Efficient definitive screening designs to optimize the freeze-drying process

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Lyophilized products

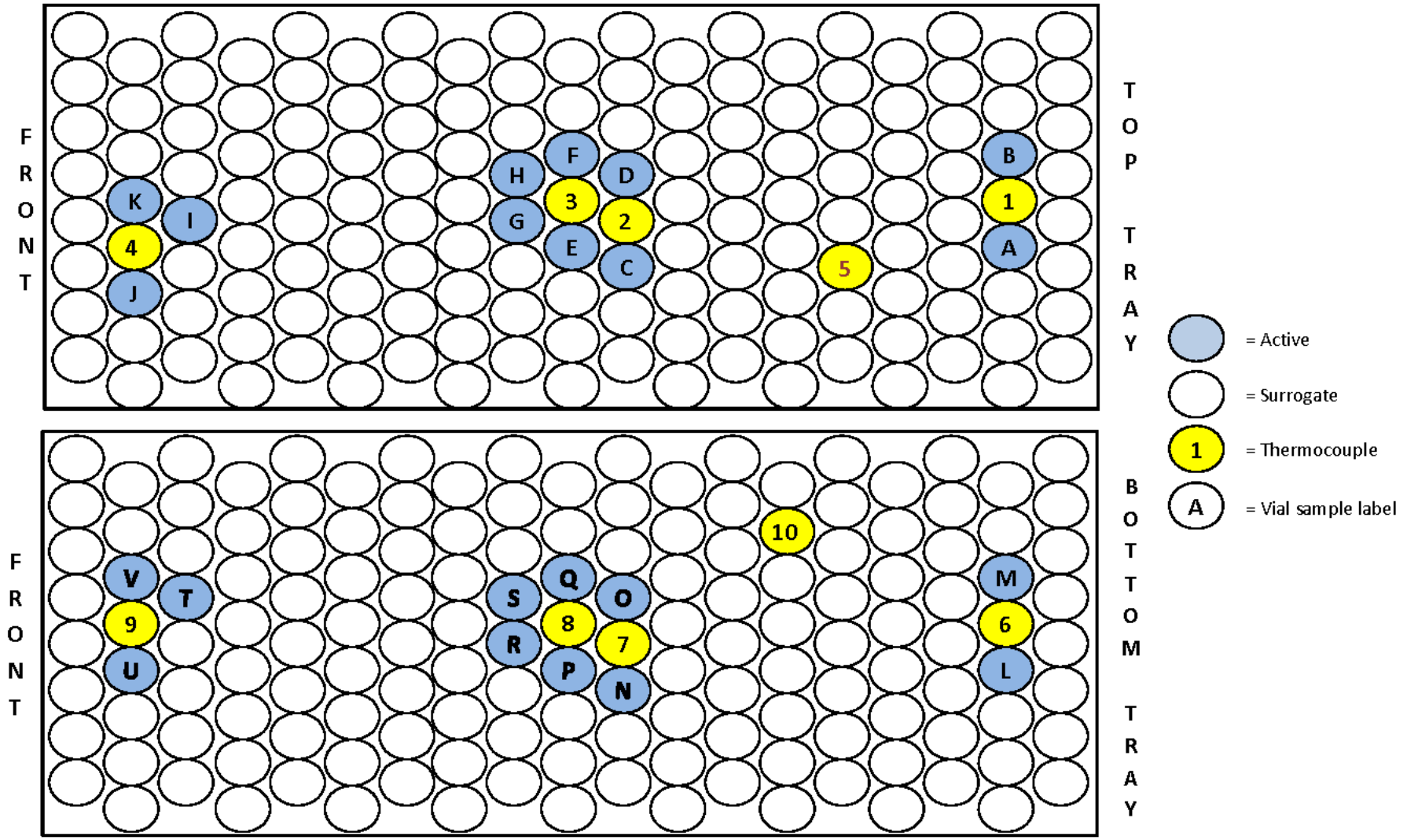
Examples:

Lyophilization

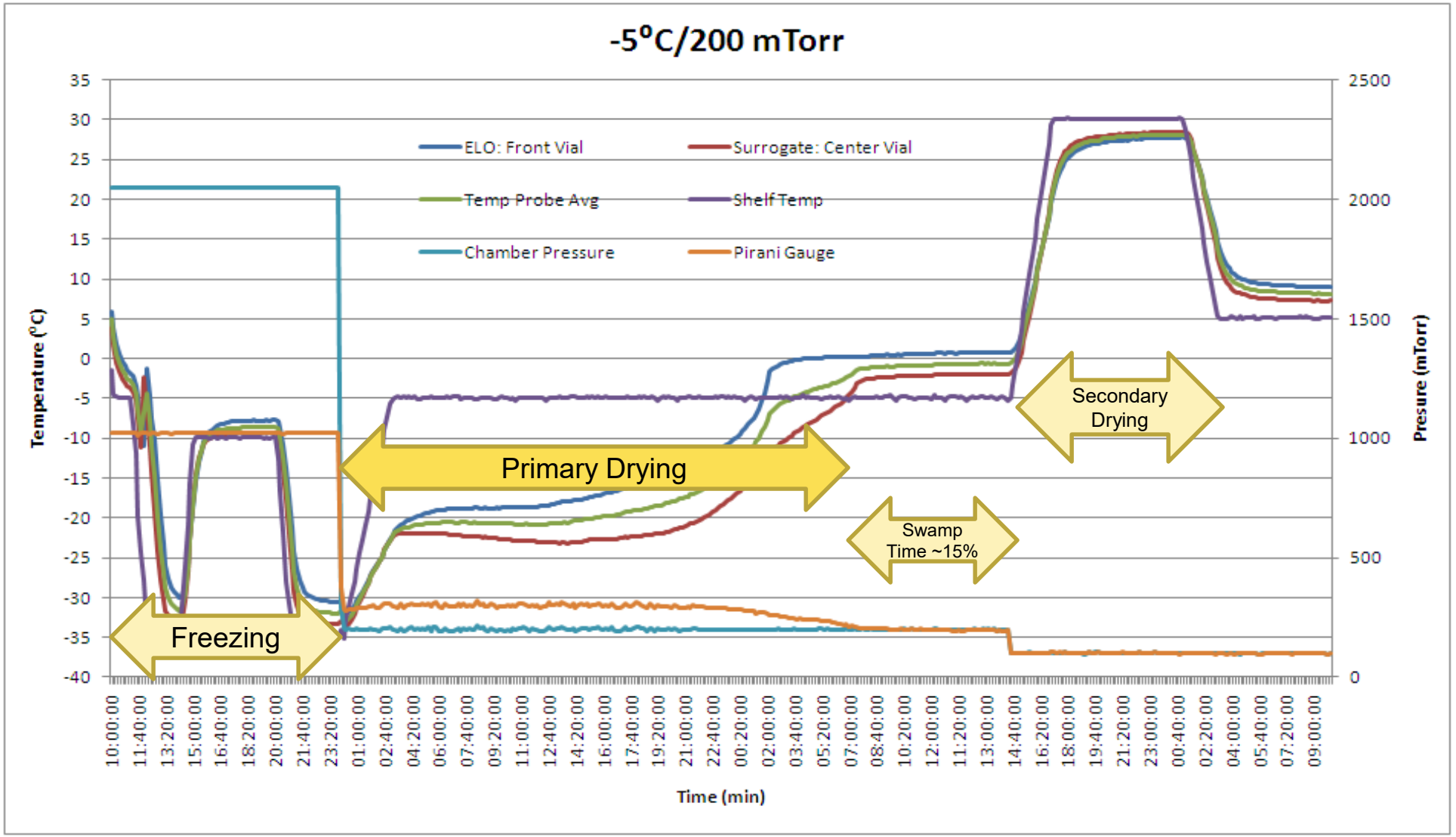
Very expensive process

It can take 1 week to finish one lyophilization run.

Lyophilization Tray Template – Sampling Center and Edge Vials



Typical Lyophilization Cycle



Design choice

Challenge

Design a study with 8 factors in less than 20+ runs with minimal risk of a follow-up study. Each lyo run takes one week to complete.

Some design options

1. Fractional factorial design: Resolution IV design in 16 runs, meaning two-factor interactions are completely confounded with other two-factor interactions.
2. Central composite design: prohibitive in terms of number of runs (over 60 runs).
3. Definitive screening design

Advantages of definitive screening designs

Reference: Jones and Nachtsheim, 2011, Journal of Quality Technology, "A Class of Three-Level Designs for Definitive Screening in the Presence of Second-Order Effects"

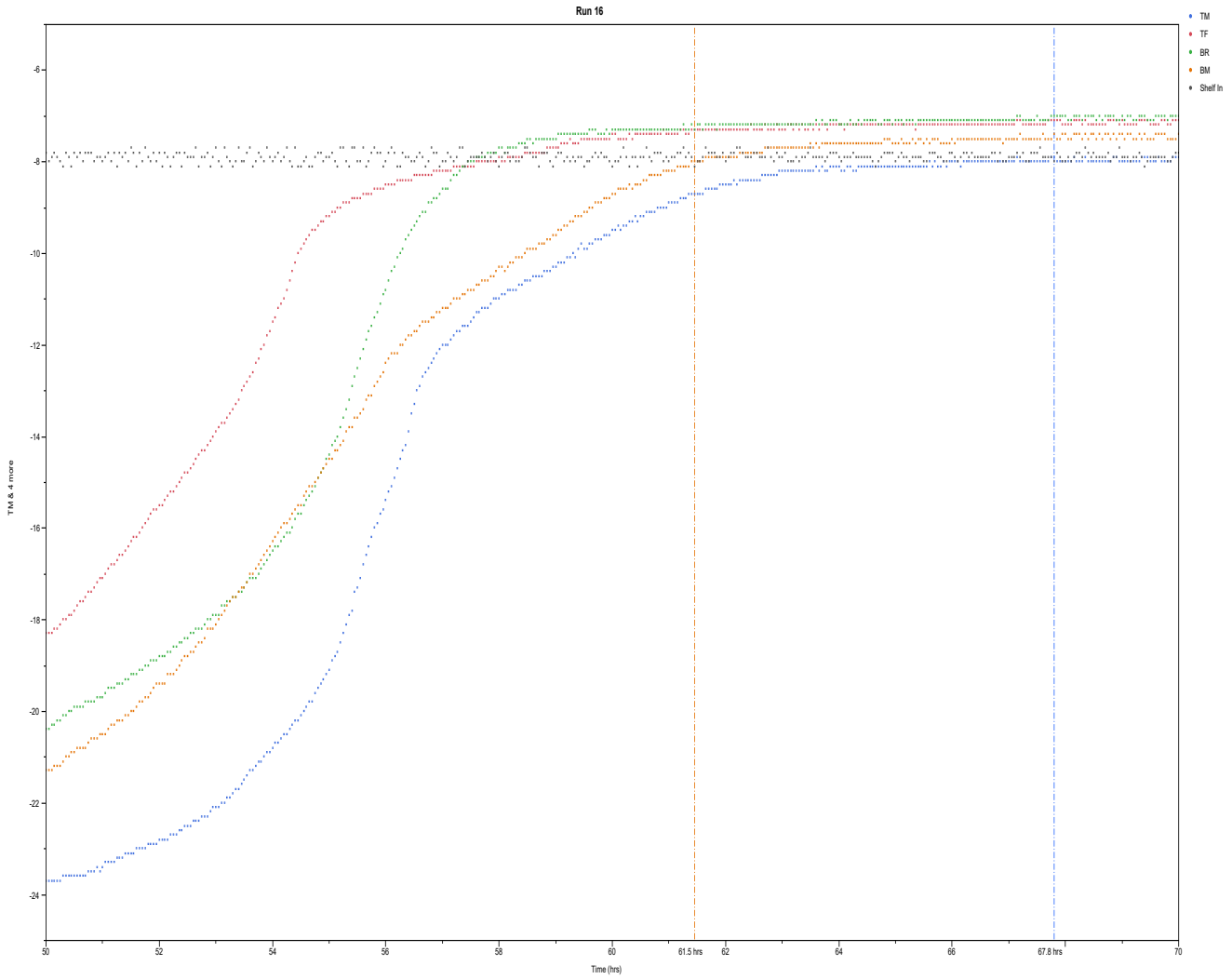
- Fewer runs: (2m+1) where m is the number of factors.
- Main effect estimates are unbiased by any second-order effect.
- Two-factor interactions are not completely confounded with other two-factor interactions, although they may be correlated.
- With 6 through (at least) 12 factors, the designs are capable of estimating all possible full quadratic models involving three or fewer factors with very high levels of statistical efficiency.

DSD with 8 factors in only 20 runs

A definitive screening DoE was designed to test the effects of eight process and formulation factors on many lyophilization responses, including primary drying time and product temperature.

DoE Parameter	Low	Middle	High
Drug Concentration (mg/mL)	10	30	50
Lyoprotectant (wt%)	6.0	7.5	9.0
Primary Drying T_{shelf} (°C)	-13	-8	-3
Chamber Pressure (mTorr)	50	100	150
Secondary Drying Duration (hours)	5.0	7.5	10.0
Temperature Ramp Rate (°C/min)	0.2	0.6	1.0
Fill Volume (mL)	6.0	7.5	9.0
Instrument	LyostarII or Virtis		

Defining the end of primary drying: Intersection of product temp and shelf temp



Run 16	Intersection of shelf temp and actual temp	
Sample	Primary drying time	Shelf Temp
TM (blue)	67.8	-8
TF	58	-8.1
BR	57.8	-8
BM (orange)	61.5	-8.1

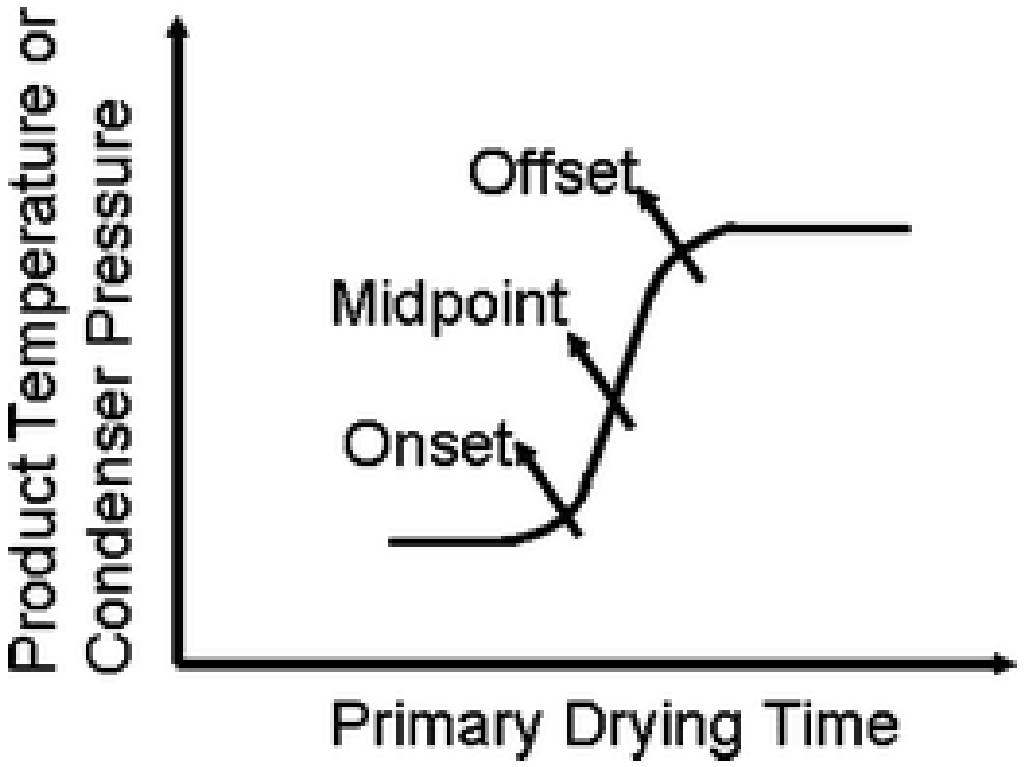
Note the difference in orange and blue thermocouples:

6.3 hours.

Defining the end of primary drying

"Product temperature approaching the shelf temperature set point (i.e., "offset" in Fig. 2) is commonly taken as an indication of the end of primary drying."

S. M. Patel, T. Doen, and M. J. Pikal, *AAPS Pharm.Sci.Tech.,* 11, **2010**



Four-parameter logistic curve:

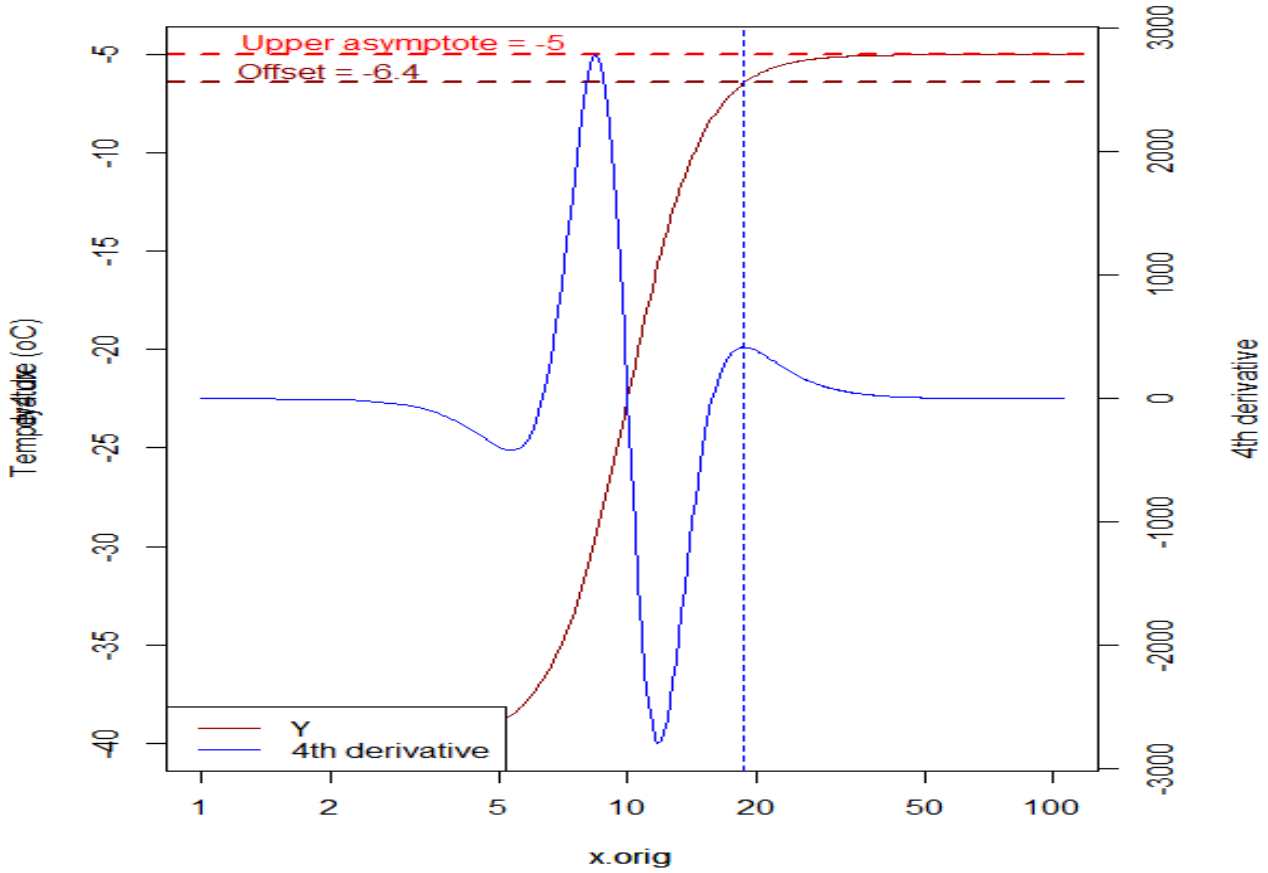
- lower asymptote c
- upper asymptote d
- Slope b
- EC50, or *e*; where 50% of the response is expected

$$f(x) = c + \frac{(d-c)}{1 + \exp\left(b(\ln x - \ln e)\right)}$$

Defining the end of primary drying
Mathematical Method: Fourth derivative of the 4-PL

$$D^4(f(x)) = (d-c)b^4e^{bx}\frac{(1-11e^{bx}+11e^{2bx}-e^{3bx})}{(1+e^{bx})^5}$$

- Need to prove that offset is reached at the maximum value of 4th derivative over the 2nd portion of the curve.
- After completing all 20 experiments, the difference in model quality between the two methods was not significant.

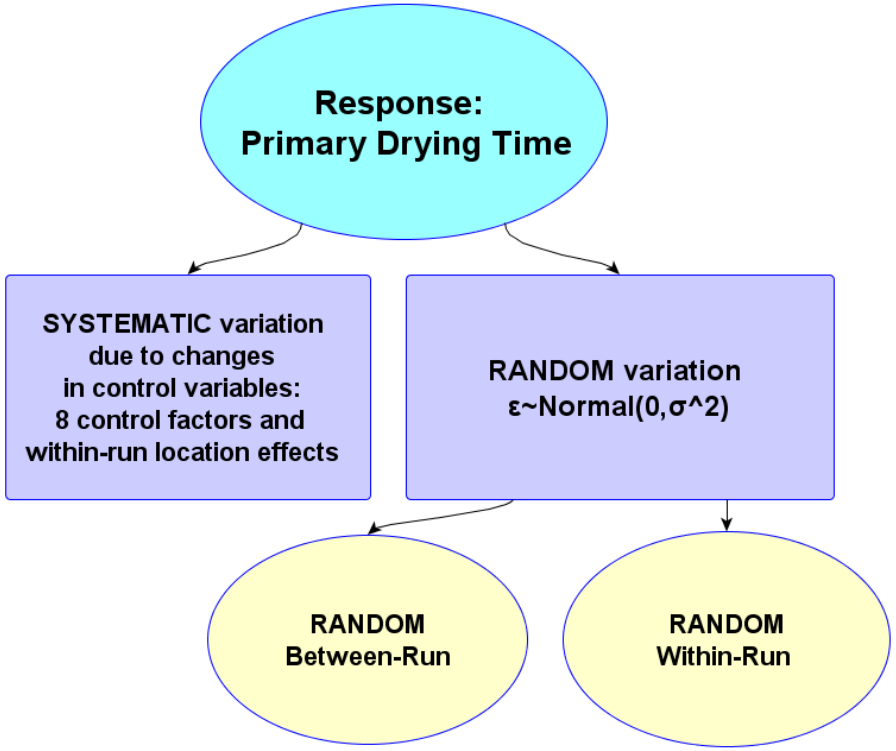


Variance component structure of the lyophilization data

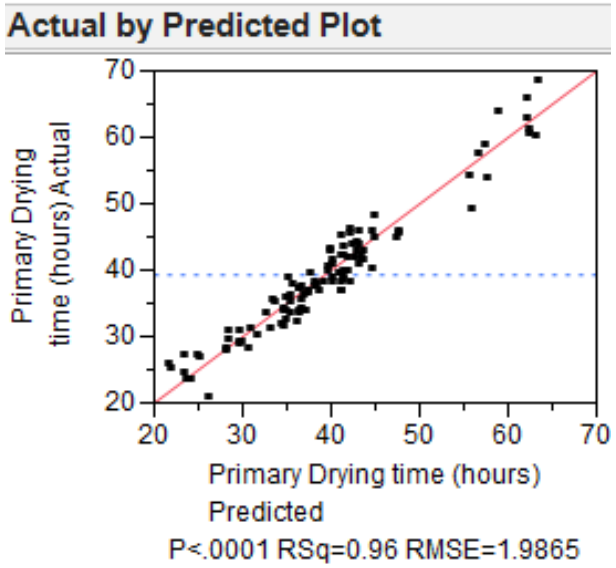
Between-run variation consists of a fixed and a random part.

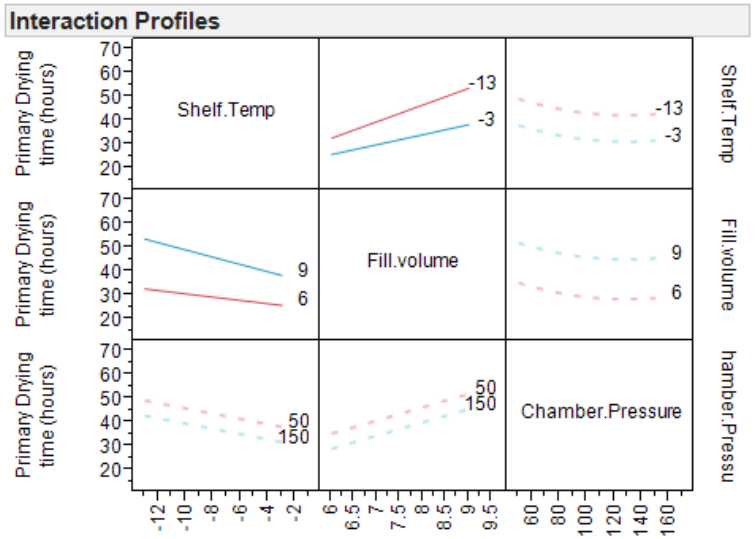
Within-run variation is due to random variation after accounting for location effects:

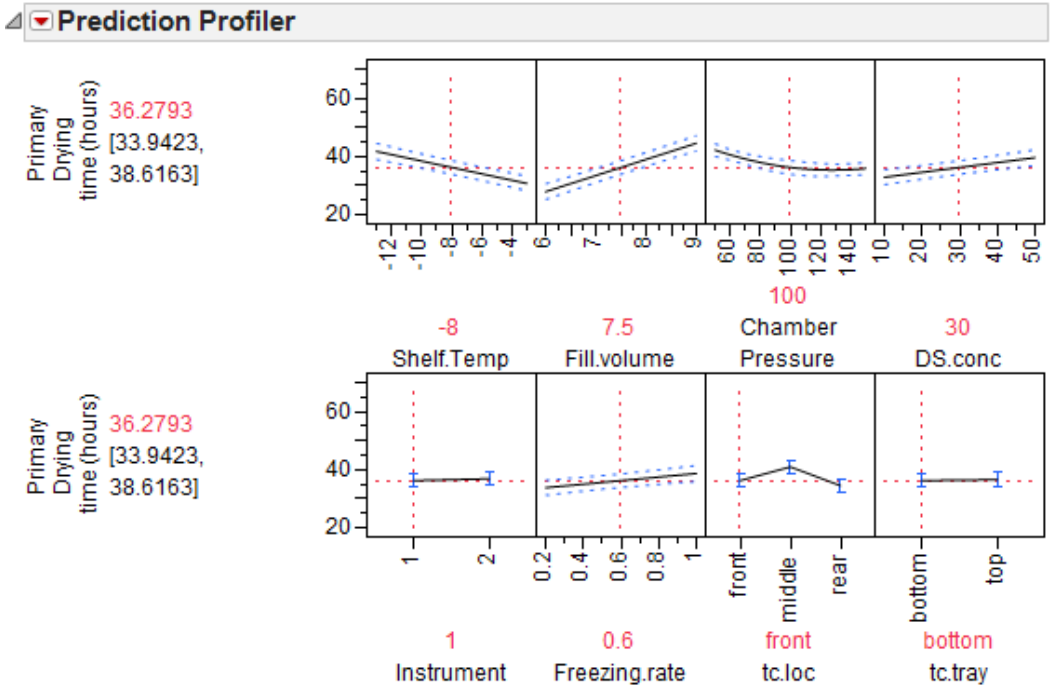
- tray position (top, bottom)
- thermocouple position (front, middle, rear)
- as well as analytical and sampling variation



Mixed Model for Primary Drying Time







Variance components Table

- Properly accounting for sources of variation leads to a decomposition of variance components into whole-plot error and split-plot error terms.
- Incorrectly pooling these two sources of variation into one leads to a more sporadic significance of effects that may not be real (inflated type I error rate, biased t-ratios and p-values).

Term	Estimate	Std Error	DFDen	t Ratio	Prob>|t|
Intercept	37.769	0.852	10.414	44.35	<.0001
Shelf.Temp(-13,-3)	-5.509	0.572	10.312	-9.63	<.0001
Fill.volume(6,9)	8.320	0.576	10.223	14.45	<.0001
Chamber.Pressure(50,150)	-3.171	0.613	9.855	-5.17	0.0004
DS.conc(10,50)	3.355	0.573	10.493	5.85	0.0001
Freezing.rate(0.2,1)	2.455	0.587	10.279	4.18	0.0018
Instrument[1]	-0.332	0.497	10.442	-0.67	0.5184
Fill.volume*Shelf.Temp	-2.089	0.665	10.624	-3.14	0.0097
Chamber.Pressure*Chamber.Pressure	2.801	1.100	10.192	2.55	0.0287
tc.loc[front]	-0.994	0.299	92.461	-3.33	0.0013
tc.loc[middle]	3.749	0.248	92.430	15.09	<.0001
tc.tray[bottom]	-0.164	0.190	92.423	-0.86	0.39

Was DSD a good choice?

Final model has:

- Six main effects: Vial Fill Volume, Shelf Temperature, Drug Substance Concentration, Chamber Pressure, Freezing Rate, and Instrument
- One quadratic effect for chamber pressure
- One two-factor interaction: Fill Volume*Shelf Temperature
- Location effects within run: tray position and thermocouple location

Definitive screening design proved to be a success.

No follow-up study is needed to further understand and optimize the freeze-drying process.

Another monoclonal antibody showed excellent agreement with this model.

Conclusions and Future Work

Process understanding

- An eight parameter mAb lyophilization DoE was completed, testing both formulation and process variables. The DoE may enable improved selection of formulation and process parameters for new lyophilization candidates and highlights relationships between parameters and product/process attributes.

- This study can be augmented to expand the design space to a lower shelf temperature, fill volume, instrument type, etc.

Business impact

- Significant savings in time and drug substance quantity for delivering drugs for clinical studies.
- Several other drugs were developed using knowledge from this study.

References

B. Jones, C.J. Nachtsheim (2011) “A Class of Three-Level Designs for Definitive Screening in the Presence of Second-Order Effects” Journal of Quality Technology, 43:1, 1-15

J. Goldman, H. More, O. Yee et al, “Optimization of Primary Drying in Lyophilization During Early-Phase Drug Development Using a Definitive Screening Design With Formulation and Process Factors” J Pharm Sci 2018 Oct 8; 107(10): 2592-2600

Acknowledgements

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