An Industry Perspective on the Application of Modeling to Lyophilization Process Scale up and transfer

10 January 2017

PepTalk

Serguei Tchessalov,
Pfizer Inc

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

SCIENCE FOR LIFE-CHANGING IMPACT

Contributing authors

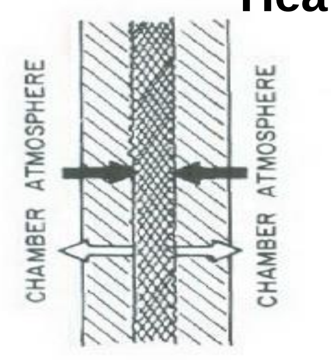
- David Latshaw, Janssen
- Suresh Nulu, Biogen
- Cherie Parkhurst-Lang, Biogen
- Geetha Govindan, Biogen
- Dawood Dassu, BPOG

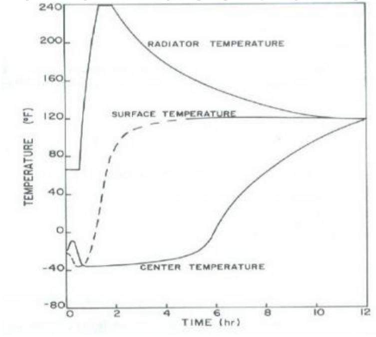
Outline

- Results of survey on the use of modeling in lyophilization process development
- Examples of primary and secondary drying models
- Primary drying model with scale up features
- Examples of applications of the scale up model
- **C**omputational **F**luid **D**ynamics modeling
- Next steps

Modeling of Drying of a slab (M. Karel, 1975)

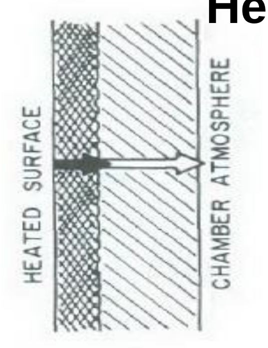
Heat and mass transfer through the dry layer





$$t = \frac{L^2 \rho (m_0 - m_f) \Delta H_s}{8 k_d (T_s - T_i)}$$

Heat transfer through frozen layer, mass transfer through dry layer



$$p_i = p_s + (k_i / b \Delta H_s)(x_d / x_i)(T_w - T_i)$$

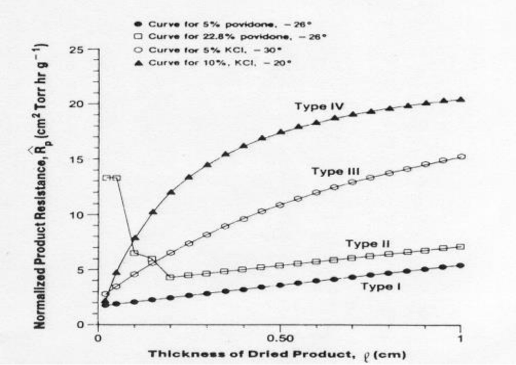
$$\int_0^L \frac{x_d}{f(x_d) - p_s} \, dx_d = \frac{b}{\rho (m_0 - m_f)} \int_0^{t_d} dt$$

Equations can be only solved by numerical methods using a *computer*

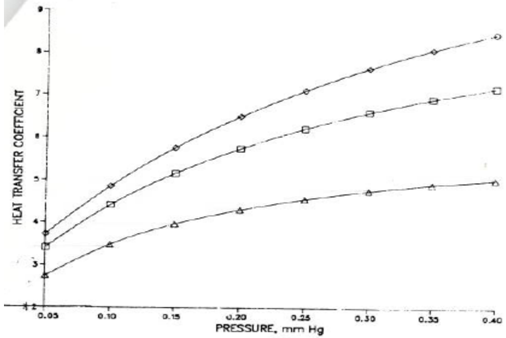
WORLDWIDE RESEARCH & DEVELOPMENT

Karel M. Heat and mass transfer in freeze-drying//Freeze-drying and advanced food technology, Ed. By Goldblith et al, London ,Academic

Vial Freeze-Drying (M. Pikal, 1985)



$$R_p = R_0 + \frac{A_1 l}{1 + A_2 l}$$



$$K_V = KC + \frac{KP * P}{1 + KD * P}$$

Steady state heat and mass transfer model

$$\left(\frac{R_p}{A_p} + R_S + nR_{tr}\right)\frac{dm}{dt} - P_0 + P_c = 0$$

$$R_S\frac{dm}{dt} - P_v + P_{tr} = 0 \qquad nR_{tr}\frac{dm}{dt} - P_{tr} + P_c = 0$$

$$0.1833\frac{dm}{dt}\left[\frac{1}{A_vK_v} + \frac{ATV}{K_{tr}} + \frac{(l_m - l)}{A_pK_I}\right] - T_S + T = 0$$

$$0.1833\frac{dm}{dt}\frac{1}{A_vK_v} - T_t + T_b = 0 \qquad 0.1833\frac{dm}{dt}\frac{1}{ATVK_{tr}} - T_S + T_t = 0$$

$$P_o = 2.6983 * 10^{10}\exp\left(\frac{-6144.96}{T}\right)$$

$$l = \frac{nl_m}{5} \qquad \Delta t_j = \frac{\Delta m}{\left({dm_j}/{dt}\right)} = \frac{\rho_I \Delta l A_p \varepsilon}{\left({dm_j}/{dt}\right)} \qquad t_j = \sum_{j=1}^{i}\Delta t_j$$

Pc=const, Ts=const

Product	Vial	Fill, ml	Tshelf, °C	Pc (Torr)	Time, hrs		Product temperature, °C	
					Exp.	Calcul.	Exp.	Calcul.
PVP (5%)	W5816	8	-5	0.1	25.8	26.9	-25.3	-24.6
Mannitol (5%)	W5816	8	-5	0.1	33.4	34.8	-20.2	-18.5
Mannitol (5%)	W5816	8	15	0.1	19.2	19.1	-14.2	-11.8
Mannitol (5%)	W5816	8	15	0.4	14.0	15.8	-11.9	-8.0

M.Pikal (1985) Use of laboratory data in freeze-drying process design: heat and mass transfer coefficients and the computer simulation of freeze-drying, J. of Parenteral Science and Technology, Vol.39, No.3/May-June, 115-139.

Vial Freeze-Drying (M. Pikal, 1985) - continued

Impact of Tproduct on drying time

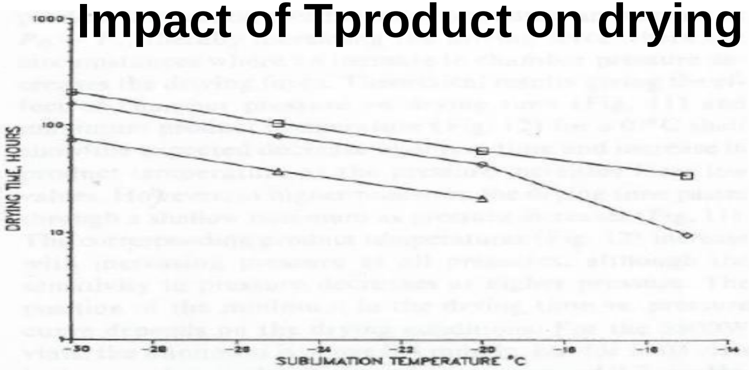


Figure 8—Effect of product temperature on drying time: chamber pressure 0.1 mmHg; 5800W vials; 8 ml fill volume: □, 5% mannitol; ◇, DOBUTREX; △, 5% *PVP*.

Impact of Tsh on Tproduct (max)

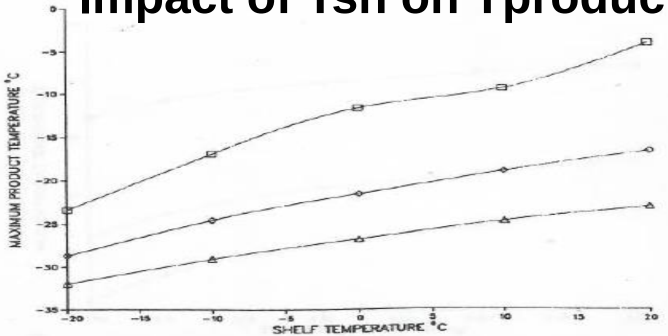


Figure 9—Effect of shelf temperature on maximum product temperature of 5% (w/w) mannitol: P_c = 0.10 mmHg; fill volume, 8 ml: □, 5800W; ◇, 5303; △, 5303 (maximum warp tray).

Impact of Tsh on drying time

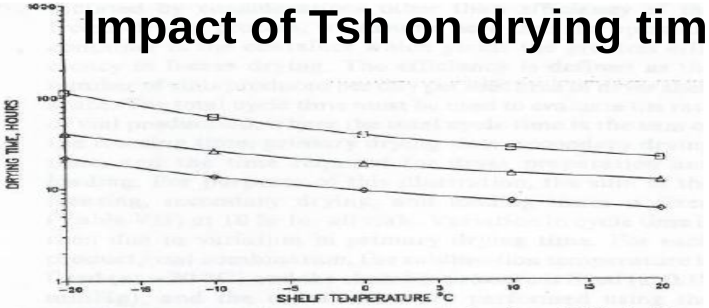


Figure 10—Effect of shelf temperature on drying time of 5% (w/w) mannitol: P_c = 0.10 mmHg; fill volume, 8 ml: □, 5800W; ◇, 5303; △, 5303 (maximum warp tray).

Impact of Pc on drying time

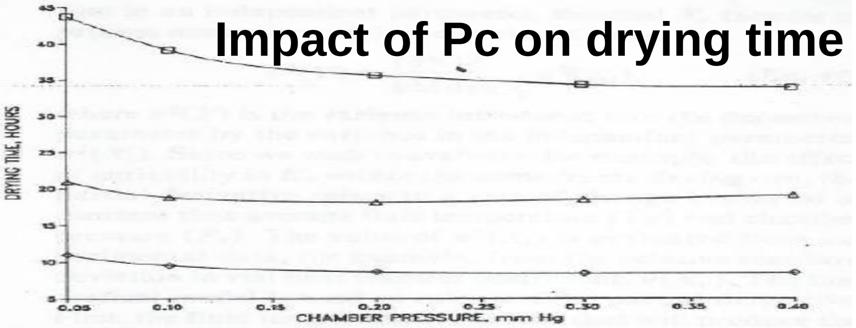
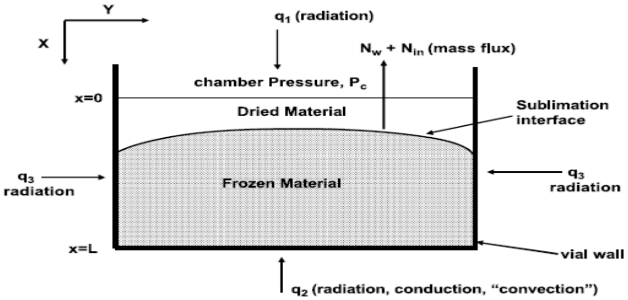
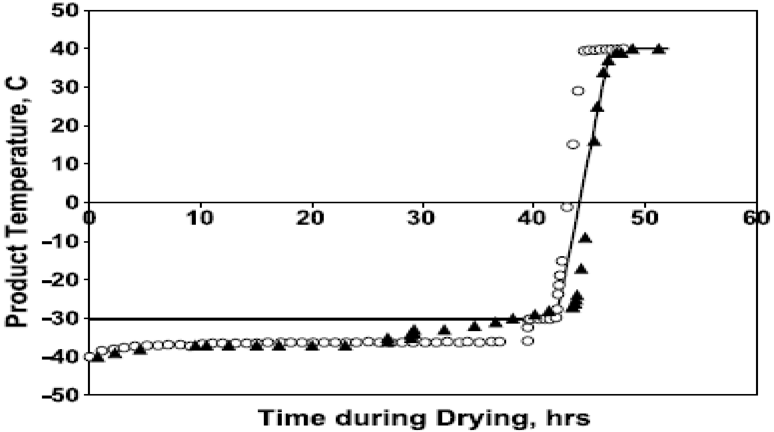
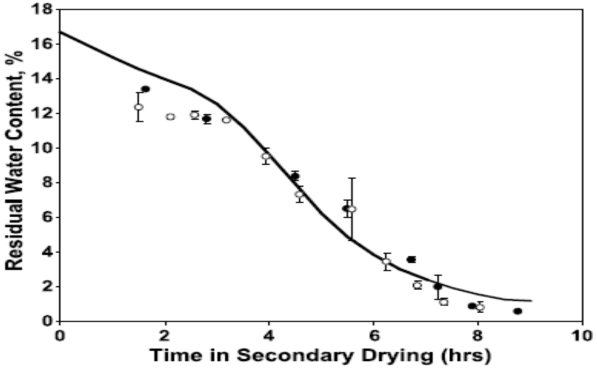


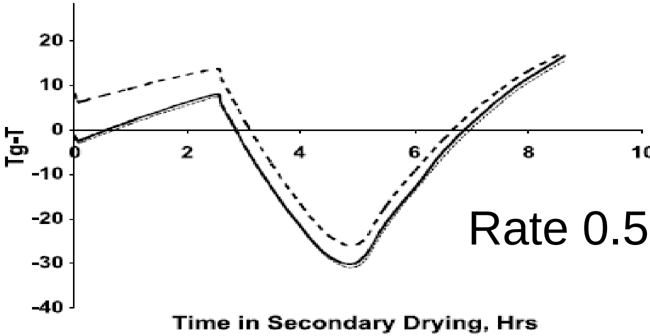
Figure 11—Effect of chamber pressure on drying time of 5% (w/w) mannitol; shelf temperature, 0 °C; fill volume, 8 ml: □, 5800W; ◇, 5303; △, 5303 (maximum warp tray).

Non-Steady State Modeling of Freeze-Drying (M. Pikal, 2005) / Passage









Rate 0.5°C/min

Pikal, M. J.; Cardon, S.; Bhugra, Chandan; Jameel, F.; Rambhatla, S.; Mascarenhas, W. J.; Akay, H. U. The nonsteady state modeling of freeze drying: in-process product temperature and moisture content mapping and pharmaceutical product quality applications. *Pharm. Dev. and Technol*. 2005, 10(1):17-32.

An Iterative Tool for Optimization of Freeze-Drying (Trelea et al., INRA, France)

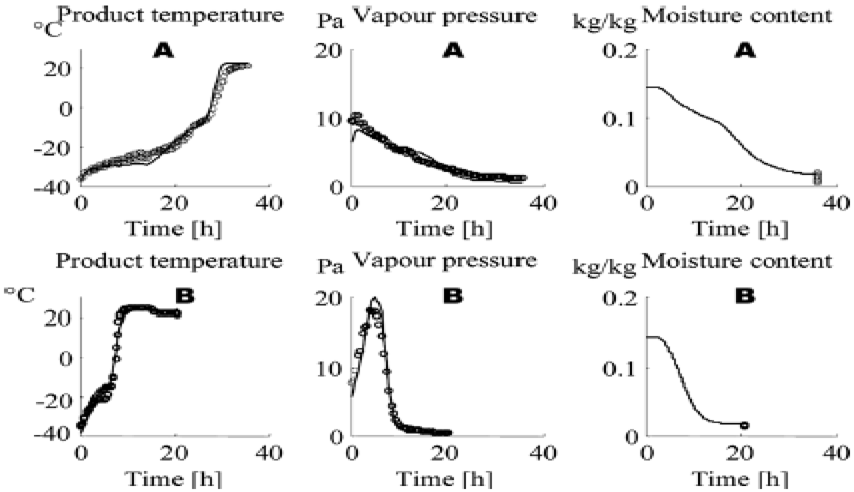
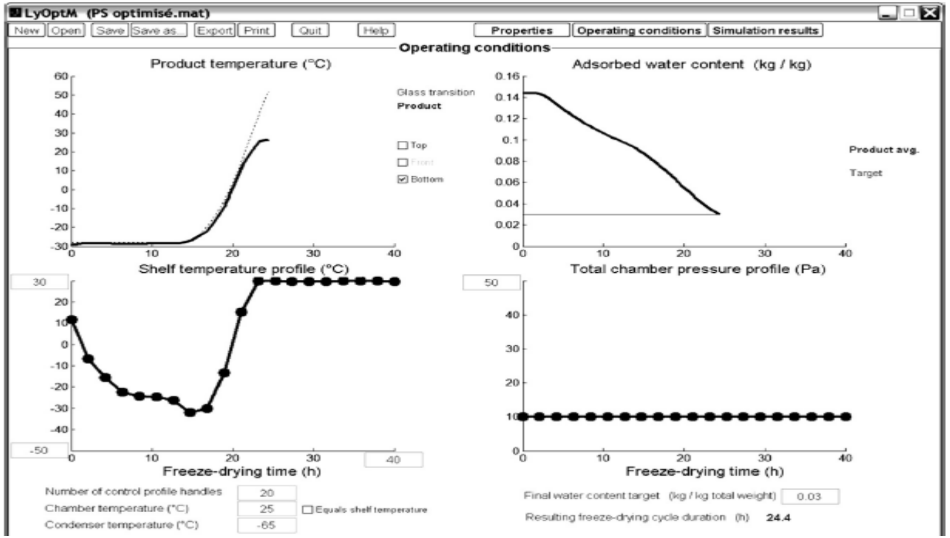


FIG. 5. Dynamic model validation. Formulation: PS. (A) Shelf temperature at −25°C and total chamber pressure at 10 Pa during primary drying. (B) Shelf temperature at +25°C and total chamber pressure at 34 Pa during primary drying. Measured values (o) and model predictions (–).



Number of control profile handles 20

Chamber temperature (°C) 25 ☐ Equals shelf temperature

Condenser temperature (°C) -65

Final water content target (kg / kg total weight) 0.03

Resulting freeze-drying cycle duration (h) **24.4**

I.C.Trelea, S. Passot, F. Fonseca, M. Martin. An interactive tool for the optimization of freeze-drying cycles based on quality criteria, *Drying Technology*, 2007, 25:741-751.

Power of Modeling: Summary to Date

- Models have been established for all three steps of freeze-drying:
  - **Freezing** (only few examples are shown in literature, there is no commercially available model)
  - **Primary drying** (Passage model, few variations of lyo calculator (Excel), one with elements of scale up included)
  - **Secondary drying** (Passage model, Excel based model is almost ready (Pikal & Sahni)
- Models could predict product temperature profile and link it to CQA's (S.Passot, Garmish, 2010)
- A commercially available model (Passage models) as well as an iterative tool for cycle optimization (Trelea et al., 2007) offered to users
- Few proprietary models, developed by companies (Pfizer, Roche, Merck)

BPOG Lyophilization Collaboration

- BPOG has been facilitating industry-led collaborations since 2006.
- The Lyophilisation collaboration started in 2014.
- 13 of the member companies below are participating in the Lyophilization collaboration.

BPOG Fill Finish Forum, Member Companies

- Abbvie
- Alexion
- Amgen
- AstraZeneca
- Bayer Healthcare
- Biogen
- BMS
- Cook Parmica
- EMD Serono
- MSD Merck Inc
- GSK Biologicals
- Ipsen
- Janssen
- Lonza
- Pfizer
- Regeneron
- Roche
- Shire

Purdue's LyoHub
Working together on best practice development
Dr Pikal (UConn)
Contributions to discussions

Value of the collaboration:

- Ensure 'minimum standards' are being followed – 'peer reviewed'
- Consolidate best practices with transparency - not just what's published .
- Easier for agencies to manage regulation - 'single best practice approach'.

Use of Modelling in the Industry (in the 13 collaborating companies)

- Lyophilization process consists of three steps: freezing, primary drying and secondary drying.
- Five companies routinely use primary drying model for process design, optimization and scale up.
- No freezing or secondary drying models are used to date

Models being used:

- Mainly, based on the steady state model of primary drying based on heat and mass transfer equations (M.Pikal, 1982, 1985)
- Single vial, 2D steady state heat-mass transfer model. Reference Tsinontides, Rajniak (1999-2001)

No. of application case-studies

Process development	5
Scale up / Tech transfer	5
Deviation analysis and decision making	2
Process optimization	5
Providing suitable information to Regulatory bodies	1

Goals of the collaboration

Goals	Current Status	Next steps
A harmonized best practice approach to modelling at the commercial scale.	• A harmonized approach at a principle level is agreed for a Primary Stage Drying Model (based on Pikal's Heat Mass Transfer for the Primary Drying Stage) • Companies may continue with different 'branch' models	• Agree how to estimate model parameters • Share new examples • Publish white papers • Develop guidelines • Engage regulatory authorities • Continue to share implementation experiences

Excel Based Primary Drying Model

$$\frac{\partial m}{\partial t} = \frac{S_{in} * (P_{Subl} - P_{Chamber})_i}{R(h)_i} = \frac{S_{out} * K_V(P) * (T_{Shelf} - T_{product})}{\Delta H_S}$$

1. Assumption – All heat received by product is used only for sublimation of water. Sublimation front moves from the top of cake parallel to the vial bottom.

2. Assumption – The contribution of radiation component to the vial heat transfer coefficient is constant within entire operation temperature range

T_{shelf} and $P_{chamber}$ could vary as function of time, as well as R(h)

$$P_1(t_i) = (P_{chamber})_i + R(h)_i 3600 (\frac{d_{out}}{d_{in}})^2 K_V(P)_i (T_{shelf} - T_{product\_bottom})_i \frac{1}{\Delta H_S}$$

$$P_2(t_i) = \exp(24.01849 - \frac{6144.96}{T_{subl\_surf} + 273})$$

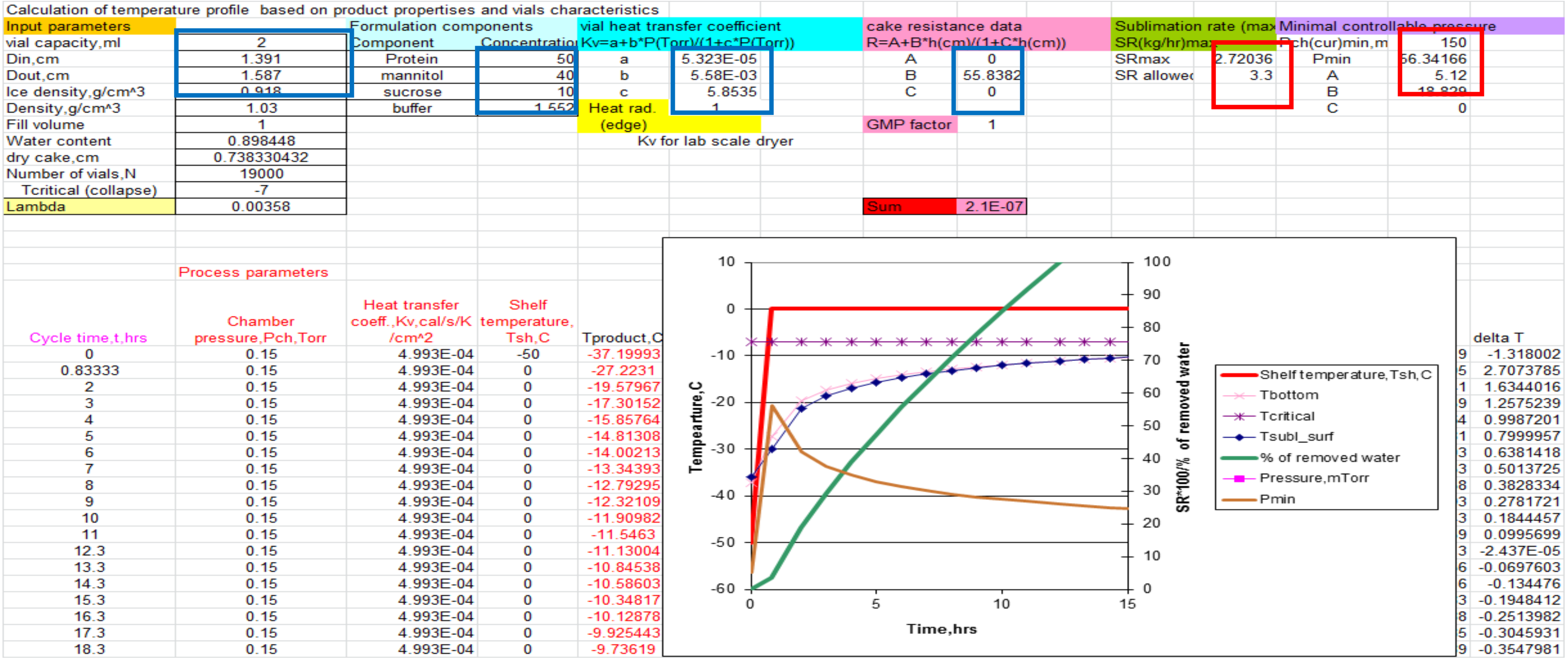
$$T_{subl\_surf} = T_{product\_bottom} - K_V(P_{ch})(T_{shelf} - T_{product\_bottom}) \frac{h_{frozen} - h_i}{\lambda_{frozen}}$$

$$Sum = \sum_{i=1}^{i} (P_1 - P_2)_i^2 \to 0$$

By varying $T_{product}$

$$PRM(\%) = \frac{m(t_i)}{\varepsilon \rho V} 100 = 100\%$$

Excel Based Primary Drying Calculation Template (lyo calculator)



Calculation of temperature profile based on product propertises and vials characteristics

Input parameters	
vial capacity,ml	2
Din,cm	1.391
Dout,cm	1.587
Ice density,g/cm^3	0.918
Density,g/cm^3	1.03
Fill volume	1
Water content	0.898448
dry cake,cm	0.738330432
Number of vials,N	19000
Tcritical (collapse)	-7
Lambda	0.00358

Formulation components

Component	Concentratio
Protein	50
mannitol	40
sucrose	10
buffer	1.552

vial heat transfer coefficient
Kv=a+b*P(Torr)/(1+c*P(Torr))

a	5.323E-05
b	5.58E-03
c	5.8535
Heat rad. (edge)	1

Kv for lab scale dryer

cake resistance data
R=A+B*h(cm)/(1+C*h(cm))

A	0
B	55.8382
C	0
GMP factor	1
Sum	2.1E-07

Sublimation rate (max
SR(kg/hr)max

SRmax	2.72036
SR allowed	3.3

Minimal controllable pressure

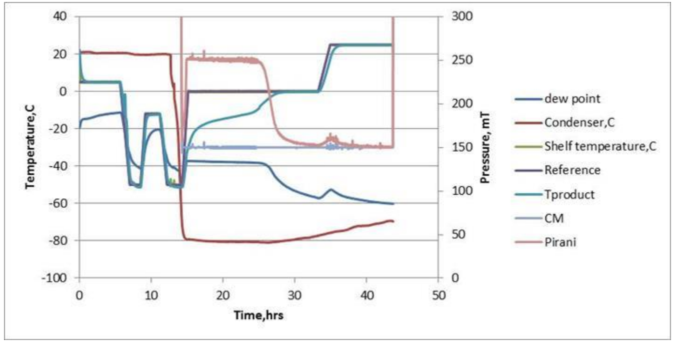
Pch(cur)min,m	150
Pmin	56.34166
A	5.12
B	18.829
C	0

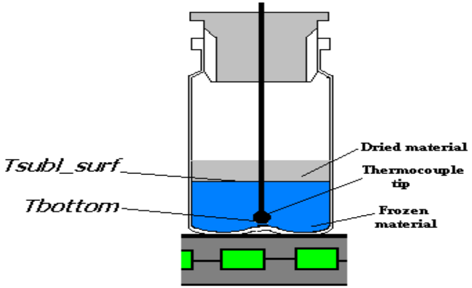
Process parameters

Cycle time,t,hrs	Chamber pressure,Pch,Torr	Heat transfer coeff.,Kv,cal/s/K /cm^2	Shelf temperature, Tsh,C	Tproduct,C		delta T
0	0.15	4.993E-04	-50	-37.19993	9	-1.318002
0.83333	0.15	4.993E-04	0	-27.2231	5	2.7073785
2	0.15	4.993E-04	0	-19.57967	1	1.6344016
3	0.15	4.993E-04	0	-17.30152	9	1.2575239
4	0.15	4.993E-04	0	-15.85764	4	0.9987201
5	0.15	4.993E-04	0	-14.81308	1	0.7999957
6	0.15	4.993E-04	0	-14.00213	3	0.6381418
7	0.15	4.993E-04	0	-13.34393	3	0.5013725
8	0.15	4.993E-04	0	-12.79295	8	0.3828334
9	0.15	4.993E-04	0	-12.32109	3	0.2781721
10	0.15	4.993E-04	0	-11.90982	3	0.1844457
11	0.15	4.993E-04	0	-11.5463	9	0.0995699
12.3	0.15	4.993E-04	0	-11.13004	3	-2.437E-05
13.3	0.15	4.993E-04	0	-10.84538	6	-0.0697603
14.3	0.15	4.993E-04	0	-10.58603	6	-0.134476
15.3	0.15	4.993E-04	0	-10.34817	3	-0.1948412
16.3	0.15	4.993E-04	0	-10.12878	8	-0.2513982
17.3	0.15	4.993E-04	0	-9.925443	5	-0.3045931
18.3	0.15	4.993E-04	0	-9.73619	9	-0.3547981

Estimation of Cake Resistance from the Cycle Data:

Kv and resistance from one product vial





$$\left(\frac{dq}{dt}\right)_i = \overset{?}{K}_V(P)S_{out}(T_{Shelf} - T_{pr\_bottom})_i$$ Eq.1

$$\left(\frac{dm}{dt}\right)_i = \left(\frac{dq}{dt}\right)_i \frac{1}{\Delta H_s}$$ Eq.2

If Kv=const when P_{ch}=const, then mass of sublimed ice at t_i

Combining Eq.1 and Eq.2

$$\Rightarrow (m_{ice})_{vial} = \int \frac{d(m_{ice})_{vial}}{dt} = \int S_{out}K_v \frac{(T_{shelf} - T_{pr\_bottom})}{\Delta H_S}$$

$$\Rightarrow K_v = \frac{2\Delta H_S (m_{ice})_{vial}}{S_{out}\sum_{i=1}^{n}(\Delta T_i + \Delta T_{i-1})(t_i - t_{i-1})}$$

Where mass of ice in the vial is known

Calculations of cake resistance

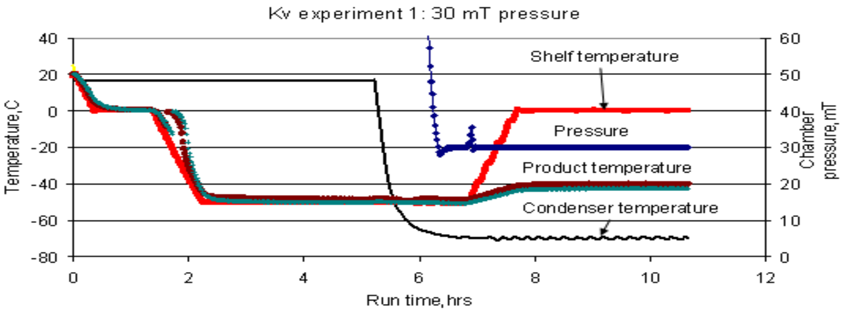
$$R_i = S_{in}\frac{(P_{subl\_surf} - P_{chamber})}{\left(\frac{d(m_{ice})_{vial}}{dt}\right)_i}$$

$$(P_{subl\_surf})_i = \exp\left(24.01849 - \frac{6144}{T_{subl\_surf} + 273}\right)$$

$$T_{subl\_surf} = T_{pr\_bottom} - \frac{dq}{dt}\frac{L_{ice}}{\lambda_{frozen}}$$

$$L_{ice} = \frac{\left(V_{fill}\rho_{sol} - \frac{m(t)}{\varepsilon}\right)}{\rho_{ice}S_{in}} = h_{max} - h_i$$

Generation of Model Inputs:
Vial Heat Transfer Coefficient (Kv) Measurements

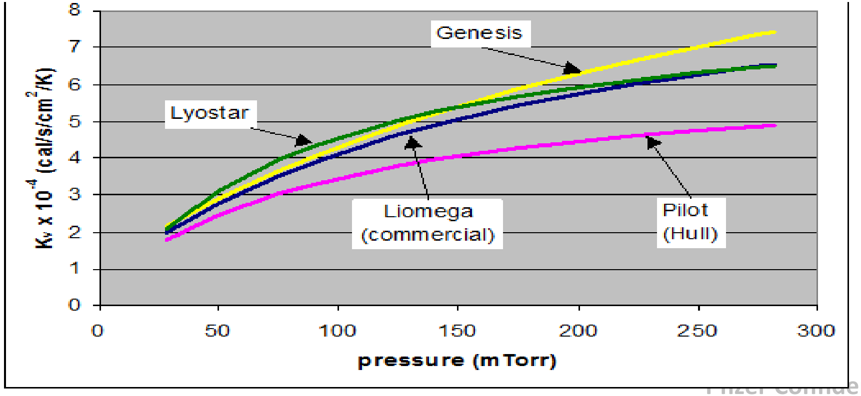


$$K_V = \frac{\Delta m \Delta H_S}{(S_V)_{Out} \int (T_{Inlet} - T_{Ice\_est}) dt}$$

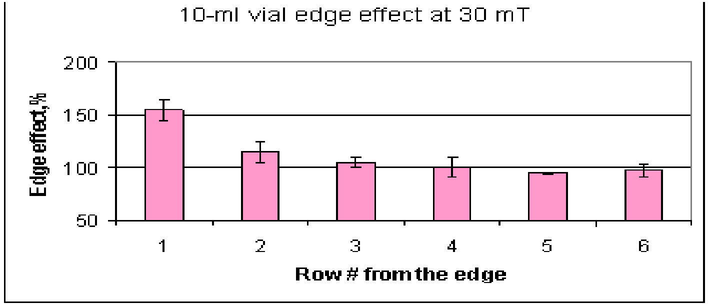
Weight loss ≤30% of total mass

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

Kv of 10 ml Schott vial



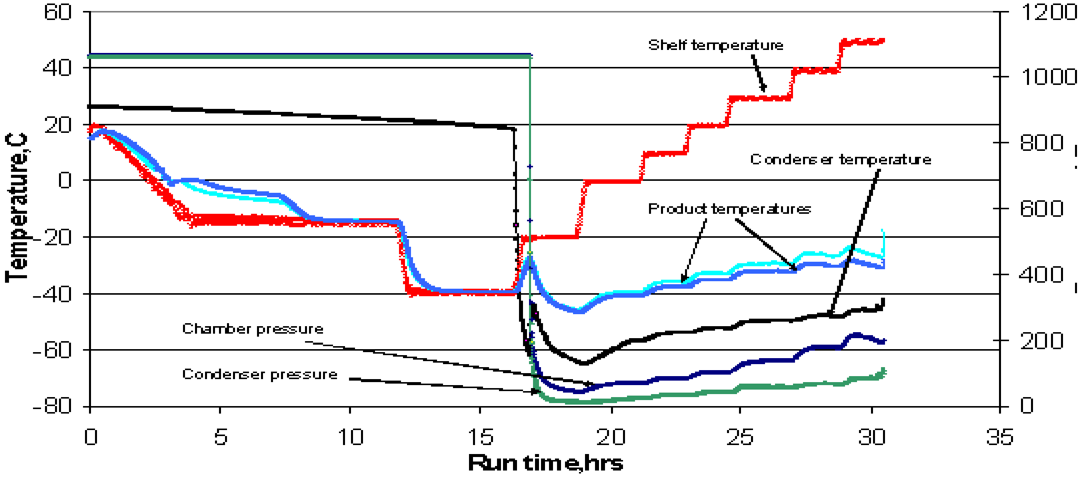
Edge effect measured for a 6 m^2 GMP dryer



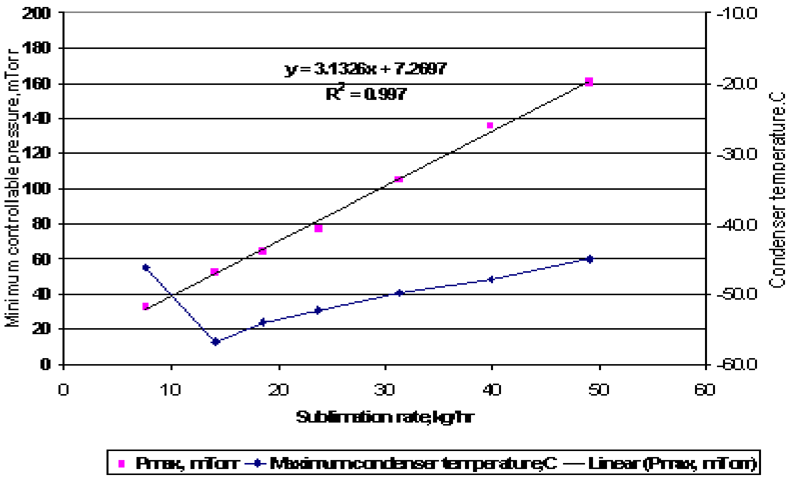
Sublimation Test on Lyomax 42

60 trays x 16.6 L~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



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

Black bags were used in experiment

Pmin=f(dm/dt) =A+B*SR+C*SR^2

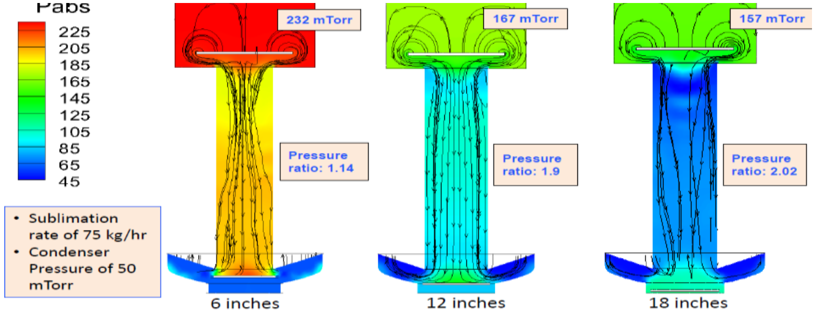
A,B,C are inputs in lyo template

When Tcond>-40C, SRmax-input in template

WORLDWIDE RESEARCH & DEVELOPMENT

Alternative to sublimation tests: CFD modeling of mass flux

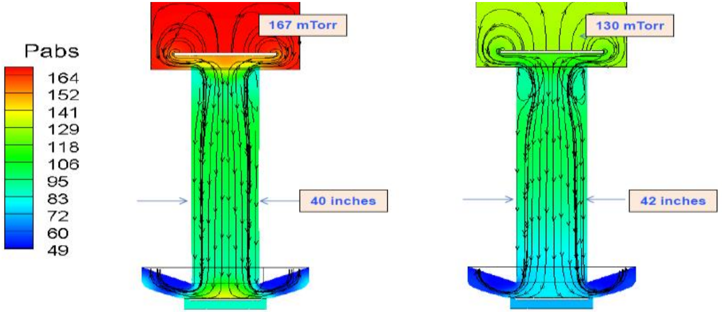
Effect of valve gap



- Sublimation rate of 75 kg/hr
- Condenser Pressure of 50 mTorr

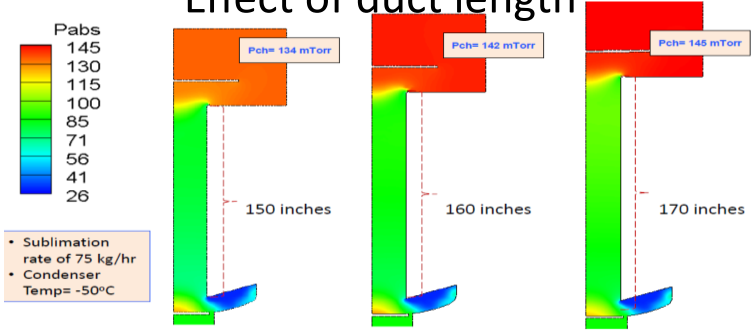
-> Chamber pressure is highest at the lowest valve gap.
-> The higher (than expected) pressure in the 18 inch case might be because of sonic conditions in the duct

Effect of duct diameter



-> At the same Sublimation rate of 75 kg/hr, the chamber pressure dropped considerably with the increase in duct diameter by two inches.

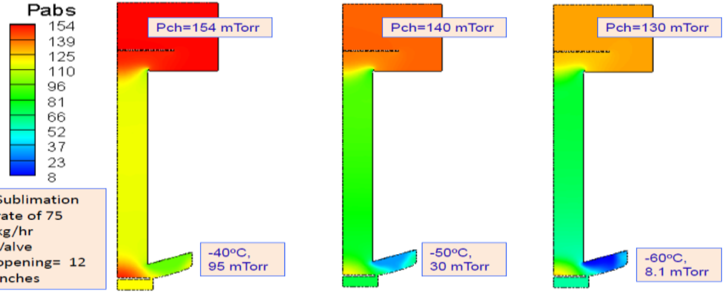
Effect of duct length



- Sublimation rate of 75 kg/hr
- Condenser Temp= -50°C

-> As can be predicted from theory, the longest duct has the highest chamber pressure.
-> However the variation in chamber pressure due to 10 inches of duct length is only a few milliTorrs

Effect of condenser temperature



- Sublimation rate of 75 kg/hr
- Valve opening= 12 inches

→As expected lowest chamber pressure corresponds to lowest condenser pressure.

Prof. Alina Alexeenko, Nikhil Varma-Purdue University

What is Needed to Generate Inputs into Primary Drying Model?

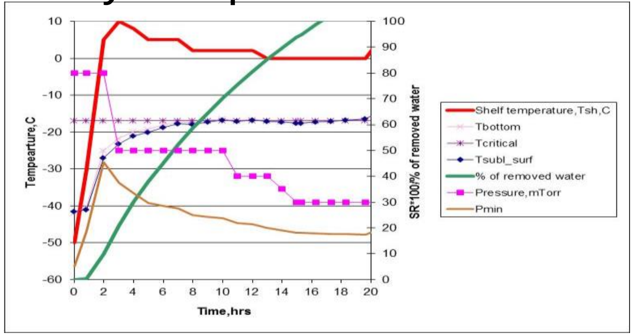
- Cake resistance
  - Cycle traces
  - TDLAS
  - MTM software
- Vial heat transfer coefficients
  - Vials of interest, water, temperature sensors, balances
  - 1 week to generate data at scale
  - TDLAS (potentially one cycle)
- Minimum controllable pressure and maximum sublimation rate
  - Trays, plastic bags, high quality water, temperature sensors to record shelf surface temperature and ice temperature
  - 1 week of experiments (3 days if freeze-dryer is not well

Advantages and Benefits of Modeling

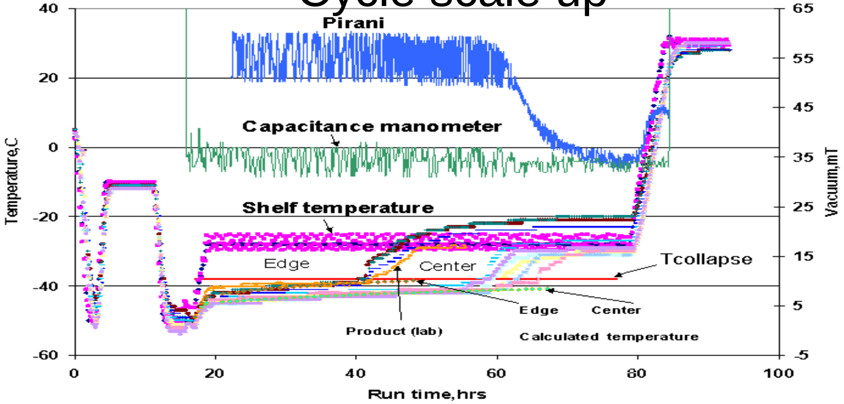
- Enables fast calculations of primary drying time and maximum product temperature – time and cost savings!
- Supports evaluation of different pressure and shelf temperature combinations to optimize product temperature profile (targeting the shortest drying time)
- Helps construction of a design space for a particular product with regard to the process parameters
- Assists in the identification of potential impact on the product at any combinations of shelf temperature/pressure/time (useful for the assessment of process deviations)
- Identify the effect of process conditions on any changes in heat and mass transfer (for example, as in the case of microcollapse)
- Allows implementation of equipment limitations into cycle design

Applications of Modeling to Freeze-Drying

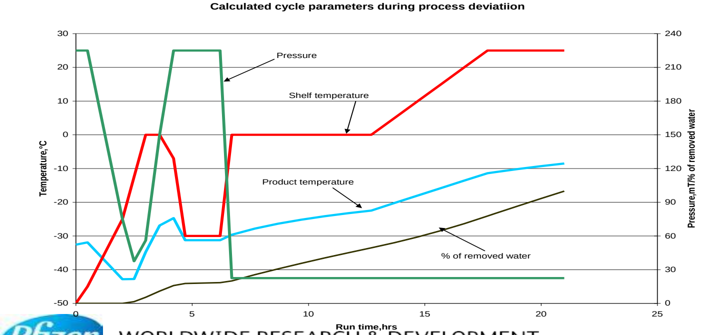
Cycle optimization



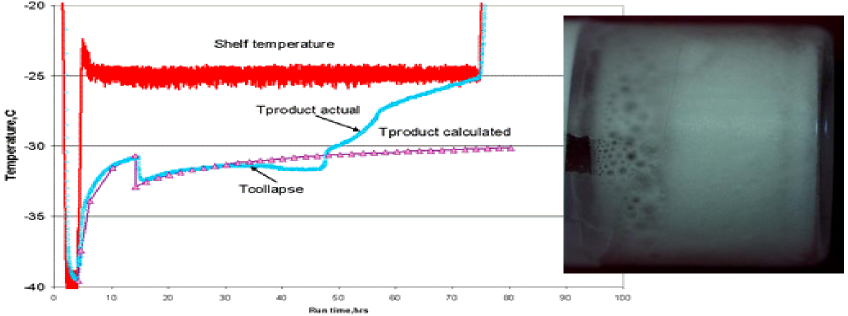
Cycle scale up



Assessment of deviations

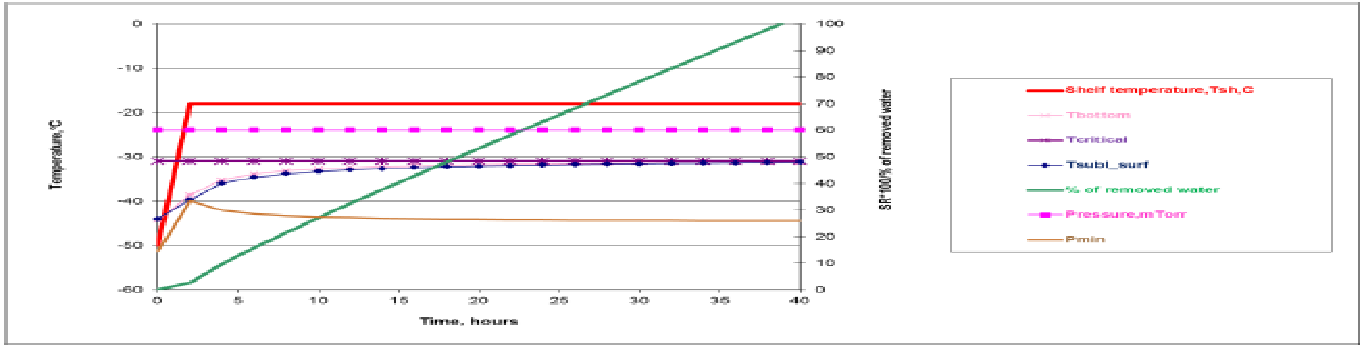


Assessment of product impact



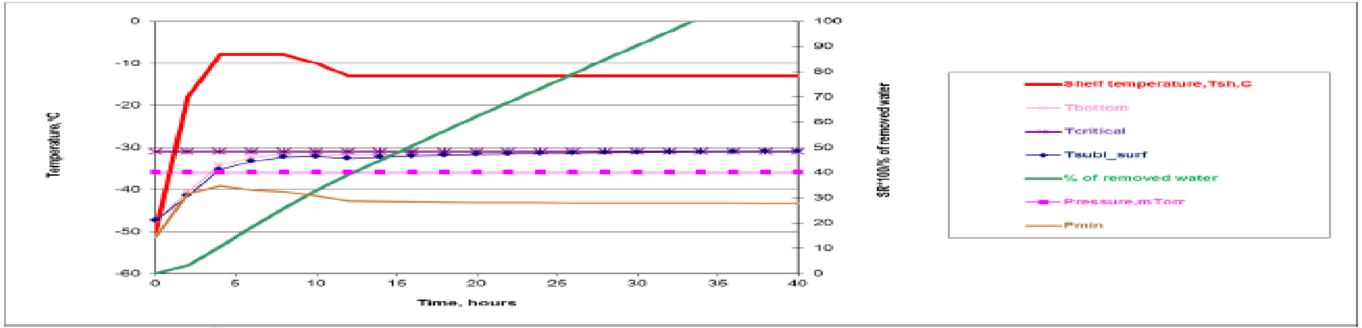
Process Optimization using the Primary drying model (Janssen)

Results – Cycle optimization alternative



<u>3 day cycle</u>
Constant chamber pressure and shelf temperature

~39 hours



<u>Variable cycle</u>
Constant chamber pressure and variable shelf temperature

~34 hours

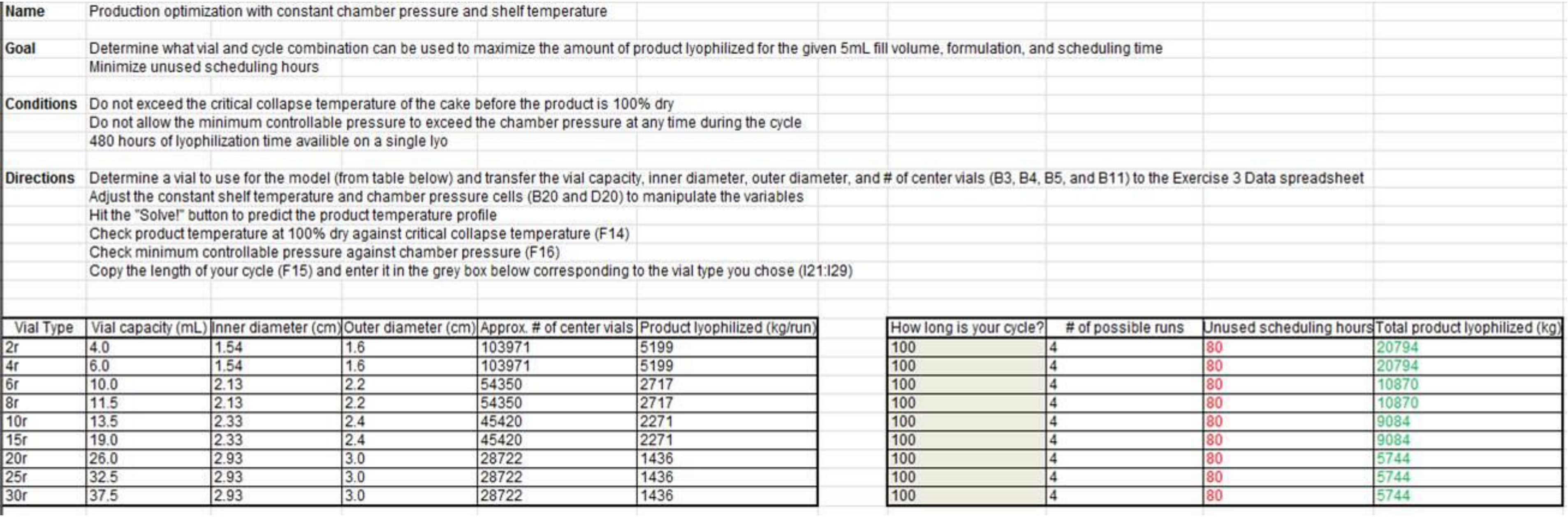
Modification of Template at Janssen (D. Latshaw)

Calculation of temperature profile based on product properties and vials characteristics

	A	B	C	D	E	F	G	H	I	J	K
2	*Input parameters*	*Value*	*Formulation components*	*Concentration (mg/mL)*	*Vial heat transfer coefficient Kv*	*Kv=a+b*P(Torr)/(1+c*P(Torr))*	*Cake resistance Rp*	*R=A+B*l(cm)/(1+C*l(cm))*	*Sublimation rate (max)*	*kg/hr*	*Minimum controll*
3	**Vial capacity,mL**	20	**Protein**	50	**a**	0	**A**	0	SRmax	3.963606924	Pch(cur)min,mT
4	**Inner vial Diam.,cm**	2.951	**Mannitol**	40	**b**	0.00978	**B**	75.18004102	**SR allowed**	3.3	Pmin
5	**Outer vial Diam.,cm**	2.975	**Sucrose**	10	**c**	25.68	**C**	5.507574822			**A**
6	**Ice density,g/cm^3**	0.918	**Buffer**	1.552	**Heat scaling factor**	1	**Resistance scaling factor**	1			**B**
7	**Density,g/cm^3**	1.03									**C**
8	**Fill volume, mL**	5	Colored concentrations should be adjusted		Colored coefficients should be adjusted		Colored coefficients should be adjusted		SR allowed should be adjusted based on equipment		
9	Water content	0.898448			Heat scaling factors should be 1 for center vials and increased for		Resistance scaling factors should be 1 base cycle and		characterization		Colored coefficients s
10	Dry cake height,cm	0.820231822			edge or corner vial		adjusted for optimization or transfers				equipment characteriz
11	**Number of vials,N**	27860									
12	**Tcritical (collapse)**	-31									
13	Lambda	0.00358			**RESULTS**						
14					**Max product temperature**	-33.7					
15	Colored values should be adjusted				**Total primary drying time (hrs)**	50.7					
16					**Minimum controllable pressure**	28.4	Note: This needs to be combined with ALL vial type contributions				
17	Sum of squared error	5.87766E-09									
18											
19		Constant chamber pressure (Torr)		Constant shelf temp (°C)							
20		0.05		-23							
21											

	A	B	C	D
22	*Cycle time,t,hrs*	*Chamber pressure (Torr)*	*Heat transfer coeff. (cal/s/K/cm^2)*	*Shelf temperature (°C)*
23	0	0.05	2.141E-04	-50
24	2	0.05	2.141E-04	-23
25	4	0.05	2.141E-04	-23
26	6	0.05	2.141E-04	-23
27	8	0.05	2.141E-04	-23
28	10	0.05	2.141E-04	-23
29	12	0.05	2.141E-04	-23
30	14	0.05	2.141E-04	-23
31	16	0.05	2.141E-04	-23
32	18	0.05	2.141E-04	-23
33	20	0.05	2.141E-04	-23
34	22	0.05	2.141E-04	-23
35	24	0.05	2.141E-04	-23
36	26	0.05	2.141E-04	-23
37	28	0.05	2.141E-04	-23
38	30	0.05	2.141E-04	-23
39	32	0.05	2.141E-04	-23
40	34	0.05	2.141E-04	-23

Use of Model to Optimize Manufacturing Process



Name	Production optimization with constant chamber pressure and shelf temperature
Goal	Determine what vial and cycle combination can be used to maximize the amount of product lyophilized for the given 5mL fill volume, formulation, and scheduling time Minimize unused scheduling hours
Conditions	Do not exceed the critical collapse temperature of the cake before the product is 100% dry Do not allow the minimum controllable pressure to exceed the chamber pressure at any time during the cycle 480 hours of lyophilization time availible on a single lyo
Directions	Determine a vial to use for the model (from table below) and transfer the vial capacity, inner diameter, outer diameter, and # of center vials (B3, B4, B5, and B11) to the Exercise 3 Data spreadsheet Adjust the constant shelf temperature and chamber pressure cells (B20 and D20) to manipulate the variables Hit the "Solve!" button to predict the product temperature profile Check product temperature at 100% dry against critical collapse temperature (F14) Check minimum controllable pressure against chamber pressure (F16) Copy the length of your cycle (F15) and enter it in the grey box below corresponding to the vial type you chose (I21:I29)

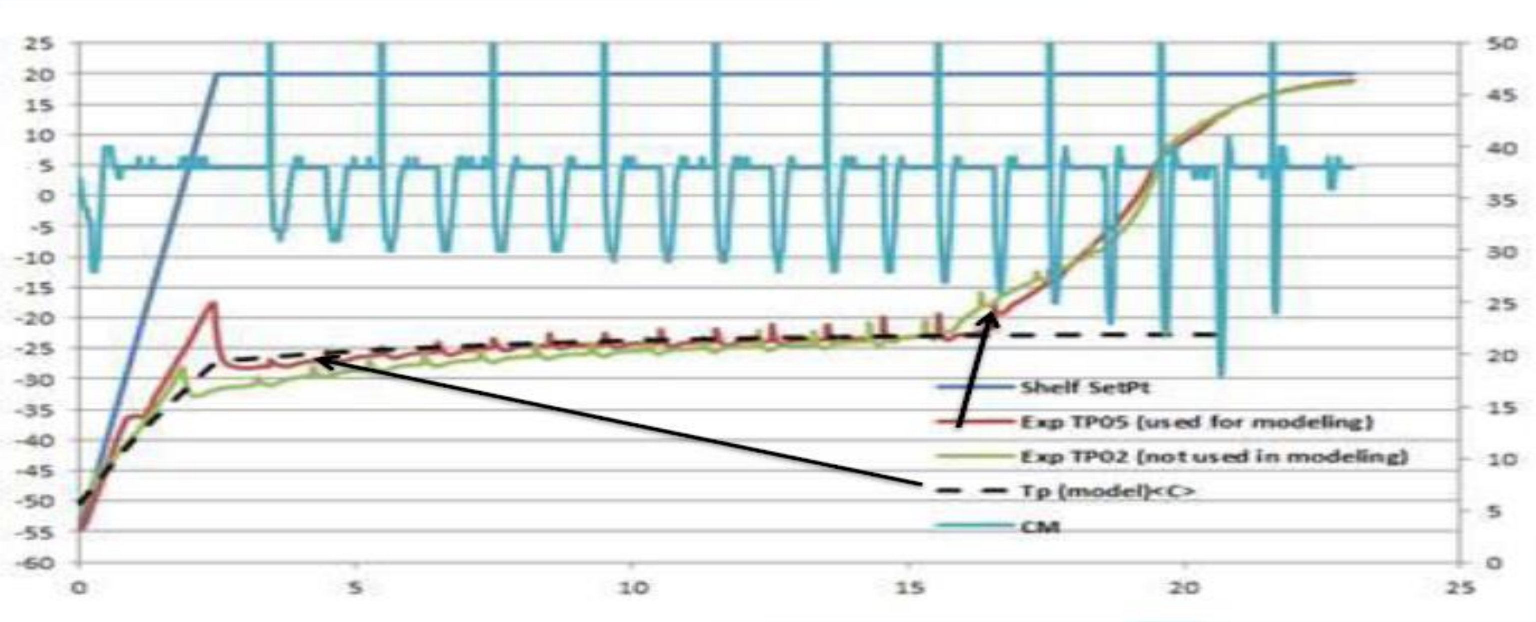
Vial Type	Vial capacity (mL)	Inner diameter (cm)	Outer diameter (cm)	Approx. # of center vials	Product lyophilized (kg/run)
2r	4.0	1.54	1.6	103971	5199
4r	6.0	1.54	1.6	103971	5199
6r	10.0	2.13	2.2	54350	2717
8r	11.5	2.13	2.2	54350	2717
10r	13.5	2.33	2.4	45420	2271
15r	19.0	2.33	2.4	45420	2271
20r	26.0	2.93	3.0	28722	1436
25r	32.5	2.93	3.0	28722	1436
30r	37.5	2.93	3.0	28722	1436

How long is your cycle?	# of possible runs	Unused scheduling hours	Total product lyophilized (kg)
100	4	80	20794
100	4	80	20794
100	4	80	10870
100	4	80	10870
100	4	80	9084
100	4	80	9084
100	4	80	5744
100	4	80	5744
100	4	80	5744

Vary vial size and fill volume to optimize commercial outcome

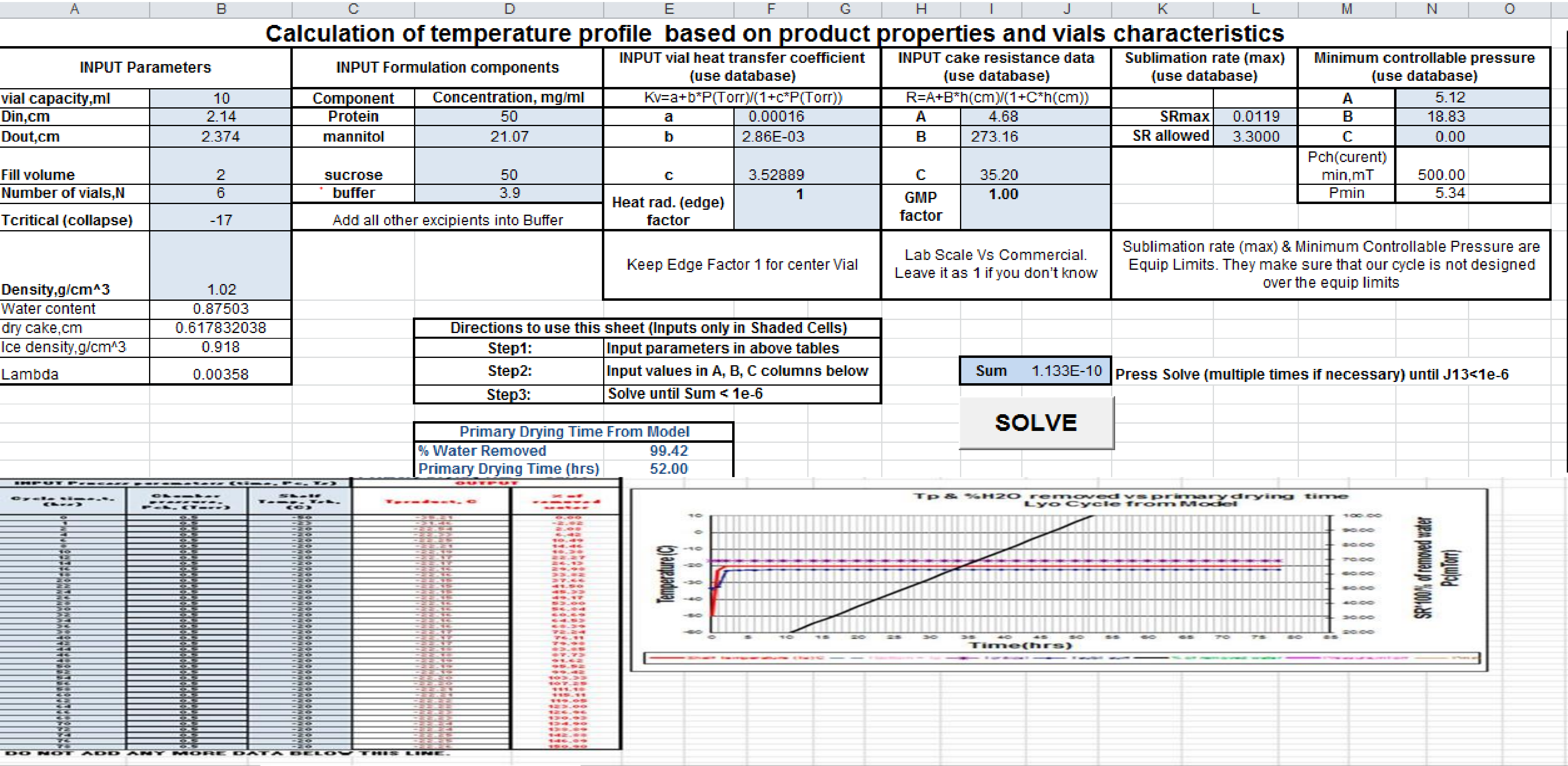
Estimation of Product Temperature Profile using the Primary Drying Model (Biogen)

Compare Experimental Data to LYO-Calculator Generated Data (exp #1)



Cherie Parkhurst-Lang, Suresh Nulu, Geetha Govindan

Template Modification at Biogen (S. Nulu)



Calculation of temperature profile based on product properties and vials characteristics

INPUT Parameters	
vial capacity,ml	10
Din,cm	2.14
Dout,cm	2.374
Fill volume	2
Number of vials,N	6
Tcritical (collapse)	-17
Density,g/cm^3	1.02
Water content	0.87503
dry cake,cm	0.617832038
Ice density,g/cm^3	0.918
Lambda	0.00358

INPUT Formulation components	
Component	Concentration, mg/ml
Protein	50
mannitol	21.07
sucrose	50
buffer	3.9

Add all other excipients into Buffer

INPUT vial heat transfer coefficient (use database)	
$K_v = a + b \cdot P(Torr)/(1 + c \cdot P(Torr))$	
a	0.00016
b	2.86E-03
c	3.52889
Heat rad. (edge) factor	1

Keep Edge Factor 1 for center Vial

INPUT cake resistance data (use database)	
$R = A + B \cdot h(cm)/(1 + C \cdot h(cm))$	
A	4.68
B	273.16
C	35.20
GMP factor	1.00

Lab Scale Vs Commercial. Leave it as 1 if you don't know

Sublimation rate (max) (use database)	
SRmax	0.0119
SR allowed	3.3000

Minimum controllable pressure (use database)	
A	5.12
B	18.83
C	0.00
Pch(curent) min,mT	500.00
Pmin	5.34

Sublimation rate (max) & Minimum Controllable Pressure are Equip Limits. They make sure that our cycle is not designed over the equip limits

Directions to use this sheet (Inputs only in Shaded Cells)	
Step1:	Input parameters in above tables
Step2:	Input values in A, B, C columns below
Step3:	Solve until Sum < 1e-6

Sum	1.133E-10

Press Solve (multiple times if necessary) until J13<1e-6

SOLVE

Primary Drying Time From Model	
% Water Removed	99.42
Primary Drying Time (hrs)	52.00

Model Limitations and Challenges in Implementation

- Limited accuracy (+/-1°C, 20% error in primary drying time)
- Significant error in prediction of time for the products with high resistance (up to 40 Torr*hr*cm^2/g at 1 cm)
- Requires generation of equipment specific inputs
  - Vial heat transfer coefficient
  - Edge effect
  - Minimum controllable pressure
  - Maximum sublimation rate
- Requires generation of product specific inputs
  - Cake resistance for a formulation
  - Cake resistance as function of process conditions (microcollapse, degree of ice nucleation

Industry Perspective on the Use of Modeling in Freeze-Drying

- Modeling could significantly reduce efforts in cycle optimization, transfer and scale up.
- Companies are currently investing in the characterization of dryers and container-closures (Kv, Pmin, SRmax).
- Companies are harmonizing modelling approach, improving primary drying template, and sharing experiences.
- Regulatory agencies will be continuously updated on this initiative.
- Through consortiums (BPOG and LyoHUB), companies will continue the advancement of application of modeling