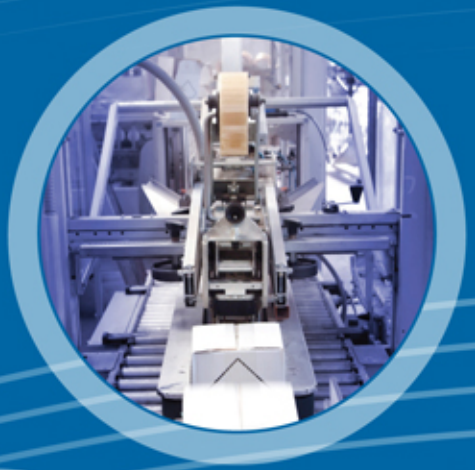
PDA Parenteral Drug Association

Connecting People, Science and Regulation

100% CCI Inspection Data of Lyophilized Product Vials:

Statistical Process Data for Proper Risk Assessment



Dr. Derek Duncan
Director Product Line

LIGHTHOUSE
The Science of Pharmaceutical Manufacturing

Industry case study: 100% CCI Inspection

- QC vials of a lyo product identified that had lost vacuum (headspace pressure should have been 0.2 atm nitrogen)
- Decision taken to run 100% inspection in short timeframe

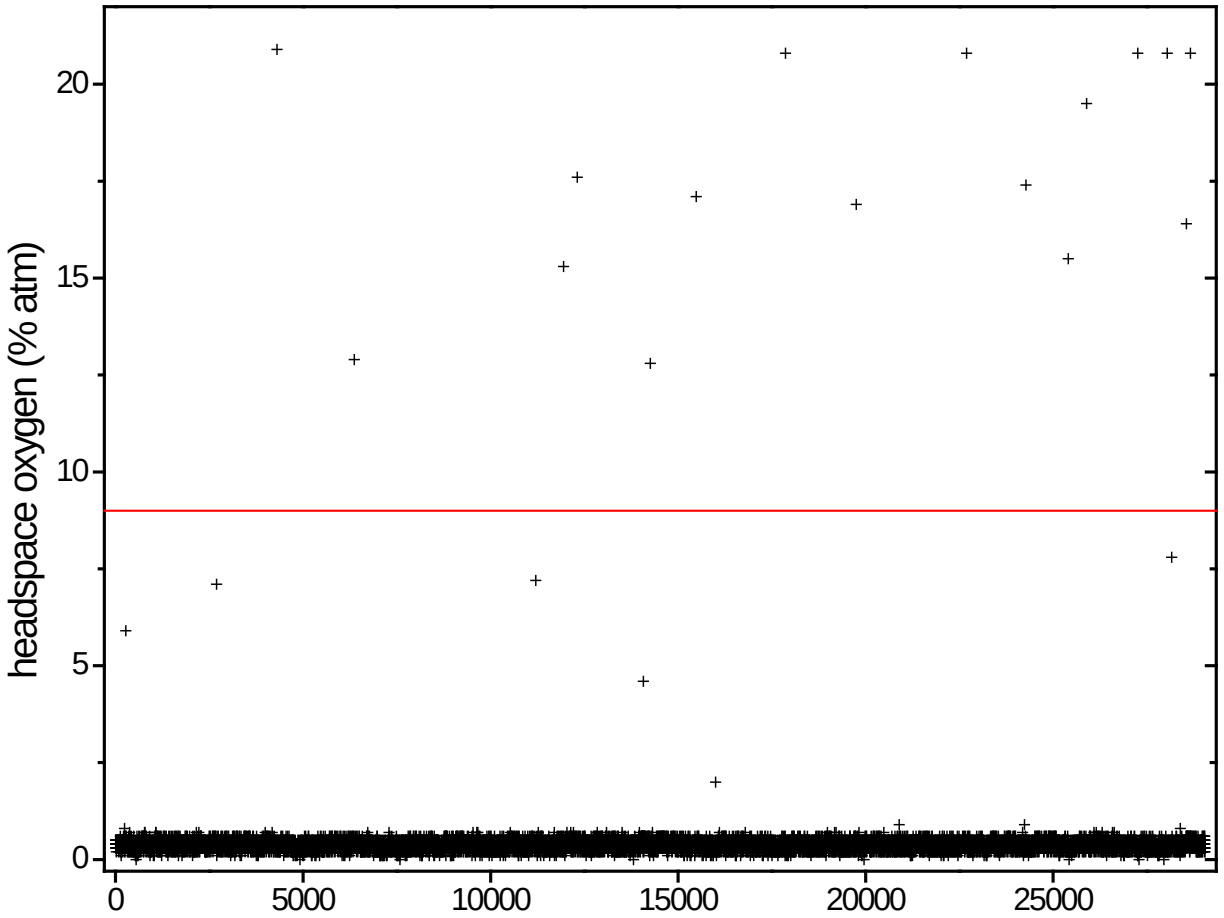
- Project schedule:

Week	Activity	Week	Activity
0	Receipt of Purchase Order	**8**	Crate and ship system
1	Machine parts manufactured	**9**	Install system and IQ, OQ
5	Test and debug machine parts	**10-11**	PQ
8	Completion of Factory Acceptance Testing	**12-13**	Perform inspection on product

Industry case study: 100% CCI Inspection

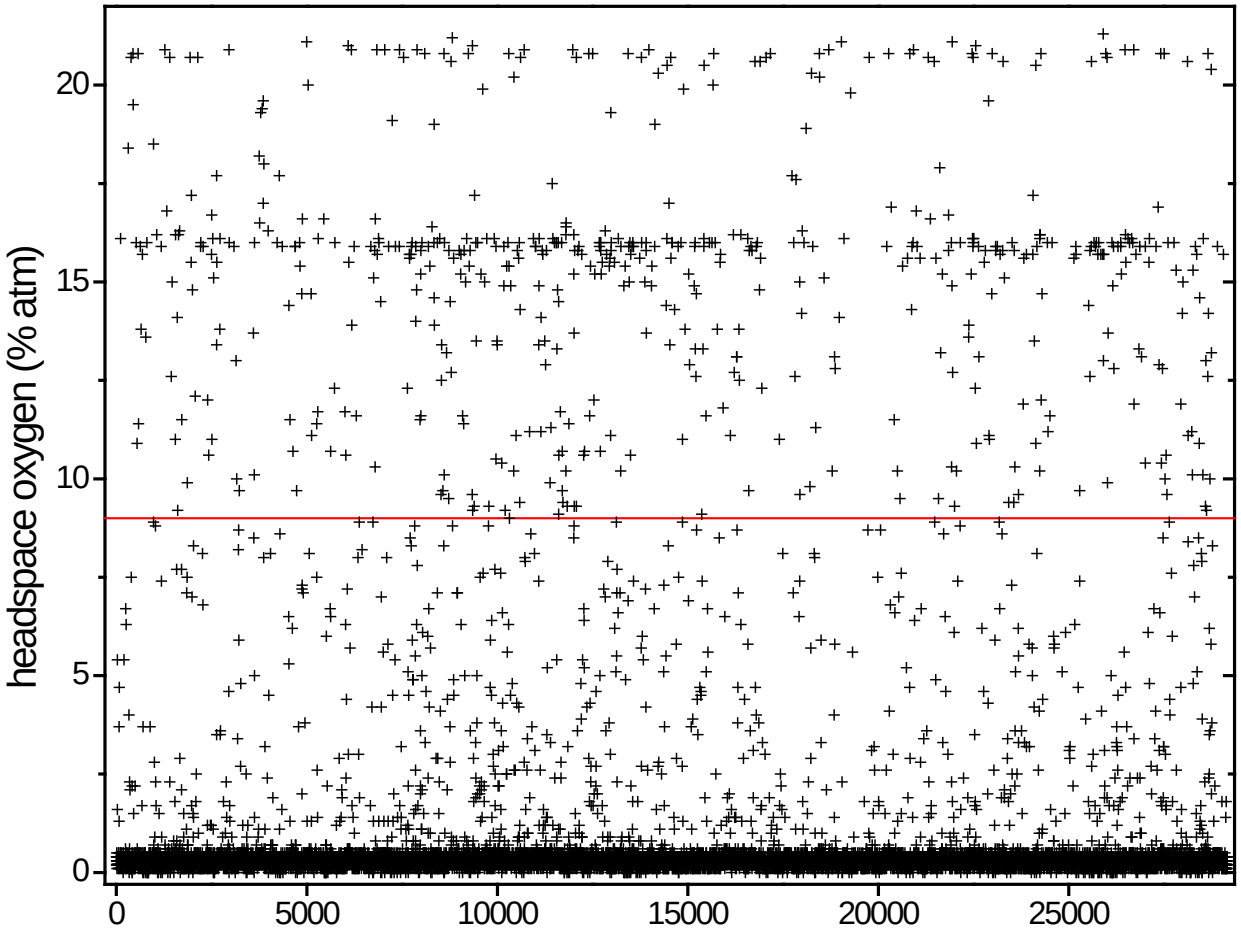
Inspection machine configured to make analytical measurement of headspace oxygen content

Industry case study: 100% CCI Inspection



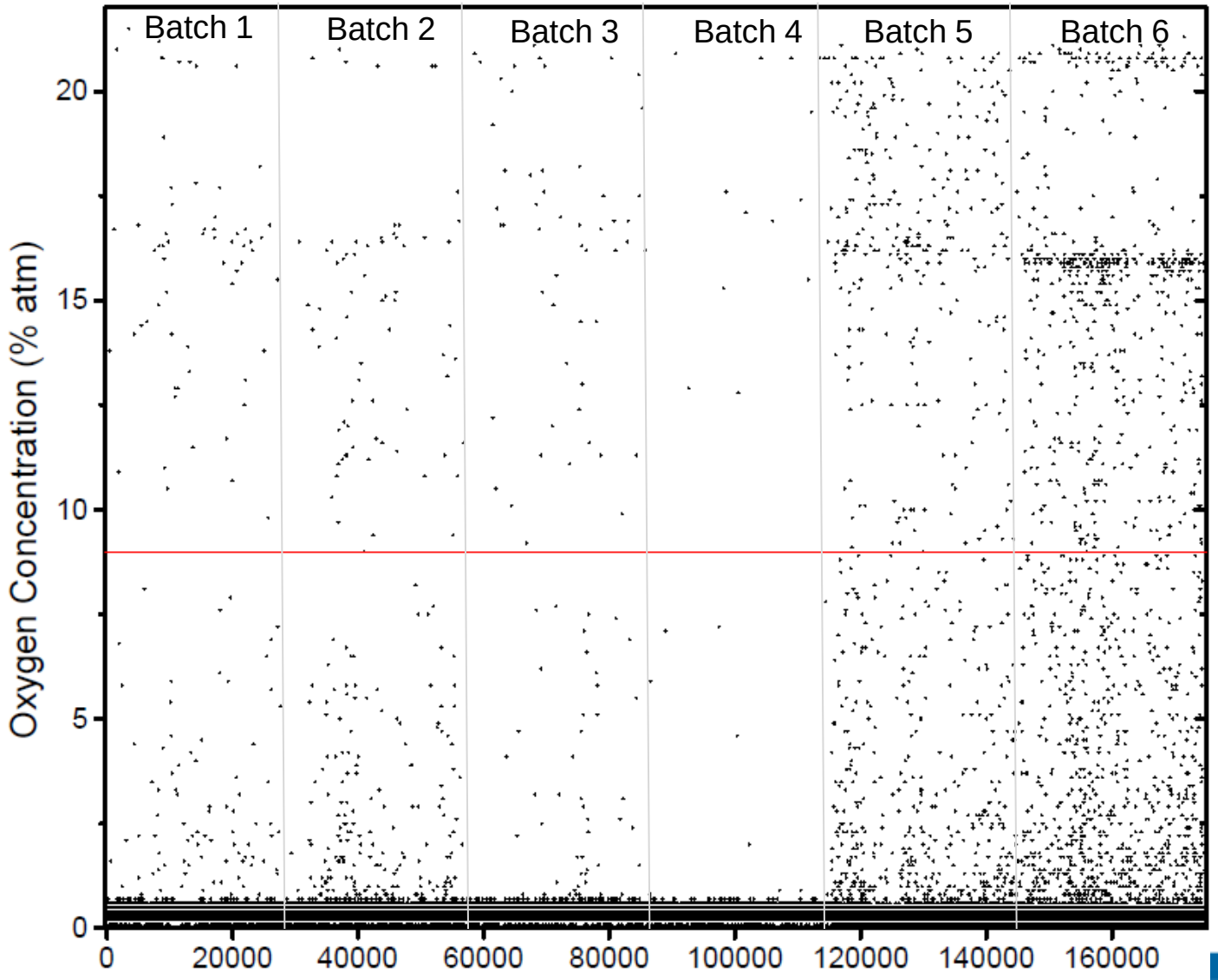
Total batch size: 29048
Number rejected: 16
Reject rate: 0.06%

Industry case study: 100% CCI Inspection



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

Industry case study: 100% CCI Inspection



Results of 6 consecutive batches

Questions

- What is a ‘typical’ container closure integrity failure rate for a batch of commercial freeze-dried product?

- How can a validated process (regularly) produce a batch having a high failure rate for a critical quality parameter?

Presentation Outline

- Container closure integrity: current regulations
- Industry 100% lyo vial CCI inspection results
- Risk assessment framework

Regulatory Guidance - EMA

- **Source:** *Good Manufacturing Practice, Annex 1: Manufacture of Sterile Medicinal Products* (Eudralex, February 2008 revision).

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.*

Regulatory Guidance - FDA

- Source: **US Food and Drug Administration, (2004) *Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*** (FDA, Rockville, MD) Paragraph VI. Components and Containers/Closures, Section B-2 Containers/Closures pg 18 Inspection of Container Closure System

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.

World Health Organization

- **Source:** WHO recommendations

Annex 1, WHO TRS 963 (revised 2007)

Containers of freeze-dried vaccine should be hermetically sealed under vacuum or after filling with pure, dry, oxygen-free nitrogen or any other gas not deleterious to the vaccine. All containers sealed under vacuum should be tested for leaks and all defective containers should be discarded.

Revised USP <1207> on CCIT

- **USP <1207> revised** (released September 2014 for comment):
  - The informational chapter on container closure integrity testing in the US Pharmacopeia has been radically updated:

"**Extensive revisions to general information chapter *Sterile Product Packaging—Integrity Evaluation* 1207** are presented for public comment in this issue of the *Pharmacopeial Forum. The original content of chapter 1207 has been revised and also subdivided into four related chapters (1207, 1207.1, 1207.2, and 1207.3) and represents the combined efforts of the USP Microbiology Expert Committee and the USP Packaging, Storage, and Distribution Expert Committee."*

- Distinguishes between PROBABILISTIC vs. DETERMINISTIC methods for CCIT

Probabilistic CCIT methods

- Microbial challenge tests
- Bubble emission tests
- Tracer liquid tests (either qualitative or quantitative measurement) *i.e. blue dye ingress*
- Tracer gas tests by sniffer probe

  - **Leakage event: Stochastic in nature**
    - Relies on a series of sequential and/or simultaneous events each associated with uncertainties
  - Results:
    - Associated with random outcomes (probability distributions)
    - Some uncertainty in findings

Deterministic CCIT methods

- Electrical conductivity and capacitance *i.e. HVLD*
- Laser-based gas headspace analysis
- Mass extraction
- Vacuum decay
- Pressure decay
- Tracer gas detection (vacuum mode) *i.e. helium leak test*

  - **Leakage event : Follows a predictable sequence**
    - Monitoring gas movement through an open leak path (at specific delta pressure or partial pressure)
    - Based on liquid presence near or in a leak path
    - Objective, quantitative data

Source reference: Dana Guazzo

Questions

- What is a ‘typical’ container closure integrity failure rate for a batch of commercial freeze-dried product?

  - **What is the quality of the vial sealing process during freeze drying?**

CCI Inspection Data Overview

Data analyzed so far to answer the question "What is a typical CCI failure rate for commercial sterile vial product?":

- 15.3 million vials manufactured 2008-2013
- 5 sterile product manufacturers
  - 2 U.S.
  - 3 EU.
- Lyo and liquid product under vacuum or partial pressure of nitrogen

Overall Results

Total no. vials inspected	**15,305,883**
Total no. vials rejected as leakers	**99,430**
Percentage	**0.65%**

Results per Product Type

- Data overview
- Overall results
- Results per product type
- Results per company
  - Vial size
  - Quarter
  - Type of failure

	Liquid	Lyo
Total no. vials	723,036	14,582,847
Total no. rejects	1,801	97,629
Percentage	0.25%	0.67%
Taking out estimated N2 purge rejects	<0.08% CCI rejects	

- In this data set, the freeze drying process produces CCI failures at a rate an order of magnitude higher than the liquid process.

Results per company

- Data overview
- Overall results
- Results per product type
- Results per company
  - Vial size
  - Quarter
  - Type of failure

	Liquid	Lyo			
Company	**A**	**B**	**C**	**D**	**E**
Total no. vials	723,036	327,178	1,586,023	491,235	12,178,411
Total no. rejects	1801	2754	4354	5002	85,519
Leaker Percentage	est. <0.08%	0.84%	0.27%	1.02%	0.70%

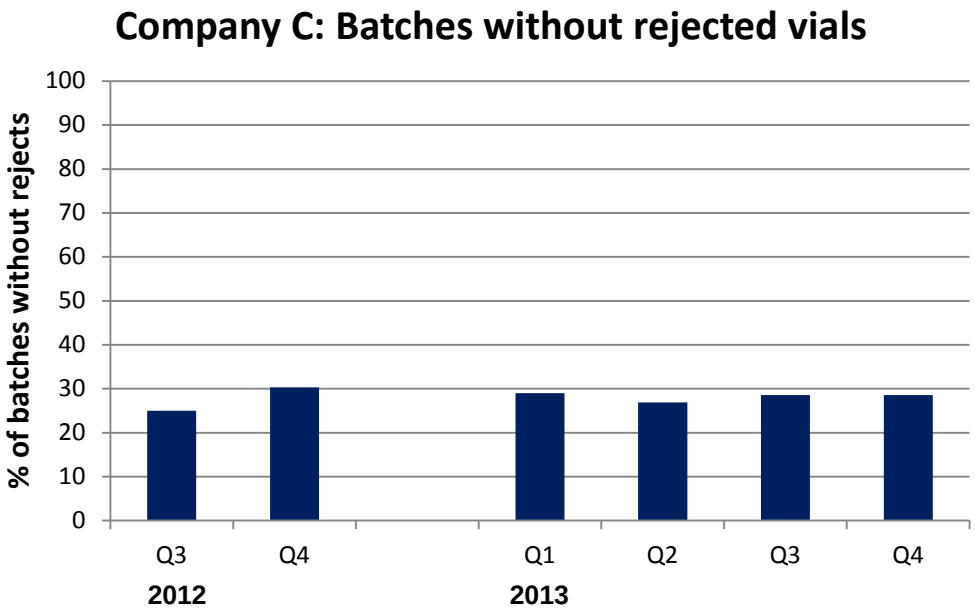
- All lyo CCI failures in the tenths of a percent.

➢ **Everyone is facing the same process challenges**

‘Zero leak’ batches

- Data overview
- Overall results
- Results per product type
- Results per company
  - Company C
  - Company E

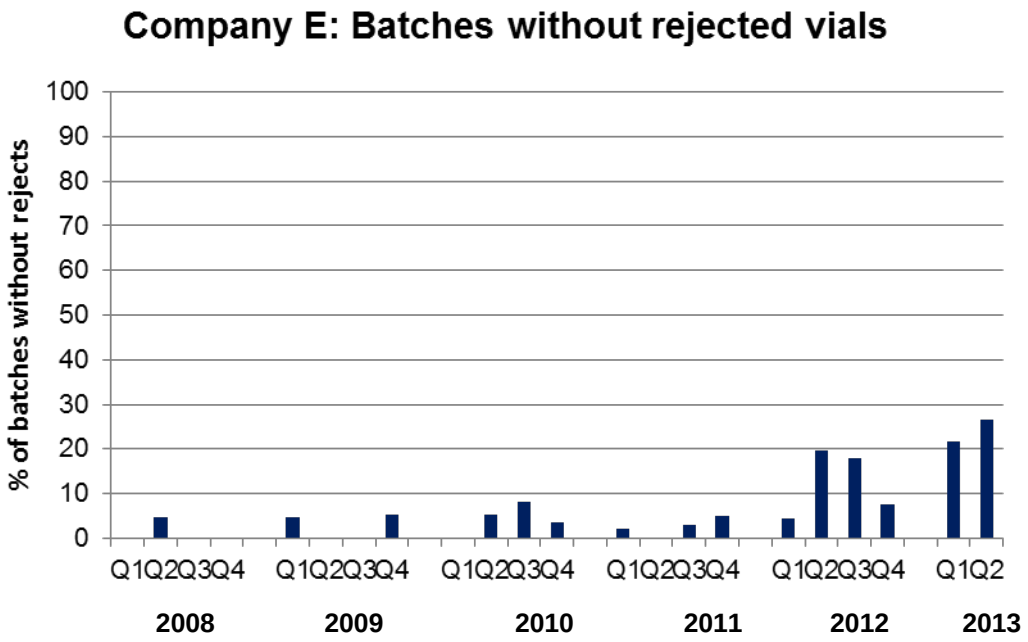
	Company C
Total No. of batches	156
Batches without rejected vials	44
Percentage	28.2%



‘Zero leak’ batches

- Data overview
- Overall results
- Results per product type
- Results per company
  - Company C
  - Company E

	Company C	**Company E**
Total No. of batches	156	**906**
Batches without rejected vials	44	**57**
Percentage	28.2%	**6.3%**



Inspection data conclusions

- CCI failure rates for lyo vials are similar to the sealing failure rate of ampoules: tenths of a %
- A validated process can still produce a batch with a high CCI failure rate
- It is difficult to produce a ‘zero leak’ batch
- The commercial freeze drying process contributes to a relatively high risk for CCI failure

Questions

- How can a validated process (regularly) produce a batch having a high failure rate for a critical quality parameter?

  - **How robustly is the vial sealing process being controlled during freeze drying?**

CCI failure risks in the freeze drying process

- Stoppering process in the lyo chamber, sticking stoppers
  - *Joe Brouwer, IMA, ISL-Freeze Drying 2013, Sao Paolo*

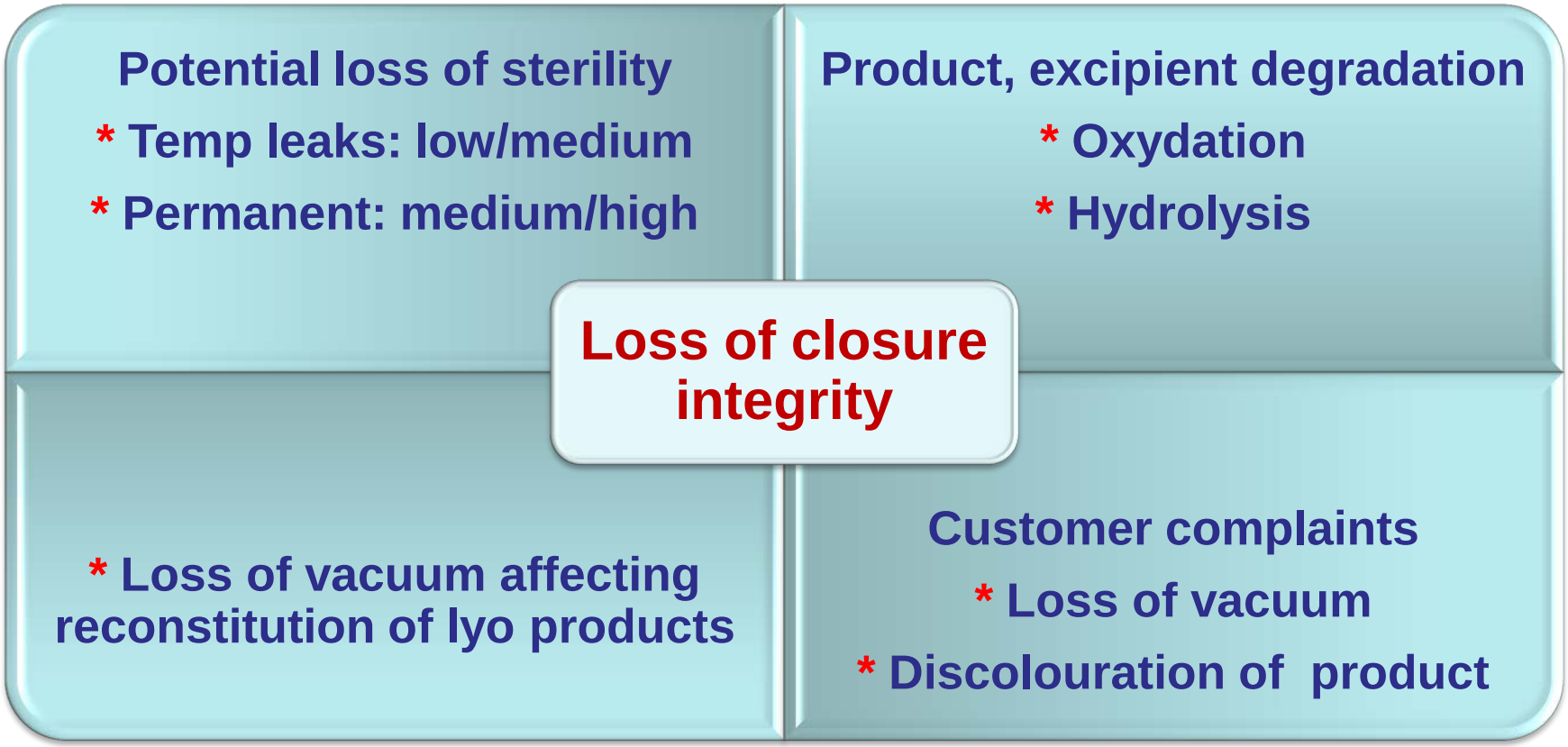
- Mismatch of packaging components, especially coated stopper / vial combinations, leading to stopper pop-up
  - *Renaud Janssen, Datwyler, PDA Freeze Drying 2011, Barcelona*
  - *Sascha Karhoefer, West, PDA Freeze Drying 2011, Barcelona*

- Extended time before vial is capped and crimped

***EU Annex 1**:*

- ***118.** The **container closure system** for aseptically filled vials is **not fully integral until the aluminium cap has been crimped** into place on the stoppered vial. Crimping of the cap should therefore be performed as soon as possible after stopper insertion.*
- ***120. Vial capping can be undertaken as an aseptic process** using sterilised caps **or** as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter **stoppered vials should be protected with a Grade A air supply until the cap has been crimped**.*

Risks associated with CCI failure



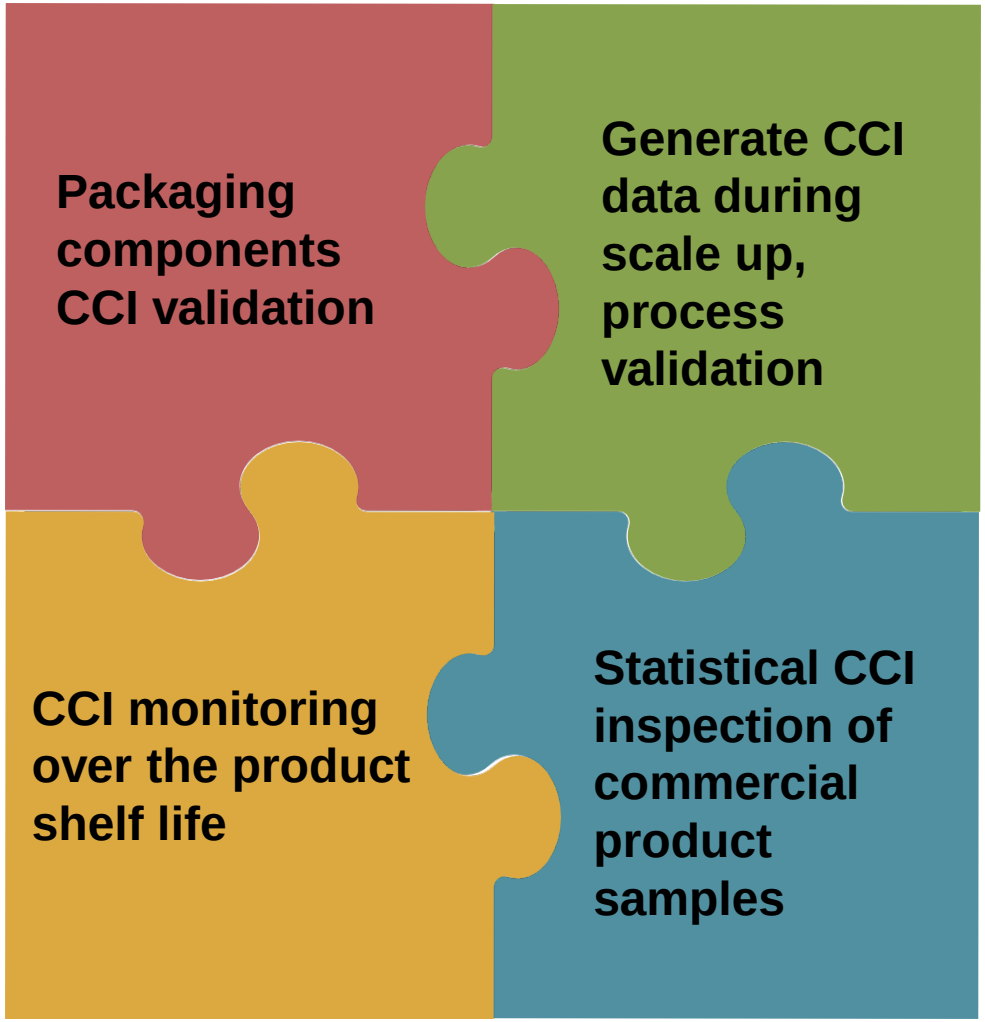
Managing the risk of CCI failure for sterile lyo product

- Thorough container closure integrity validation in packaging development
- **Generate statistical CCI data whenever possible** from samples produced with the actual process: clinical batches, scale-up placebo batches, validation batches

  (QbD approach; 2011 FDA guidance on Process Validation)
- Statistical inspection/monitoring of commercial batches
- CCI quality monitoring in stability program

Managing the risk of CCI failure for sterile lyo product

- Zero failures in CCI validation studies



- When package is introduced into process, is closure maintained?
- Zero failures over product shelf life
- Is process kept under control well enough to robustly maintain CCI?

“Ideal future process”

PAT, QbD, new FDA Process Validation guidance…

- Identify process parameters critical to freeze dried vial seal integrity
- Identify parameter range for achieving/maintaining CCI through generation of statistical ‘proof data’
- Monitor the process to assure critical parameters are in acceptable range

Discussion

- How to gain a statistical confidence that the freeze drying process is properly sealing sterile freeze dried product vials?
- How much risk to container closure integrity is acceptable?
- Can (parts of) Annex 1 be revised to give clearer guidance for ensuring good seal integrity of freeze dried product vials?

Acknowledgements

- Jeanette Evers, LIGHTHOUSE

Thank you for your attention!