QUANTUM: MULTI-PURPOSE LYO PROCESS QUANTITATION, ANALYSIS & CONTROL

Speaker
Arnab Ganguly, Ph.D. Technology Manager at IMA Life North America (Freeze Drying division)
Alan Rhoden, Ph.D. PAT Manager, Manufacturing Process Analytics and Control at Pfizer Inc.

| **April 9, 2018**

Lyo Process Development

IMA WEBINAR

QUANTUM: MULTI-PURPOSE LYO PROCESS QUANTITATION, ANALYSIS & CONTROL

Challenges in freeze drying

From the FDA's guideline on freeze-drying process (UCM074909)

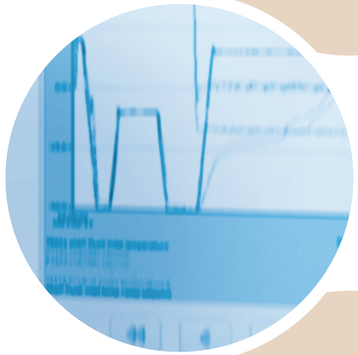
- "It is necessary to **monitor the leak rate** periodically to maintain the integrity of the system. It is also necessary, should the leak rate **exceed specified limits**, to determine the actual leak site for purposes of repair."
- "Leakage into a lyophilizer may originate from various sources. As in any vacuum chamber, leakage can occur from the atmosphere into the vessel itself. Other sources are media employed within the system to perform the lyophilizing task. These would be the **thermal fluid circulated through the shelves** for product heating and cooling…"

Challenges in freeze drying

- **Silicone oil detection**
  - Silicone oil can originate from silicone oil shelf circuit or from the product itself (stoppers)
  - Small leakage in large system can be hard to detect
  - Once detected, not only the last produced batch may be lost, as suspicion can be raised on previous batches too
- **Vacuum leaks**
  - Vacuum system must be monitored periodically
  - Searching for vacuum leak is always a time consuming operation impacting the turn around time
- **Monitoring primary and secondary end points**
  - Present solutions are indirect measurements with insufficient accuracy
  - Absence of methods to determine secondary drying end point with quantification of residual moisture

QUANTUM - Mass Spectrometer

PROCESS: PRIMARY AND SECONDARY DRYING



PROCESS: NON AQUEOUS SOLVENTS

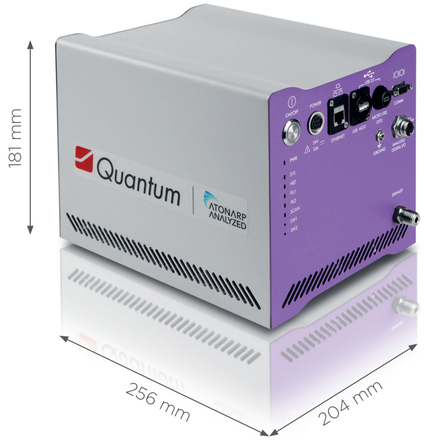
MOTIVATION

DETECT, **QUANTIFY** AND CONTROL

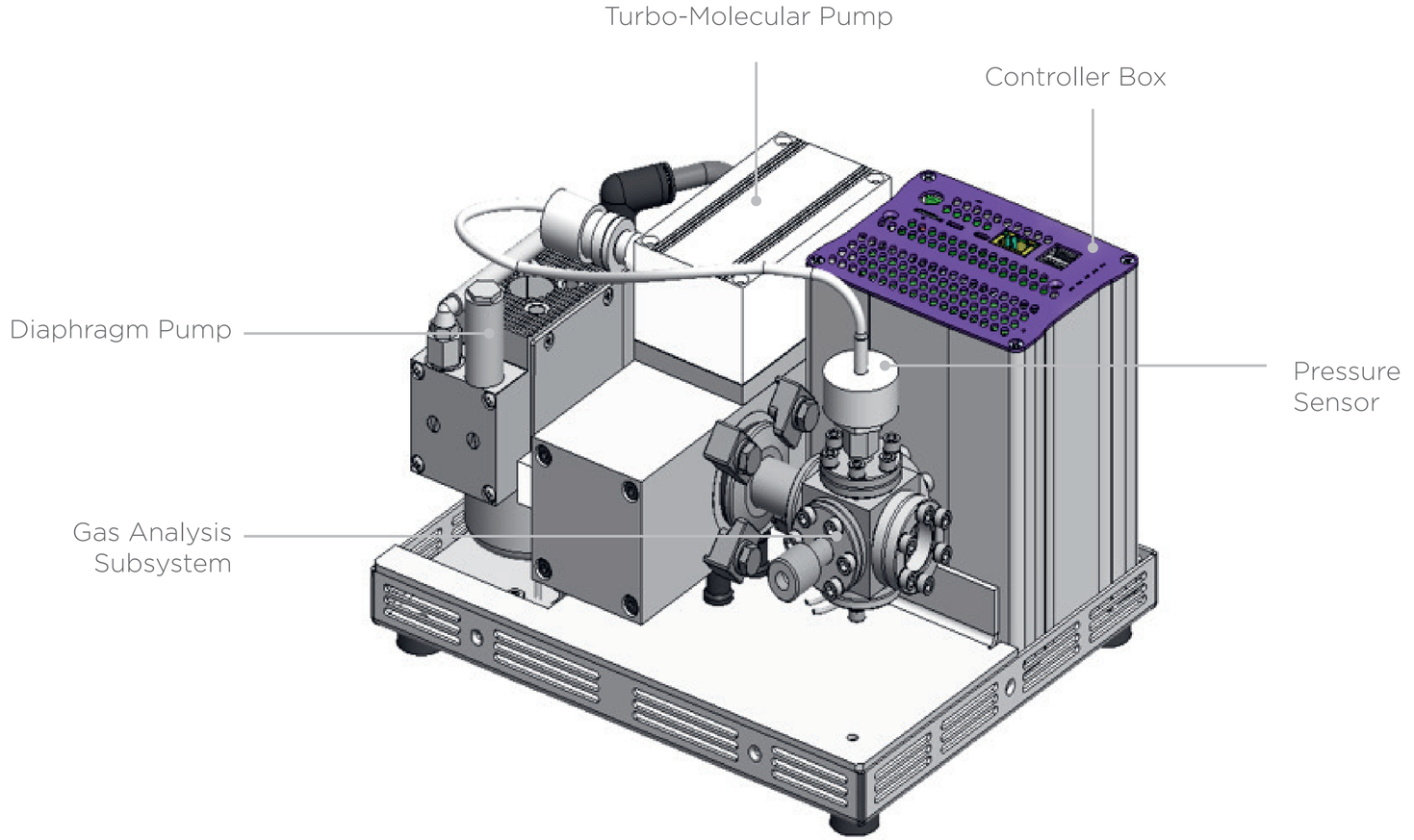
DETECTION: SILICONE OIL LEAKS

DETECTION: VACUUM LEAKS

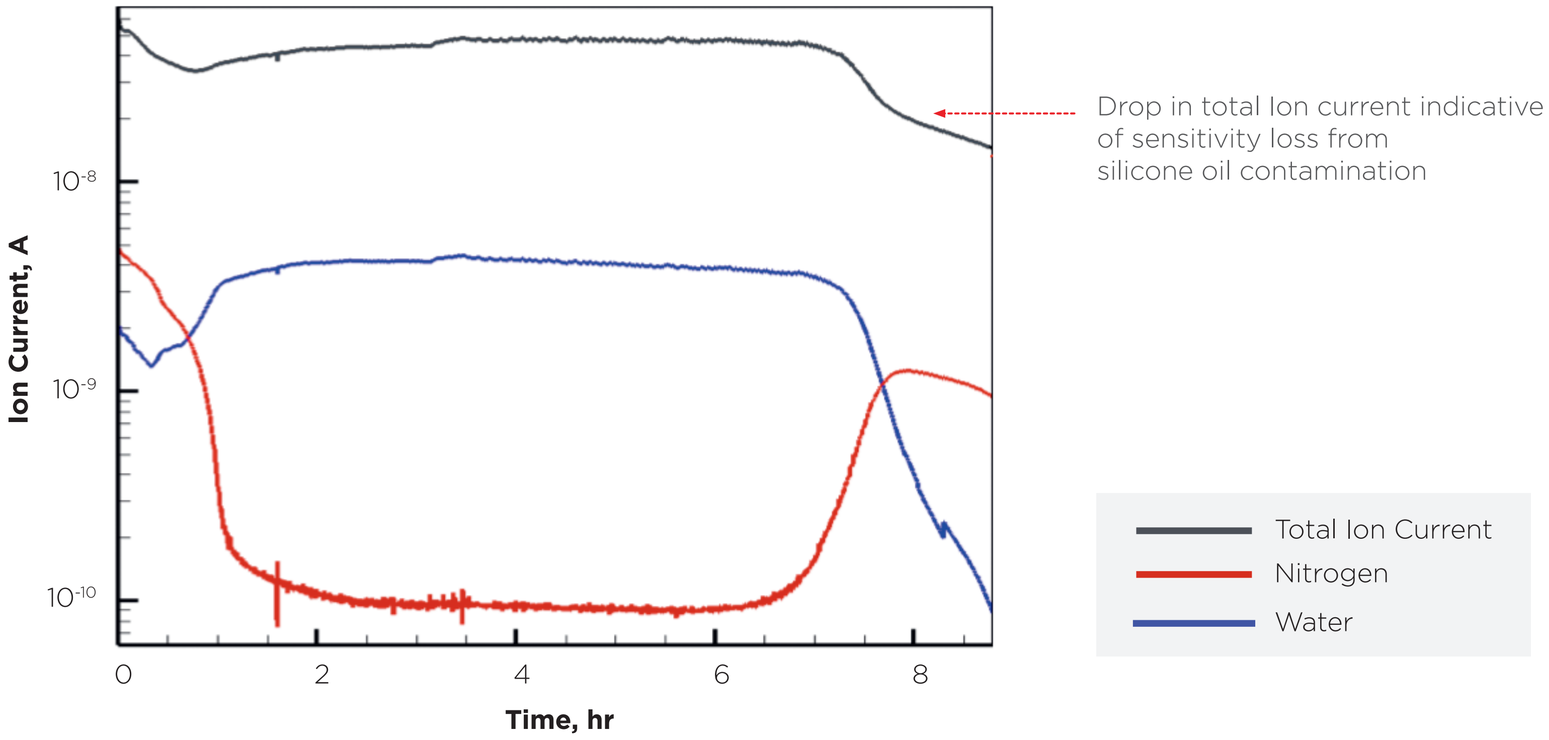
QUANTUM - Mass Spectrometer



QUANTUM Mass Spec Sensor Unit:
Ion Source + Mass Filter + Faraday Cup



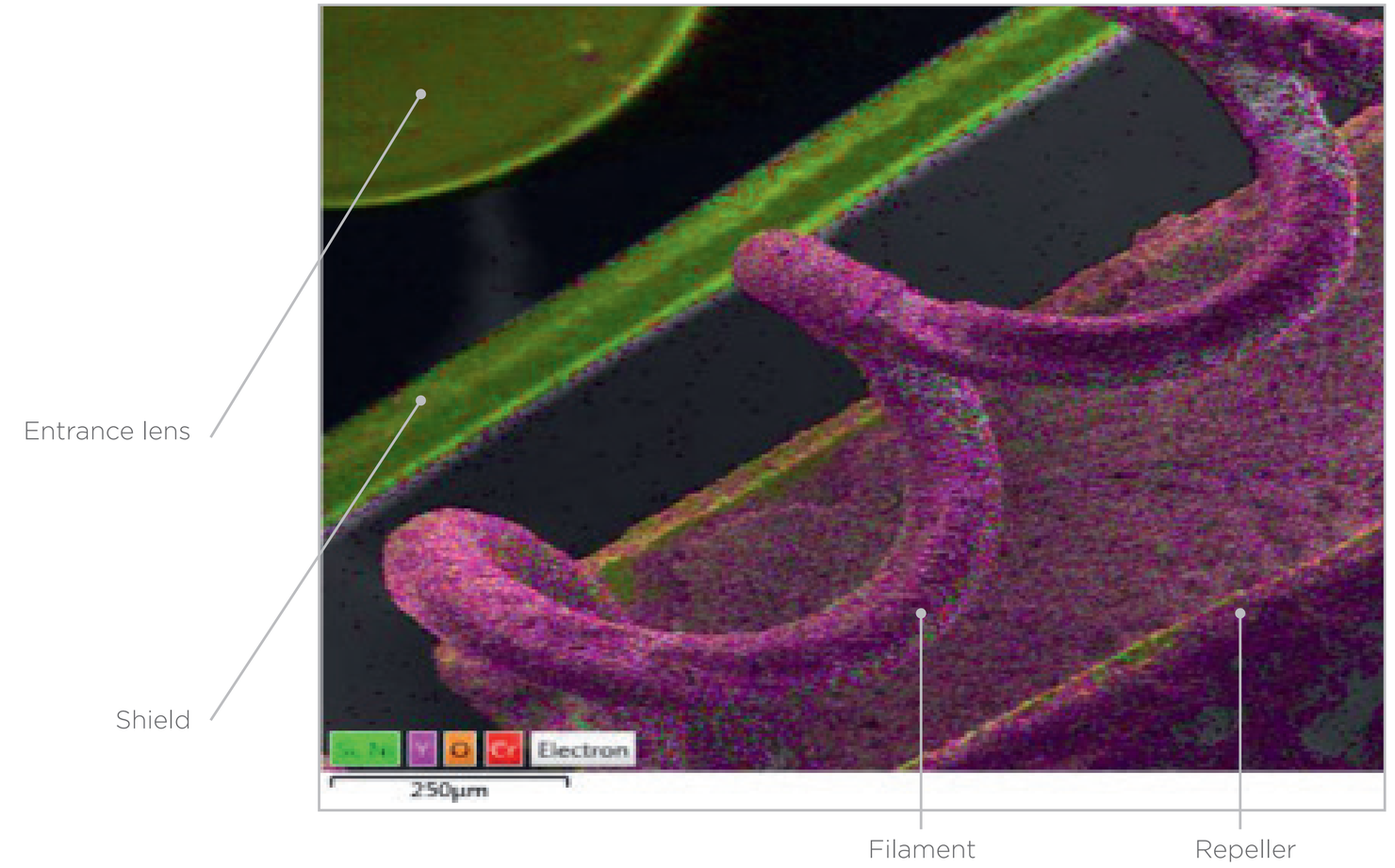
Silicone oil contamination detection



The challenge in detection of silicone oil in application to freeze drying lies in the apparent loss in sensitivity due to the formation of silicone oxide over time.

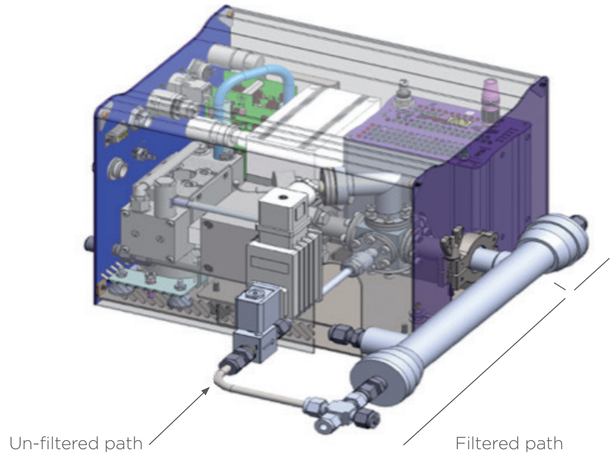
Destructive Testing of Mass Spec

- A destructive test was performed on the mass spec
- The mass analyzer was destructively disassembled
- Subjected to SEM-EDS for elemental composition analysis

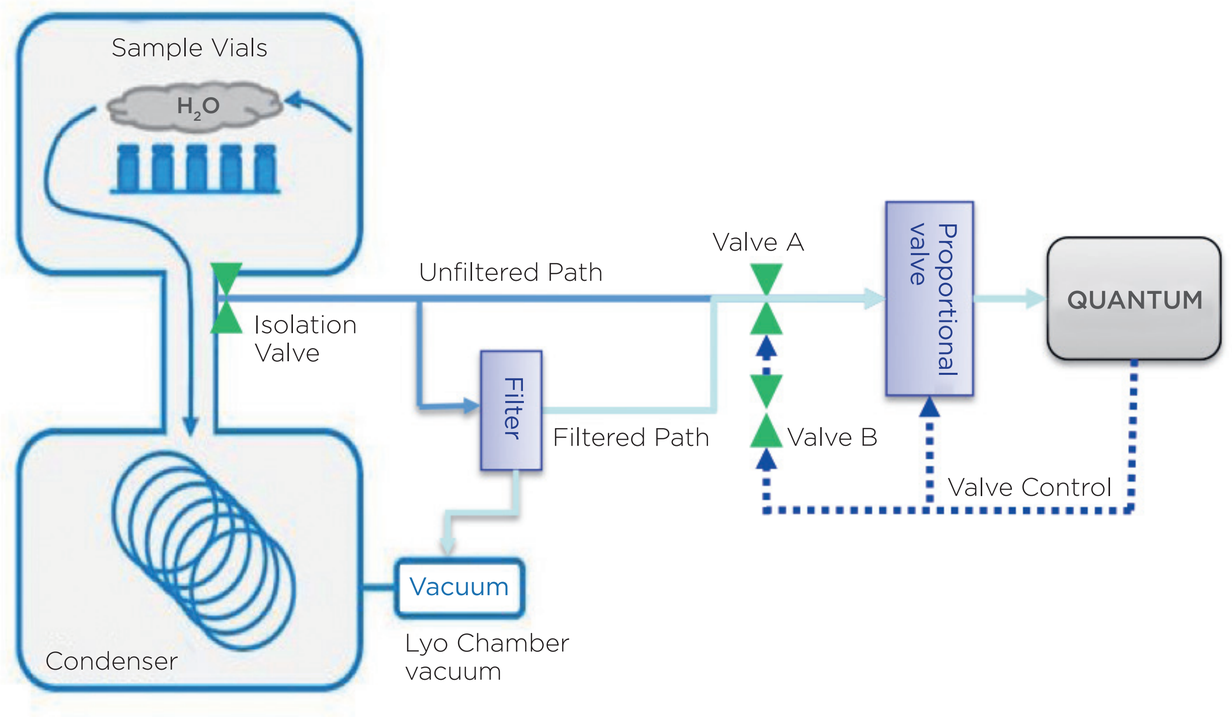


EDS analysis revealed coating of silicone inside the analyzer even in trace concentration exposure, leading to drop in sensitivity.

QUANTUM - Filtering system




Filter

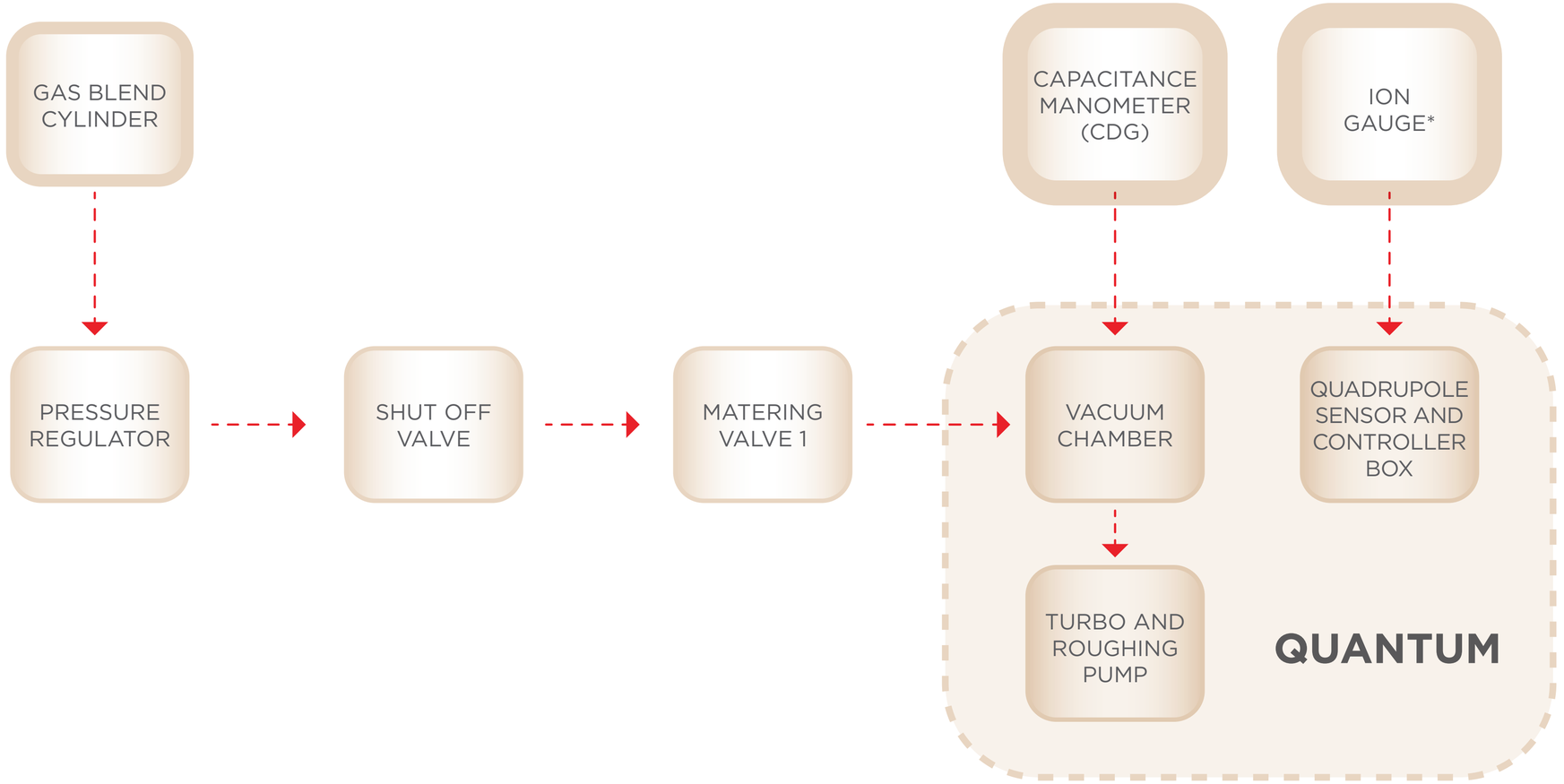


A filter is added to the system to prevent silicone oil contamination.
In absence of such filter, the detector would need to be periodically replaced.

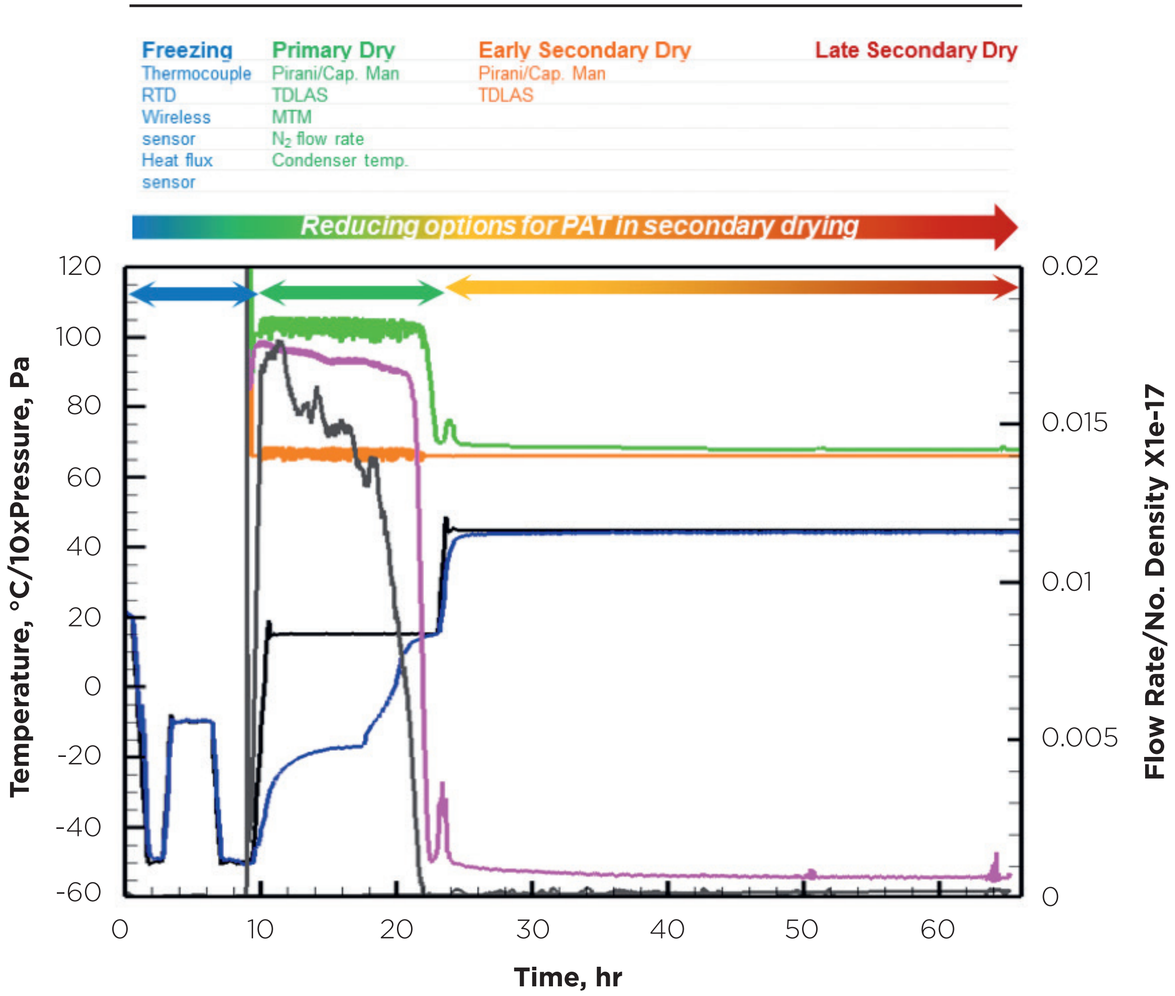
QUANTUM - A customized device

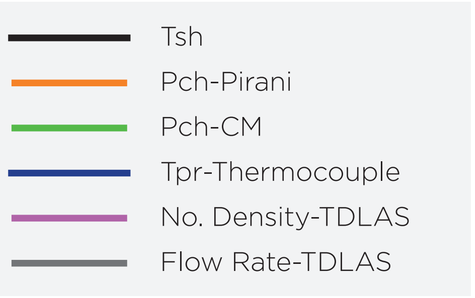
Specification/feature	Quantum	Other MS solutions	Benefits
Silicone oil filter	Patented micro pore silicone oil filter selectively blocks oil contaminants	No filter solution	• Prevents mass spec sensor from build-up of silicone oil. Increases reliability and extends period between maintenance
Quantitative and accurate	**Operates at 1mTorr** (1.3µbar) allowing QUANTUM factory **calibration against gold standard Capacitance Diaphragm** Gauge for quantitative pressure measurements	Semi-quantitative	• Guaranteed quantitative measurements • Highly accurate • Less calibration required
Ultra-Compact suitability for system retrofit	**Small size** ~0.01m^3 with integrated vacuum pumps. Higher operating pressure	External pumps required lower operating pressure	• Small highly integrated system enables quick and easy retrofit of lyophilization chambers bringing mass spec benefits to exiting capital equipment owners
Faraday Cup detector No drifty Electron Multiplier	Increased sensitivity to 5x10^{-13} Torr	Electron multiplier requires lower pressure	• FC offers similar accuracy to EM but measurements are highly reproducible w/ much less calibration and high system up-time
Cloud-Connectivity	Data analytics and chemometrics options in development using cloud-based data services	No solution	• Capital efficient services based deployment model • Facilitates ‘future proof’ tool deployment • Remote tool configuration for process improvement

QUANTUM - Factory Calibration Setup

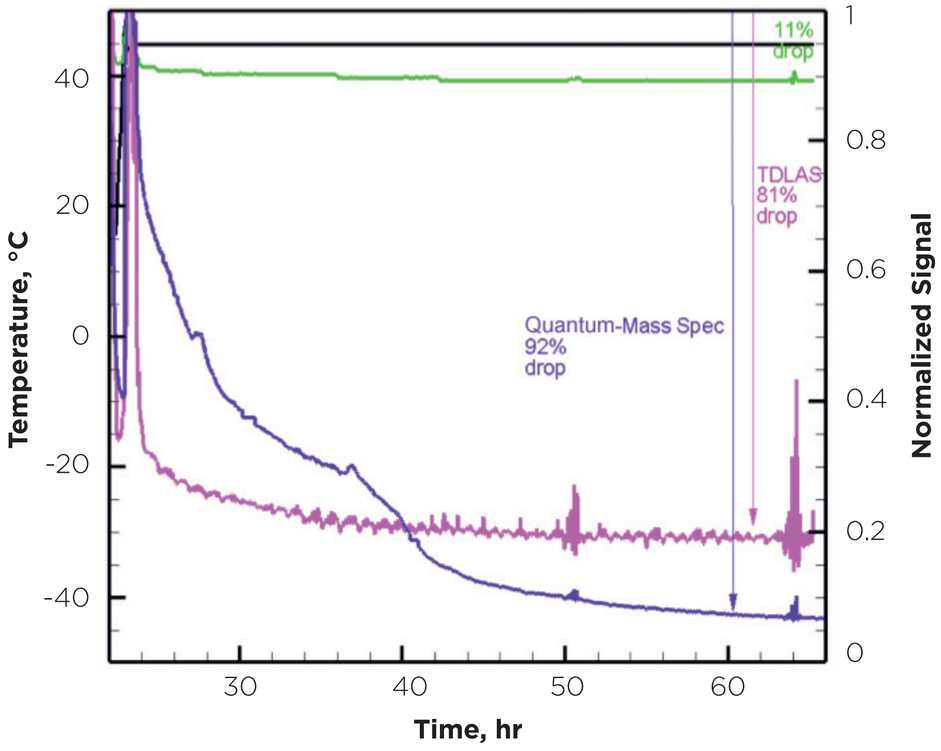


* Ion gauge used primarily to set the zero of the CDG (capacitance manometer)


Freezing
Primary Dry
Early Secondary Dry
Late Secondary Dry
Thermocouple
RTD
Wireless
sensor
Heat flux
sensor
Pirani/Cap. Man
TDLAS
MTM
N_2 flow rate
Condenser temp.
Pirani/Cap. Man
TDLAS
Reducing options for PAT in secondary drying
Temperature, °C/10xPressure, Pa
Flow Rate/No. Density X1e-17
Time, hr
120
100
80
60
40
20
0
-20
-40
-60
0.02
0.015
0.01
0.005
0
0
10
20
30
40
50
60


Tsh
Pch-Pirani
Pch-CM
Tpr-Thermocouple
No. Density-TDLAS
Flow Rate-TDLAS

Comparison of Secondary Drying Signal Between Pirani/TDLAS and Mass Spec



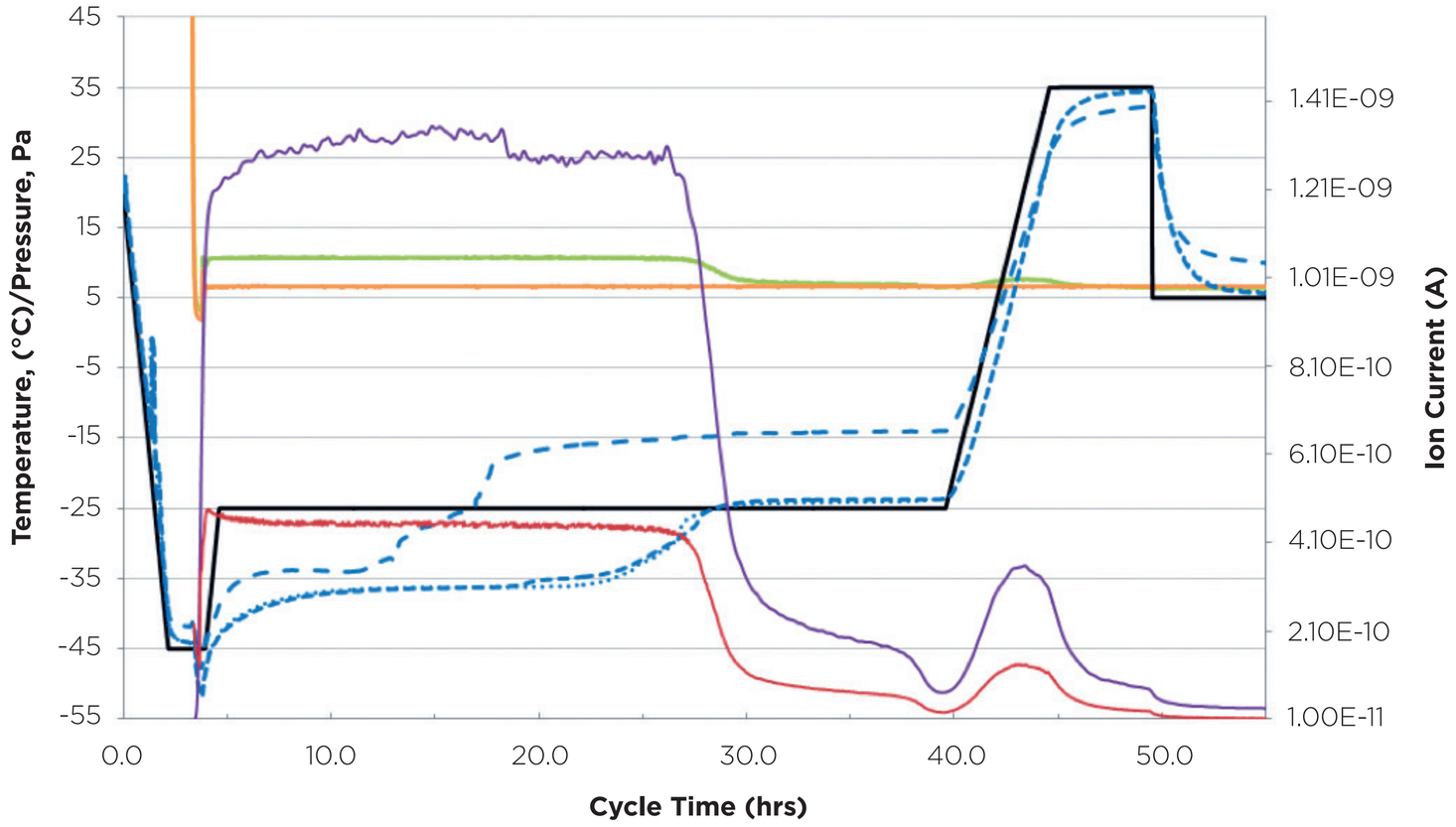
Tsh

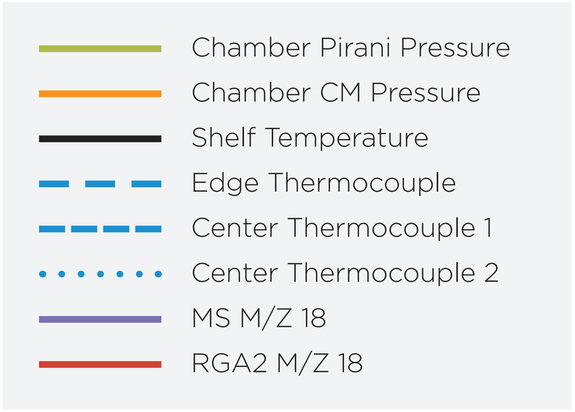
Norm-Pirani
(11% drop in signal)

Norm-TDLAS (No. Dens.)
(81% drop)

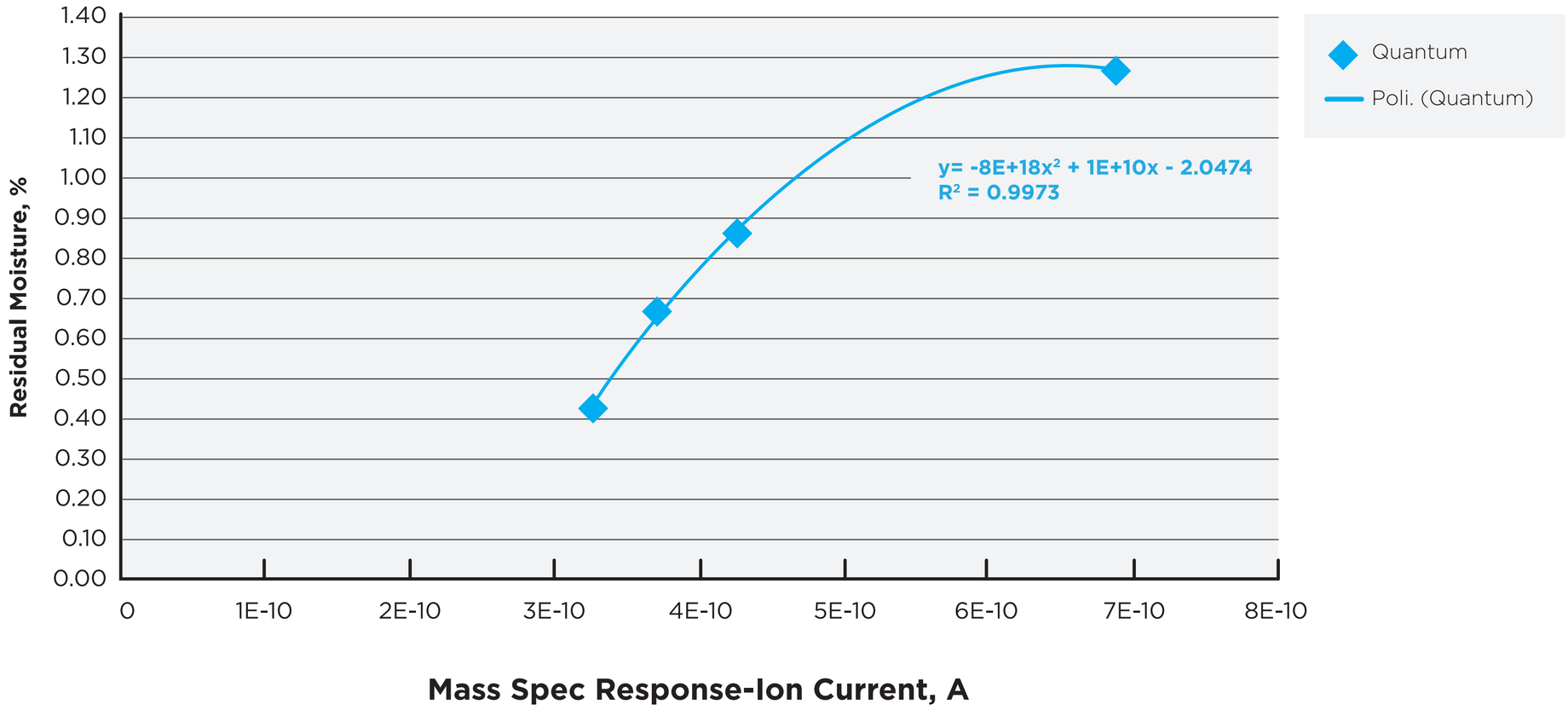
Norm Quantum
(92% drop)

5% Sucrose: Comparison of Secondary Drying Signal Between Pirani and Mass Spec

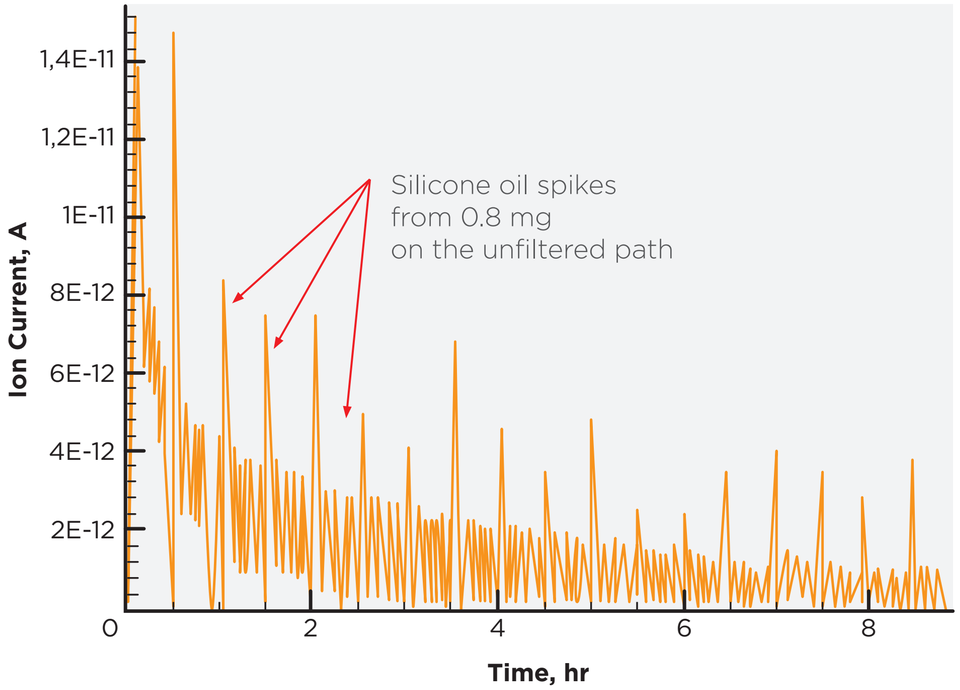


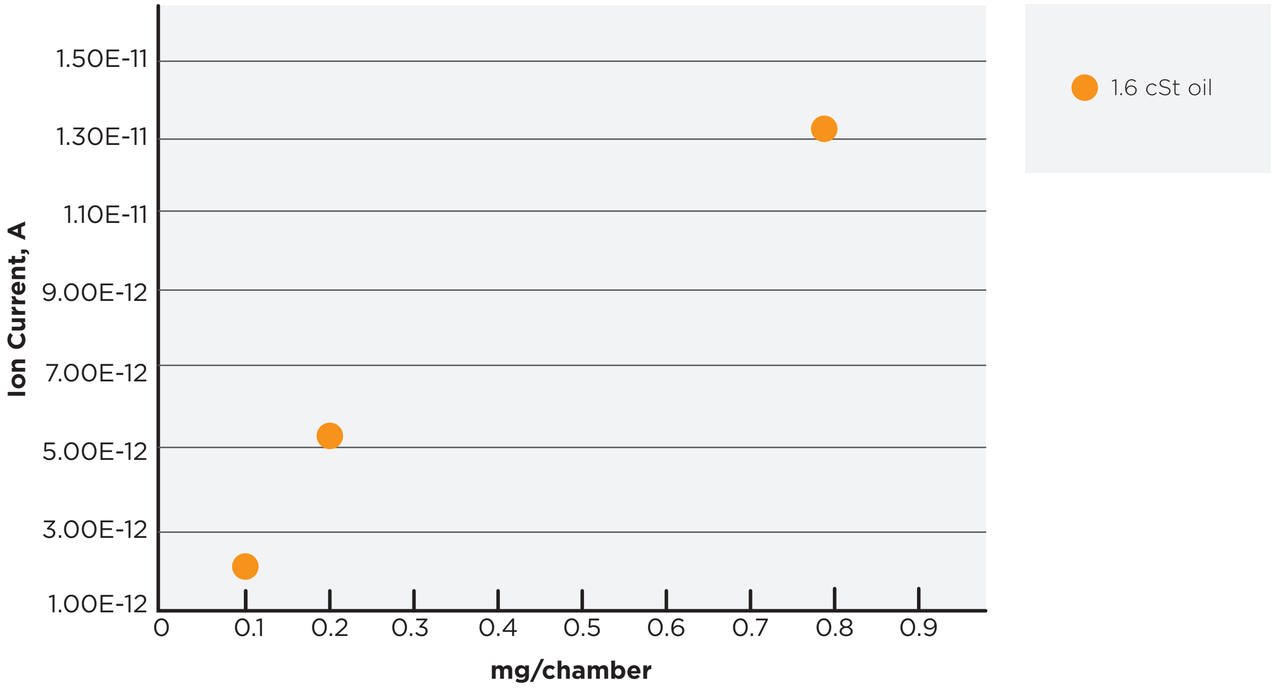


Mass Spec to predict residual moisture



Silicone oil calibration

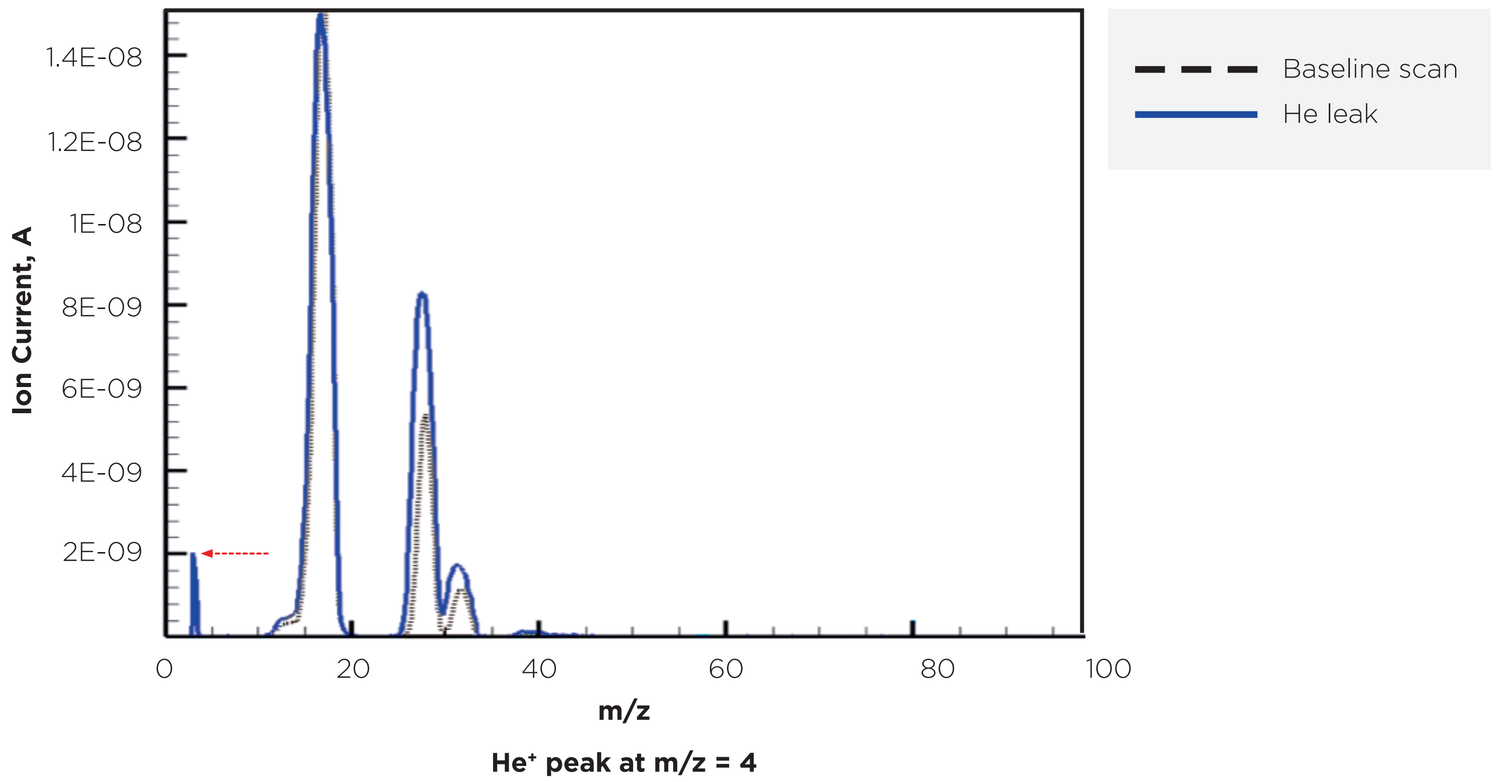




Detection down to 0.1 mg in 1.0 m^3 chamber

System leak check: He leak detection

- Detection and identification of system leaks are performed today using a cumbersome vacuum cart and He supply source
- This can be eliminated using a permanently mounted Mass Spec
- Tested here using an external He supply at the source of the leak and sensed using a mass spec system connected to the side of the production dryer chamber.



Operation modes: stand alone

- **Maintenance mode used for silicone oil and He leak detection**
  - Run Mass Spec pre CIP/SIP
    - Open valve to Mass Spec, run CIP/SIP, load batch
  - Not recommended for in process use (eg. water vapor)
  - Data sent to computer (picked by customer)
  - Alarms (visual) generated based on silicone oil levels

Operation modes: integrated

- **In process mode used for silicone oil, water vapor, He leak and non aqueous solvent detection**
  - Data sent to freeze dryer SCADA with historian backup
  - Alarms (visual) generated based on analyte levels directly on FD SCADA
  - Run Mass Spec pre CIP/SIP or during cycle in continuous operation

Quantum

Thank you for your attention!

Questions?

lab4life@imalife.com

Aseptic Processing & Freeze Drying Solutions