Real Time Release strategy for dissolution testing in continuous manufacturing

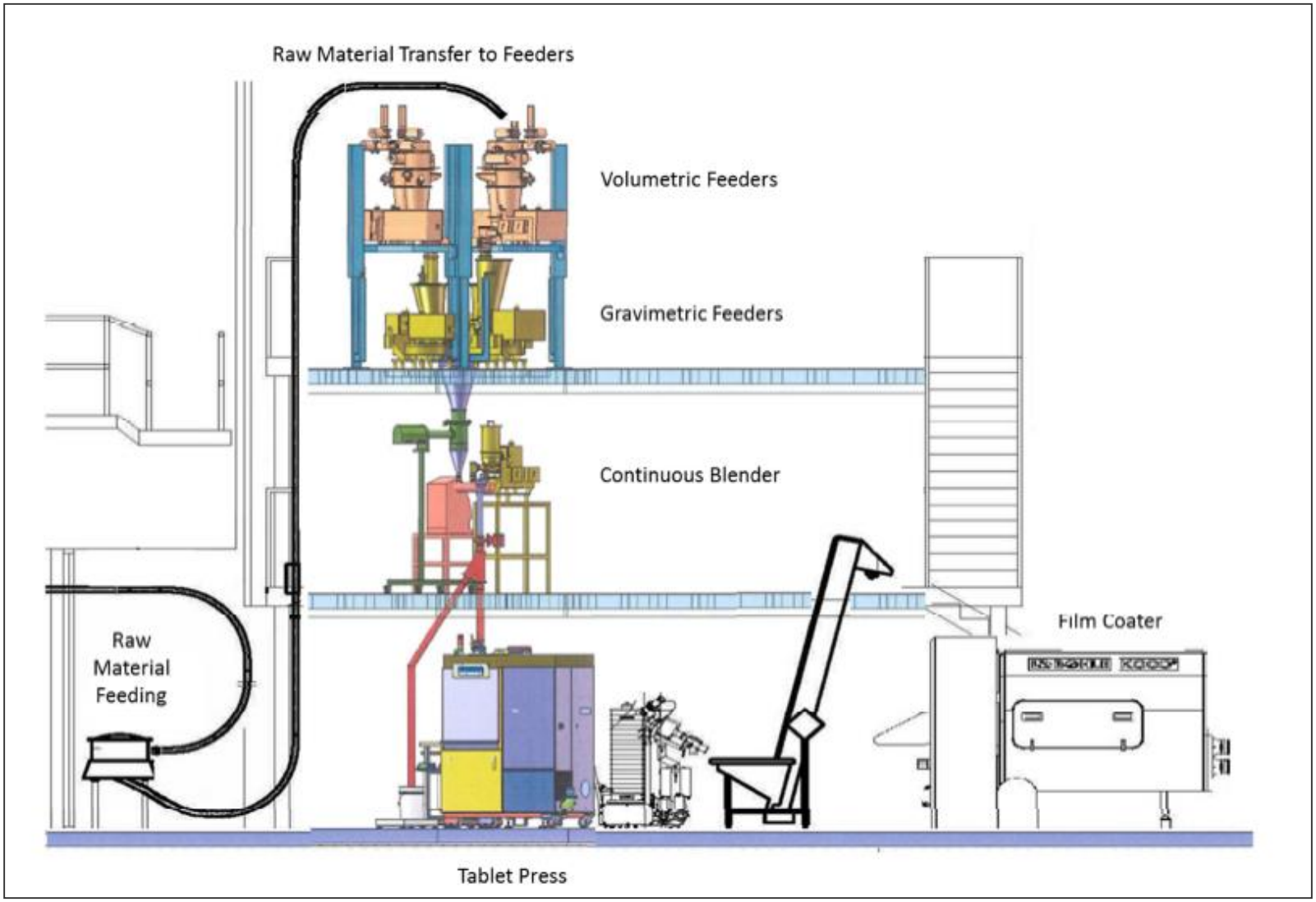
Melinda, *Tree of Life*
Melinda's artwork reflects her journey living with HIV.

Dwaine Banton, Principal Statistician
June 18, 2019 | Manufacturing and Applied Statistics

Outline

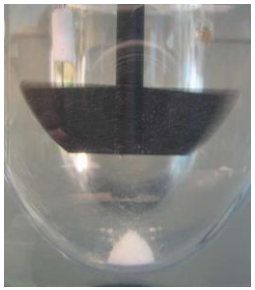
- The continuous manufacturing process
- Dissolution testing
- Surrogate model for dissolution: using a more convenient measurement as a substitute for an intended end-point ("biomarker" for manufacturing)
- Methodology:
  - Use of DoE to orthogonalize process factor effects and assaying process
  - Non-linear modeling of full dissolution profile and connection with process factors
- Case Study

Continuous Manufacturing (CM)



Dissolution Testing

The Dissolution Apparatus



Importance of dissolution testing

- characterizing the biopharmaceutical quality of a product at different stages in the pharmaceutical product's life cycle.
- In early drug development, in vitro dissolution properties are supportive for choosing and evaluating formulation candidates.
- In vitro dissolution data supports evaluation and interpretation of effects on bioavailability within gastrointestinal conditions.
- Dissolution is one of the three primary tests used to release a finished drug product:

Surrogate model for dissolution

- Use of near-infrared (NIR) spectroscopy to get real time measurements of content
  - Validation of HPLC-NIR calibration
- Multivariate measurement of content by NIR and dissolution at various time points for each observational unit
- Response vector modeled as a function of time and process factors
- Conditional predictive distribution of dissolution at any time point given content by NIR and process factor settings

DoE example considerations for dissolution assay

- 6 batches manufactured
- Balanced sequence of Batches to vessels for Baths A , B
- 12 dissolution runs with 6 HPLC runs
- Operator and HPLC run are confounded

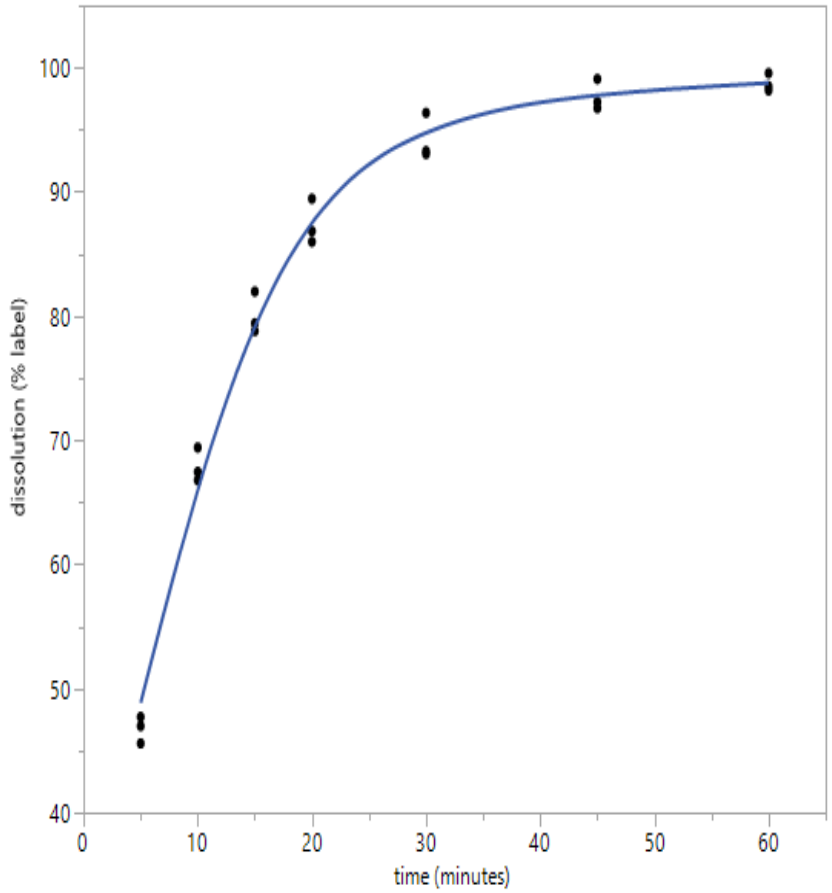
Operator	Bath	Vessel						Apparatus	HPLC Run
		V1	V2	V3	V4	V5	V6		
1	A	R1	R2	R3	R4	R5	R6	A	1
	B	R2	R3	R4	R5	R6	R1	B	
	A	R3	R4	R5	R6	R1	R2	A	2
	B	R4	R5	R6	R1	R2	R3	B	
	A	R5	R6	R1	R2	R3	R4	A	3
	B	R6	R1	R2	R3	R4	R1	B	
2	B	R1	R2	R3	R4	R5	R6	B	4
	A	R2	R3	R4	R5	R6	R1	A	
	B	R3	R4	R5	R6	R1	R2	B	5
	A	R4	R5	R6	R1	R2	R3	A	
	B	R5	R6	R1	R2	R3	R4	B	6
	A	R6	R1	R2	R3	R4	R1	A	

Non-linear dissolution model

- Three parameter Weibull Model, reparametrized to accommodate desired release rate
- Let $\lambda = ln\left(\frac{1}{1-\gamma}\right)$, $0 < \gamma < 1$, then

$$E[Y|t, \theta_1, \theta_2, \theta_3, \lambda\,] = \theta_1\left[1 - e^{-\lambda\left(\frac{t}{\theta_2}\right)^{\theta_3}}\right]$$

- θ_1 is dissolution extent parameter
- θ_2 is time to achieve $\gamma\theta_1$% dissolution



Hierarchical Model and conditional expectation

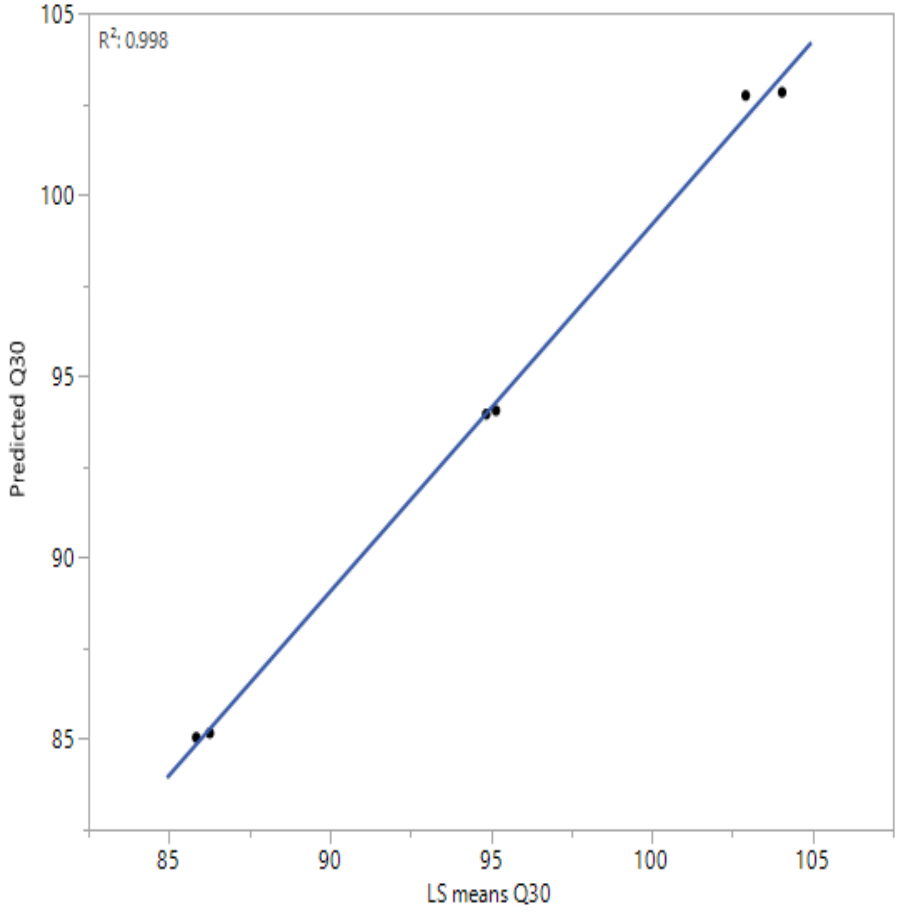
- Fit $y|t,\boldsymbol{\theta}\sim N\left(\theta_1 * \left[1-e^{-\lambda\left(\frac{t}{\theta_2}\right)^{\theta_3}}\right],\sigma\right)$
- $\boldsymbol{\theta},\text{Content}_{\text{NIR}}|X,B\sim MVN(XB,\Sigma)$
- Determine the conditional expectation of the Weibull parameters:

$$\boldsymbol{\theta}^* \equiv E\left[\boldsymbol{\theta}|\text{Content}_{\text{NIR}},\boldsymbol{x_{pred}},\text{data}\right]$$
$$= \left(\boldsymbol{x_{pred}} * B[,1:3]\right)^T + \left(\frac{\Sigma[1:3,4]}{\Sigma[4,4]}\right)$$
$$* \left(\text{Content}_{\text{NIR}} - \boldsymbol{x_{pred}} * B[,4]\right)$$

- Make predictions for dissolution at any given time point, for any particular process factors settings: $y_{pred}|t,\boldsymbol{\theta}^*$

Case Study and model validation

- 6 validation batches manufactured
- 2 batches each at 90%, 100%, and 110% target API
- Empirical dissolution at 30 minutes (Q30) measured in 12 vessels
- Surrogate model applied using Nir measurements



Thank you

Melinda, *Tree of Life*
Melinda's artwork reflects her journey living with HIV.

dbanton@its.jnj.com

June 18, 2019

Janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson


janssen
PHARMACEUTICAL COMPANIES OF
Johnson & Johnson