Innovative Solutions for the Headspace Gas Monitoring of Glass Packages with Lyo Products

Andrea Simonetti
Convel Srl, Italy

Agenda

- Intro & Background
- Laser-Based Headspace Gas Monitoring
- Regulatory Overview
- Technology and Systems
- Case Study
- Summary and Wrap up

Laser-Based Headspace Gas Analysis “HGA”

- Key points:
  - Method used for the inspection of finished sterile product
  - Non destructive / non invasive
- Applications: Parenteral sterile drugs as O_2 sensitive and Lyophilized
  - Any modification in the headspace pressure, moisture or oxygen level may result in:
    - ✓ Degradation of the active drug
    - ✓ Reduction of drug potency
    - ✓ Decrease in product shelf life

Regulatory Overview: Sterile Products

- EU GMP Annex 1: Requirements for sterile drugs packaged under sub-atmospheric pressure:
  - *"Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period"*
- USP <1207> Package Integrity Evaluation Sterile Products
  - *"Sterility, Product Formulation Content, and Gas Headspace Content must be Preserved: …the package should prevent product formulation escape and product contamination by external liquid or solid matter or by microorganisms, but in addition, the package must preserve the gas headspace content or absolute pressure. Preservation of headspace content and/or pressure is needed to maintain product stability within physicochemical specification limits, and/or to aid end-user product access…"*

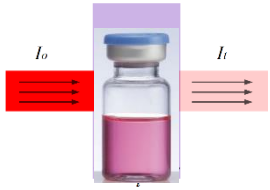
HGA: Background

- Target:

1. Investigation of the closure integrity of pharmaceutical finished containers
   - ✓ Packages sealed under vacuum: leakages determine a rise in headspace pressure towards atmospheric levels
   - ✓ Packages sealed at or near atmospheric pressure of an inert gas as N_2 and exposed to air: leakages cause oxygen ingress into the headspace
2. Verification of the maintenance of the proper headspace conditions for products packaged under modified atmosphere or under negative pressure
   - ✓ Filling / N_2 Purging / Stoppering failures can be easily detected, reported and fixed

HGA: Principle

- Technique: TDLAS "Tunable Diode Laser Absorption Spectroscopy"



  - TDLAS measurement based on the Beer-Lambert Law
  - Diode laser beam, transmitted through container headspace region and received by a detector after passing through the container itself
  - Light transmitted at a wavelength is a function of the concentration of the target gas
  - Beam wavelength optimized for measurements of distinct gases and substances:
    - ✓ Oxygen: λ = 760 nm
    - ✓ Moisture: λ = 1854 nm
    - ✓ Carbon dioxide: λ = 2000 nm

Lambert – Beer law:

Absorption $A = \log_{10}(I_0/I_1)$

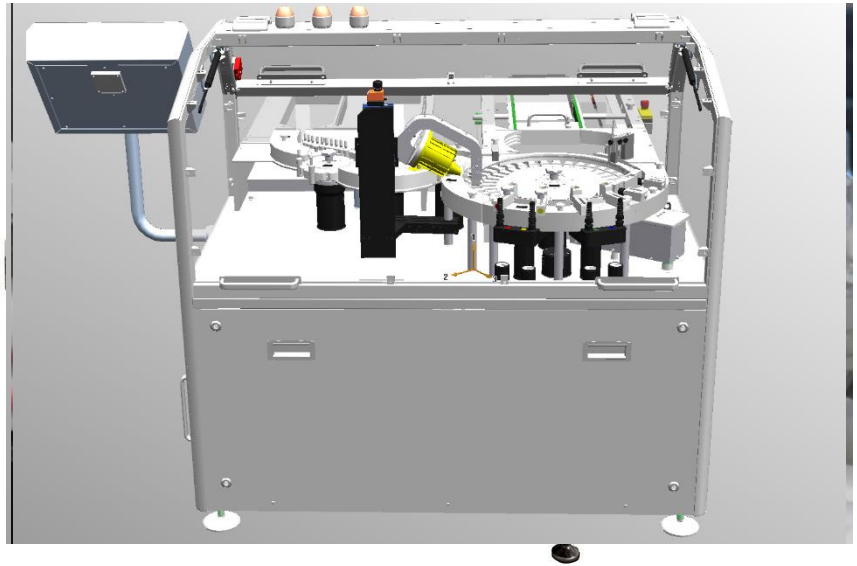
HGA: Technology and Systems

- Laser System:
  - Transceiver + reflector
  - Adjustment in height and slope
  - Spindle for stable container rotation

- **1. Bench top solution**
  - 1 laser sensor
  - Multi-format
  - Batch sample inspection

HGA: Technology and Systems (cont'd)

- **2. Fully automated solution**
  - 100% In-line / Off-line inspection
  - More laser sensors can be installed to increase accuracy and resolution



- **3. Combined solutions**
  - Visual Inspection + HGA
  - Traditional Container Closure Integrity + HGA

Case Studies: Abstract

- *Measuring the performance of a Headspace Gas Analysis equipment*
  - Oxygen laser sensor
  - 2 equipment inspection speed setting
  - 2 headspace atmosphere configuration
    - ✓ Vacuum
    - ✓ Modified atmosphere (N_2 + O_2)
- **Case 1**: 1 laser installed, 8000 cph, Vacuum standards
- **Case 2**: 1 laser installed, 16000 cph, Oxygen standards

Case Studies: Certified Traceable Standards

- Certified traceable standards with different O_2 levels

  1. Headspace under vacuum
  2. Headspace modified atmosphere (N_2)

- Method of manufacturing standard samples:

  a) Airtight chamber, sample inside
  b) Establish full vacuum condition
  c) Switch to desired vacuum level (Case 1); connect with certified gas mixture N_2-O_2 (Case 2)
  d) Stopper and seal the container

Case Study 1: Headspace Under Vacuum

- 6 different O2 levels: obtained by evacuating the container headspace

Standard Sample #	Headspace sub-atmospheric pressure mbar (abs)	Headspace O_2 partial pressure mbar (abs)	O_2 Level [%]	Samples Picture
SV1	0	0	0	
SV2	20	4,15	0,41	
SV3	40	8,29	0,83	
SV4	60	12,4	1,24	
SV5	80	16,6	1,66	
SV6	100	20,7	2,07	

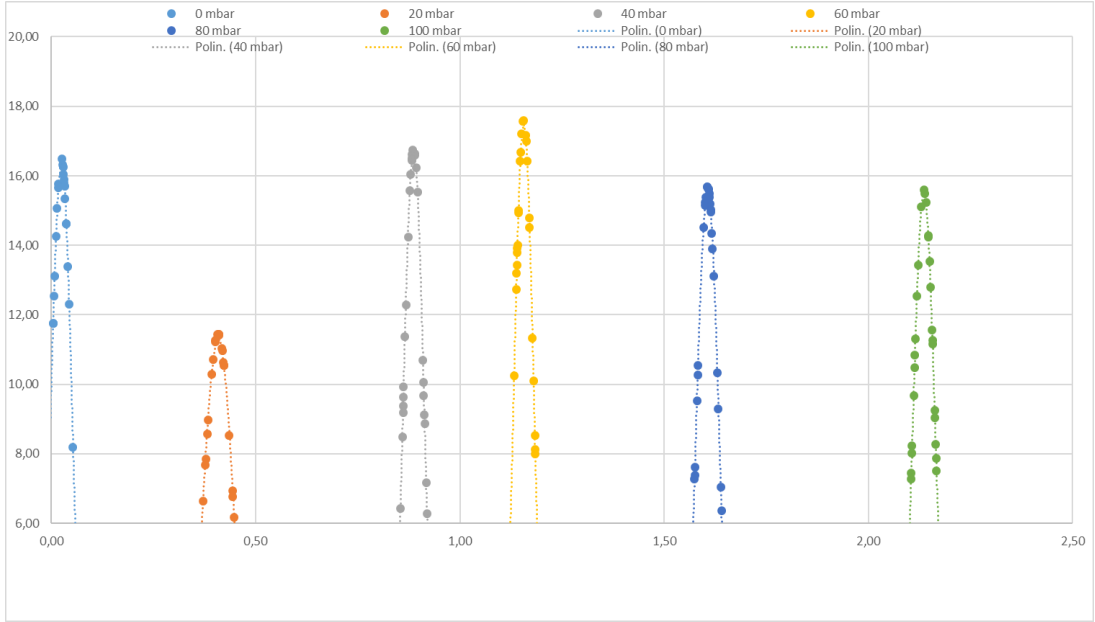
Case Study 1: Findings

Sampling ID#	SVI - 0 mbar		SV2 - 20 mbar		SV3 - 40 mbar		SV4 - 60 mbar		SV5 - 80 mbar		SV6 - 100 mbar		
	abs press	O2 %	abs press	O2 %	abs press	O2 %	abs press	O2 %	abs press	O2 %	abs press	O2 %	
1	1,56	0,03	19,40	0,40	43,09	0,89	55,03	1,14	77,73	1,61	103,71	2,15	Measured levels
2	1,76	0,04	20,99	0,43	44,93	0,93	56,95	1,18	77,80	1,61	102,75	2,13	
3	-0,41	-0,01	18,24	0,38	43,24	0,90	57,41	1,19	77,18	1,60	104,35	2,16	
4	1,54	0,03	19,75	0,41	42,56	0,88	56,04	1,16	80,32	1,66	103,06	2,14	
5	0,40	0,01	18,19	0,38	44,40	0,92	54,65	1,13	77,68	1,61	101,53	2,10	
6	3,10	0,06	18,92	0,39	42,44	0,88	55,56	1,15	77,86	1,61	101,96	2,11	
7	-1,56	-0,03	19,35	0,40	43,95	0,91	54,07	1,12	78,01	1,62	100,87	2,09	
8	0,56	0,01	20,38	0,42	43,88	0,91	55,18	1,14	77,60	1,61	104,85	2,17	
9	2,08	0,04	19,09	0,40	41,88	0,87	55,80	1,16	77,49	1,61	104,05	2,16	
10	0,69	0,01	18,42	0,38	44,28	0,92	56,47	1,17	74,89	1,55	103,59	2,15	
…	-0,14	0,00	18,52	0,38	41,61	0,86	56,82	1,18	79,05	1,64	103,58	2,15	
150	-0,38	-0,01	19,66	0,41	43,99	0,91	56,20	1,16	76,27	1,58	103,20	2,14	
AVG	1,19	0,02	19,70	0,41	42,79	0,89	55,79	1,16	77,50	1,61	103,06	2,14	
STDDEV	1,17	0,02	1,68	0,03	1,15	0,02	1,09	0,02	1,23	0,03	1,23	0,03	

- 150 measurements: headspace abs pressure / Oxygen level
- Accuracy needed while implementing standards – keep the process under control

Case Study 1: Findings (cont'd)

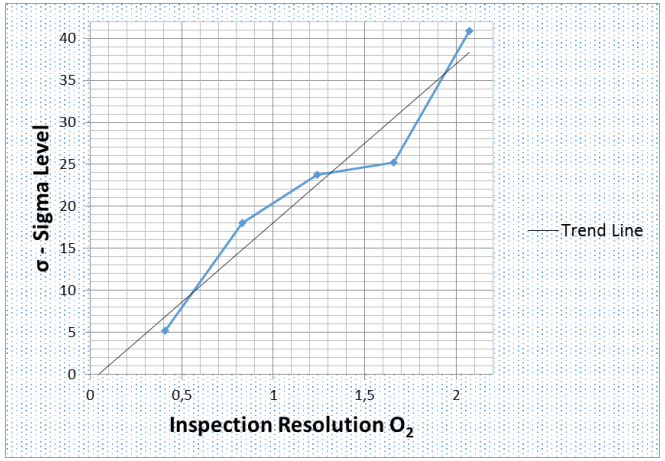
- Headspace measurements made on:
  - Standards: 0, 20, 40, 60, 80, 100 mbar (abs)
  - Inspection time = 200 msec
  - Production speed 8000 cph
  - Histograms are plots of the measurements for each standard
  - Accuracy and resolution demonstrated



Case Study 1: Findings (cont'd)

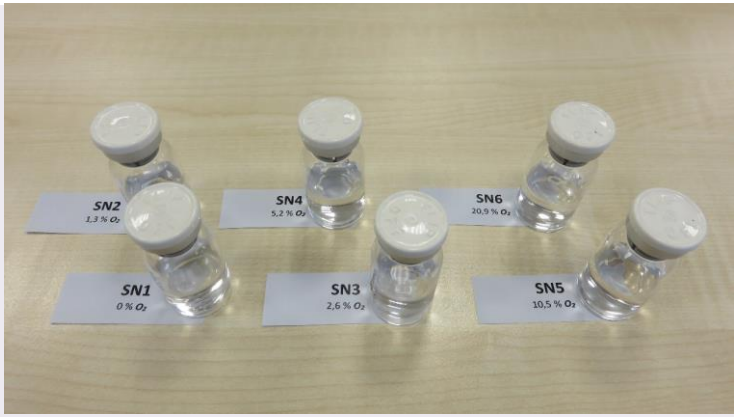
- Other results:
  - Equipment can distinguish between the O2 levels investigated
  - Sigma levels calculated as a function of O2 resolution
  - Prevision model:
    - ✓ 3σ Process
    - ✓ Inspection resolution = 0,2% O2

Resolution O2	Reference		Inspection Time (msec) 200	Sigma Level
0,41	SVI	SV2	5,21	
0,41	SV2	SV3	7,35	
0,41	SV3	SV4	5,77	
0,41	SV4	SV5	8,55	
0,41	SV5	SV6	10,53	
0,83	SVI	SV3	18,08	
1,24	SVI	SV4	23,74	
1,66	SV2	SV6	25,26	
2,07	SVI	SV6	40,86	



Case Study 2: Headspace Under Modified Atmosphere

- 6 different O2 levels: nitrogen overlay in the container headspace

Standard Sample #	Headspace pressure mbar (abs)	O_2 Level [%]	Pictures
SN1	800	0	
SN2	800	1,3	
SN3	800	2,6	
SN4	800	5,2	
SN5	800	10,4	
SN6	800	20,9	

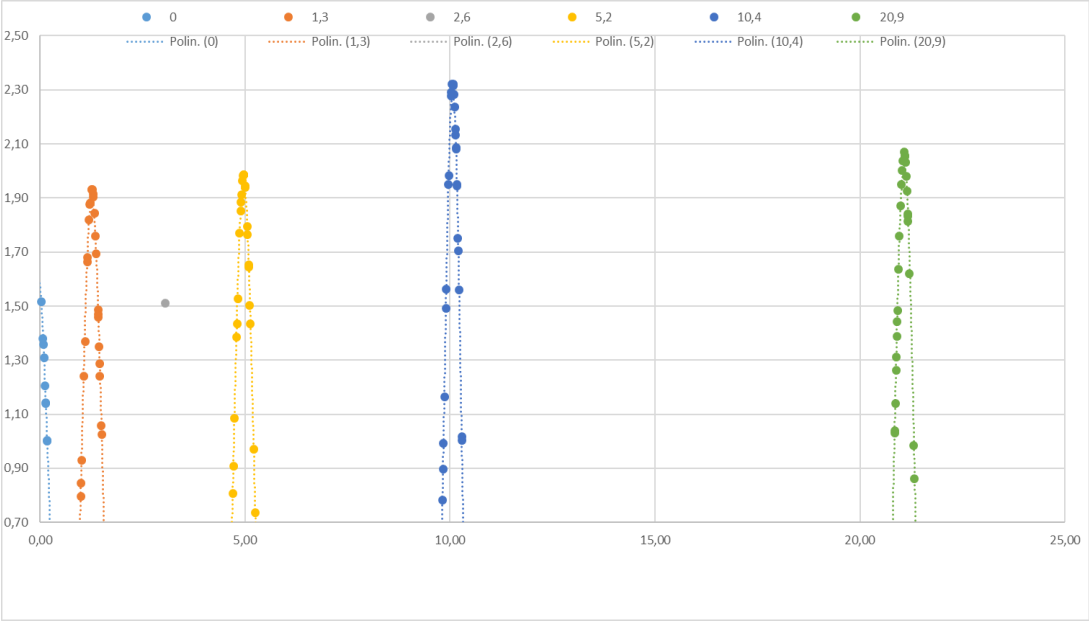
Case Study 2: Findings

- 150 measurements:
  - ✓ Oxygen levels on the set of certified standards
  - ✓ Statistical picture of the system performance

Sampling ID#	SN1 - O% O2	SN2 - 1,3% O2	SN3 - 2,6% O2	SN4 - 5,2% O2	SN5 - 10,4% O2	SN6 - 20,9% O2	
	O2 %	O2 %	O2 %	O2 %	O2 %	O2 %	
1	-0,27	0,76	3,08	5,01	10,10	20,79	Measured levels
2	0,32	0,99	3,02	5,26	9,81	21,11	
3	0,03	1,33	2,97	4,94	10,22	20,88	
4	-0,23	1,27	3,60	5,06	9,80	20,89	
5	-0,43	1,00	2,94	5,13	10,03	21,08	
6	-0,37	1,42	3,33	4,91	9,96	21,21	
7	0,14	1,19	3,45	4,63	10,08	20,96	
8	0,12	1,46	3,31	4,80	10,05	20,90	
9	-0,29	1,49	3,07	5,27	10,41	20,85	
10	-0,16	1,50	3,38	5,07	9,90	21,10	
…	0,17	1,16	3,04	4,96	10,15	21,17	
150	0,07	0,87	3,07	4,87	10,14	21,02	
AVG	-0,07	1,27	3,20	4,97	10,06	21,07	
STDDEV	0,24	0,21	0,23	0,20	0,17	0,19	

Case Study 2: Findings (cont'd)

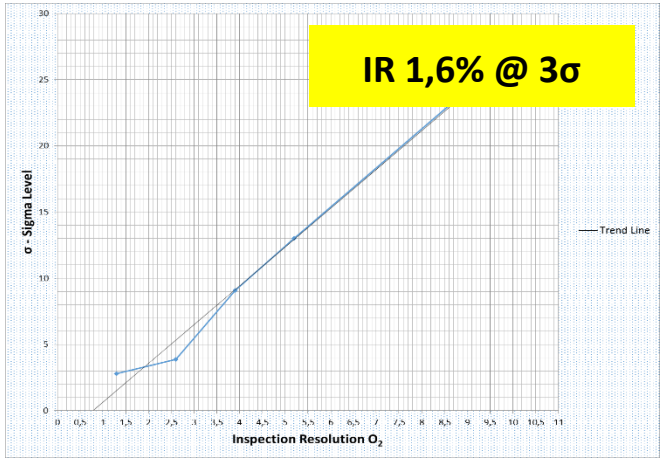
- Headspace measurements made on:
  - Standards 0; 1,3; 2,6; 5,2; 10,4; 20,9 % O2
  - Inspection time = 100 msec
  - Production speed 16000 cph
  - O2 levels of interest can be distinguished



Case Study 2: Findings (cont'd)

- Correlation between inspection parameters:
  - A decrease in inspection time results in…
    - ✓ An increase of production speed
    - ✓ A decrease of σ
    - ✓ An increase of inspection resolution
  - Possible approach:
    - ✓ Set the desired sigma level
    - ✓ Design the most suitable equipment configuration
      - Production speed / Inspection Time
      - Number of HGA Laser units to be installed

Resolution O2	Reference		Inspection Time (msec)	
			100	
1,30	SN1	SN2	2,79	Sigma Level
1,30	SN2	SN3	4,30	
2,60	SN3	SN4	3,86	
5,20	SN4	SN5	13,03	
10,50	SN5	SN6	28,65	
20,90	SN1	SN6	53,96	
2,60	SN1	SN3	6,89	
3,90	SN2	SN4	9,09	
7,80	SN3	SN5	15,22	



Summary and Conclusions

- Laser Based HGA is Non Destructive, Deterministic, Quantitative, Quick
- Immediate feedback about headspace gas levels enables
  - Detection of failures
  - Process characterization and improvement
- Scalability:
  - Lab system: batch sample inspection
  - Automated system: 100% In-Process controls
  - Combination equipment: headspace gas monitoring + visual inspection + traditional CCI

Summary and Conclusions (cont'd)

- The presented case studies provide a roadmap for selecting and configuring a HGA process as a function of:
  - Headspace gas composition
  - Equipment speed / Inspection time
  - Expected quality: Sigma Level, Inspection Resolution…
- Studies under developments:
  - Employ HGA to establish container closure integrity
    - ✓ calculate leakage rate / equivalent hole size
  - Implement a robust method for manufacturing the certified standards