Developing Transferable Freeze Drying Protocols Using Accuflux® and a MicroFD®

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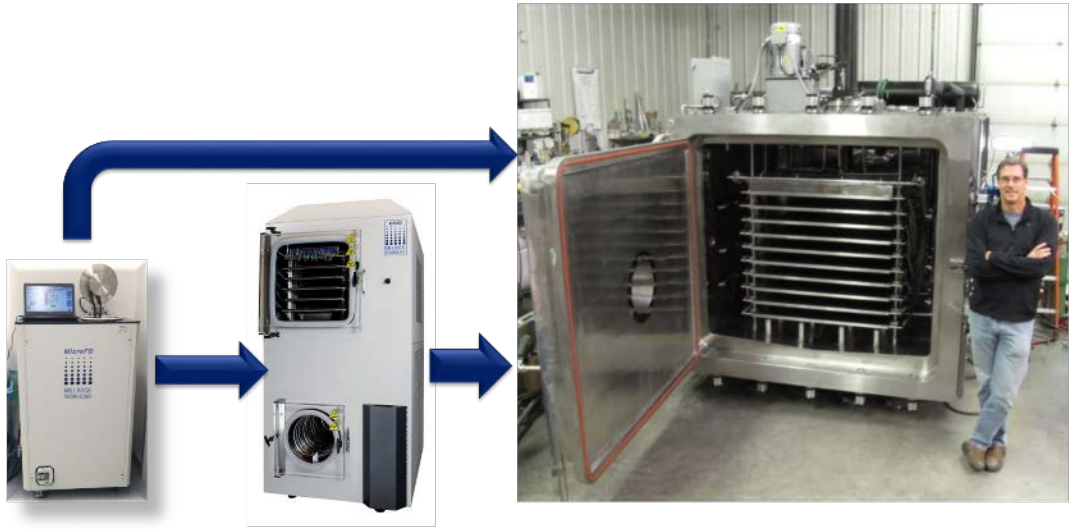

Peptalk 2017, San Diego

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Scale-up and Transfer

“The goal is to maintain an equivalent product temperature ‘thermal history’ between the lab and commercial processes.”

Principles of Lyophilization Cycle scale-up - Tchessalov, Dixon, Warne

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Vial Heat Transfer Coefficient - Kv

1. Kv can be used to help with transfer of protocols between different freeze dryers

2. Methods to determine Kv
   A. Kv Gravimetric – Method to determine Kv by measuring the weight loss per time during a short primary drying cycle
   B. Kv AccuFlux – Method to determine Kv by measuring heat flow
      i. AccuFlux – Heat Flow Measurement using a heat flux sensor between the shelf and vials

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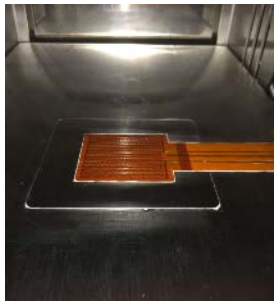
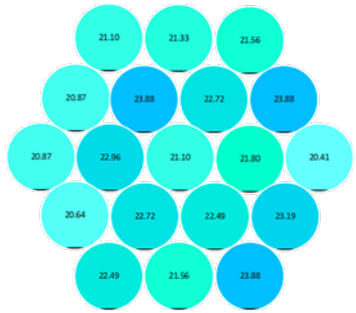
Objective

1. Compare Kv Accuflux to Kv Gravimetric in a REVO Lab Scale Freeze Dryer (6 sf)



2. Compare Kv AccuFlux vs Kv Gravimetric in a MicroFD (19 Vials)



3. Develop Protocols in the MicroFD® and Transfer to the Revo
   A. Review ‘Thermal History’

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Kv Gravimetric

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Measuring Kv Gravimetrically

1. Add Water to Vials
   A. 336 Vials, 5ml fill, 10 ml vial with igloo stopper
   B. T_{Shelf} = -20°C, $P_{Chamber}$ = 100 mT

2. Weigh Each Vial and Mark its Location on the Shelf

3. Freeze and Start Primary Drying
   A. Freeze at 0.5°C/min to -40

4. Stop Primary Drying when Drying is stable
   A. At Steady State Before the sublimation surface changes
   B. IE: 300 minutes into run

5. Weigh Each Vial Calculate the Mass Loss per Time
   A. For our experiments – Time was determined during steady state in Primary Drying

6. Calculate Kv Grav
   A. Per Vial for a map – 336 calculations
   B. Based on Batch Average Product Temp and Shelf Temp

$$Kv\ grav = \frac{\left(\frac{dm}{dt}\right)Hs}{Av(Ts - Tb)}$$

dm/dt = Mass loss/Time – Batch Avg
Ts = Shelf Temperature – Batch Avg
Tb = Product Temperature - Batch Avg
Hs = Heat of Sublimation
Av = Area (OD) per vial

Millrock Revo

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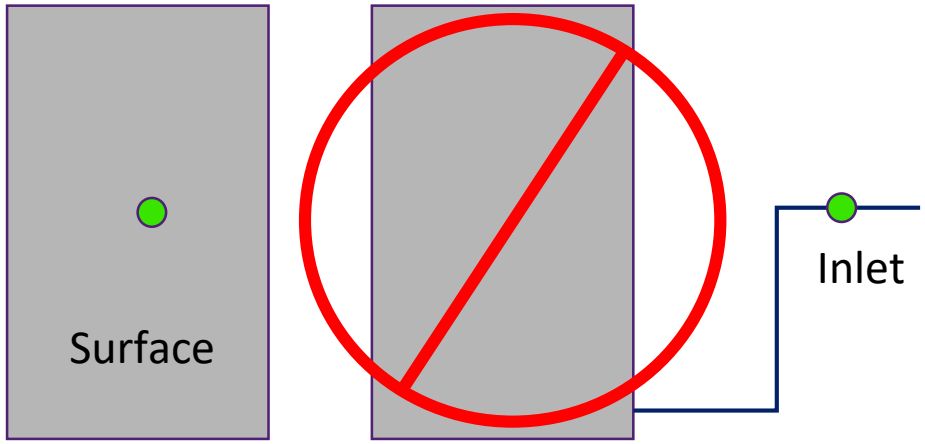
Be Consistent in Measurement between Systems

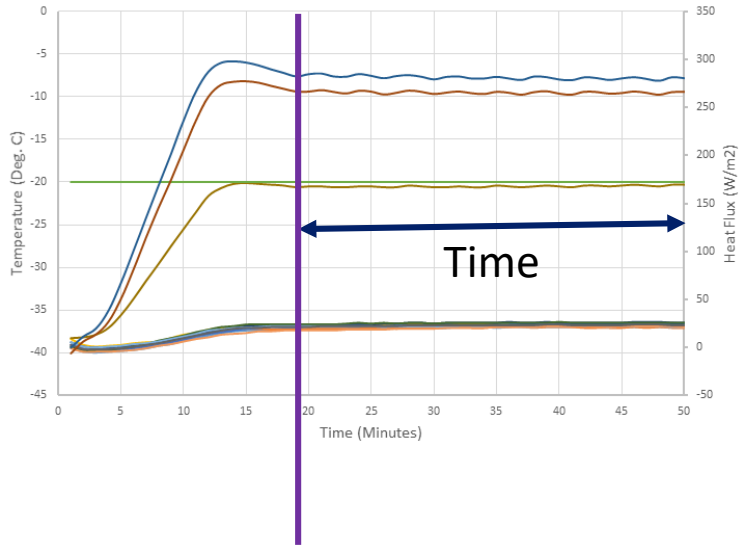
1. T_{Shelf} surface, not T_{Shelf} inlet
   A. T_{Shelf} surface provides the true Kv value
   B. Using T_{Inlet} will produce different results on different systems

2. $T_{Product}$ – Batch Average

3. Time - Be consistent
   A. We used a quick ramp to set point and timed from steady state!

4. Always use partially stoppered vials





Experimental aspects of Measuring Kv – Lindsay Wegiel

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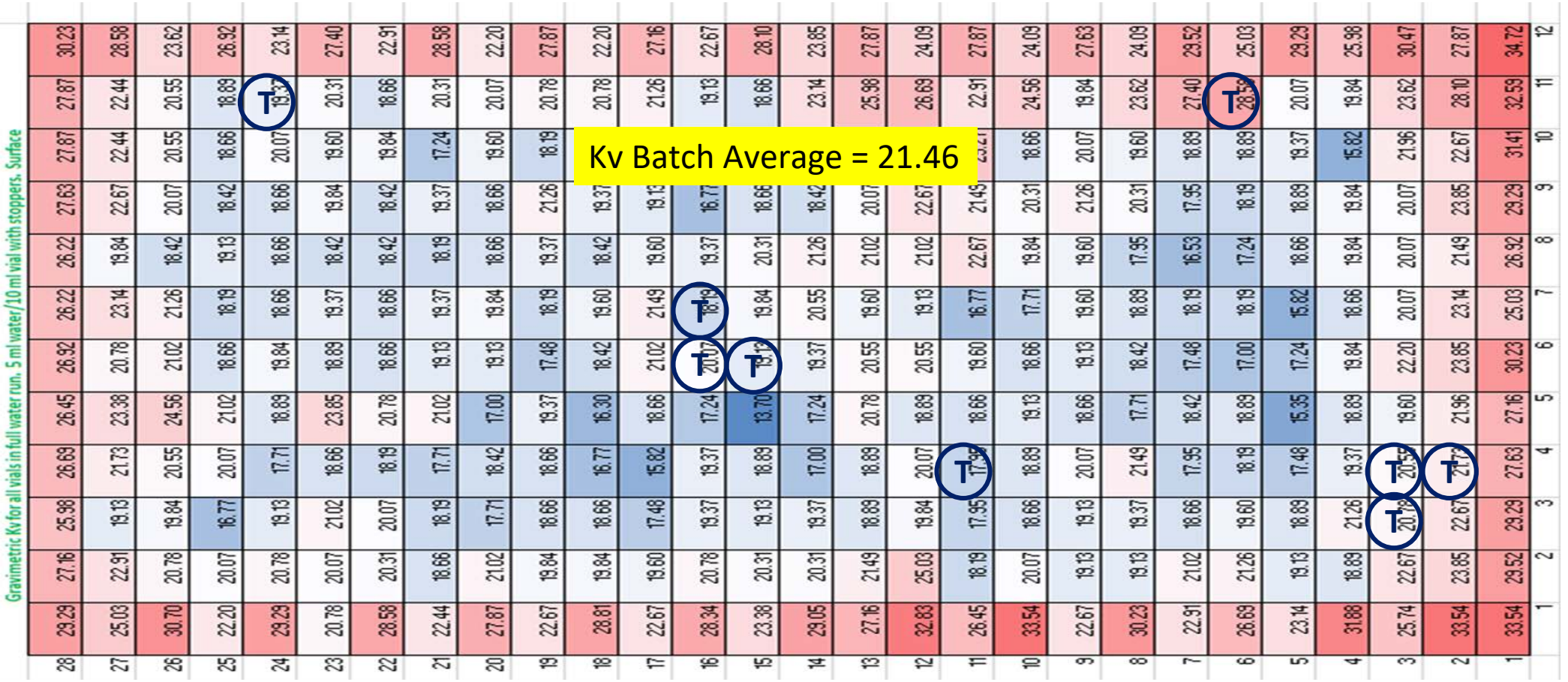
Kv Gravimetric 'Heat' Map – 12" x 24" shelf

10ml Vial, 5ml H_2O, Tshelf -20C, 100mT

Kv Gravimetric Based on
$T_{Shelf\_Surface}$ (-20.3 °C)



Kv in W/sqM/C

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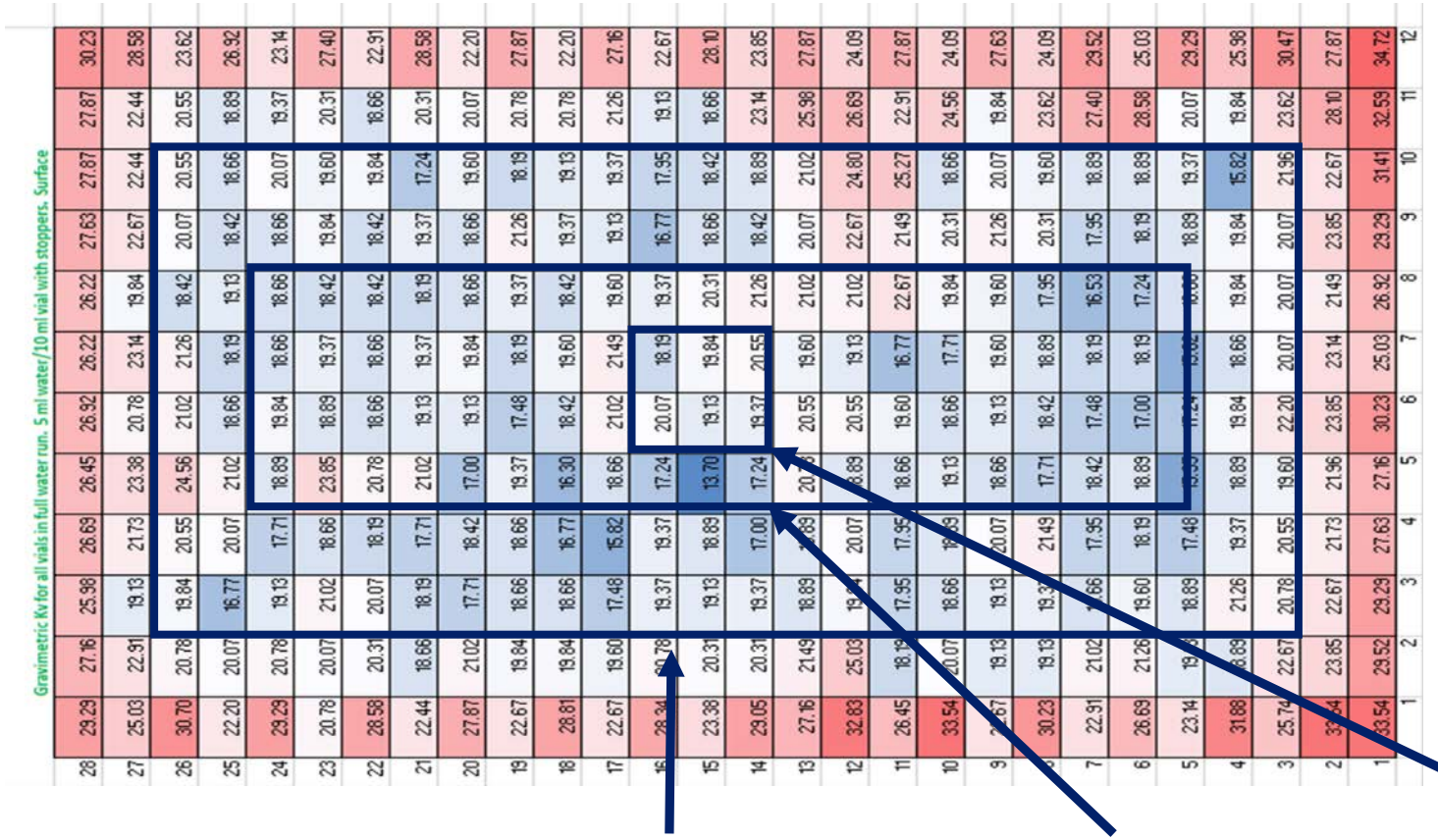
Kv Variation Depending on Vial Selection – Full Shelf (12” x 24”)



Front

Columns x Rows	12 x 28		8 x 24		4 x 20		6 Center vials
Kv Grav – Shelf Temp	21.46		19.18		18.92		18.90

Kv in W/sqM/C

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Kv Gravimetric

1. Advantages
   A. Data can be selected for desired results
      i. Batch Average vs Center Vials vs Edge Vials
2. Disadvantages
   A. Labor intensive and Time consuming
   B. Subject to error due to the large number of manual measurements
   C. Must use the batch average product temperature
   D. Calculation of time is subjective
      i. Wait for stable sublimation
   E. Challenge to get Kv Gravimetrically for Production Units

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Kv Determination Using AccuFlux®

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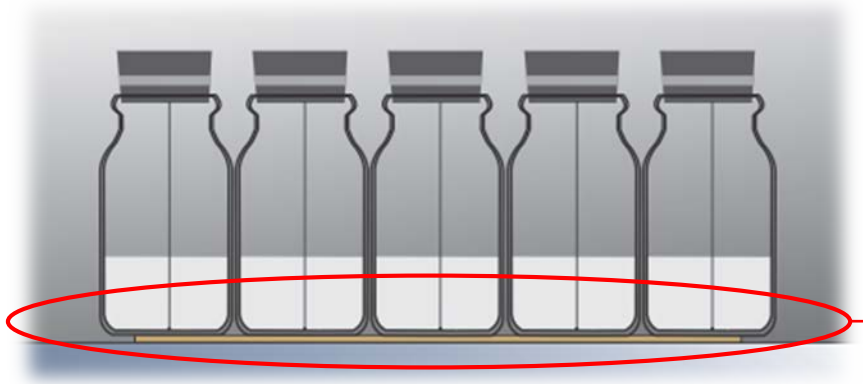
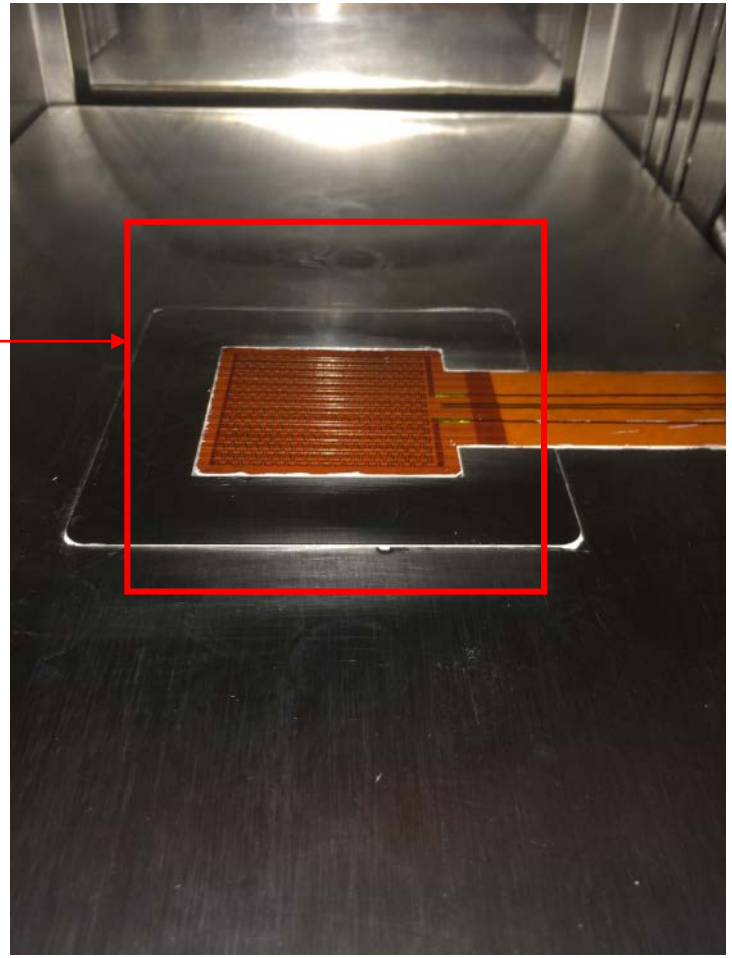
AccuFlux®





- AccuFlux Sensor Size : ~ 2.5” x 2.5”
  - Installed directly on the surface of the shelf
- Measures
  - Heat Flux from Shelf to Vial
  - Shelf Surface Temperature
- Output in : Watts/m^2 = Joules/sec/m^2

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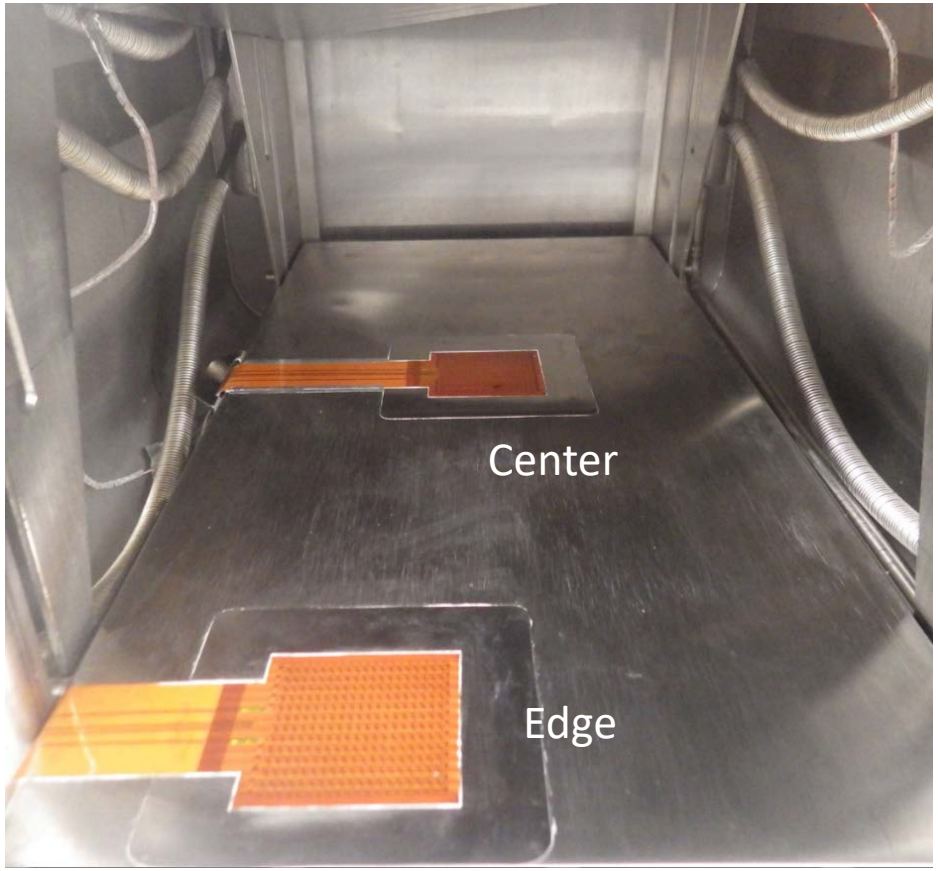
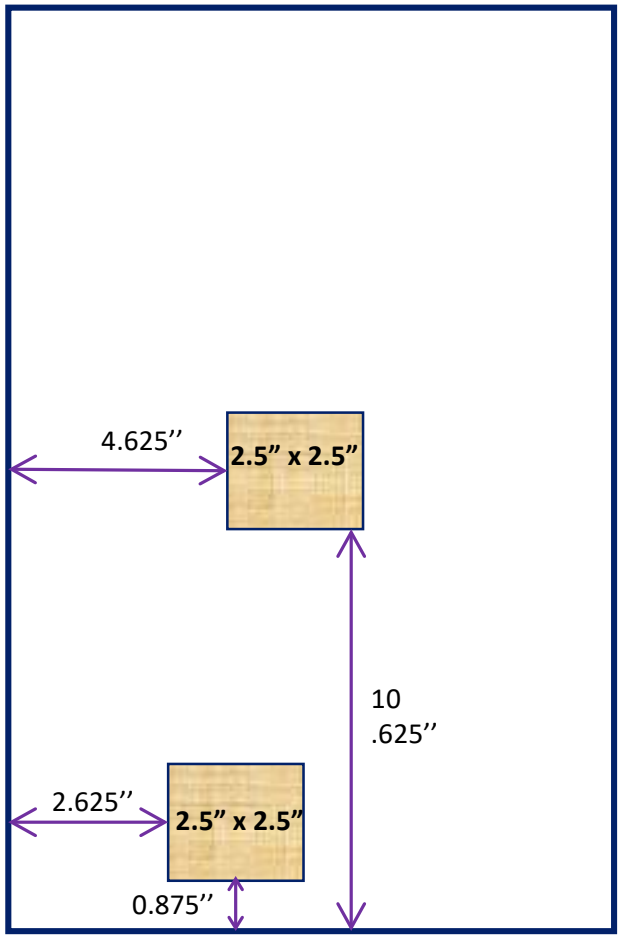
Sensor Location on Shelf (12”x 24”)





Front

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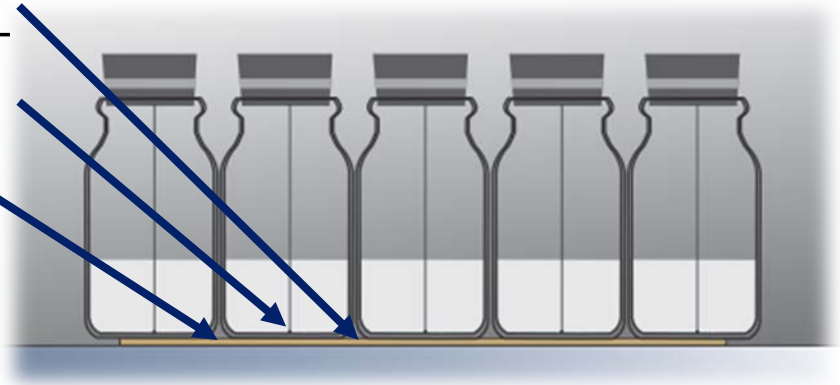
Kv Determination Using AccuFlux

$$Kv\ AccuFlux\ Shelf\ = \frac{HF\ Shelf}{(T_s - T_b)}$$



$Kv\ Other$

- Radiation
- Gas Conduction
- And Other Sources of Heating and Cooling

Kv = Kv AccuFlux Shelf + Kv Other

Gas Conduction, Radiation

How do we determine Kv without measuring Kv Other?

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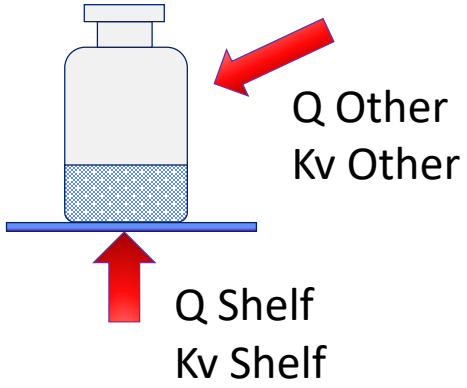
Kv Determination Using AccuFlux



To find Kv :

- Perform a Full Primary Drying Cycle
  - Measure Kv Accuflux at Steady State

- Determine the Amount of Heat Flow from the Shelf vs the Total Heat of Sublimation

- Divide Kv AccuFlux by % Q Shelf to get Kv Total

$$Kv\ AccuFlux\ Shelf\ = \frac{HF\ Shelf}{(T_s - T_b)}$$
at steady state

$$\%\ Q\ Shelf\ = \frac{QShelf\ Accum}{(\Delta\ Hs\ * mass)}$$

$$Kv\ AccuFlux\ total = \frac{Kv\ AccuFlux\ Shelf}{\%\ Q\ Shelf}$$

HF – Heat Flux (W/sqM)
Hs – Heat of Sublimation (2834 J/g)
Mass – Mass of material sublimating
Kv AccuFlux – Heat Flow from Shelf
%Q Shelf – Heat flow measured divided by Total Heat of Sublimation
Kv total – Vial Heat Transfer Coeff

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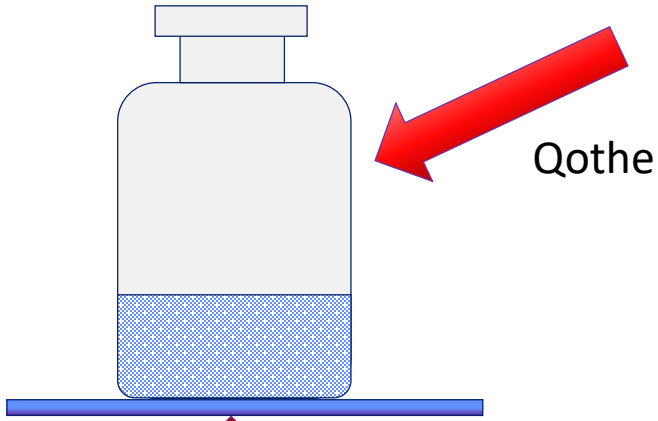
Kv Total Example

Variable	Value	UOM	Comment
Kv AccuFlux Measured	15.1	W/sqM/C	Measured at Steady State During Primary Drying
Q Shelf Total Measured	4,285,612	J	Measured by AccuFlux for Full Primary Drying Cycle
Q Sublimation	4,761,792	J	Mass of Material x Heat of Sublimation
% Q Shelf	90%		Q Shelf / Q Sublimation
Kv AccuFlux Total	16.78		Kv AccuFlux / % Q Shelf



$$Kv\ AccuFlux = 15.1$$

$$Q\ Shelf\ Accum = 4{,}285{,}612$$

$$Q\ Sublimation = 4761792\ J$$

$$\%\ Q\ Shelf = \frac{Q\ Shelf\ Accum}{Q\ Sublim} = \frac{4{,}285{,}612\ J}{4{,}761{,}792\ J} = 90\%$$

$$Kv\ Total = \frac{Kv\ AccuFlux}{\%\ Q\ Shelf} = \frac{15.1}{.90} = 16.78$$

Kv in W/sqM/C

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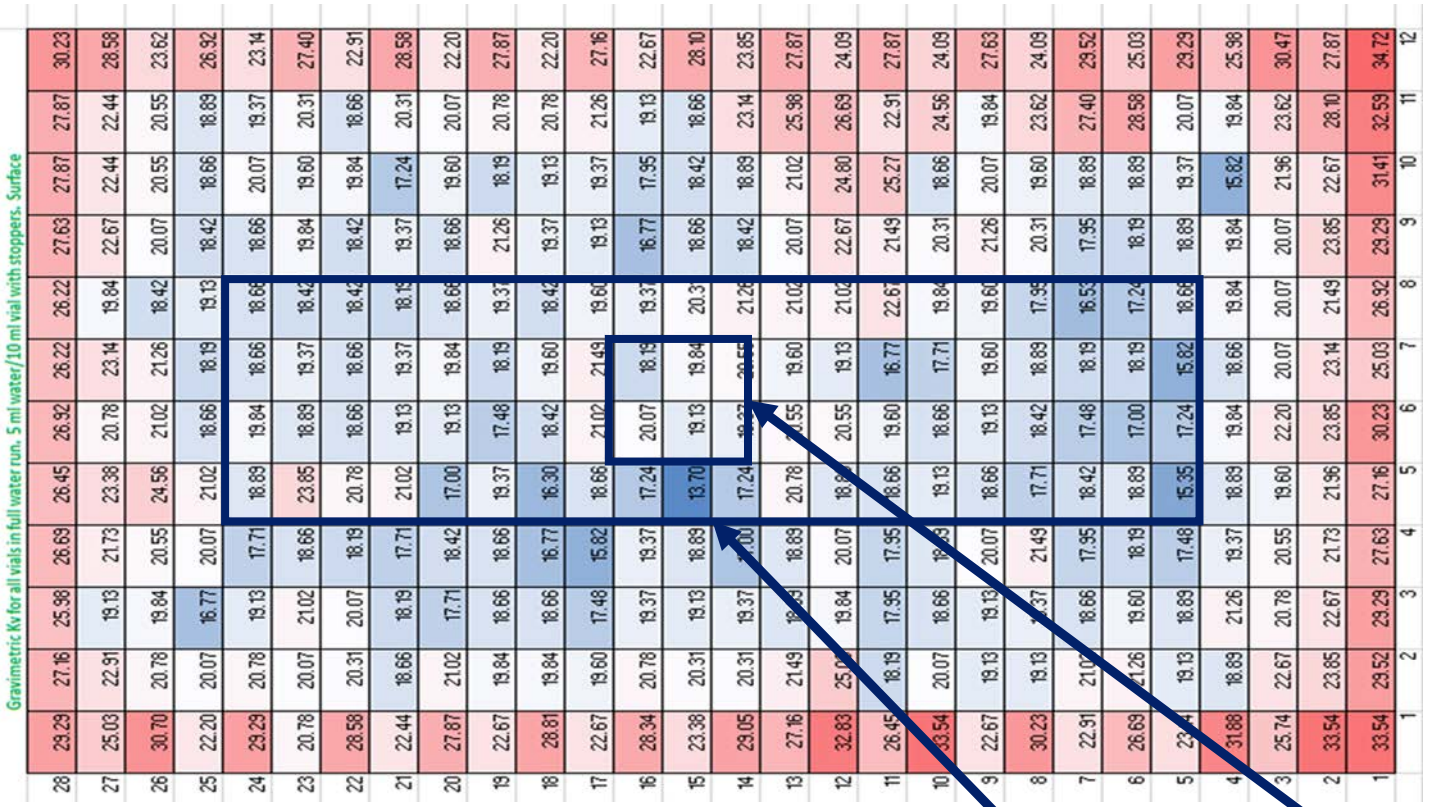
Kv AccuFlux vs Kv Gravimetric for Center Vials



Columns x Rows	12 x 28		8 x 24		4 x 20		6 Center vials
KV Grav Center	21.46		19.18		18.92		18.90
Kv Grav StDEV	3.88		1.57		1.55		
Kv Accuflux Center					18.01		18.01

Within +/- 2.5 %!

Kv in W/sqM/C

Great Correlation!

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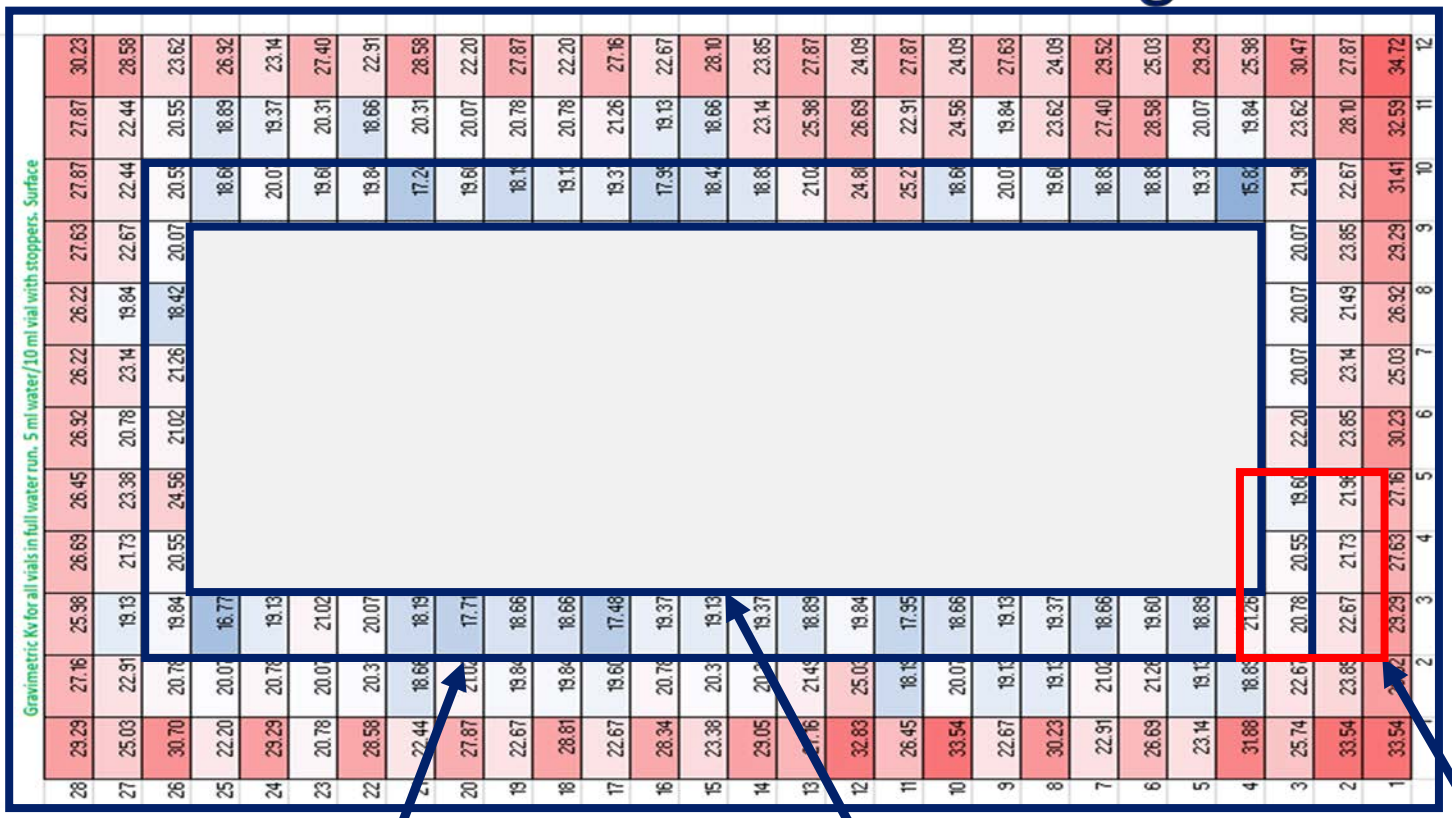
Kv AccuFlux vs Kv Gravimetric for Edge Vials



Range	Outer 2 rings		Outer 3 rings		Accuflux Edge vials
KV Grav Edge	24.50		23.08		23.48
Kv AccuFlux Edge	23.71		23.71		23.71

Great Correlation!

Kv in W/sqM/C

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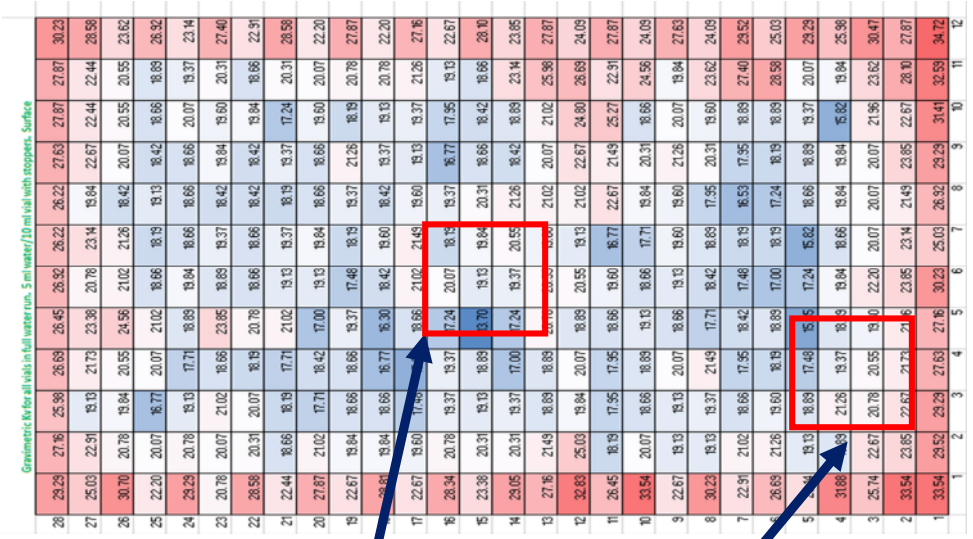
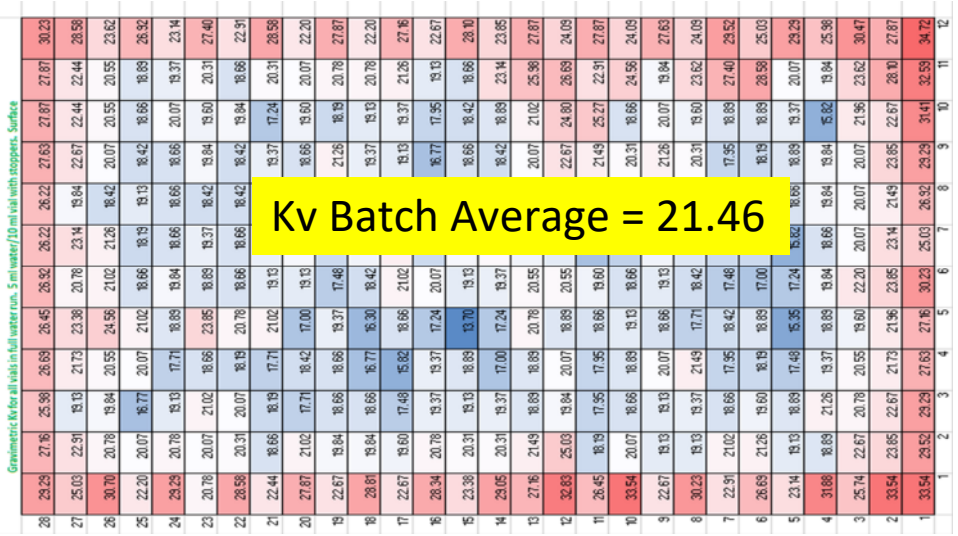
Conclusion: Kv AccuFlux Correlates to Kv Gravimetric





Kv Batch Average = 21.46

Kv AccuFlux Center	Kv AccuFlux Edge
18.01	23.71

Kv AccuFlux Avg	Kv Gravimetric
20.86	21.46

Kv Accuflux Avg = (Kv Center + Kv Edge) / 2

Kv in W/sqM/C

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Determine Kv AccuFlux and Kv Gravimetric Correlation in a MicroFD®

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What is the MicroFD®?

1. Process Small Batch – 19 vials or less

2. Latest PAT Technologies
   A. Controlled Nucleation
   B. AccuFlux Heat Flow measurement and control
   C. LyoSIM – Center and Edge Vial simulation
   D. LyoPAT Control System

3. Determines All Critical Process Parameters
   A. Kv - Vial Heat Transfer Coeff
   B. dM/dt - Mass Flow
   C. Rp - Cake Resistance
   D. ….

4. Ability to Test the Effects of
   A. Freezing Methods
   B. Drying Conditions

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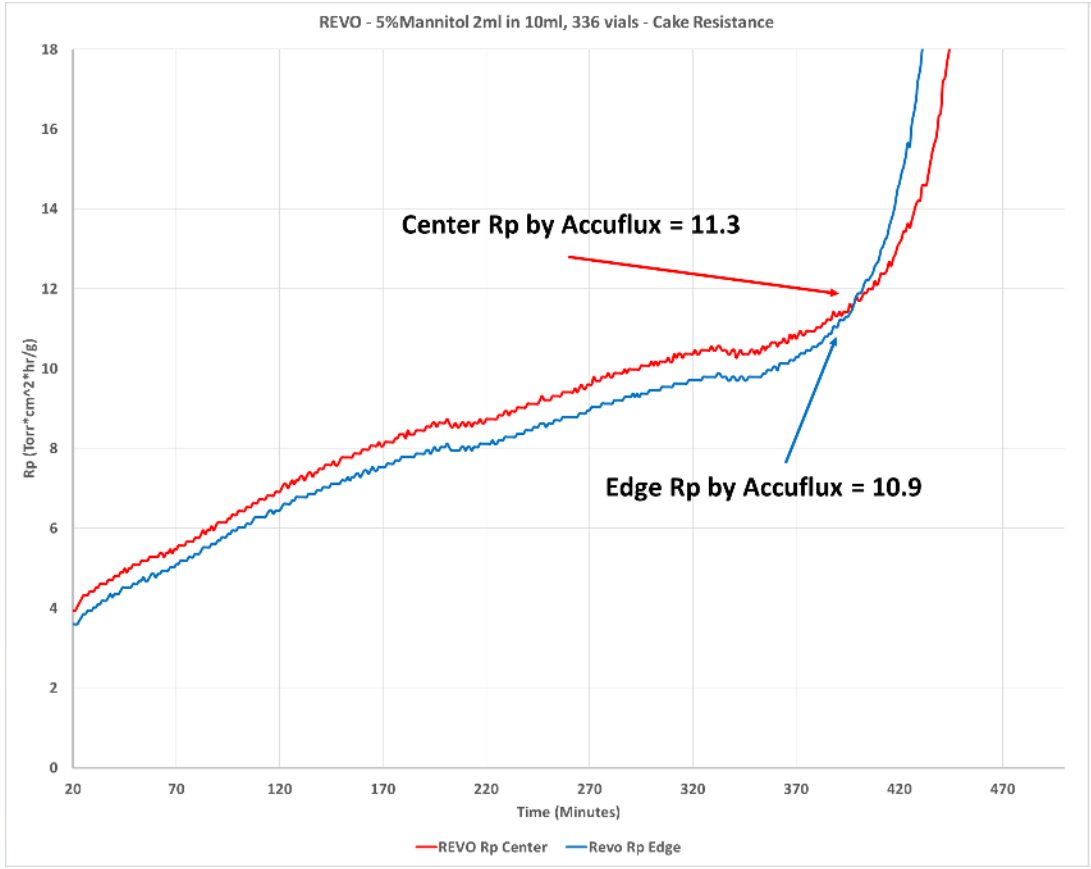
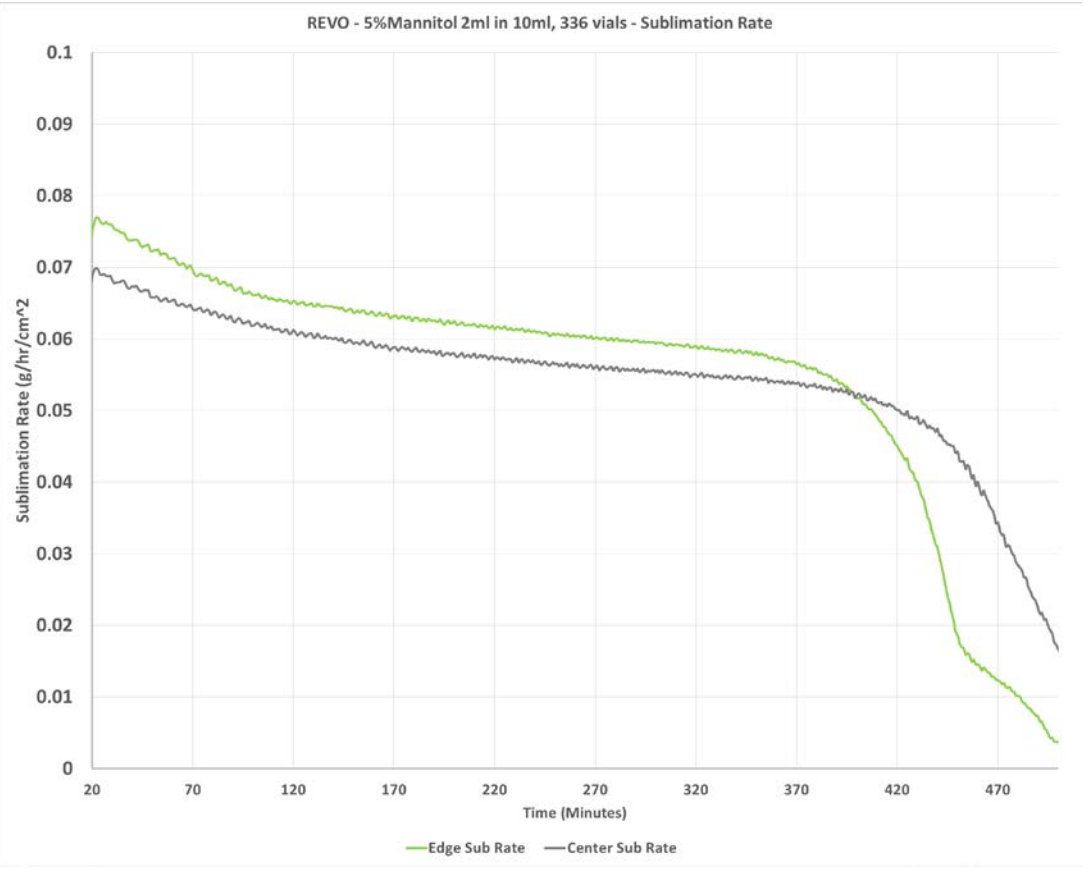
LyoPAT Example – Cake Resistance and Mass Flow





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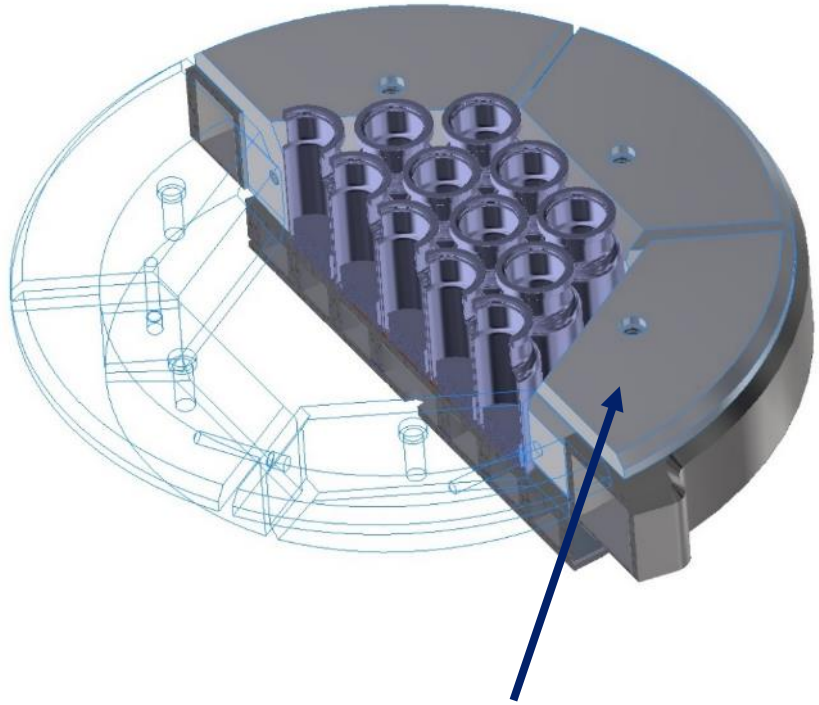
LyoSIM®– Modeling Center or Edge Vials

- Temperature Controlled Ring
  - Closely coupled to the vial stack
  - Independent control from shelf
  - Tracks/follows product temperature!
  - With Conduction Blocks for Different Sized Vials

- Model Center or Edge Vials By Programming the LyoSIM Temperature



Removable thermal conductors to accommodate different vials

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How is LyoSIM used?

LyoSIM temperature can be programmed to follow the temperature of the product to simulate either center or edge vials

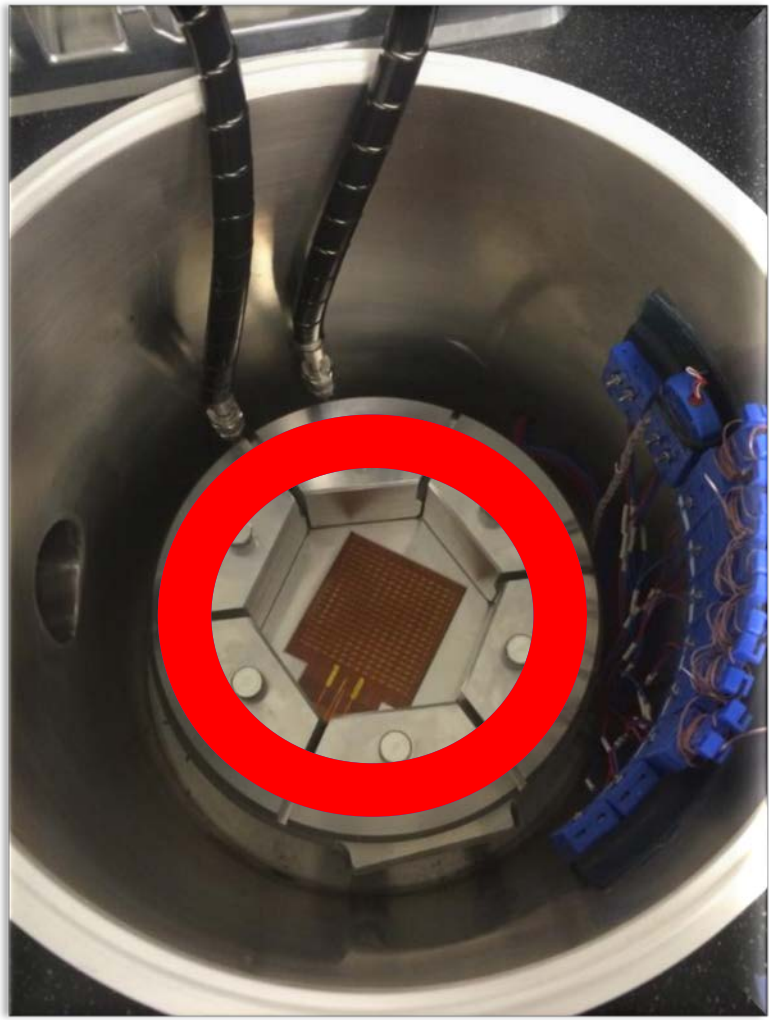
Primary Drying:

i. Center Vial Effect

- $T_{LyoSIM} =< T_{product}$
- E.g.: LyoSIM Temperature $=T_{product}$ - 2 °C

ii. Edge Vial Effect

- $T_{LyoSIM} > T_{product}$
- E.g: LyoSIM Temperature = $T_{product}$ + 5 °C



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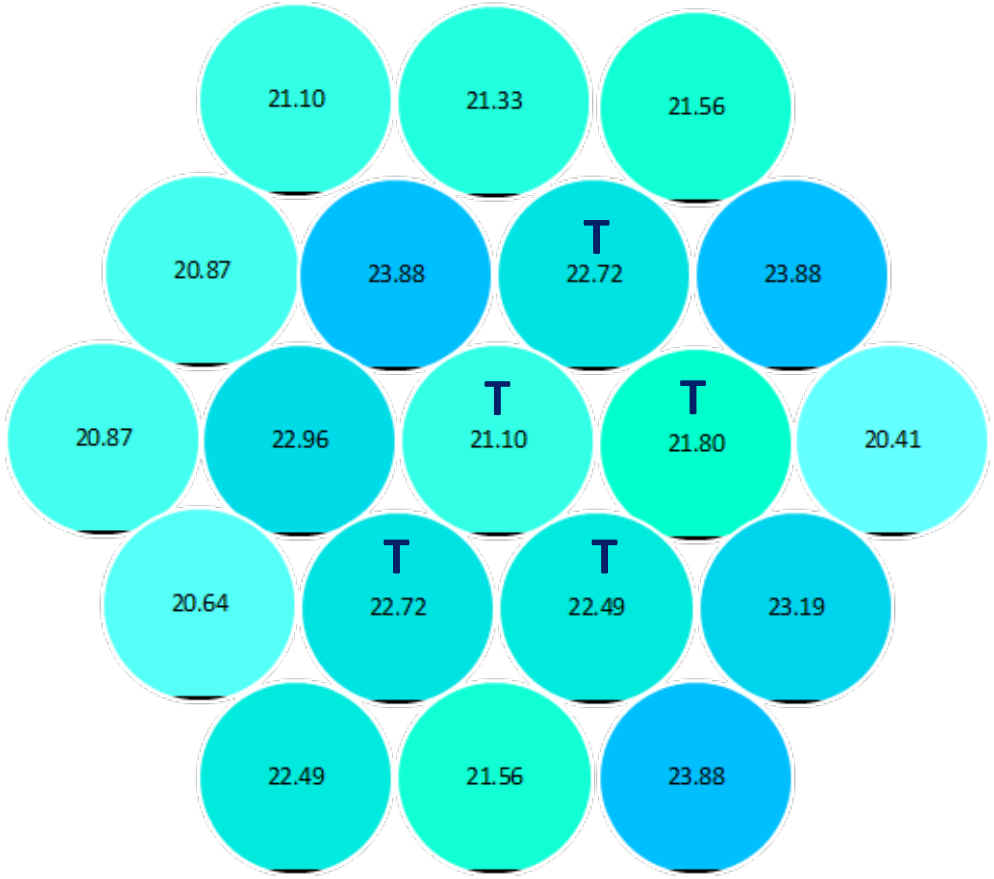
MicroFD Kv Gravimetric Results (center vial simulation)

Gravimetric	Kv (W/m^2-C)
Batch Average	22.08
Inner 7 vials	22.53
Outer 12 vials	21.82
MicroFD 19-vial STDEV	1.12
REVO center vial (4x20) StDEV	1.55

All 19 vials behave like center vials!



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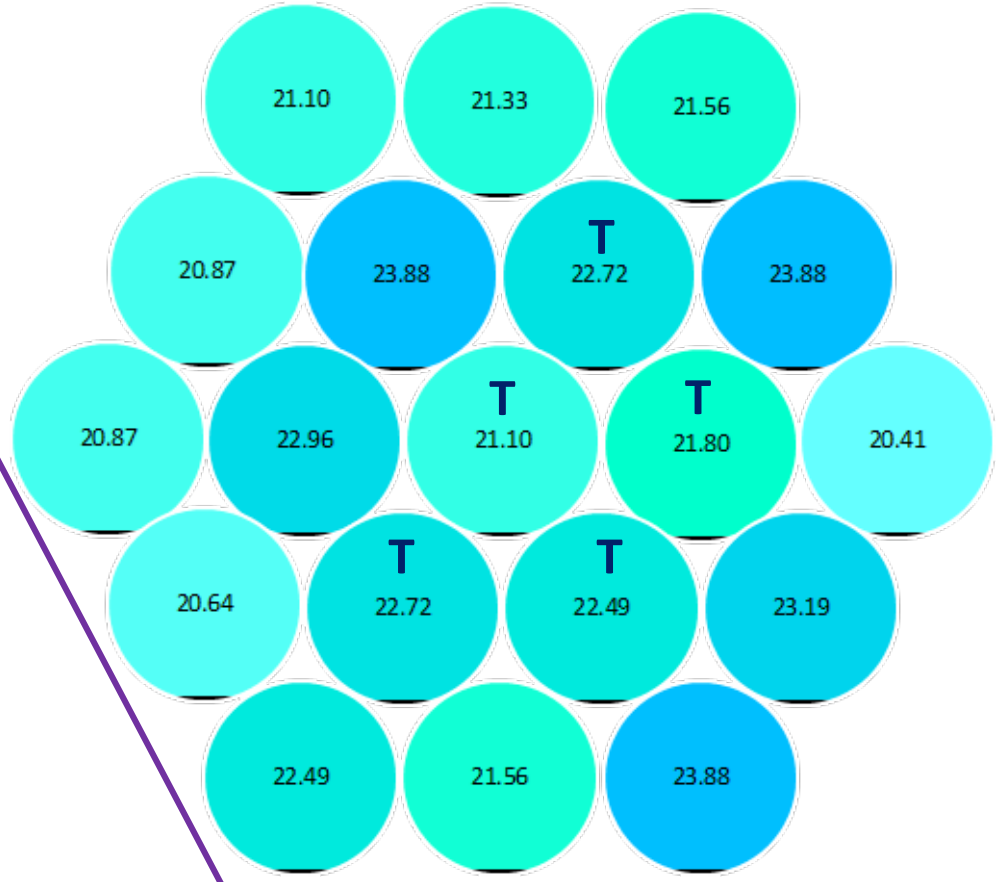
MicroFD Kv Gravimetric Results vs Kv Accuflux (center vials)

Gravimetric	Kv (W/m^2-C)
Batch Average	22.08
Inner 7 vials	22.53
Outer 12 vials	21.82
STDEV	1.12
Accuflux	**Kv (W/m^2-C)**
Kv AccuFlux Shelf@300min	12.5
%Q Shelf	56.4%
Kv AccuFlux Total after full run	22.16



Great Correlation!

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Protocol Transfer from MicroFD to REVO Using Kv AccuFlux

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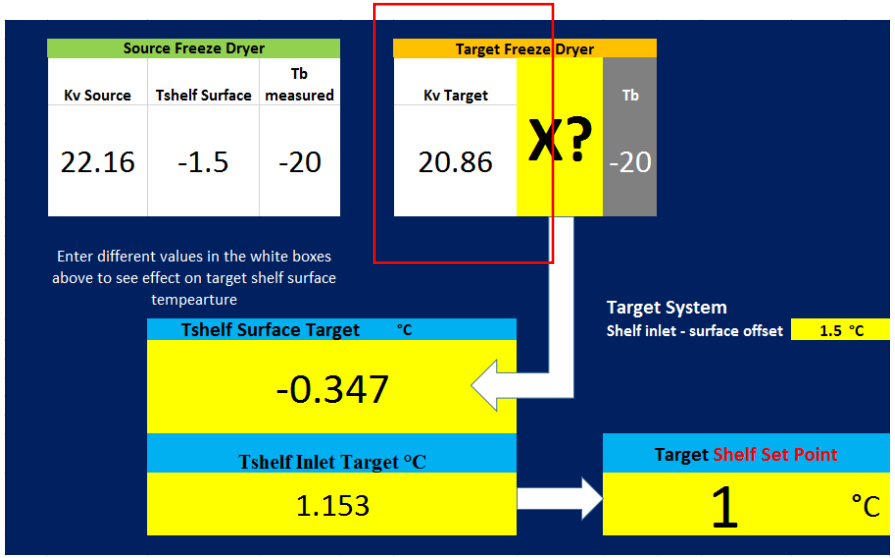
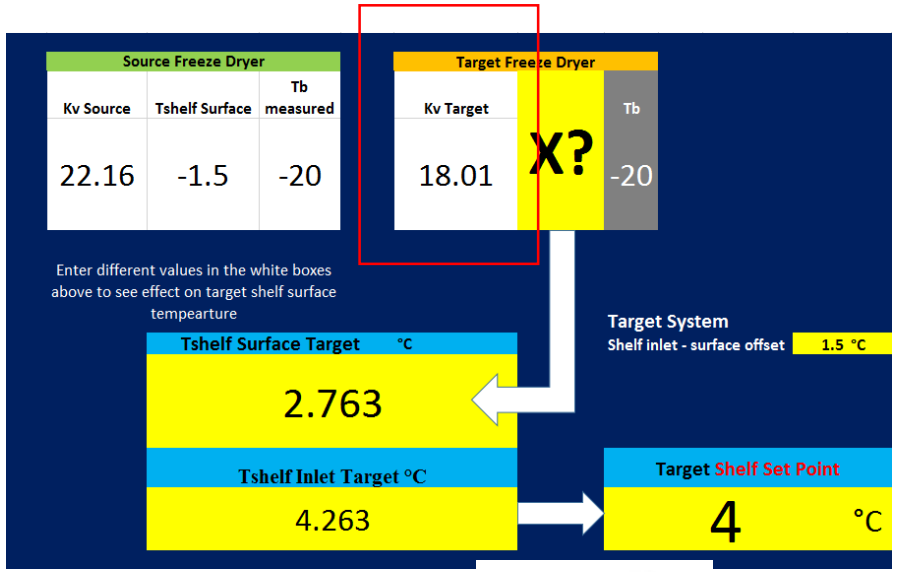
Protocol Transfer using Kv

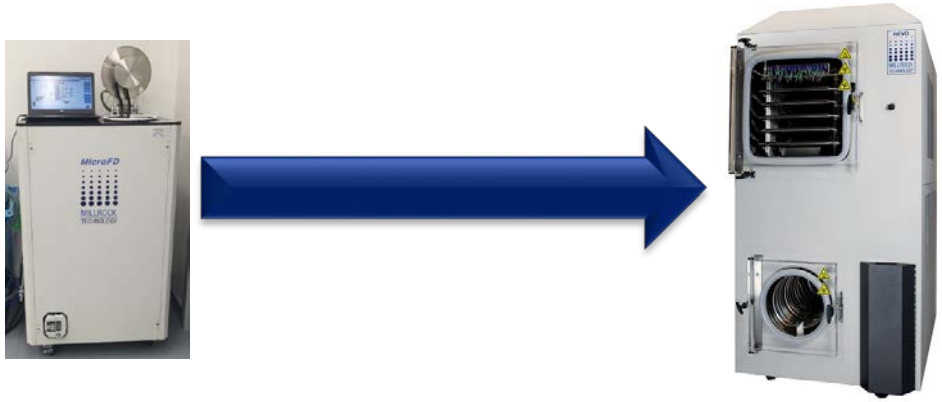
Kv AccuFlux Batch Average



Kv AccuFlux Center Vials



Kv Source – MicroFD
Kv Target – REVO



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5% Mannitol Experiments – Cycle Information

Setup	MicroFD	REVO
Material	5% Mannitol	5% Mannitol
Vial size	10 mL	10 mL
Fill Volume	2ml	2ml
Number of vials	19	336

Protocol	MicroFD	REVO	REVO
Freezing	0.5 °C/min to -40 °C	0.5 °C/min to -40 °C	0.5 °C/min to -40 °C
Annealing for 2 hours	-15 °C	-15 °C	-15 °C
Kv Accuflux	22.16	20.86 (Batch Avg)	18.01 (Center Kv)
Primary Drying Shelf	0 °C	0 °C	+ 4 °C
Primary Drying Vacuum	100 mT	100 mT	100 mT

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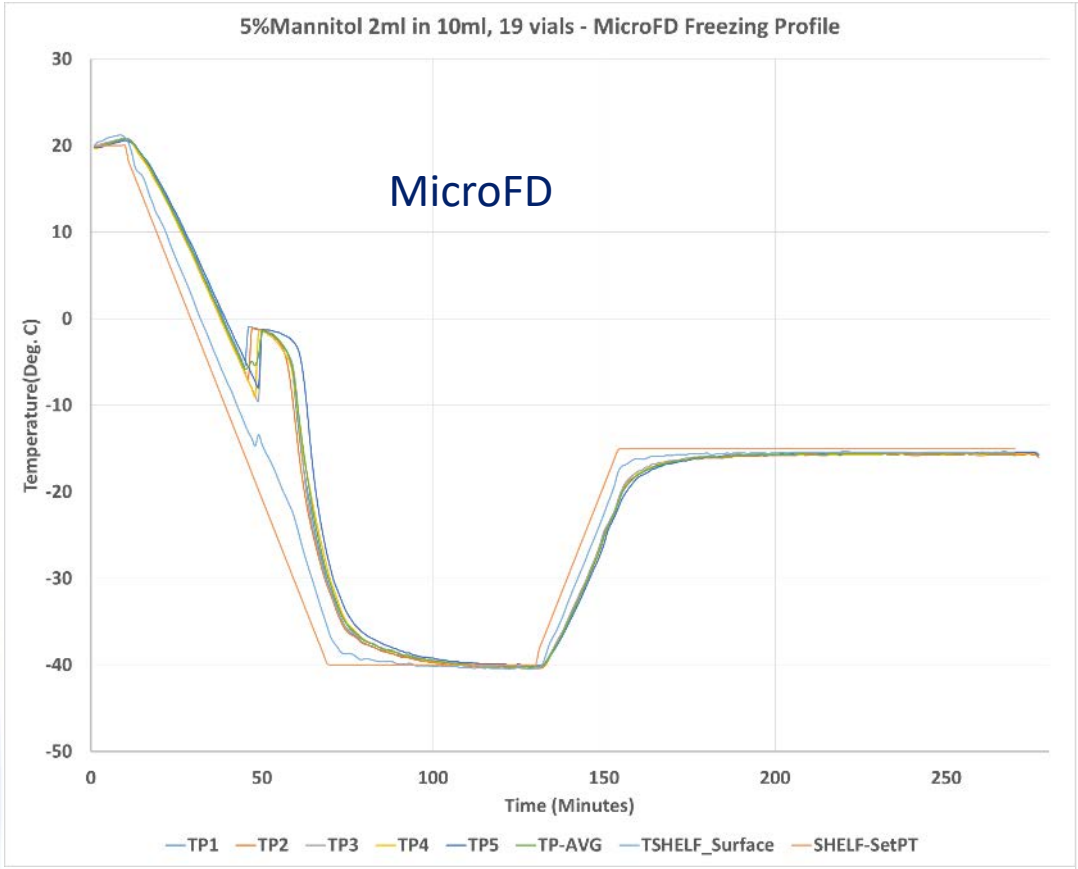
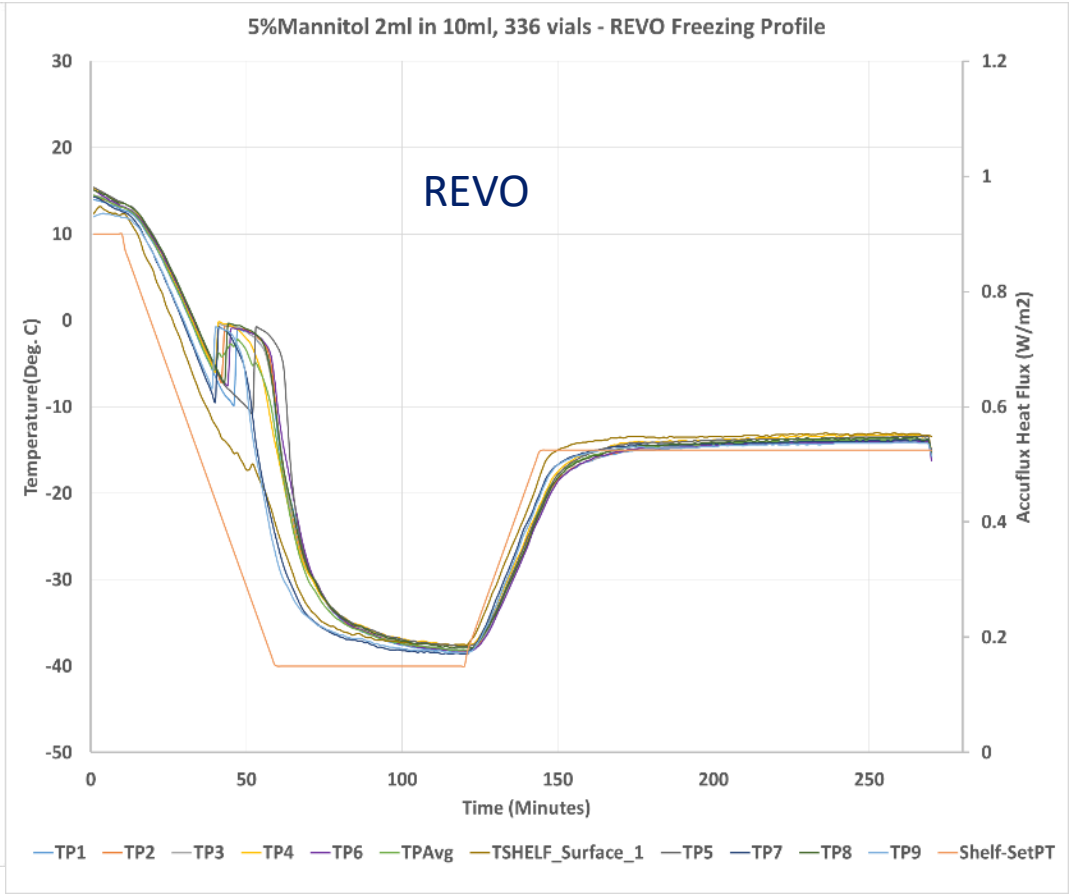
Freezing Comparison between MicroFD and REVO (without HF)





5% Mannitol 2ml fill in 10ml vials

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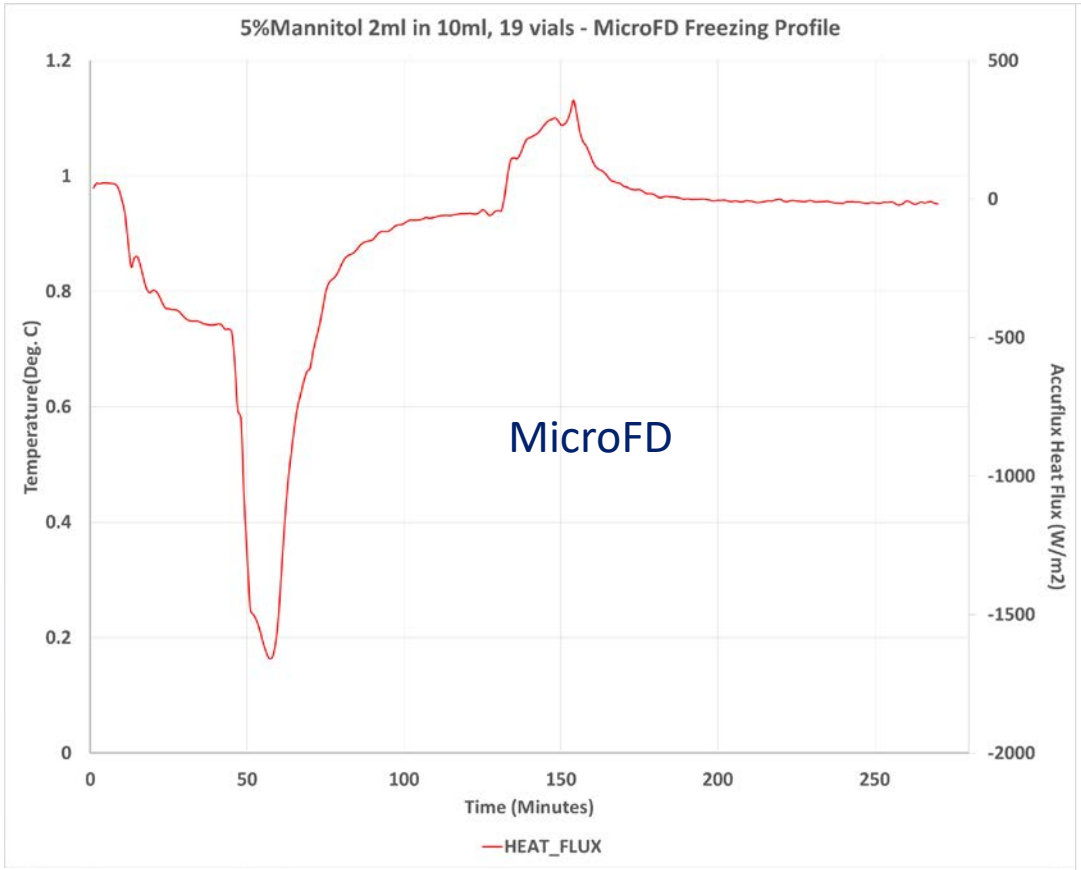
Freezing Comparison between MicroFD and REVO – Heat Flow



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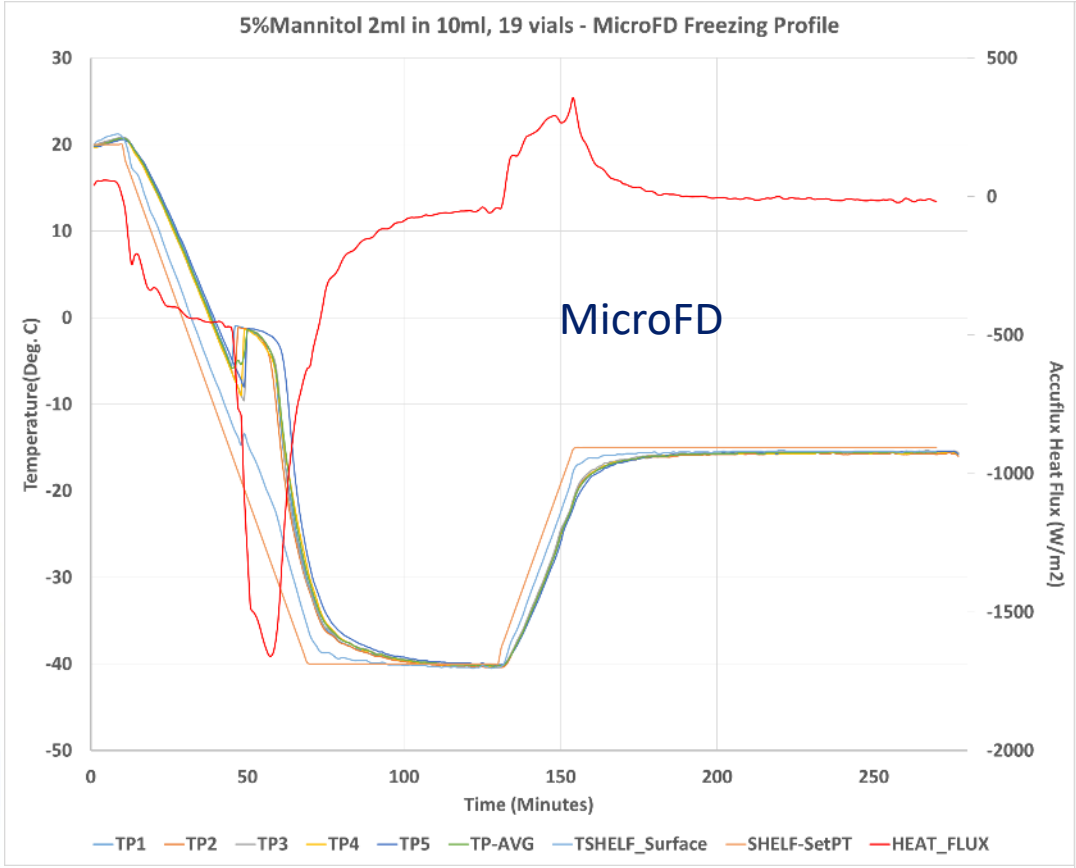
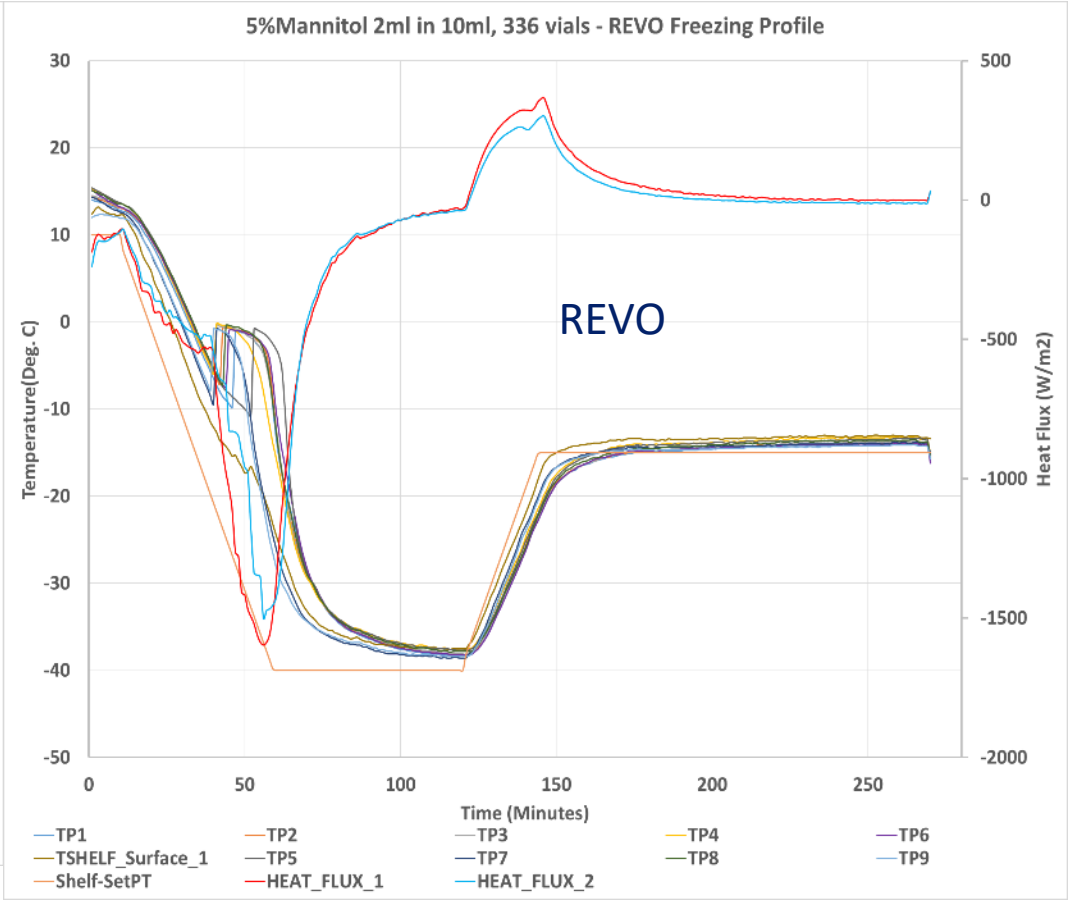
Freezing Comparison between MicroFD and REVO





5% Mannitol 2ml fill in 10ml vials

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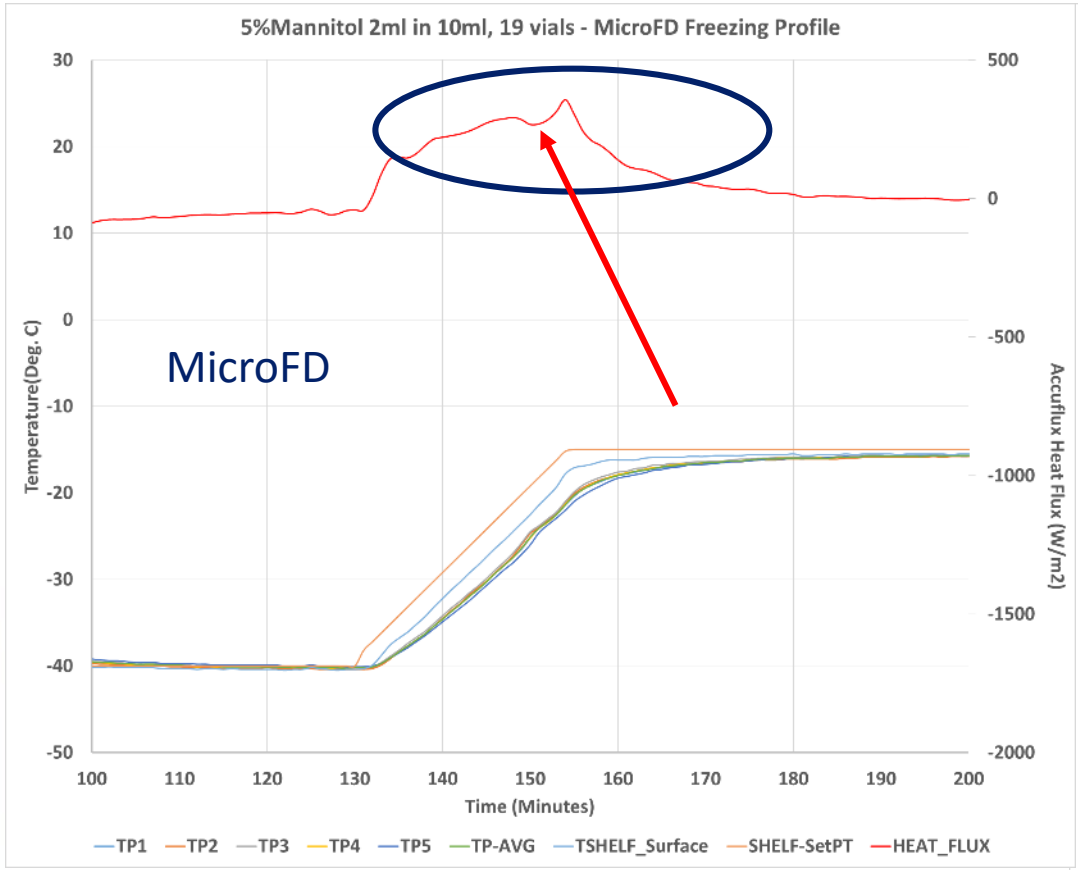
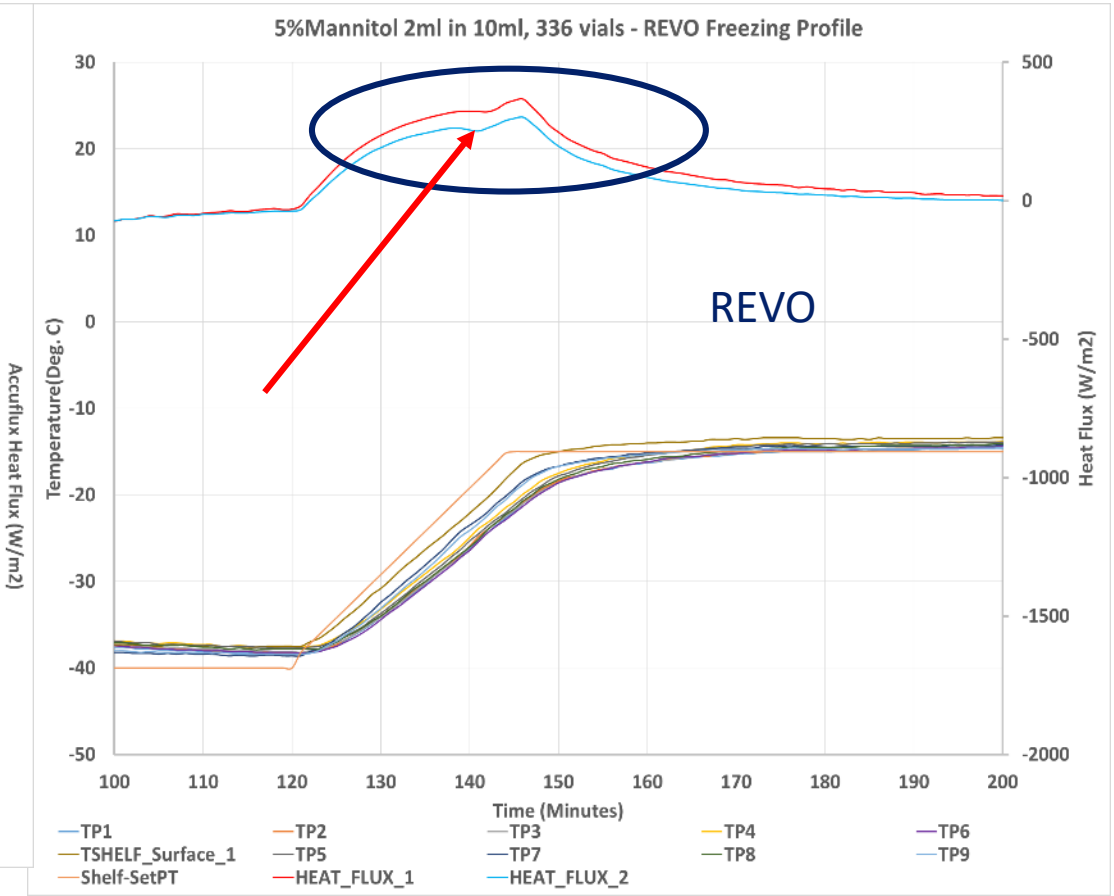
Freezing Comparison between MicroFD and REVO – Secondary Crystallization?





5% Mannitol 2ml fill in 10ml vials

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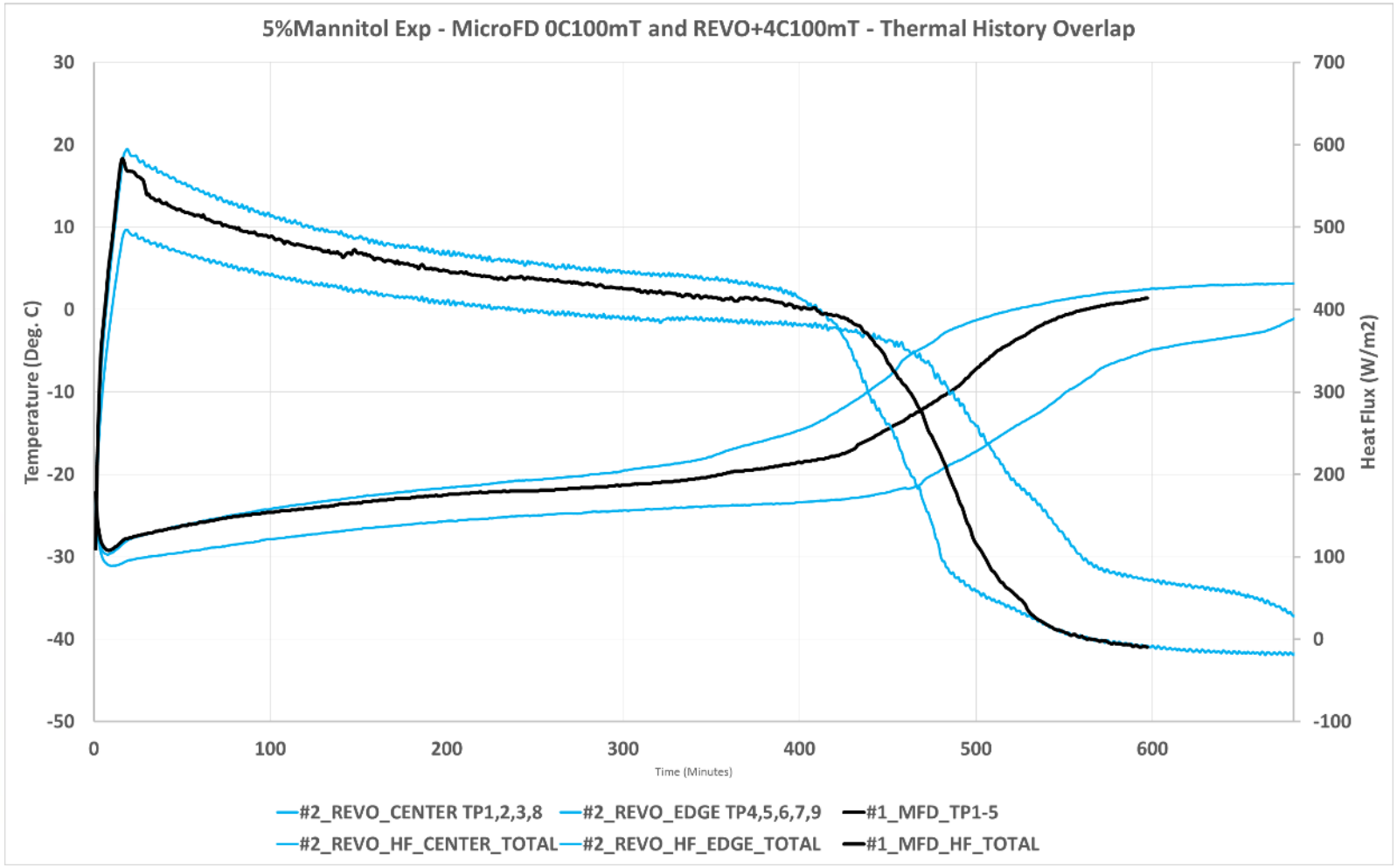
MicroFD and REVO – Baseline Thermal History Overlap



MicroFD@ 0C 100mT

REVO@ 0C 100mT

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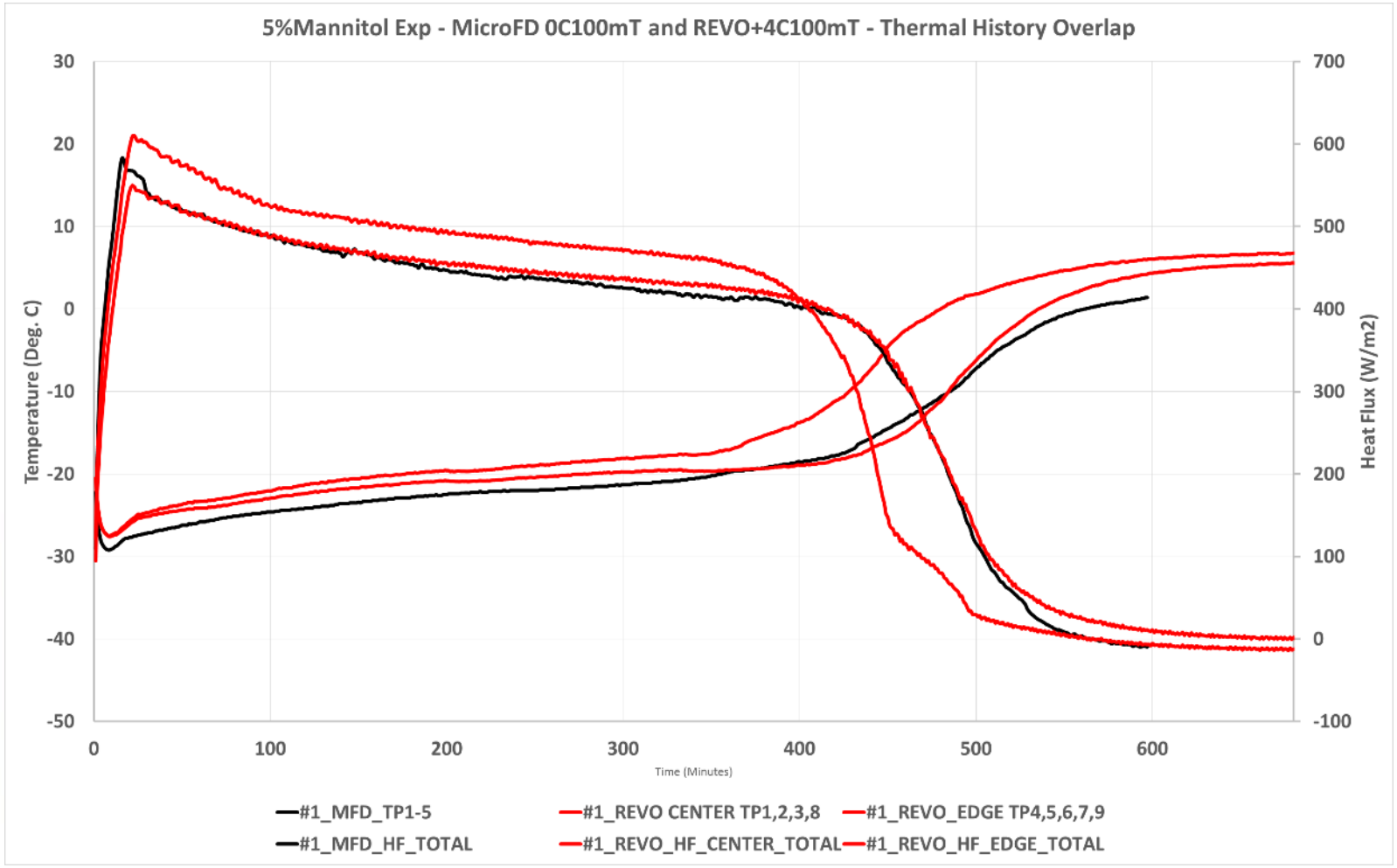
MicroFD and REVO – Transfer Thermal History Overlap



MicroFD@ 0C 100mT

REVO@ +4C 100mT

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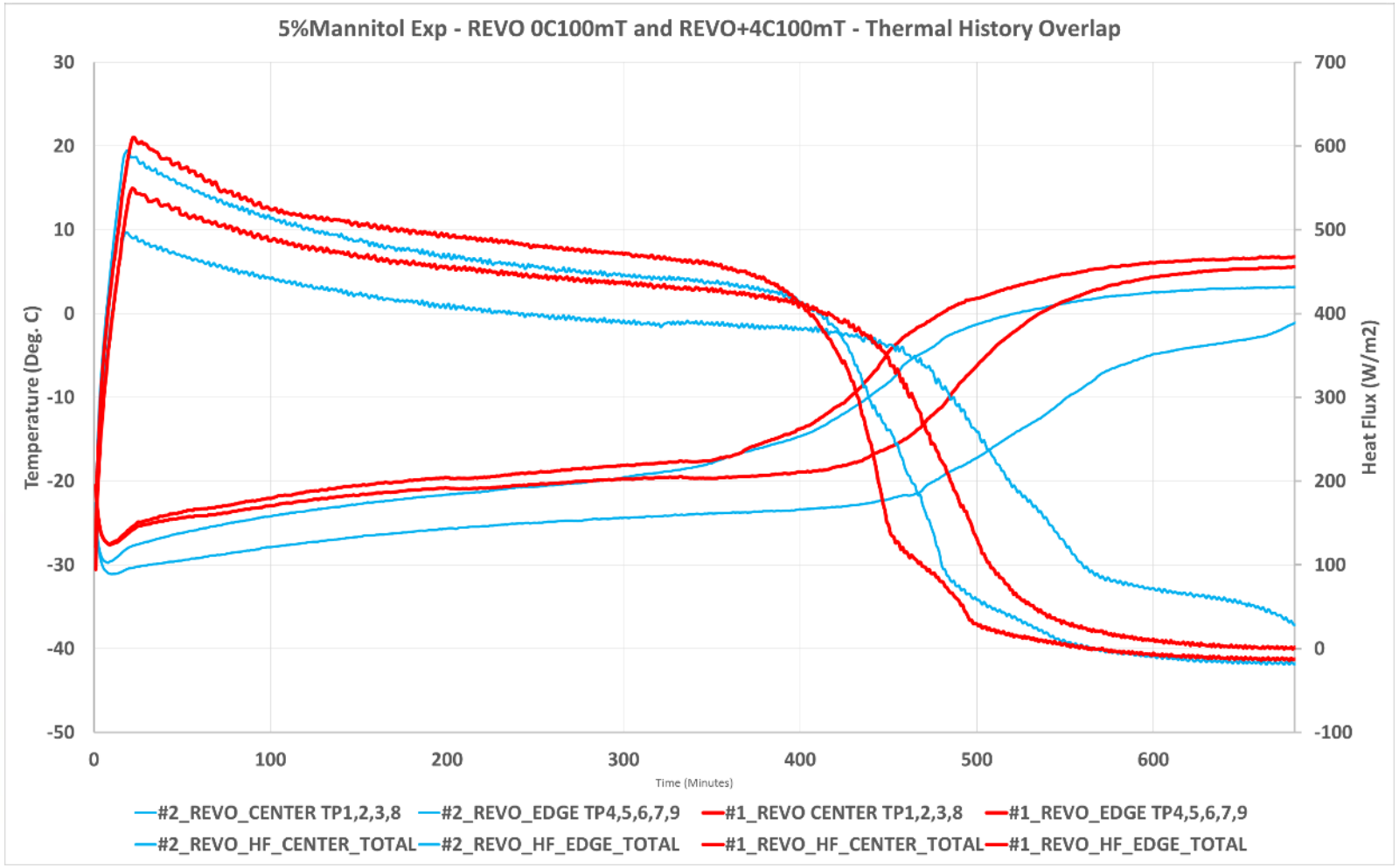
REVO Baseline vs REVO Transfer – Thermal History Overlap



REVO@ 0C 100mT

REVO@ 4C 100mT

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CONCLUSIONS

- Kv AccuFlux can replace Kv Gravimetric.
  - Accuflux eliminates the need to weigh vials before and after the run and eliminates data entry for calculating Kv.
- The MicroFD can be used to develop and transfer a cycle successfully.

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Next: Develop Optimized Transferable Protocols Using 19 Vials

Experiments in progress!

MicroFD

Revo

Quanta

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Thank you!

Questions?

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MicroFD and REVO Kv AccuFlux and Kv Gravimetric

-20°C 100mT	Kv AccuFlux Center	Kv Grav Center	Kv Grav Center	Kv Grav Center	Kv AccuFlux Edge	Kv Grav Edge Outer 2 rings	Kv Grav Edge Outer 3 rings	Kv Grav Accuflux Edge vials	Batch Average Kv Grav	Batch Average Kv Accuflux
MicroFD	22.16	22.08 (19 vials)	22.53 (Inner 7)	21.82 (Outer 12)	/	/	/	/	/	/
MicroFD*	20.66	20.47	20.88	20.23	/	/	/	/	/	/
REVO	18.01	19.18 (8x24 vials)	18.92 (4x20 vials)	18.90 (6 center vials)	23.71	24.50	23.08	23.48	21.46	20.86
REVO*	17.40	18.49	18.24	18.23	22.23	23.63	22.25	22.65	20.70	19.82

*Measured using shelf inlet temp

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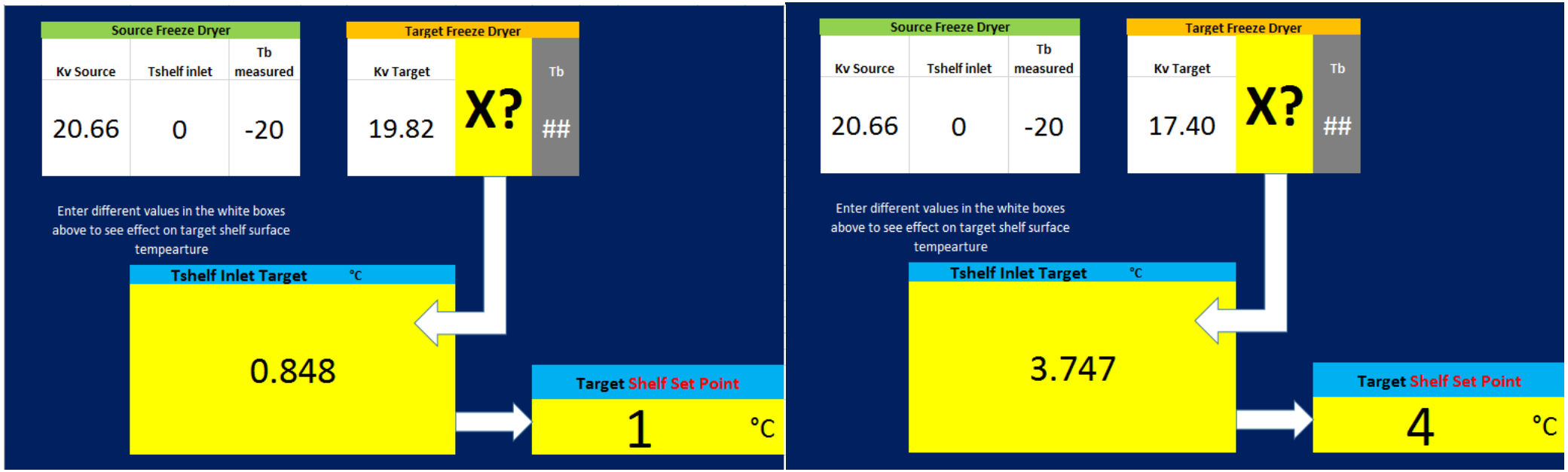
Transfer using Kv inlet results



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Shelf Temperature Transfer Concept

$$Ts\_surface_{target} = \left(\frac{Kv\ Source}{Kv\ Target}\right) \times (Ts_{surface_{source}} - Tb_{source}) + Tb_{target}$$

Goal - Maintain the same level of heat flow going into the vial during the run in both systems	
Assumptions:	Heat Flux source - Heat Flux Target
	Tb source - Tb target
User equivac Kv in both systems	Using LyoPAT
	or Gravimetrically

Units of measure	
Kv	W/m^2-C
Heat Flux	W/m^2-C
Ts	C
Tb	C

Source Freeze Dryer		
Kv Source	Tshelf Surface	Tb measured
22.16	-1.5	-20

Target Freeze Dryer		
Kv Target		Tb
18.01	X?	-20

Enter different values in the white boxes above to see effect on target shelf surface tempearture

Target System
Shelf inlet - surface offset 1.5 °C

Tshelf Surface Target °C
2.763

Tshelf Inlet Target °C
4.263

Target Shelf Set Point
4 °C

MicroFD
Source

Revo
Target

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