GLOBAL SUPPLY

The Utilization of Mass Spectrometry for Equipment and Process Monitoring in Lyophilization

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We make difficult choices, but we <u>never</u> compromise Quality, Compliance or Safety.

Acknowledgments

- Takeshi Sato, Principal Scientist, Atonarp
- Dave Debo at IMA Life
- Vamsi Mudhivarthi, IMA Life/Pfizer Inc.
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- Ben Lyons, Nicole Bundy, Jacob Pantazis, Pfizer Inc.

What we set out to do

Co-develop from the ground up a bespoke mini mass spectrometer that could be used to monitor Lyophilization; in particular, help us to determine the end point of primary and secondary drying. We also wanted a system that could be used to monitor for silicone oil leaks and be used as a way to perform He leak testing.

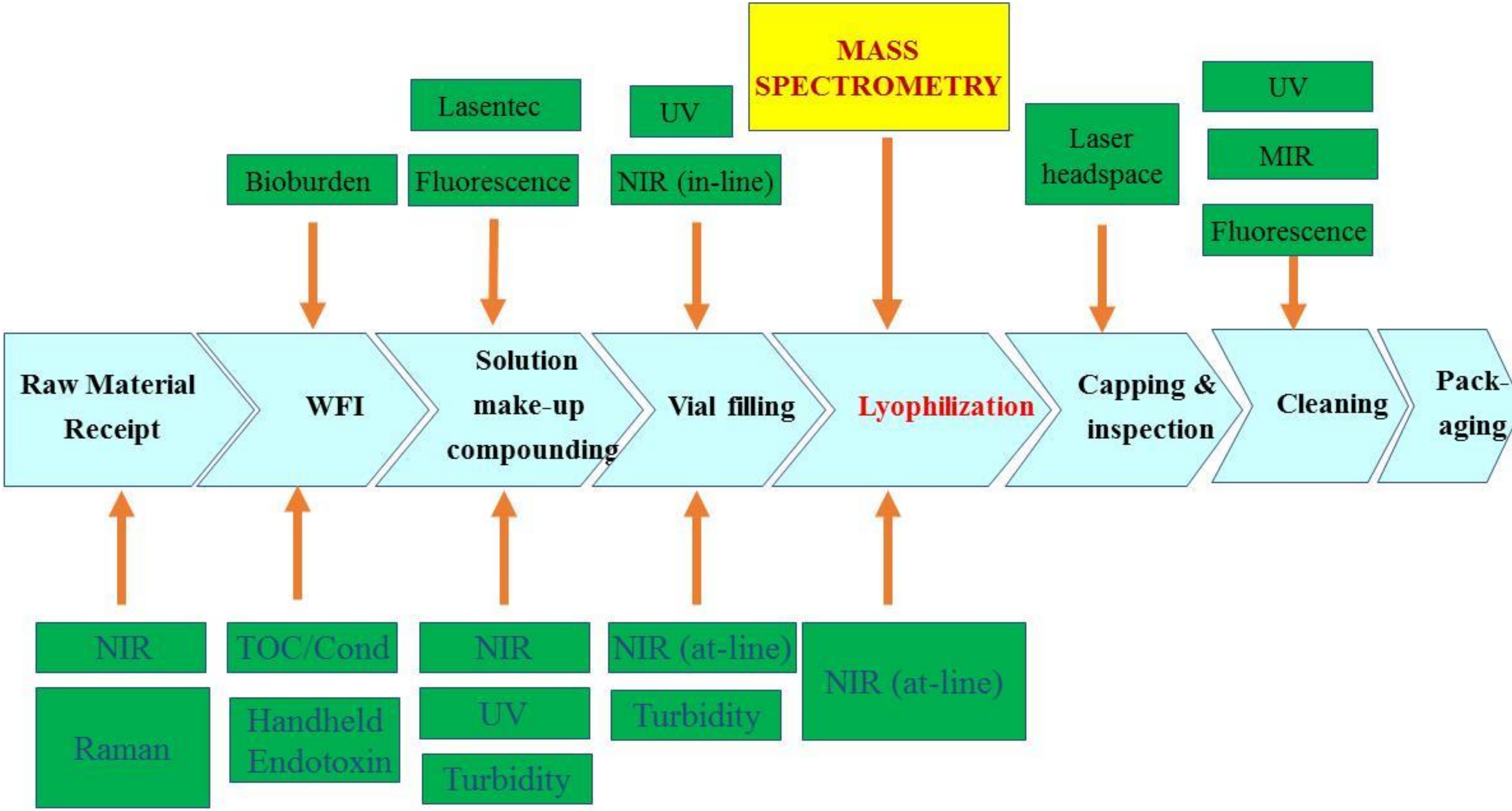
Process Analytical Technology - Definition

The FDA CGMP September 2004

PAT is considered to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

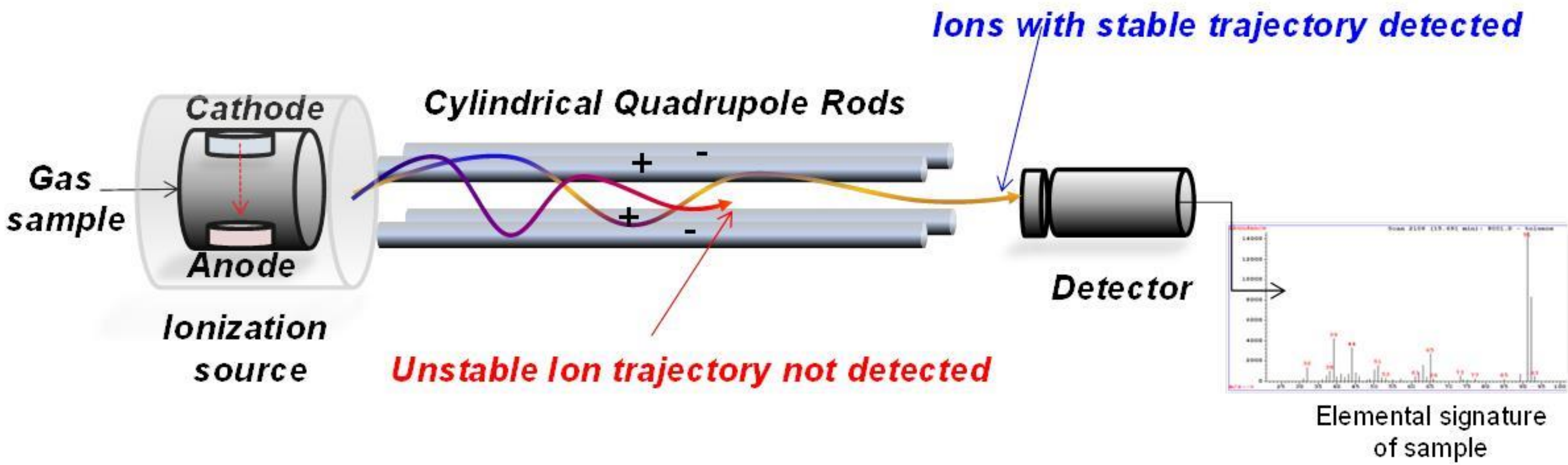
PAT is synonymous with process understanding

Application of PAT in support of Aseptic Manufacturing



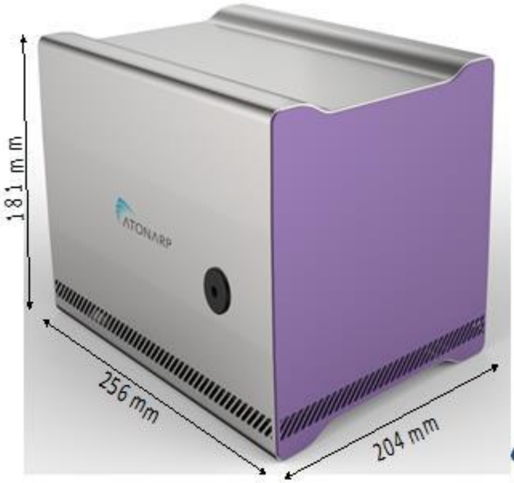
What is Mass Spectrometry?

- Method used to identify chemical species (example, gas composition) by measuring the mass-to-charge ratio (m/z) and partial pressure of gas-phase ions
- Spectra are plotted as m/z ratio vs. abundance (detector response)
- In pharma since early ’80s: Test sensitivity to detect silicone oils in trace concentrations in product chamber from heat transfer fluid, hydraulic fluids

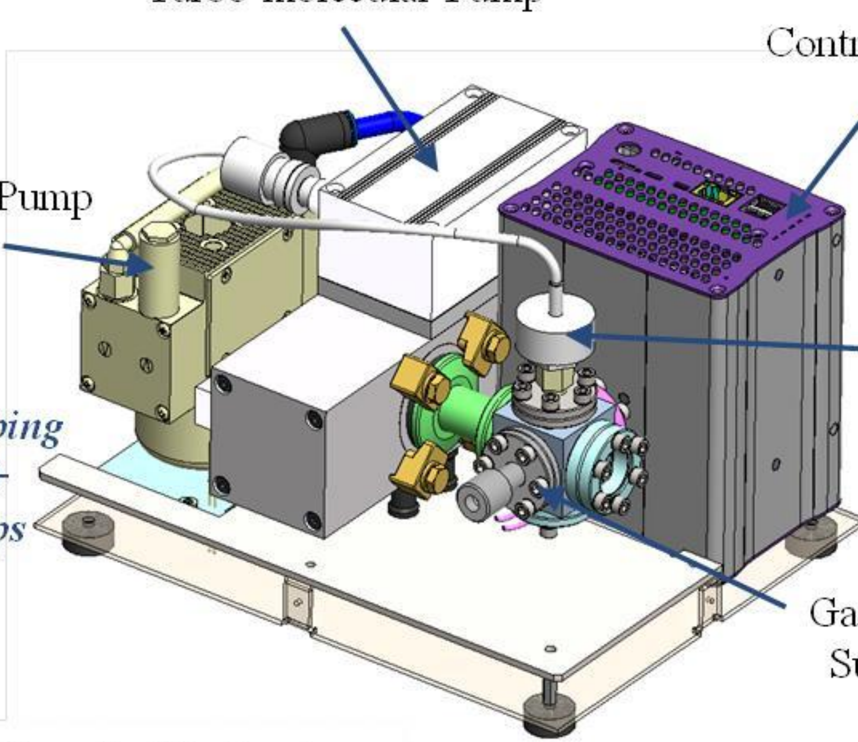


Mass Spectrometry: Why choose this technique?

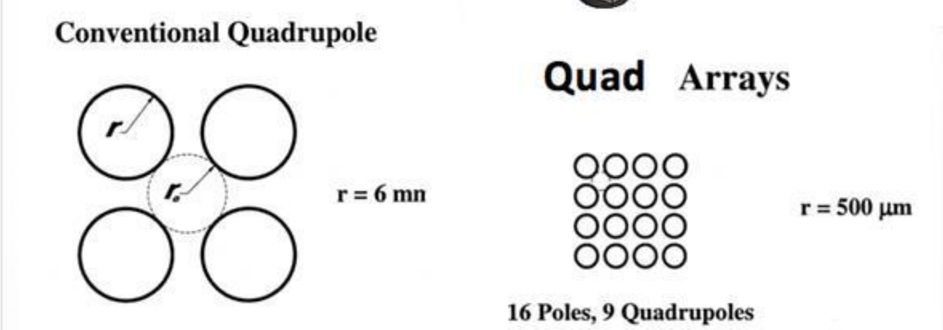
The AMS Mass Spectrometer



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

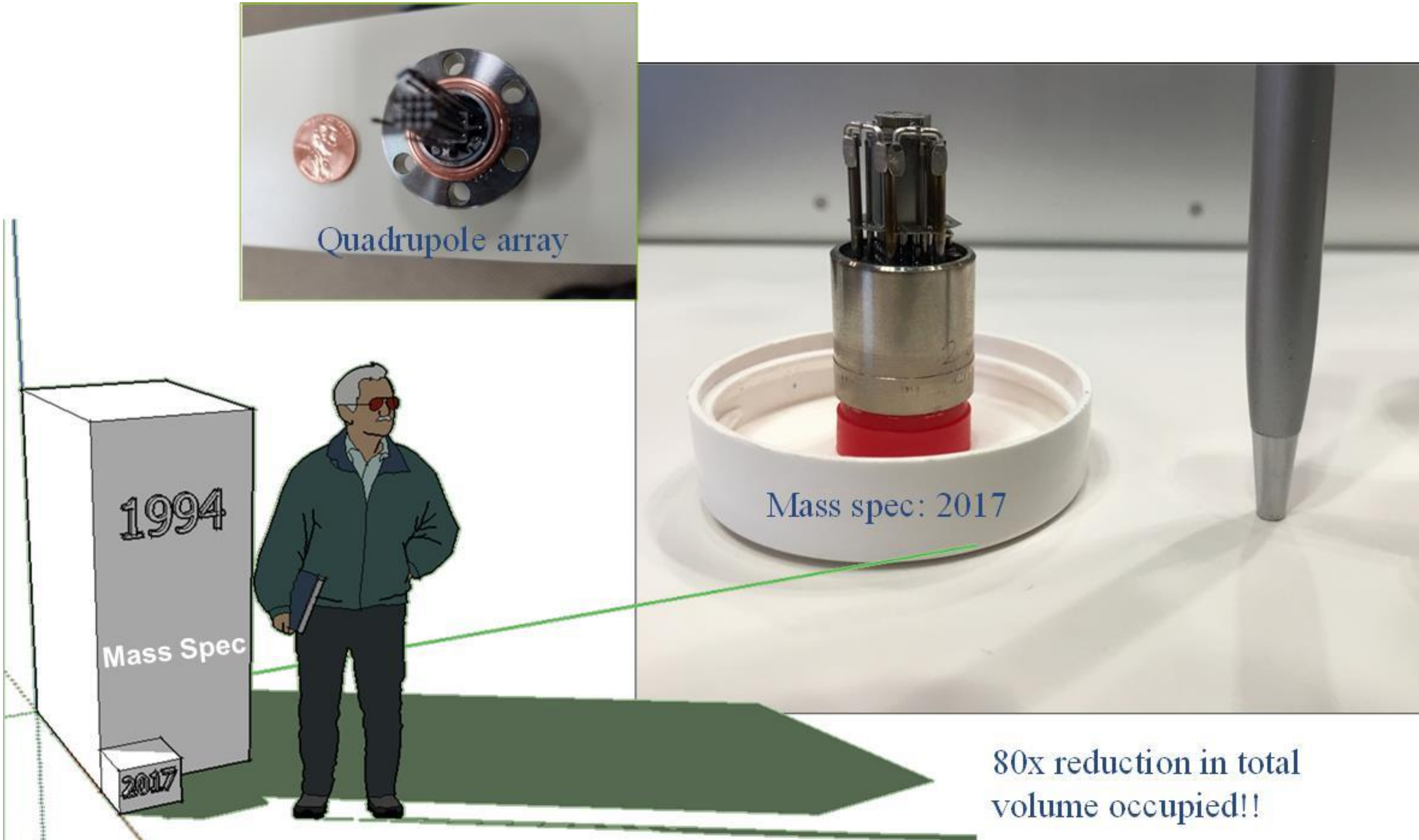


contained pumping system: Turbo + Roughing pumps



12x reduction in electrode size compared to any other quadrupole

1994 to 2017 Miniaturization



80x reduction in total volume occupied!!

Key Distinguishing Features

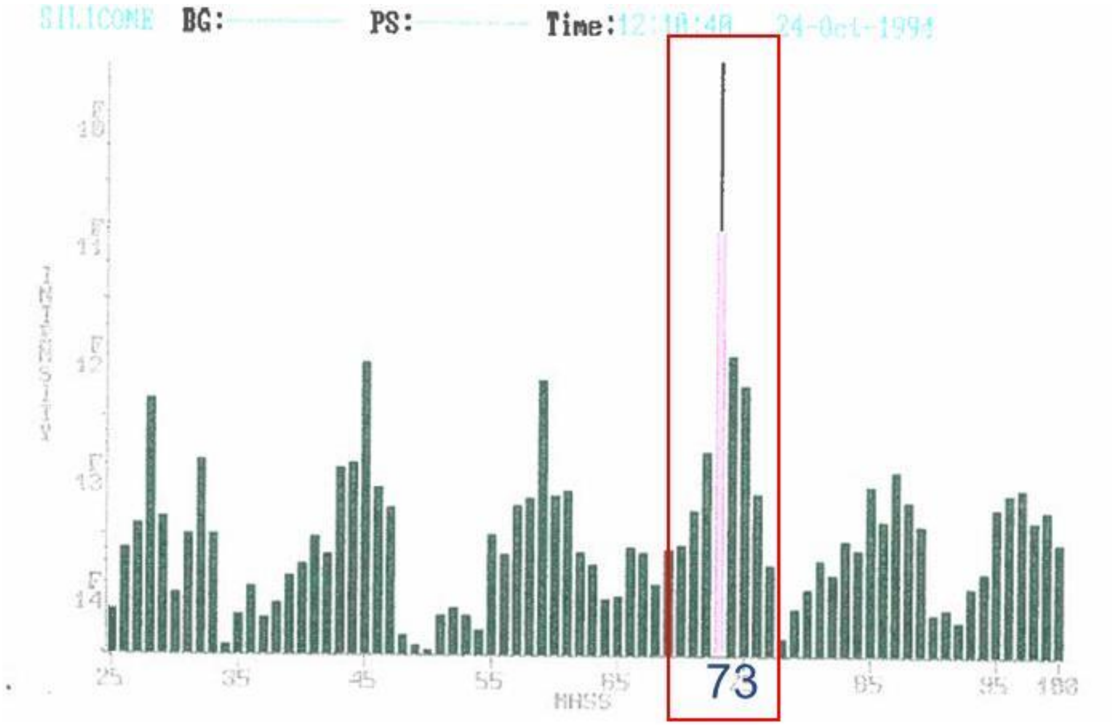
- Typical Residual Gas Analyzer (RGA) requires external pumps to operate at low pressure due to its bulky quadrupole design
- The AMS operates at high pressure (Three orders of Magnitude) due its miniature, distributed quad array,
  - larger number of gas molecules to be converted into +ve ions.
- Use of stable Faraday detector down to the ppm sensitivity
  - Typical RGAs with fewer cations require use of a Electron Multiplier as a detector down to the ppm sensitivity
- Small footprint
  - Integrated sensor componentry (ion source, quad array filter, FC detector)

Regulatory Stance for Leakage

- From the FDA's document on Freeze-Drying inspection (UCM074909)
  - "Leakage into a lyophilizer (freeze-dryer) may originate from various sources… These would be the **thermal fluid circulated through the shelves** for product heating and cooling…"
  - "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**…"

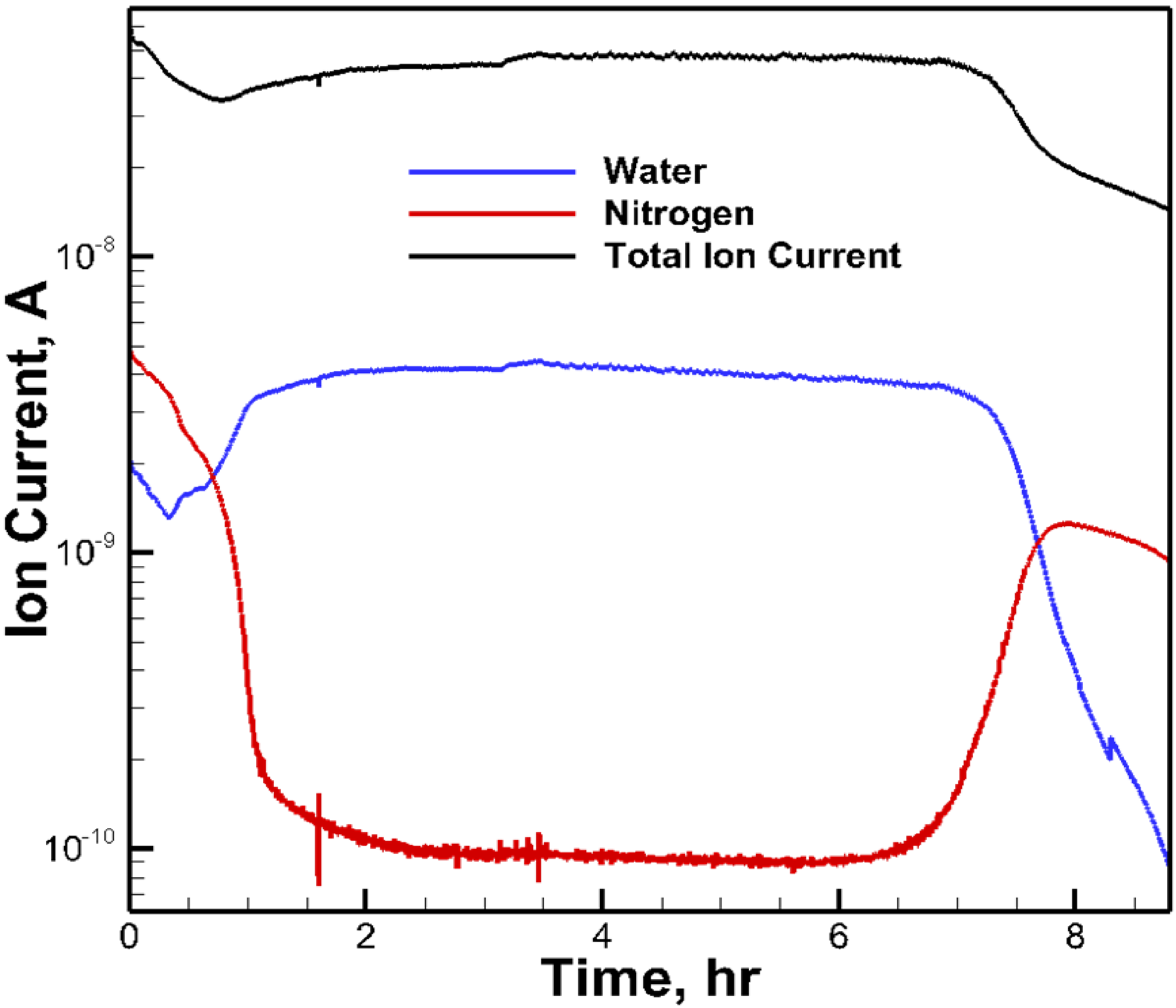
Detection of Silicone Oil

Mass Spectrograph



Implemented primarily for silicone oil mass 73 detection: successfully

Challenges: Need for application specific solution

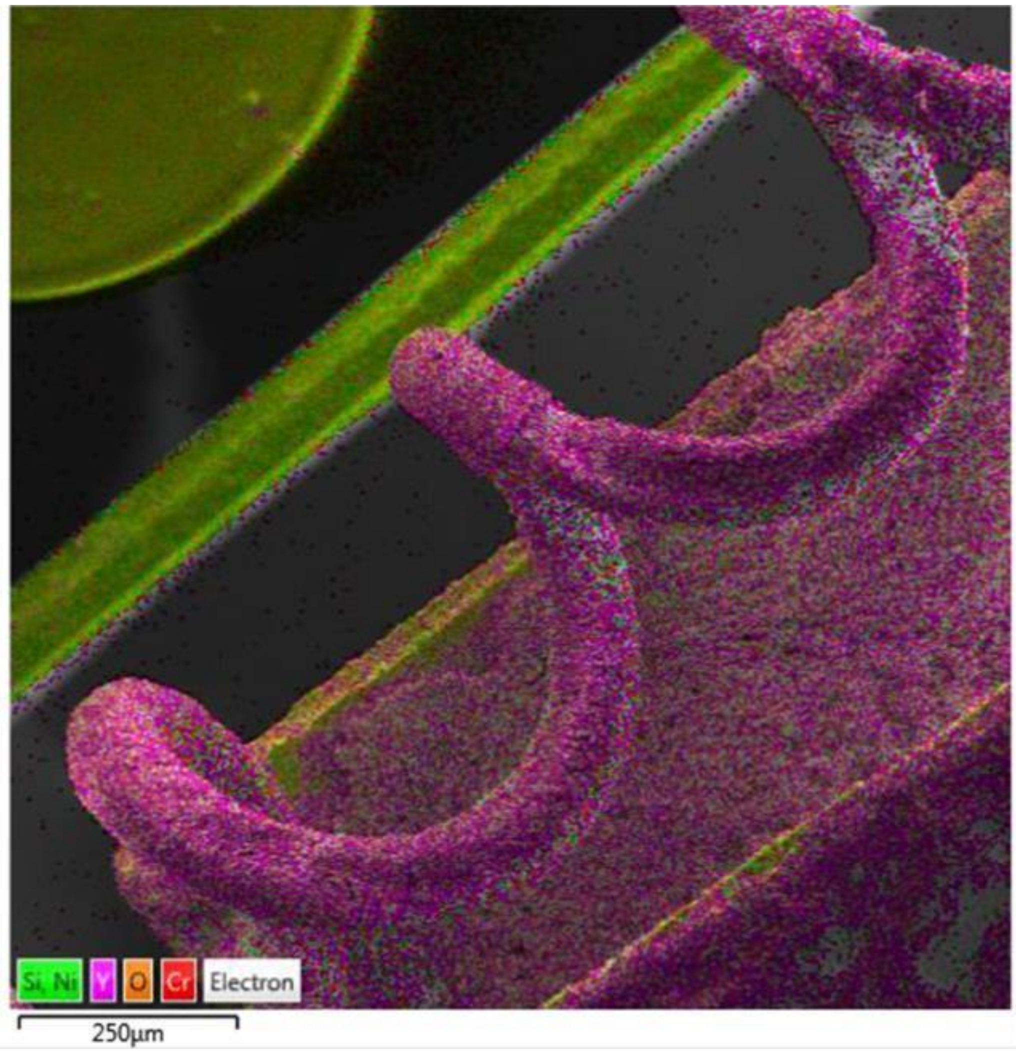


Drop in total ion current indicative of sensitivity loss from silicone oil contamination

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

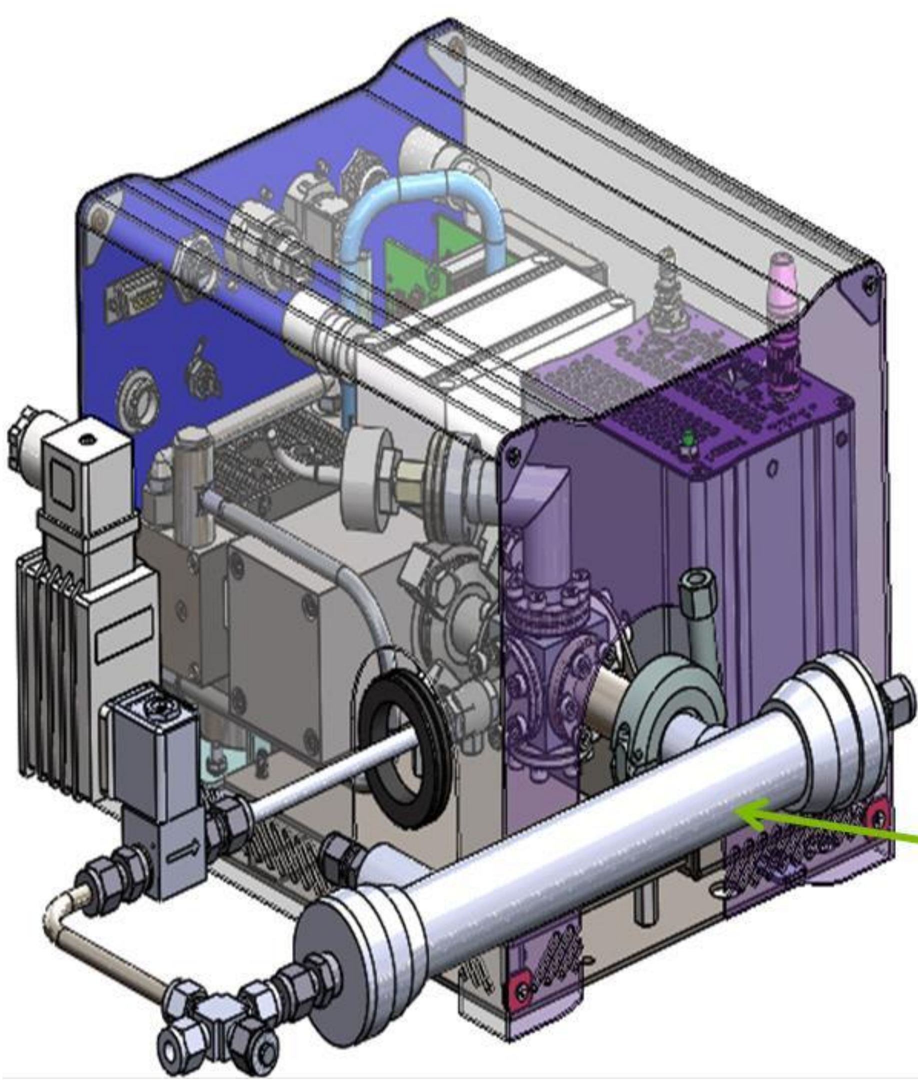
Analysis: Destructive Testing of Mass Spec

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

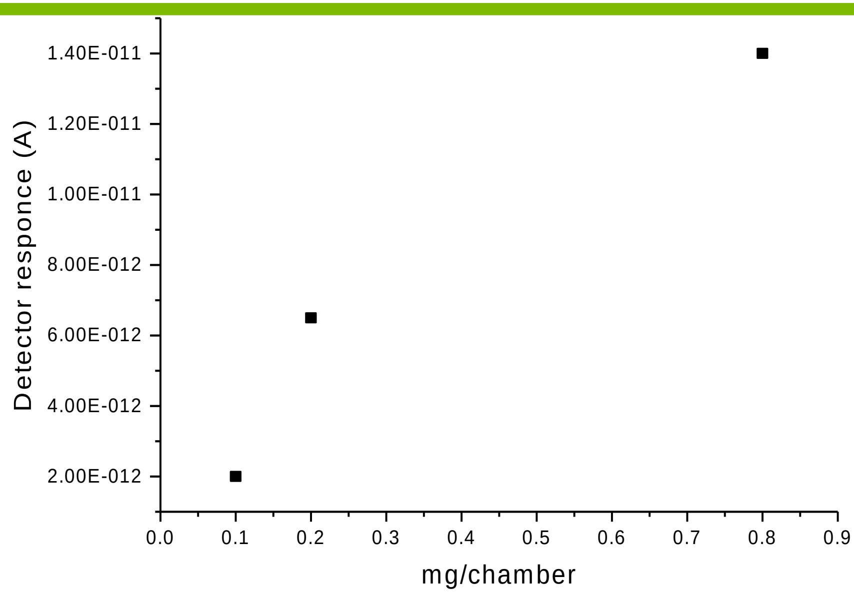


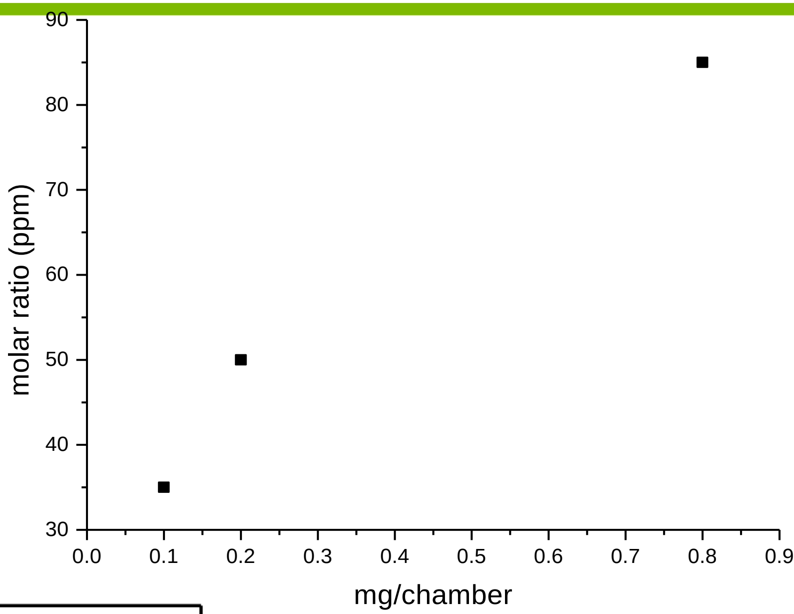
EDS analysis revealed coating of silicone inside the analyzer even in trace concentration exposure, leading to drop in sensitivity

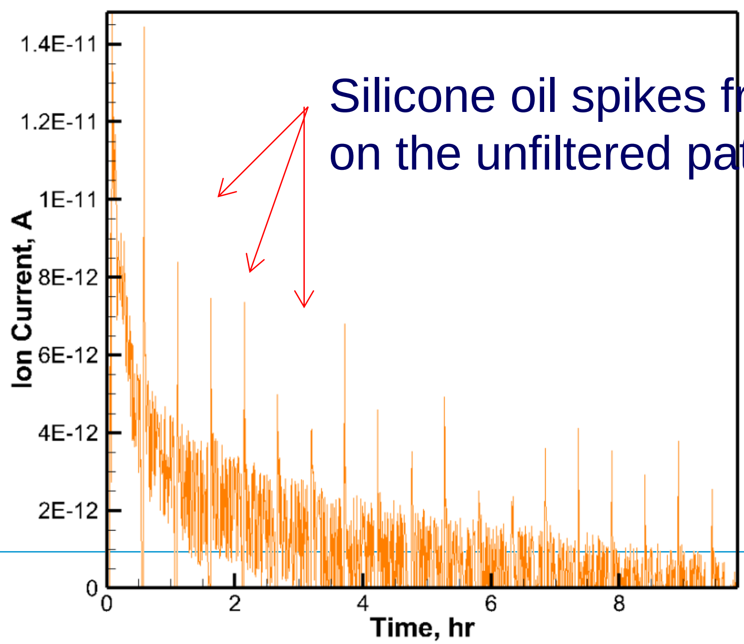
AMS with attached Silicone Oil Filtration System



Silicone Oil Calibration



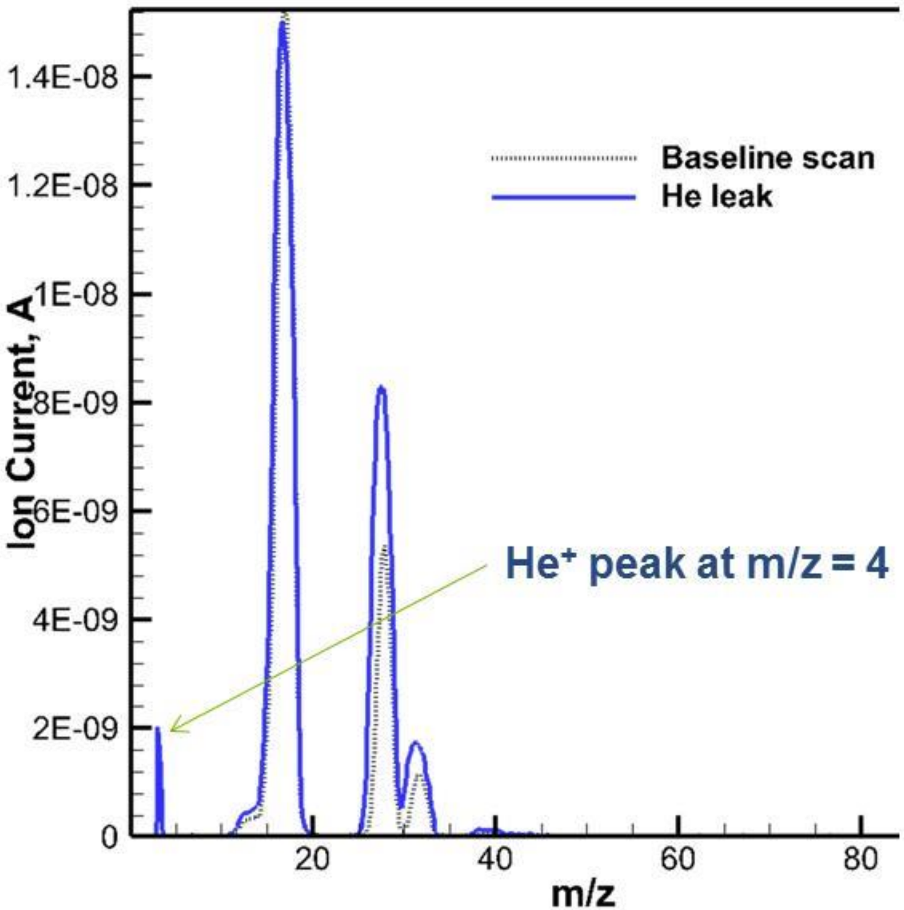




Silicone oil spikes from 0.8 mg on the unfiltered path

Detection down to 0.1 mg in 1.0 m^3 chamber

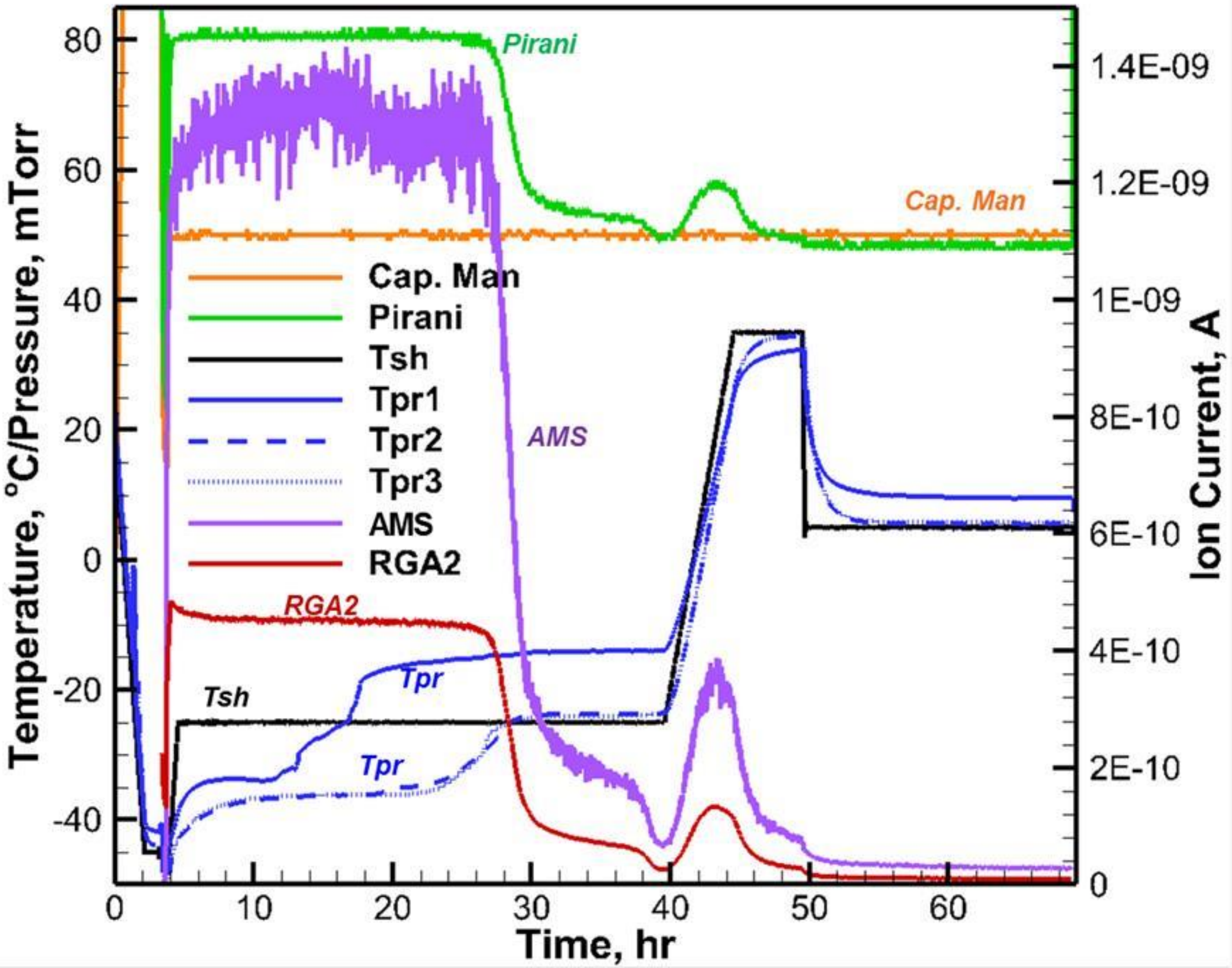
System Leak Check: He Leak Detection



- 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 three different mass spec/RGA systems connected to the side of the production dryer chamber

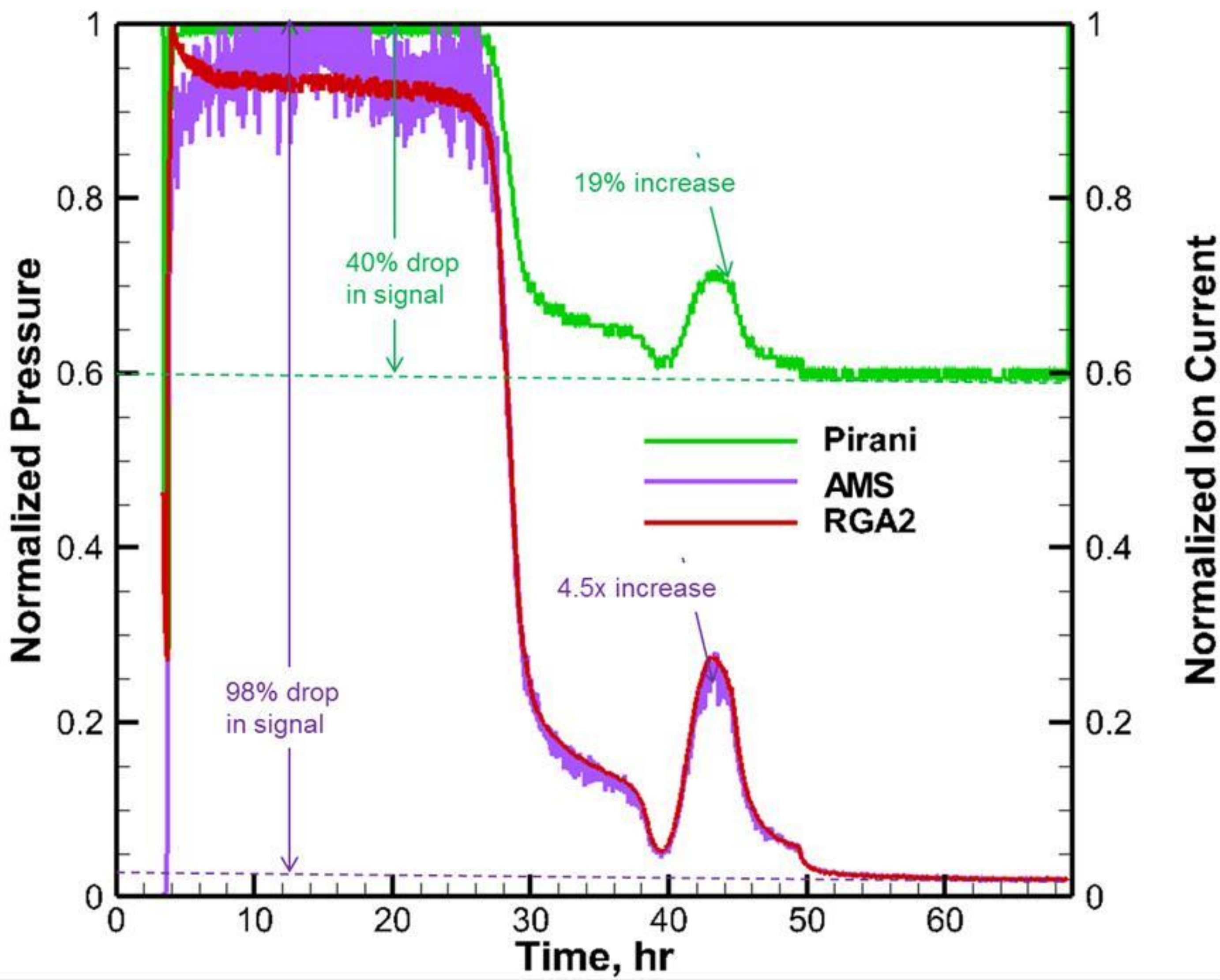
Cycle Monitoring: 5% w/v Sucrose, 2.7 mL fill in 20 mL vials

- Tsh(1^0 dry=-25 ˚C)
- Pch= 50 mT
- Tsh(2^0 dry= 35 ˚C)
- Ramp: 0.2 ˚C/min
- Product thermocouple locations
  - Tpr1: Edge
  - Tpr2: Center
  - Tpr3: Center



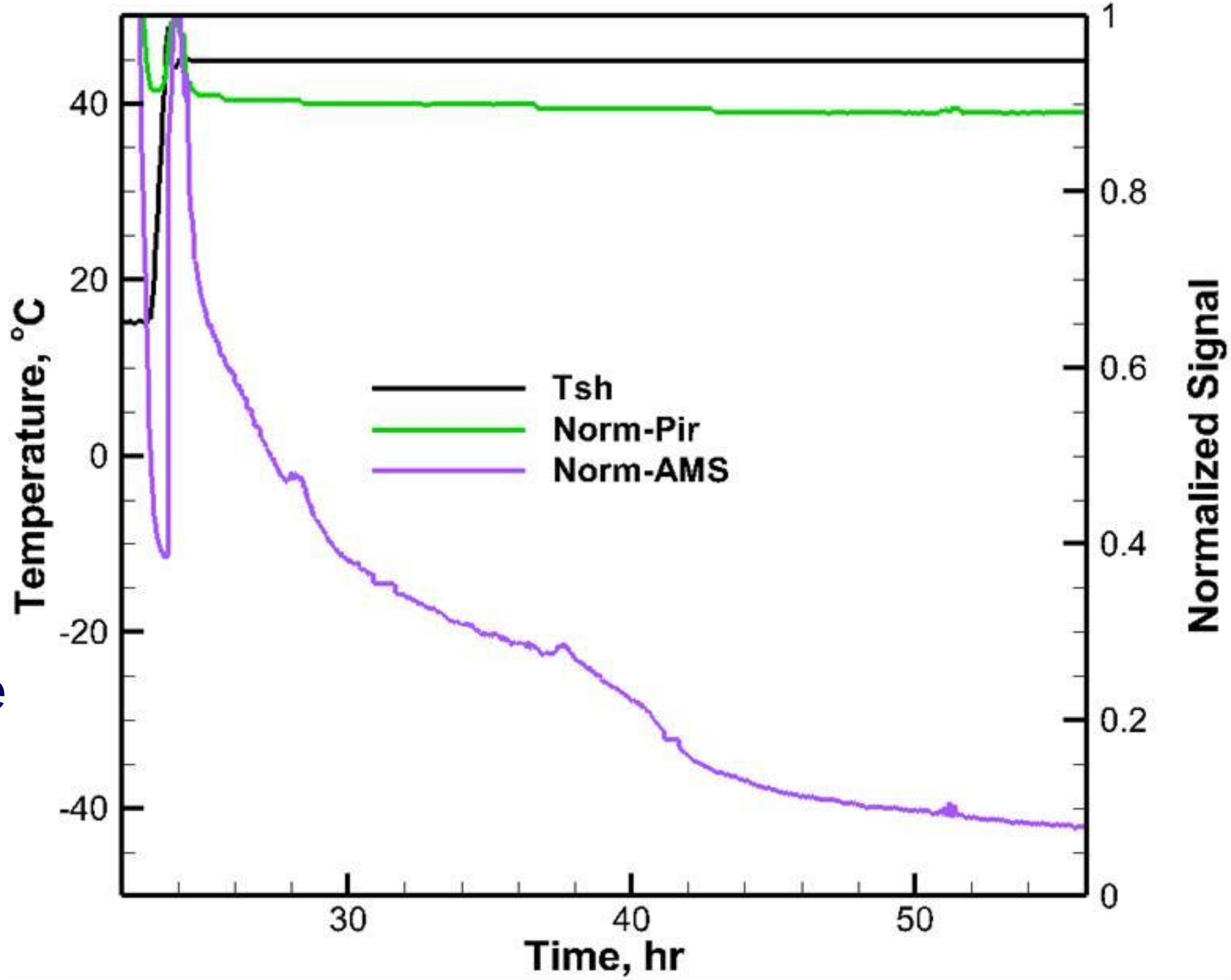
Normalized Data

- Data normalized by setting the largest value during the process to "1"
- Mass spectrometers can be used to monitor lyophilization processes real-time
- Primary and secondary drying end points can be determined



Comparison of Secondary Drying Signal Between Pirani and Mass Spec

- A key step during a lyo cycle is to determine when secondary drying is completed. It is also where Pirani technology is at the limits of its dynamic range.
- This can be demonstrated by comparing it with the water signal from a mass spectrometer, which shows continued water loss/drying after the Pirani has plateaued



Sample Thief Cycle: 5% w/v Sucrose, 2.7 mL fill in 20 mL vials

- Tsh(1^{0}dry=-25 ˚C)
- Pch= 50 mT
- Tsh(2^{0}dry= 40 ˚C)
- Ramp: 0.2 ˚C/min
- Product thermocouple locations
  - Tpr1: Edge
  - Tpr2: Center
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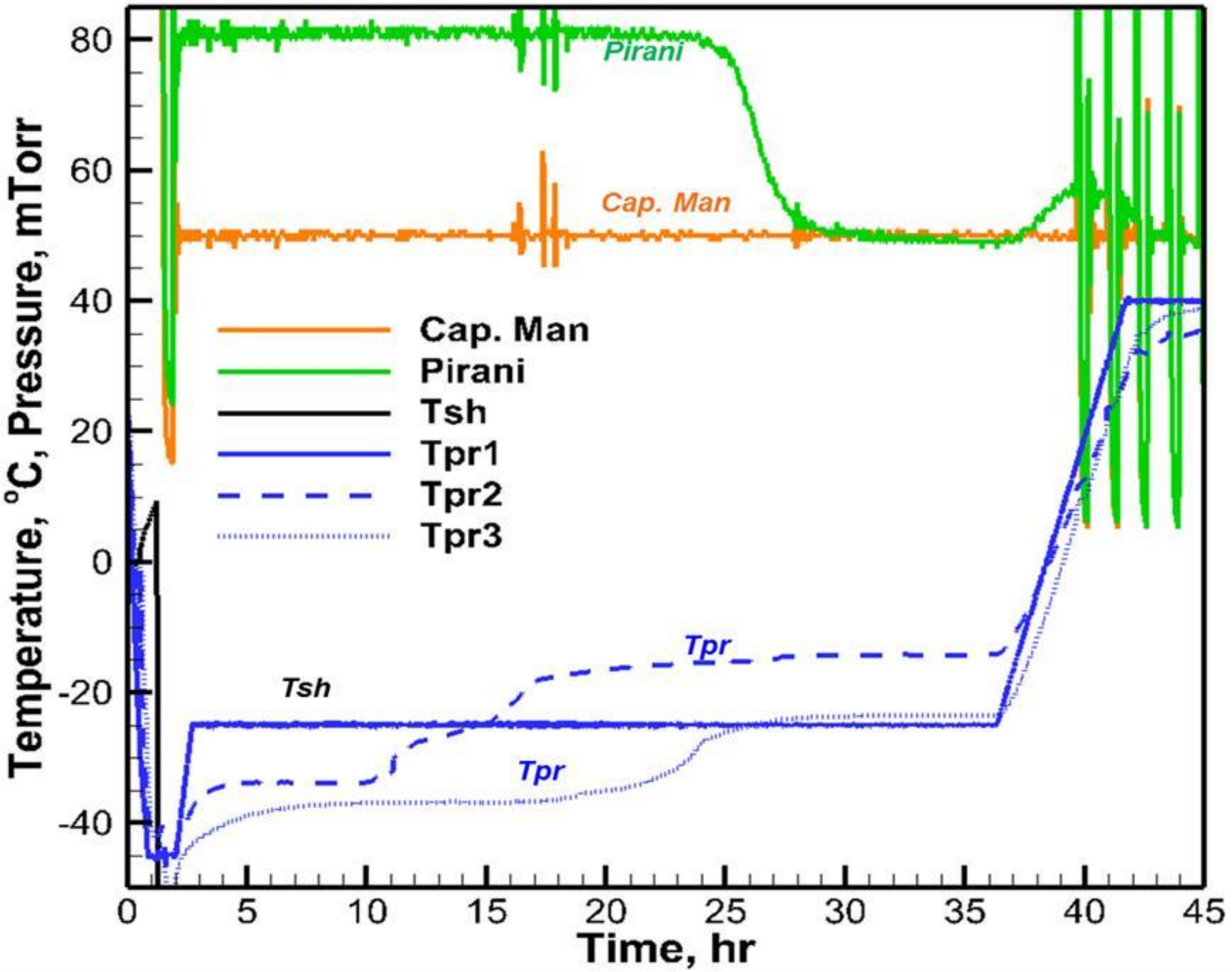
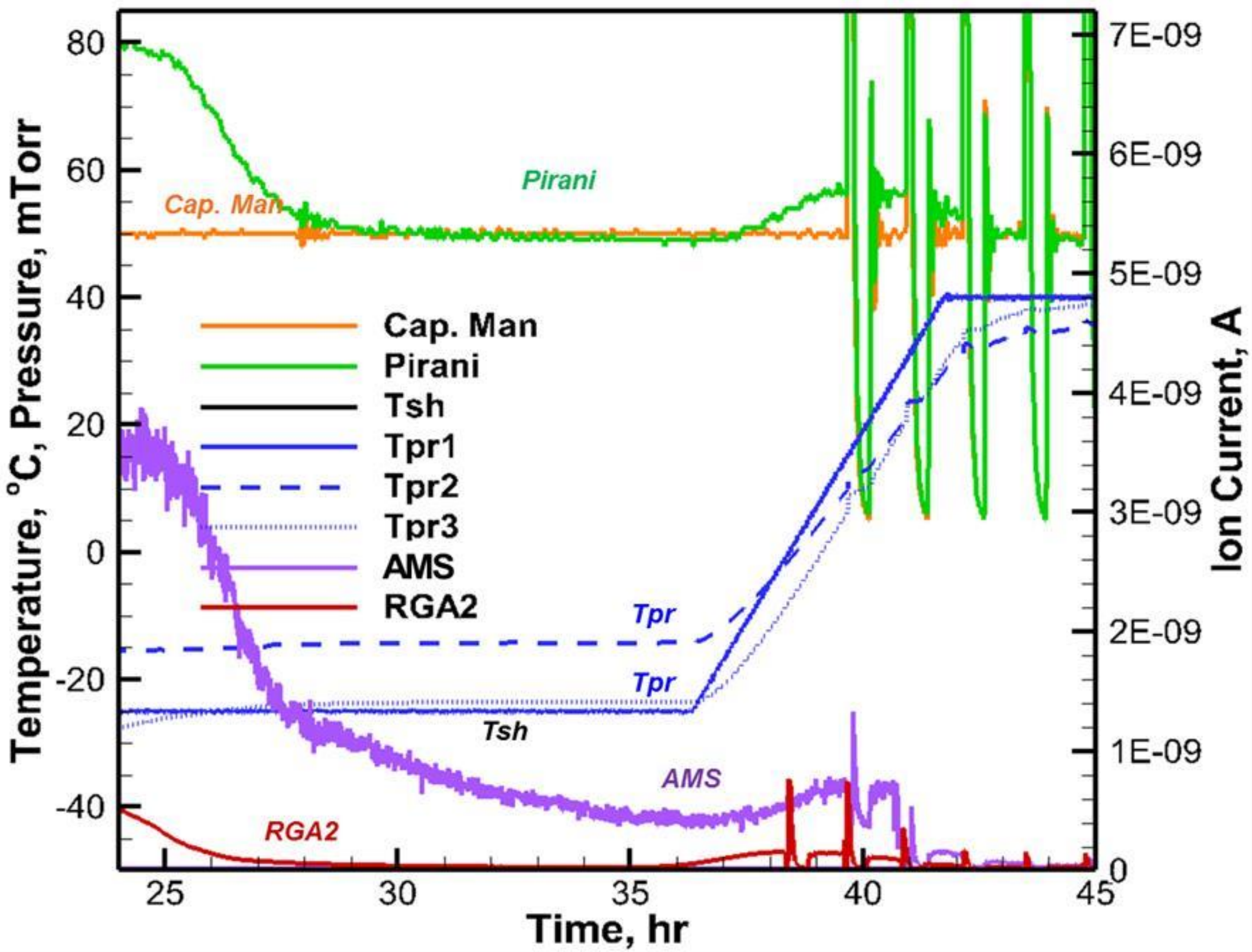


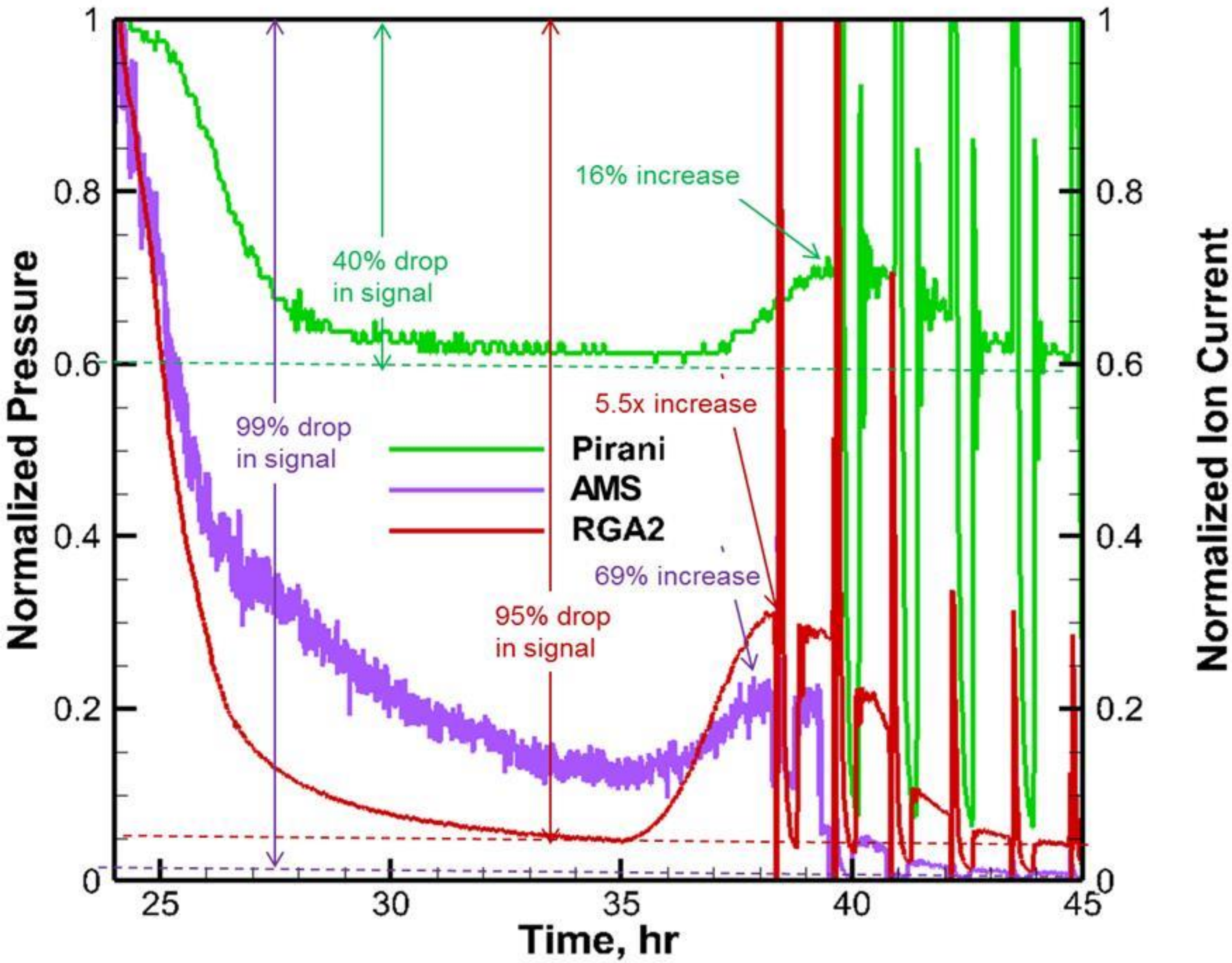
Sample Thief Cycle: End of Primary and Secondary Drying

- Tsh(1^0dry=-25 ˚C)
- Pch= 50 mT
- Tsh(2^0dry= 40 ˚C)
- Ramp: 0.2 ˚C/min
- Product thermocouple locations
  - Tpr1: Edge
  - Tpr2: Center
  - Tpr3: Center



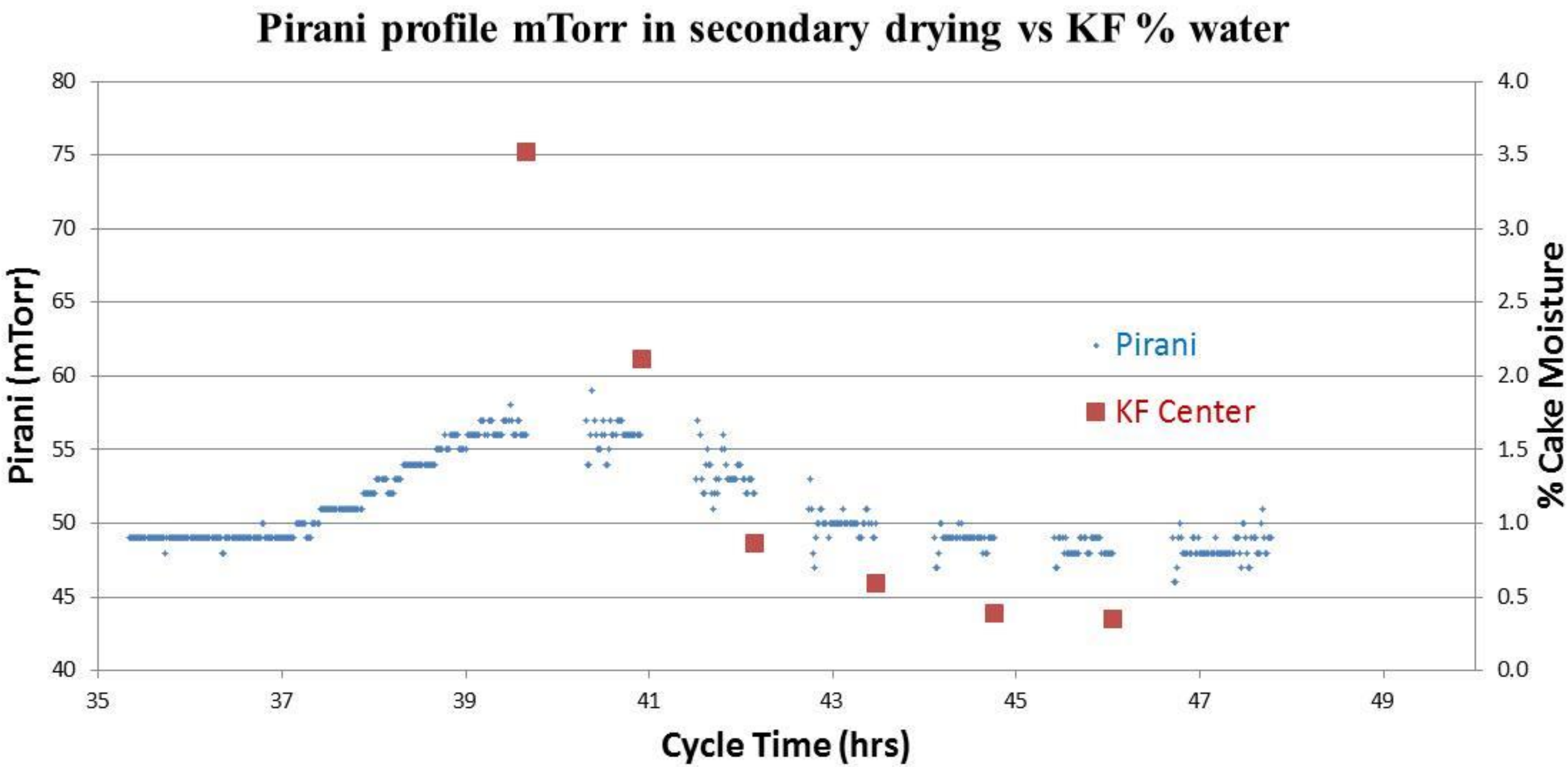
Sample Thief Cycle: Normalized Data

- Tsh(1^{0}dry=-25 ˚C)
- Pch= 50 mT
- Tsh(2^{0}dry= 40 ˚C)
- Ramp: 0.2 ˚C/min
- Data normalized by setting the largest value during the process to “1”

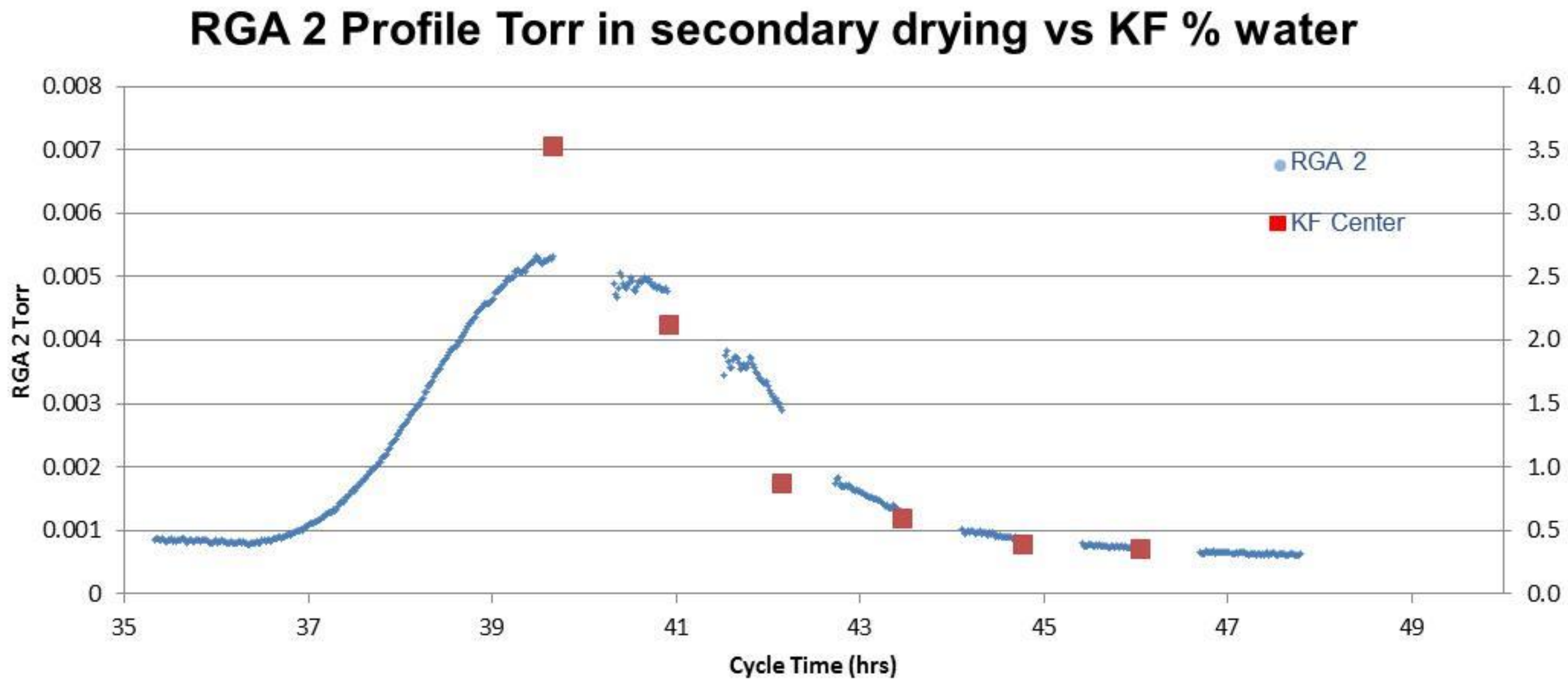


Secondary Drying: Pirani Gauge

Traditionally the Pirani gauge is used to help determine critical endpoints for primary and secondary drying during a lyo cycle

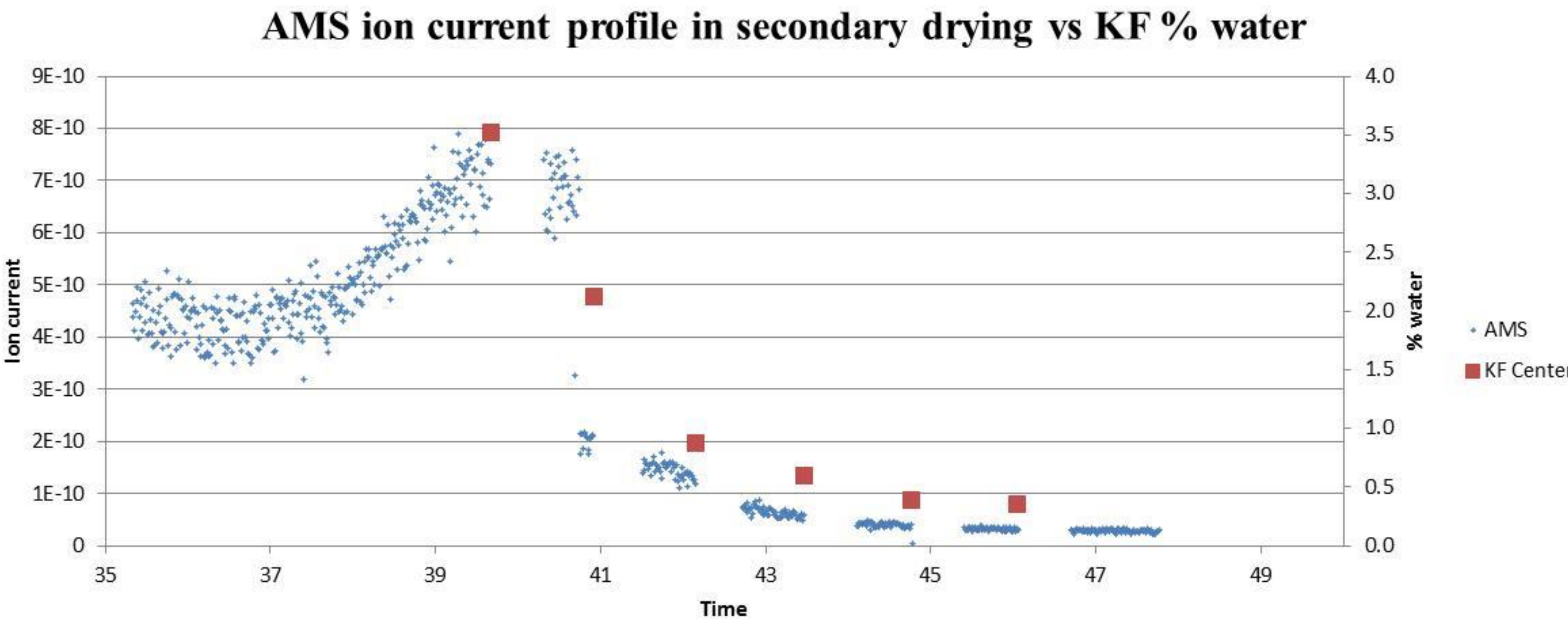


Secondary Drying: RGA 2



Signal from a RGA can be dealt with as a pressure measurement or as ion current flow and compared to residual water content in the lyo cake obtained from KF.

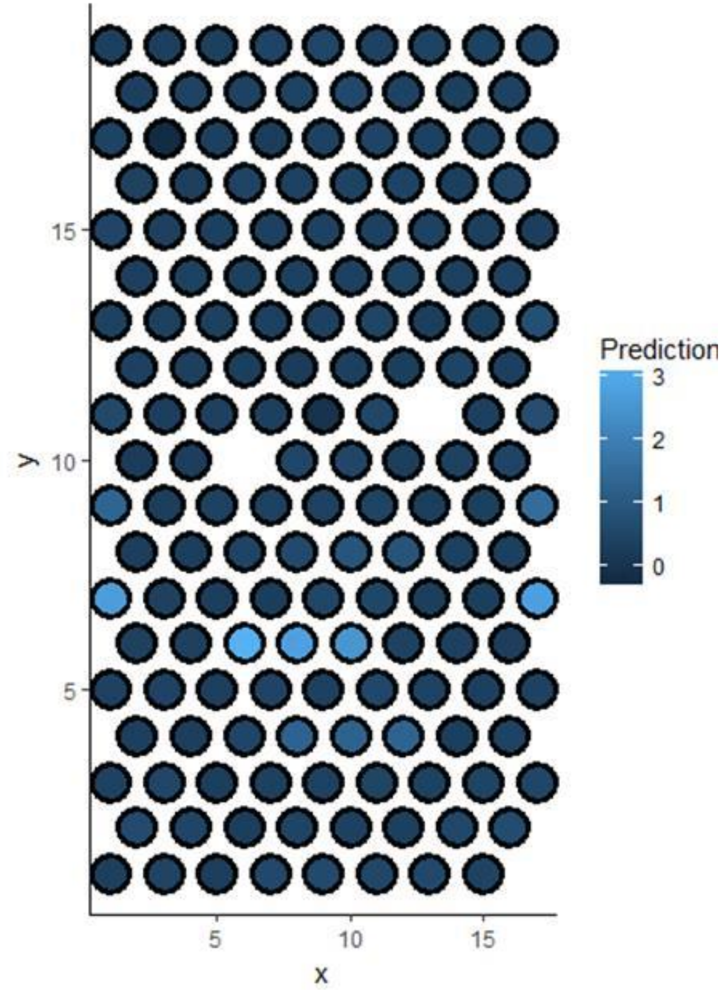
Secondary Drying: AMS



Raw signal from an AMS can be dealt with as a pressure measurement or as ion current flow and compared to residual water content in the lyo cake obtained from KF.

NIR Moisture Map

- A complete picture of the moisture distribution, effectively, a shelf map can be generated without performing destructive, time consuming, and hazardous KF on all vials.
  - Missing positions had inserted thermocouples.
- This type of map can reveal and confirm interesting features of a lyo shelf
  - At end of cycle the vials at the front of the lyo are on average slightly dryer than those at the back
  - high degree of uniformity of the drying process is evident



Overcoming Challenges

Status

- Philosophical Challenges
  - Why introduce new data? → Value added and industry landscape
  - Production downtime
- Technical Challenges
  - Quantitation → In Progress
    - Silicone Oil
    - Water
  - Impact of silicone oil on detector → Silicone oil filtration
- Logistics of implementation
  - New vs retrofit of existing dryers
  - Cost of equipment → Return on investment
  - Space and mounting considerations → Miniaturization of systems
  - Systems integration
  - Production downtime
  - Maintenance and lifespan → In Progress

Justification for Implementation

Regulatory requirements

Improvement in product quality

Reduction in cycle times

Increase capacity

Reduction in costs for our customers

Reduction in costs for us

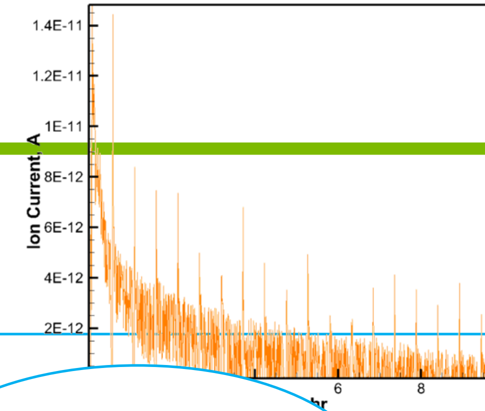
Increased process understanding

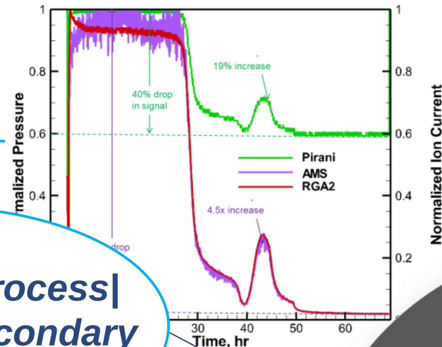
Improve measurement capabilities

Reduction in waste

Reduction in down-time

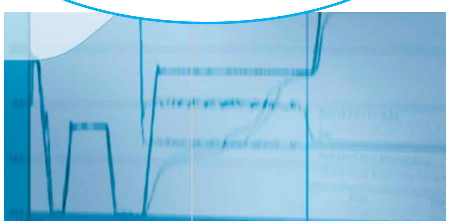
Next Steps: make predictive and quantifiable measurements



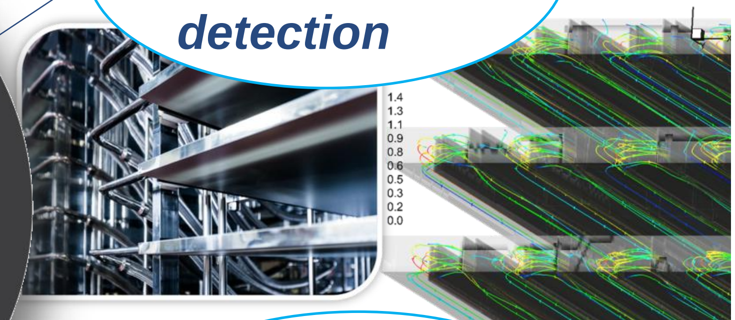


Motivation

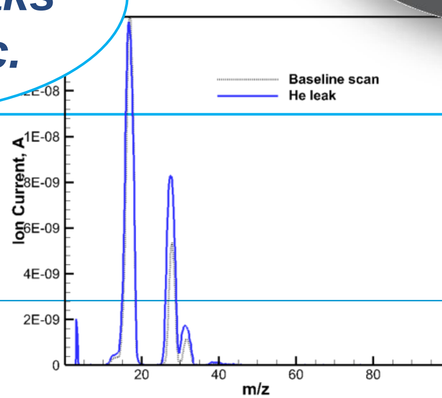
Quantitative Process| Primary and Secondary drying



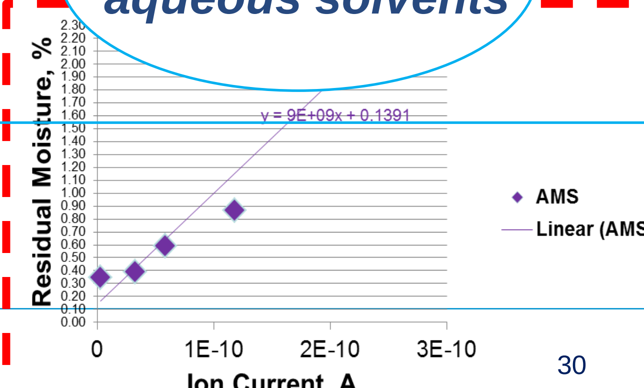
Quantitative silicone oil detection



System Leaks He , O_2 etc.



Quantitative non aqueous solvents



Questions