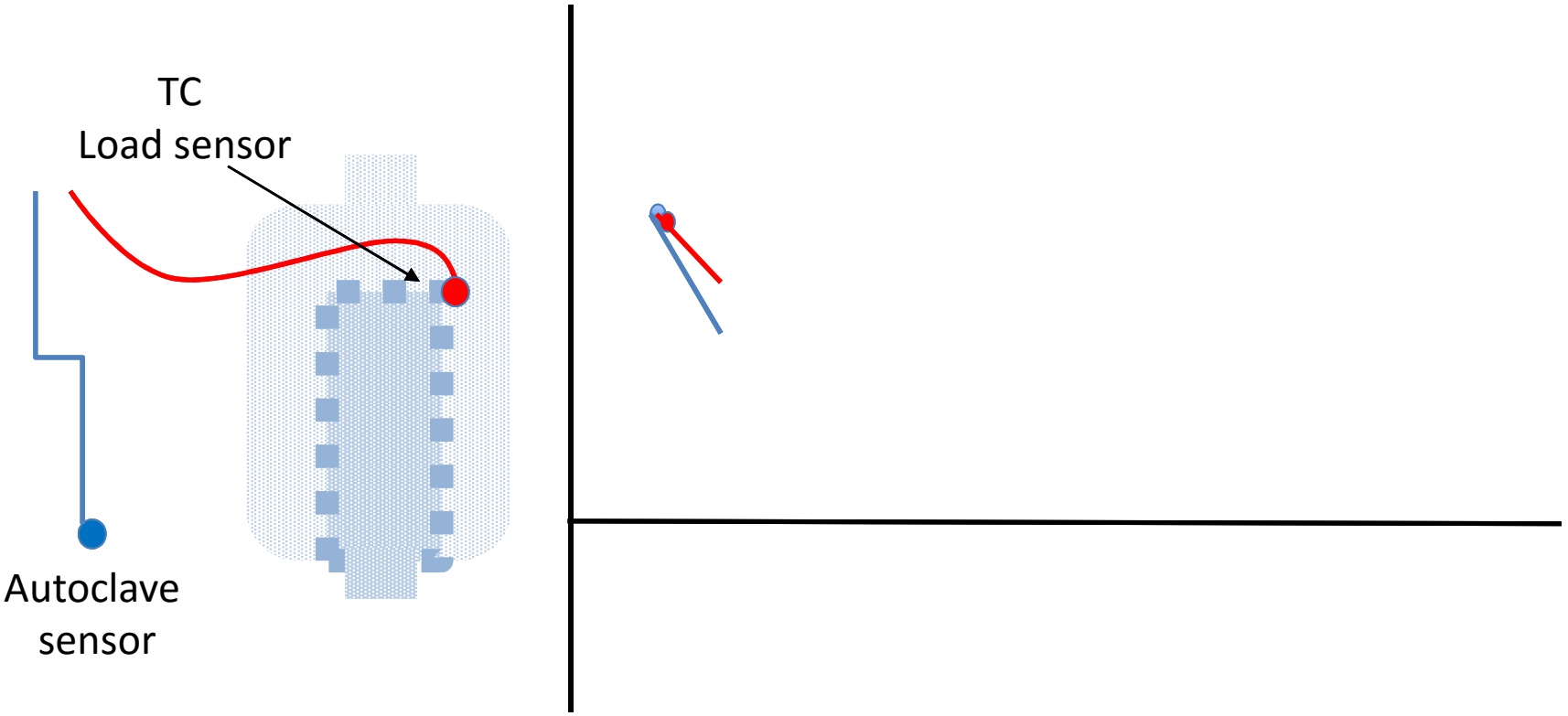

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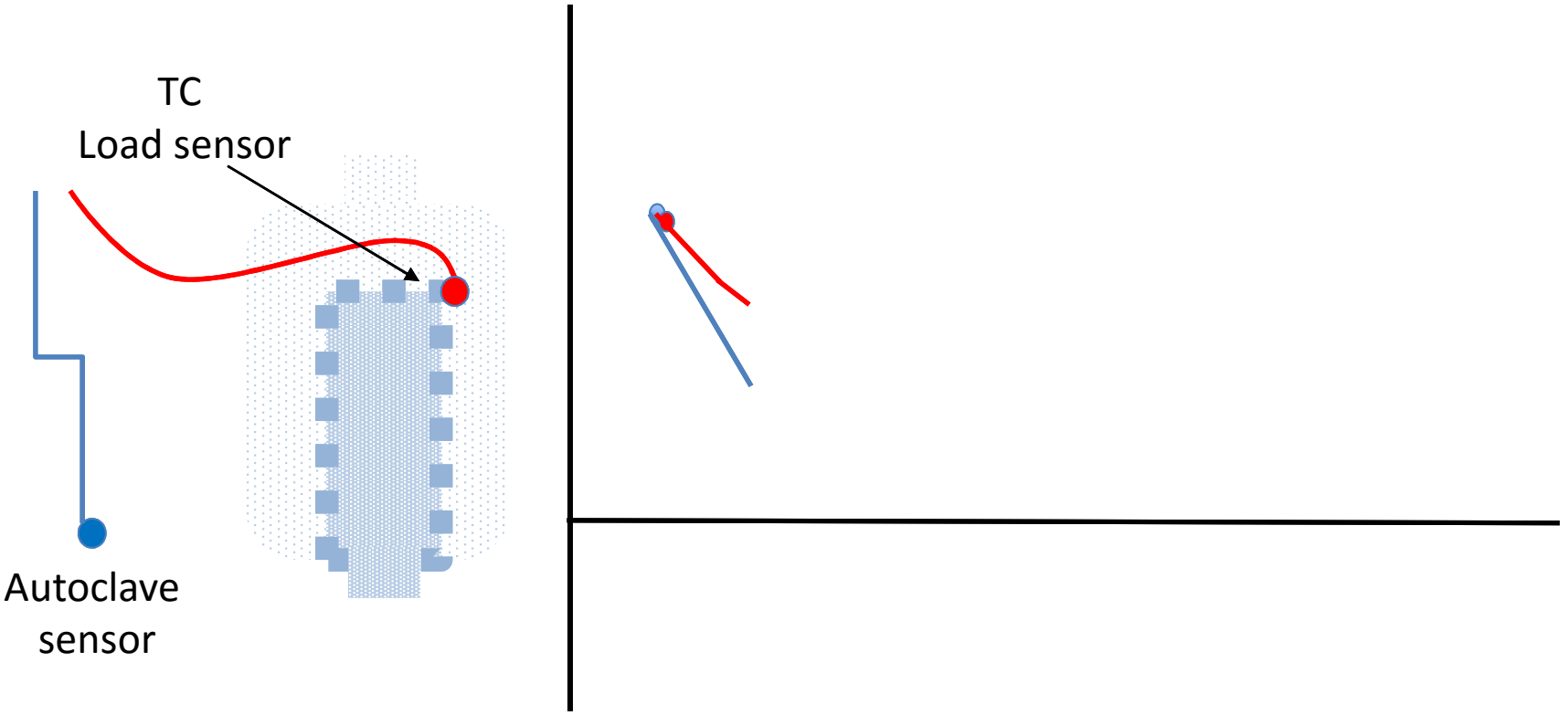

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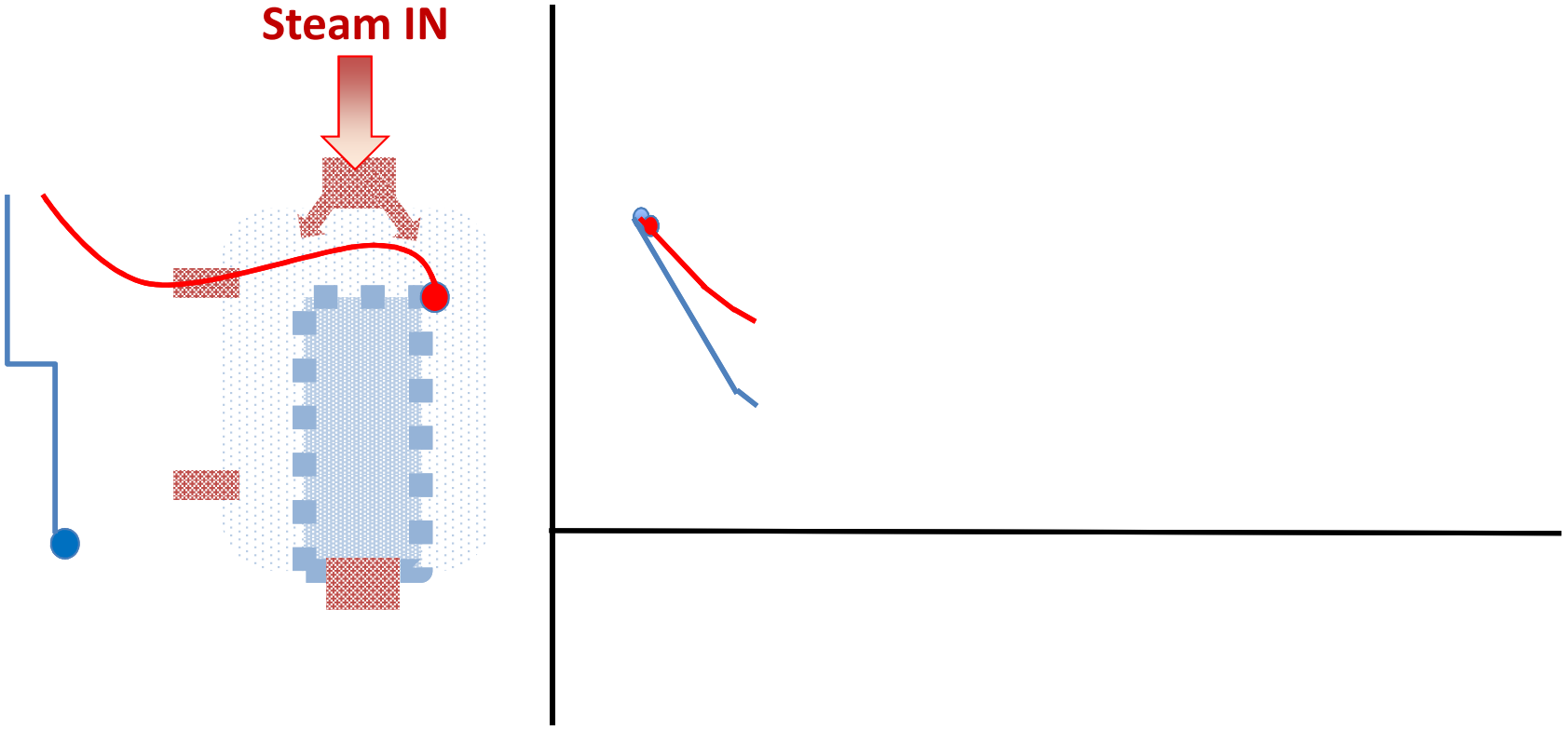

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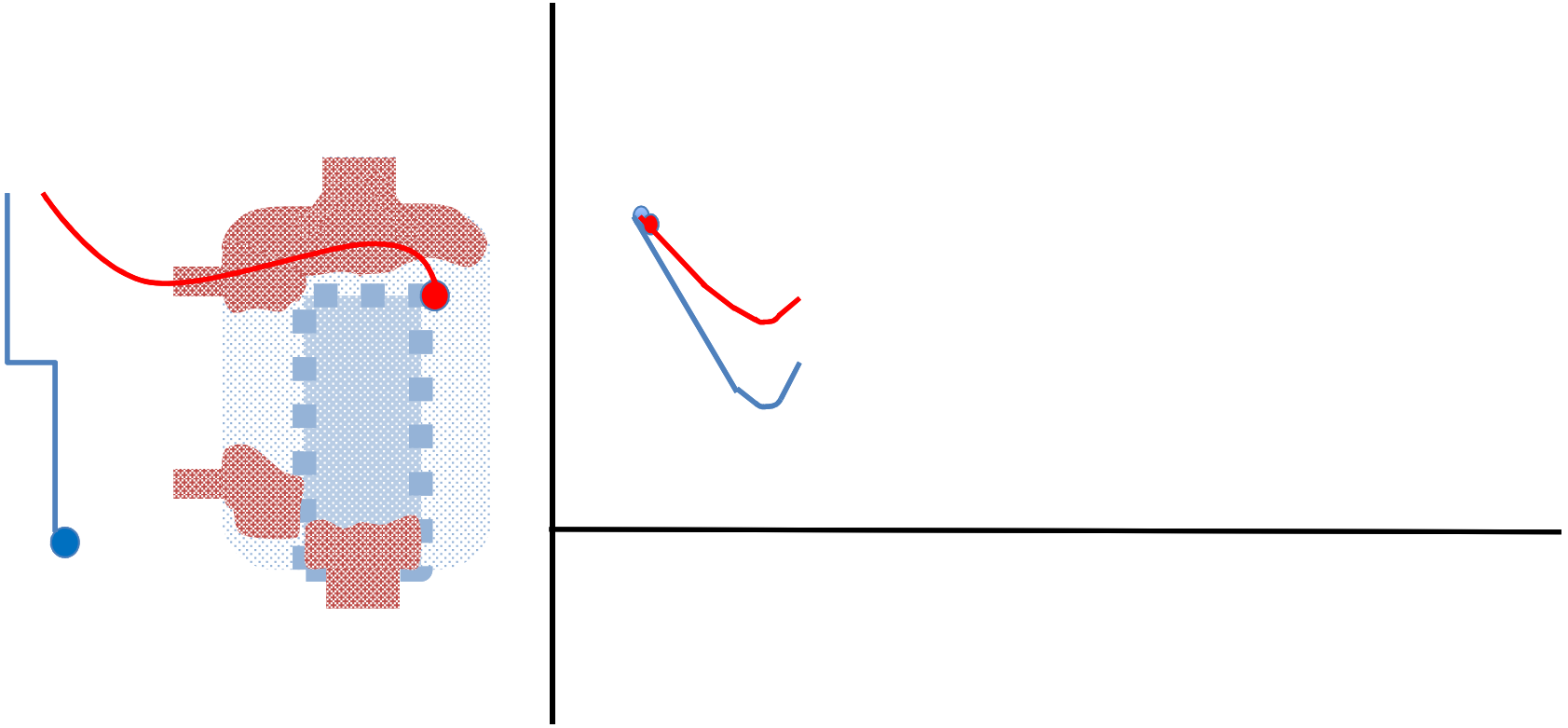

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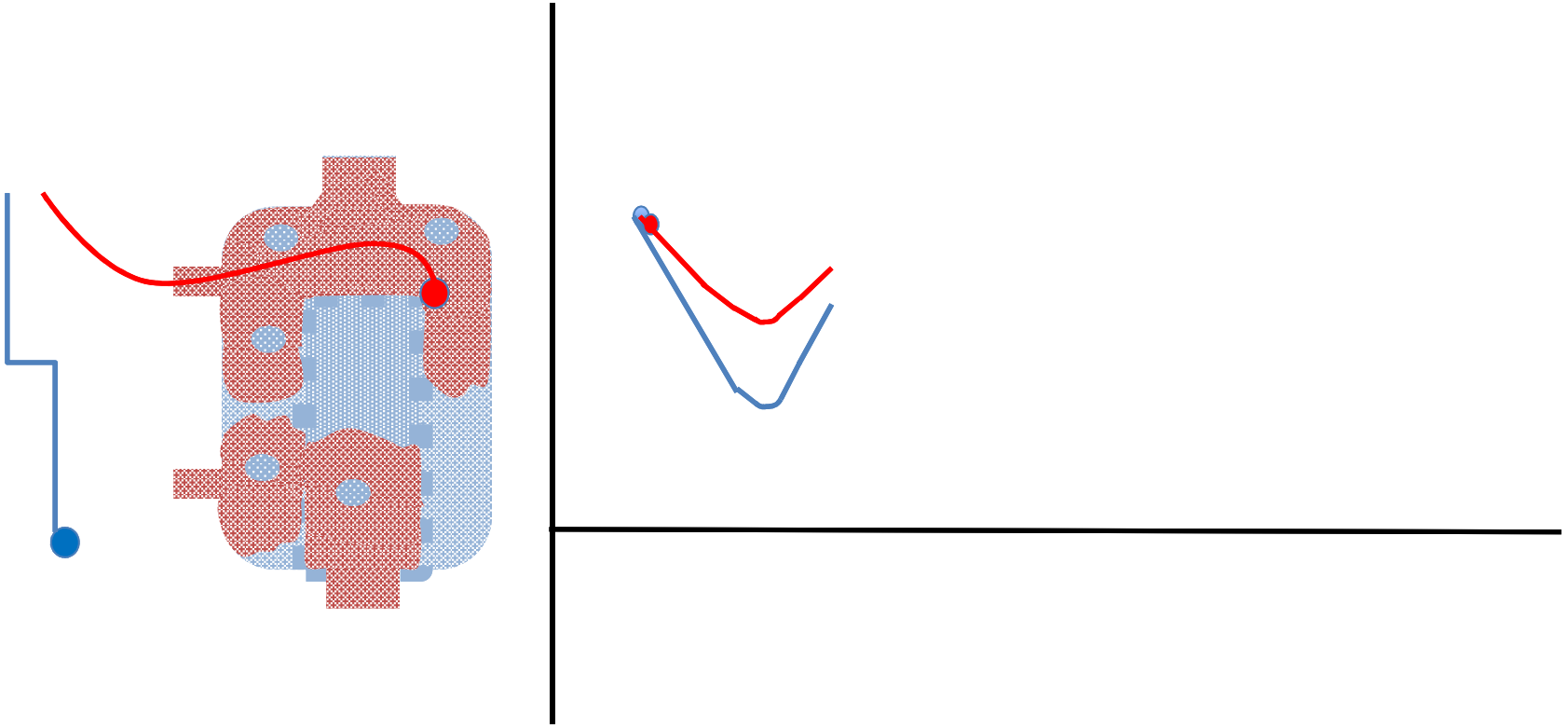

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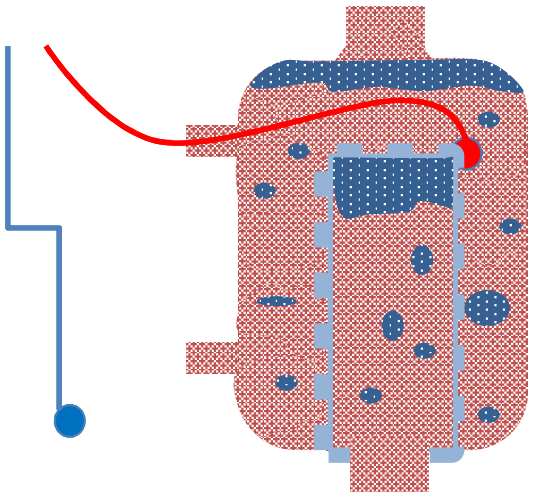

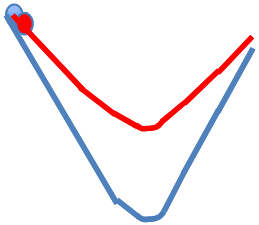

TEMPERATURE CHARATERICS AS SHOWN: NOT AT SCALE

DRAWING ONLY FOR EDUCATIONAL PURPOSES, NOT MEANT TO BE TRUE / REALISTIC

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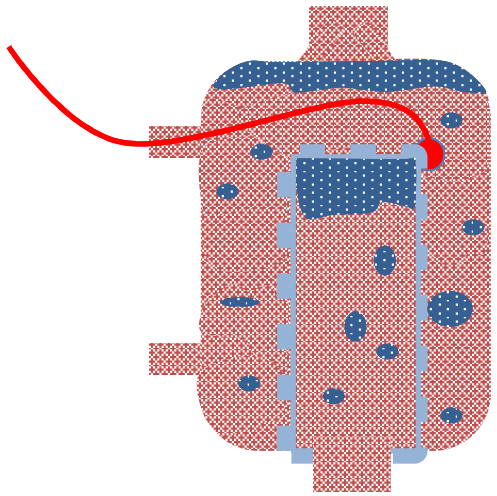
POINTS TO CONSIDER

- Was the right spot chosen for the TC (Thermo Couple) ?
- What will happen, if the filter is placed up-side down in the autoclave



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POINTS TO CONSIDER

- Validation/Qualification should be considered/planned at the start of the project/R&D-phase.
  It is often stated that validation is a status, and –to a lesser extent- function-testing

- Information from third-parties (if qualified) may be used during validation/qualification activities

  *Note that the Inspection will examine your qualification, **not** the qualification of (any) third parties.*

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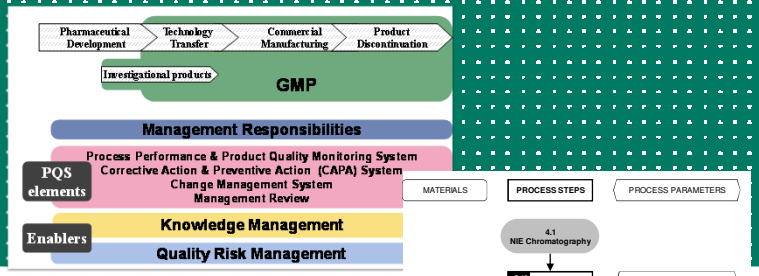
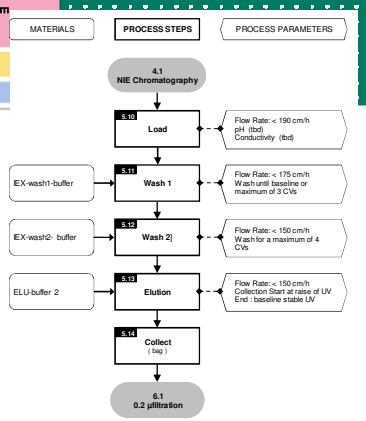
PROCESS VALIDATION (PV)





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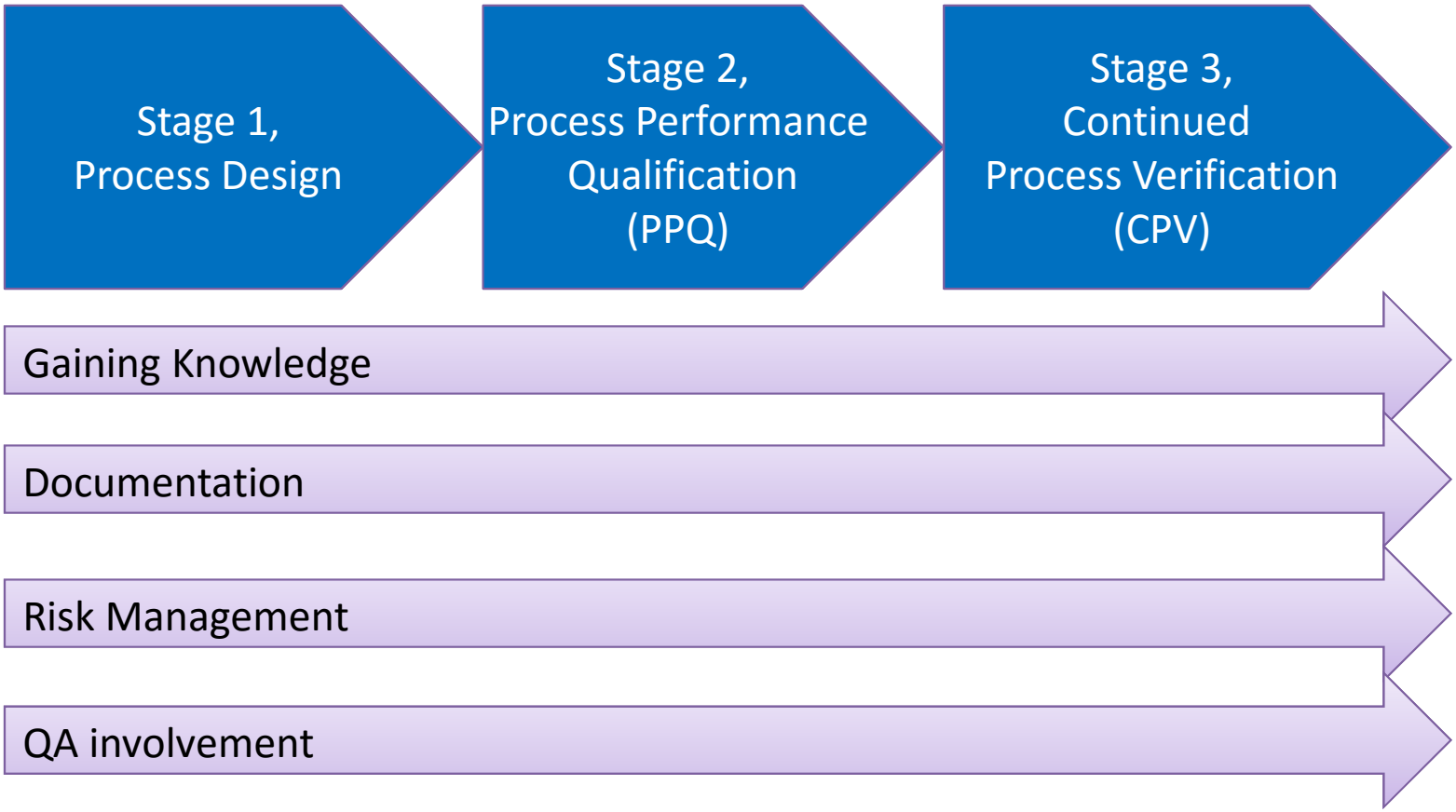
LIFE-CYCLE AND PROCESS VALIDATION



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VALIDATION OF ANALYTICAL METHODS

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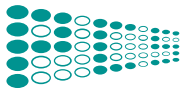

VALIDATION OF ANALYTICAL METHODS

Analytical Methods Validation (AMV)

- Analytical methods have to be validated unless the used method is mentioned in the related Pharmacopoeia or in any other recognized, common source

- The suitability of all used testingmethods has to be verified one way or the other:
  - Under actual testing circumstanes
  - As well as being documented

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VALIDATION OF ANALYTICAL METHODS

Methods have to be validated taking into account the ICH Q2 guidelines.

ICH Q2: Validation of Analytical Methods

- Identification tests
- Quantitative tests for impurity values
- Limit testing for impurities
- Quantitative tests for the level of the active compoment in samples of the product

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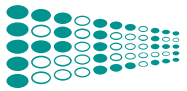
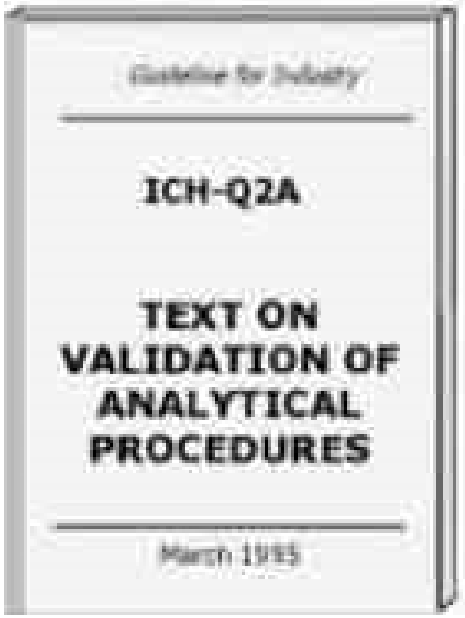


CHARACTERISTICS (1)

Typical validation characteristics:



- Range – lowest & highest
- Linearity – calibration line
- Accuracy – compared to the standard
- Precision – the same value, **always**
  - Reproducability (circle investigation)
  - Intermediate Precision (different labs, analysts etc.)
  - Repeatability (same sample, one after another)
- Specificity – Am I (accidentally) measuring other ingredients as well?

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CHARACTERISTICS (2)

Typical validation characteristics:

- Detection Limit – observable, not quanitify-able
- Limit for quantify-ability – to what amount can I attribute a number?
- Robustness – pre-validation, what does- and what does not matter for the end result (e.g. temperature, oxidation, matrix-effects).

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SHIPPING VALIDATION (& HOLDING)

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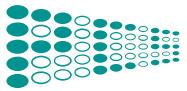

SHIPPING VALIDATION (GDP)

New Guideline (GDP)

- Know the Supply Chain, and Holding Conditions
- Holding Containers: Leachables/Extractables
- Cold Chain
- Counterfeits

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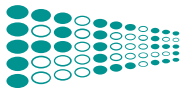

RE-VALIDATION / EVALUATION

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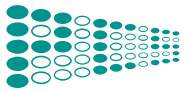

EVALUATION

Evaluate at:

- Environmental Monitoring Data
- System Review (automation!)
- Annual/rolling Product Review
- Change Control with (most probably) no impact
- Continuous Monitoring / Trending (processes, cleaning, shipping,……) , OOT's

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RE-VALIDATION

Laminair Air Flow “cabinets” and HVAC – according Annex I / ISO 14644

- HEPA-Filter integrity
- Flow patterns
- Recovery time
- Debiet JK1
- Particles (in operation and during idling)

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Diapositive 42

JK1 Troughput / Discharge (welke van de twee)?
Julian Koster; 22/05/2015

RE-VALIDATION

- Sterilisation-processes (e.g. autoclave)
  - Steam quality
  - Vacuum leak test
  - Air filter
  - Loads (not all over again)

- Aseptic Handling
  - Gowning
  - Operator / Team Qualification
  - Media Fill

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RE-VALIDATION

- Temperature-Controlled Environments
- After Changes
  - After a big change
  - After many small changes (that accumulate to a big change)
- After deviations / OOS's
- At alterations of (common) insights

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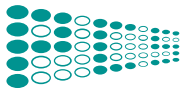

QUESTIONS ?

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THANK YOU FOR YOUR ATTENTION

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