




# Method development

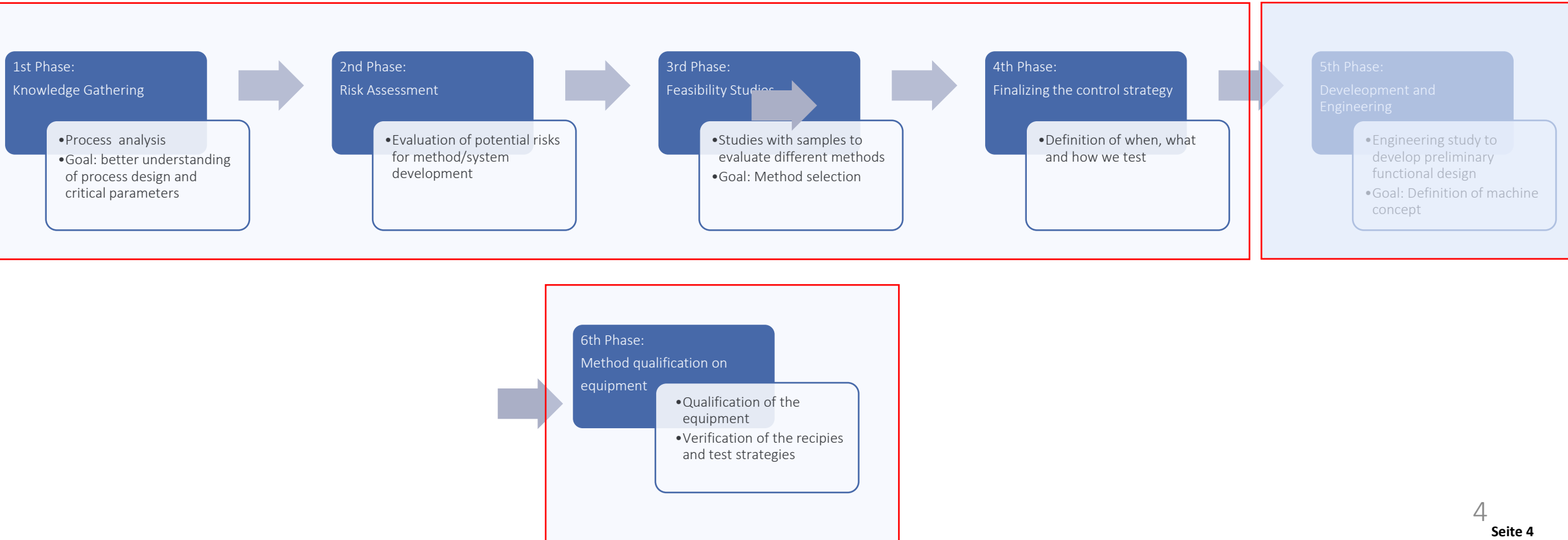
27.02.2020 | Dr. M. Kahl

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- A large red square is positioned on the left side of the slide, with a smaller orange square located at its bottom-right corner.
- 1. Concept Overview**
  - 2. Knowledge Gathering**
  - 3. Risk assessment**
  - 4. Implementation on equipment – feasibility study**
  - 5. Final selection of method and strategy**
  - 6. Implementation on equipment**
  - 7. Definition of method parameters**
  - 8. (Engineering / equipment / implementation)**
  - 9. Method qualification / validation**

# Concept Overview

# Concept Overview

## Method selection & development (according USP1220)



# Knowledge gathering

# Concept development

## Knowledge Gathering

- **What:**

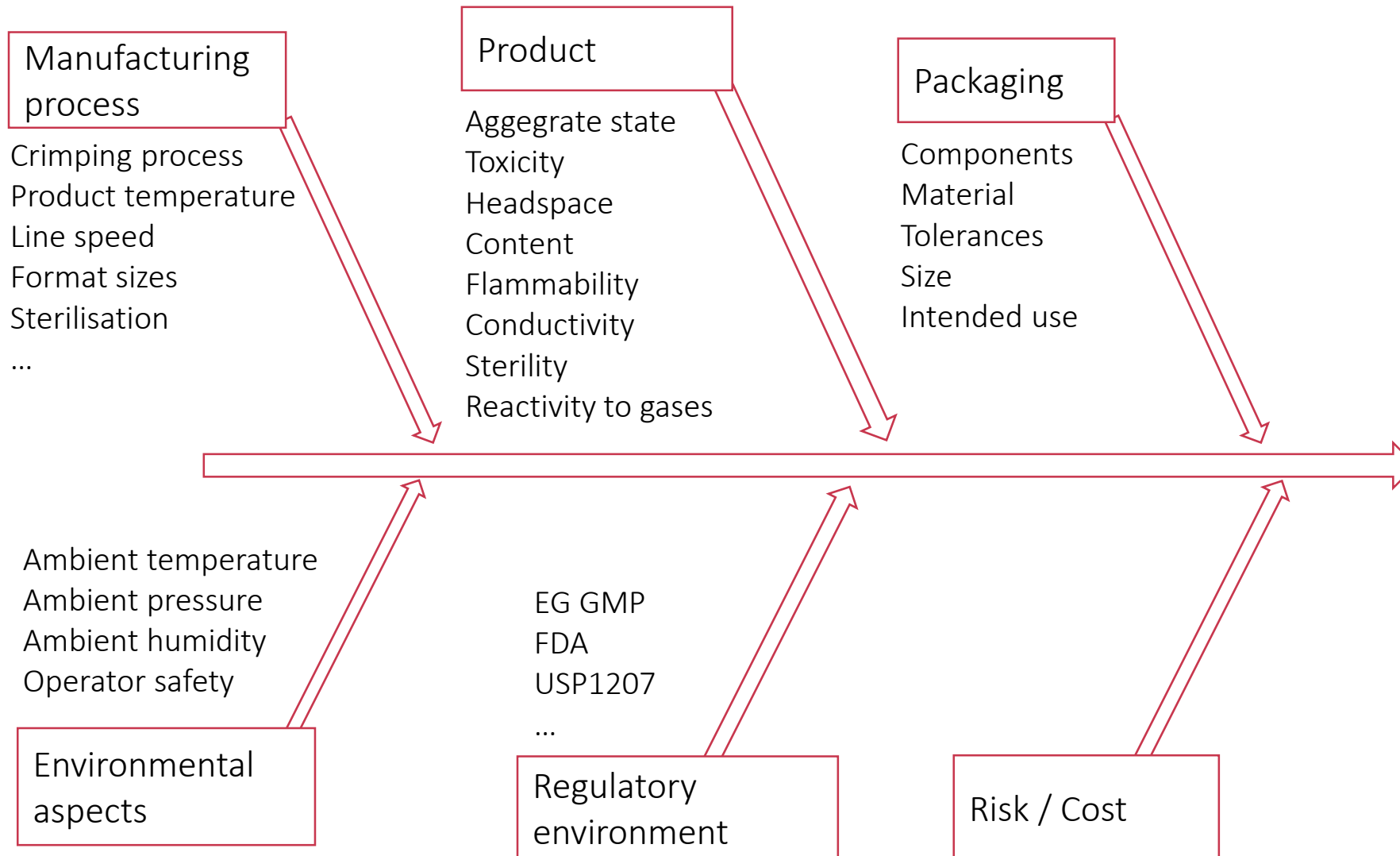
- Package design analysis
- Manufacturing Process analysis
- Gathering all information needed to design a fitting testing strategy

- **How:**

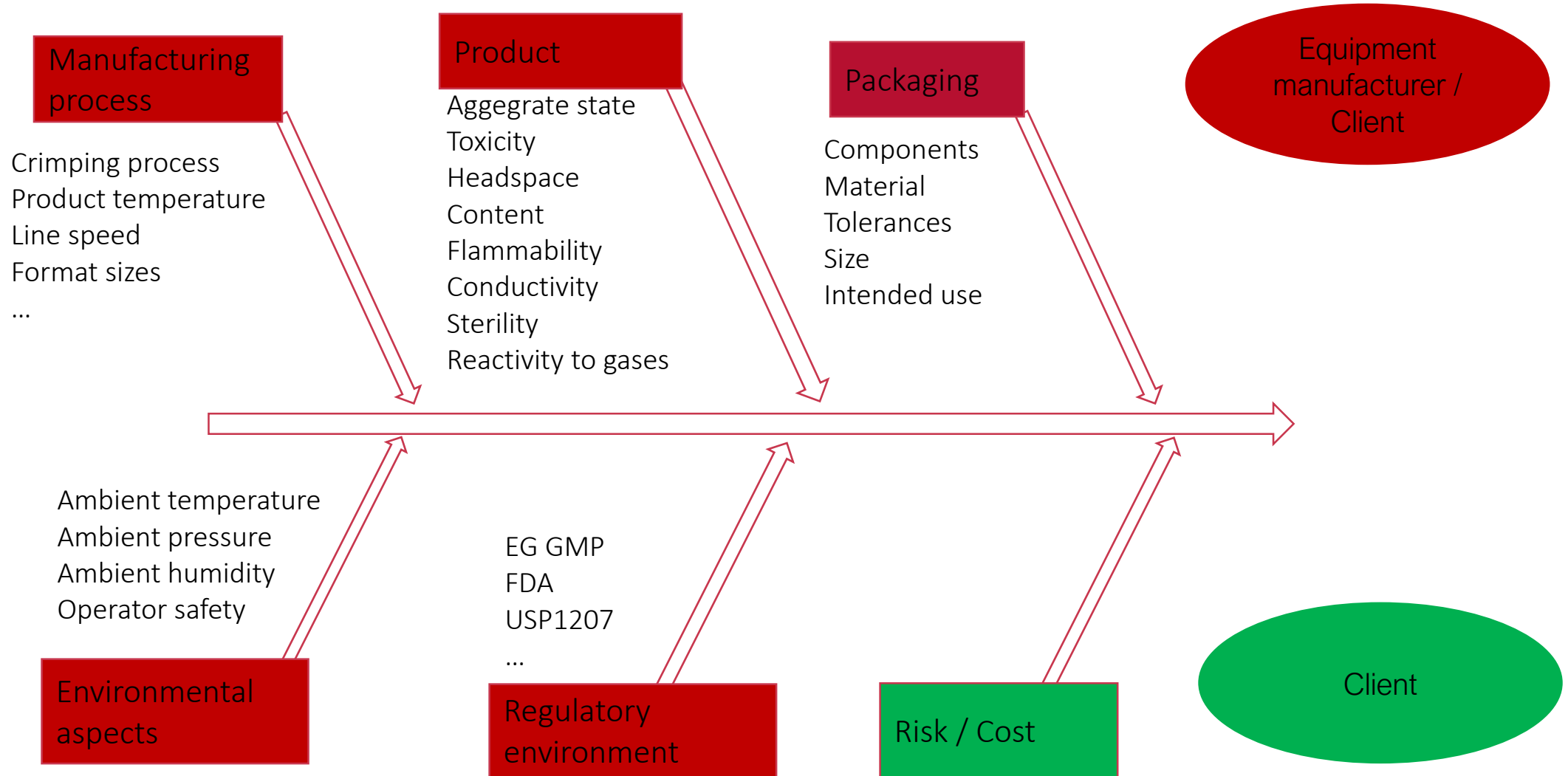
- Workshop at site
- Clustering of topics
- Include all departments (production, QA, QC, Development, Engineering, Global ...)
- If needed consult in process development if process is not fixed yet

# Knowledge gathering workshop

## Get all process information – What can influence test performance?



# Client vs. equipment manufacturer view





# Risk assessment

# Concept development

## Joint Risk assessment

### What:

- Risk Assessment (Acc. to ICH Q9 – QUALITY RISK MANAGEMENT)
- Process FMEA
- Common understanding
- Include information from knowledge gathering

### How:

- Workshop where FMEAs are merged
- Do FMEA twice – customer / supplier perspective
- Consolidation of risk assessments

### NOTE:

- Can be combined with the first workshop

FMEA																			
				Produktname		Änderungsstand		Datum											
				Produktnummer		erstellt durch													
				Modell/System/Fertigung		verantwortlich													
Element/ Funktion	n°	mögliche Fehler / Fehlfunktion		Fehlerursache		Fehlerfolge		Derzeitiger Zustand				empfohlene Maßnahme		Zuständigkeit		Verbesserter Zustand			
		Vermeidungs- Maßnahme	Entdeckungs- Maßnahmen	Bedeutung 1-10	Auftreten 1-10	Entdeckung 1-10	RPZ Risiko- prioritäts- zahl	Bedeutung 1-10	Auftreten 1-10	Entdeckung 1-10	RPZ Risiko- prioritäts- zahl	getroffene Maßnahme	Bedeutung 1-10	Auftreten 1-10	Entdeckung 1-10	RPZ Risiko- prioritäts- zahl			
Motorwelle	1	Bruch der Welle	Belastung nicht korrekt erkannt	Totalausfall	Standardtests	keine	8	6	10	480	Belastung durch geeigneten Berechnungsansatz	Herr Mustermann	neuer überarbeiteter Belastungstest	8	2	7	112		
	2	Spiel in der Lageranordnung	unexakte Funktionserfüllung	Lockern der Lagermutter im Betrieb	Befestigung mit Drehmomentschlüssel	keine	3	8	10	240	Zusätzliche Sicherung der Lagermutter	Herr Mustermann	Konterung der Mutter mit zweiter Mutter	1	8	10	80		
	3																		
	4																		
	5																		

Legende		
Auftreten	Bedeutung	Entdeckung
Wahrscheinlichkeit des Fehlers (Fehler ist möglich)	des Fehlers (Auswirkung auf den Kunden)	Wahrscheinlichkeit der Entdeckung des Fehlers (vor Auslieferung an Kunden)
unwahrscheinlich <span style="background-color: #90EE90; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 1	kaum wahrnehmbar <span style="background-color: #90EE90; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 1	hoch <span style="background-color: #90EE90; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 1
sehr gering <span style="background-color: #90EE90; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 2-3	unbedeutender Fehler <span style="background-color: #90EE90; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 2-3	mäßig <span style="background-color: #90EE90; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 2-3
gering <span style="background-color: #FFD700; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 4-6	mäßig schwerer Fehler <span style="background-color: #FFD700; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 4-6	gering <span style="background-color: #FFD700; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 4-6
mäßig <span style="background-color: #FFA500; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 7-8	schwerer Fehler <span style="background-color: #FFA500; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 7-8	sehr gering <span style="background-color: #FFA500; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 7-8
hoch <span style="background-color: #FF4500; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 9-10	äußerst schwerer Fehler <span style="background-color: #FF4500; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 9-10	unwahrscheinlich <span style="background-color: #FF4500; border: 1px solid black; display: inline-block; width: 15px; height: 10px;"></span> 9-10

Implementation on  
equipment –  
feasability studys



# Differential pressure



# Definition method parameters

## Differential pressure

Goal:

- Determine the parameters of the recipes

Use of negative samples:

- determine first estimate for the time intervals of test sequence
- determine the noise of the test system
- determine the noise introduced for by tolerance variations of the negative samples
- for a single station use for example 30 negative sample

Use of positive samples:

- test sequence of positive samples
- functional controls
- positive samples

Needed:

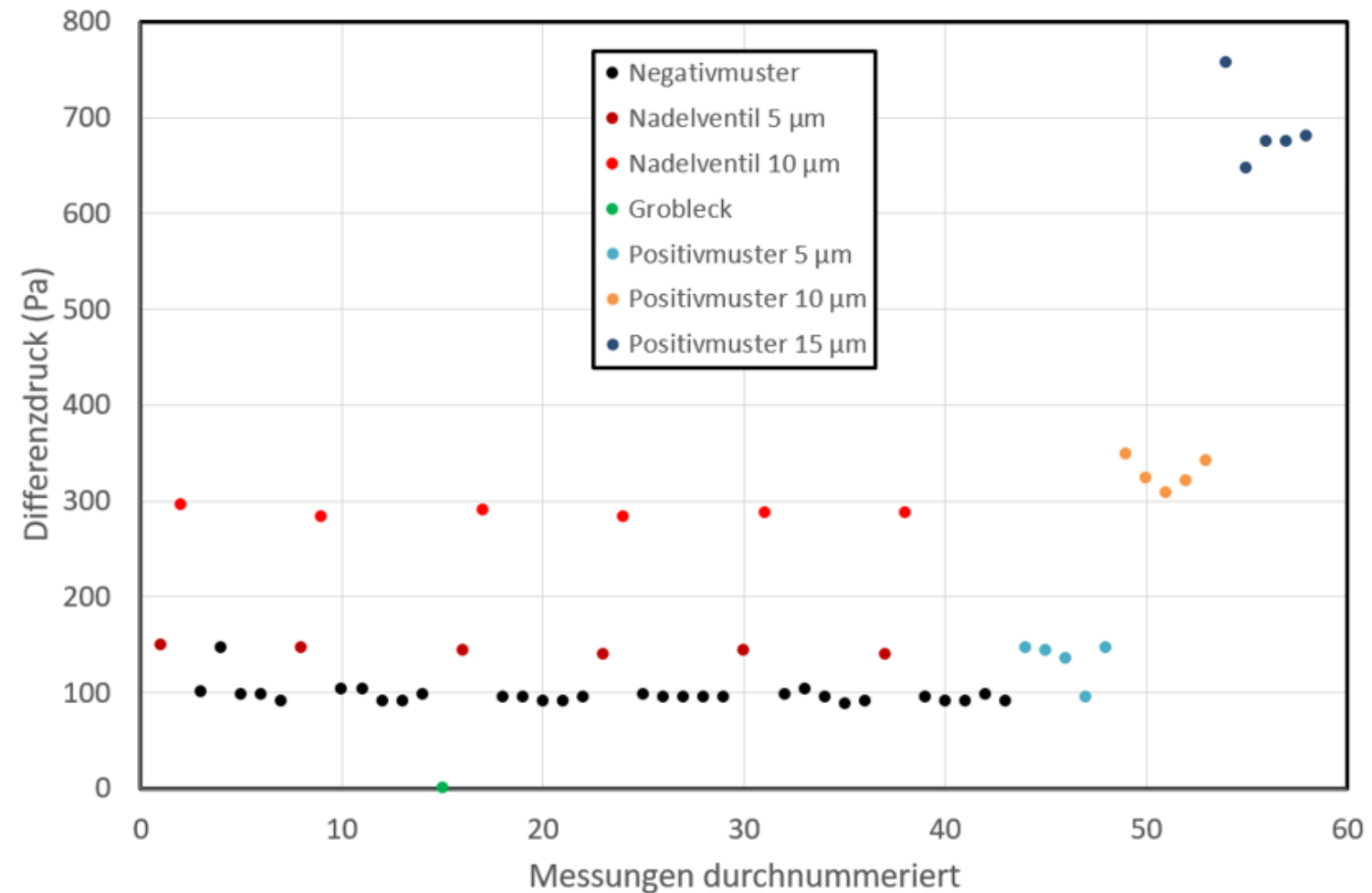
- Negative samples
- Positive samples
- Functional tests

# Definition method parameters

## Differential pressure – sample sequence

- Example for measurement done for 6H vial
- consecutive measurement of
  - repeat six times
    - self test (functional test)
    - negative samples
  - do coarse leak in-between
  - positive samples
    - flow under designed limit of machine
    - flow at designed limit of machine
    - flow over designed limit of machine

Gemessene Differenzdrücke - 6H





Headspace



# Definition method parameters

## Headspace analysis

Goal:

- Design of machine determines the detection limit
- Determine the waiting time

Needed:

- Positive samples

Design of machine:

- Machine parameters will determine the detection limit
- Adapt machine layout to fit application demands (speeds, integration time, formats, ...)
- Calculate LoD

Air ingress in case of leaky vial:

- conditions of gas in container at closing will determine the potential air ingress
- Modell the air ingress to determine the time needed to get to LoD



# Definition method parameters

## Headspace analysis – air ingress model

Calculation:

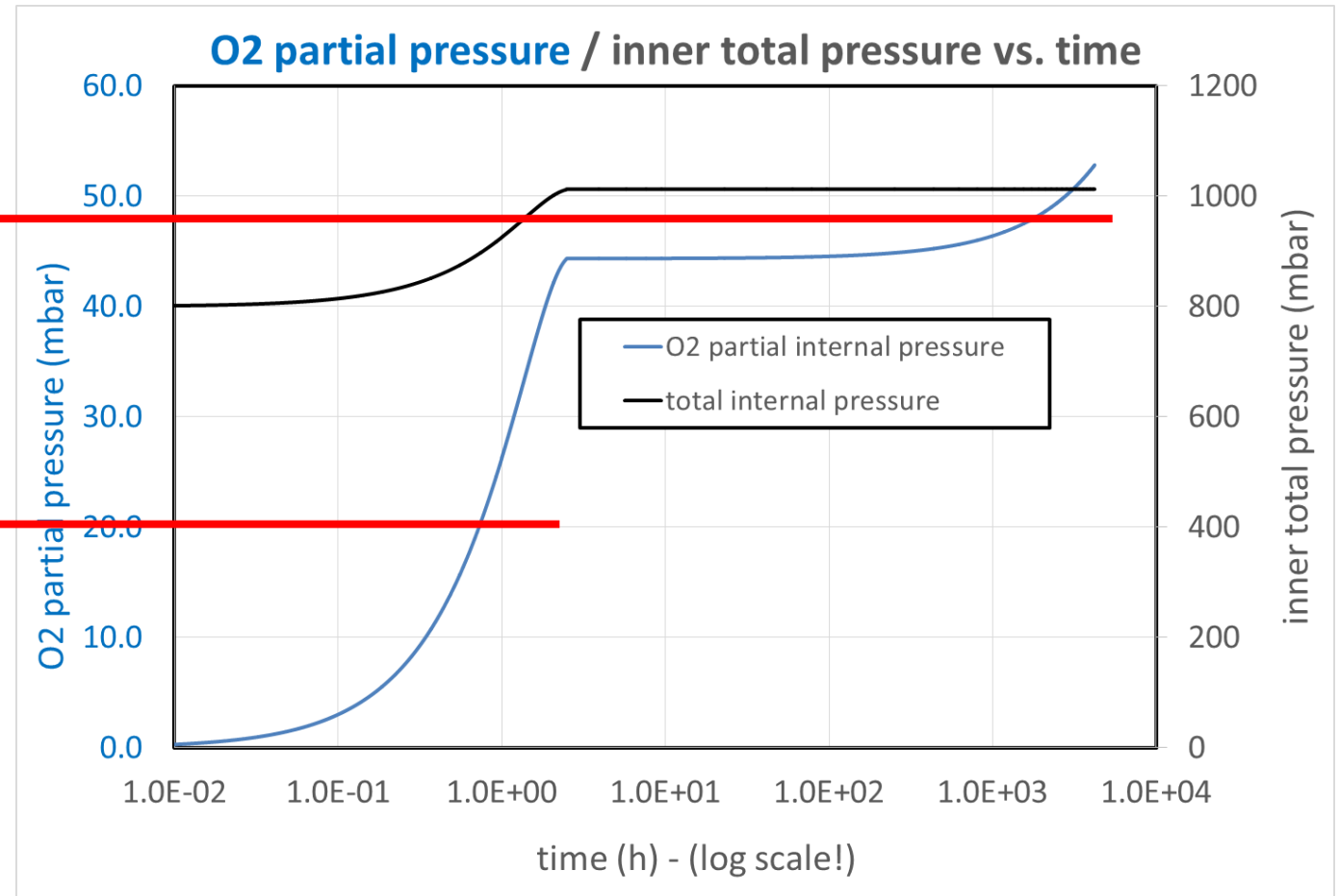
- 10 ml vial, 10  $\mu\text{m}$  leak (orifice)
- 800 mbar nitrogen overlay

Machine config. 1

- long waiting time
- “high” oxygen concentration
- depending on testing speed

Machine config. 2

- short waiting time
- low oxygen concentration
- air ingress model
- for 100 % multiple test stations needed





High Voltage



# Definition method parameters

## HV

### Goal:

- determine the test geometry of electrodes needed to test different areas
- determine the needed HV levels to detect the leaks present
- noise levels, influence of container tolerances, tolerances of setup, of handling
- test times, test strategies, test speed
- determine the handling strategy

### Needed:

- Positive samples

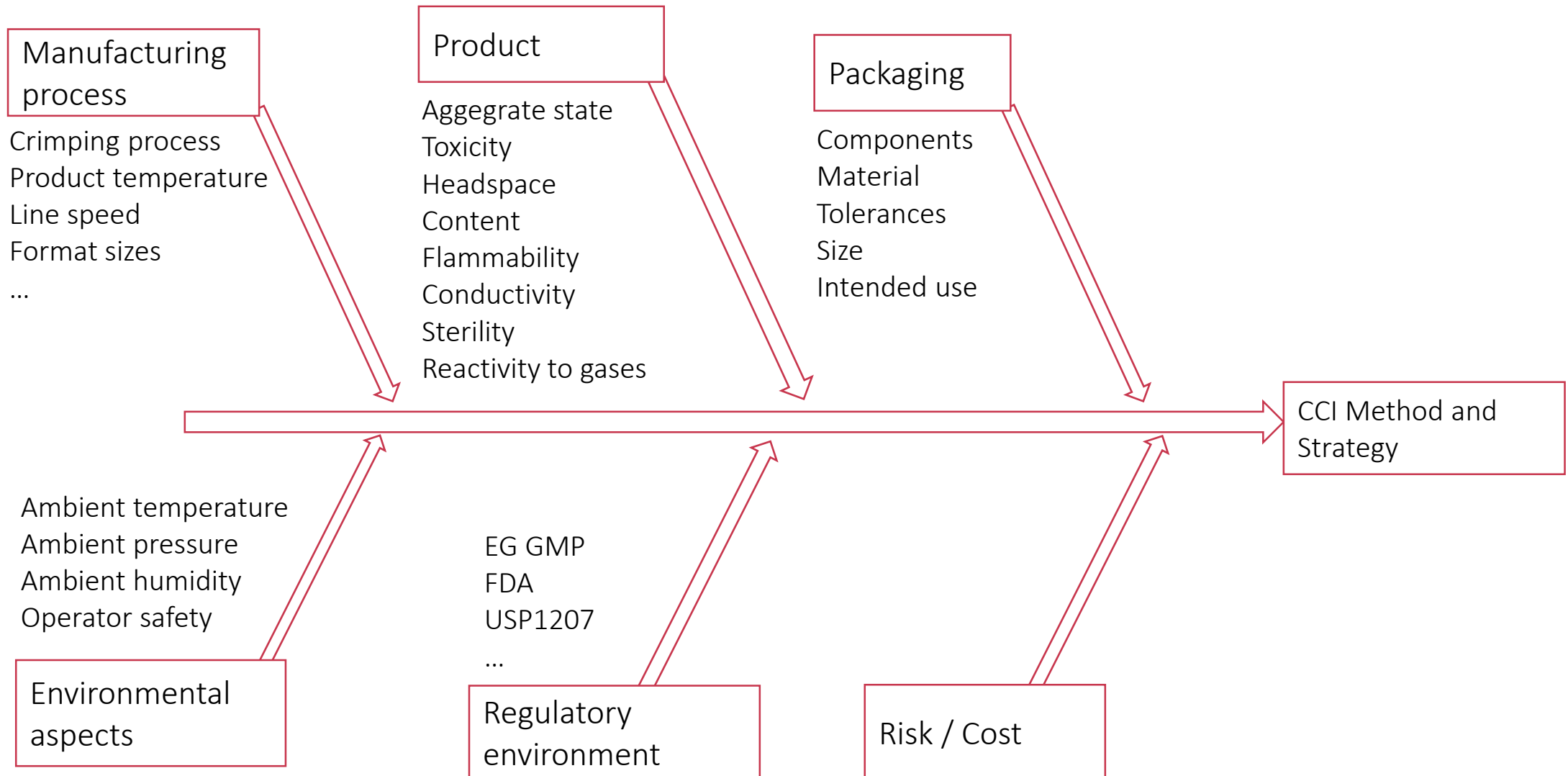
### Design of machine:

- Machine parameters and process will determine the detection limit
- Adapt machine layout to fit application demands (speeds, integration time, formats, ...)
- Calculate LoQ, LoD

# Final selection of method and strategy

# Knowledge gathering workshop

## Get all process information – What can influence test performance?



# Concept development

## Definition of Analytical Control Strategy

- Definition of testing strategy in general
- At which point in the overall process will we test (where in the production process)
- to what extend (IPC/100%)
- Which technology will be put in place for which step in the process
  - filled container
  - empty container
  - intermittent process steps
- link strategy to inspection technologies / other technologies
  - visual inspection
  - other product quality related inspections (e.g. NIR)
  - labeling / laser marking / track and trace

# Definition of method parameters

# Concept development

## Definition of Method Parameters

Concept for machine design

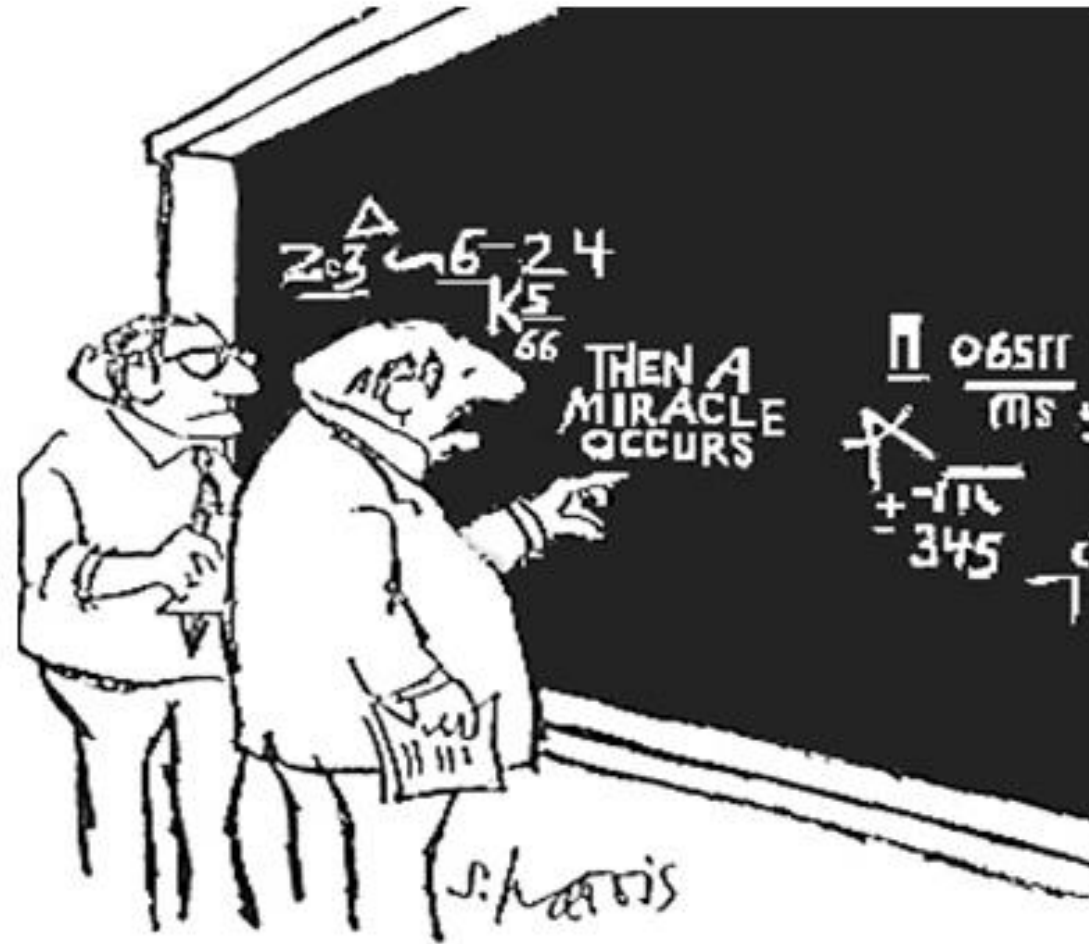
- Lab / semi automatic / or inline machine (according to test strategy to be set in place)
- Inline machine concept
  - test method
  - first idea on handling concept
- Parametrization of method and technology
  - DP (times, pressure levels, volumes ...)
  - HSA (integration times, optical path length, calibration strategies ...)
  - HVLD (voltage levels, speeds, electrode configurations, testing areas ...)
  - FS (forces, handling ...)



# Engineering and implementation on equipment

# Concept development

Engineering / Machine / Testing



"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO."

# Method validation



Concept



# Concept for qualification/validation

## Add on to PQ

Check developed recipes for validity:

- load the proper recipe for the format to be tested
- use a sequence of samples to check the function of the test system
  - negative samples from client from line
  - functional tests in place
  - positive controls – depending on test technology
    - leak to liquid on inside
    - leak to headspace
  - positive controls
    - DP: leaks to headspace and liquid (if applicable)
    - HSA: generate standards with controlled tracer gas concentrations
    - HV: positive samples
    - FS: positive samples with leaks to liquid and headspace (if present)
- verify positive samples with orthogonal method (Helium leak test, air flow, ...)

# Concept for qualification/validation

## Example for test plan

Sample	Negatives	Functional Below MALL	Functional At MALL	Positive Below MALL	Positive At MALL	Positive Over MALL	Coarse
NEG01	X						
NEG02	X						
NEG...	X						
NEG30	X						
NEG01	X	X					
NEG...	X	X					
NEG05	X	X					
NEG06	X		X				
NEG...	X		X				
NEG10	X		X				
COARSE							X
POS01				X			
POS...				X			
POS05				X			
POS06					X		
POS...					X		
POS10					X		
POS11						X	
POS...						X	
POS15						X	

### Negative controls and functional tests

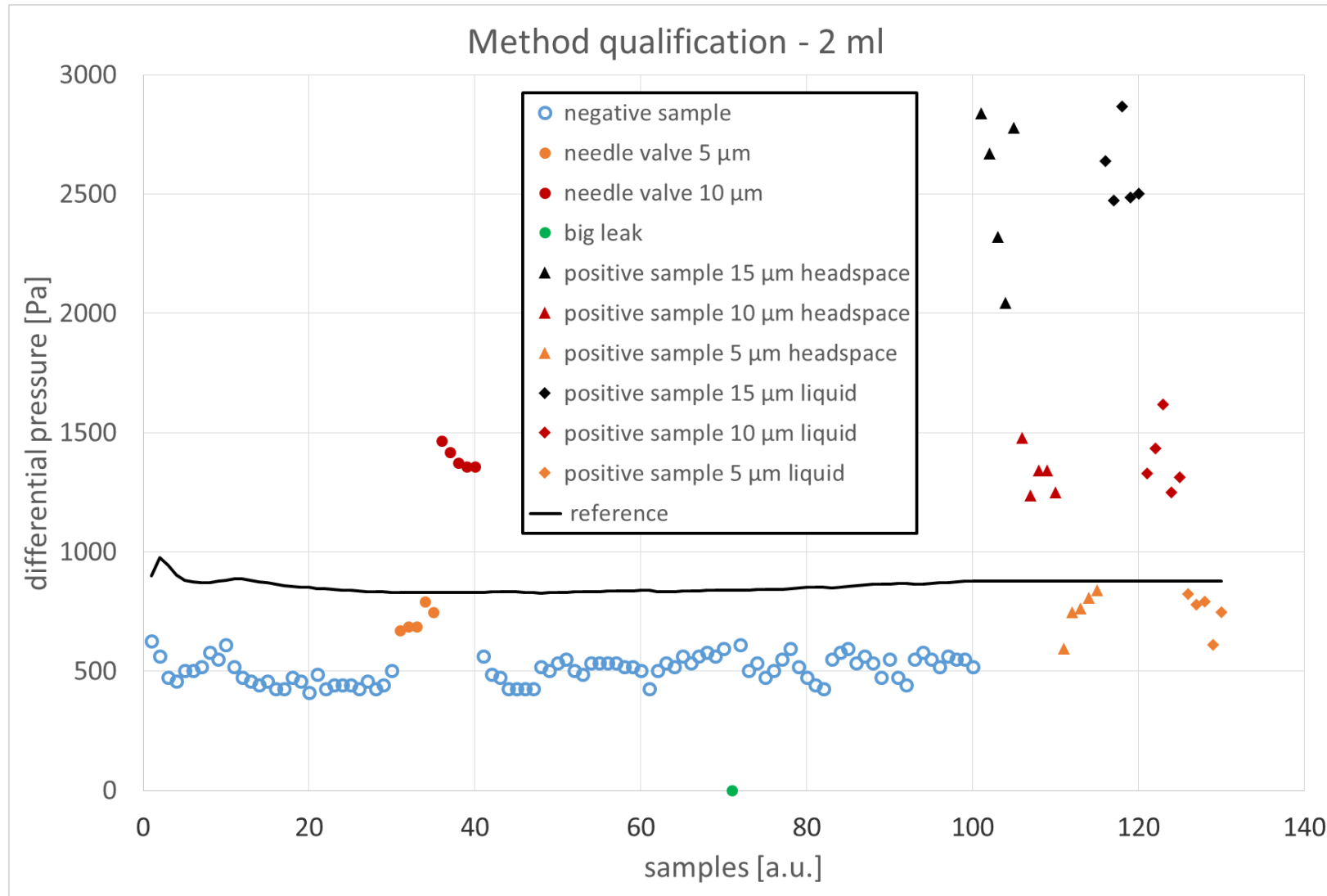
- repeat pattern of negative samples and functional tests
  - depending on machine (inline vs. offline)
  - depending on number of test chambers
  - depending on test sensitivity

- coarse leak

- positive samples

# Concept for qualification/validation

## Example for data



# Being sure.



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