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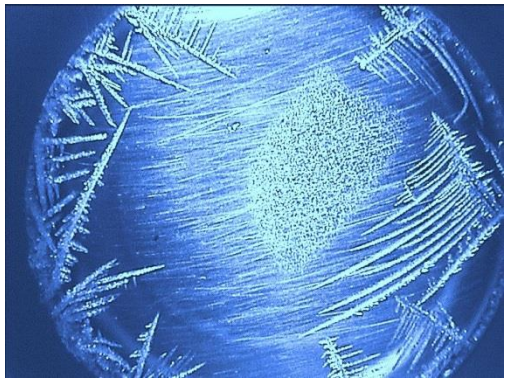
Centre for Metrology MIKES

MIKES METROLOGY



Traceable humidity measurements in the pharmaceutical industry

Workshop: Improved measurement standards for humidity at high temperatures: impact on the industry

INRIM, Torino, Italy, 12th July 2018

Richard Högström, VTT MIKES, Finland

HIT

EMPIR EURAMET
The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

MIKES METROLOGY

Contents

- Needs of pharmaceutical industry
- Challenges in current practice
- Developments within HIT project
  - Dynamic calibration procedures
  - Calibrators
- Conclusion

Contributors

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Case: Orion

- Orion Oyj is a globally operating Finnish pharmaceutical company (listed on Nasdaq Helsinki)
- In the EMPIR HIT project improved humidity calibration methods were developed for pharmaceutical industry in collaboration with Orion

Needs of pharmaceutical industry

https://libindustrym.en.made-in-china.com/product/dBUmxVolvTpG/China-Pharmaceutical-Temperature-Humidity-Stability-Test-Chamber.html

https://www.pharmaceutical-technology.com/contractors/contract/orion/

- Stringent quality standards for monitoring environmental conditions (e.g. relative humidity) in test chambers and at manufacturing sites
- Industry needs cost-effective calibration procedures, preferably on-site methods to minimize down time due to calibration

Challenges in current industry practice

http://www.directindustry.com/prod/voetsch-industrietechnik/product-16219-424389.html

https://www.otm.sg/humidity-measurement-instruments.html#.W0QzW8cUnUQ

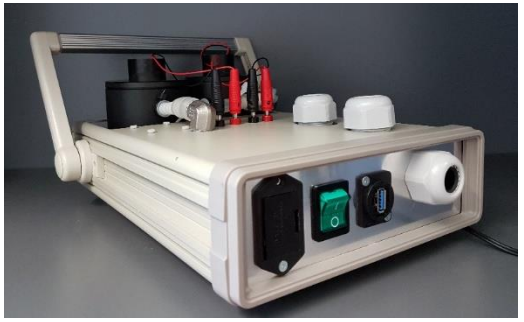
https://www.rotronic.com/en/hygrogen2-s.html

- Calibrations are performed at static conditions:
  - Time consuming, i.e. expensive
    - Costs limit the number of measurement points → representativeness of results?
    - Hysteresis often significant but not included
  - In many cases RH probes are used at non-static conditions
- On-site calibration methods:
  - Salt solutions: low cost, but labourous and limited (static) calibration points
  - Calibrators: more flexible, but expensive

Developments in HIT project

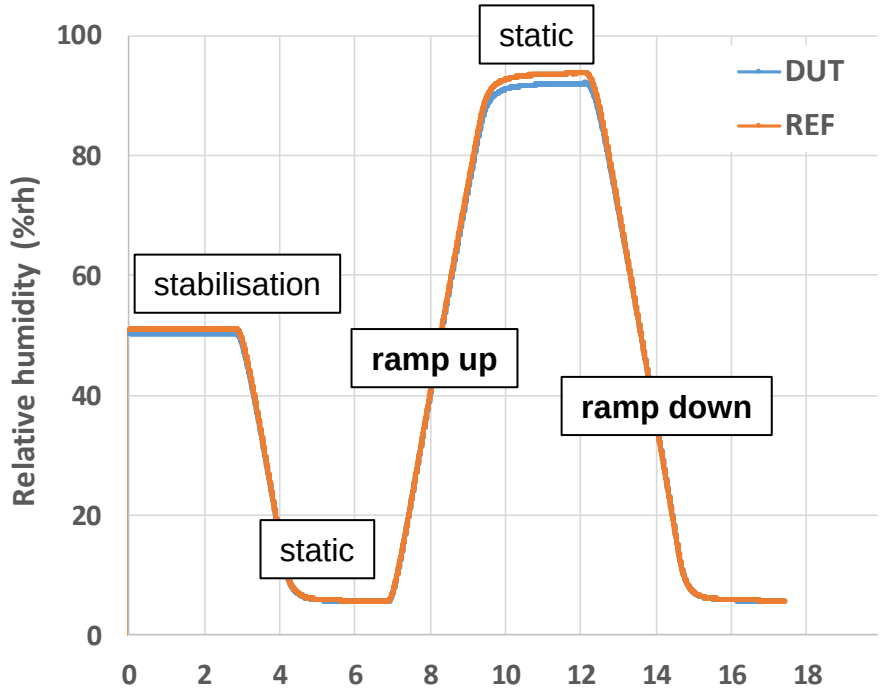
Target: Development of an efficient but comprehensive calibration procedure based on measurements at non-static conditions

- In-laboratory calibrations
  - Calibrator for non-static calibrations
- On-site calibrations
  - Humidity calibrators for fast non-static calibrations on-site

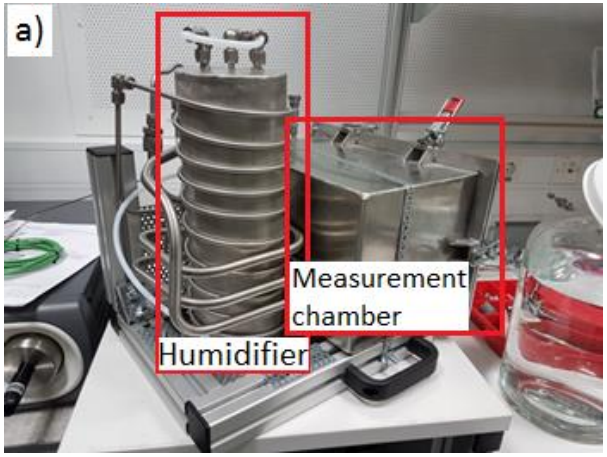


Non-static calibration procedure

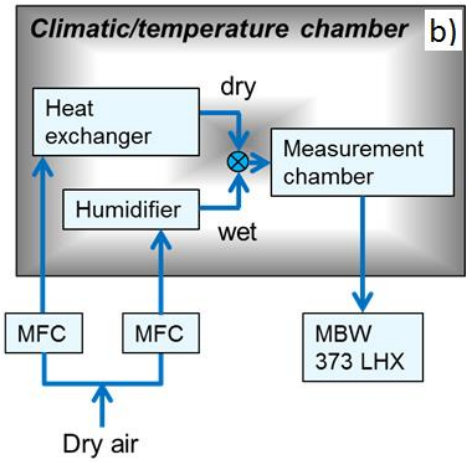
- Fast
- Coverage over full humidity range
- Hysteresis is included

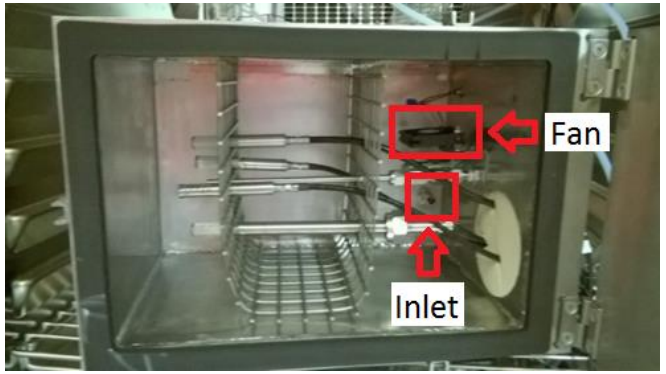


In-laboratory calibrations:
A new modular humidity calibration setup



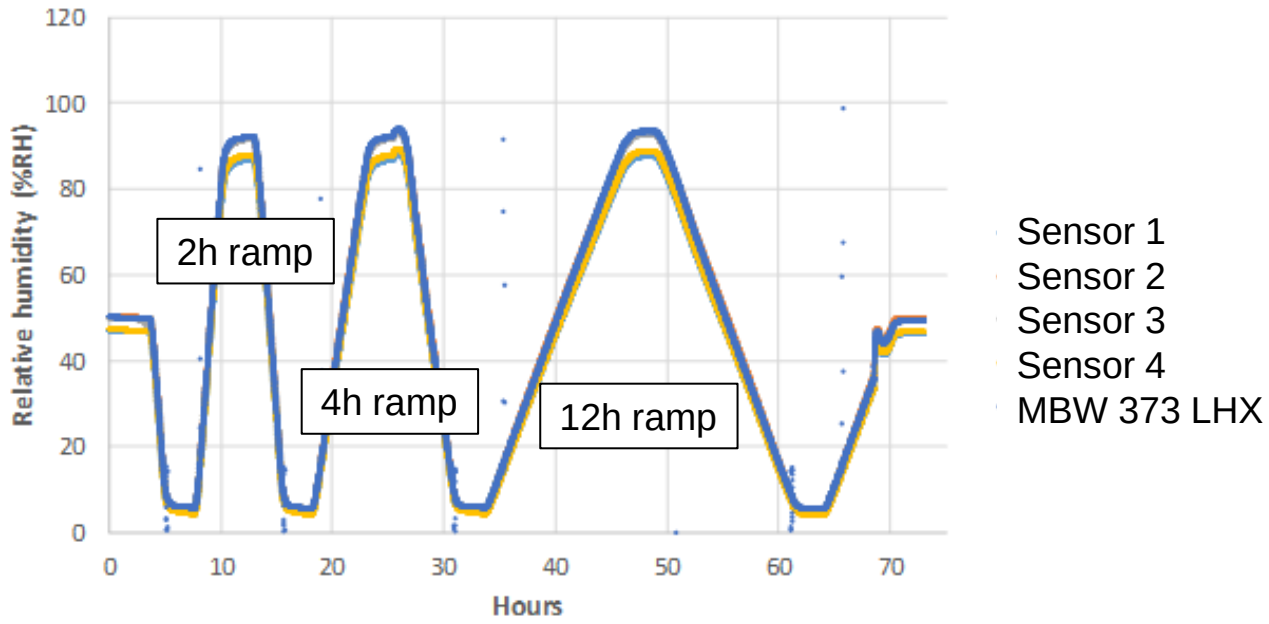
- Humidity is generated by mixing dry and humid air using mass flow controllers
- Heater in the humidifier to compensate for evaporative cooling
- Quick couplings for easy assembling
- Fully automated (computer control)



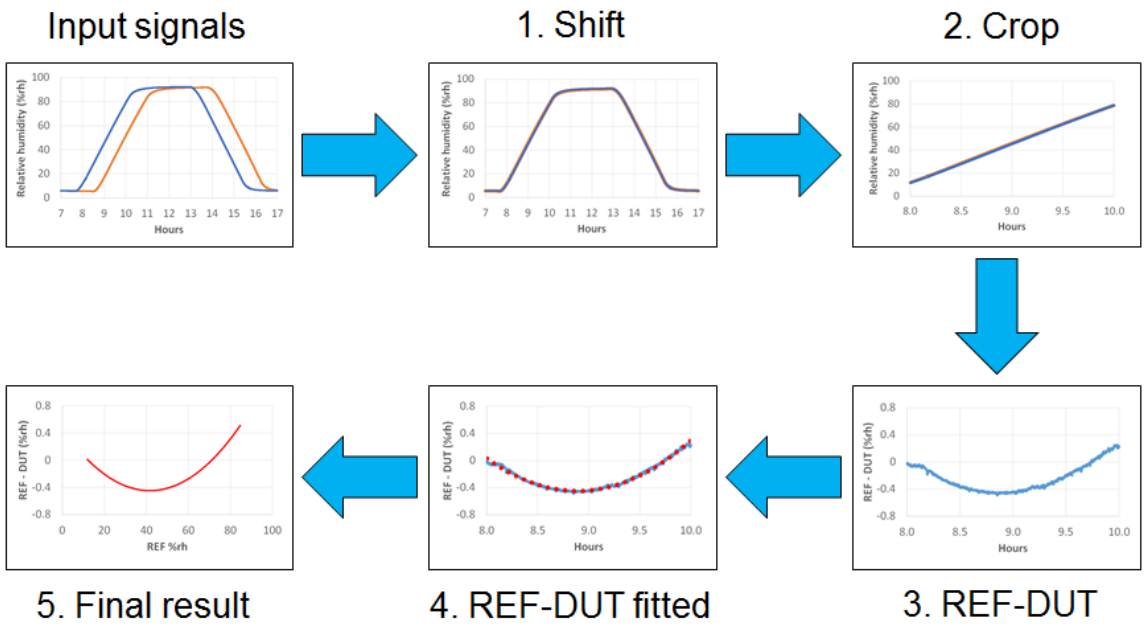


Non-static calibration procedure

- Study of measurement scheme:
  - Influence of ramp speed?
  - Comparability to static calibration?

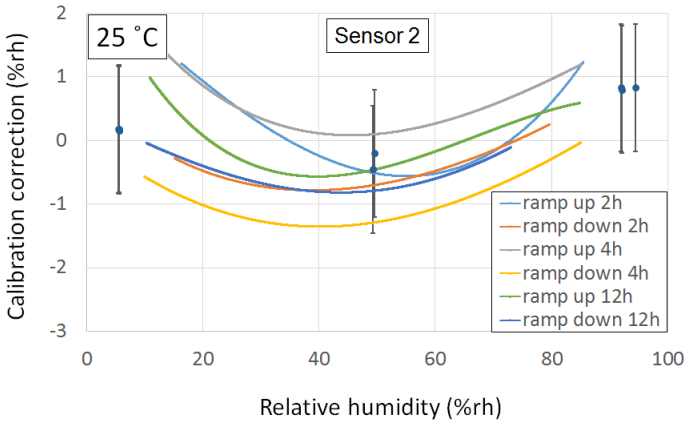


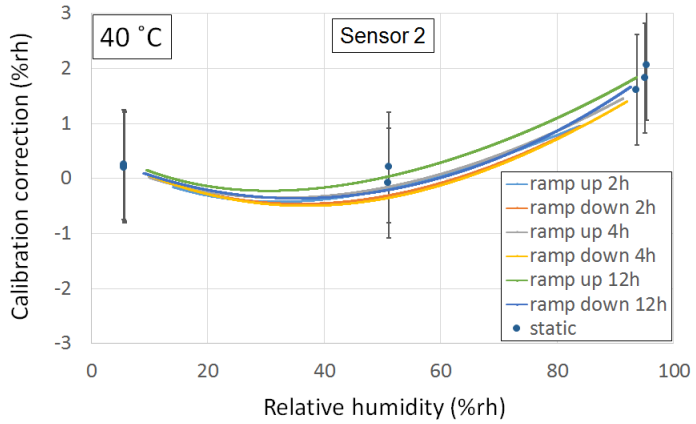
Signal processing scheme

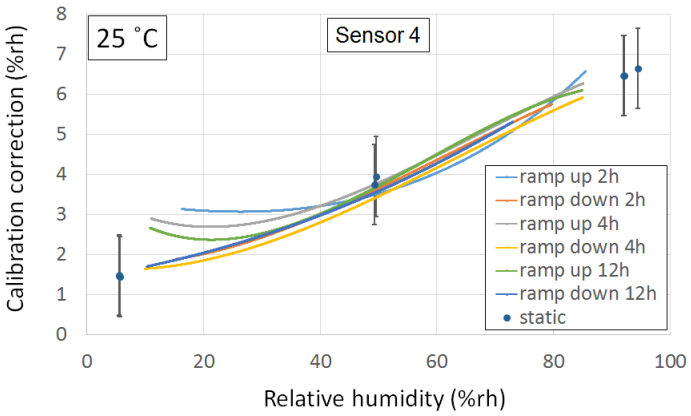


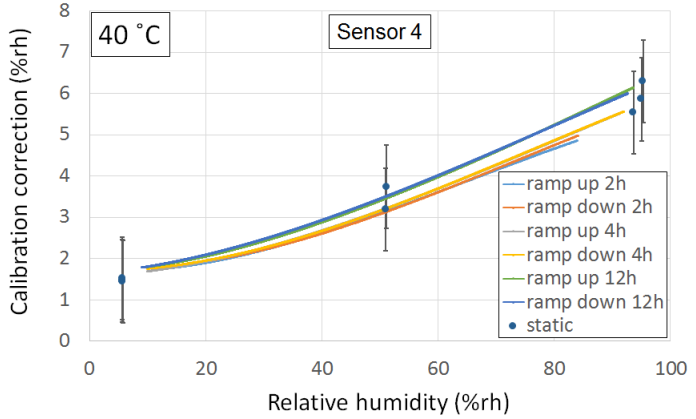
1. Delay compensation - different time constants cause shift in signal
2. Linear part of ramp selected
3. Calibration correction calculated (REF-DUT)
4. Fitting of REF-DUT data
5. Results presented as calibration correction curve as function of relative humidity

Non-static calibration results 1/2



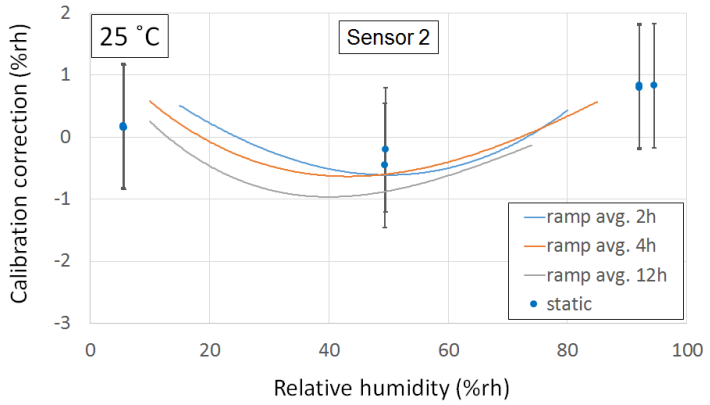


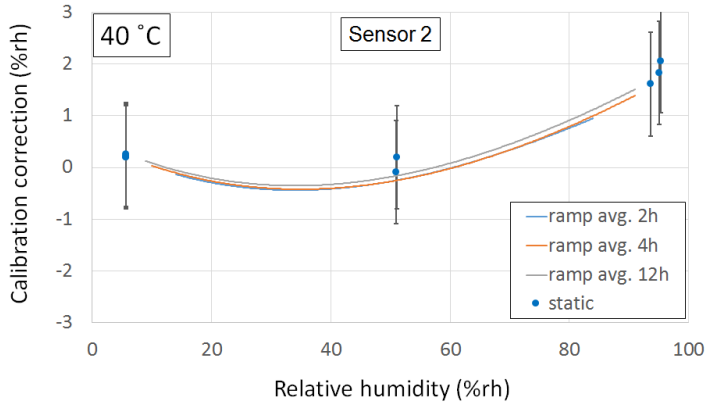


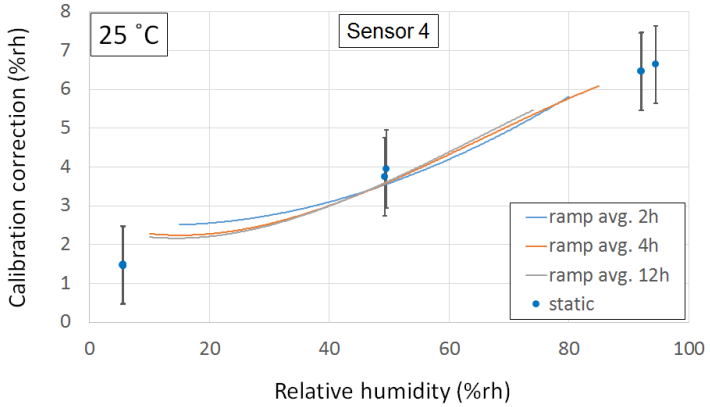


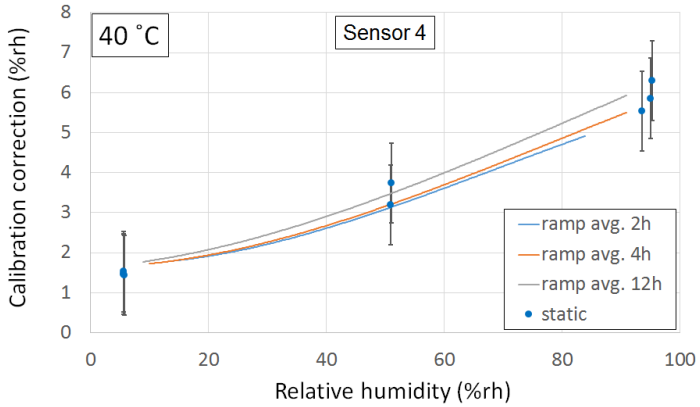
- Non-static calibration results match fairly well with static calibration
- Hysteresis larger at 25 ˚C and for 2h and 4h ramps compared to 12h ramps
- At 25 ˚C and lower humidities (20 %rh and below) small discrepancies found (Note: T_d = 0 ˚C at 20 %rh and 25 ˚C)

Non-static calibration results 2/2



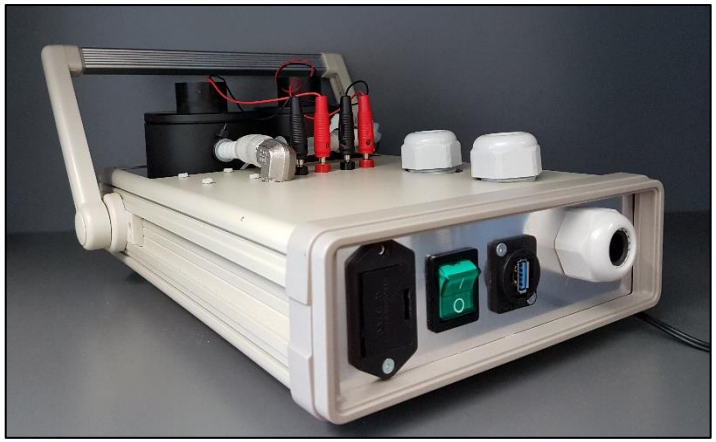


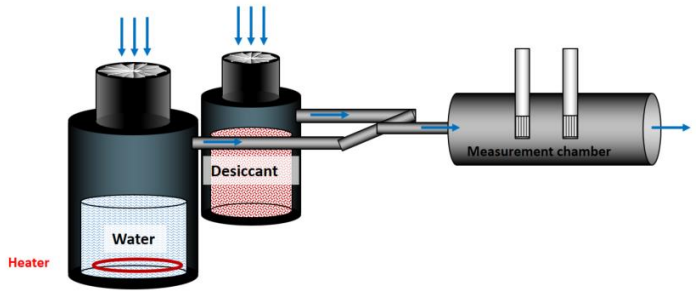




- Averaging ramp up and down gives similar results for different ramp speeds and compared to the static calibration
- Small discrepancy found at lower humidities is probably caused by the slower response of the MBW at sub zero dew-points

On-site calibrations: Humidity calibrator for non-static calibrations

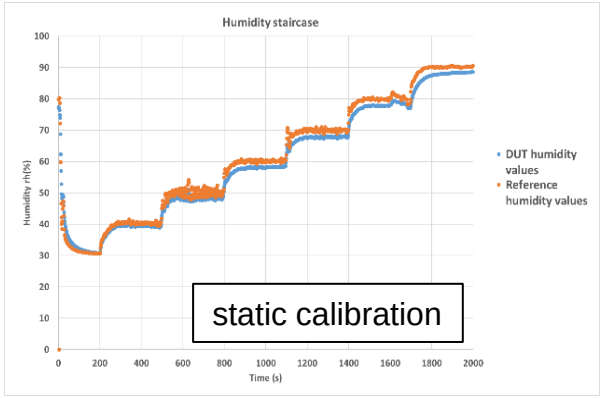




- Humidity is generated by mixing dry and humid air using voltage controlled fans
- Calibration is based on comparison against a reference sensor (traceably calibrated elsewhere)
- Fully automated calibration

  → **Demonstrations at Orion**

Demonstration at Orion



- Feedback:
  - Connectivity of factory measurement system prevents the use of a dynamic calibration approach
  - Even in static operation, 30 % to 50 % reduction in overall calibration time is expected
  - If temperature calibration option is added, the reduction is expected to be even larger

Conclusion

- Non-static calibration procedure has a potential of decreasing the calibration time by up to 50 %
- Time constants of sensors varies significantly → validation against static calibration is necessary
- Use of chilled mirror hygrometer as a reference is challenging
- Our design with flow control using fans provides a simple and cost-effective approach for a field humidity calibrator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Thank you

Challenges in current industry practice

- Calibrations are performed at static conditions:
  - Time consuming, i.e. expensive
    - Limited number of measurement points → representativeness of results?
    - Hysteresis often significant but not included
  - In many cases RH probes are used at non-static conditions
- On-site calibration methods:

Salt solution	Calibrators
+ low cost	+ flexible
- laborous - limited (static) calibration points	- expensive - static calibrations