



Transient humidity measurements in sterile storage of pharmaceuticals

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EMPIR



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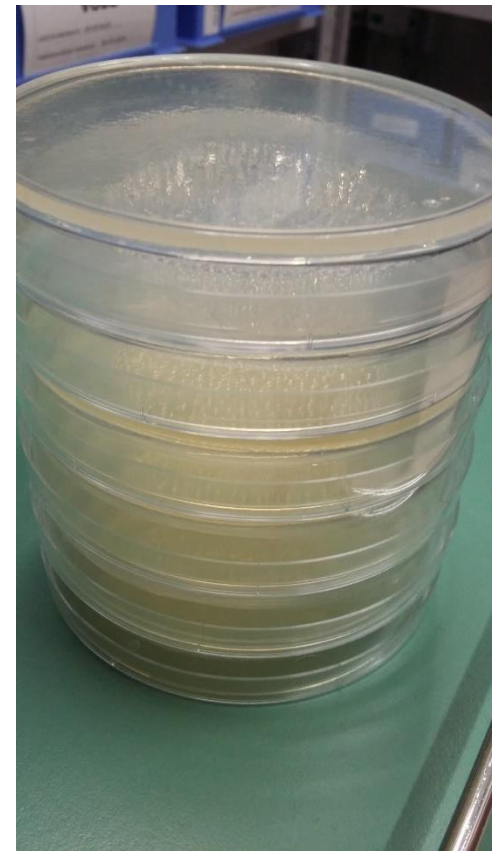
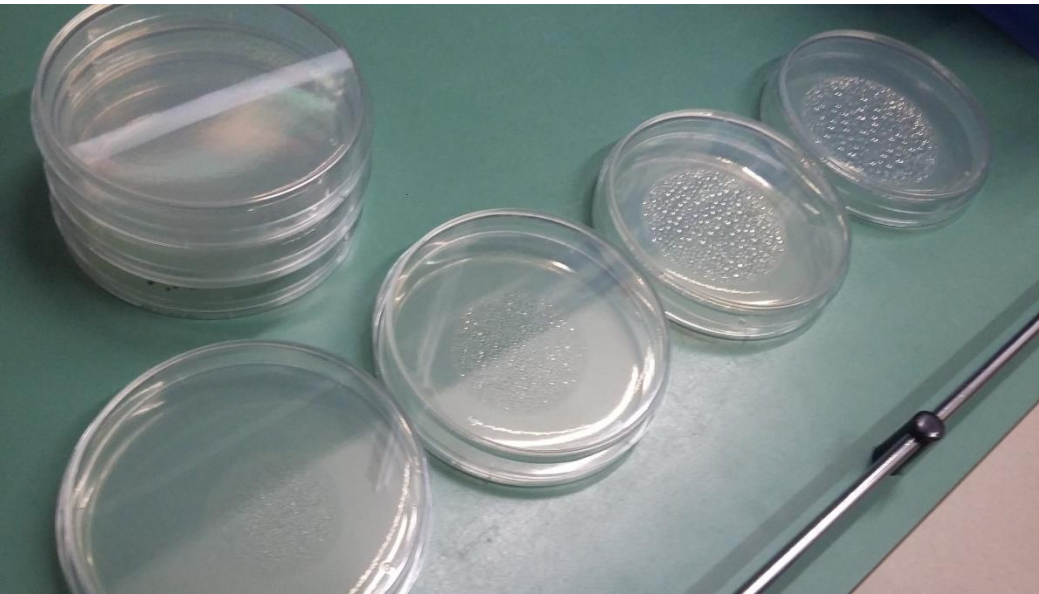
Microbial growth

- sterile process in Lek d.d. (part of Sandoz / Novartis)
- microbiological quality control of water samples
- samples prepared at room conditions (R2A agar)
- stacked Petri dishes (PDs), typically in batches of 6
- temperature of incubator: 30°C to 35°C
- time of incubation: 5 to 7 days or longer at 20°C to 28 °C, or at least 5 days at 30°C to 35°C



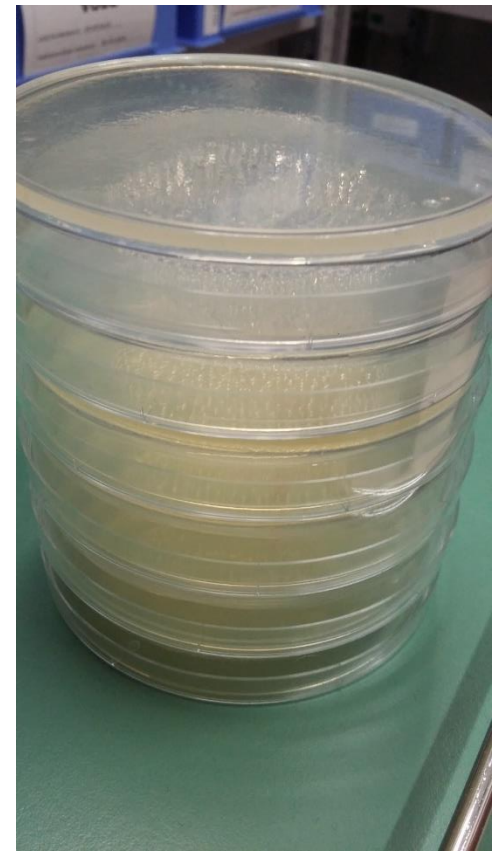
Microbial growth

- inside PDs high accumulation of water vapor (high humidity)
- condensation forming (on the inside) after 2 to 3 days (transient)
- not in all PDs in the stack



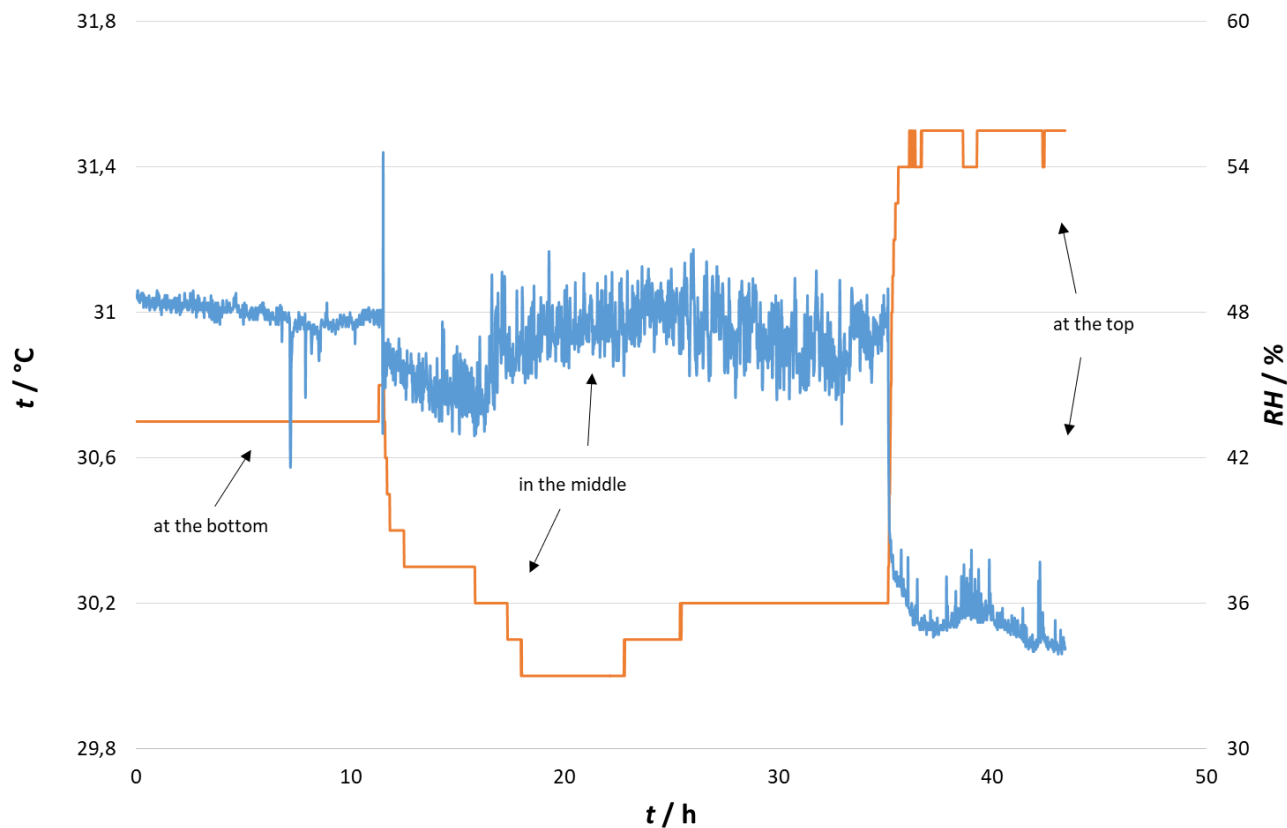
Condensation issue

- the source of water vapor inside – agar - same effect as with sterile purified water (SPW)
(initial suspect was also microbial growth process)
- potential causes of condensation:
 - temperature of incubation (storage)
 - humidity of incubation (tightness of the PD cover)
 - endothermic / exothermic growth process
 - evaporative cooling
 - thermal conductivity between PDs in a stack
 - cold spots
 - temperature shocks



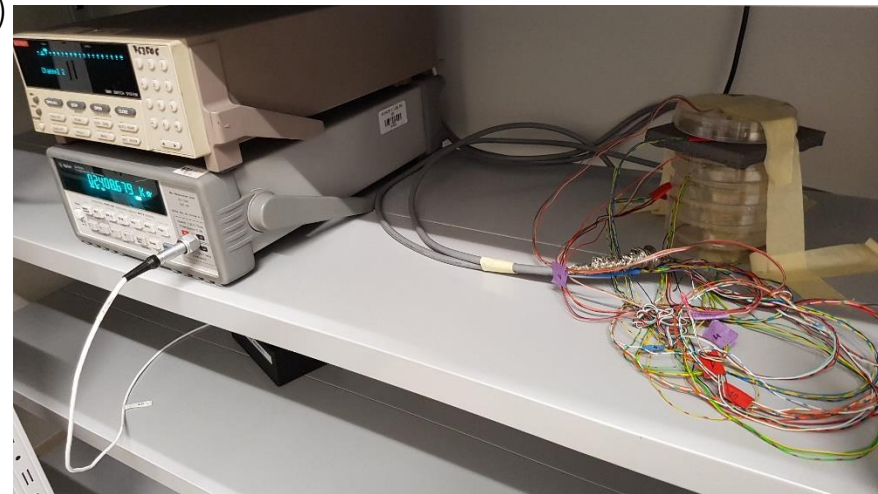
Measurement setup

- initially measured T&RH on top, in the middle and at the bottom of the stack (small T&RH loggers used) – switched positions



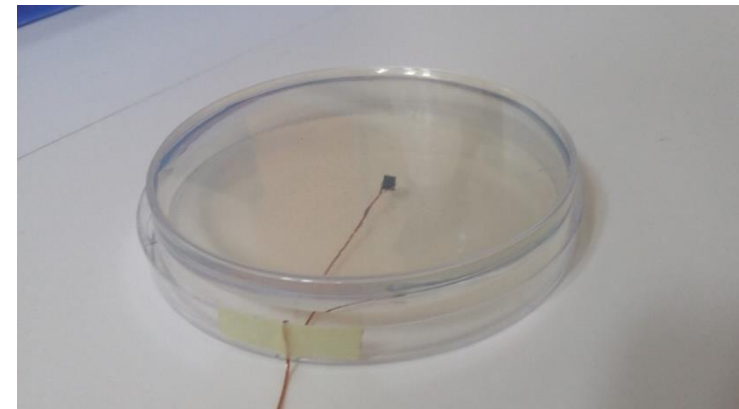
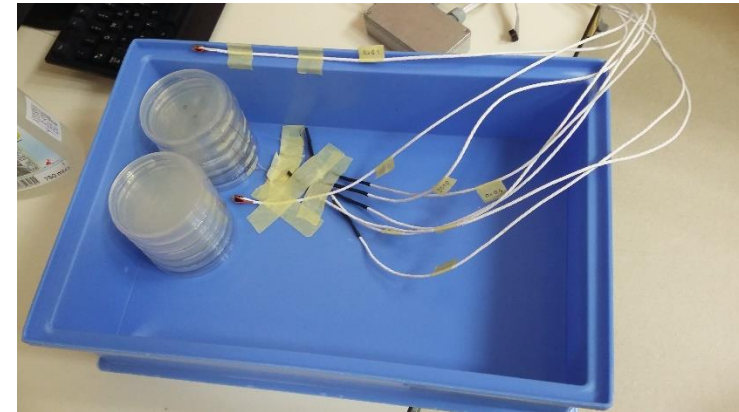
Measurement setup

- because of their size and mass, the stacks had to be split – top and bottom half three PDs
- deviation from real conditions – heat conduction between PDs, convection (in the split space), mass of the logger
- smaller calibrated thermistors were used instead
(uncertainty below 0,01 °C; differential measurement - profile)

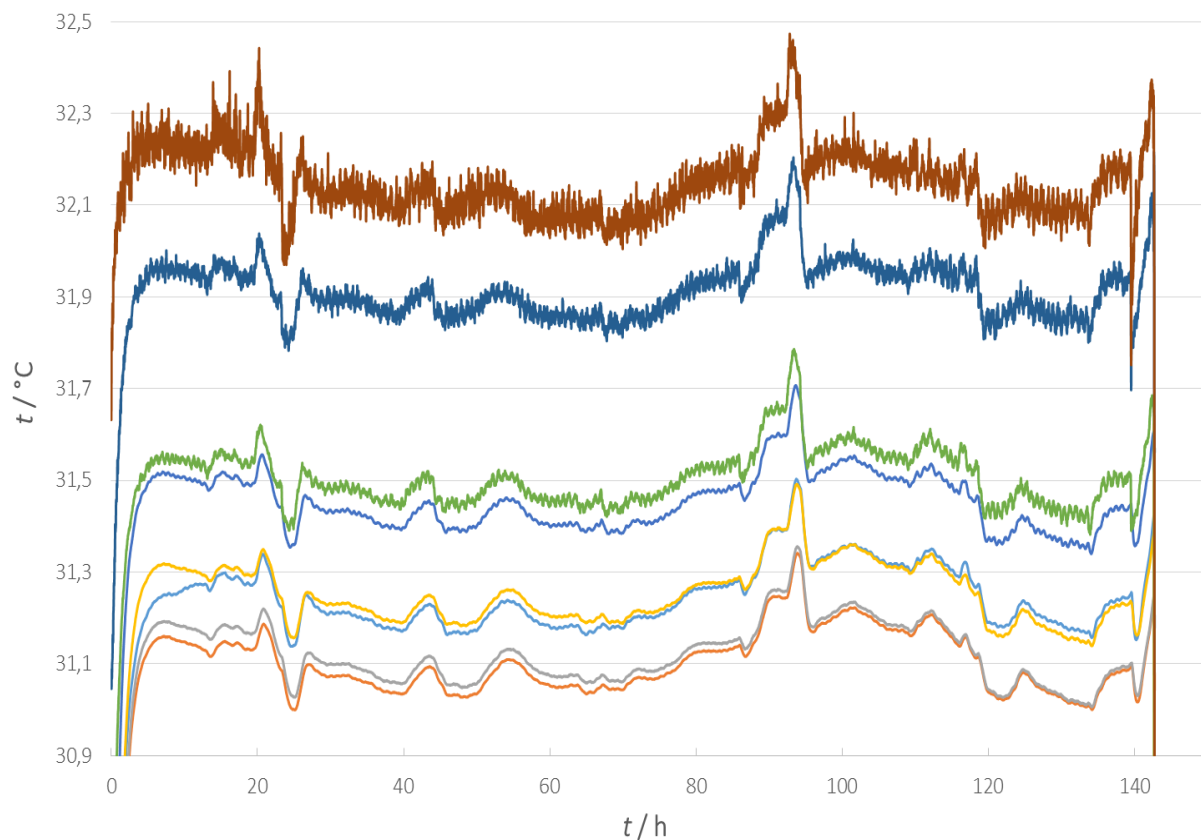


Measurement setup

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- allows high spatial resolution – below 0,1 °C/cm corresponding to less then 1 %rh/cm
- small RH capacitive sensors were used inside the PDs
- outside humidity proved not significant (PDs covers tight enough)



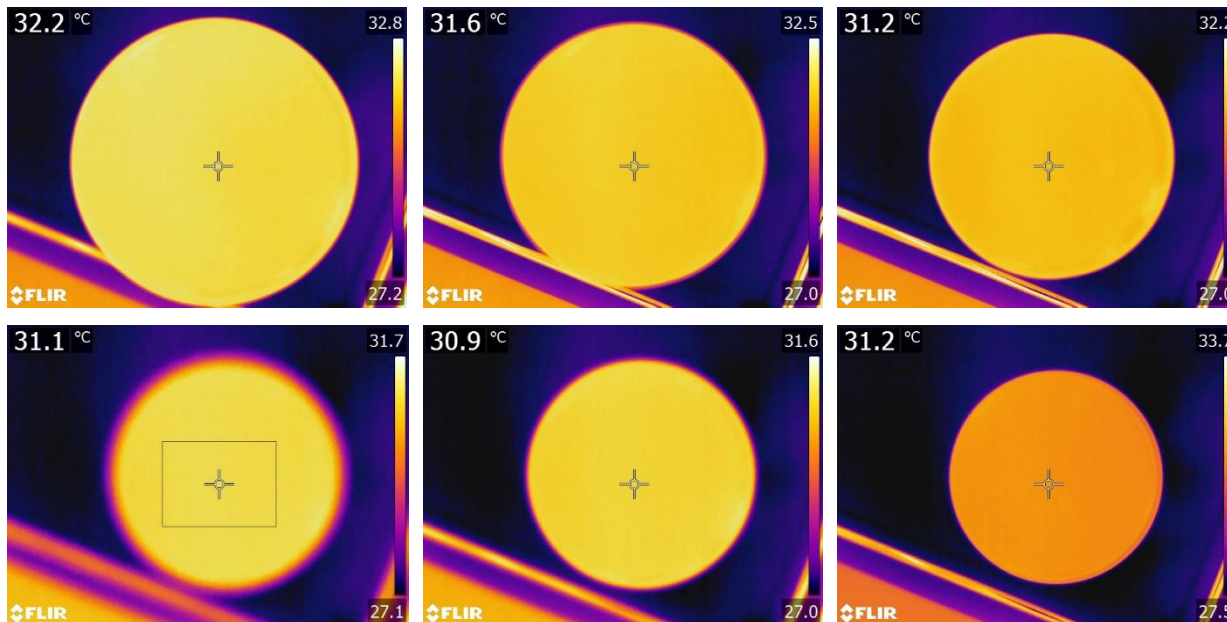
Temperature profile of the stack



6	31,95 °C
5	31,48 °C
4	31,28 °C
3	31,13 °C
2	31,15 °C
1	31,28 °C

Petri dish 1 (bottom) Petri dish 2 Petri dish 3 Petri dish 4 Petri dish 5 (1/2) Petri dish 5 (2/2) Petri dish 6 (top) Plastic case

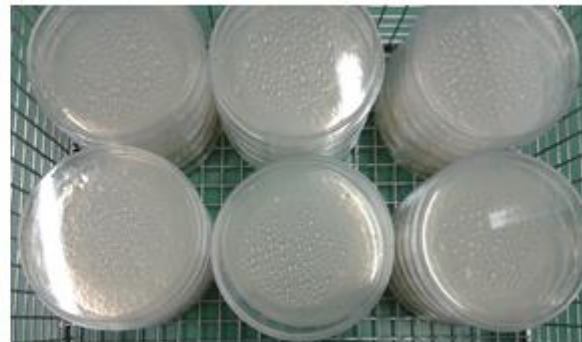
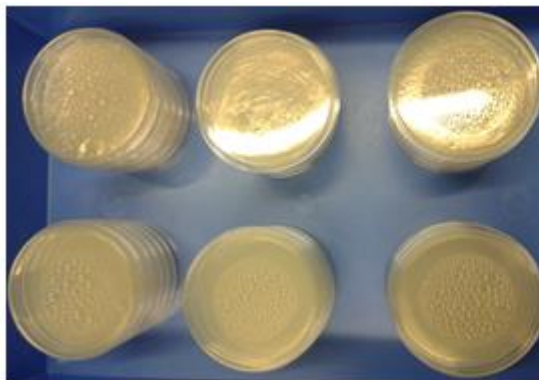
Temperature profile of the stack



6	32,2 °C
5	31,6 °C
4	31,2 °C
3	31,1 °C
2	30,9 °C
1	31,2 °C

Testing

- the level of condensation corresponded to temperature cold spots
- in collaboration with Lek d.d. (Sandoz/Novartis) the potential parameters that could decrease the condensation were explored
- first, we switched the plastic containers with the mesh basket



effect:
0

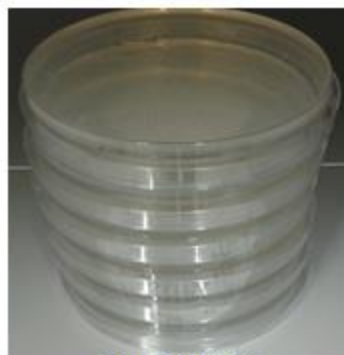
0 no effect
+ improved (less cond.)
++ very improved

Testing

- different incubation temperature



30-35 °C (I30)



20-25 °C (I31)



30-35 °C (I11)

effect:

0

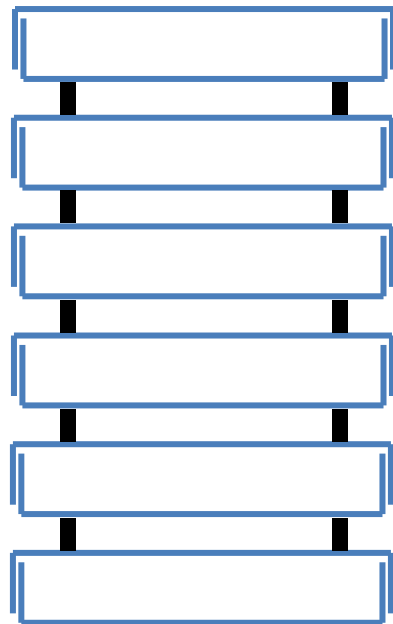
+ / ++

+

0 no effect
+ improved (less cond.)
++ very improved

Testing

- *spacers* between individual PDs in a stack (no forced convection)

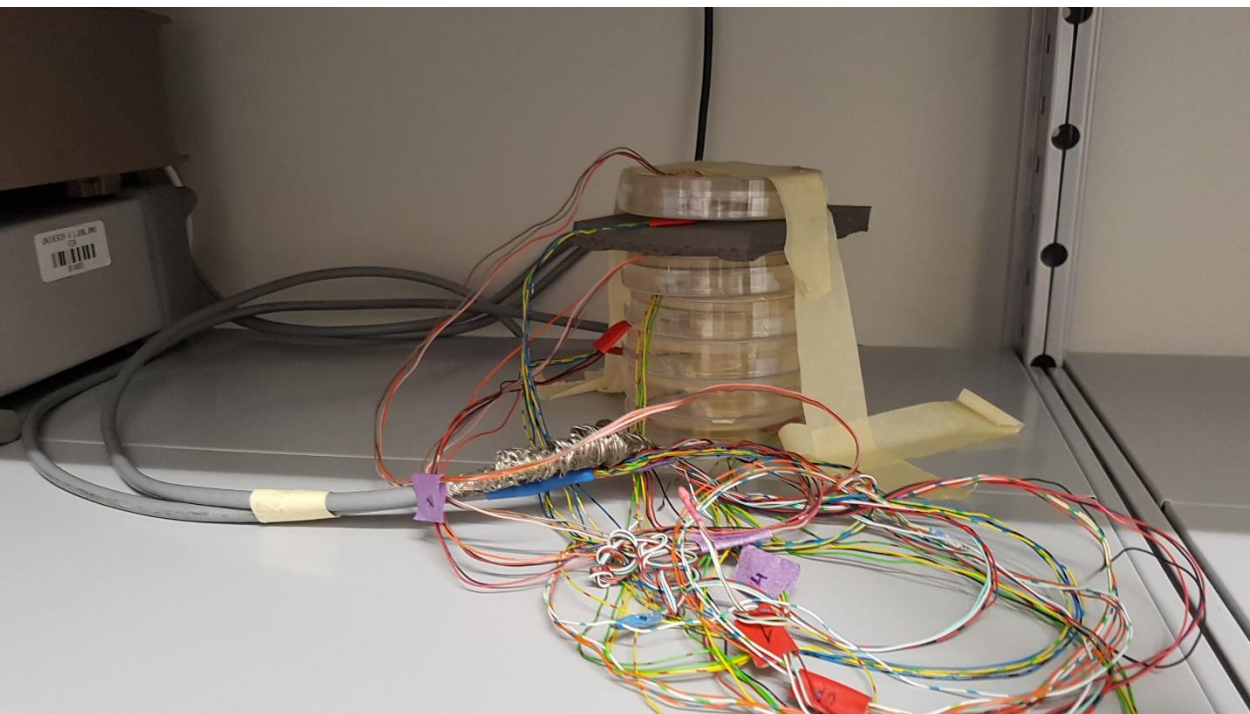


effect:
0

0 no effect
+ improved (less cond.)
++ very improved

Testing

- *isolation* between individual PDs in a stack
- better horizontal temperature gradients (condensation over smaller area)

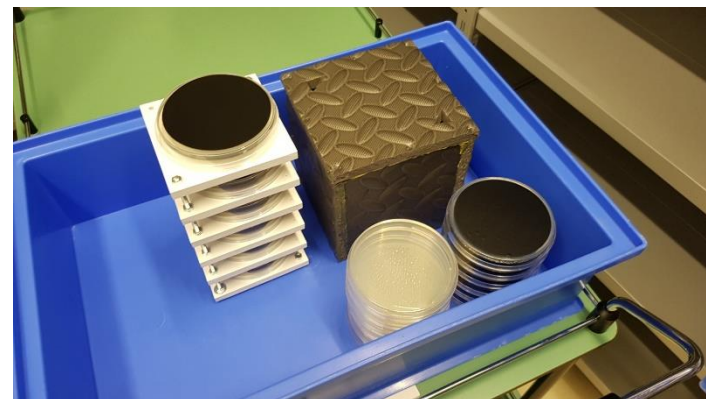
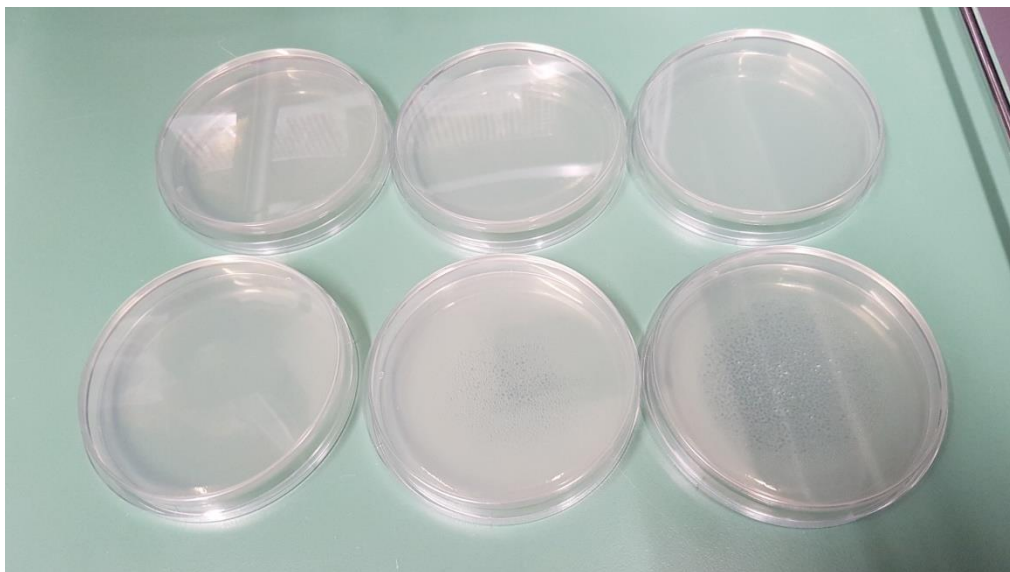


effect:
0/+

0 no effect
+ improved (less cond.)
++ very improved

Testing

- whole stack cover isolation (as pictured + alu and plastic wrap)



effect:
+ / ++

0 no effect
+ improved (less cond.)
++ very improved

Testing

- separate Petri dishes
(stacks of different sizes)

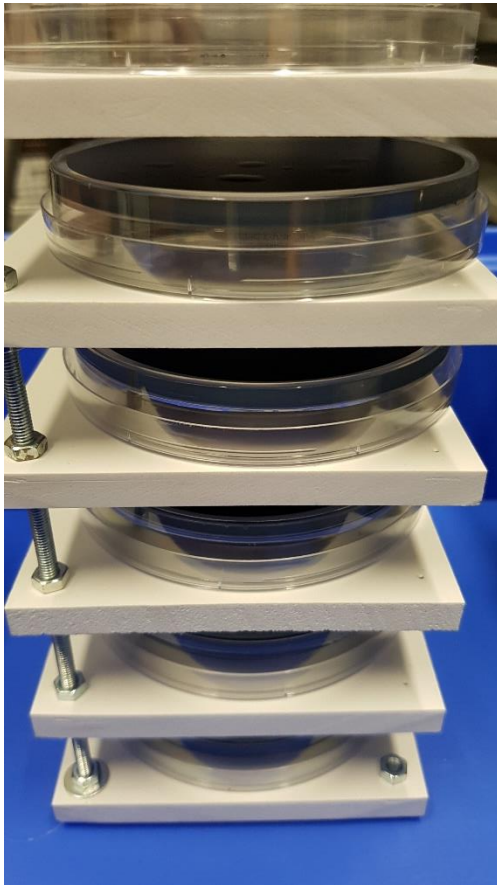


effect:
0

0 no effect
+ improved (less cond.)
++ very improved

Testing

- *spacing and isolation (shelving)* individual PDs in a stack



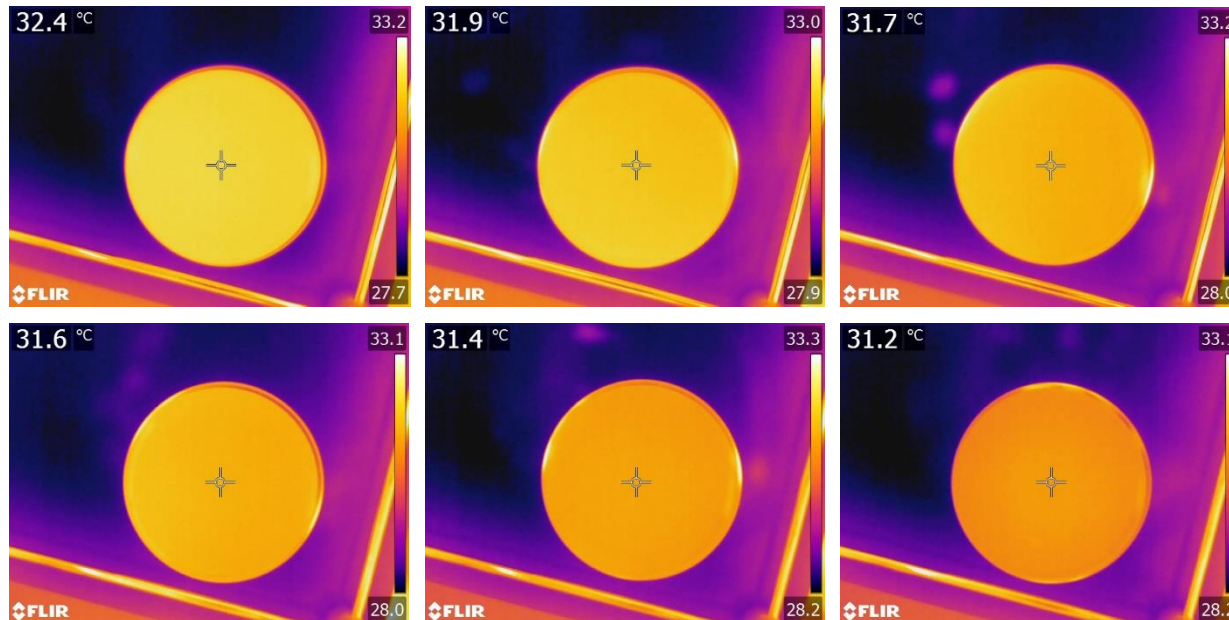
effect:

++

0 no effect
+ improved (less cond.)
++ very improved

Testing

- spacing and isolation (shelving)* individual PDs in a stack



6	32,4 °C
5	31,9 °C
4	31,7 °C
3	31,6 °C
2	31,4 °C
1	31,2 °C

Conclusions

- a special measurement setup was designed and used to confirm spatial gradients
- different tests were performed in order to minimize condensation - some measures proved successful (+/++) – lowered risk in subsequent analysis
- limited number of tests (pharma, sterile environment, strict protocols, availability of premises,...)

Potential follow-up

- more measurements in the sample preparation phase
- modelling of heat fluxes would be interesting (*some parameters like air flow, turbulances would be difficult to set*)