AUTOMATED DETECTION OF CONTAINER CLOSURE DEFECTS

Wolfram Schindler, Robert Bosch Packaging Technology GmbH

Sept 12, 2019 PDA MO Valley Chapter: Fall Dinner Event

BOSCH

Why CCIT?

Ensure sterility and other product quality attributes. Leak defects are risk for microbial ingress, oxygen and moisture ingress, loss of vacuum.

Maintaining headspace may imply stricter CCI requirements than maintaining sterility.

"...specified leakage limits help to ensure the contained product meets and maintains sterility and relevant physiochemical specifications" USP <1207>

"*Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period*" EU GMP Annex 1

"*Package integrity verification occurs during three product life cycle phases: 1) development and validation of the product-package system, 2) product manufacturing, and 3) commercial product shelf-life stability assessments*" USP <1207>

CCIT & visual inspection

2008

EMA_GMP_Revised_Annex_1_2008.pdf

117. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

123. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.

2017 (Draft, 2017-Dec-21)

2017_12_pc_annex1_consultation_document.pdf

8.18 Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. Form-Fill-Seal Small Volume Parenteral (SVP) & Large Volume Parenteral (LVP) bags, glass or plastic ampoules, should be subject to 100% integrity testing. Samples of other containers should be checked for integrity utilising validated methods and in accordance with QRM, the frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A statistically valid sampling plan should be utilized. It should be noted that visual inspection alone is not considered as an acceptable integrity test method.

8.19 Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate, pre-determined period and during shelf life.

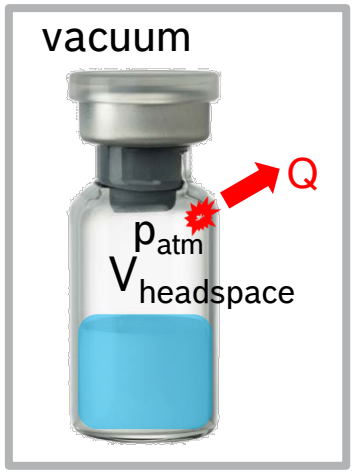
8.20 The container closure integrity validation should take into consideration any transportation or shipping requirements.

- **Visual and CCI inspection have increasingly been seen as being complementary**
- More attention to robust CCI studies, validation of CCIT methods, and generation of science-based, statistical data
- „Statistically valid“ sometimes means 1000‘s of samples. When is 100% batch testing appropriate?

CCIT technologies for automated inspection

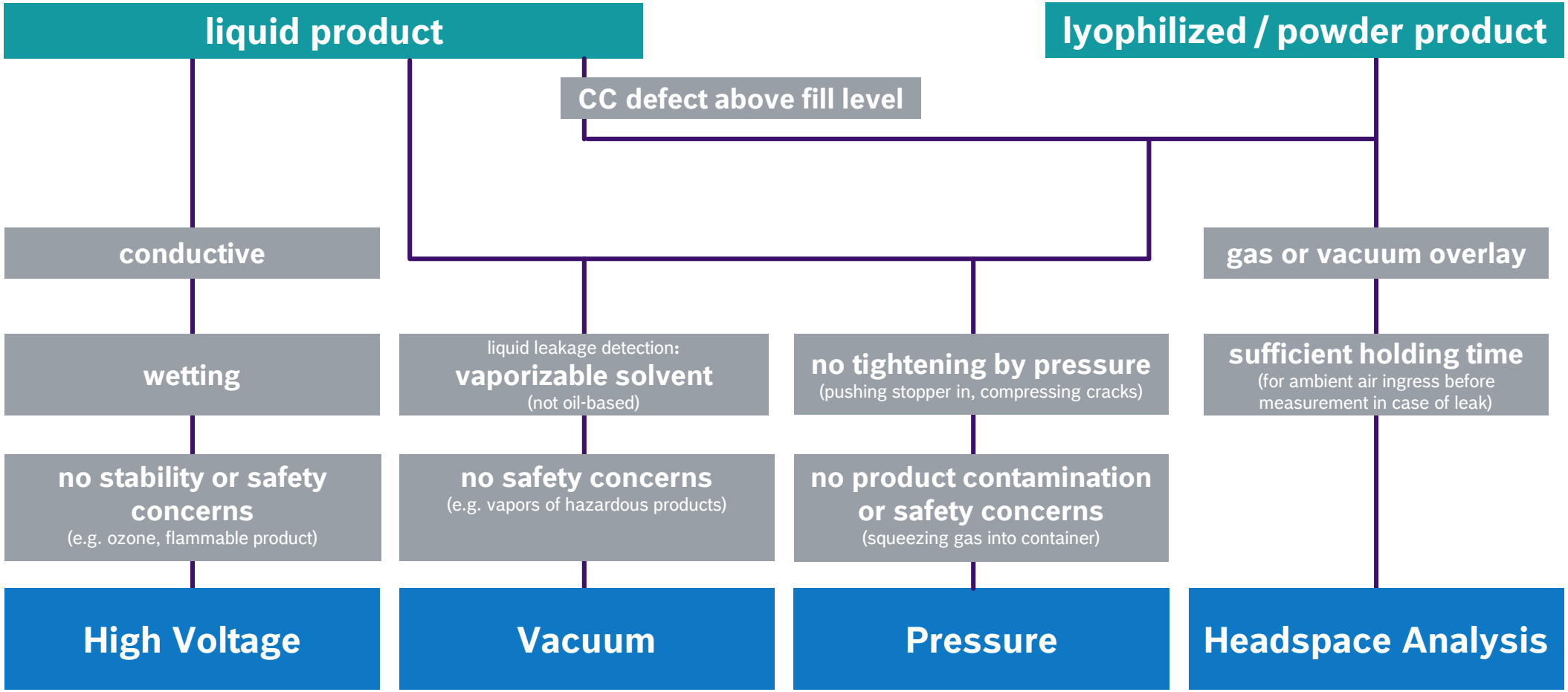
Laser-based headspace analysis

High voltage leak detection



Vacuum leak detection

Selection of the adequate CCIT technology



Accurately identify leaking vs non-leaking product packages

- Appropriate accuracy, precision, linearity, range, specificity, robustness, detection (and quantitation) limit
- Limit of detection smaller or as close to the maximum allowable leak limit as possible → determine the residual risk
- Consider product interference like clogging (may depend on storage conditions!) or cake moisture (may affect HSA total pressure measurement signal quality, depends on storage conditions!)
- Besides leak presence, also size, location of interest?
- What are adequate reference standards, positive controls, realistic defects?

Reference standards and positive controls

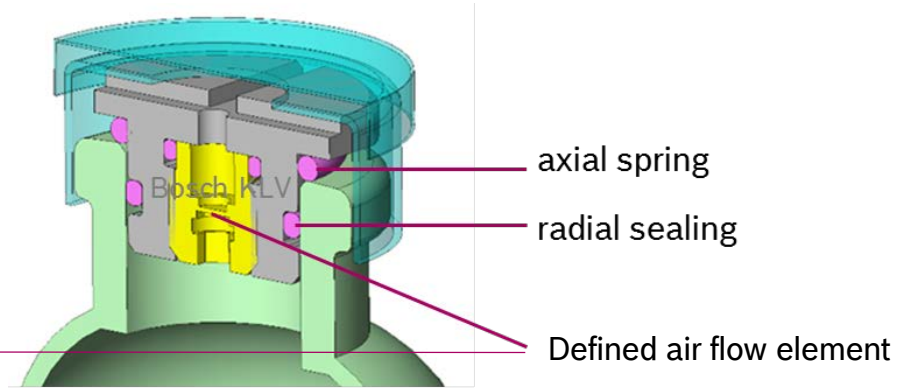
Reference standards

determine detection capability, routine performance check, yielding defined signal but not necessarily due to a leak.
HSA: flame-sealed glass container at certified pressure and/or oxygen level
Vacuum decay: Dummy replicating external and inner volume, comprising an air flow calibrated leak
HVLD: Empty container (lower limit), dummy with defined impedance (upper limit)

Positive controls

validate method detection limit, prove leaks at **specific package locations** can be detected, determine the **impact of product presence** (fill volume, oxidation, moisture release, conductivity, viscosity, surface tension, clogging) and other conditions (storage time, temperature)

Reference standard for air leak



- Same conditions for calibration, verification and product measurement: same headspace volume (→“pressure reservoir”), same measurement cycle.
- Laser-drilled hole or hollow fiber as air flow element
- Leak rate of the air flow element are determined and certified using a with calibrated flow meter
- Flexibility to set different leak sizes, bracketing the acceptance criteria

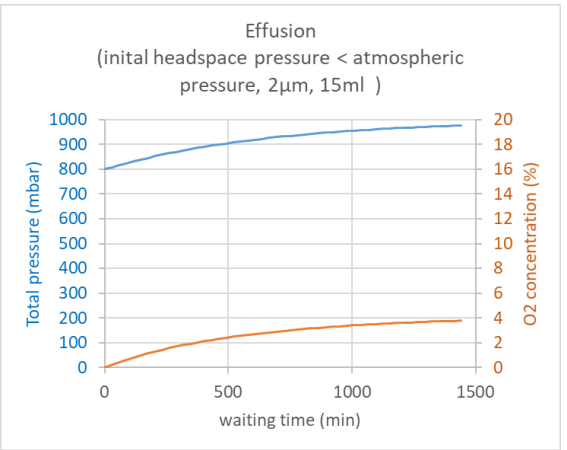
HSA case study: oxygen concentration measurement

- Study on new vial/stopper combination for freeze dried product. Sub-batches per shelf.
- 22 mm vials, nitrogen backfill at 800 mbar, 200 vpm
- Determine distribution (from manual sampling: “be prepared for >2% rejects”)
- Propose reject limit

When leaking to atmospheric pressure (in air), headspace oxygen concentration reaches 200mbar*20% / 1000 mbar = **4%.** After, further oxygen ingresses much slower by diffusion.

Leak size	**Time* to reach 3%** (starting from 800mbar, V=15ml)
2 µm	12 h
5 µm	2 h
10 µm	30 min
100 µm	20 sec

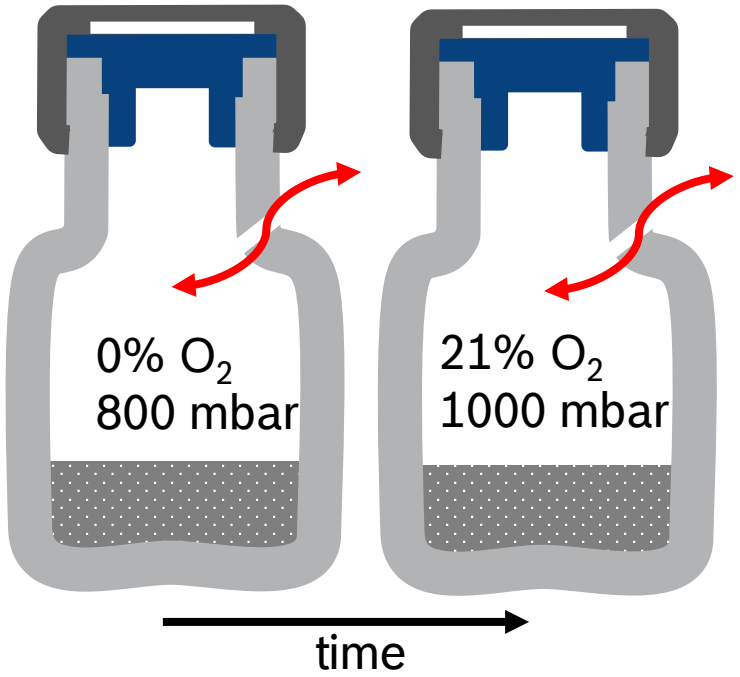
*may depend on defect characteristics



Permanent and temporary leaks

Permanent leak

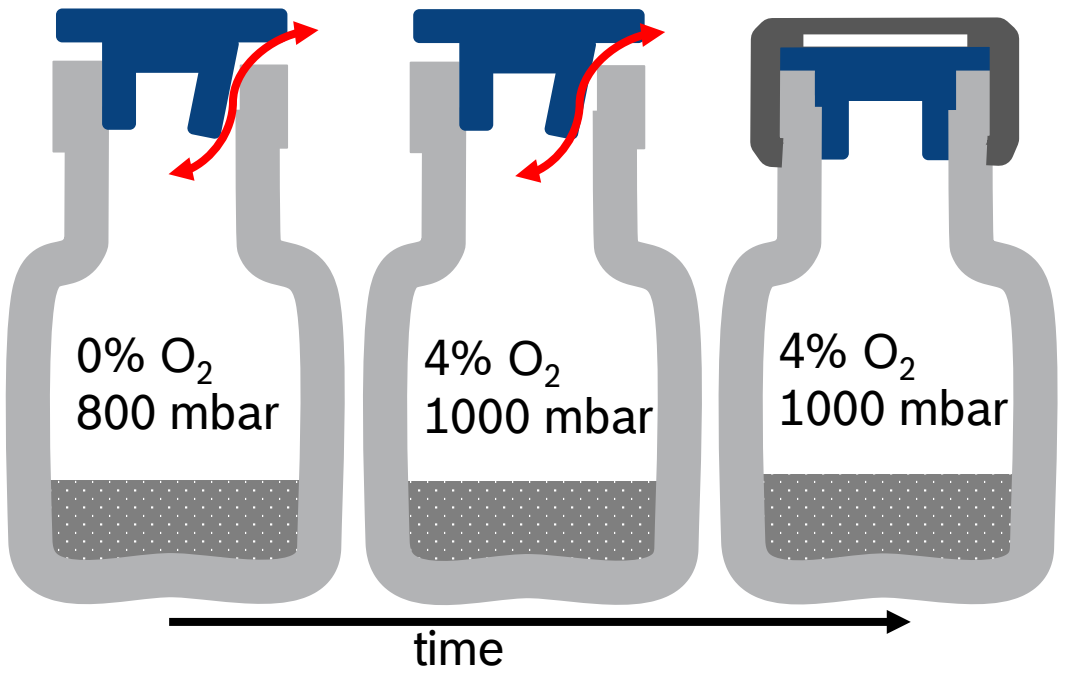
continuous gas exchange,
headspace equalizes to ambient



temporary leak

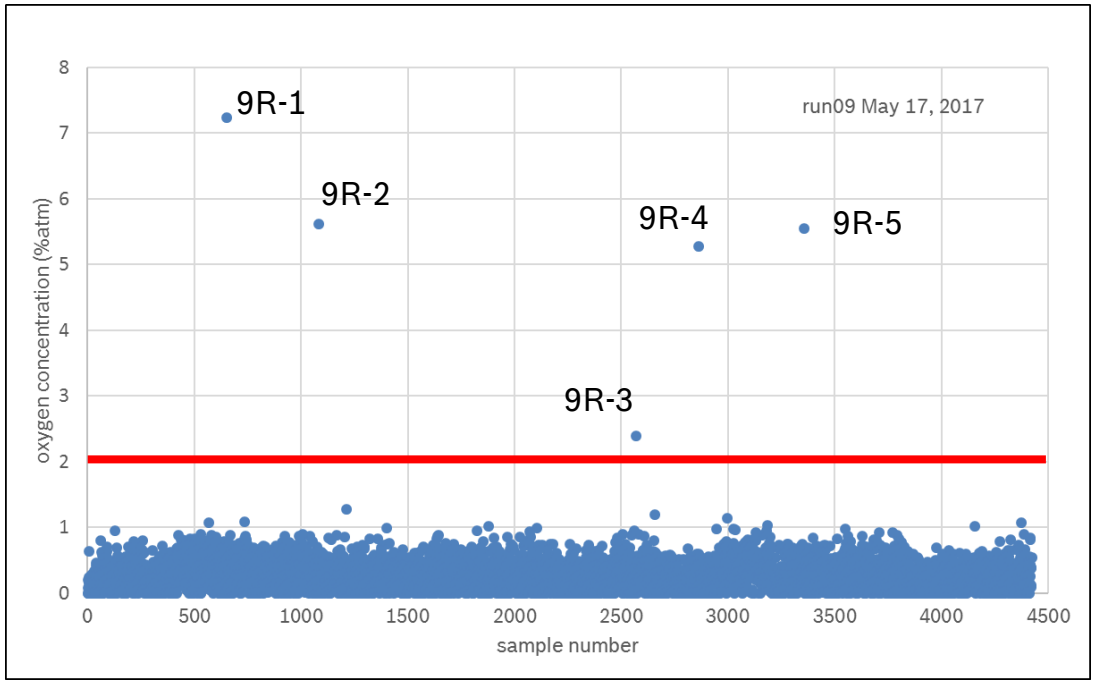
leaky before crimping („stopper pop-up“), stored in air

sealed before measurement



Headspace analysis detects both permanent and temporary leaks.
Longer holding time helps to detect smaller permanent leaks.

HSA study: Individual values of one shelf



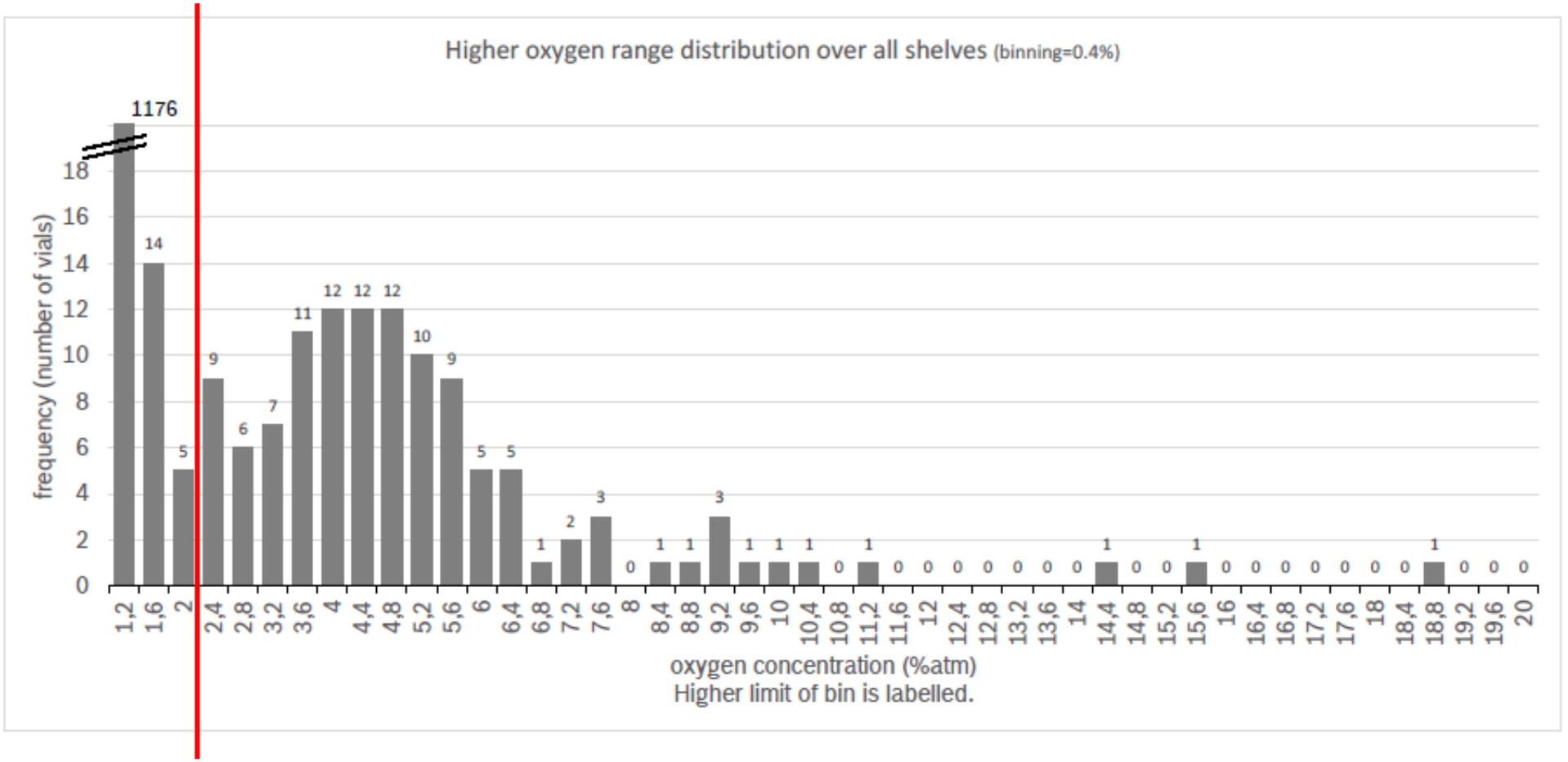
- SD of 4%atm reference standard: 0.25%atm
- Mean of good vials: 0.3%atm
- Rejected vials have been measured again 30 turns in recirc mode and compared to benchtop measurements

Machine reject limit set to 2%atm

All values in %atm

	Machine, each sample measured 30 times (at 200 vials/min)				Benchtop, each sample measured once	
Sample	**Mean Value**	**Min**	**Max**	**SD**	**Single**	**Difference between machine mean and benchtop**
9R-1	7,09	6,60	7,50	0,21	7,31	-0,22
9R-2	5,12	4,60	5,40	0,22	5,45	-0,33
9R-3	1,98	1,60	2,40	0,23	2,10	-0,12
9R-4	4,64	4,00	5,00	0,23	5,06	-0,42
9R-5	4,91	4,20	5,40	0,25	5,30	-0,39

HSA study: Oxygen concentration distribution

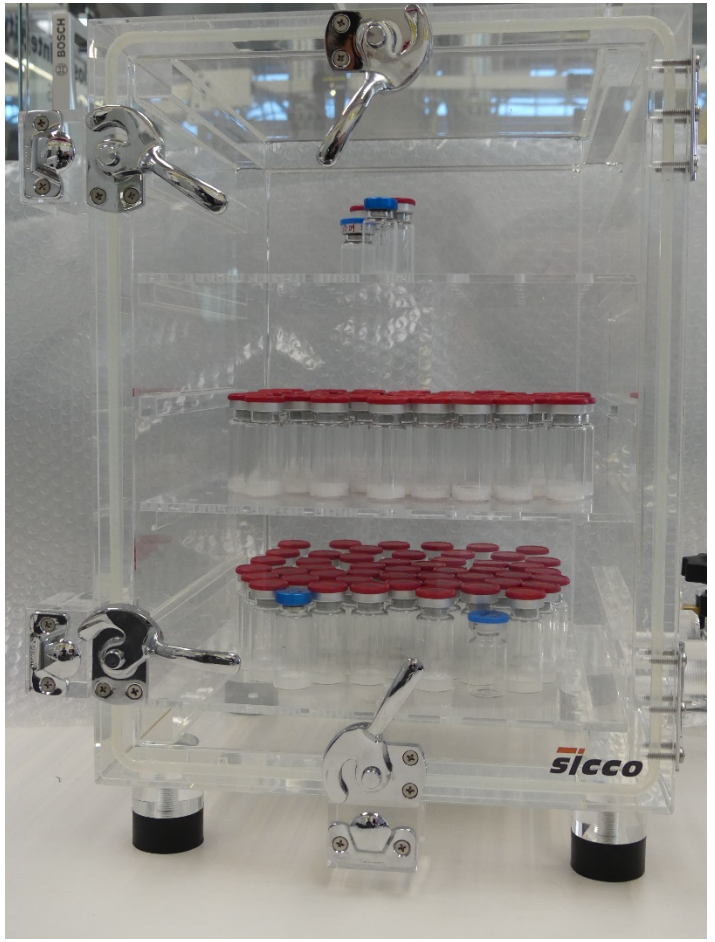


HSA study: Different results per shelf

	Sampling with benchtop		**Automated 100% testing**				
	Rejects, limit 3%atm		Total	Rejects, limit 3%atm	Reject rate (%), limit 3%atm	Rejects, limit 2%atm	Reject rate (%), limit 2%atm
Shelf_01	0/100		4186	14	0,33	18	0,43
Shelf_02	0/100		4345	27	0,62	35	0,81
Shelf_03	0/100		4399	5	0,11	6	0,14
Shelf_04	0/100		4420	7	0,16	8	0,18
Shelf_05	2/100		4425	11	0,25	11	0,25
Shelf_06	0/100		4418	11	0,25	14	0,32
Shelf_07	0/100		4418	3	0,07	3	0,07
Shelf_08	0/100		4200	2	0,05	2	0,05
Shelf_09	0/100		4423	4	0,09	5	0,11

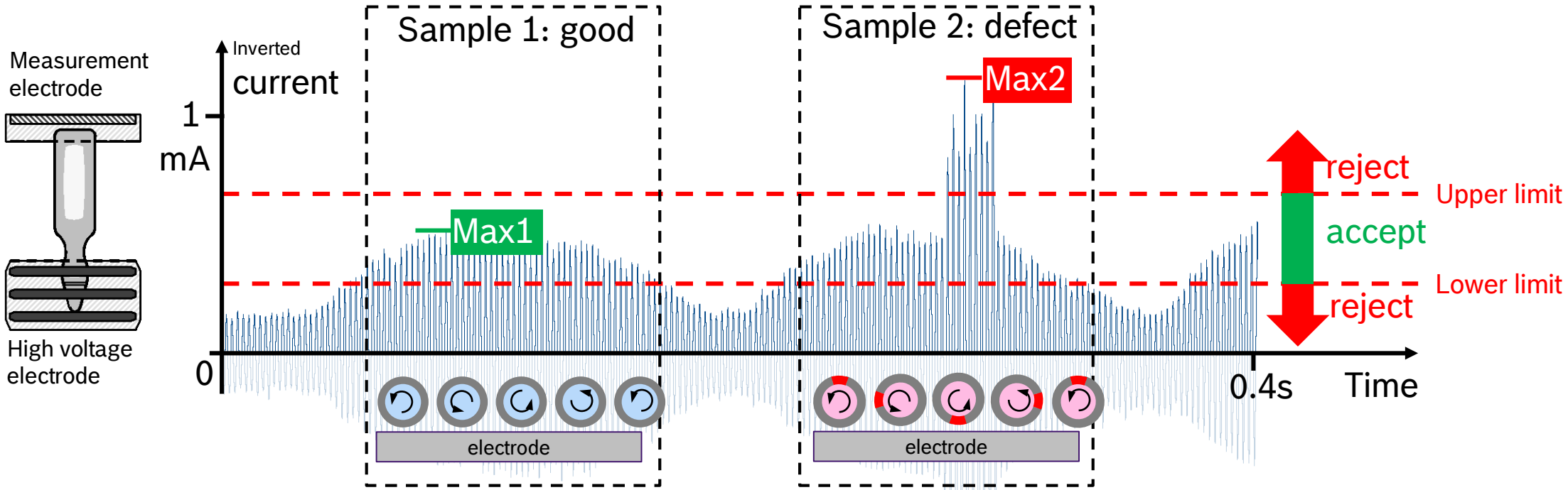
HSA study: Permanent or temporary leak

sample	O_2 conc. (%atm) Before vacuum exposure	O_2 conc. (%atm) After vacuum and subsequent nitrogen exposure	O_2 conc. (%atm) difference
Positive controls (vials quipped with special lid comprising laser-drilled holes)			
aperture 5-08 („2µm“)	21	5,50	-15,44
aperture 10-09 („5µm“, 6R vial)	21	1,44	-19,79
2-R7	18,62	18,60	-0,02
2-R13	15,19	15,28	0,09
2-R20	13,84	13,82	-0,02

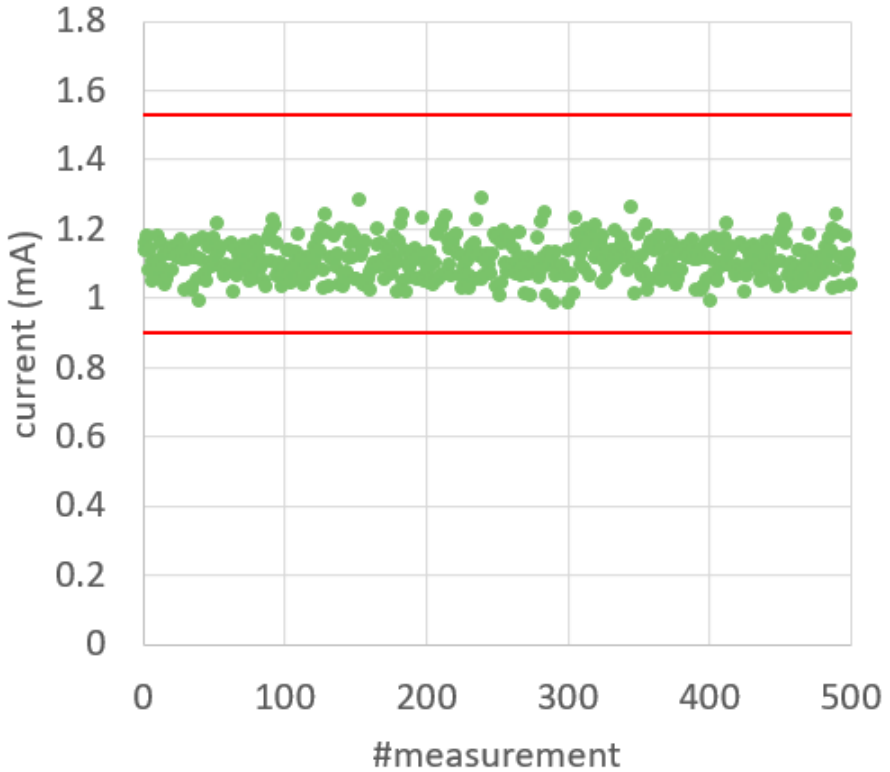


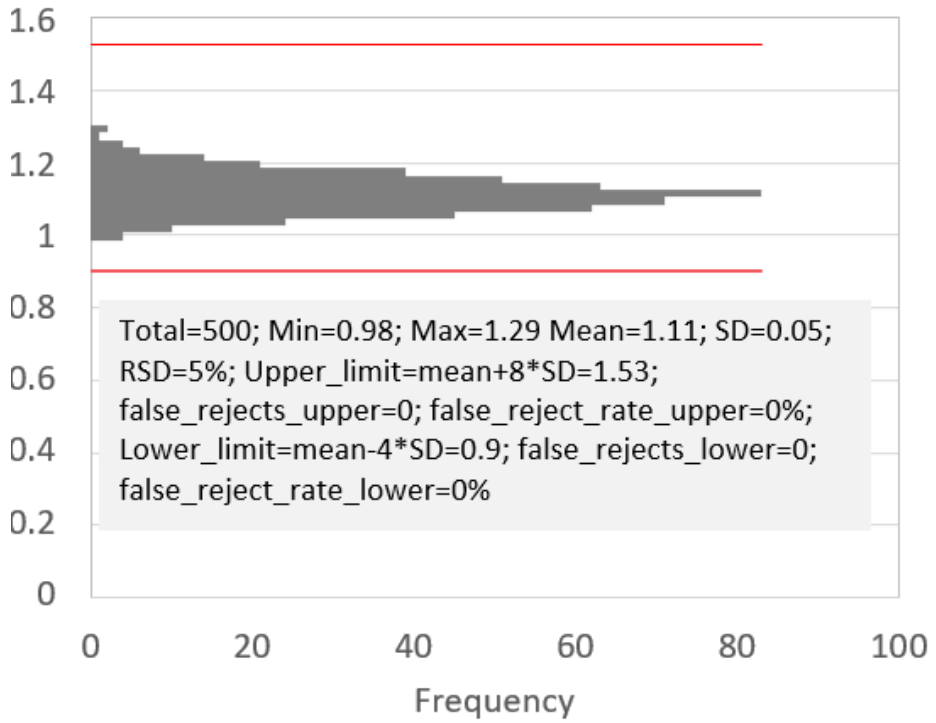
Other than control samples, oxygen concentration of rejected vials did not change → temporary leaks

High voltage leak detection principle



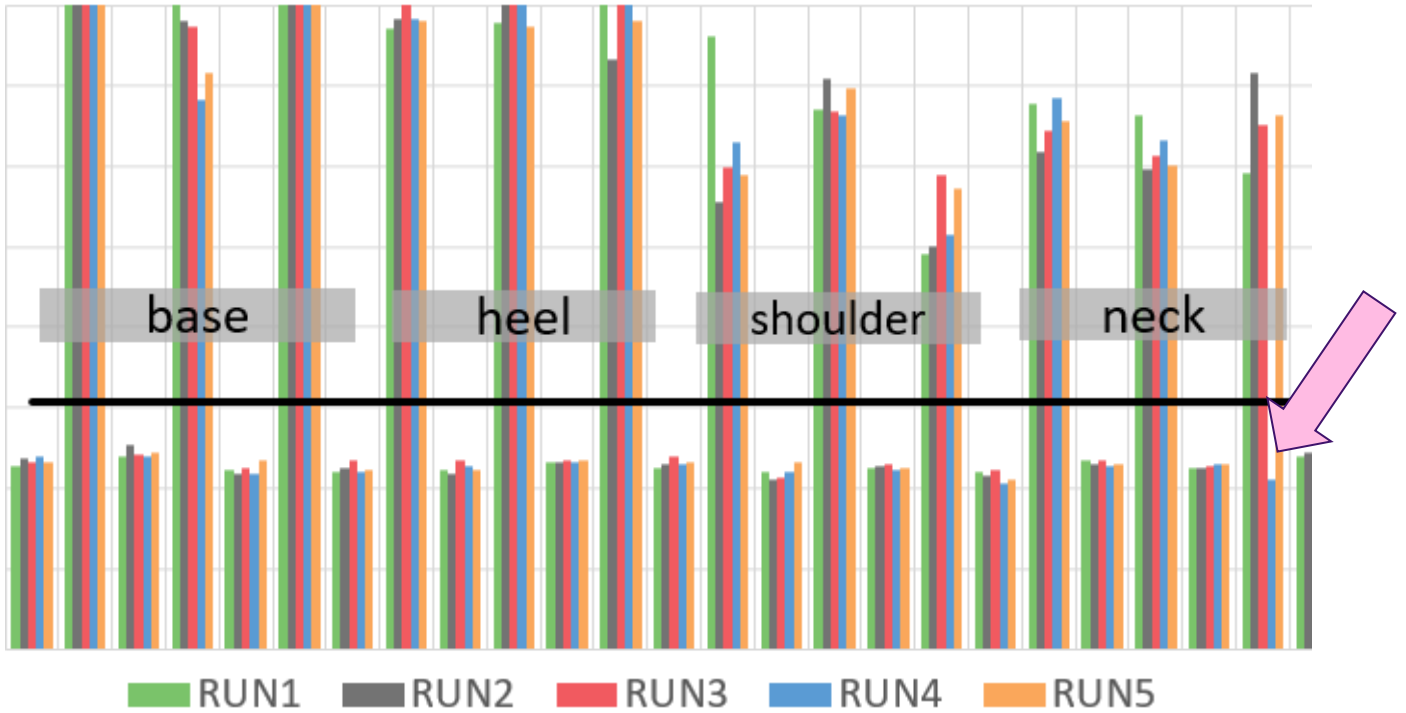
HVLD recipe creation /1





- Determine distribution of bulk good containers, individually for each station (covering different regions)
- Derive statistically based reject limit, e.g. 8*Stddev above mean

HVLD recipe creation /2



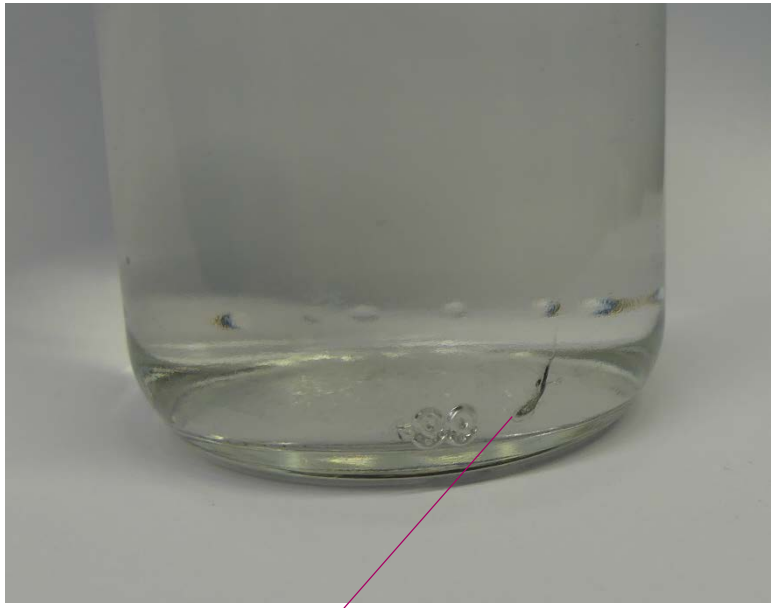
One defect not detected in one run (but NOT due to too strict limit)

- Verify recipe settings and evaluate detection performance by testing positive and negative controls (here each sample 5 runs)

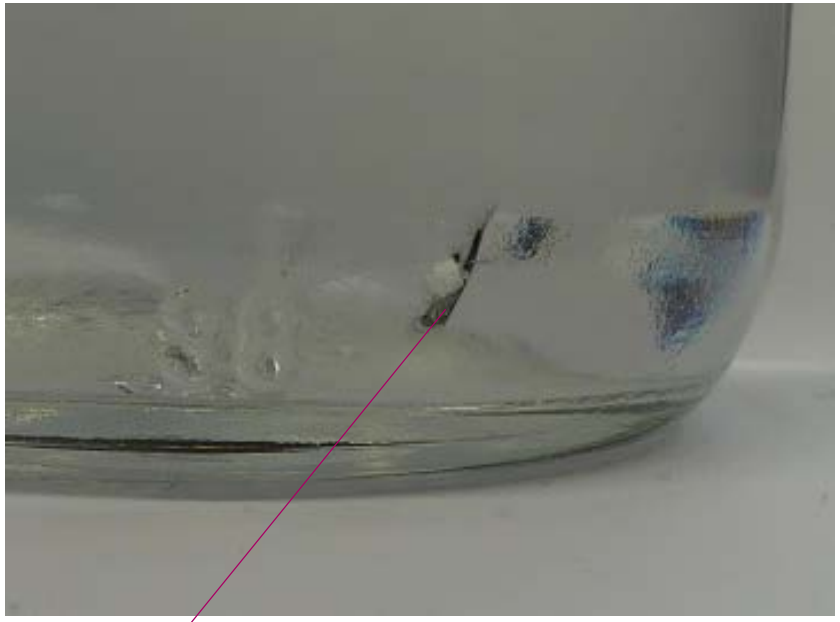
HVLD test of molded glass vial showing product crust

Sample 1: 100ml molded, filled with syrup A, unknown storage time

Crust in heel region, as proved.
Clearly detected with HVLD.



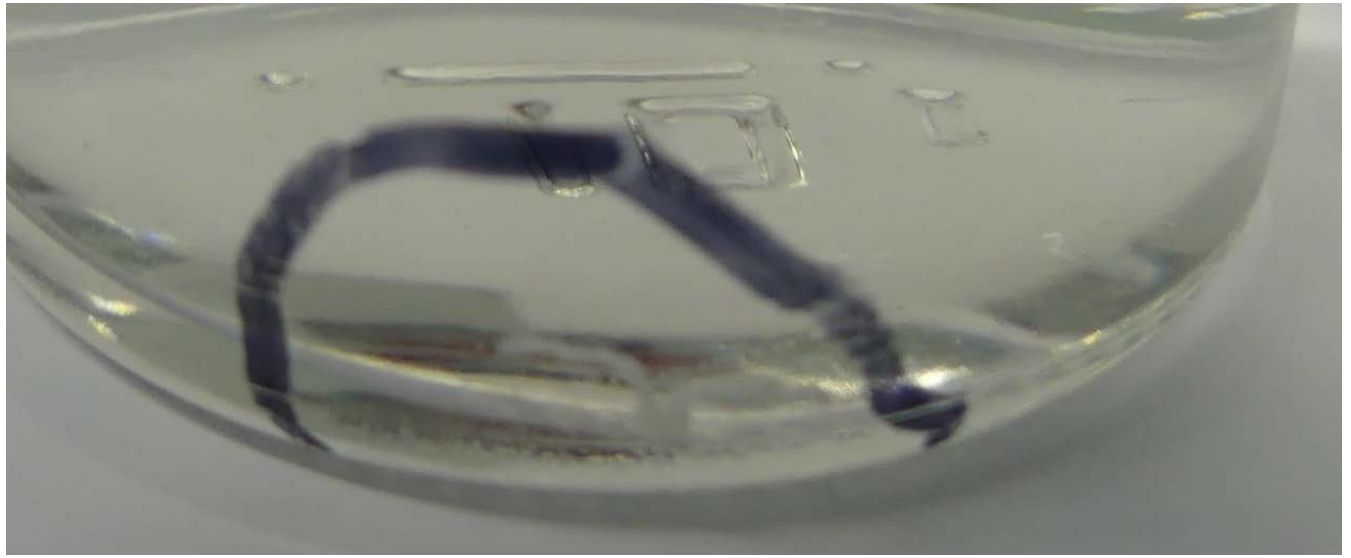
crack after wiped-down



crust grew back after one day (small spot only), repeatable

HVLD test of molded glass vial showing product crust

Sample 2: 50ml molded, filled with syrup B, unknown storage time



After wiping, crust did not grow again. Negative both according to HVLD and subsequent blue dye test.

→ Visual inspection seems more suitable. However, HVLD for freshly filled product to be evaluated

CCIT in combination with visual inspection

CCIT downstream

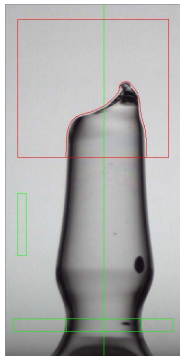
- when mostly visually detectable defects
- When visual inspection process (mechanical handling) induces CCI risk

CCIT upstream

when samples ejected by visual inspection are to be further analyzed for clear accept/reject.

Visual pre-inspection station / pre-sorting recommended

- Prevent glass breakage in inspection system
- Avoid contamination of inspection machine
- Minimize danger to operator (hazardous product, broken glass)
- Deep scratches (potential risk for crack)



Conclusions

- Deterministic CCIT methods are complementary to visual inspection
- Collected data is used to validate the CCIT method and helps to understand and improve processes
- Consider 100% CCIT as part of process validation.
- Consider 100% CCIT for batch release of critical product, particularly when percentage of non-conforming product is low (hard to find by sampling a small number)

Backup slides

Advantages of CCIT over sterility testing

1. Such alternate methods may detect a breach of the container and/or closure system prior to product contamination;
2. Some of the alternate methods used to evaluate container and closure integrity can conserve samples that may be used for other stability tests;
3. Alternative test methods may require less time than sterility test methods which require at least seven days incubation; and
4. The potential for false positive results may be reduced with some alternative test methods when compared to sterility tests.

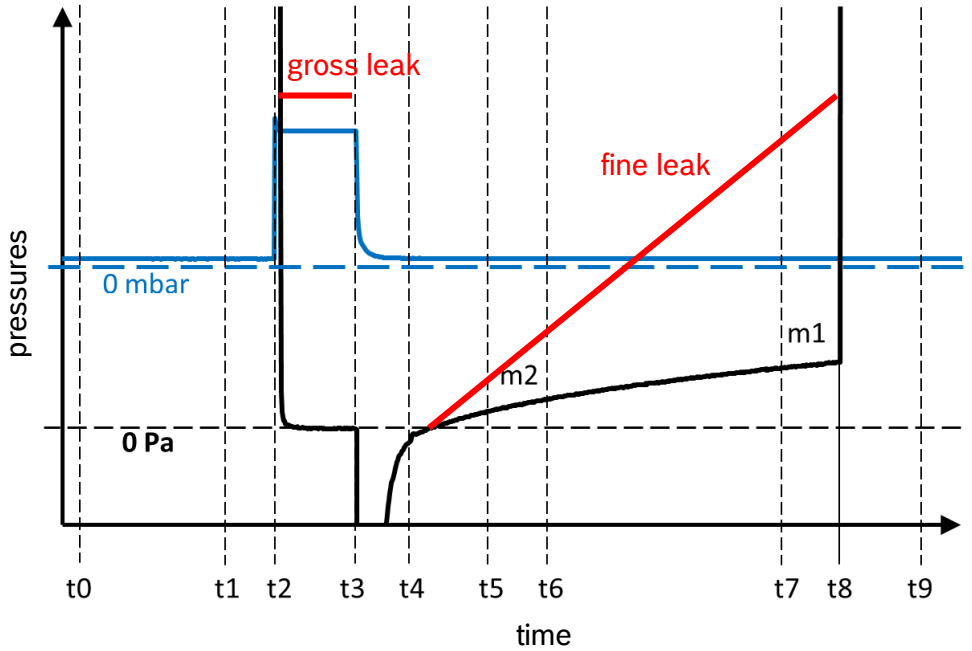
Source: US Food and Drug Administration, 2008. Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products

BUT: CCIT is NOT sterility testing. An intact container may hold insterile product, a defective container may still be able to protect sterile product

Vacuum decay test

- Non-destructive, deterministic, reliable & established method
- Containers are exposed to vacuum within special test chambers
- Measurement of changes in chamber pressure to detect leakages
- Integral measurement regardless of defect position, if leak channel is permeable
- Detection of both gas and liquid leakages, if vacuum below vapor pressure (water: 23 mbar at 20°C)
- Risk of false accepts: some products may clog the leak channel → only store shortly before measurement

Signals of absolute (blue) and differential (black) pressure sensor



Headspace Analysis

Laser light matches frequency of target molecule

Amount of absorbed laser light is dependent on concentration of target molecule in headspace