PDA Visual Inspection Meeting
Hyatt Regency Bethesda
October 22, 2009

Raised Stopper Detection: Visual Inspection versus Headspace Inspection

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LIGHTHOUSE
The Science of Pharmaceutical Manufacturing

Presentation Outline

- Background of stopper pop-up
- Analysis of stopper pop-up after lyophilization
  - Gas flow models
  - Experiments
- Strategies for addressing stopper pop-up in manufacturing
- Concluding remarks

Stopper Pop-up

Definition of Problem

- Stoppers are partially inserted to vials prior to lyo cycle
- Lyo chamber and vial headspace pressure are set at end of cycle and shelves are raised/lowered to press stoppers into vial and achieve closure
- Stoppers can “pop-up” after shelves are raised allowing gas ingress which poses risk to product stability and sterility as well the ability to reconstitute.
- Leaks can be temporary, stopping once cap is applied or can be permanent, allowing gas ingress continuously
- What is the best way to detect and remove vials that have lost container closure integrity: visual inspection or headspace analysis?

Risk

- Sterility-
  - Potential exists for microbial ingress
    - Temporary leaks-low to medium risk
    - Permanent leaks-medium to high
    - Depends on leak rate (defect size) and microbial concentration
- Stability-
  - Oxidation
    - Temporary/permanent leaks-high risk
  - Hydrolysis
    - Temporary/permanent leaks-high risk
- Customer complaints-
  - Loss of vacuum
  - Discoloration of product

Regulatory Aspects

Source: US Food and Drug Administration, (2004) G*uidance for Industry. Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* (FDA, Rockville, MD)

A container closure system that permits penetration of microorganisms is unsuitable for a sterile product. Any damaged or defective units should be detected, and removed, during inspection of the final sealed product. ……. If damage that is not readily detected leads to loss of container closure integrity, improved procedures should be rapidly implemented to prevent and detect such defects.

Paragraph VI. Components and Containers/Closures, Section B-2 Containers/Closures pg 18 Inspection of Container Closure System

Source: Eudralex, (2008) *Volume 4: Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice, Annex 1: Manufacture of Sterile Medicinal Products* (Eudralex, February 2008 revision).

121. Vials with missing or displaced stoppers should be rejected prior to capping….

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

Recalls

Top 5 Reasons for FDA Reported Recalls - 2006

1. Subpotent product
2. Defective container
3. Lack of sterility assurance
4. Impurity / degradation products
5. cGMP deviations (failure to perform or document required activities)

Source: Famulare, J (2007) "CDER Compliance Update," PDA/FDA Joint Regulatory Conference

LIGHTHOUSE *Projects*

European manufacturer:

- 3M vials recalled, root cause: Stopper pop-up
- Product stability issue-Solution turned yellow-Customer complaints
- European health authorities involved

US contract manufacturer:

- Observed significant stopper pop-up when using coated stoppers
- Issue identified during process development
- Process altered to reduce incidence

US manufacturer:

- Customer complaints due to loss of vacuum
- FDA involved

US manufacturer:

- Batches of lyo product showing 2% loss of CCI due to stopper pop-up
- Issue identified during lab testing

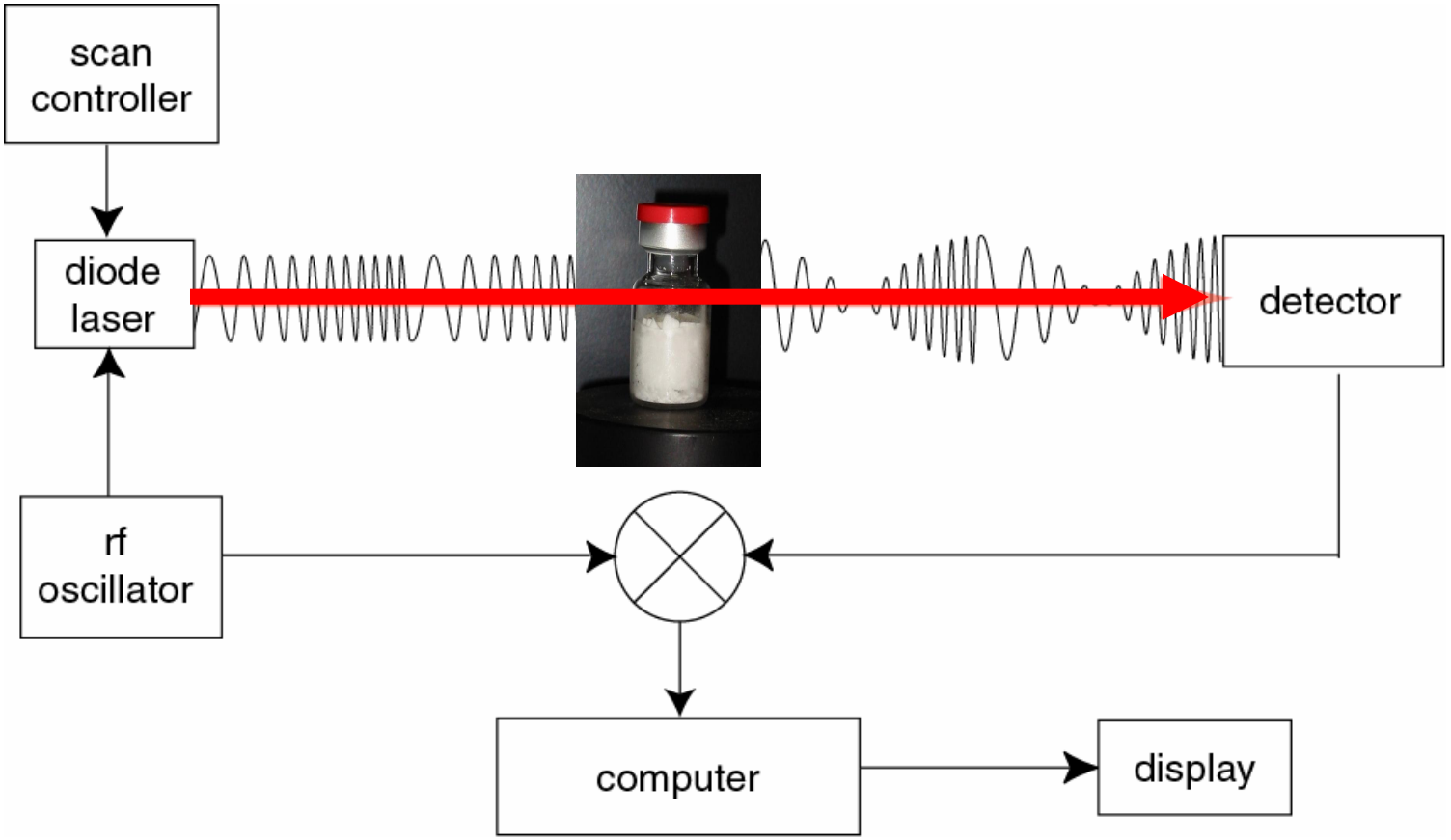
-In cases where product entered the market place customer complaints and stability related issues triggered investigations.
-In all cases 100% inspection was implemented and customer complaints were significantly reduced.

Molecular Spectroscopy of Water Vapor and Oxygen using Tunable Diode Lasers

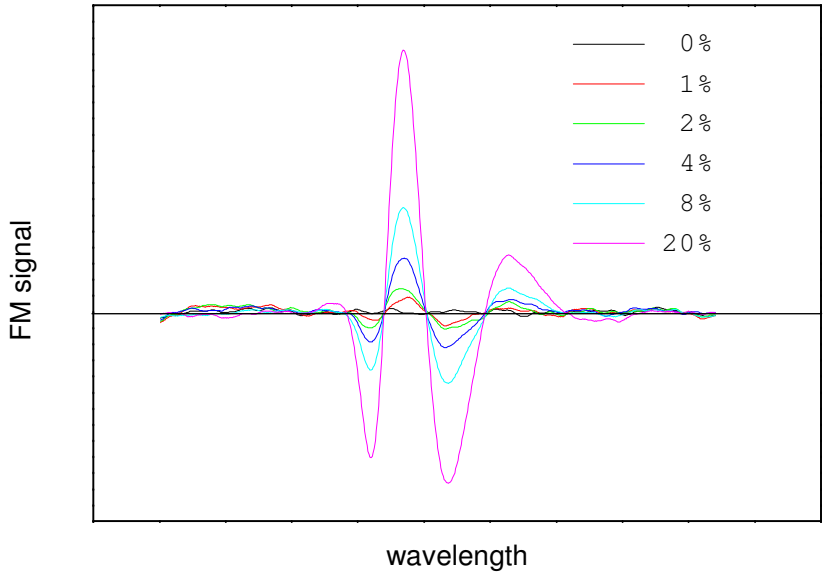
Molecules of Interest to the Pharmaceutical Industry

- Water vapor
  - Stability indicator in freeze dried and solid dosage product
  - Indicator of microbial growth--water activity
  - Can be used to measure total pressure through collisional broadening effect of other gases on residual headspace water vapor
- Oxygen
  - Stability indicator in many liquid and freeze dried product
  - Can be used as leak indicator for products sealed under inert gases and/or vacuum--air ingress to headspace
- Our current focus is on measuring oxygen and water vapor in small volume sealed containers. Nondestructive headspace inspection

Laser Measurement Technology

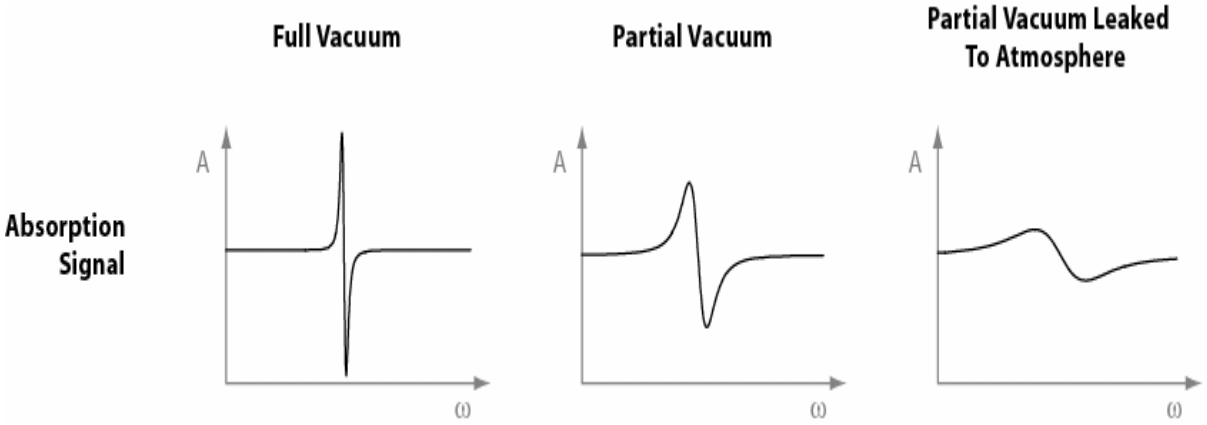


Headspace Gas Analysis



Oxygen ingress

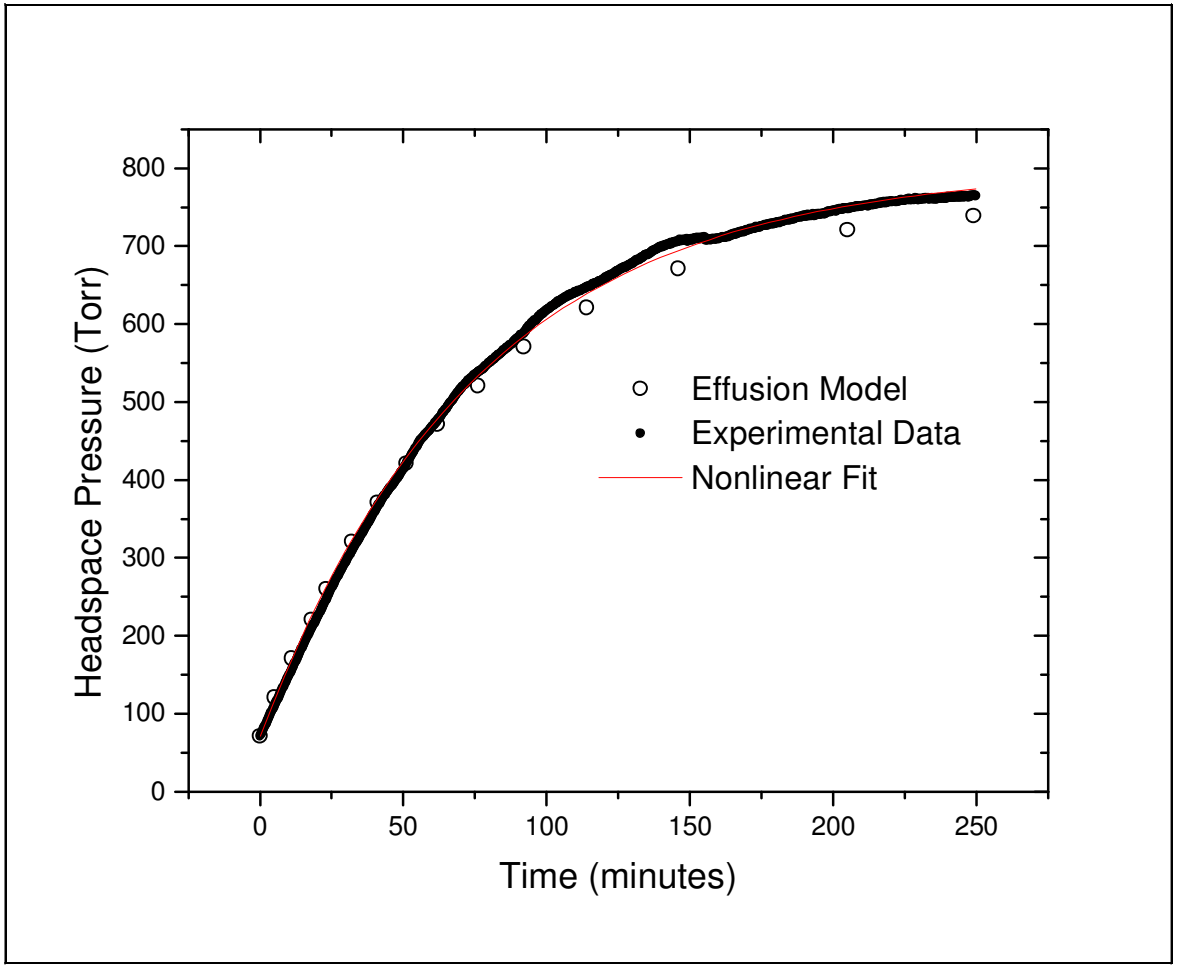
Collisional broadening of water vapor by air or nitrogen



Gas Flow Physics Applied to Container Closure Integrity

Source:
Veale, James R. “New Inspection Developments.” Practical Aseptic Processing Fill and Finish Ed. Jack Lysfjord. Davis Healthcare International Publishing/PDA Bethesda, 2009. 305-372

Effusive Flow: Vials under vacuum $\Delta P > 0$ $\Delta p > 0$



$$\frac{\partial P}{\partial t} = \frac{kT}{V}\frac{\partial N}{\partial t}$$

$$\frac{\partial N}{\partial t} = ZA_0 = \frac{PA_0}{(2\pi mkT)^{\frac{1}{2}}}$$

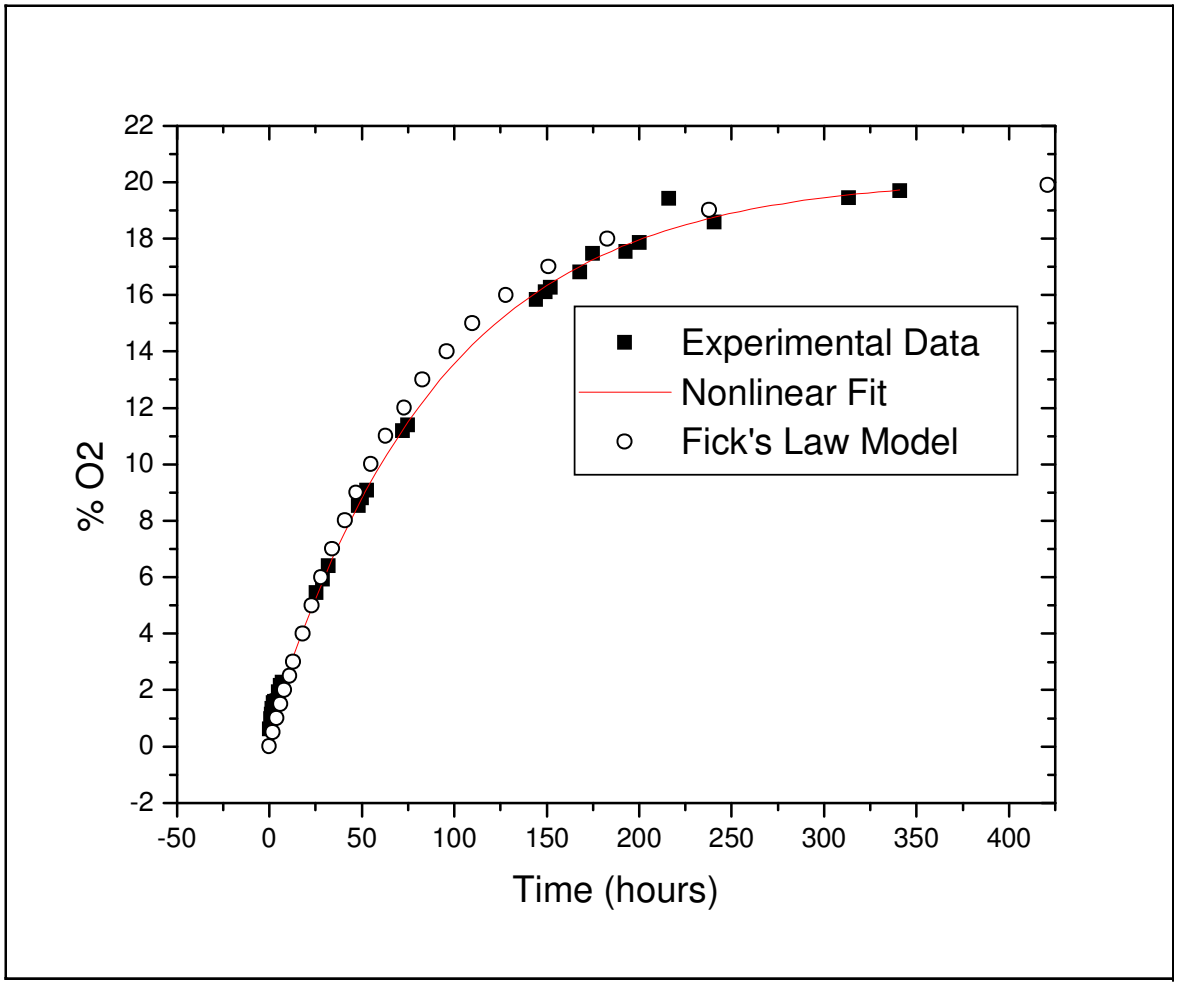
$$t = -\ln\left[\frac{P_0 - P_i}{P_0 - P_f}\right]\left(\frac{2\pi m}{kT}\right)^{\frac{1}{2}}\frac{V}{A_0}$$

5 micron diameter defect in a 10cc vial. Starting pressure: 71 torr

Effusion

Pressure rise (torr)	Oxygen rise (% atm)	t(minutes)	t(hours)	t(hours)	t(days)
0	0.0	0	0	0	0
50	1.3	5	1	8	2
100	2.6	10	1	17	4
150	3.9	16	2	26	7
200	5.3	22	2	34	9
250	6.6	28	3	47	12
300	7.9	36	4	60	16
350	9.2	44	5	73	19
400	10.5	53	6	89	23
450	11.8	64	7	107	28
500	13.2	77	8	128	33
550	14.5	92	10	153	40
600	15.8	111	12	185	48
650	17.1	138	14	230	60
700	18.4	181	19	302	79
750	19.7	309	32	515	134
		5 micron hole	**2 micron hole**	**0.5 micron hole**	**0.2 micron hole**

Diffusive Flow: Vials not under vacuum $\Delta P = 0 \;\; \Delta p > 0$



$$J_z = -D\frac{\partial n}{\partial z}$$

$$\frac{\partial N}{\partial t} = J_z A_0 = -DA_0\frac{\partial n}{\partial z}$$

$$t(s) = -\ln\left[\frac{p_0 - p_i}{p_0 - p_f}\right]\frac{Vz}{DA_0}$$

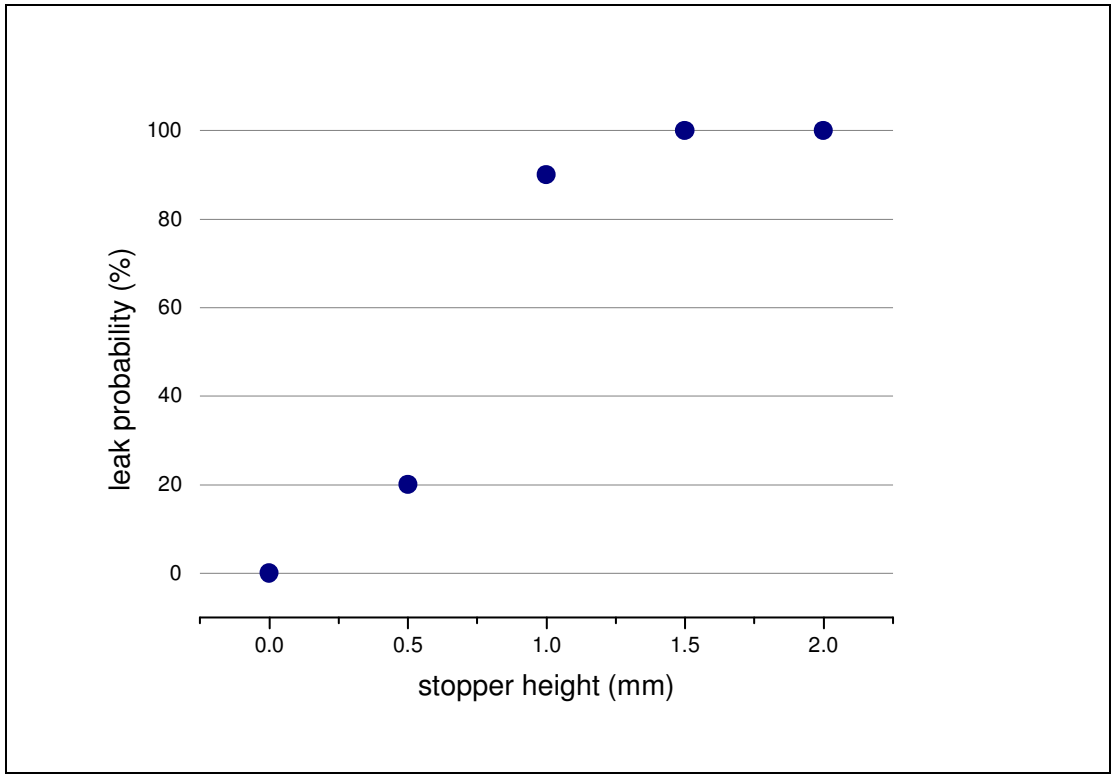
6 micron defect in a 20cc vial.

Leak times for various defect diameters: 10cc vial-Diffusion Model

Partial Pressure Rise(atm)	Oxygen Concentration Rise (% atm)	t(days)	t(days)	t(weeks)	t(years)
0	0	0	0	0	0
0.005	0.5	<1	4	9	1
0.01	1	1	8	19	2
0.02	2	3	17	39	5
0.04	4	6	36	81	10
0.08	8	13	81	185	22
0.12	12	23	143	327	39
0.15	15	34	212	484	58
0.20	20	84	527	1204	145
		5 micron hole size	**2 micron hole size**	**0.5 micron hole size**	**0.2 micron hole size**

Stopper Pop-up Experiments

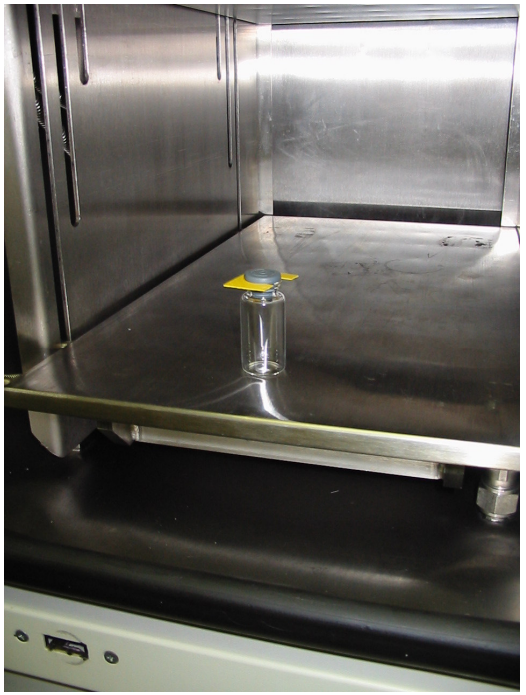
Probability of gas ingress as a function of stopper height



Stopper Pop-up Study

Samples/Materials/Equipment:

- 10cc clear tubing vials/grey siliconized stoppers/Lyostar I/benchtop FMS
- plastic shims (0.5, 1.0, 1.5, 2.0mm)



Parameters:

- N=30 vials*40 conditions=1200 measurements
- Five stopper heights (0-2mm)
- Four vial headspace pressures (0-570 torr)
- Two closure processes:
  - Back fill with N2, **Raise, Release** and Vent with air
  - Back fill with N2, **Raise, Hold** and Vent with air

Analysis:

- Leak probability (did a vial leak?) Measurable rise in pressure or oxygen
- Leak rates (how much did a vial leak?) Equivalent defect diameter

Experimental Equipment

Lyo Star I Freeze Dryer

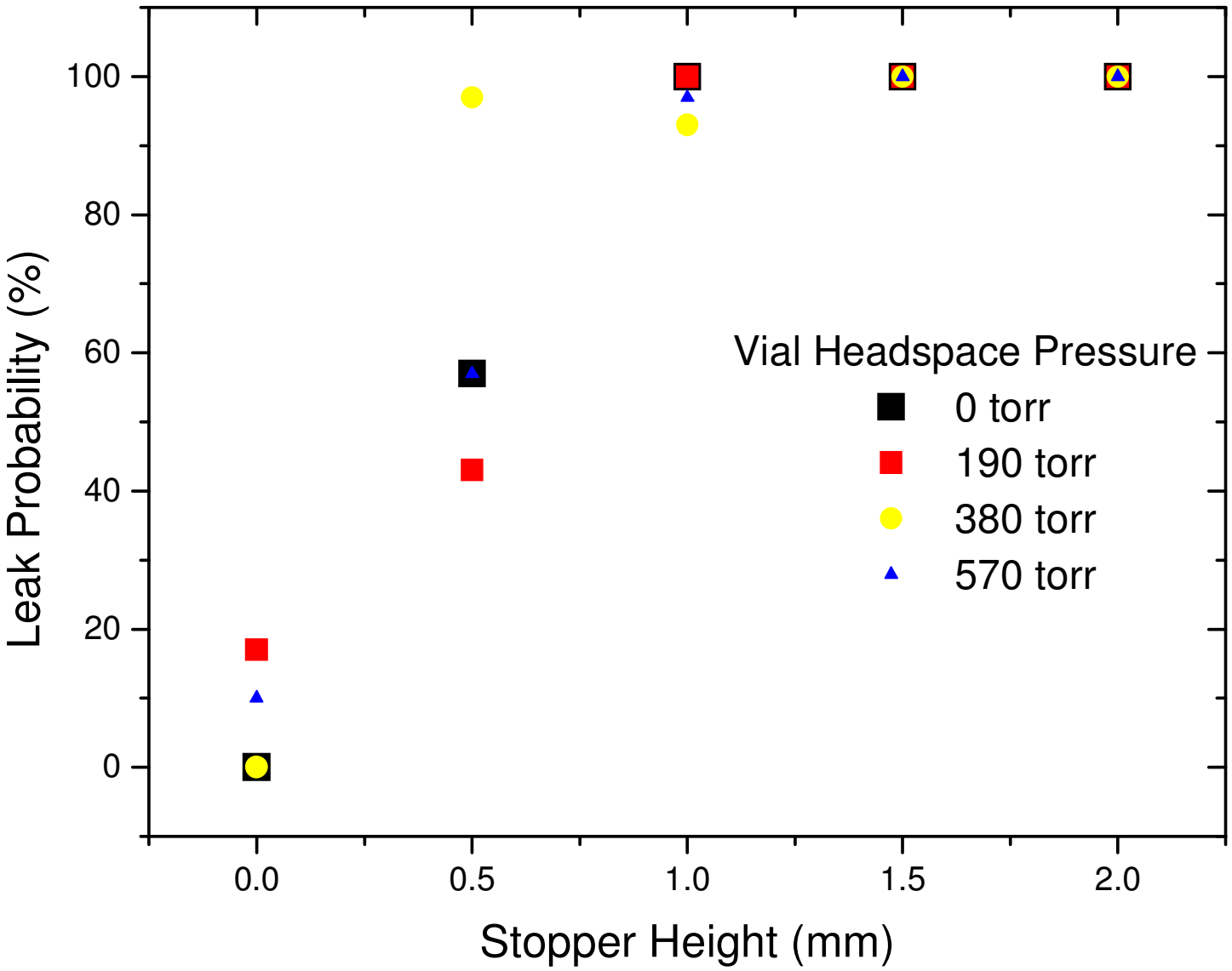
FMS-760 Headspace Oxygen Analyzer

FMS-1400 Headspace Pressure Analyzer

Data Table-Close and release

	Close + Release				
			P=P0	P0<P<Atm	P=Atm
P=0	Shim	Avg O2	No Leak	Effusive Leak	Total Leak
	0.0	0.1	100%	0%	0%
	0.5	10.2	43%	7%	50%
	1.0	18.8	0%	3%	97%
	1.5	18.2	0%	0%	100%
	2.0	18.6	0%	0%	100%
P=190	Shim	Avg O2	No Leak	Effusive Leak	Total Leak
	0.0	0.8	83%	13%	3%
	0.5	6.0	57%	3%	40%
	1.0	19.4	0%	0%	100%
	1.5	19.1	0%	0%	100%
	2.0	19.4	0%	0%	100%
P=380	Shim	Avg O2	No Leak	Effusive Leak	Total Leak
	0.0	0.2	100%	0%	0%
	0.5	17.8	3%	0%	97%
	1.0	16.7	7%	0%	93%
	1.5	19.2	0%	0%	100%
	2.0	19.2	0%	0%	100%
P=570	Shim	Avg O2	No Leak	Effusive Leak	Total Leak
	0.0	0.5	90%	n/a	10%
	0.5	11.2	43%	n/a	57%
	1.0	18.7	3%	n/a	97%
	1.5	19.4	0%	n/a	100%
	2.0	19.5	0%	n/a	100%

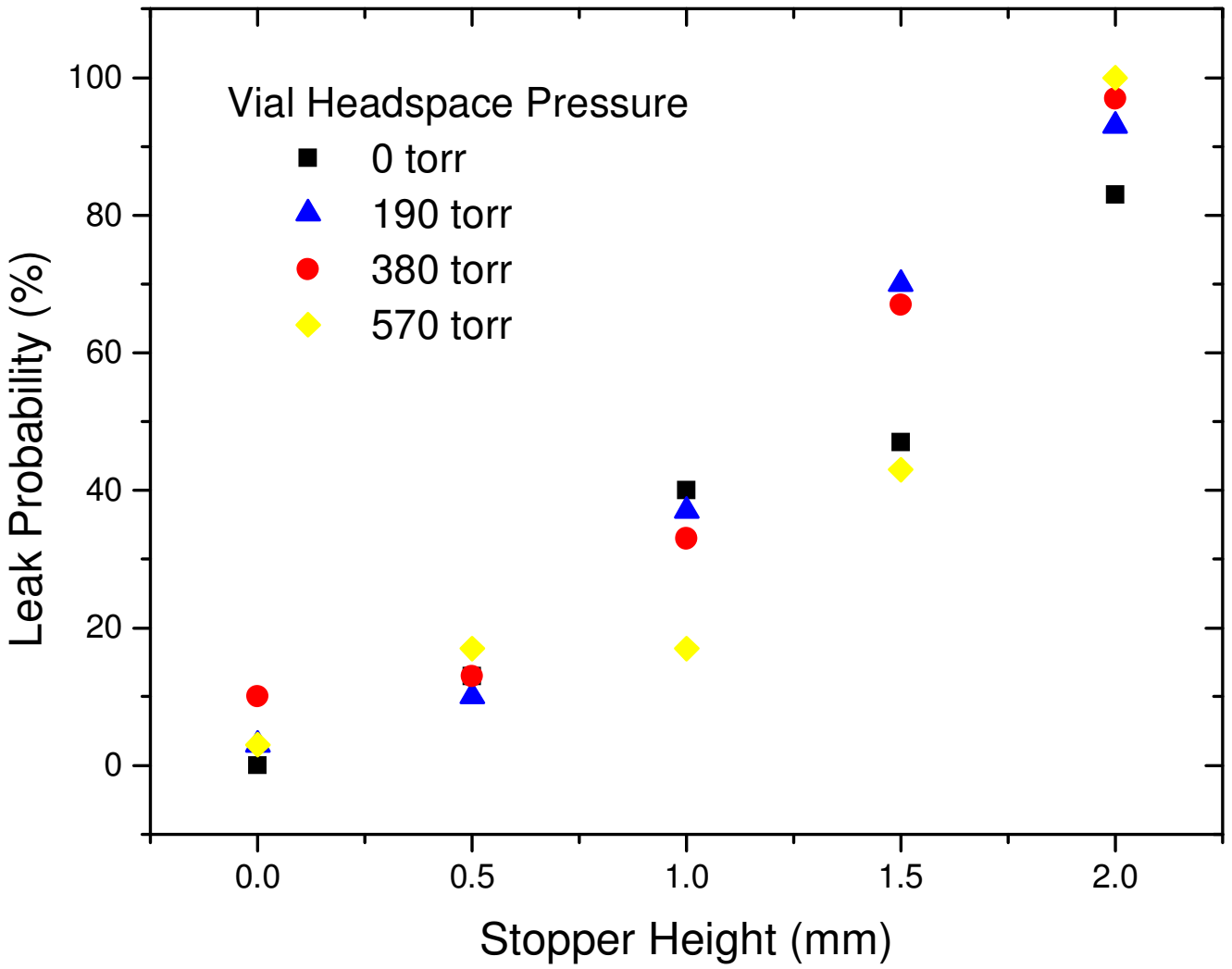
Data Graph-Close and release



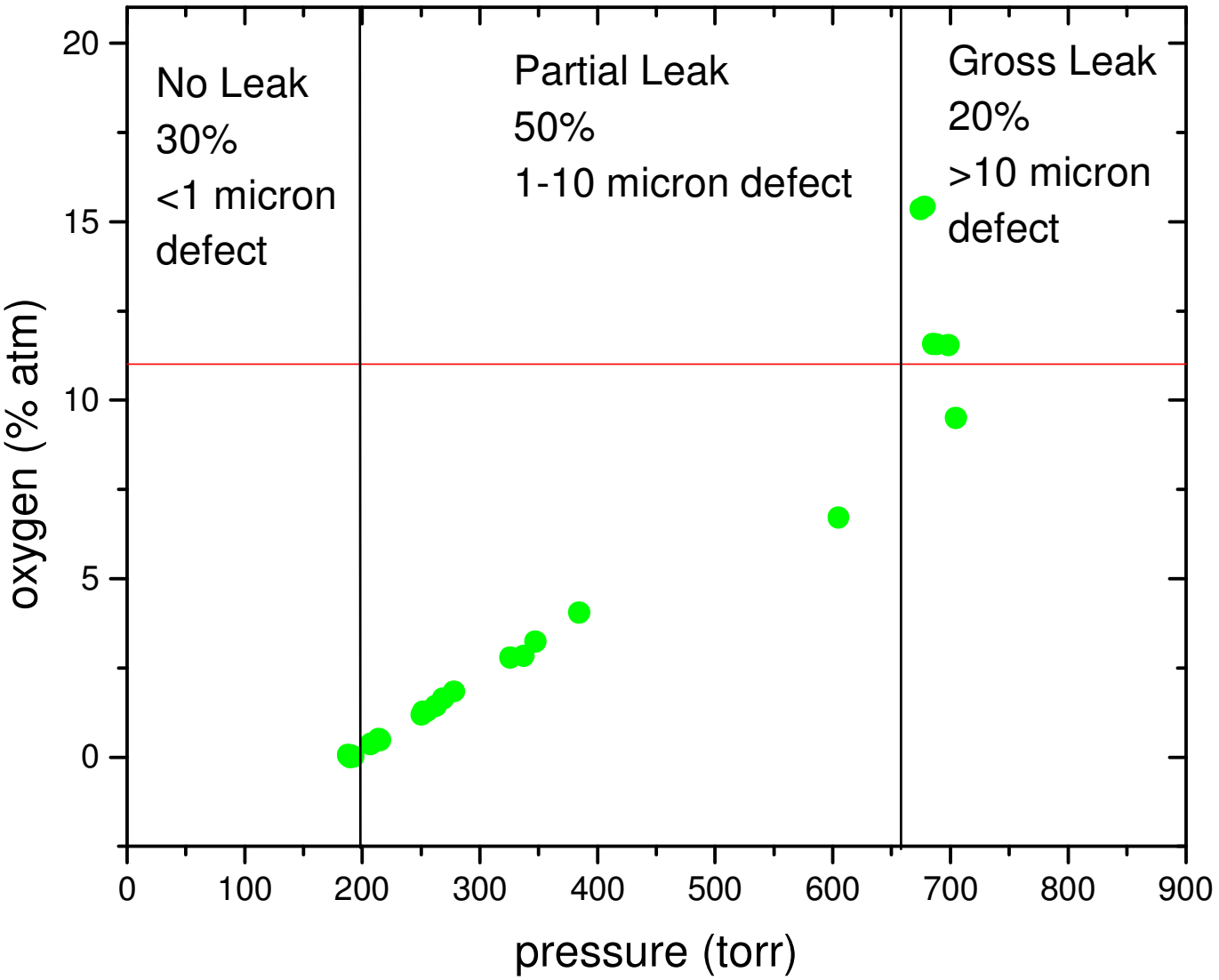
Data Table-Close and hold

	Hold Closed				
			P=P0	P0<P<Atm	P=Atm
P=0	Shim	Avg O2	No Leak	Effusive Leak	Total Leak
	0.0	0.1	100%	0%	0%
	0.5	0.8	87%	13%	0%
	1.0	1.9	60%	37%	3%
	1.5	6.7	53%	17%	30%
	2.0	14.8	17%	7%	77%
P=190	Shim	Avg O2	No Leak	Effusive Leak	Total Leak
	0.0	0.2	97%	0%	3%
	0.5	1.0	90%	7%	3%
	1.0	1.9	63%	23%	13%
	1.5	6.7	30%	50%	20%
	2.0	14.7	7%	17%	77%
P=380	Shim	Avg O2	No Leak	Effusive Leak	Total Leak
	0.0	0.4	90%	3%	7%
	0.5	0.6	87%	0%	13%
	1.0	0.7	67%	23%	10%
	1.5	3.7	33%	20%	47%
	2.0	17.4	3%	3%	93%
P=570	Shim	Avg O2	No Leak	Effusive Leak	Total Leak
	0.0	0.3	97%	n/a	3%
	0.5	0.5	83%	n/a	17%
	1.0	0.6	83%	n/a	17%
	1.5	2.2	57%	n/a	43%
	2.0	19.4	0%	n/a	100%

Data Graph-Close and hold



N=30 Close and hold, P=190 torr, 1.5mm shim



Manufacturing Case Study

Commercial scale CCI testing

- Lyo product
  - 30cc vial
  - 155 torr nitrogen
- Some vials were found in lab testing to have lost vacuum. Decision to test 100% in short timeframe
- Lighthouse has an automated system available for short term lease.
- Schedule:

Week	Activity
0	Receipt of Purchase Order
1	Release machine parts for modification
5	Test and debug machine parts
8	Completion of Factory Acceptance Testing
8	Crate and ship system
9	Install system and IQ, OQ
10-11	PQ
12-13	Perform inspection on product
14	Breakdown system and return to LIGHTHOUSE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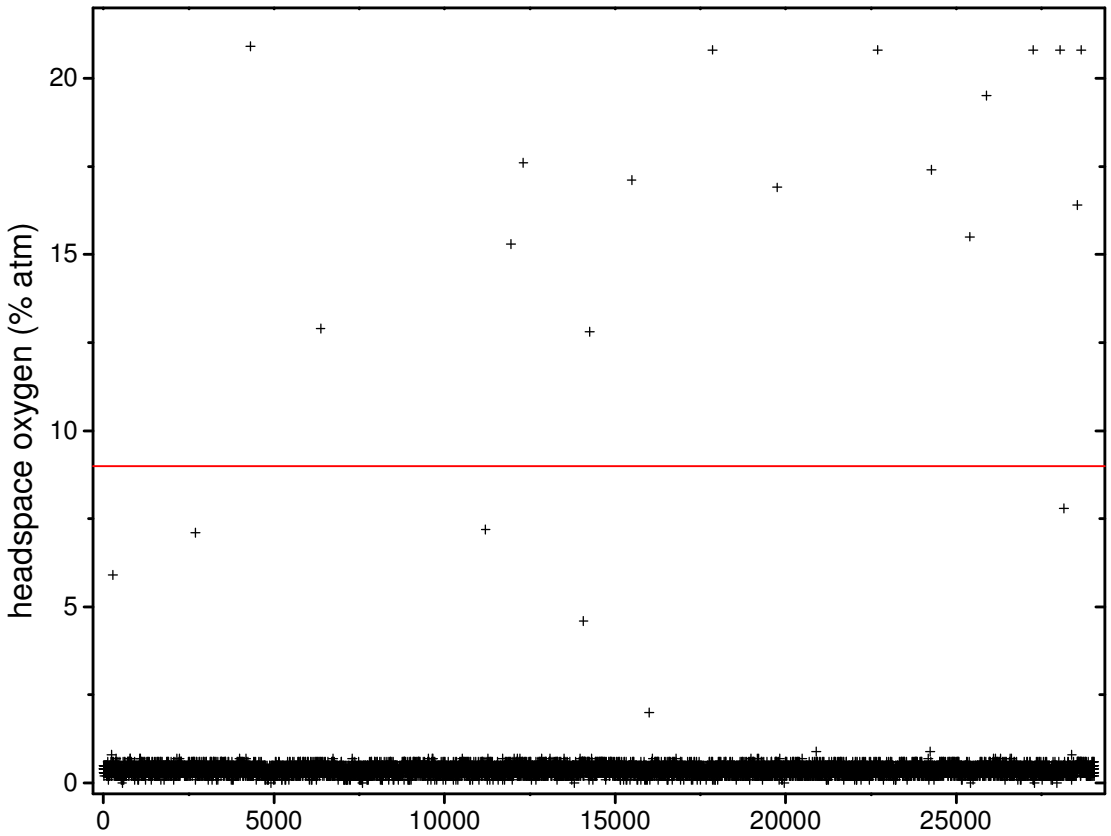
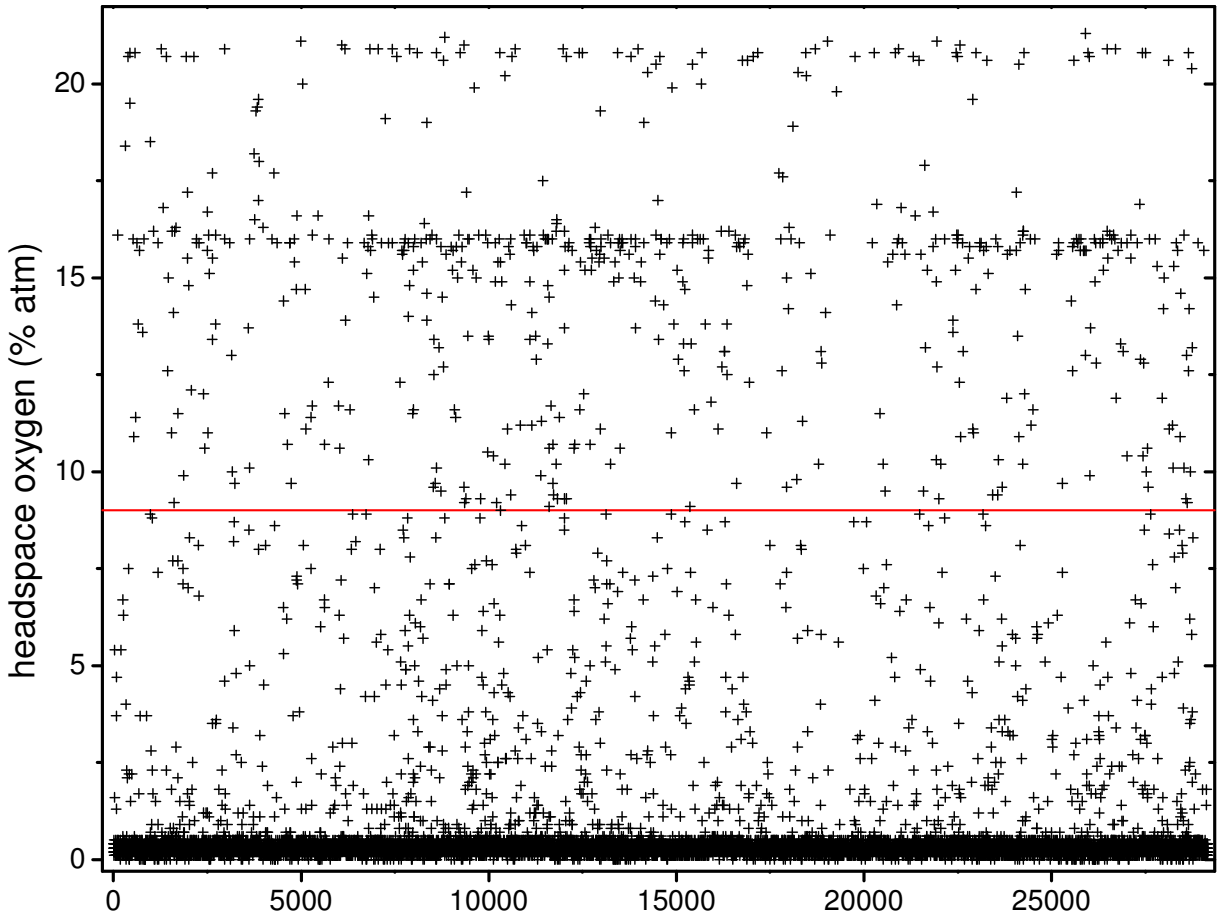
Case Study: Oxygen Monitoring for Leak Detection



Total batch size: 29048
Number rejected: 16
Reject rate: 0.06%

Case Study: Oxygen Monitoring for Leak Detection



Total batch size: 29156
Number rejected: 568
Reject rate: 1.95%

VISTA-200 In-Line System:

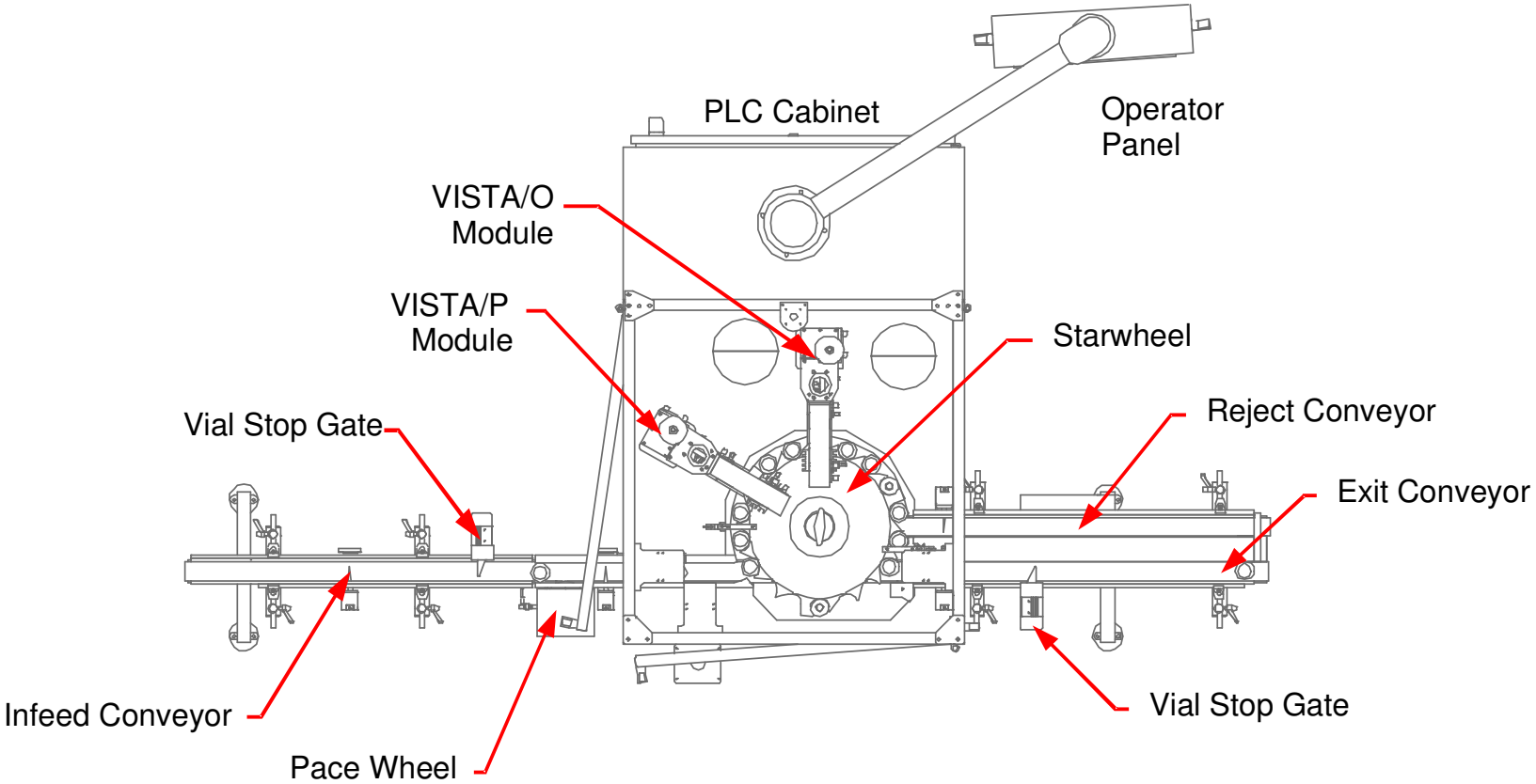
Single starwheel design

-minimum number change parts

-rapid change over

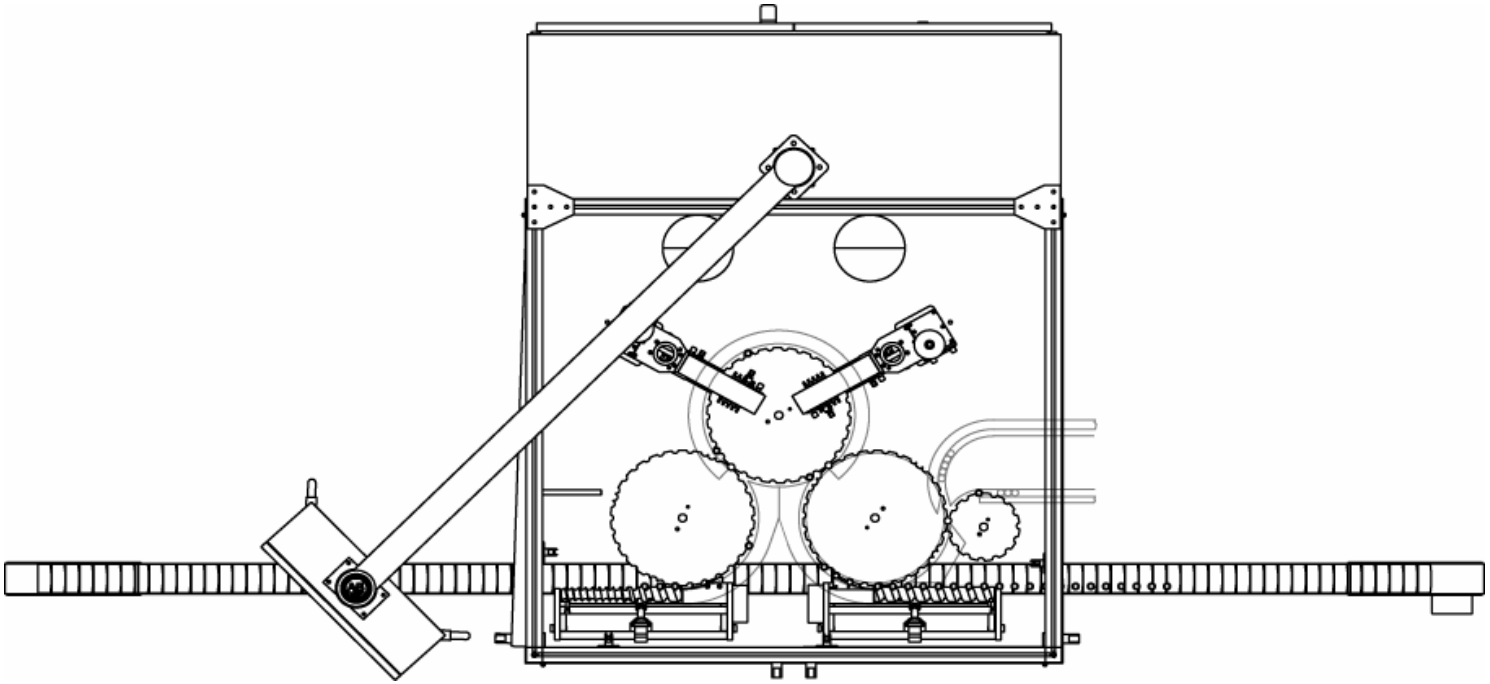
Speed range: 200 vpm

Measurement capability: Oxygen, Vacuum, Moisture



VISTA-400 Automated System:

Multiple starwheel design
Speed range: 400 vpm
Measurement capability: Oxygen, Vacuum, Moisture



Concluding Remarks-stopper pop-up

- Vials leak independent of stopper height and backfill pressure.
- Leak probability and leak rates can be altered by process steps.
  - Close, hold and vent vs. Close, release and vent
- Leak rates, for a given set of parameters, will vary continuously from small to large.
- Headspace analysis can identify those vials that have lost container closure integrity due to stopper pop-up.

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Thank you for your time

Questions?

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