Methodology of lyophilizers characterization to enable modeling of process parameters during cycle scale up

Serguei Tchessalov

BioTherapeutics, Pharmaceutical Sciences

Pfizer Inc

Outline

- **Lyophilizers characterization: why do we need it?**
- **Characterization tests review**
- **Primary drying modeling**
- **Examples of lyophilization cycle scale up using primary drying model**

Lyophilizer characterization: why do we need it?

Typical manufacturer practice (FAT): “Dry and empty” tests

1. **Maximum cooling and warming rates (inlet temperature), minimum shelf temperature, shelf temperature uniformity (shelf surface temperature measurements at steady state conditions)**
2. **Condenser cooling rate and minimum temperature**
3. **Vacuum performance-evacuation rate, minimum chamber pressure in empty lyophilizer**
4. **Sublimation test: freeze-drying of certain amount of water using cycle specified by the customer**

Typical lyophilization scale up issues:

- **Differences in cake resistance between laboratory and production samples**
- **Differences in heat transfer between commercial and laboratory freeze-dryers**
- **Variations in resistance to mass flow during primary drying from lyophilizer to lyophilizer**
- **Shelf surface temperature variations due to differences in mass and design**
- **Differences in process control and design (temperature and pressure control, capacitance manometer vs. Pirani, condenser temperature and capacity, internal condenser vs external etc.)**

In most cases, we could not transfer or scale up lab scale lyo process without adaptation to the commercial dryer.

References on scale up issues

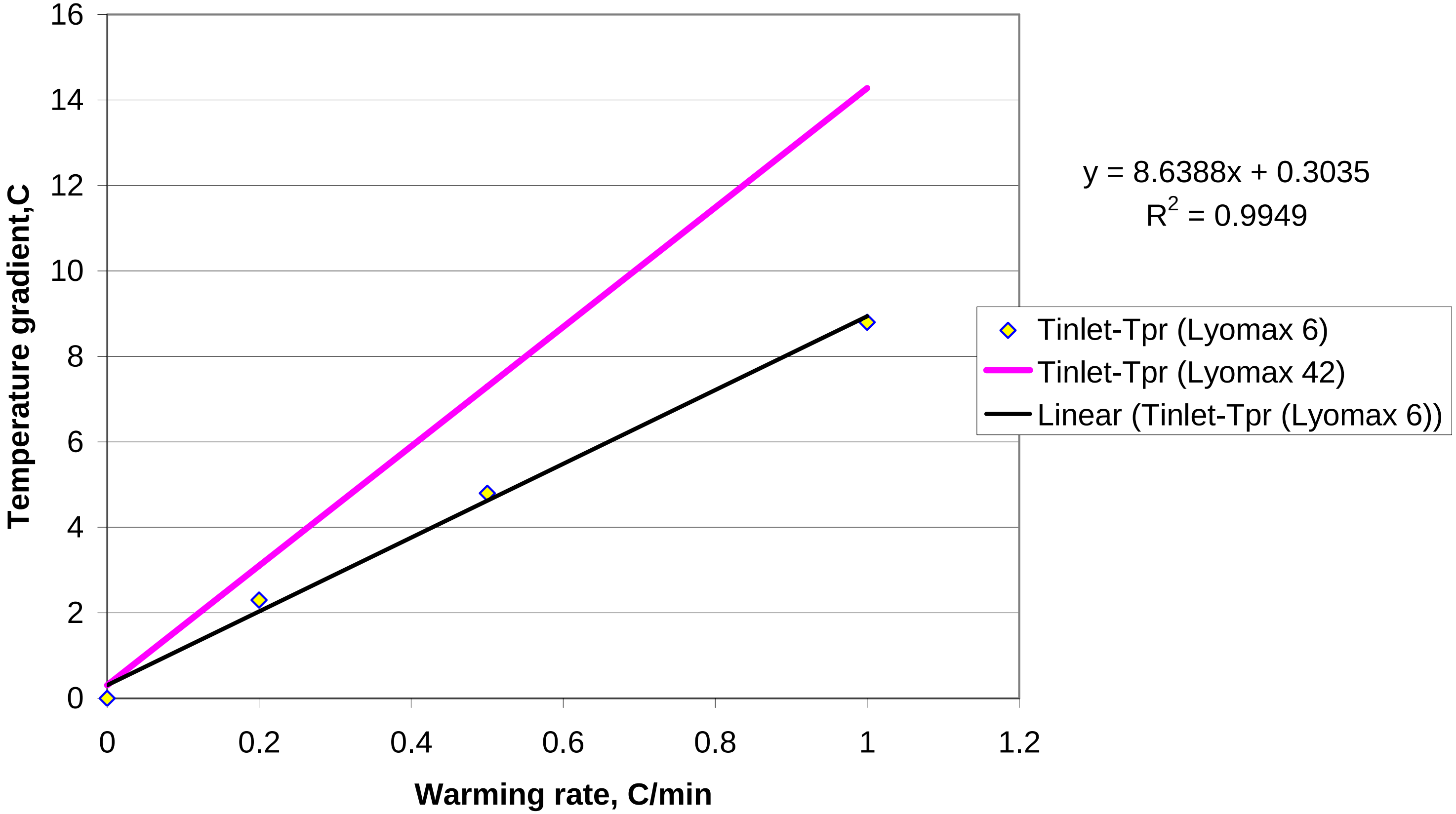
- **E.Trappler. Scale-up strategy for a lyophilization process. *American Pharmaceutical Review*. Volume/Issue 4:55-60 (2001)**
- **T.Jennings. Transferring the Lyophilization Process from One freeze-dryer to Another. *American Pharmaceutical Review*. Volume 5, issue 1, Spring:34-42 (2002).**
- **S.Tsinontides,P.Rajniak,D.Pham,W.Hunke,J.Placek,S.Reynolds. Freeze drying-principles and practice for successful scale-up to manufacturing. *International J.of Pharmaceutics*.280: 1-16(2004)**
- **W.Kuu,L.Hardwick,M.Akers. Correlation of laboratory and production freeze drying cycles. *International J.of Pharmaceutics*.302: 56-67(2005)**
- **S.Rambhatla, M. Pikal .Heat and mass transfer scale-up issues during freeze drying: I. Atypical radiation and the edge vial effect. *AAPS PharmSciTech*. 4(2), article 14:1-10 (2003)**
- **S.Rambhatla, R. Ramot, C. Bhugra, M. Pikal .Heat and mass transfer scale-up issues during freeze drying: II. Control and characterization of the degree of supercooling. *AAPS PharmSciTech*. 5(4), article 58:1-9 (2004)**
- **S.Rambhatla S; Tchessalov S; Pikal Michael J Heat and mass transfer scale-up issues during freeze - drying , III: control and characterization of dryer differences via operational qualification tests. AAPS PharmSciTech (2006), 7(2), E1-E10**
- **S. Tchessalov, D. Dixon, N. Warne. Principles of lyophilization cycle scale-up. American Pharmaceutical review, March-April 2007**

Additional testing of loaded lyophilizer

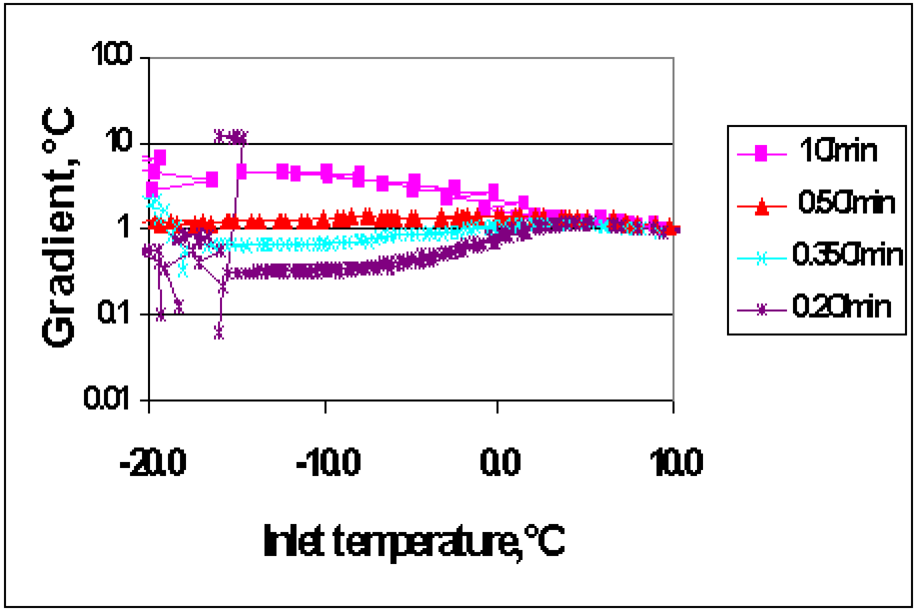
1. Effect of cooling/warming rates on temperature gradients across the shelf
2. Sublimation mapping
3. Sublimation tests to measure minimum controllable pressure as a function of sublimation rate
4. Maximum sublimation rate in respect to condenser load and choked flow
5. Vials heat transfer coefficients measurements
6. Power shut down tests

Freezing step scale up: effect of dryer size (Lyomax 6 vs. Lyomax 42)

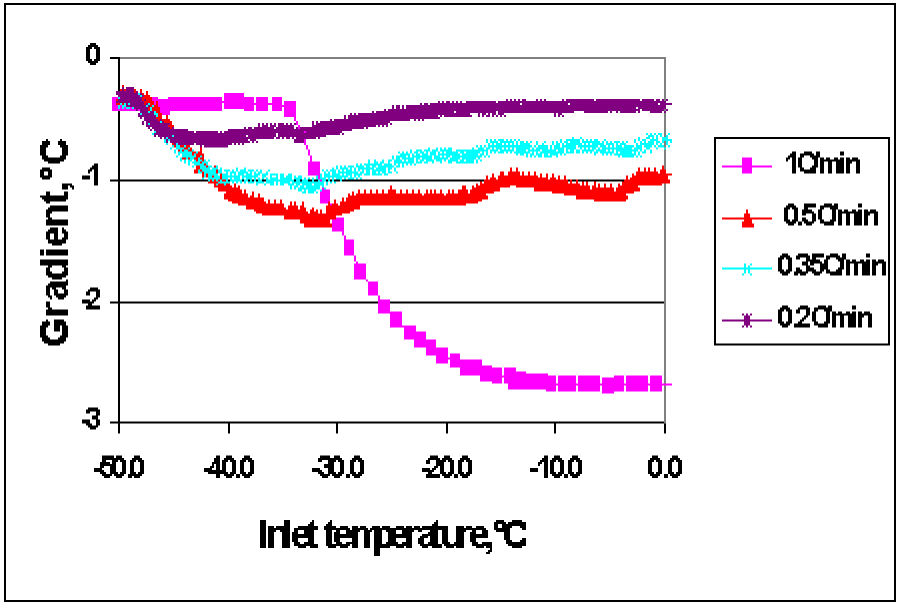
Effect of warming rate on temperature gradient between inlet temperature and product temperature for the vial in center of shelf 3



Choosing optimal rates during freezing: effect of ramp rates on product temperature difference across the shelf (center vial- corner vial, Lyomax 42)



Cooling



Warming

Material: water

Recommendation: Cooling and warming rates should not exceed 0.5°C/min to keep product temperature gradient across the shelf close to 1°C. This recommendation is applicable for many dryers (Telstar, Edwards, SP Industries)

Sublimation mapping: using filled vials to assess freeze-dryer performance

- Pros

1. Kv and edge effect could be estimated for fully loaded dryer (at one pressure set point)
2. Freeze-dryer hot and cold spots can be identified
3. Vacuum and refrigeration systems performance for a given cycle could be confirmed using relatively cheap material (water or buffer)

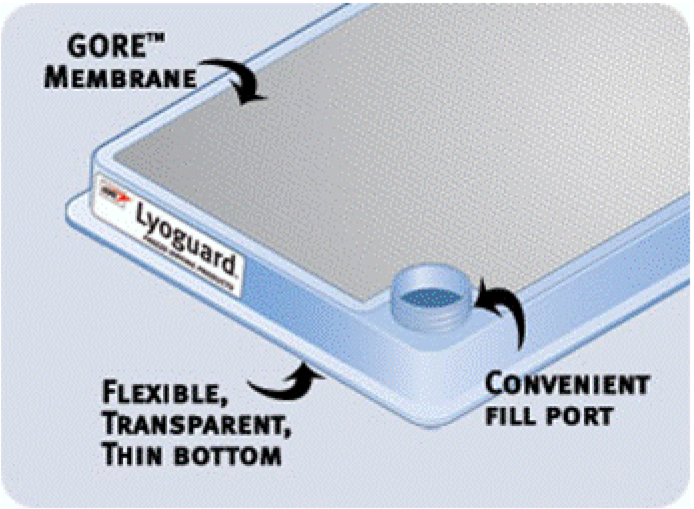
- Cons

1. Vials and stoppers could be expensive
2. Additional experiments are needed to establish the design space

Sublimations tests: Experiment set up

Black garbage bags versus Lyoguard trays

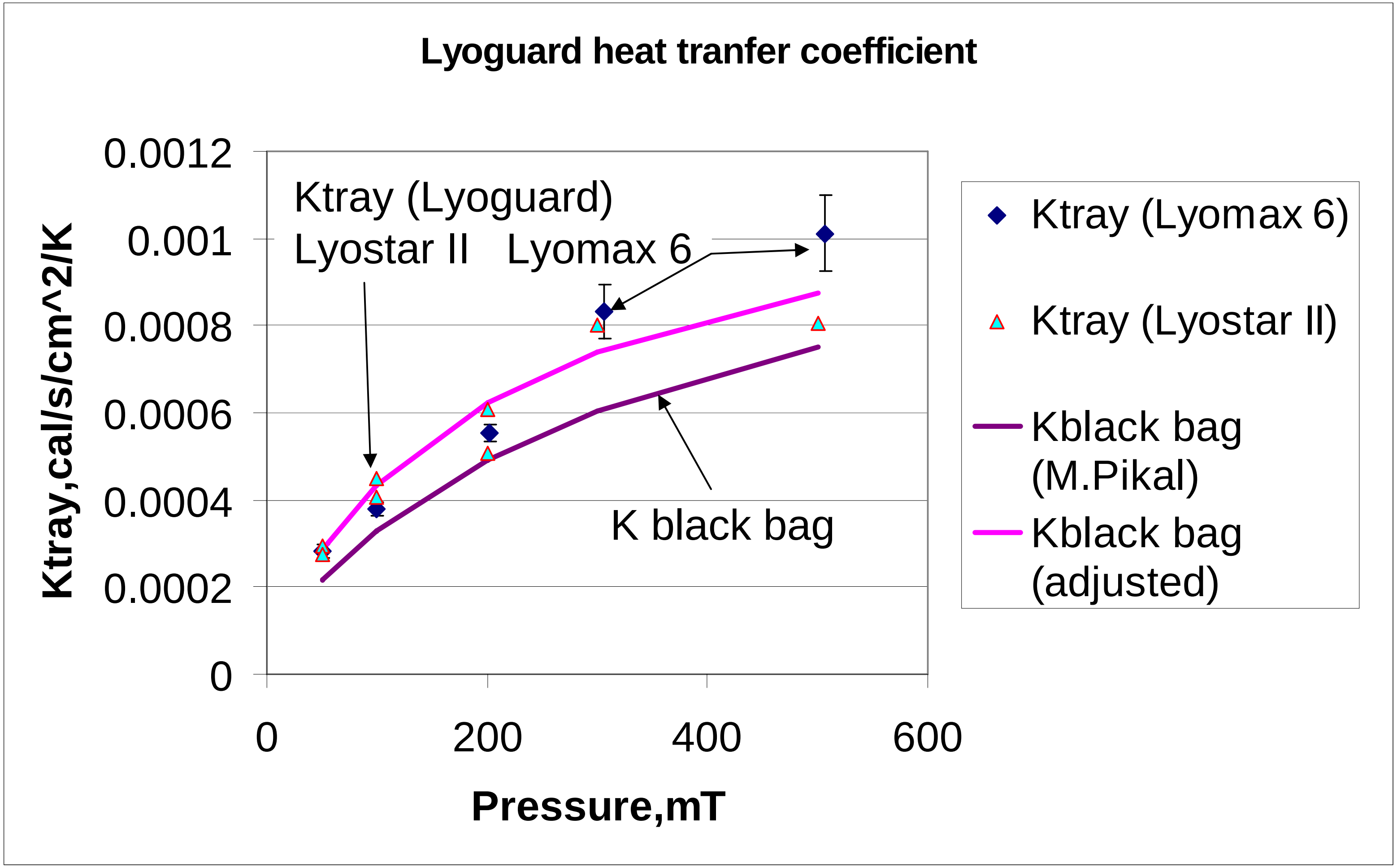
Leaky but no limitation on thickness of ice



Very convenient in sublimation tests. Maximum ice height is 2 cm (short sublimation tests).

Kbag=f(P) is known for both containers

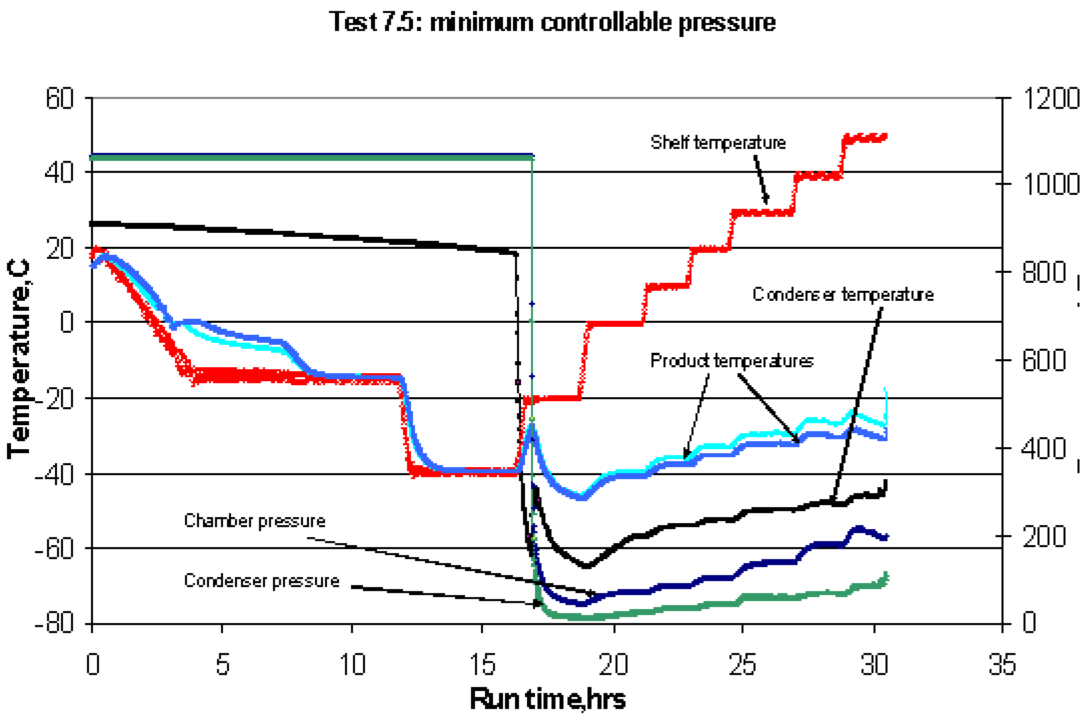
Container heat transfer coefficient as a function of pressure: Comparison between Lyoguard tray and black bag



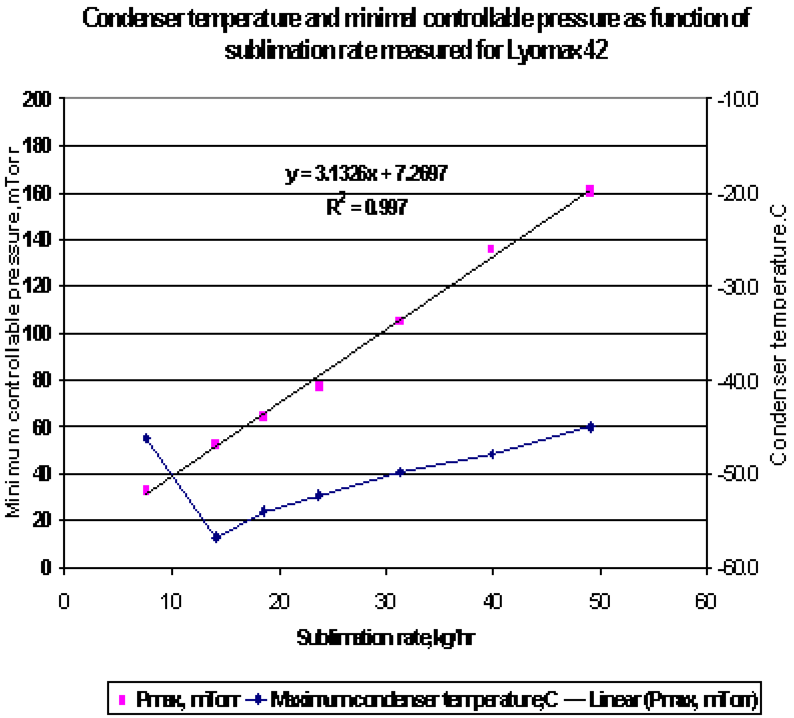
Reference for black bag heat transfer coefficient: S.Rambhatla and M.Pikal in Lyophilization of pharmaceuticals, AAPS press, 2004(p.94)

Sublimation test on Lyomax 42

60 trays x 16.6L~1000L filled. Actual weight loss during sublimation ~352 kg.



Test 7.5: minimum controllable pressure



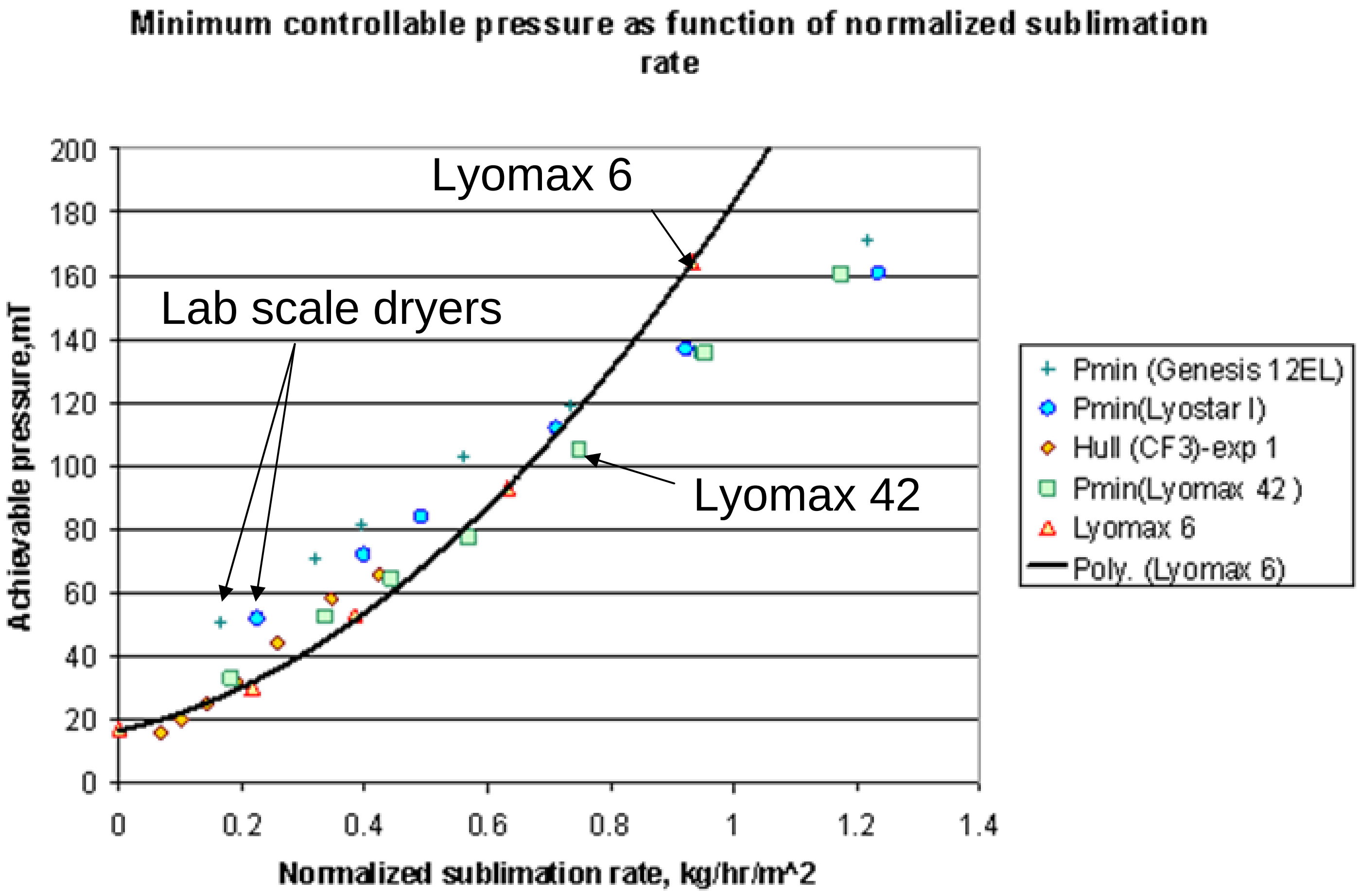
Condenser temperature and minimal controllable pressure as function of sublimation rate measured for Lyomax 42

$$\frac{dm}{dt}\left(\frac{kg}{hr*m^2}\right)=K_{Tray}B(T_{shelf\_surface}-T_{ice\_bottom})$$

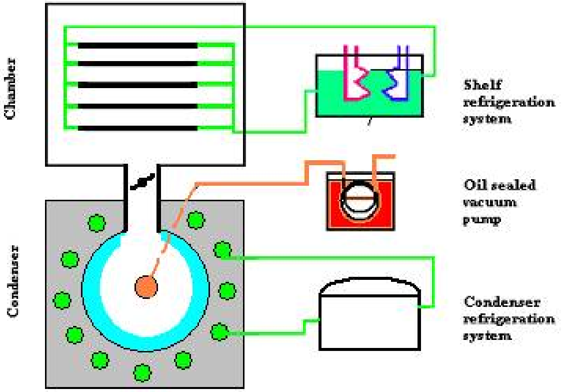
Pmin=f(dm/dt) input in lyo template

Black bags were used in experiment

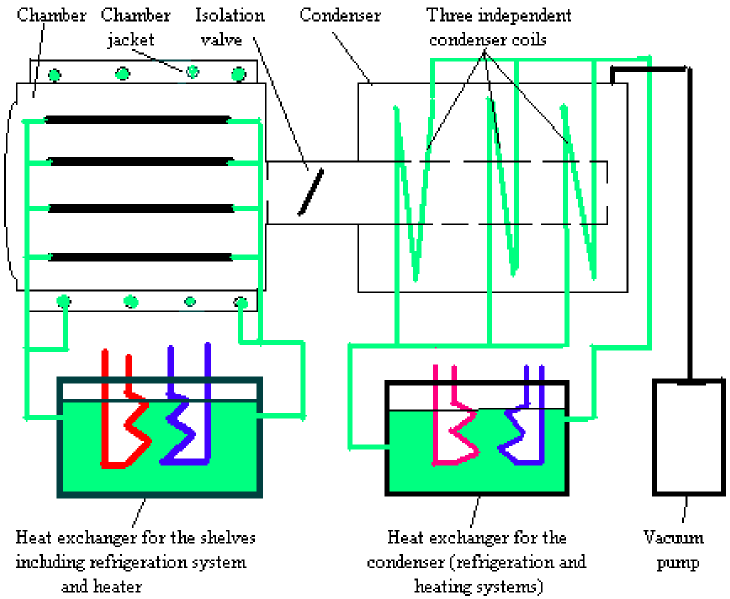
Comparison between freeze-dryers



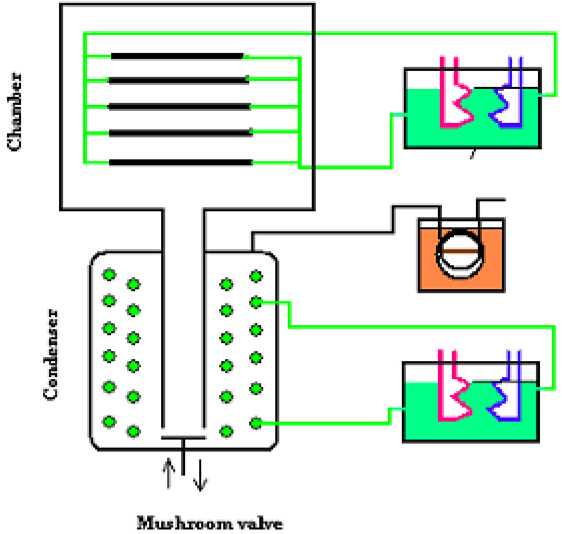
Comparison between laboratory and commercial dryers



Genesis



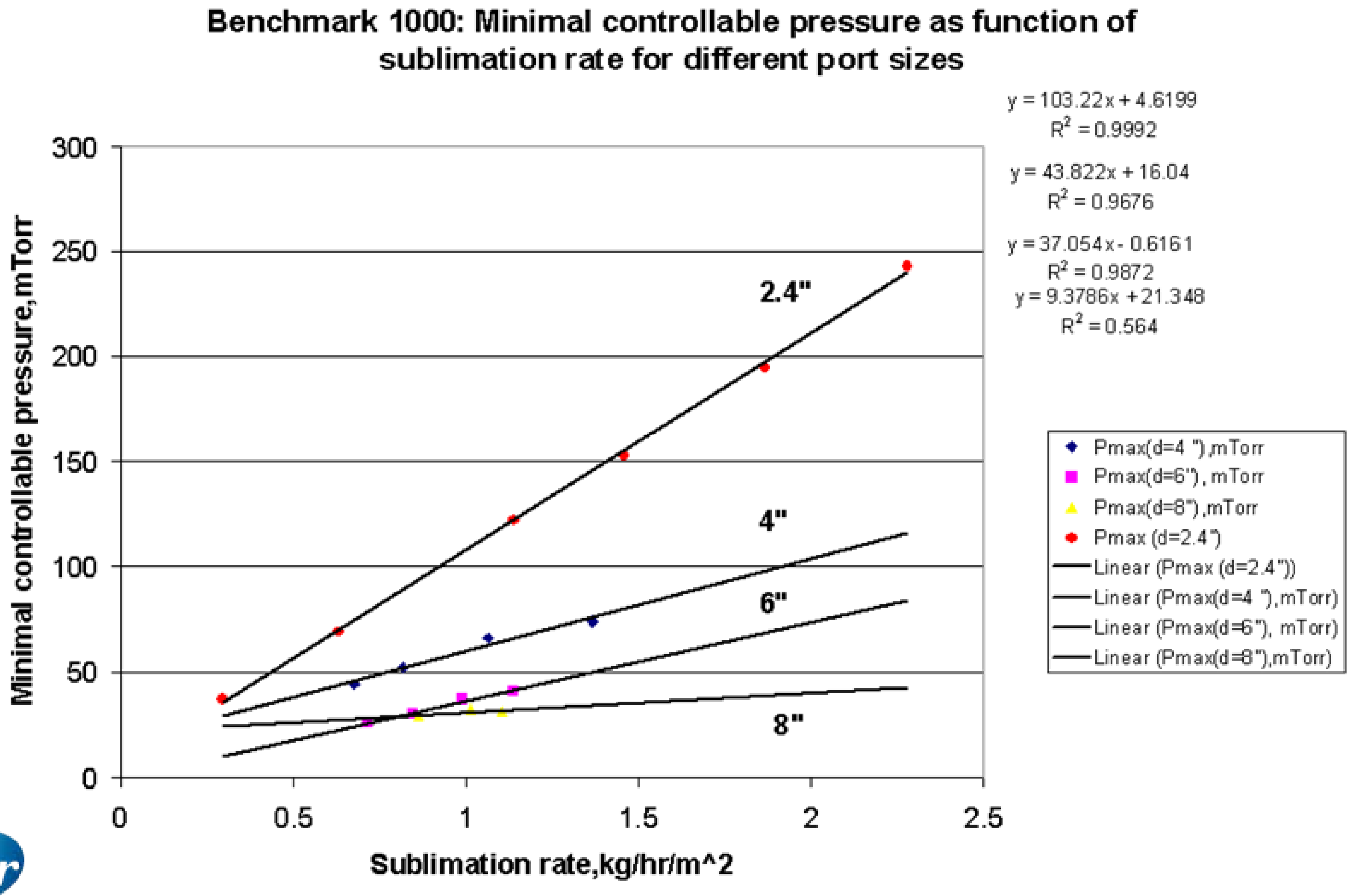
Benchmark 1000



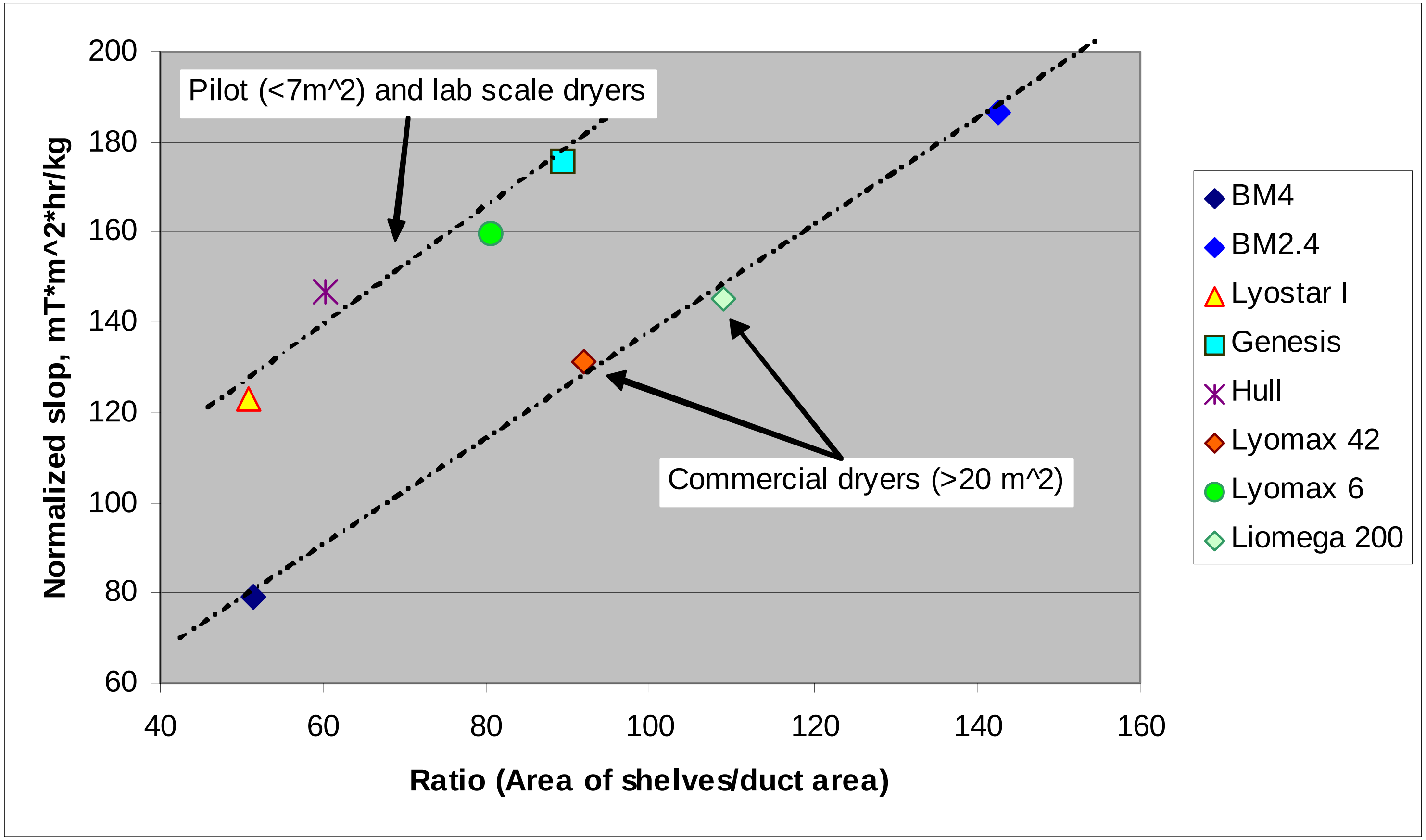
Lyomax 42

	Genesis (Laboratory)	Benchmark (laboratory)	Lyomax (commercial)
Surface area, Sa	0.56m^2	0.42m^2	42m^2
Duct area (Sd)/ diameter (Dduct)	0.008m^2/ 0.01m	0.03m^2/ 0.02m	0.45m^2/ 0.76m
Ratio, Sa/Sd	71	14	93

Effect of port size on minimal controllable pressure (Benchmark 100)



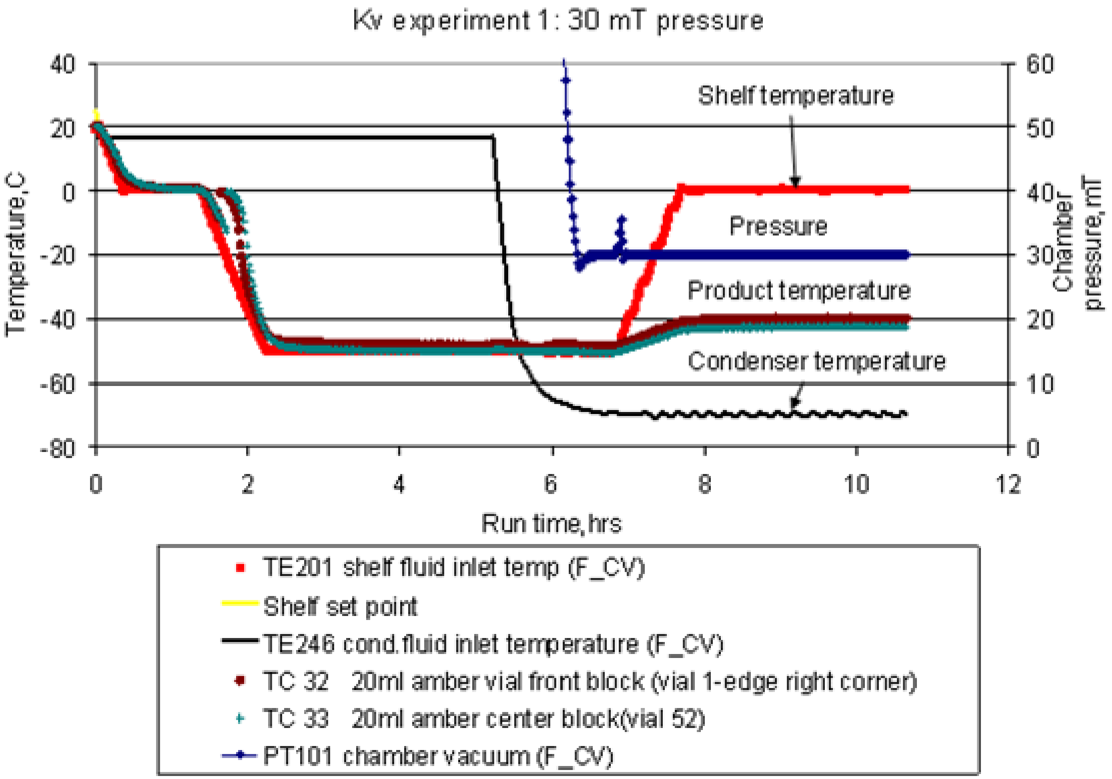
Correlation between slope and lyophilizer geometry



$$P_{Min}(mT) = P_0 + Sl * SR(kg/hr)$$

$$Norm\_Slope = Sl * A(m^2)$$

Kv measurements

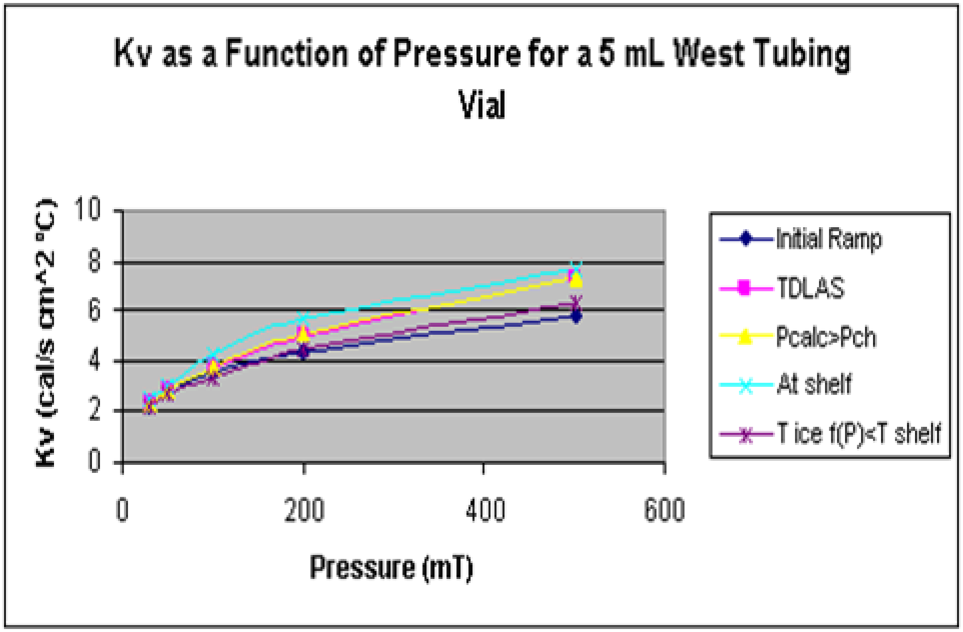


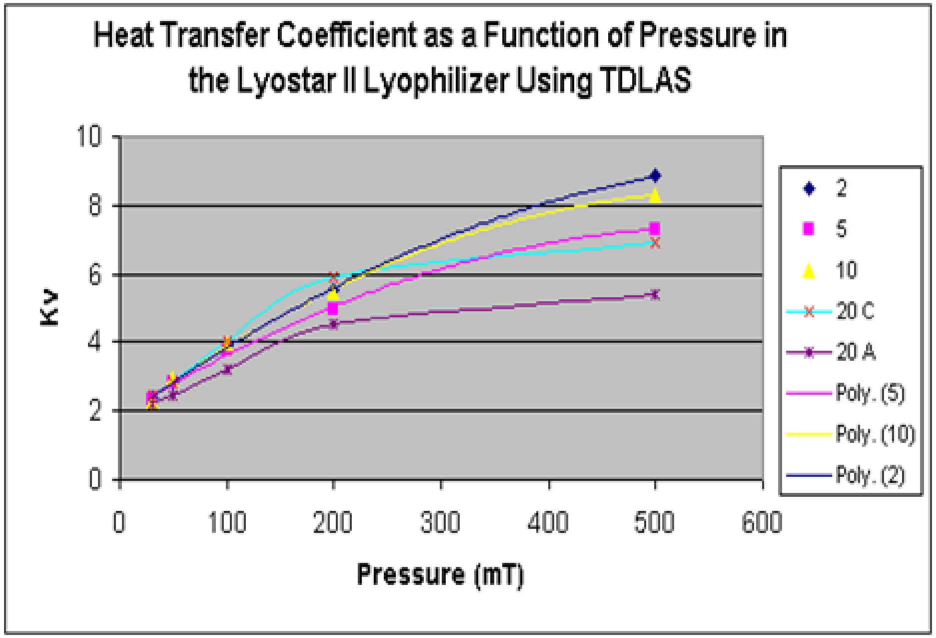
Weight loss ≤30% of total mass

$$K_V = \frac{\Delta m \Delta H_S}{(S_V)_{Out} \int (T_{Inlet} - T_{Ice\_est})dt}$$

Weight loss ≥ 50% of total mass – Heat transfer surface area is reduced: Underestimation of Kv value.

Kv as function of pressure for different vials estimated by 5 different methods



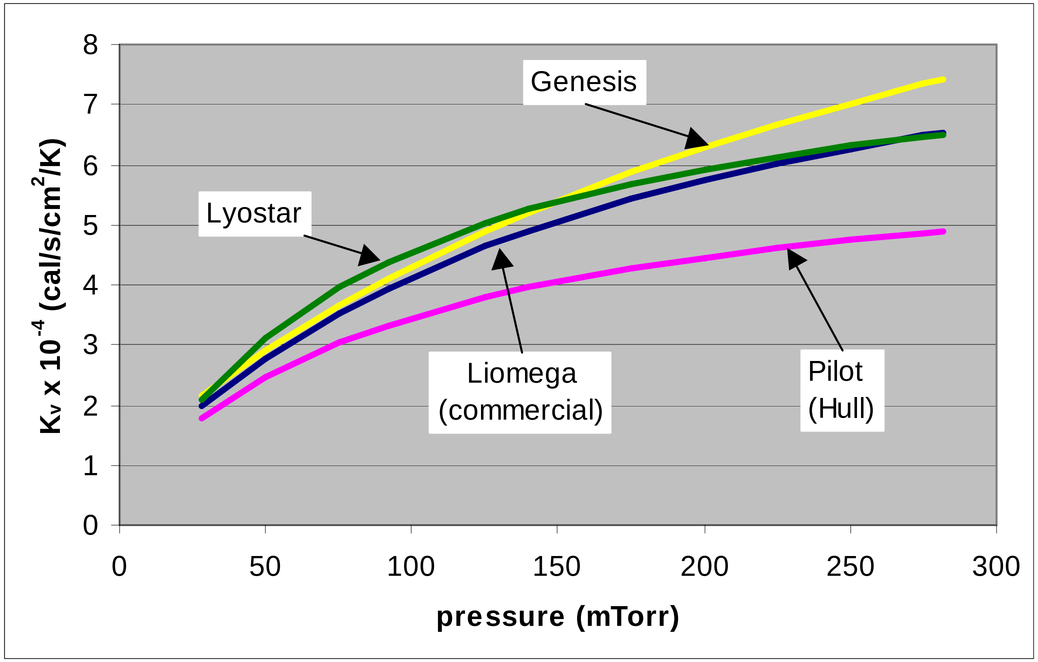


5-ml vial Kv: 1.Tsh=const > 2.TDLAS~ ~3.Psubl>Pch > 4.Tpr(Pch)> 5.Initial ramp

TDLAS method: 2-ml>10-ml>5-ml> >20-ml(clear)>20-ml (amber)

Kv=f(Pch)- input in lyo template
Should be measured for individual freeze-dryer.

Kv measurements: comparison between laboratory, pilot and commercial dryers (10-ml Schott vials)



$$K_V = K_{radiation} + K_{contact} + K_{gas}$$

$$K_{gas} = \frac{\alpha \Lambda_0 P_{ch}}{1 + l_V \left(\frac{\alpha \Lambda_0}{\lambda_0}\right) P_{ch}}$$

$$K_{radiation} = \sum A_i \varepsilon_i \sigma (T^4_{surface} - T^4_{product})$$

Shelf emissivity, distance between shelves, vial geometry and heat transfer through the shelf itself all could impact Kv

$$K_V = a + \frac{bP_{chamber}}{1 + cP_{chamber}} \longrightarrow$$

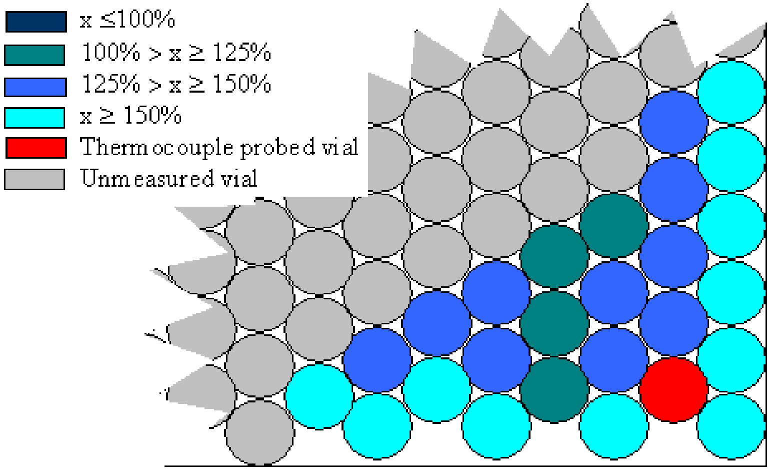
Lyo characterization generates a,b,c coefficients for specific vial type/size in specific lyophilizer

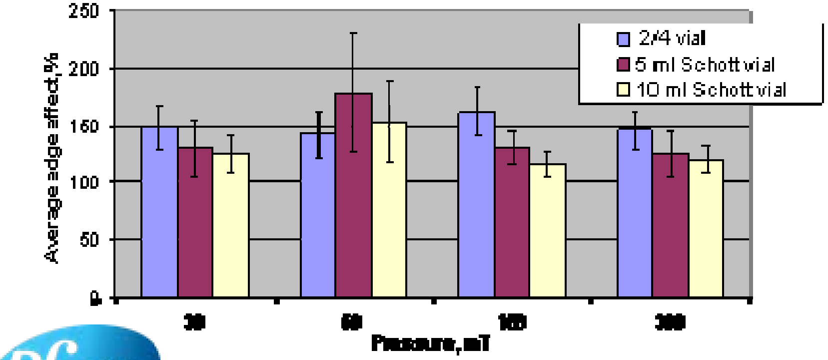
Edge effect for different freeze-dryers

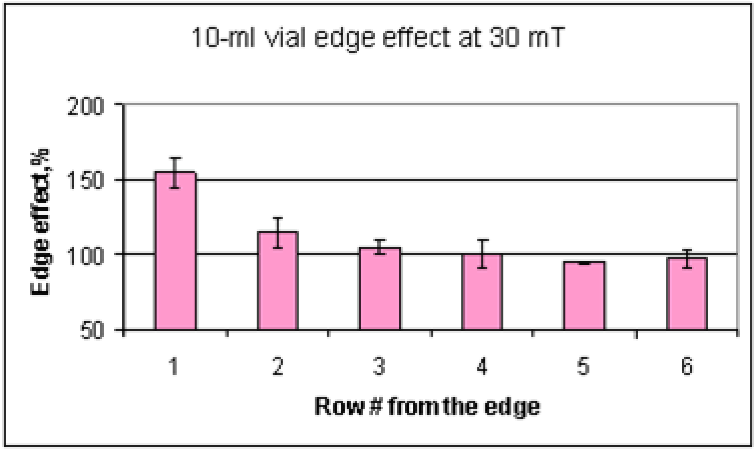
Hull clinical dryer
(bottomless trays)

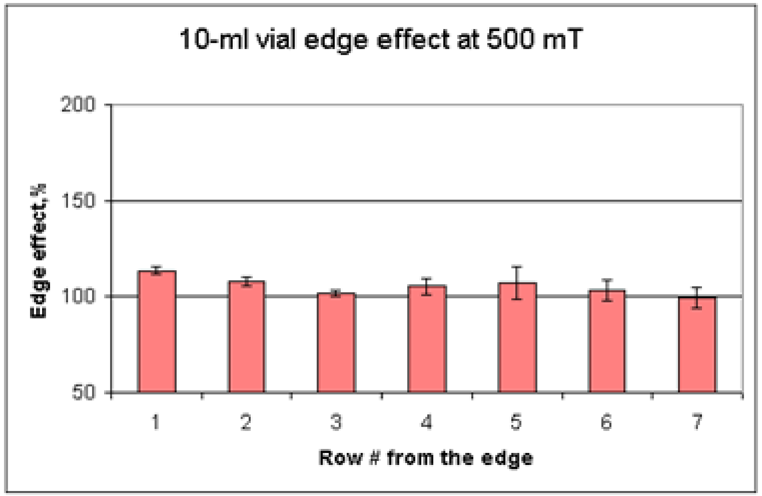
Lyomax 6 (no trays)

2/4 Schott vials $P_{chamber}$ = 30 mTorr



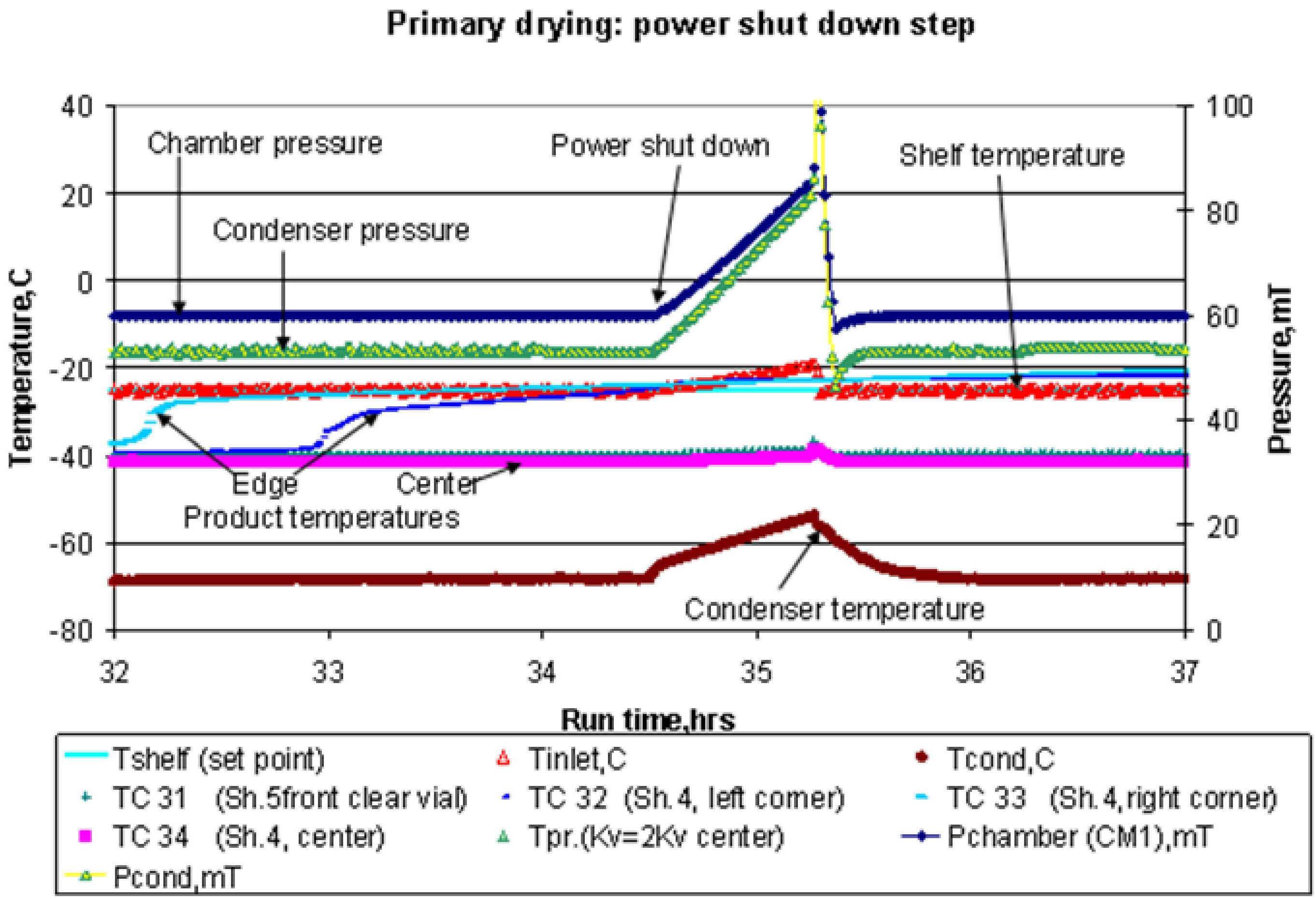






Kv(edge)=Factor*Kv(center)- input in lyo template

Power shut down test



Product temperature and pressure increase in Lyomax 6 during 45-min power shut down test

Parameter		Initial value	Final value	Rate of change	Value after pressure spike
Average surface temperature (bottom) of shelf #4,°C		-25.8	-26.5	-0.93 °C/hr	-25.9
Condenser temperature (measured by RTD attached to the coil), °C		-69.9	-63.7	8.27 °C/hr	-58.4
Product temperature	Tc31-Sh5-front	-39.8	-38.1	2.27 °C/hr	-37.5
	Tc32-Sh4-left corner	-24.3	-23.0	1.73 °C/hr	-22.9
	Tc33-Sh4-right corner	-23.9	-22.8	1.47 °C/hr	-22.7
	Tc34-Sh4-center	-41.3	-39.9	1.87 °C/hr	-38.7
Chamber pressure, mT		60.0	85.4	33.9 mT/hr	109.8
Condenser pressure, mT		53.3	83.1	39.7 mT/hr	109.2

Pressure spike that occurred when power was restored could be notable.

Simple Steady State model (SSSM) of primary drying

$$P_{subl\_surf} = P_{ch} + \frac{R(h)_i}{\Delta H_S}\frac{S_{out}}{S_{in}} K_V(P_{ch})(T_{shelf} - T_{product\_bottom})3600 = P_1$$ Eq.1

$$(P_{sublsurf})_i = \exp(24.0185 - \frac{6145}{(T_{subl\_surf})_i}) = P_2$$ Eq.2

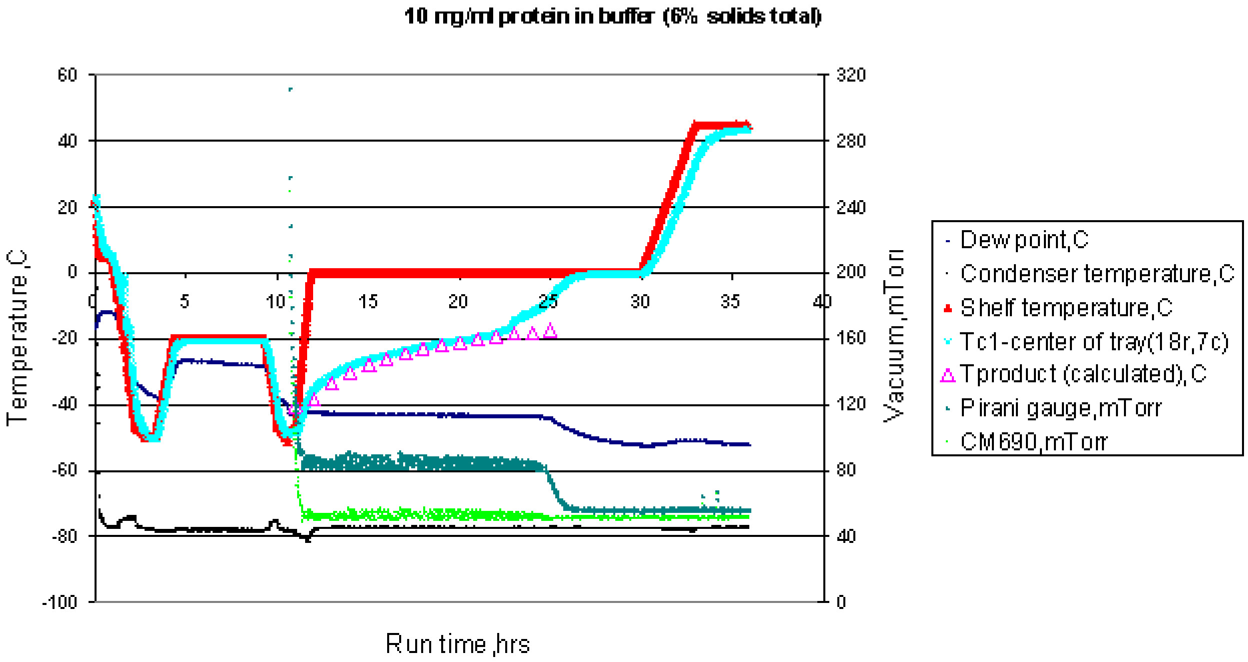
$$T_{subl\_surf} = T_{product\_bottom} - K_V(P_{ch})(T_{shelf} - T_{product\_bottom})\frac{h_{frozen} - h_i}{\lambda_{frozen}}$$ Eq.3

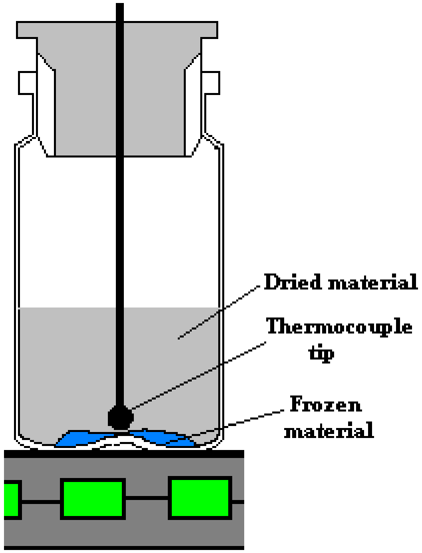
Using Solver $\sum (P_1 - P_2)^2 \to \min$ Eq.4

$$PRW\ (t_i) = \frac{((m_{ice})_{vial})_i}{(m_{ice})_{vial}}100$$ Eq.5

Tproduct (bottom and sublimation surface)=f(Tsh and Pch)

Comparison between calculated and actual temperature profiles



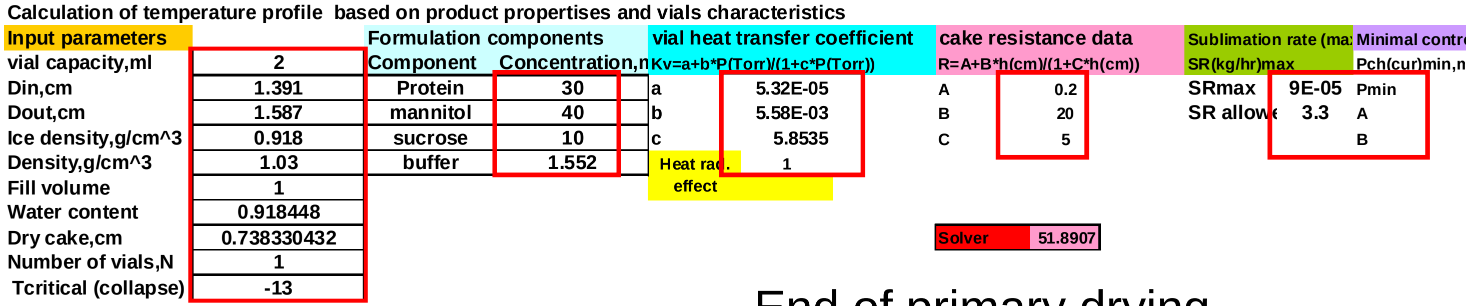


Error in temperature prediction ≤1°C.

Error in primary drying time prediction ≤10% (up to 30% at Tsh<-25°C).

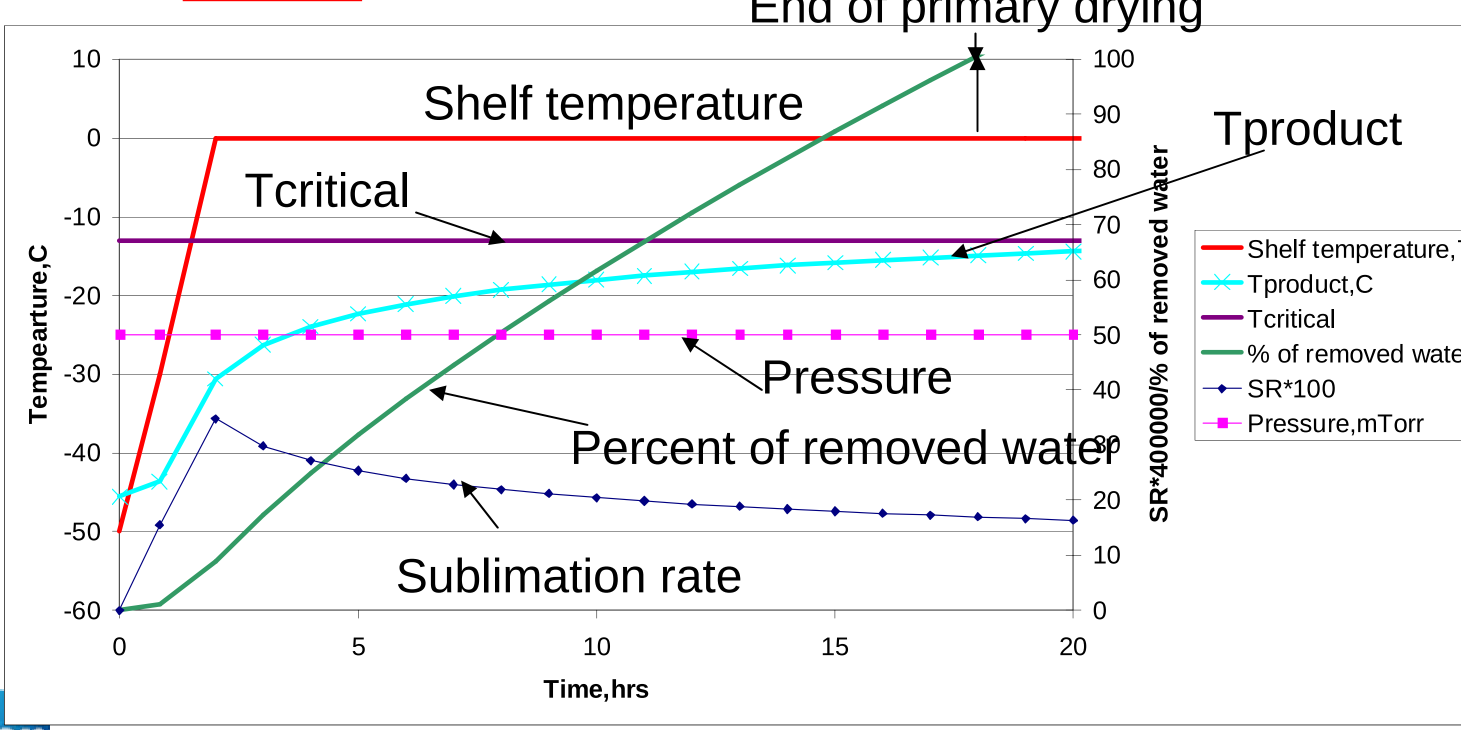
Calculation time-seconds

Application of sublimation and Kv tests

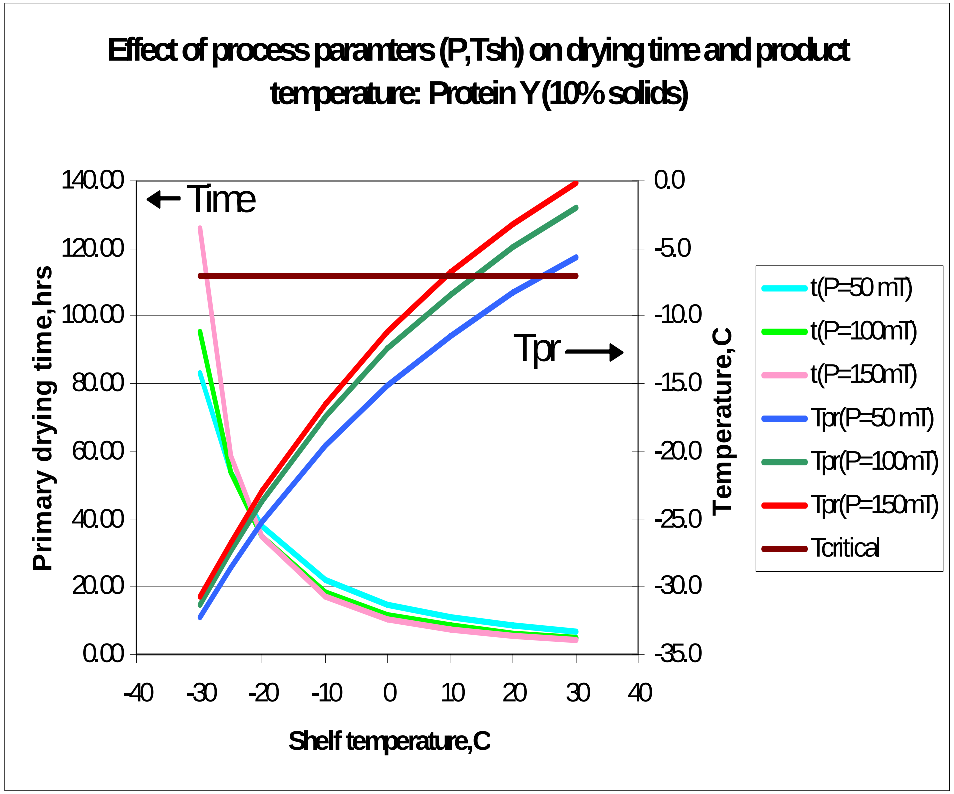


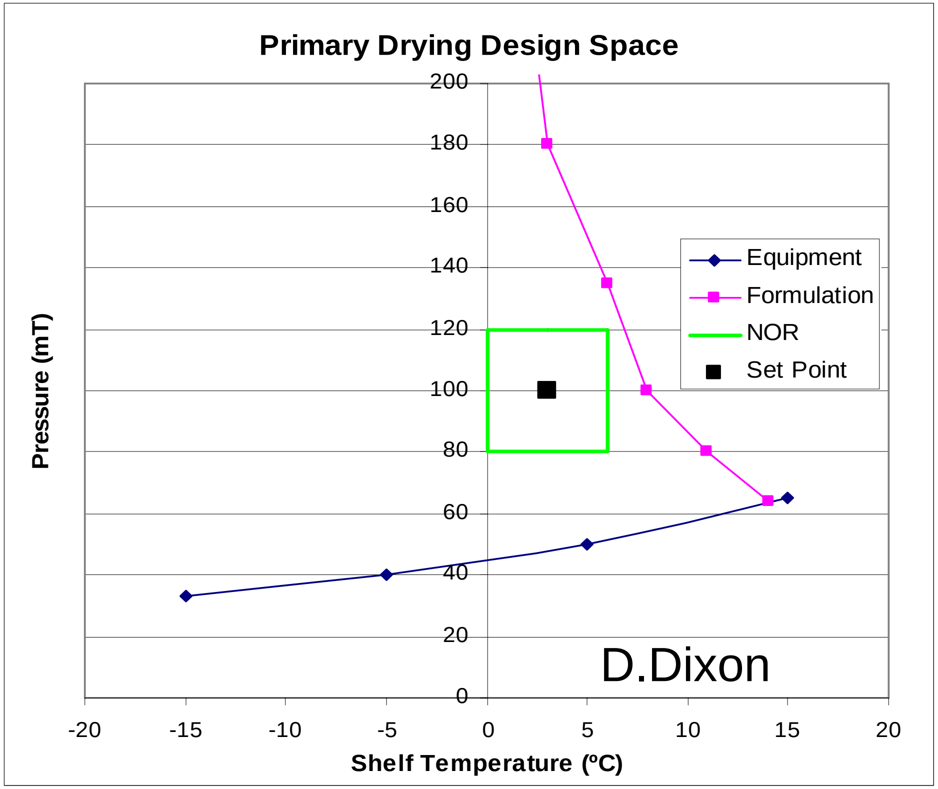
Calculation of temperature profile based on product propertises and vials characteristics

Input parameters		**Formulation components**		**vial heat transfer coefficient**		**cake resistance data**		**Sublimation rate (ma**		**Minimal contr**
vial capacity,ml	**2**	**Component**	**Concentration,n**	**Kv=a+b*P(Torr)/(1+c*P(Torr))**		**R=A+B*h(cm)/(1+C*h(cm))**		**SR(kg/hr)max**		**Pch(cur)min,n**
Din,cm	**1.391**	**Protein**	**30**	**a**	**5.32E-05**	**A**	**0.2**	**SRmax**	**9E-05**	**Pmin**
Dout,cm	**1.587**	**mannitol**	**40**	**b**	**5.58E-03**	**B**	**20**	**SR allow**	**3.3**	**A**
Ice density,g/cm^3	**0.918**	**sucrose**	**10**	**c**	**5.8535**	**C**	**5**			**B**
Density,g/cm^3	**1.03**	**buffer**	**1.552**	**Heat rad. effect**	**1**					
Fill volume	**1**									
Water content	**0.918448**									
Dry cake,cm	**0.738330432**					**Solver**	**51.8907**			
Number of vials,N	**1**									
Tcritical (collapse)	**-13**									



Primary drying design space



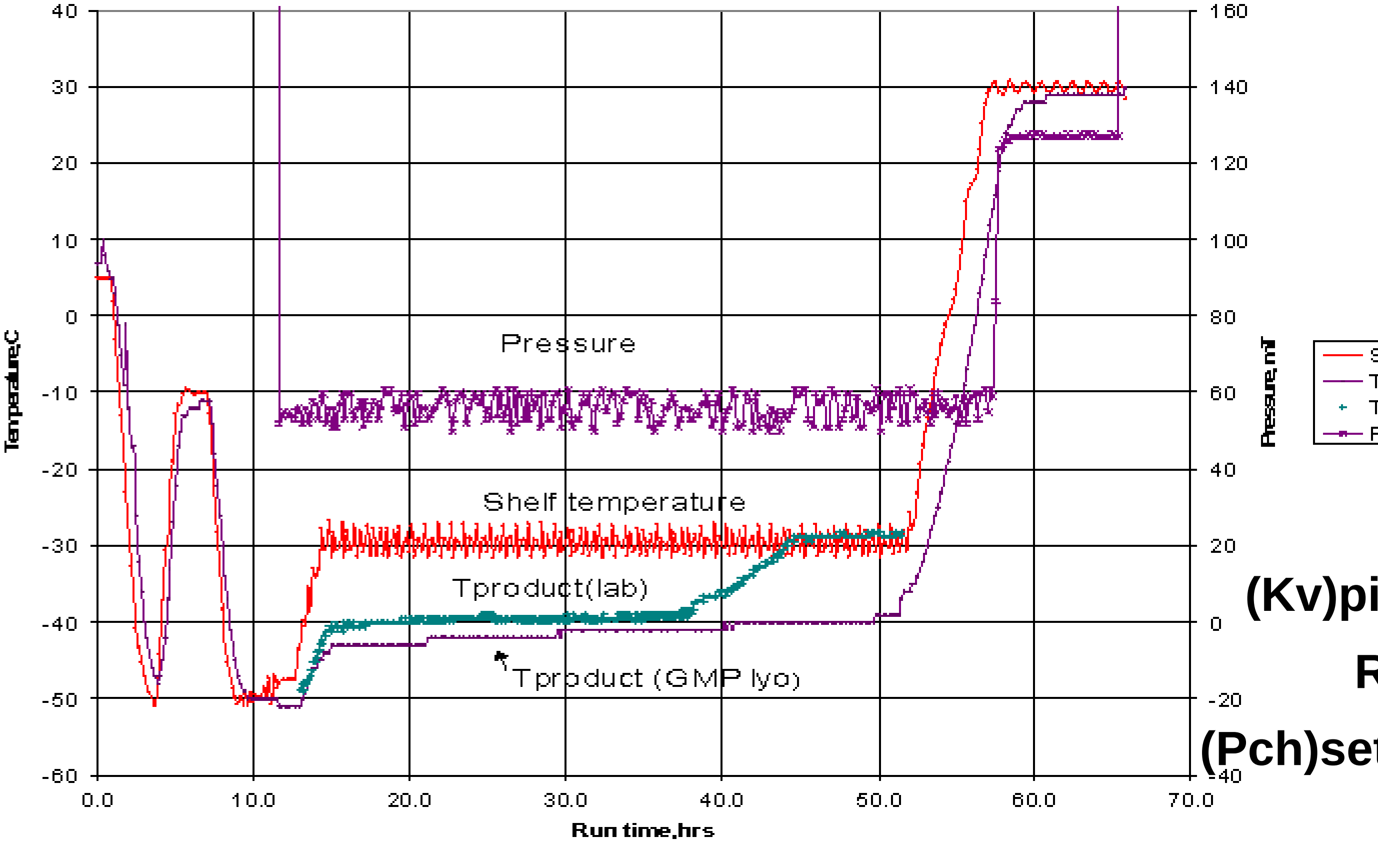


Design space in respect to process parameters (Tsh, Pch) and drying time (Kv and cake resistance should be known)

Design space in respect to process parameters (Tsh, Pch) and equipment limitations (minimum controllable pressure as function of sublimation rate)

Example of primary drying scale up:

using laboratory cycle set points in pilot lyophilizer



(Kv)pilot<(Kv)lab

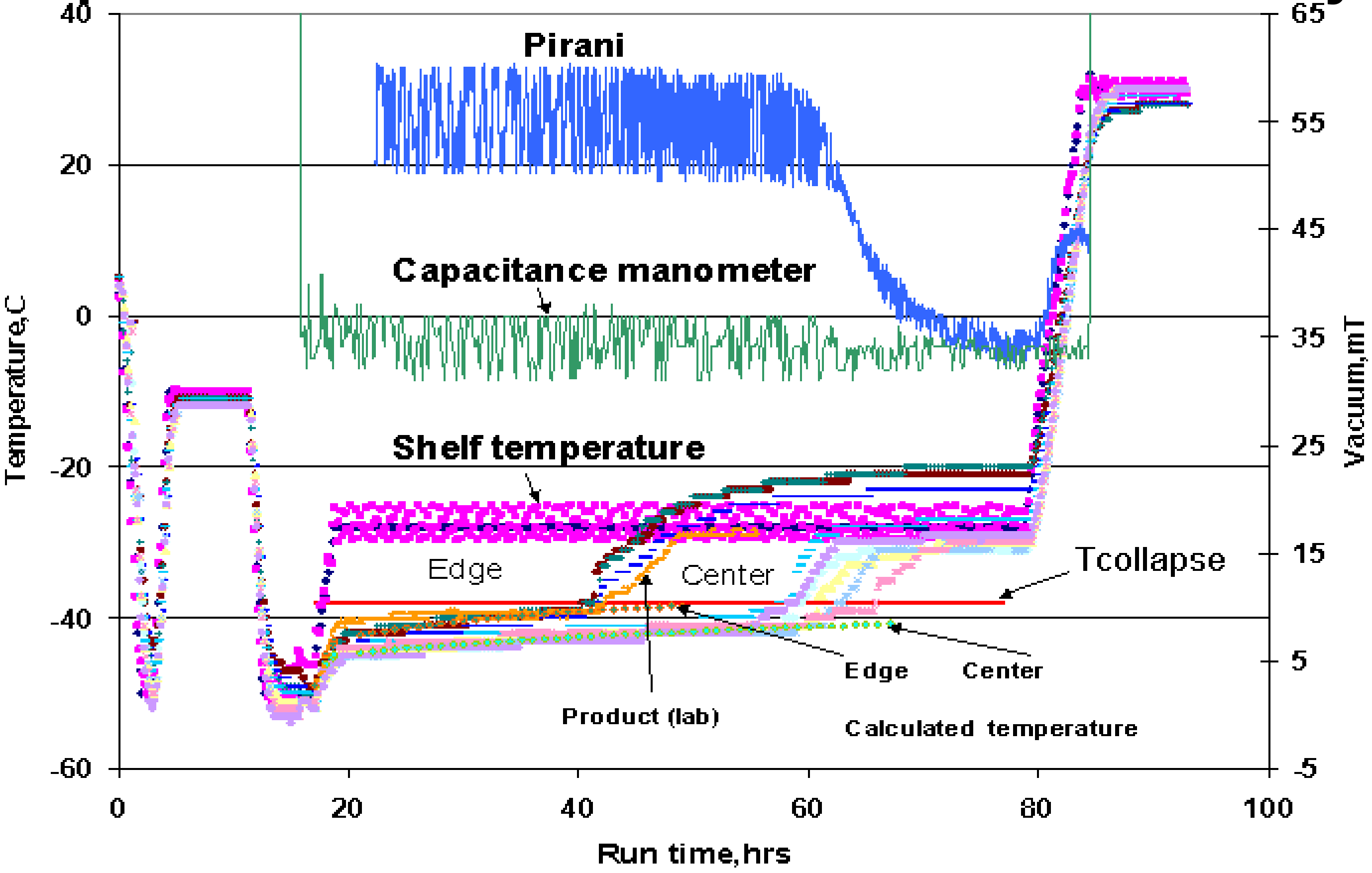
$R_{pilot}>R_{Lab}$

(Pch)set-(Pch)act=9-10mT

Scale up from laboratory to the pilot lyophilizer:

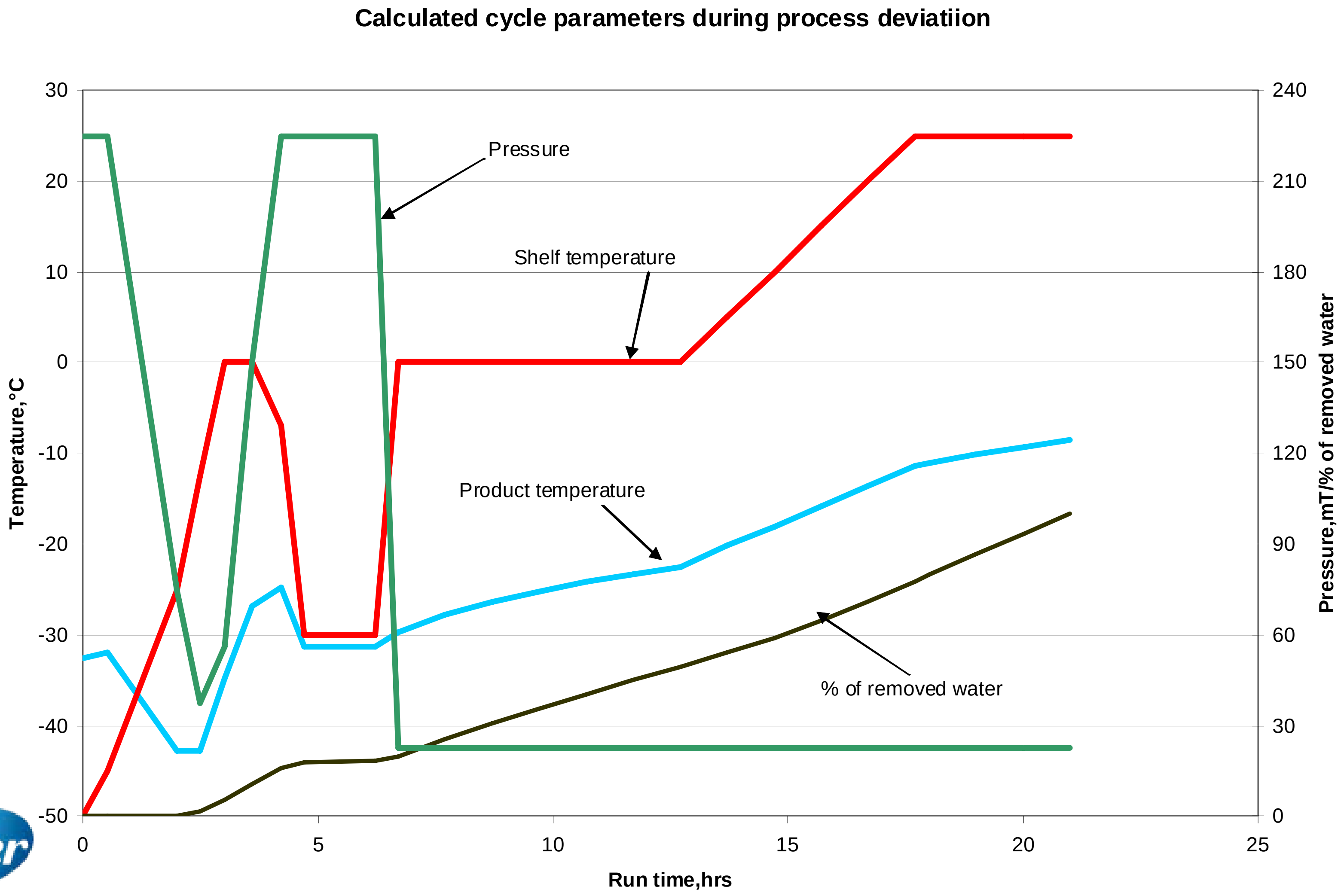
use a model to establish the link between two lyophilizers when Kv of this particular vial is known for both freeze-dryers

- Tshelf was Increased from -30 to -25°C
- Pchamber was decreased from 60 mT to 35 mT
- Kv(edge)=1.5 Kv(center)
- Cake resistance was assumed being increased by 50%



Material: 4.5% solids sucrose-based formulation containing NaCl

Support of commercial deviations using modeling of primary drying



Acknowledgements

Andover DPD

- Dan Dixon
- Brian Wilbur
- Anthony Gudinas
- Jason Rossi
- Mike Schmidt
- Susan Knowles
- Christian Ruitberg
- William Evans
- Nick Warne
- Ron Peeples

Grange Castle

- Tim McCoy
- Paula Lalor
- Michael Darwent
- Orla McGarvey
- Herwig Muehleder
- Owen Moore
- Jim Roycroft
- BOC Support Group

- Michael Pikal,UCONN

Pearl River

- Andrew Schafranek
- Garry Forrest
- Robby Mohammed
- Kris Pushlar
- Maurice Trinidad
- Tok Han
- Frank Williams,
(IMA Edwards)

Algete

- Angel Vitores
- Teresa Uriarte
- Elisabet Griera