Compressed Gas Testing in Controlled Environments

Industry Trends and Best Practices

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Outline

1. Regulations and Guidance
2. Design of an Effective Sampling Plan
3. Overview of Methods and Qualification
4. Industry Feedback – Current Practices and Trends

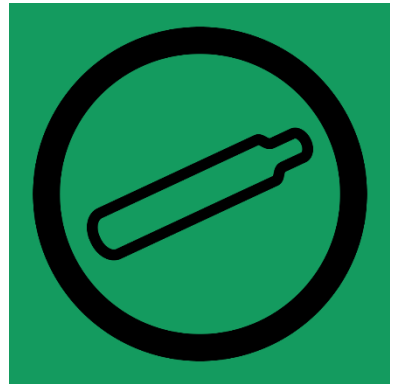
Disclaimer

- The information in this seminar is given for the purposes of education and discussion
- It is not intended to be, and it should not be used as a substitute for regulations or regulatory guidance
- Decisions and actions should be based on the relevant regulations, guidance documents and pharmacopeial chapters
- Statements and opinions expressed are of the presenter and are not necessarily the views of MilliporeSigma or Alcon Laboratories

Regulations & Guidance

Why Test Compressed Gases?

- Compressed gases are used in direct and indirect contact with final product
- Gas contaminants can effect product quality, stability and efficacy
- Compressed gases introduced into aseptic areas should be of the same, or better ISO classification as environment utilized in
- Critical, but often overlooked utility used in pharmaceutical production
- Organisms can exist and grow in compressed gases[1]



- [1]Zinger, Meier, MBV

Regulations and Guidance

1) FDA "Guideline on Sterile Drug Products Produced by Aseptic Processing", 2004

2) ISO 8573 consists of the following parts, under the general title *Compressed air*:

– *Part 1: Contaminants and purity classes*
– *Part 2: Test methods for oil aerosol content*
– *Part 3: Test methods for measurement of humidity*
– *Part 4: Test methods for solid particle content*
– *Part 5: Test methods for oil vapour and organic solvent content*
– *Part 6: Test methods for gaseous contaminant content*
– ***Part 7: Test method for viable microbiological contaminant content***
– *Part 8: Test methods for solid particle content by mass concentration*
– *Part 9: Test methods for liquid water content*

Regulations & Guidance

Specifications for Air Cleanliness (Non-Viable) (m^3)

ISO 14644-1 –Revised 2015

ISO Class number (*N*)	Maximum allowable concentrations (particles/m^3) for particles equal to and greater than the considered sizes, shown below[a]					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
1	*10*[b]	d	d	d	d	e
2	100	*24*[b]	*10*[b]	d	d	e
3	1 000	237	102	*35*[b]	d	e
4	10 000	2 370	1 020	352	*83*[b]	e
5	100 000	23 700	10 200	3 520	832	d, e, f
6	1 000 000	237 000	102 000	35 200	8 320	293
7	c	c	c	352 000	83 200	2 930
8	c	c	c	3 520 000	832 000	29 300
9[g]	c	c	c	35 200 000	8 320 000	293 000

Regulations & Guidance

EU Annex 1 Specifications for Air Cleanliness (Viable) (m3) and Contact Plates

Grade/ ISO	**Air Sample cfu/m^3**	Settle Plates cfu/≤ 4 Hours	Contact Plates cfu/plate	Glove prints 5 fingers cfu/glove
A/5	**<1**	<1	<1	<1
B/5	**10**	5	5	5
C/7	**100**	50	25	-
D/8	**200**	100	50	-

Regulations & Guidance

What the guidance addresses:

- Classification of compressed gas purity
- Types of contaminants to monitor (solid, liquid, oil)
- Specifications based on ISO Class or Grade

What the guidance does not address:

- Sampling conditions
- Sample Volume/Time
- Testing frequency
- Type of media to be used
- Method of sampling (beyond Slit-to-Agar method specified in ISO 8573
- Safety Considerations

Design of an Effective Sampling Plan

Sampling Plan

Where to Sample

- For initial Qualification, sample from entire system

- Routine monitoring:
  - Select worst-case locations based on qualification results
  - Sample at use point furthest from filtration or source

Sampling Plan

Testing Performed

- Non-viable Particulates
- Microbial Content
  - For inert gas systems with no Oxygen, this includes anaerobic testing.
- Hydrocarbon
- Dew Point

Sampling Plan

How Often to Sample

- Based on Classification in Area of Use
  - Grade A/B: Risk-based assessment
  - Grade C/D: Quarterly (industry standard)

- Can reduce frequency with historical data

Sampling Plan

Control Limits

- Based on Classification as well
- Microbial and NVP limits should match those of surrounding air.
- Hydrocarbon/Dew Point: Based on use and required classification.

TABLE 1- Air Classifications[a]

Clean Area Classification (0.5 um particles/ft^3)	ISO Designation[b]	≥ 0.5 µm particles/m^3	Microbiological Active Air Action Levels[c] (cfu/m^3)	Microbiological Settling Plates Action Levels[c,d] (diam. 90mm; cfu/4 hours)
100	5	3,520	1[e]	1[e]
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

a- All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity.
b- ISO 14644-1 designations provide uniform particle concentration values for cleanrooms in multiple industries. An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A.
c- Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.
d- The additional use of settling plates is optional.
e- Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

Overview of Methods and Qualification

Environmental Monitoring of Compressed Gases

Different applications of compressed air/gas in the pharmaceutical industry

Blanketing:

- To maintain constantly a protective layer of gas on top of a substance.
  - In process (tank)
  - Final packaging

Purging:

- To fill and rinse a reactor

Stirring

- To mix and store liquids

Cleaning

Environmental Monitoring of Compressed Gases

Common pharmaceutical compressed gases monitored for microbial content

- Air
- Nitrogen
- Carbon Dioxide
- Argon
- Oxygen

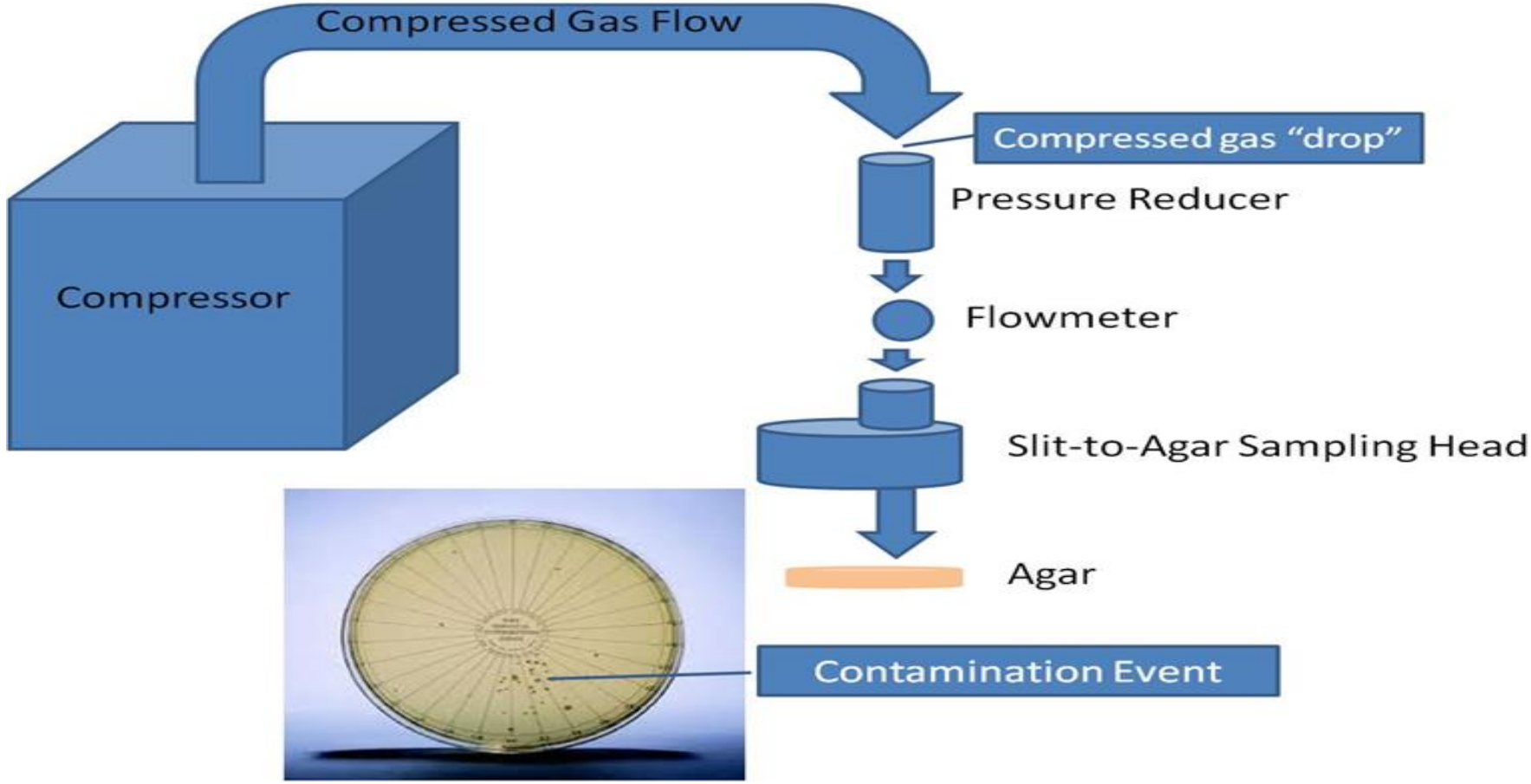
Any gases that come into contact with the product and container closure system should be monitored.

"A compressed gas should be of appropriate purity (e.g., free from oil) and its microbiological and particle quality after filtration should be equal to or better than that of the air in the environment into which the gas is introduced."(FDA, 2004)This statement should be interpreted as meaning that incoming compressed gas should be held to the same standard and alert/action levels as the air sampling in the aseptic environment.

Environmental Monitoring of Compressed gases –Tim Cser and Anne Connors. PDA Technical Book, Environmental Monitoring Volume 7

Microbial Testing Methods

Sampling per ISO 8573



Microbial Testing Methods

Several commercial test systems available.

Similar basic function.

Differ in complexity and design.

- User or Machine regulation of airflow
- Growth medium configuration
- Closed/Open system

Overview of Methods

Slit-to-Agar Sampler

- Pressure is reduced to atmospheric conditions with a regulator (usually manual)
- Air is impacted through slit, directly onto nutrient agar (usually 150 mm plate)
- Sample time of 1 cubic meter dependent on flow rate of instrument

Overview of Methods

Filtration

- A filter holder is assembled with a 47 mm filter disc and autoclaved
- Pressure is reduced to atmospheric pressure using a regulator
- Sample volume is determined by sample pressure/time
- After sampling, filters are aseptically transferred onto growth media and incubated

Overview of Methods

Impaction

- Impaction principle based on Centrifugal, Anderson Principle, Sieve Impaction
- Sample device or air sampler attachment is connected to compressed gas line
- In many samplers, a regulator is necessary to adjust line ambient pressure
- Sample gas is impacted directly onto agar plate, or strip
- Time of sample dependent on sampler flow rate and gas pressure

Overview of Methods

Comparison of common commercially available instruments

Method	Ease of Use	Sensitivity	Regulation of air flow	Sample Time	Workflow	Safety
Slit to Agar (Standard)						
Filtration						
Traditional Impaction						
Pressurized Impaction Sampler						

 Above standard  In-line with standard  Below standard technology

Industry Feedback – Current Practices and Trends

Industry Survey Overview

- **Objectives**

❖Gain an understanding about current methods utilized in Pharma

❖ Understand what regulatory guidance is most closely followed

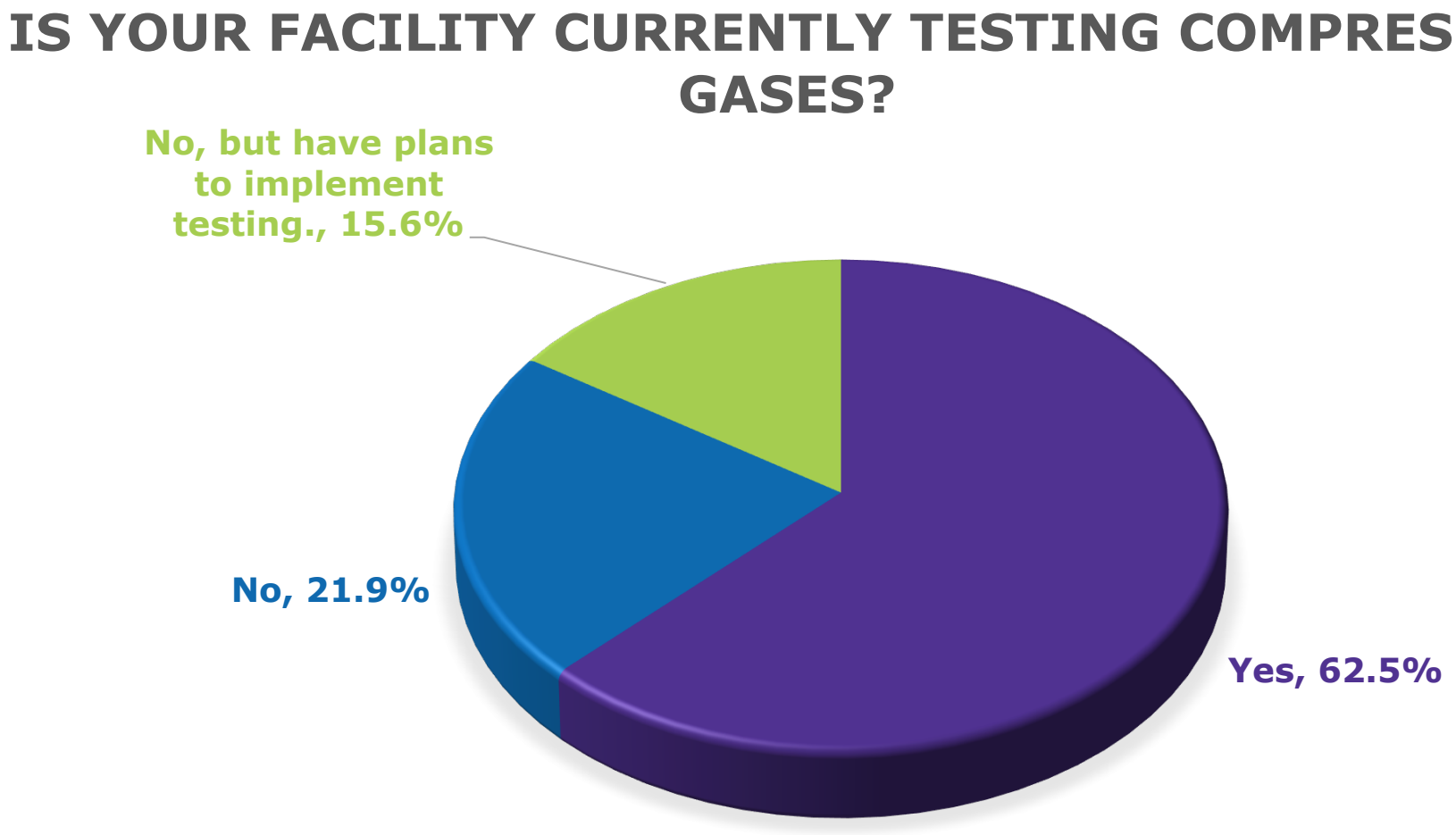
❖ Understand trends in compressed gas testing technology

❖ Uncover common concerns in compressed gas sampling that are relevant to discussion

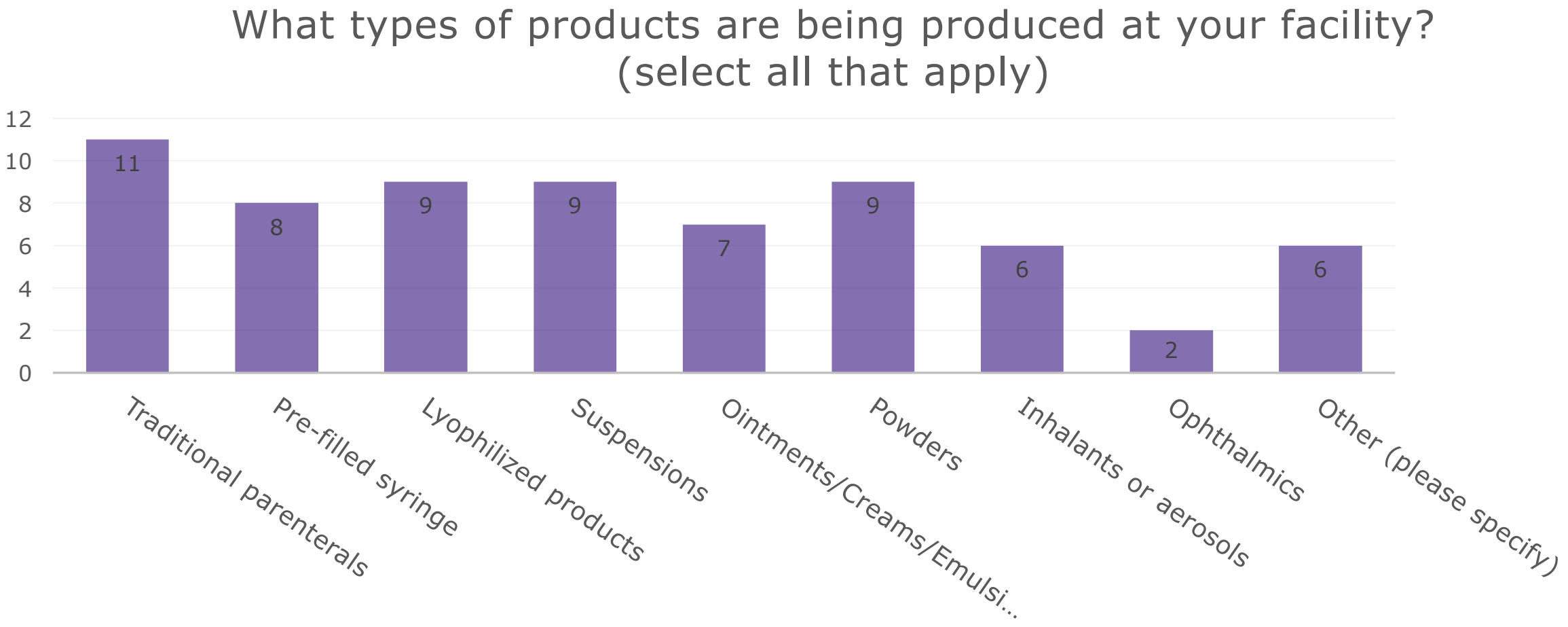
- **Summary**

- Total of 32 respondents across the Pharma industry
- Representation of a wide variety of product types and manufacturing processes

Industry Survey Overview



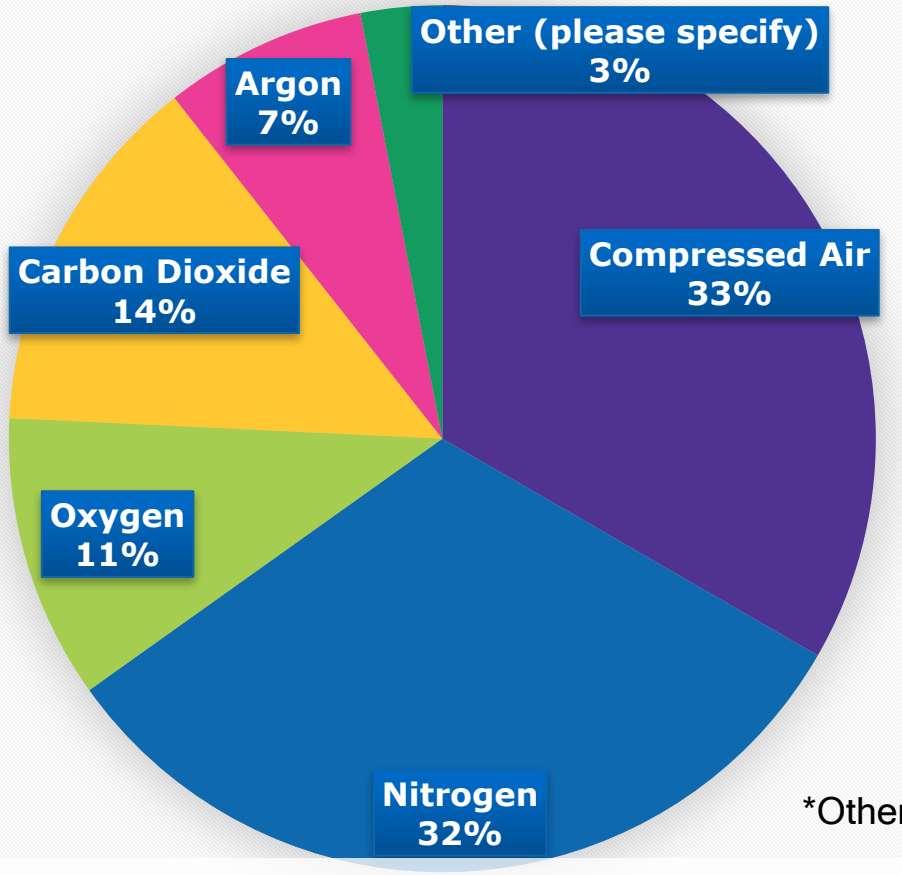
Industry Survey Overview



- Other answers included: Cell culture, Proteomics, Tablets/Capsules, Bulk Production

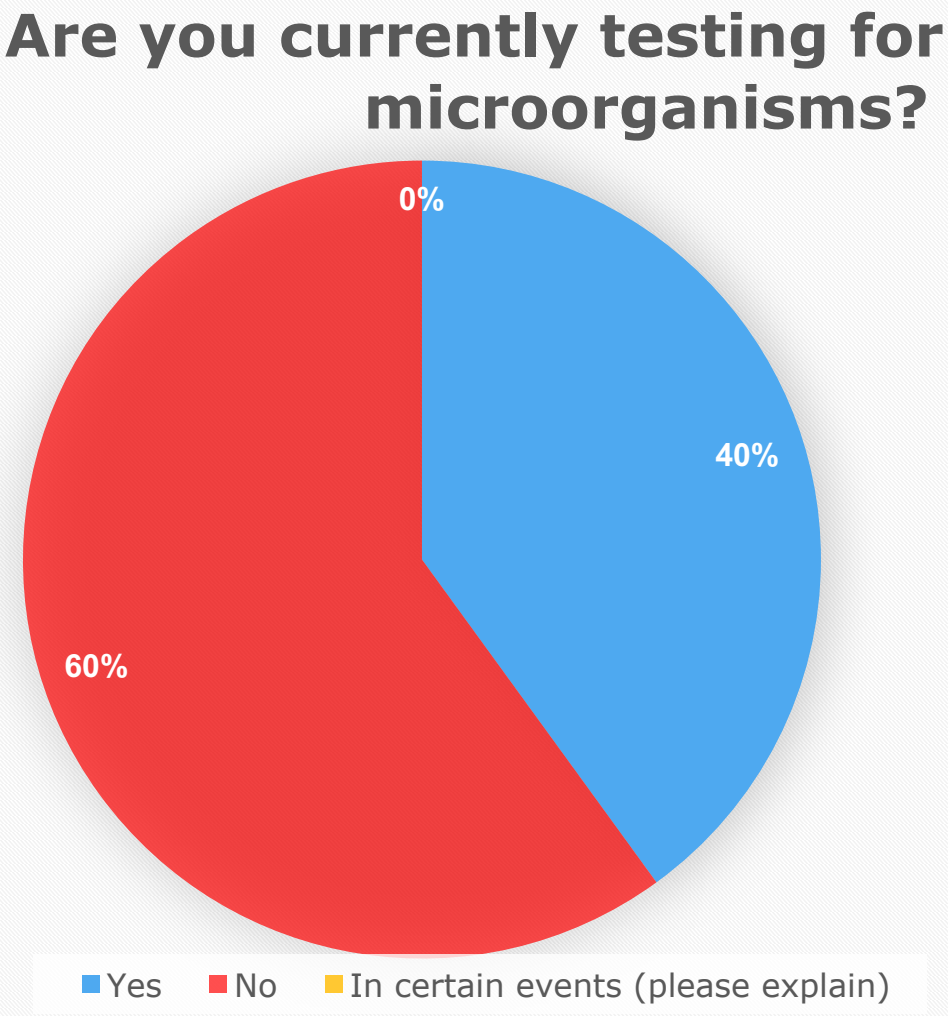
Industry Survey Overview

What types of gases are currently tested at your facility? (Select all that apply)



*Other: Isobutane, Dimethyl Ether

Industry Survey Overview



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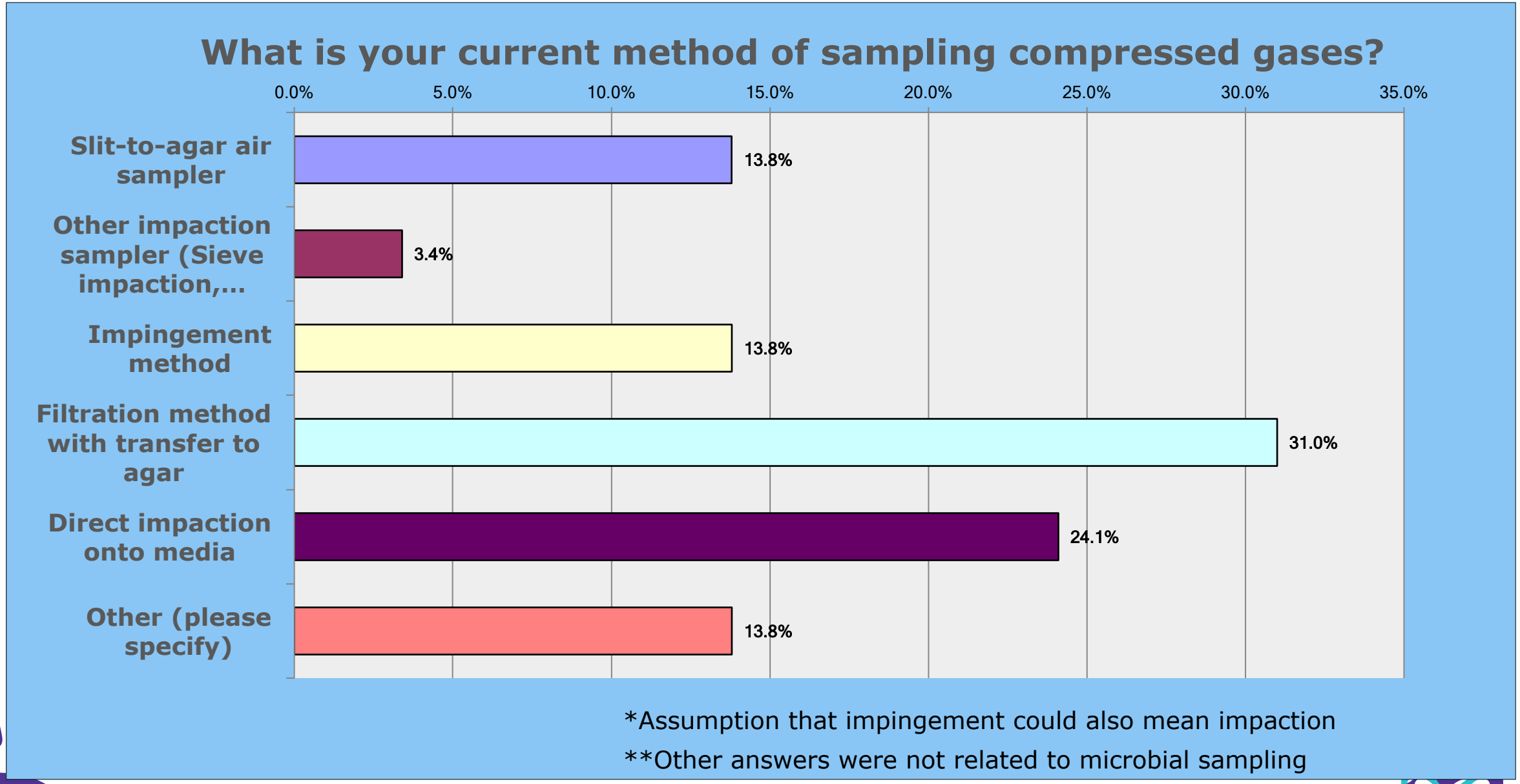
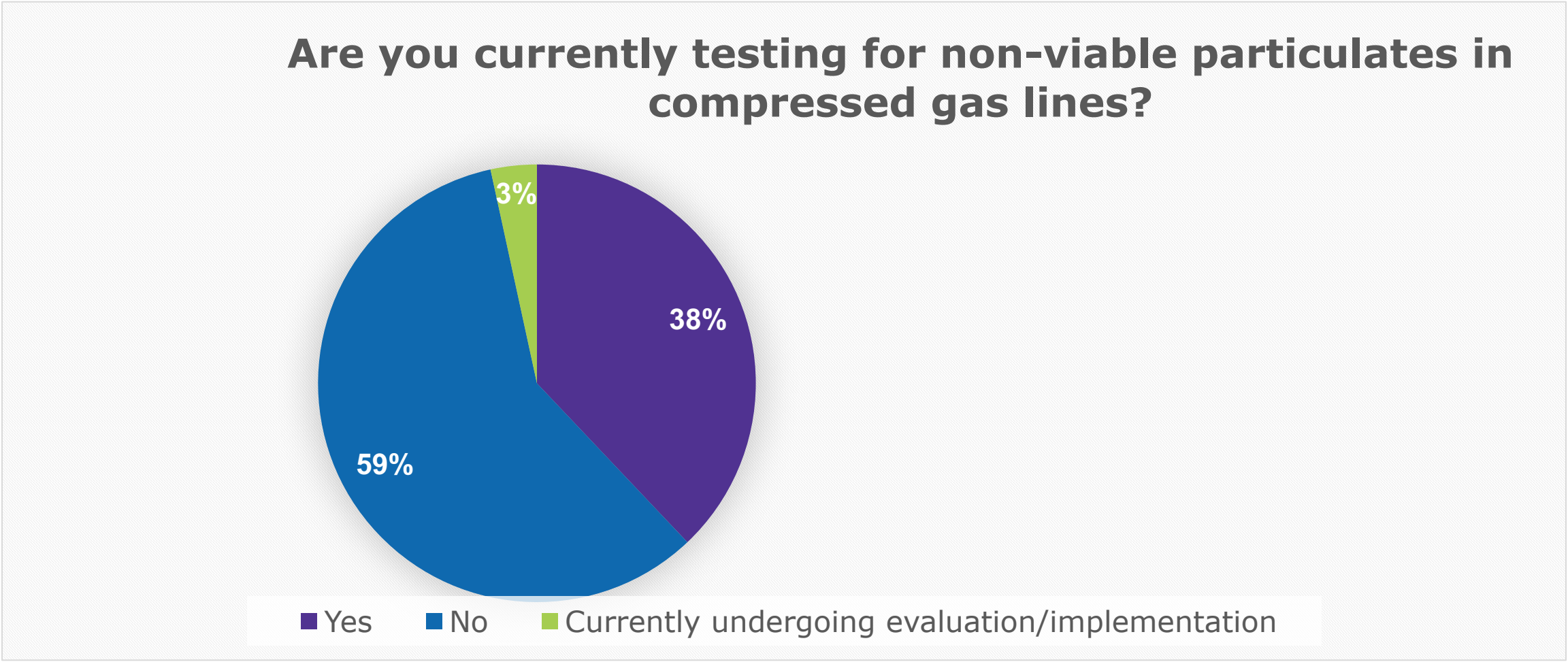


*Assumption that impingement could also mean impaction

**Other answers were not related to microbial sampling

Industry Survey Overview



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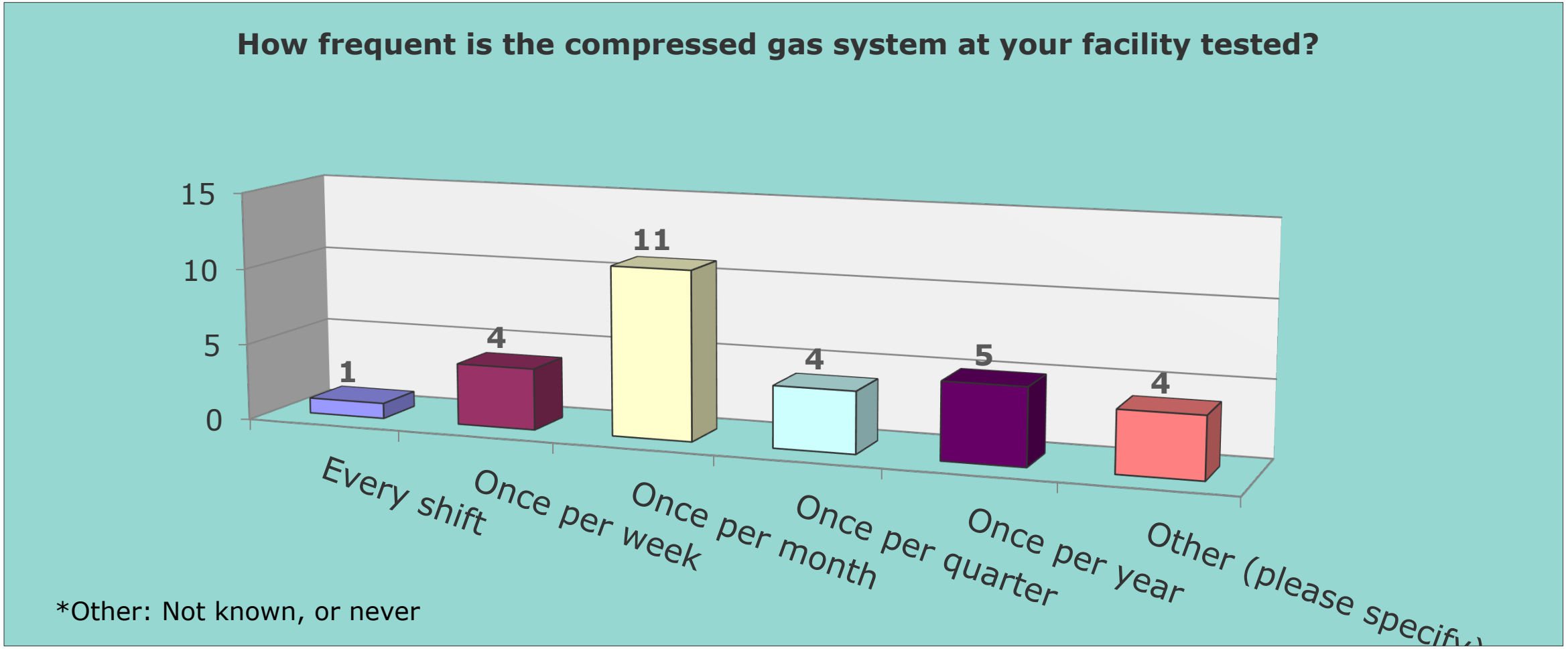
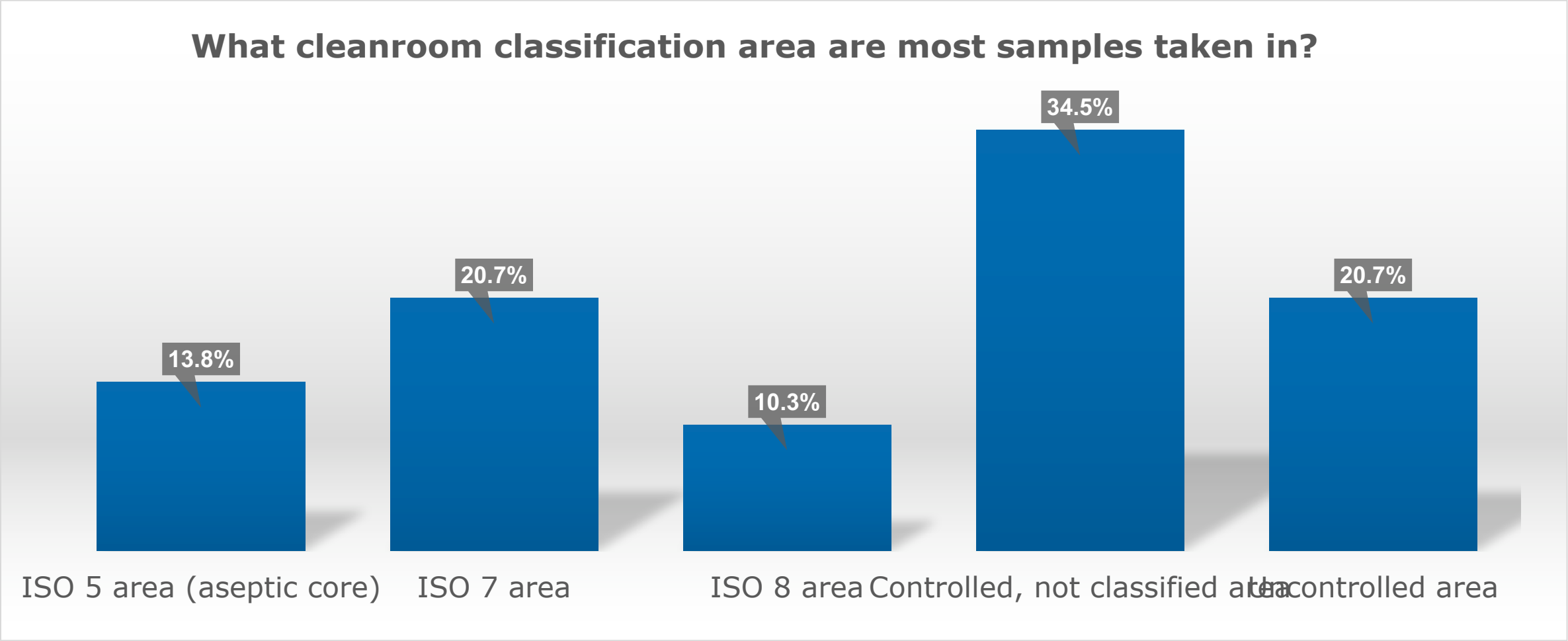


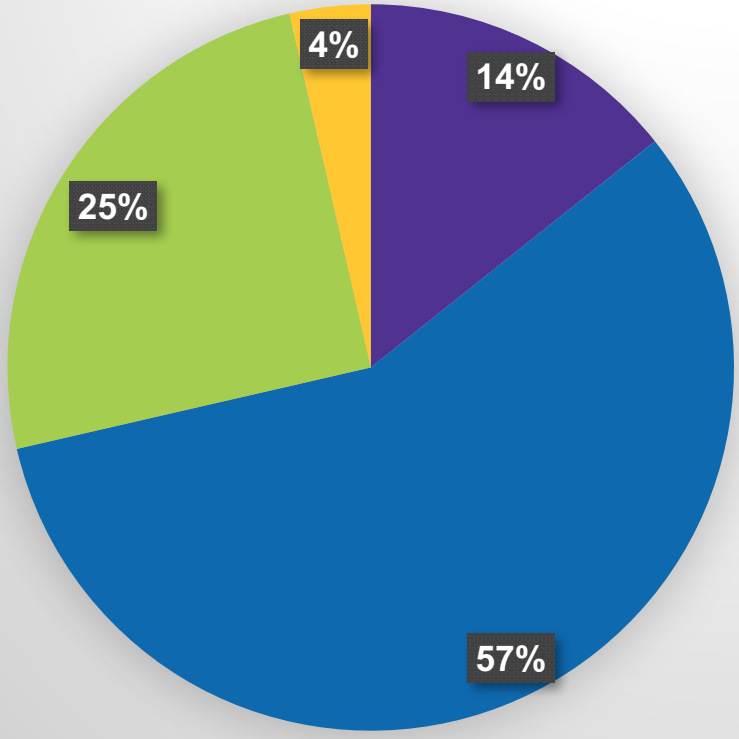
*Other: Not known, or never

Industry Survey Overview



Industry Survey Overview

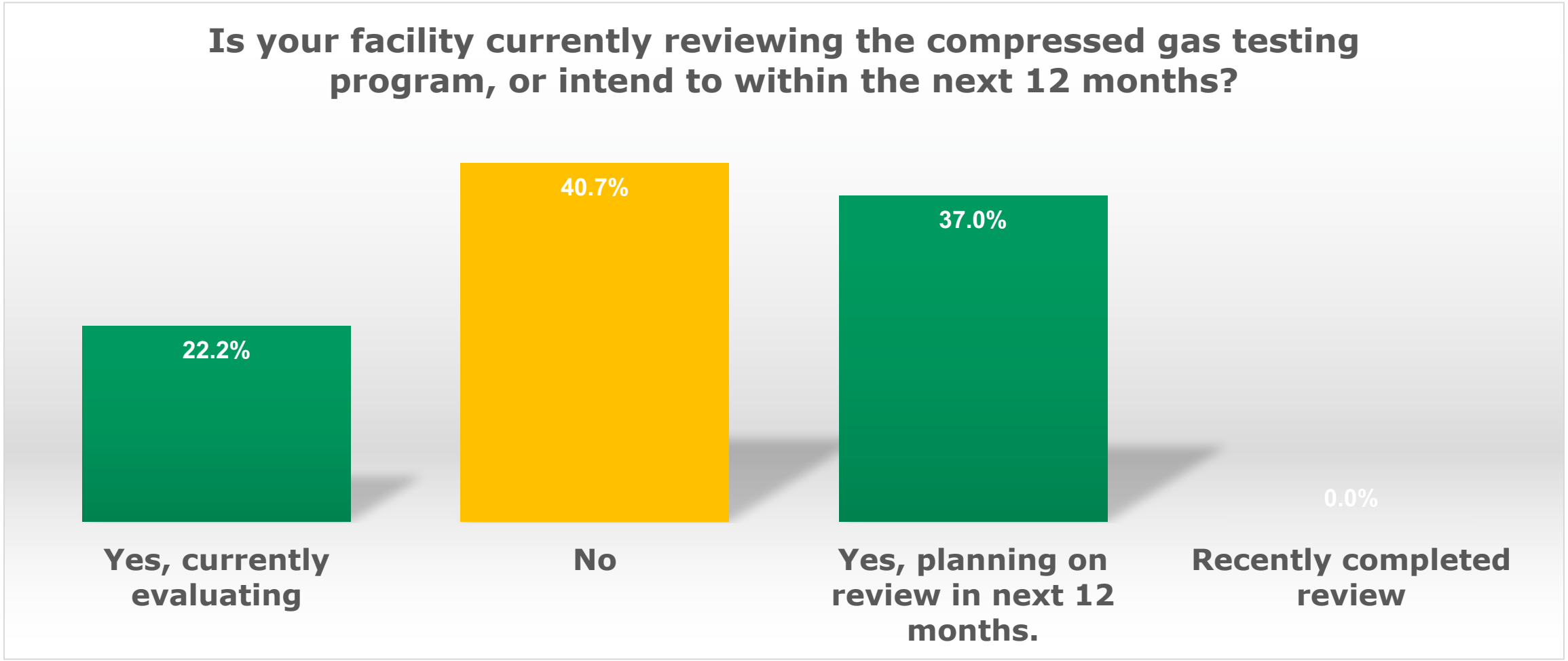
What standard or guidance is most closely followed for compressed gas testing at your facility?



- ISO 8573
- FDA Guidance -Sterile Drug Products Produced by Aseptic Processing
- ISPE Good Practice Guide: Process Gases
- Other (please specify)

Other Answer: Not known

Industry Survey Overview



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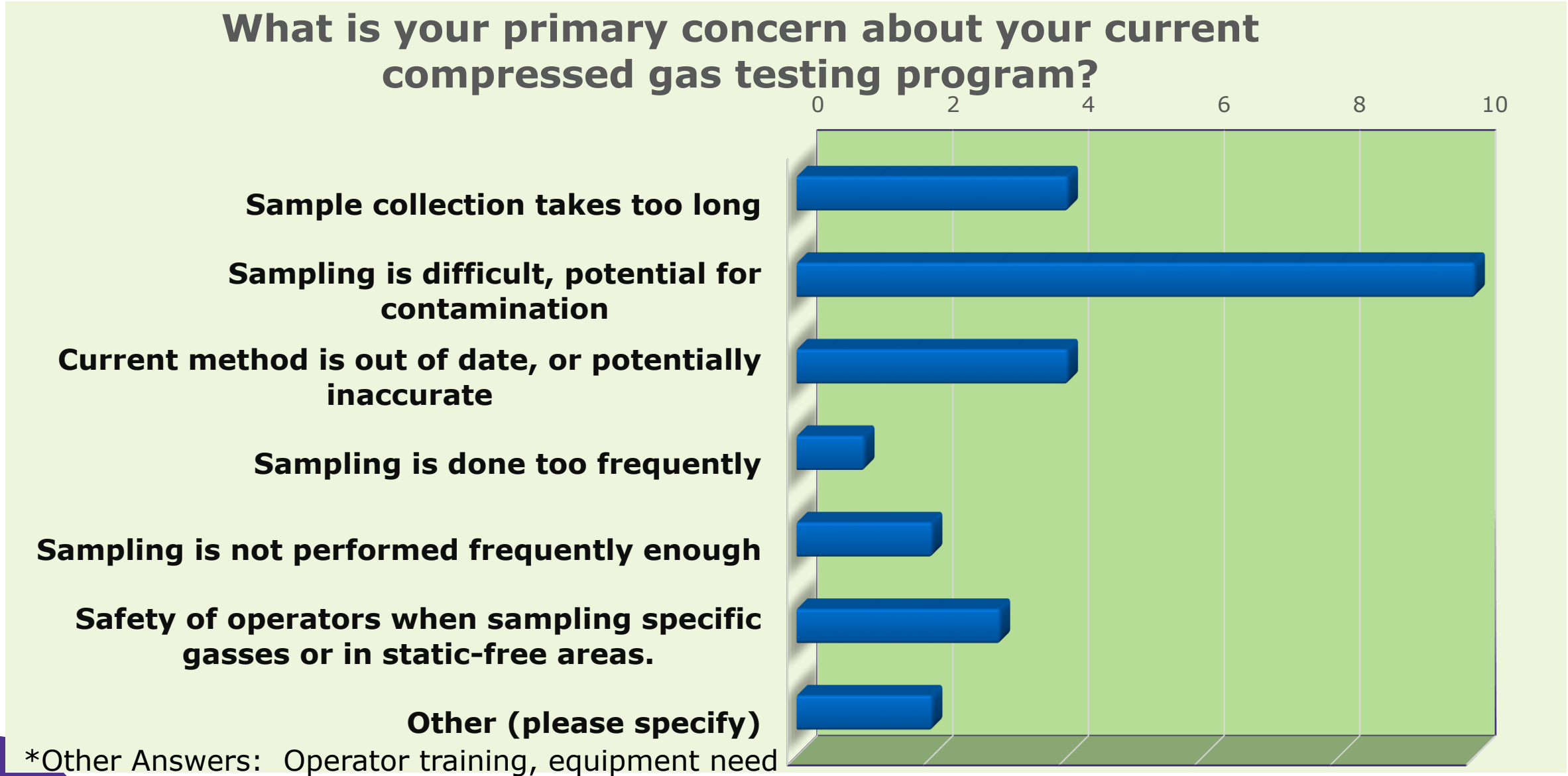

*Other Answers: Operator training, equipment need

Key Findings

- Majority of respondents are monitoring compressed gases at least once per month, or more
- Surprise in common use of filtration and direct impaction methods
- Not all manufacturing in ISO Class 5 are monitoring per each shift
- Trend is to evaluate current compressed gas testing program
- Main concerns include:
  - Sampling is difficult
  - Sampling is time consuming
  - Sample method is out of date

MAS 100 CG EX (Explosion Proof)

- Sample is taken under pressure, ensuring full air flow regulation
- Automatic Decompression cycle ensures sample accuracy
- In accordance with the guidelines for pressure vessels 97/23/EG
- SNCH 02 ATEX 3418 guidelines for explosion risk areas
- Utilizes Standard 90mm plates
- 5 compressed gas types are pre-programmed (including oxygen)

Q&A Session

Thank You!