

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

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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

Vial Heat Transfer Coefficient - K_v

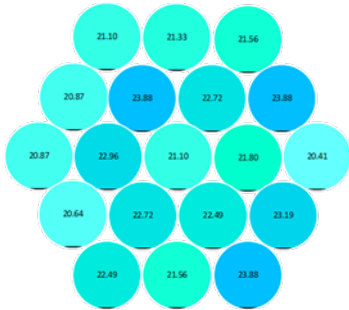
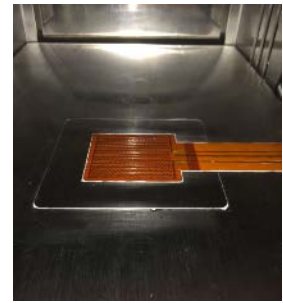
1. K_v can be used to help with transfer of protocols between different freeze dryers

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

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'

Time	Temp	Pressure	Flow	Weight	Moisture	Volume	Area	Perimeter	Centroid
10	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
11	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
12	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
13	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
14	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
15	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
16	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
17	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
18	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
19	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
20	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
21	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
22	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
23	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
24	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
25	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
26	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
27	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
28	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
29	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78
30	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78	20.78





Kv Gravimetric

Measuring Kv Gravimetrically

1. Add Water to Vials
 - A. 336 Vials, 5ml fill, 10 ml vial with igloo stopper
 - B. $T_{\text{Shelf}} = -20^{\circ}\text{C}$, $P_{\text{Chamber}} = 100 \text{ mT}$
2. Weigh Each Vial and Mark its Location on the Shelf
3. Freeze and Start Primary Drying
 - A. Freeze at $0.5^{\circ}\text{C}/\text{min}$ 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

$$Kv_{grav} = \frac{\left(\frac{dm}{dt}\right)H_s}{Av(T_s - T_b)}$$

dm/dt = Mass loss/Time – Batch Avg

T_s = Shelf Temperature – Batch Avg

T_b = Product Temperature - Batch Avg

H_s = Heat of Sublimation

Av = Area (OD) per vial

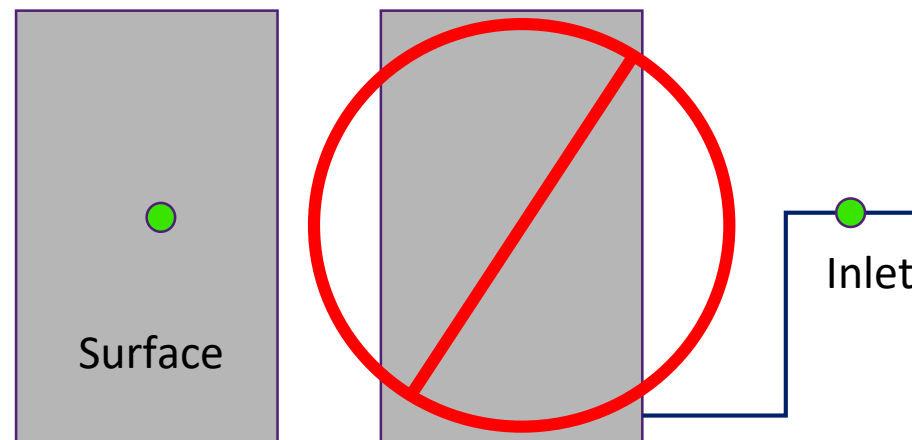


Millrock
Revo

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



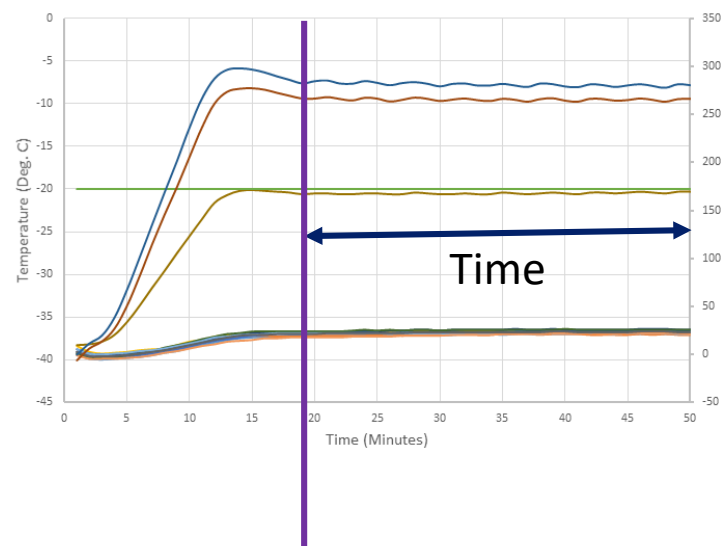
2. T_{Product} – Batch Average

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



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

10ml Vial, 5ml H₂O, Tshelf -20C, 100mT

Kv Gravimetric Based on
T_{shelf_surface} (-20.3 °C)

Gravimetric Kv for all vials in full water run. 5 ml water/10 ml vial with stoppers. Surface

28	29.29	27.16	25.98	26.69	26.45	26.92	26.22	26.22	27.63	27.87	27.87	30.23
27	25.03	22.91	19.13	21.73	23.38	20.78	19.84	22.67	22.44	22.44	22.44	28.58
26	30.70	20.78	19.84	20.55	24.56	21.02	18.66	18.42	20.07	20.55	20.55	23.62
25	22.20	20.07	16.77	20.07	21.02	18.66	18.19	19.13	18.42	18.66	18.66	26.92
24	29.29	20.78	19.13	17.71	18.89	19.84	18.66	18.66	18.66	20.07	18.37	23.14
23	20.78	20.07	21.02	18.66	23.85	18.89	18.42	19.37	19.84	19.60	20.31	27.40
22	28.58	20.31	20.07	18.19	20.78	18.66	18.42	18.66	18.42	19.84	18.66	22.91
21	22.44	18.66	18.19	17.71	21.02	19.13	19.37	18.19	19.37	17.24	20.31	28.58
20	27.87	21.02	17.71	18.42	17.00	19.13	18.66	18.66	18.66	19.60	20.07	22.20
19	22.67	19.84	18.66	18.66	19.37	17.48	19.37	18.19	19.37	21.26	18.19	27.87
18	28.81	19.84	18.66	16.77	16.30	18.42	18.42	19.60	18.42	19.37	20.78	22.20
17	22.67	19.60	17.48	15.82	18.66	21.02	19.60	21.49	19.60	19.13	21.26	27.16
16	28.34	20.78	19.37	19.37	17.24	20.07	19.37	16.77	16.77	16.77	19.13	22.67
15	23.38	20.31	19.13	18.89	13.70	19.13	19.84	20.31	18.66	18.66	18.66	28.10
14	29.05	20.31	19.37	17.00	17.24	19.37	20.55	21.26	18.42	23.14	23.85	23.85
13	27.16	21.49	18.89	18.89	20.78	20.55	19.60	21.02	20.07	25.98	27.87	27.87
12	32.83	25.03	19.84	20.07	18.89	20.55	19.13	21.02	22.67	26.69	24.09	24.09
11	26.45	18.19	17.95	17.95	18.66	19.60	16.77	22.67	21.49	22.91	27.87	27.87
10	33.54	20.07	18.66	18.89	19.13	18.66	17.71	19.84	20.31	18.66	24.56	24.09
9	22.67	19.13	19.13	20.07	18.66	19.13	19.60	21.26	20.07	19.84	27.63	27.63
8	30.23	19.13	19.37	21.49	17.71	18.42	18.89	17.95	20.31	19.60	23.62	24.09
7	22.91	21.02	18.66	17.95	18.42	17.48	18.19	16.53	17.95	18.89	27.40	29.52
6	26.69	21.26	19.60	18.19	18.89	17.00	18.19	17.24	18.19	18.89	28.58	25.03
5	23.14	19.13	18.89	17.48	15.35	17.24	18.66	18.89	19.37	19.37	20.07	29.29
4	31.88	18.89	21.26	19.37	18.89	19.84	18.66	19.84	15.82	19.84	25.98	25.98
3	25.74	22.67	20.78	20.55	19.60	22.20	20.07	20.07	21.96	23.62	30.47	30.47
2	33.54	23.85	22.67	21.77	21.96	23.85	23.14	21.49	23.85	22.67	28.10	27.87
1	33.54	29.52	29.29	27.63	27.16	30.23	26.92	29.29	31.41	32.59	34.72	34.72

Kv Batch Average = 21.46

Front

Kv in W/sqM/C

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

Gravimetric Kv for all vials in full water run, 5 ml water/10 ml vial with stoppers. Surface

28	29.29	27.16	25.98	26.69	26.45	26.92	26.22	26.22	27.63	27.87	27.87	27.87	30.23
27	25.03	22.91	19.13	21.73	23.38	20.78	23.14	19.84	22.67	22.44	22.44	22.44	28.58
26	30.70	20.78	19.84	20.55	24.56	21.02	21.26	18.42	20.07	20.55	20.55	20.55	23.62
25	22.20	20.07	16.77	20.07	21.02	18.66	18.19	19.13	18.42	18.66	18.66	18.66	26.32
24	29.29	20.78	19.13	17.71	18.89	19.84	18.66	18.66	18.66	20.07	19.37	19.37	23.14
23	20.78	20.07	21.02	18.66	23.85	18.89	19.37	18.42	19.84	19.60	20.31	20.31	27.40
22	28.58	20.31	20.07	18.19	20.78	18.66	18.66	18.42	18.42	19.84	18.66	18.66	22.91
21	22.44	18.66	18.19	17.71	21.02	19.13	19.37	18.19	19.37	17.24	20.31	20.31	28.58
20	27.87	21.02	17.71	18.42	17.00	19.13	19.84	18.66	18.66	19.60	20.07	20.07	22.20
19	22.67	19.84	18.66	18.66	19.37	17.48	18.19	19.37	21.26	18.19	20.78	20.78	27.87
18	28.81	19.84	18.66	16.77	16.30	18.42	19.60	18.42	19.37	19.13	20.78	20.78	22.20
17	22.67	19.60	17.48	15.82	18.66	21.02	21.49	19.60	19.13	19.37	21.26	21.26	27.16
16	28.34	20.78	19.37	19.37	17.24	20.07	18.19	19.37	16.77	17.95	19.13	19.13	22.67
15	23.38	20.31	19.13	18.89	13.70	19.13	19.84	20.31	18.66	18.42	18.66	18.66	28.10
14	29.05	20.31	19.37	17.00	17.24	19.37	20.55	21.26	18.42	18.69	23.14	23.14	23.95
13	27.16	21.49	18.89	20.78	20.78	20.55	19.60	21.02	20.07	21.02	25.98	25.98	27.87
12	32.83	25.03	19.13	20.07	18.89	20.55	19.13	21.02	22.67	24.80	26.69	26.69	24.09
11	26.45	18.19	17.95	17.95	18.66	19.60	16.77	22.67	21.49	25.27	22.91	22.91	27.87
10	33.54	20.07	18.66	19.84	19.13	18.66	17.71	19.84	20.31	18.66	24.56	24.56	24.09
9	27.67	19.13	19.13	20.07	18.66	19.13	19.60	19.60	21.26	20.07	19.84	19.84	27.63
8	30.23	19.13	19.37	21.49	17.71	18.42	18.89	17.95	20.31	19.60	23.62	23.62	24.09
7	22.91	21.02	17.66	17.95	18.42	17.48	18.19	16.53	17.95	18.89	27.40	27.40	29.32
6	26.69	21.26	19.60	18.19	18.89	17.00	18.19	17.24	18.19	18.69	28.58	28.58	25.03
5	23.14	19.13	18.89	17.48	18.89	17.24	18.66	18.66	18.89	19.37	20.07	20.07	29.29
4	31.88	18.89	21.26	19.37	18.89	19.84	18.66	19.84	19.84	15.82	19.84	19.84	25.98
3	25.74	22.67	20.78	20.55	19.60	22.20	20.07	20.07	20.07	21.96	23.62	23.62	30.47
2	33.54	23.85	22.67	21.73	21.96	23.85	23.14	21.49	23.85	22.67	28.10	28.10	27.87
1	33.54	29.32	29.29	27.63	27.16	30.23	25.03	26.32	29.29	31.41	32.59	32.59	34.72

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



Kv Gravimetric

1. Advantages

- A. Data can be selected for desired results
 - i. Batch Average vs Center Vials vs Edge Vials

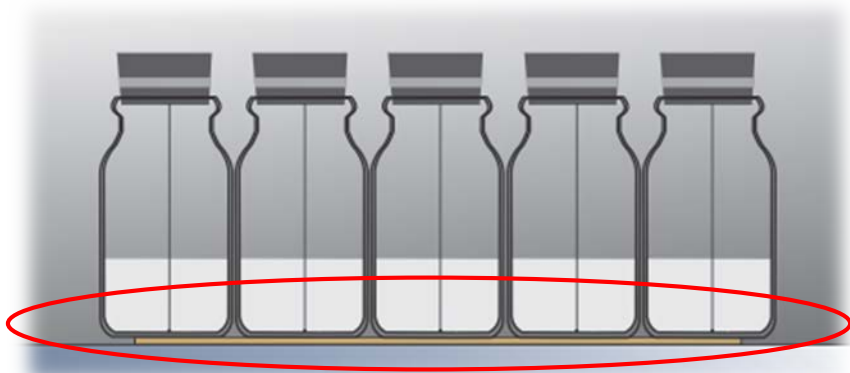
2. Disadvantages

- 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

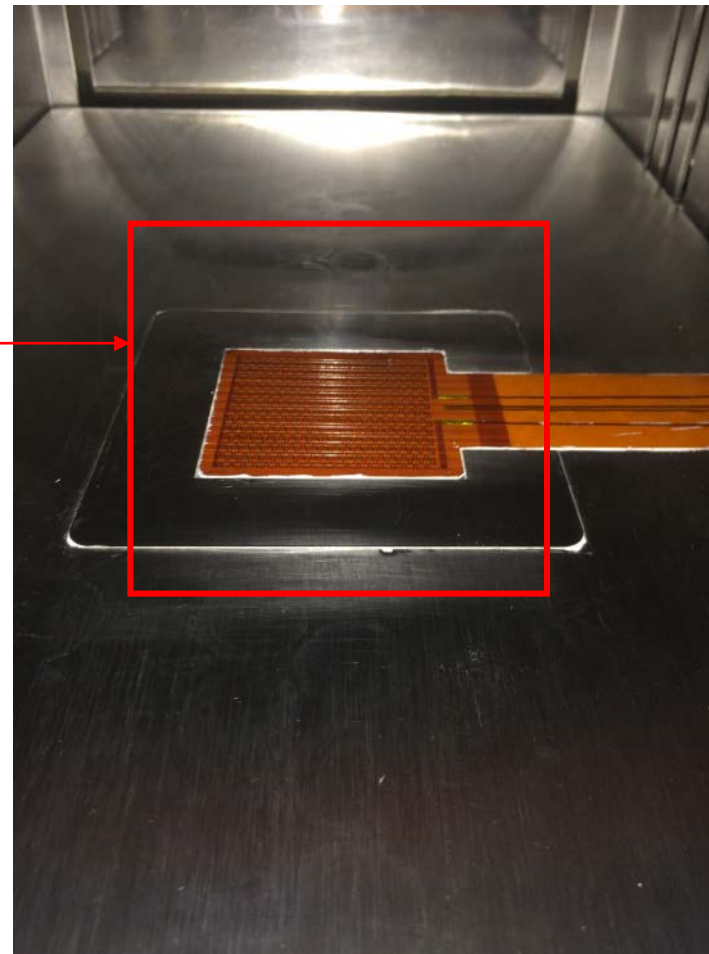


Kv Determination Using AccuFlux[®]

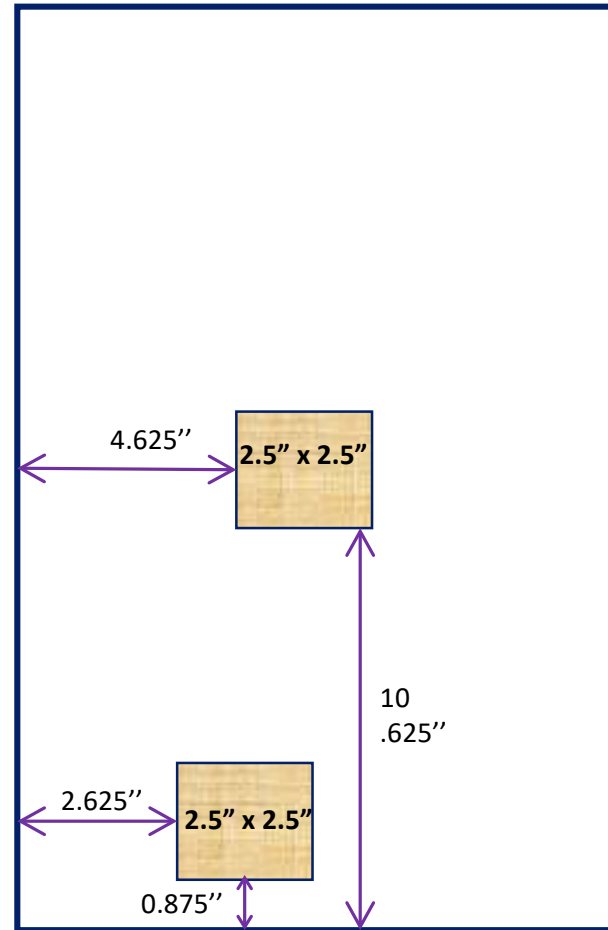
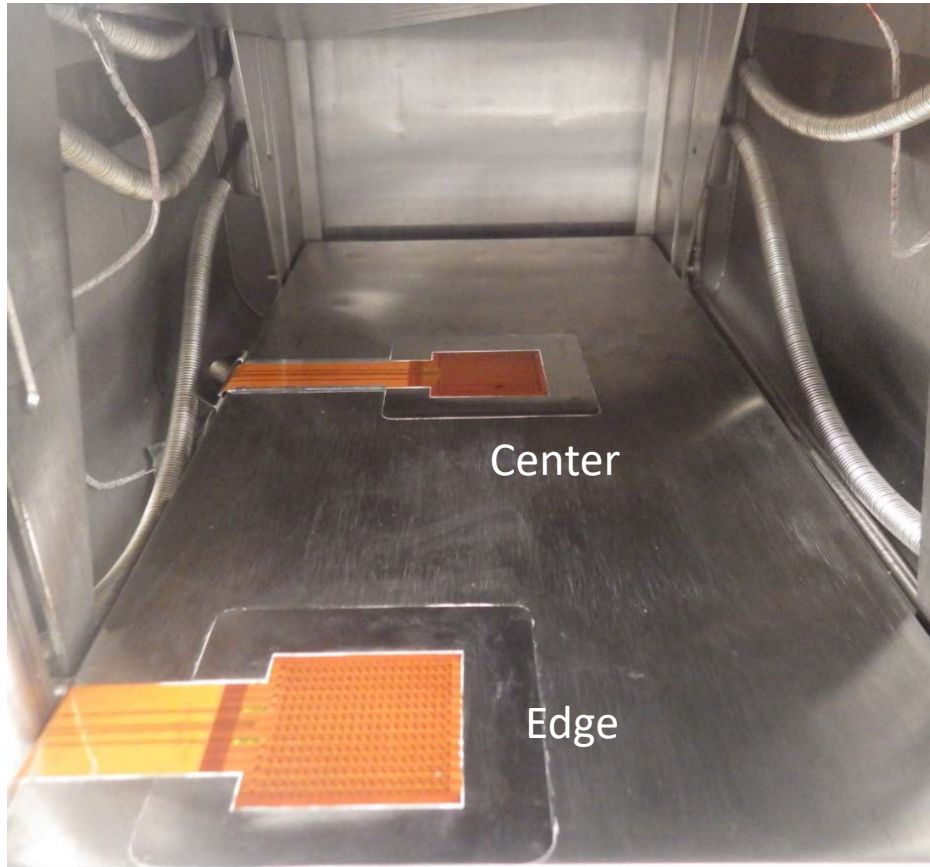
AccuFlux[®]



- 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 : $\text{Watts/m}^2 = \text{Joules/sec/m}^2$



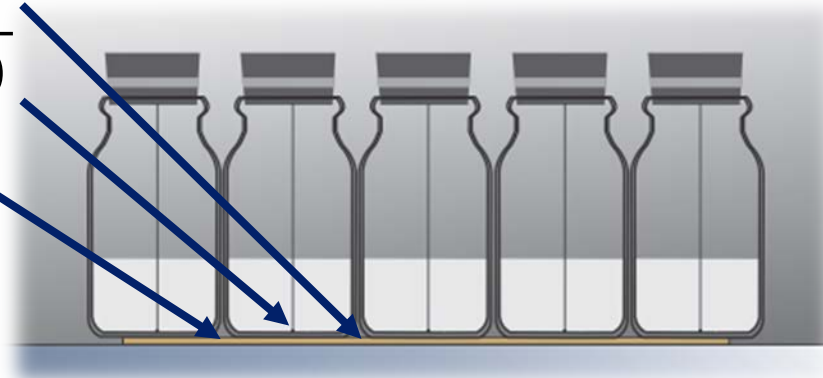
Sensor Location on Shelf (12" x 24")



Front

Kv Determination Using AccuFlux

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



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

$$Kv = Kv \text{ AccuFlux Shelf} + Kv \text{ Other}$$

Gas Conduction, Radiation

How do we determine Kv without measuring Kv Other?

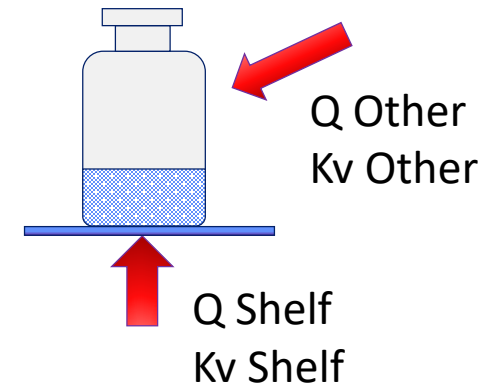
Kv Determination Using AccuFlux

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



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

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

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

HF – Heat Flux (W/sqM)

Hs – Heat of Sublimation (2834 J/g)

Mass – Mass of material sublimating

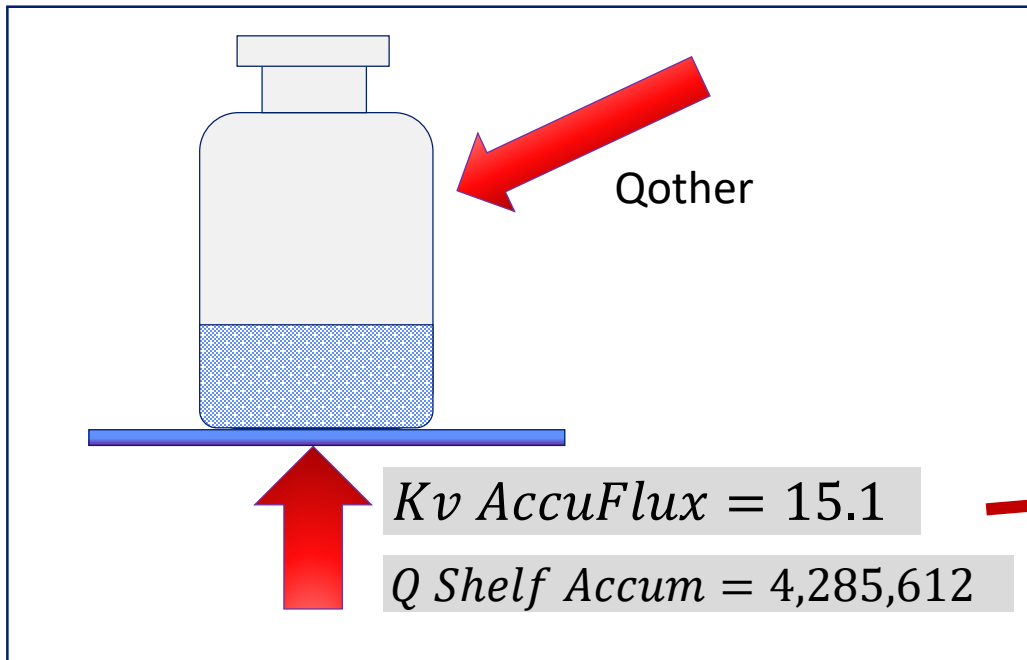
Kv AccuFlux – Heat Flow from Shelf

%Q Shelf – Heat flow measured divided by Total Heat of Sublimation

Kv total – Vial Heat Transfer Coeff

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



$$Q \text{ Sublimation} = 4761792 \text{ J}$$

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

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

Kv in W/sqM/C

Kv AccuFlux vs Kv Gravimetric for Edge Vials

Gravimetric Kv for all vials in full water run, 5 ml water/10 ml vial with stoppers. Surface

28	29.29	27.16	25.98	26.69	26.45	26.92	26.22	26.22	27.63	27.87	27.87	30.23
27	25.03	22.91	19.13	21.73	23.38	20.78	23.14	19.84	22.67	22.44	22.44	28.58
26	30.70	20.78	19.84	20.55	24.56	21.02	21.26	18.42	20.07	20.55	20.55	23.62
25	22.20	20.07	16.77							18.66	18.89	26.92
24	29.29	20.78	19.13							20.07	19.37	23.14
23	20.78	20.07	21.02							19.66	20.31	27.40
22	28.58	20.3	20.07							19.84	18.66	22.91
21	22.44	18.66	18.19							17.2	20.31	28.58
20	27.87	21.02	17.71							19.66	20.07	22.20
19	22.67	19.84	18.66							18.1	20.78	27.87
18	28.81	19.84	18.66							19.1	20.78	22.20
17	22.67	19.60	17.48							19.3	21.26	27.16
16	28.34	20.78	19.37							17.95	19.13	22.67
15	23.38	20.3	19.13							18.4	18.66	28.10
14	29.05	20.7	19.37							18.8	23.14	23.85
13	21.76	21.45	18.89							21.0	25.98	27.87
12	32.83	25.03	19.84							24.8	26.69	24.09
11	26.45	18.1	17.95							25.2	22.91	27.87
10	33.54	20.07	18.66							18.6	24.56	24.09
9	22.67	19.1	19.13							20.07	19.84	27.63
8	30.23	19.1	19.37							19.6	23.62	24.09
7	22.91	21.02	18.66							18.8	27.40	29.52
6	26.69	21.26	19.60							18.8	28.58	25.03
5	23.14	19.1	18.89							19.3	20.07	29.29
4	31.88	18.66	21.26							15.8	19.84	25.98
3	25.74	22.67	20.78	20.55	19.60	22.20	20.07	20.07	20.07	21.9	23.62	30.47
2	33.54	23.85	22.67	21.73	21.96	23.85	23.14	21.49	23.85	22.67	28.10	27.87
1	33.54	23.29	23.29	27.16	27.16	30.23	25.03	26.32	29.29	31.41	32.59	34.72

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

Conclusion: Kv AccuFlux Correlates to Kv Gravimetric

Gravimetric Kv for all trials in full water runs. 5 ml water/10 ml air with stoppers. Surface

28	25.23	27.16	25.98	26.68	26.45	26.92	26.22	26.22	27.63	27.67	27.67	30.23
27	25.03	22.91	19.13	21.73	23.36	20.78	23.14	19.84	22.67	22.44	22.44	28.58
26	30.70	20.78	19.84	20.55	24.56	21.02	21.26	18.42	20.55	20.55	20.55	23.62
25	22.20	20.07	16.77	20.07	21.02	18.66	18.19	19.13	18.42	18.66	18.66	26.92
24	28.28	20.78	19.13	17.71	18.89	19.84	18.66	18.66	20.07	19.37	19.37	23.14
23	20.78	20.07	21.02	18.66	23.95	18.89	19.37	18.42	19.84	19.84	20.31	27.40
22	28.58	20.31	20.07	18.19	20.78	18.66	18.66	18.42	19.84	18.66	22.91	
21	22.44	18.66	18.19	17.71	21.02	19.13	19.37	18.19	19.37	17.24	20.31	28.58
20	27.67	21.02	17.71	18.42	17.00	19.13	19.84	18.66	19.84	19.84	20.07	22.20
19	22.67	19.84	18.66	18.66	19.37	17.46	18.19	19.37	21.26	18.19	20.78	27.67
18	28.58	19.84	18.66	16.77	16.30	18.42	19.60	18.42	19.37	19.13	20.78	22.20
17	22.67	19.60	17.46	18.66	21.02	21.49	19.60	19.13	19.37	21.26	27.16	
16	26.34	20.78	19.37	19.37	17.24	20.07	19.13	19.37	16.77	17.95	19.13	22.67
15	23.36	20.31	19.13	18.89	13.70	19.13	19.84	20.31	18.66	18.42	18.66	28.10
14	29.05	20.31	19.37	17.00	17.24	19.37	20.55	21.26	18.42	18.89	23.14	23.95
13	27.16	21.49	18.89	18.89	18.89	18.89	21.02	20.07	21.02	21.02	25.98	27.67
12	32.83	25.03	19.84	20.07	18.89	20.55	19.13	21.02	22.67	24.90	26.69	24.09
11	26.45	18.19	17.95	17.95	18.66	19.60	16.77	22.67	21.49	25.27	22.91	27.67
10	33.54	20.07	18.66	18.89	19.13	19.66	17.71	19.84	20.31	18.66	24.56	24.09
9	22.67	19.13	19.13	20.07	18.66	19.13	19.60	19.60	21.26	20.07	19.84	27.63
8	30.23	19.13	19.37	21.49	17.71	18.42	18.89	17.95	20.31	19.60	23.62	24.09
7	22.91	21.02	18.66	17.95	18.42	17.46	18.19	16.53	17.95	18.89	27.40	28.52
6	26.69	21.26	19.60	19.13	18.89	17.00	19.13	17.24	18.19	18.89	28.58	25.03
5	28.58	19.13	18.66	17.46	15.35	17.24	15.92	18.66	18.89	19.37	20.07	28.28
4	31.68	18.89	21.26	19.37	18.9	19.84	18.66	19.84	15.92	19.84	25.98	
3	25.74	22.67	20.78	20.55	19.00	22.20	20.07	20.07	21.96	23.62	30.47	
2	33.54	23.65	24.57	21.73	21.6	23.85	23.14	21.49	23.85	22.67	28.10	27.67
1	33.54	29.52	29.29	27.63	27.16	30.23	25.03	26.92	29.29	31.41	32.59	34.72

Gravimetric Kv for all trials in full water runs. 5 ml water/10 ml air with stoppers. Surface

28	29.29	27.16	25.98	26.68	26.45	26.92	26.22	26.22	27.63	27.67	27.67	30.23
27	25.03	22.91	19.13	21.73	23.36	20.78	23.14	19.84	22.67	22.44	22.44	28.58
26	30.70	20.78	19.84	20.55	24.56	21.02	21.26	18.42	20.07	20.55	20.55	23.62
25	22.20	20.07	16.77	20.07	21.02	18.66	18.19	19.13	18.42	18.66	18.66	26.92
24	28.28	20.78	19.13	17.71	18.89	19.84	18.66	18.66	20.07	19.37	19.37	23.14
23	20.78	20.07	21.02	18.66	23.95	18.89	19.37	18.42	19.84	19.84	20.31	27.40
22	28.58	20.31	20.07	18.19	20.78	18.66	18.66	18.42	19.84	18.66	22.91	
21	22.44	18.66	18.19	17.71	21.02	19.13	19.37	18.19	19.37	17.24	20.31	28.58
20	27.67	21.02	17.71	18.42	17.00	19.13	19.84	18.66	19.84	19.84	20.07	22.20
19	22.67	19.84	18.66	18.66	19.37	17.46	18.19	19.37	21.26	18.19	20.78	27.67
18	28.58	19.84	18.66	16.77	16.30	18.42	19.60	18.42	19.37	19.13	20.78	22.20
17	22.67	19.60	17.46	18.66	21.02	21.49	19.60	19.13	19.37	21.26	27.16	
16	26.34	20.78	19.37	19.37	17.24	20.07	19.13	19.37	16.77	17.95	19.13	22.67
15	23.36	20.31	19.13	18.89	13.70	19.13	19.84	20.31	18.66	18.42	18.66	28.10
14	29.05	20.31	19.37	17.00	17.24	19.37	20.55	21.26	18.42	18.89	23.14	23.95
13	27.16	21.49	18.89	18.89	18.89	21.02	20.07	21.02	21.02	21.02	25.98	27.67
12	32.83	25.03	19.84	20.07	18.89	20.55	19.13	21.02	22.67	24.90	26.69	24.09
11	26.45	18.19	17.95	17.95	18.66	19.60	16.77	22.67	21.49	25.27	22.91	27.67
10	33.54	20.07	18.66	18.89	19.13	19.66	17.71	19.84	20.31	18.66	24.56	24.09
9	22.67	19.13	19.13	20.07	18.66	19.13	19.60	19.60	21.26	20.07	19.84	27.63
8	30.23	19.13	19.37	21.49	17.71	18.42	18.89	17.95	20.31	19.60	23.62	24.09
7	22.91	21.02	18.66	17.95	18.42	17.46	18.19	16.53	17.95	18.89	27.40	28.52
6	26.69	21.26	19.60	19.13	18.89	17.00	19.13	17.24	18.19	18.89	28.58	25.03
5	28.58	19.13	18.66	17.46	15.35	17.24	15.92	18.66	18.89	19.37	20.07	28.28
4	31.68	18.89	21.26	19.37	18.89	19.84	18.66	19.84	15.92	19.84	25.98	
3	25.74	22.67	20.78	20.55	19.00	22.20	20.07	20.07	21.96	23.62	30.47	
2	33.54	23.65	24.57	21.73	21.6	23.85	23.14	21.49	23.85	22.67	28.10	27.67
1	33.54	29.52	29.29	27.63	27.16	30.23	25.03	26.92	29.29	31.41	32.59	34.72

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



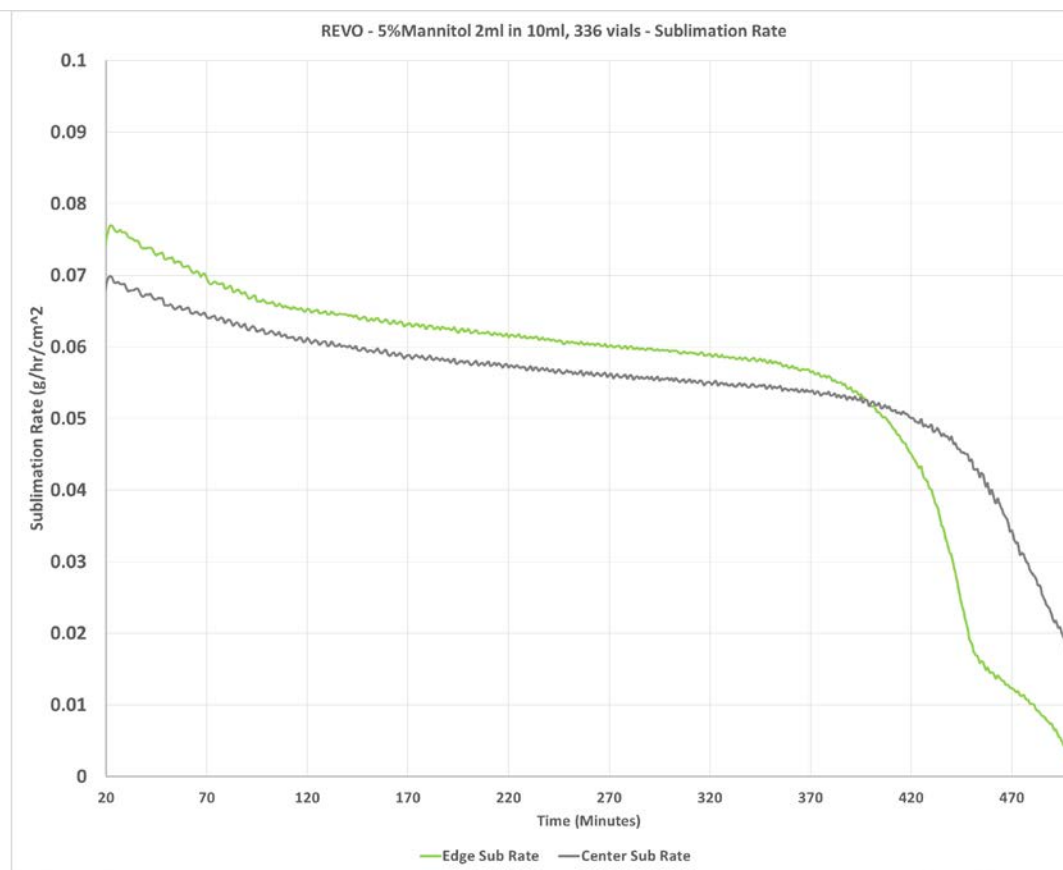
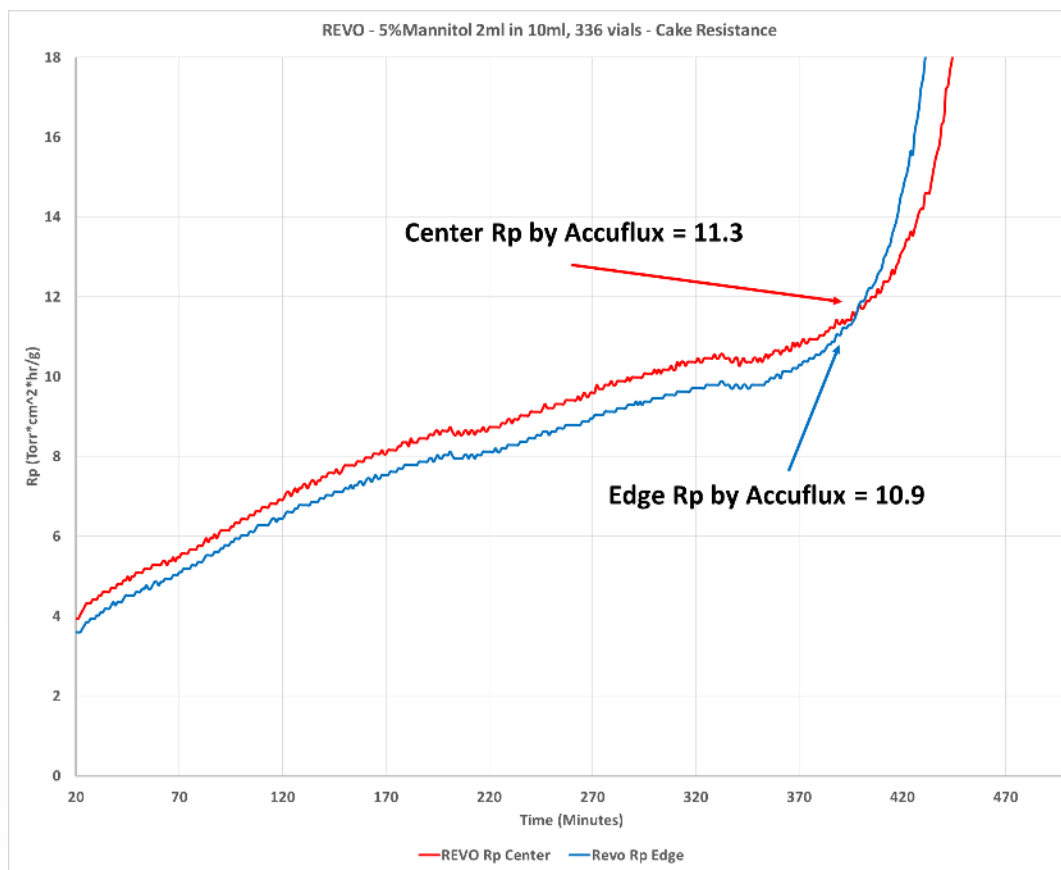
Determine Kv AccuFlux and Kv Gravimetric Correlation in a MicroFD[®]

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. K_v - Vial Heat Transfer Coeff
 - B. dM/dt - Mass Flow
 - C. R_p - Cake Resistance
 - D.
4. Ability to Test the Effects of
 - A. Freezing Methods
 - B. Drying Conditions

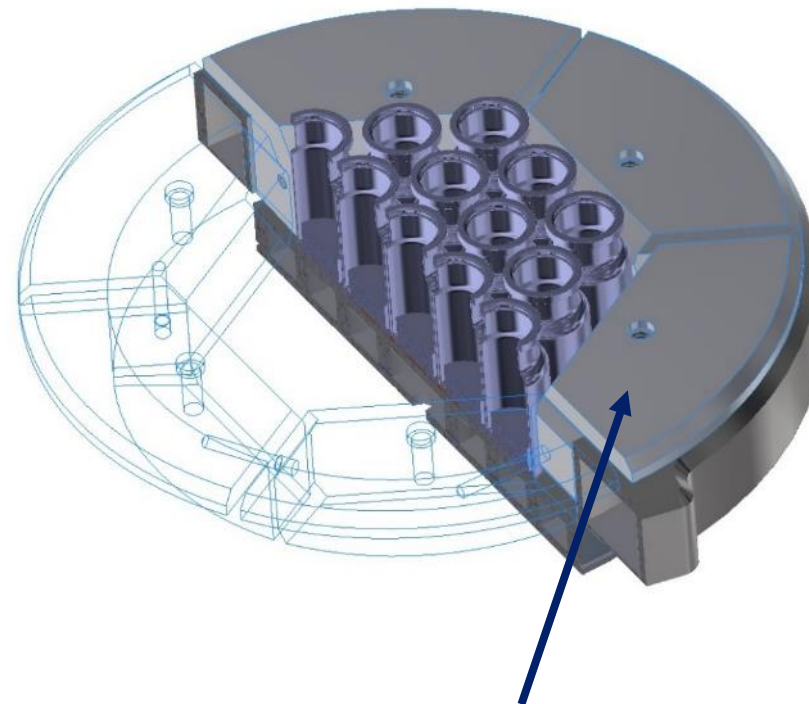


LyoPAT Example – Cake Resistance and Mass Flow



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

How is LyoSIM used?

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

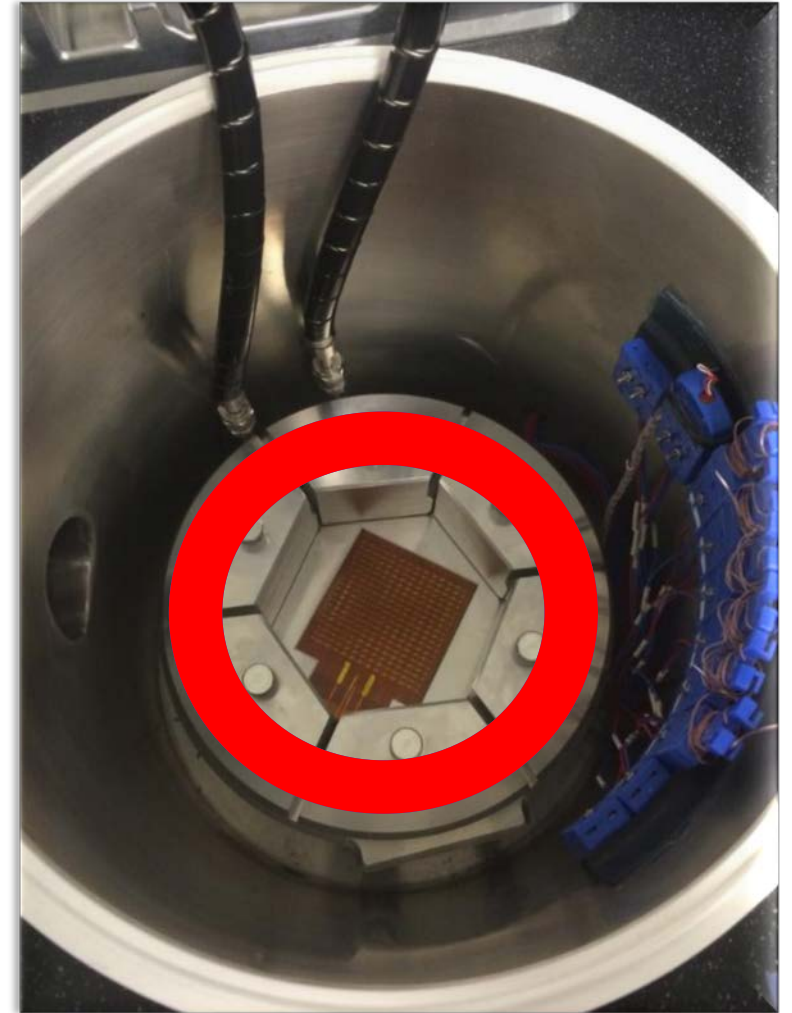
Primary Drying:

i. Center Vial Effect

- $T_{\text{LyoSIM}} \leq T_{\text{product}}$
- E.g.: LyoSIM Temperature = $T_{\text{product}} - 2\text{ }^{\circ}\text{C}$

ii. Edge Vial Effect

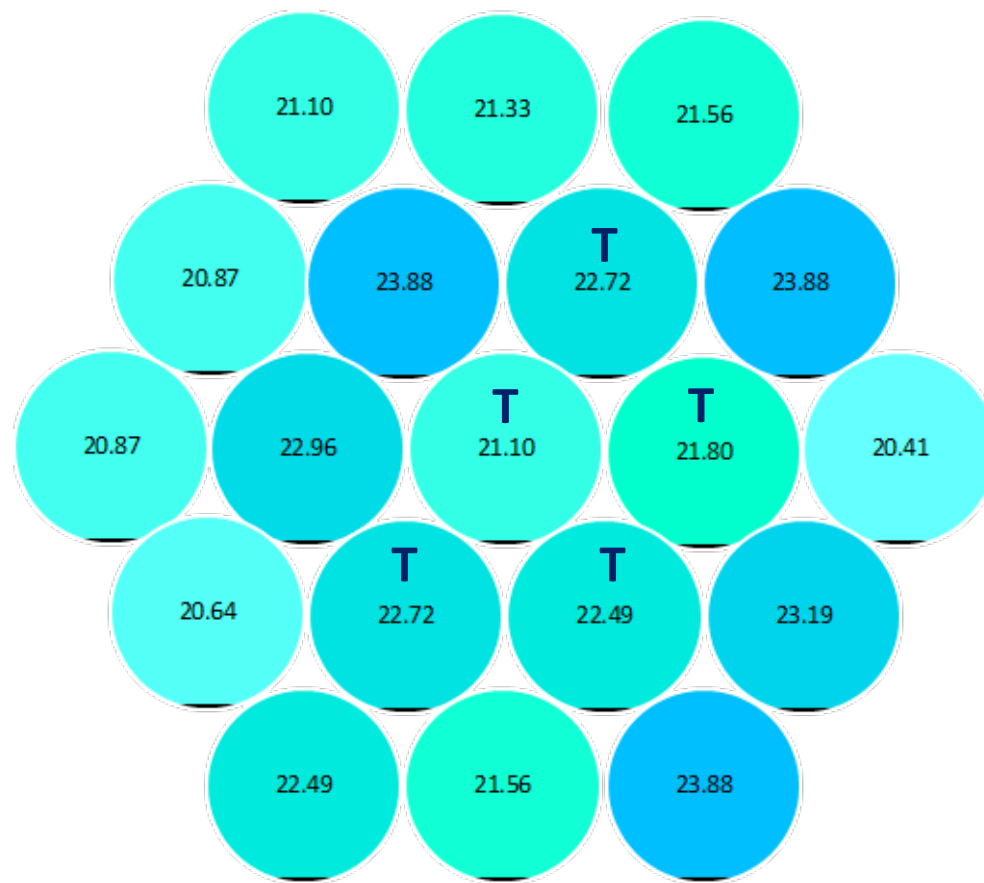
- $T_{\text{LyoSIM}} > T_{\text{product}}$
- E.g.: LyoSIM Temperature = $T_{\text{product}} + 5\text{ }^{\circ}\text{C}$



MicroFD Kv Gravimetric Results (center vial simulation)

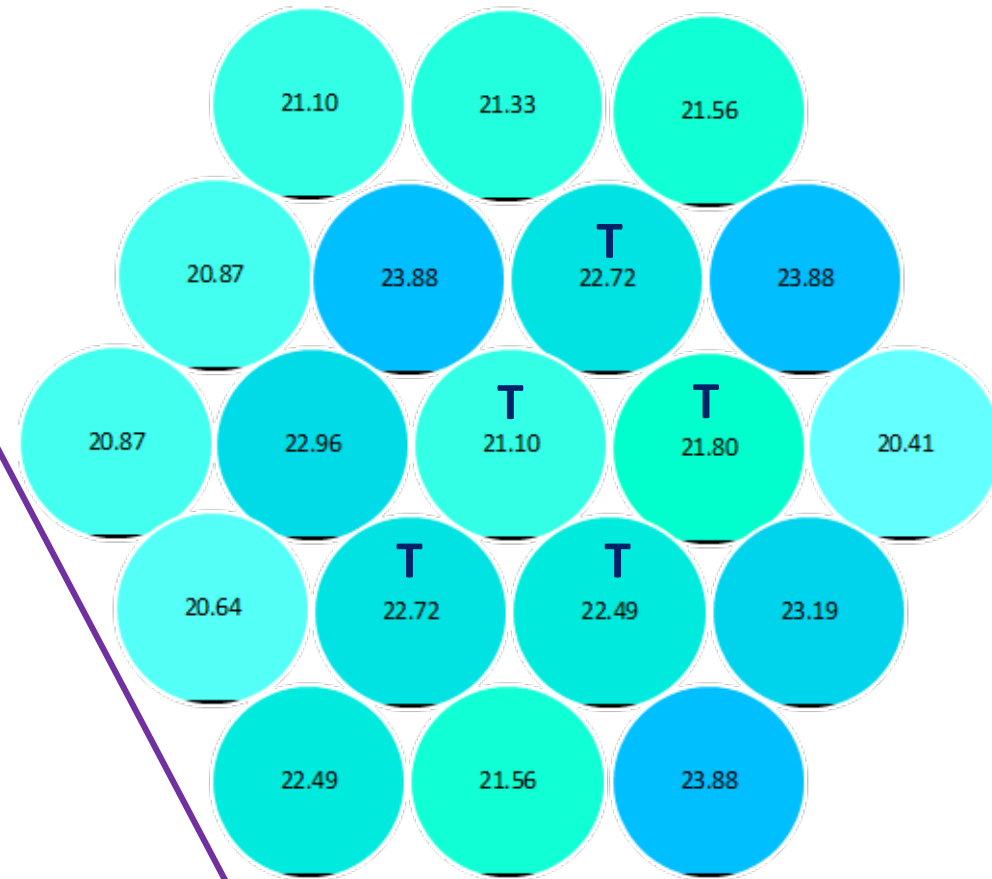
Gravimetric	Kv (W/m ² -C)
Batch Average	22.08
Inner 7 vials	22.53
Outer 12 vials	21.82
MicroFD 19-vial STDEV	1.12
REVO center vial (4x20) StDEV	1.55

All 19 vials behave like center vials!



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!



Protocol Transfer from MicroFD to REVO Using Kv AccuFlux

Protocol Transfer using Kv

Kv AccuFlux Batch Average

Source Freeze Dryer			Target Freeze Dryer		
Kv Source	Tshelf Surface	Tb measured	Kv Target	Tb	
22.16	-1.5	-20	20.86	X?	-20

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

Target System
Shelf inlet - surface offset 1.5 °C

Tshelf Surface Target °C
-0.347

Tshelf Inlet Target °C
1.153

Target Shelf Set Point
1 °C

Kv AccuFlux Center Vials

Source Freeze Dryer			Target Freeze Dryer		
Kv Source	Tshelf Surface	Tb measured	Kv Target	Tb	
22.16	-1.5	-20	18.01	X?	-20

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

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

Kv Source – MicroFD
Kv Target – REVO

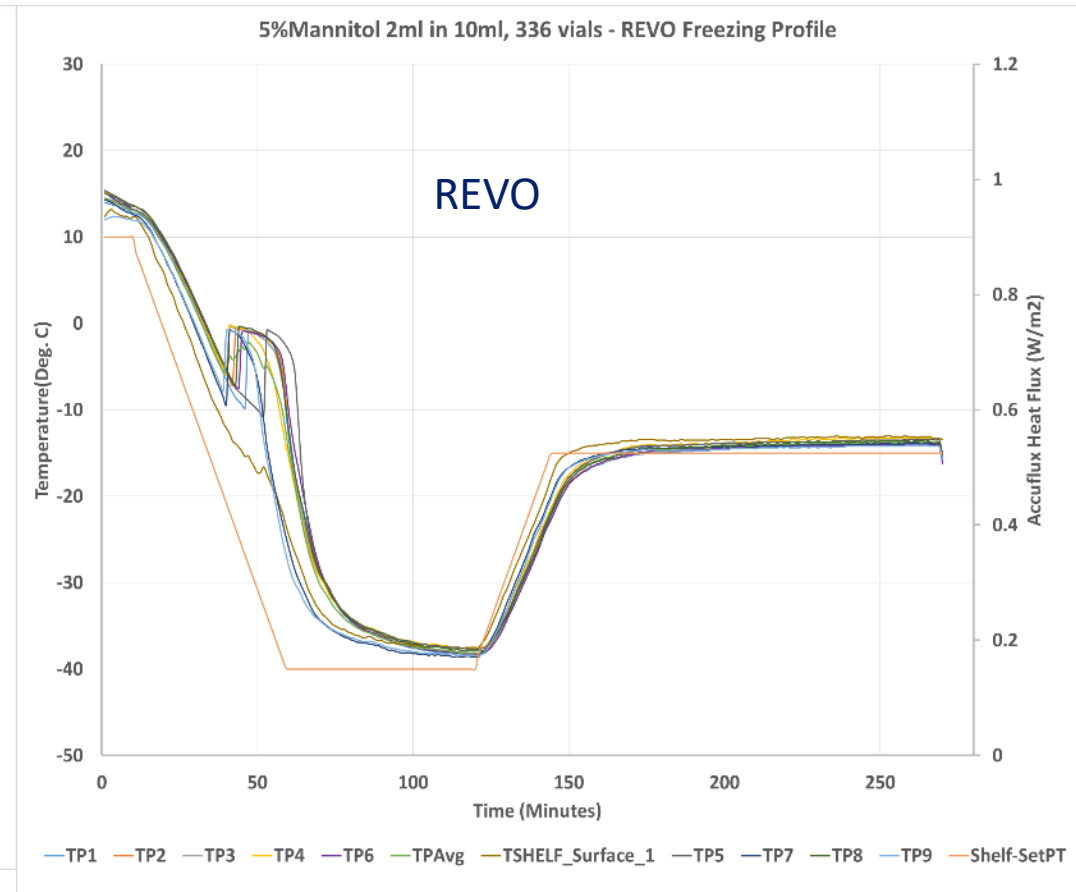
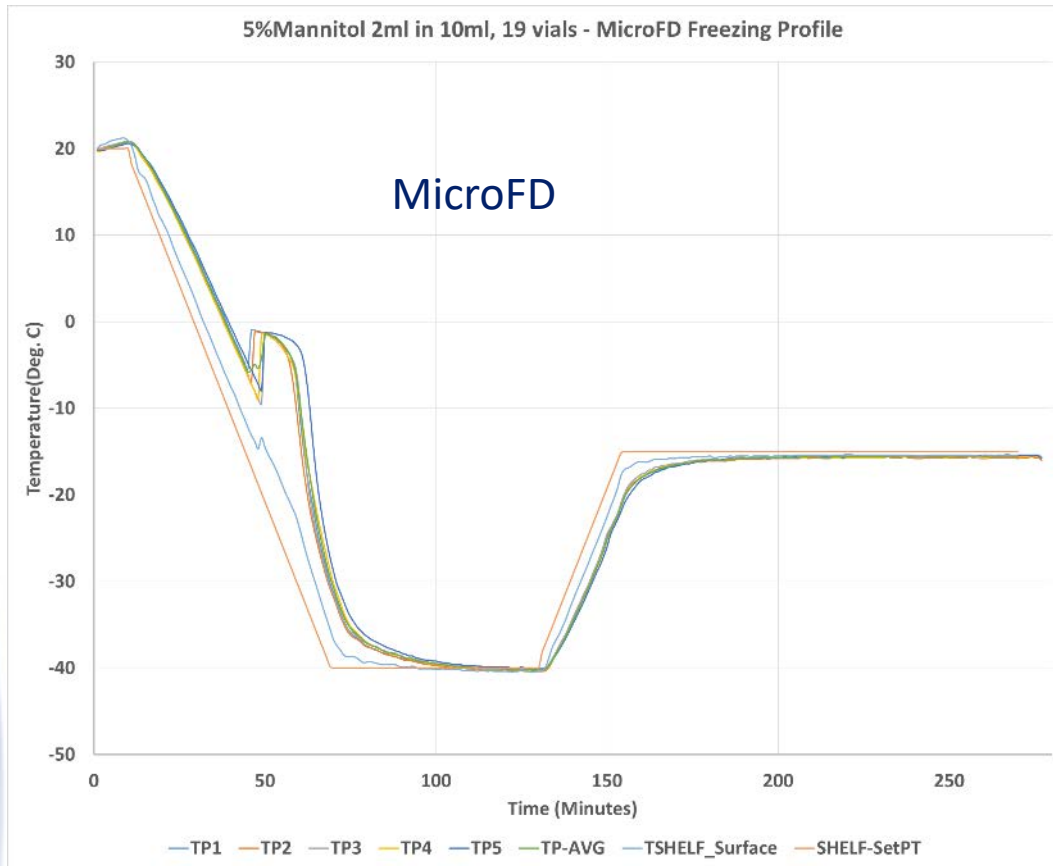


5% Mannitol Experiments – Cycle Information

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

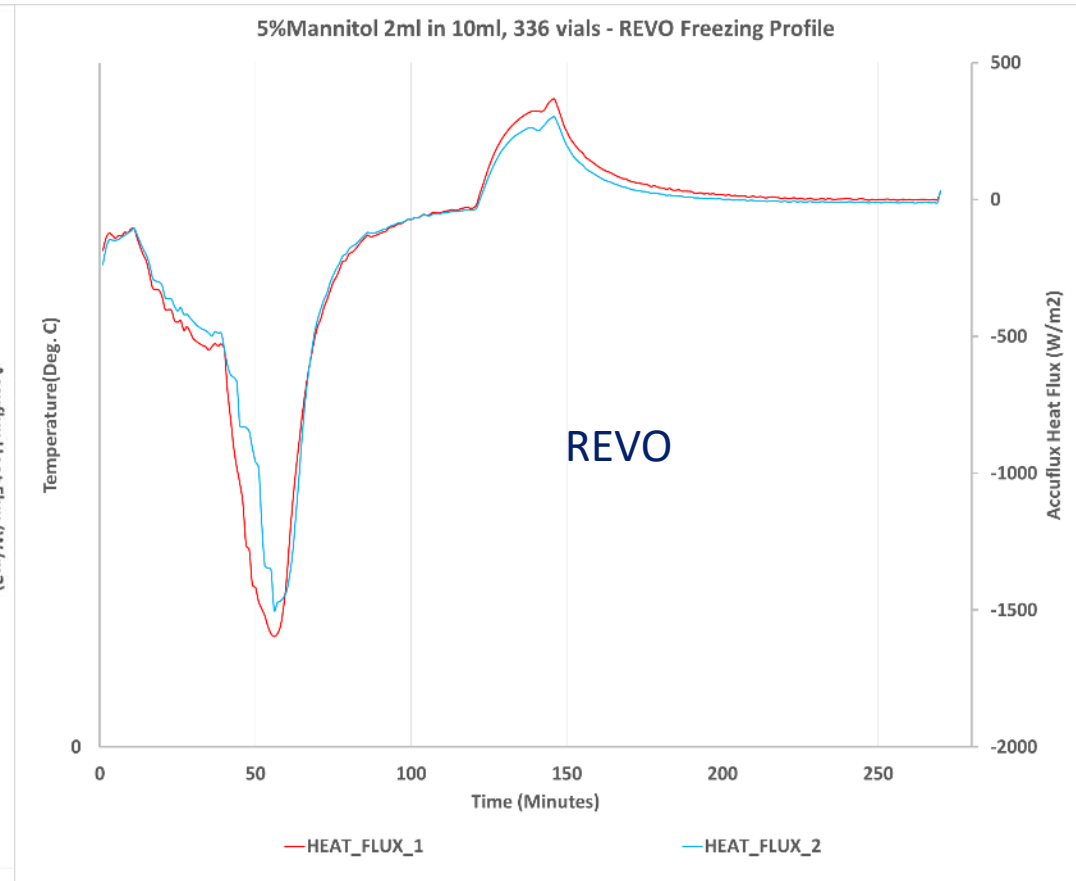
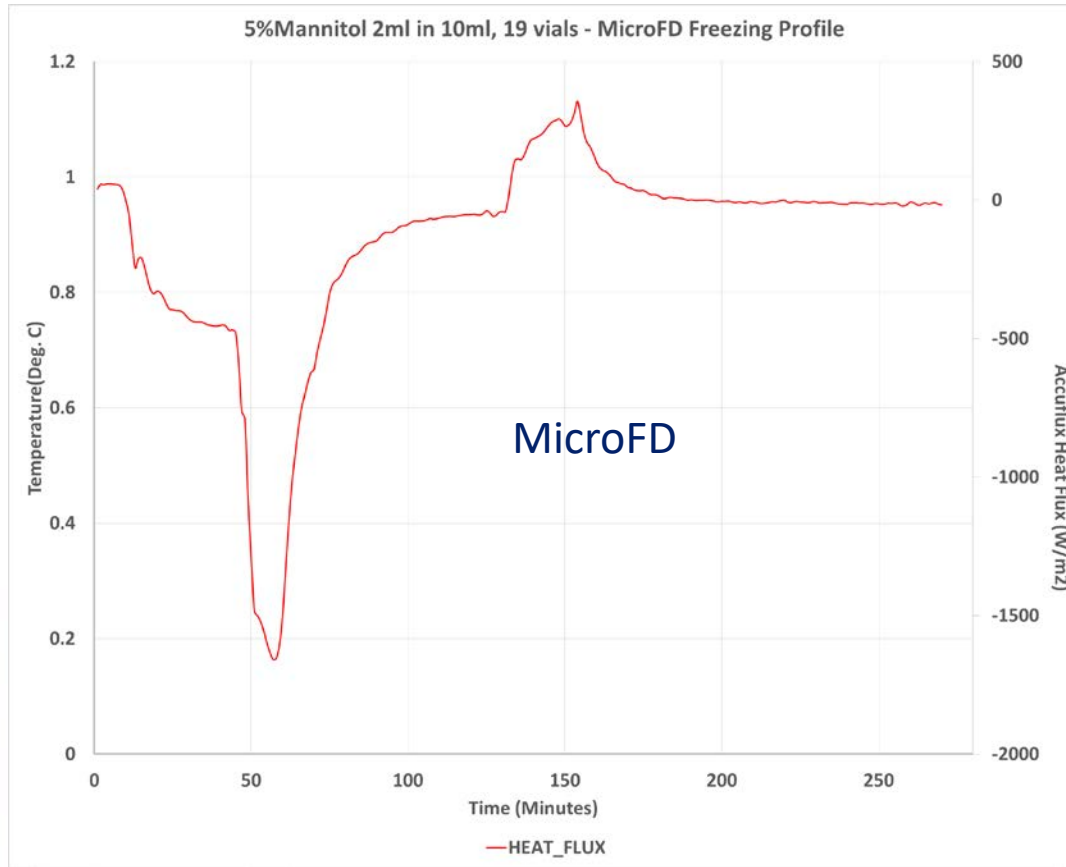
Protocol	MicroFD	REVO	REVO
Freezing	0.5 °C/min to -40 °C	0.5 °C/min to -40 °C	0.5 °C/min to -40 °C
Annealing for 2 hours	-15 °C	-15 °C	-15 °C
Kv Accuflux	22.16	20.86 (Batch Avg)	18.01 (Center Kv)
Primary Drying Shelf	0 °C	0 °C	+ 4 °C
Primary Drying Vacuum	100 mT	100 mT	100 mT

Freezing Comparison between MicroFD and REVO (without HF)

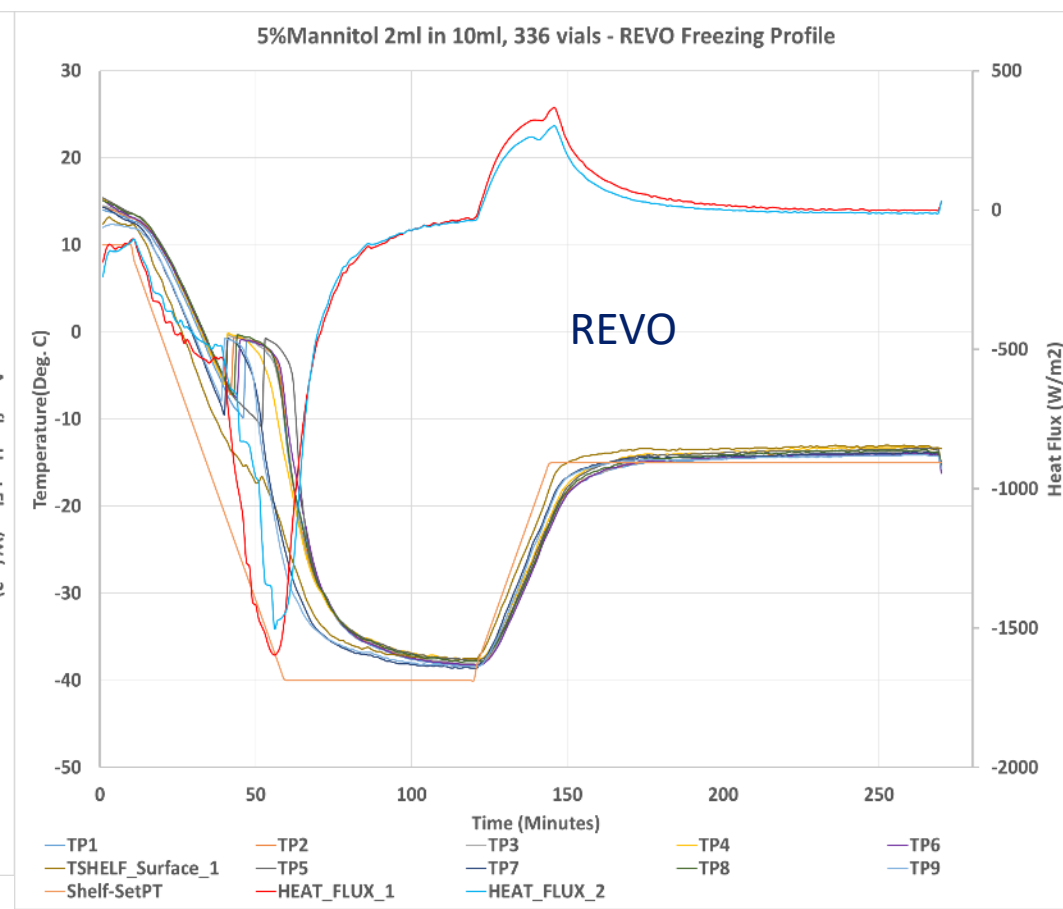
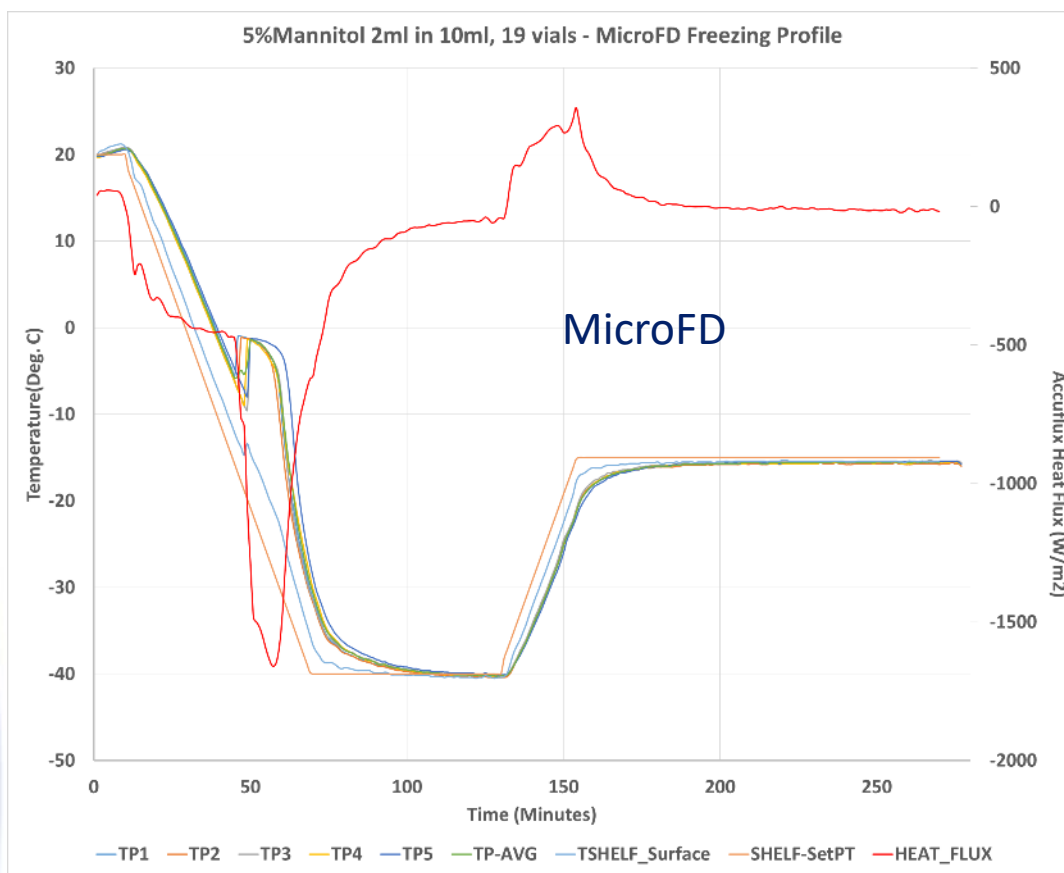


5% Mannitol 2ml fill in 10ml vials

Freezing Comparison between MicroFD and REVO – Heat Flow

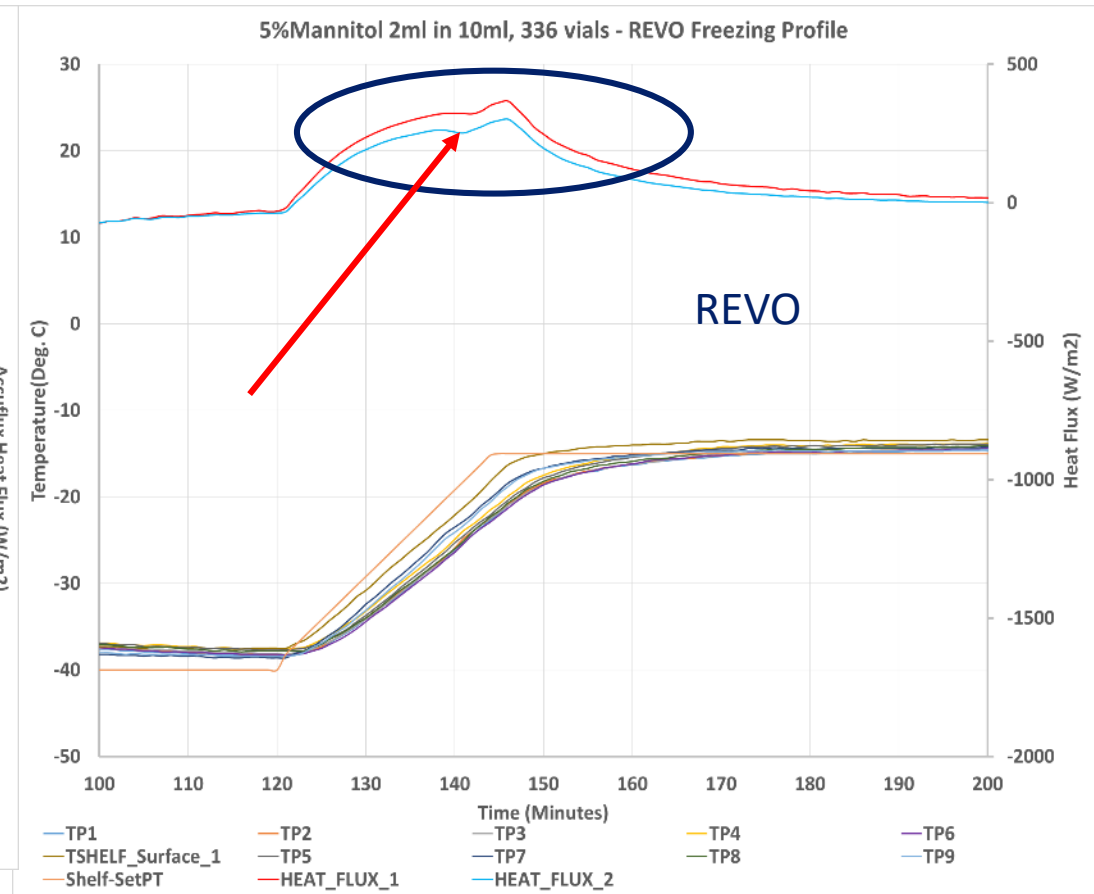
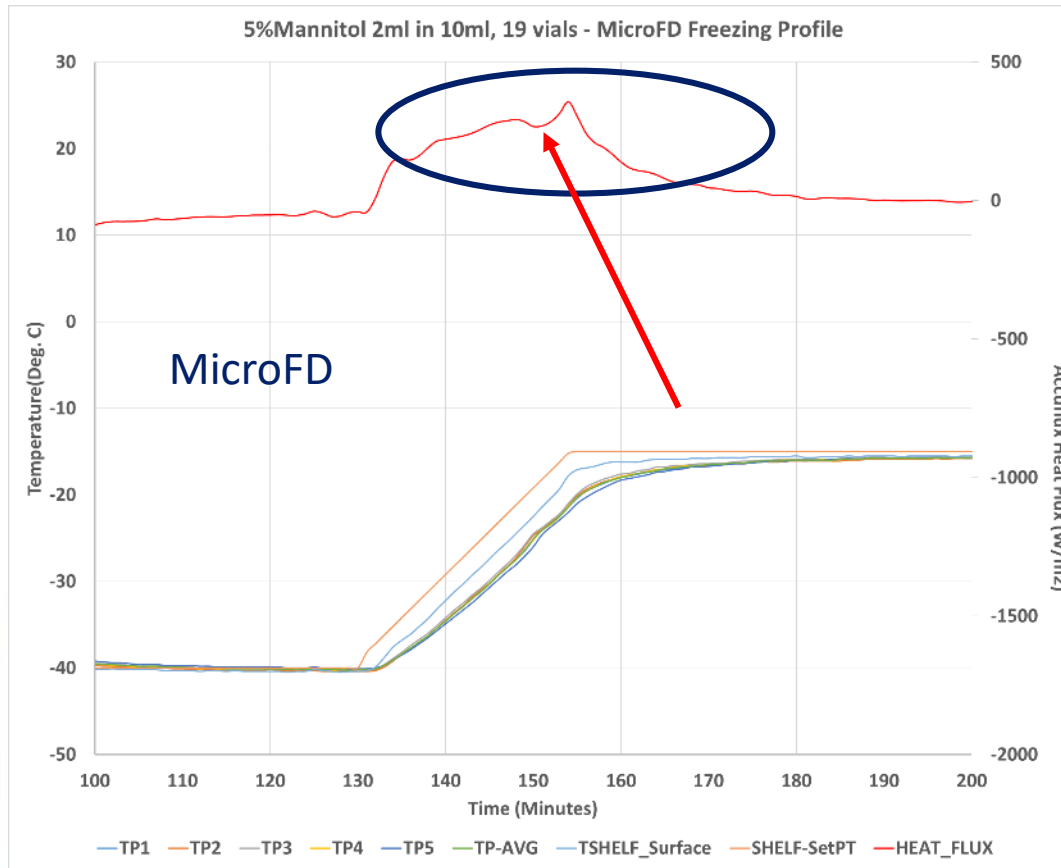


Freezing Comparison between MicroFD and REVO



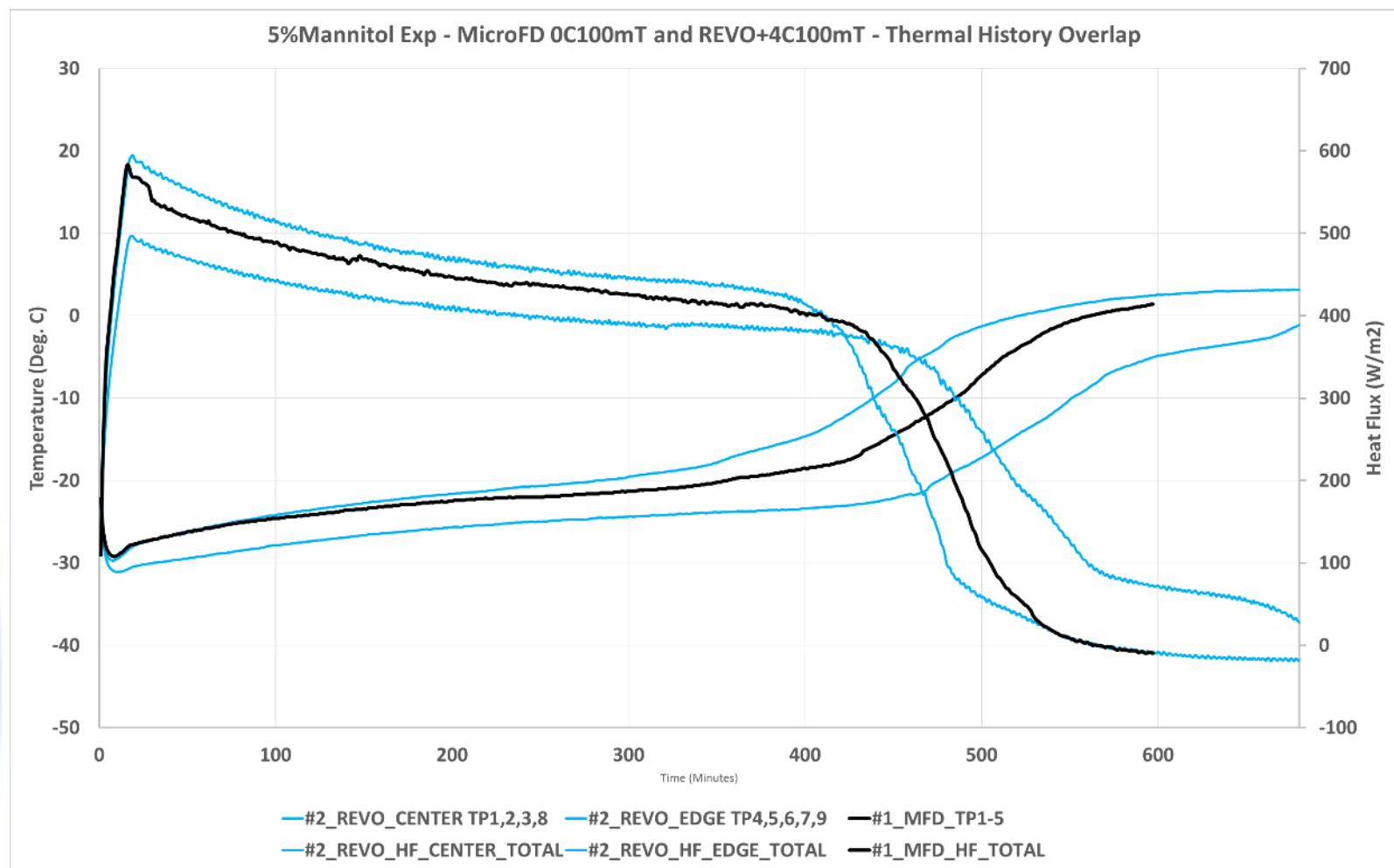
5% Mannitol 2ml fill in 10ml vials

Freezing Comparison between MicroFD and REVO – Secondary Crystallization?



5% Mannitol 2ml fill in 10ml vials

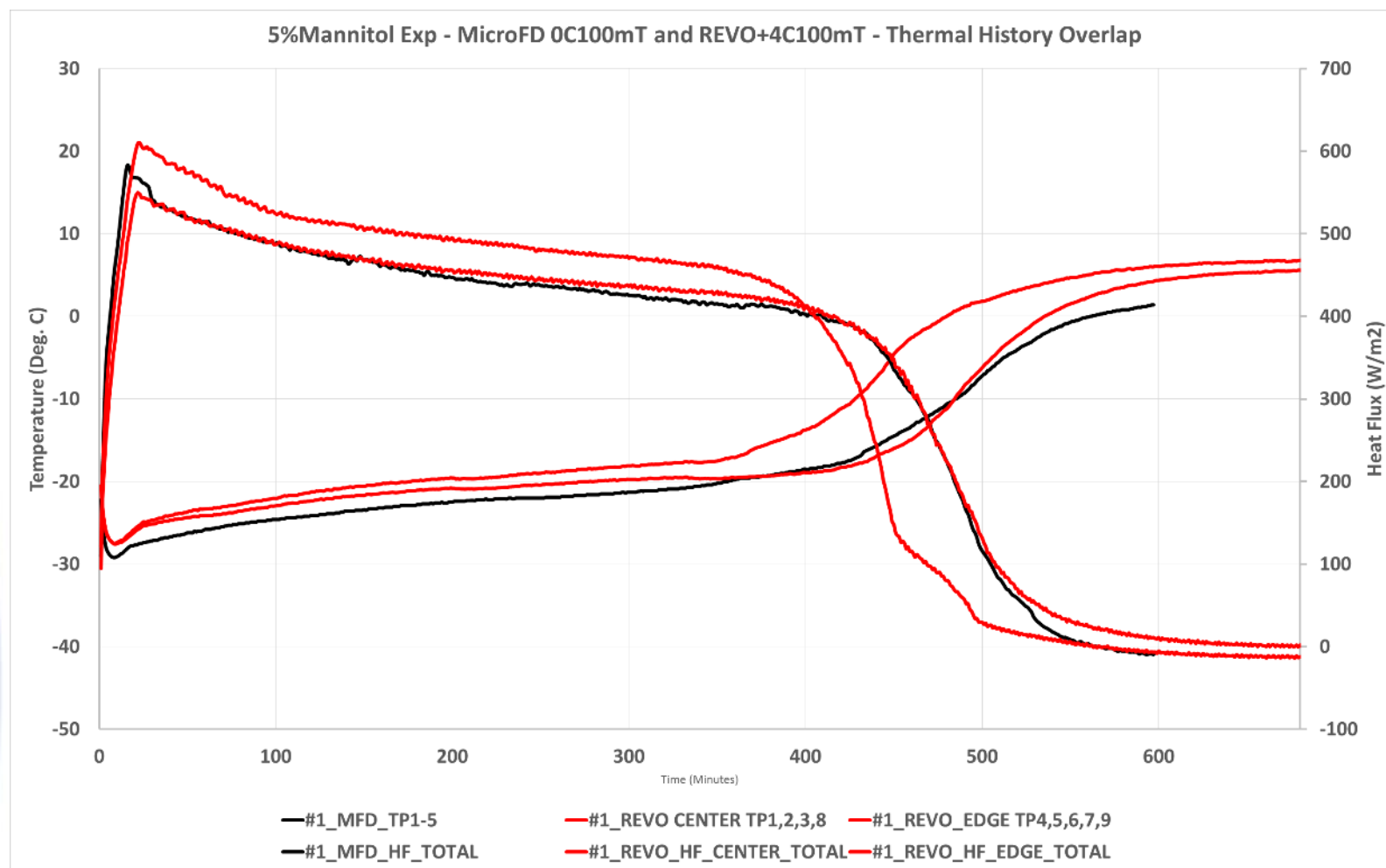
MicroFD and REVO – Baseline Thermal History Overlap



MicroFD@ 0C 100mT

REVO@ 0C 100mT

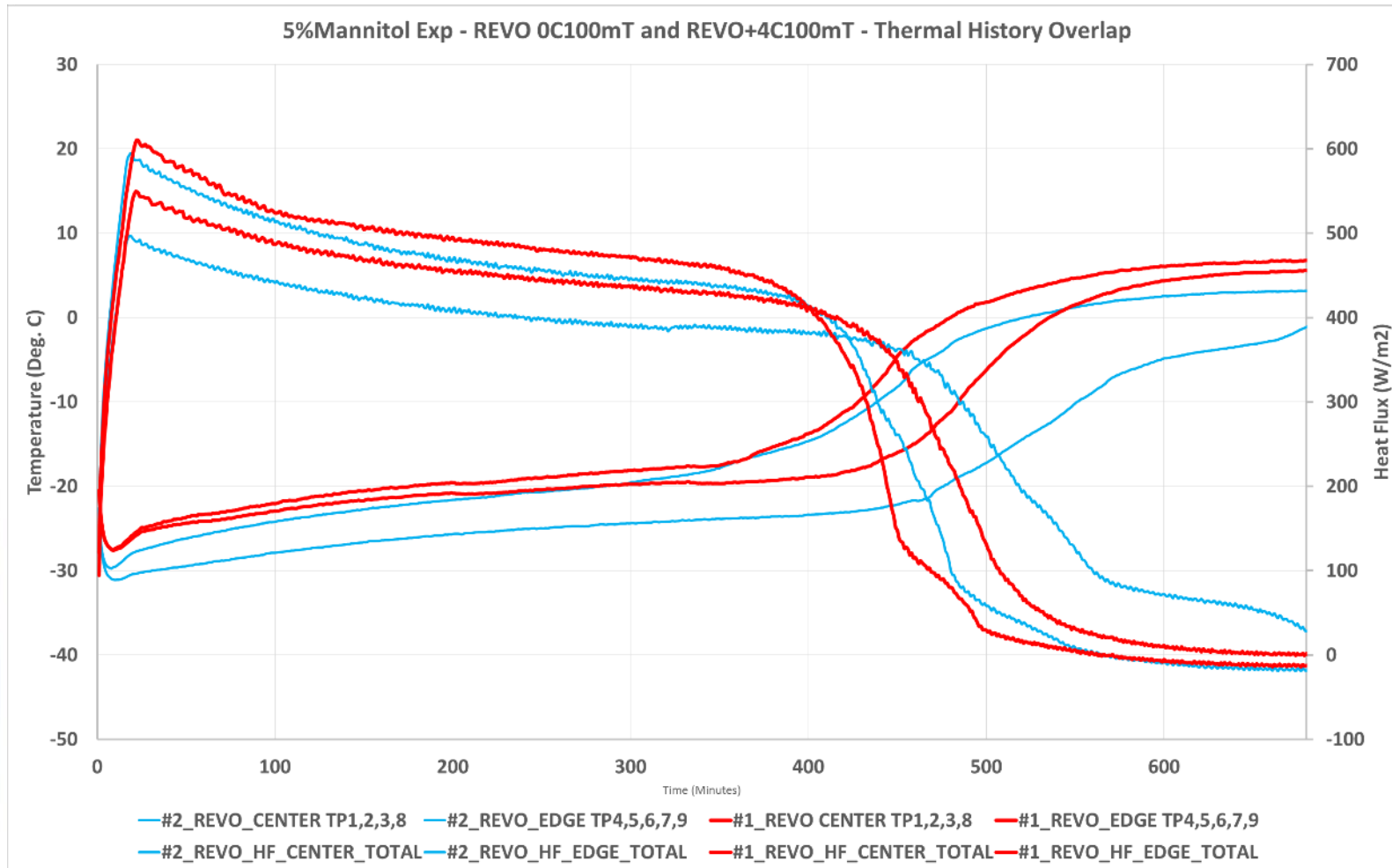
MicroFD and REVO – Transfer Thermal History Overlap



MicroFD@ 0C 100mT

REVO@ +4C 100mT

REVO Baseline vs REVO Transfer – Thermal History Overlap



REVO@ 0C 100mT

REVO@ 4C 100mT

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.

Next: Develop Optimized Transferable Protocols Using 19 Vials

Experiments in progress!



MicroFD



Revo



Quanta



Thank you!

Questions?

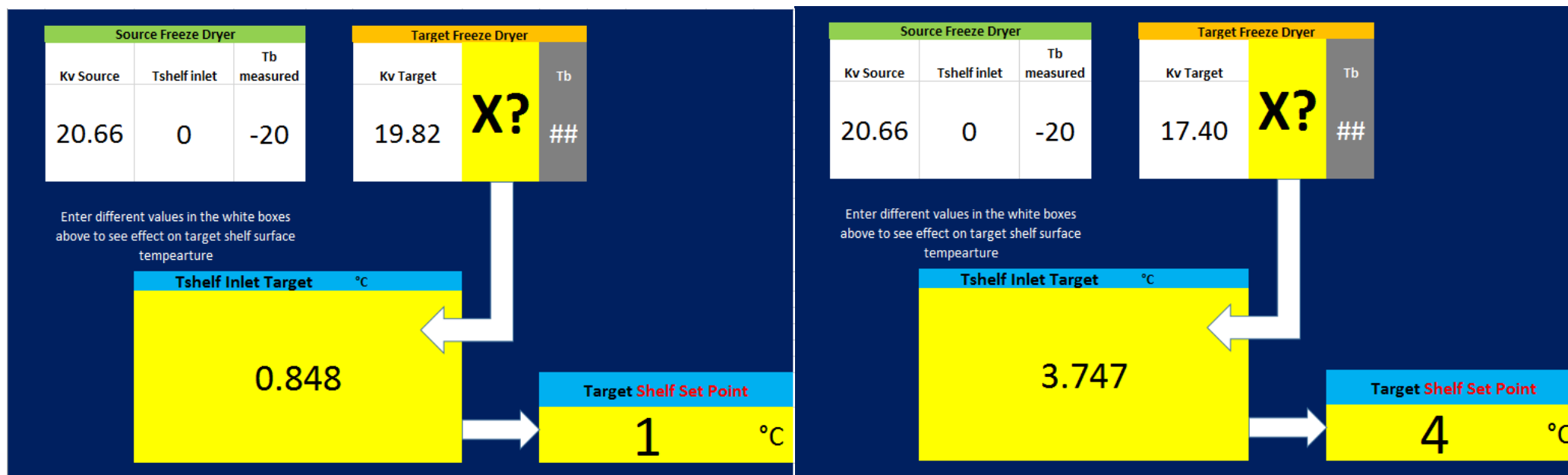
tn@millrocktech.com
845-339-5700

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

Transfer using Kv inlet results



Shelf Temperature Transfer Concept



MicroFD
Source

$$T_{s_surface_target} = \left(\frac{Kv_Source}{Kv_Target} \right) \times (T_{s_surface_source} - T_{b_source}) + T_{b_target}$$

Goal - Maintain the same level of heat flow going into the vial during the run in both systems			Units of measure		
Assumptions:	Heat Flux _{source} = Heat Flux _{Target}		Kv	W/m ² ·°C	
	T _{bsource} = T _{btarget}		Heat Flux	W/m ² ·°C	
User requires Kv in both systems	Using LysPAT or Geometrically		T_r	°C	
			T_b	°C	

Source Freeze Dryer			Target Freeze Dryer		
Kv Source	Tshelf Surface	T _b measured	Kv Target	T _b	T _b
22.16	-1.5	-20	18.01	X?	-20

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

Tshelf Surface Target °C <div style="background-color: yellow; padding: 5px; font-size: 24px; margin: 5px auto;">2.763</div>	Target System Shelf inlet - surface offset 1.5 °C
Tshelf Inlet Target °C <div style="background-color: yellow; padding: 5px; font-size: 24px; margin: 5px auto;">4.263</div>	Target Shelf Set Point <div style="background-color: yellow; padding: 5px; font-size: 24px; margin: 5px auto;">4 °C</div>



Revo
Target