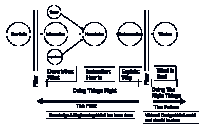
API Development

- Science
  - Effect of Starting Materials, Reagents, and Raw Materials
  - Particle Engineering
  - Understanding of Physical Sciences
    - Heat and mass transfer considerations, with and without chemical reactions
    - Use of empirical and semi-empirical modeling
    - Etc
- Risks
  - Assumptions built into models
  - Etc
- Note: Process Understanding Pyramid. Work from top down and explain why we are where we are



API Development

Macroscopic Mass Balance

$$\frac{d}{dt} m_{i,tot} = -\Delta w_i + w_i^{(m)} + r_{i,tot}$$

w_i=mass flow rate of the *i*th species past bounding planes
$w_i^{(m)}$=mass flow rate of the *i*th species via diffusion
$r_{i,tot}$ = rate of production/reaction of *i*th species

Macroscopic Momentum Balance

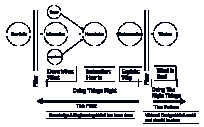
$$\frac{d}{dt}\mathbf{P} = -\Delta\left(\frac{\langle \upsilon^2 \rangle}{\langle \upsilon \rangle}\mathbf{w} + p\mathbf{S}\right) + \mathbf{F}^{(m)} - \mathbf{F} + m_{tot}\mathbf{g}$$

Macroscopic Energy Balance

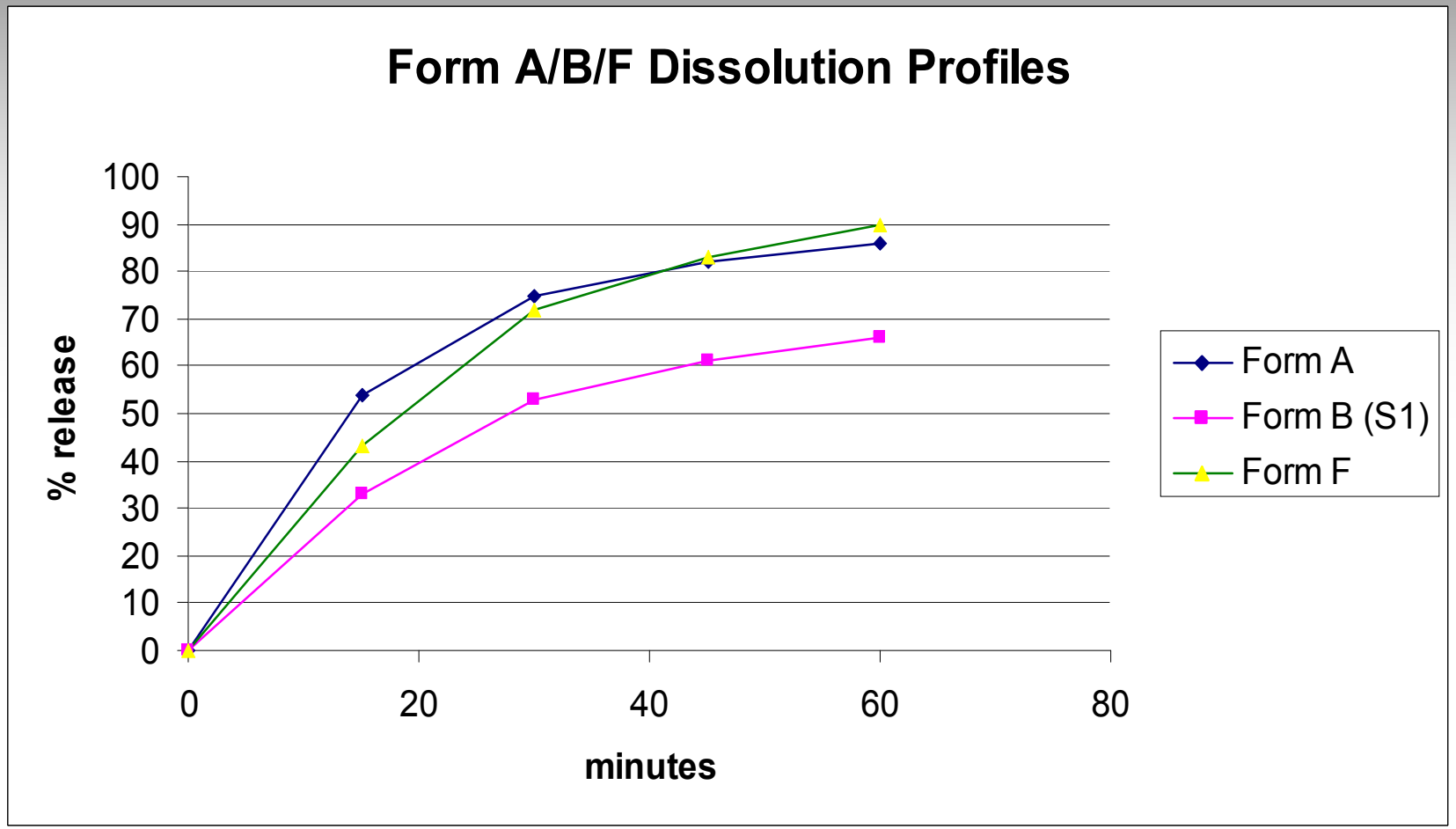
$$\frac{d}{dt} E_{tot} = -\Delta\left[\left(U + pV + \frac{1}{2}\frac{\langle \upsilon^3 \rangle}{\langle \upsilon \rangle} + \Phi\right)w\right] + Q^{(m)} + Q - W$$

Macroscopic Mechanical Energy Balance

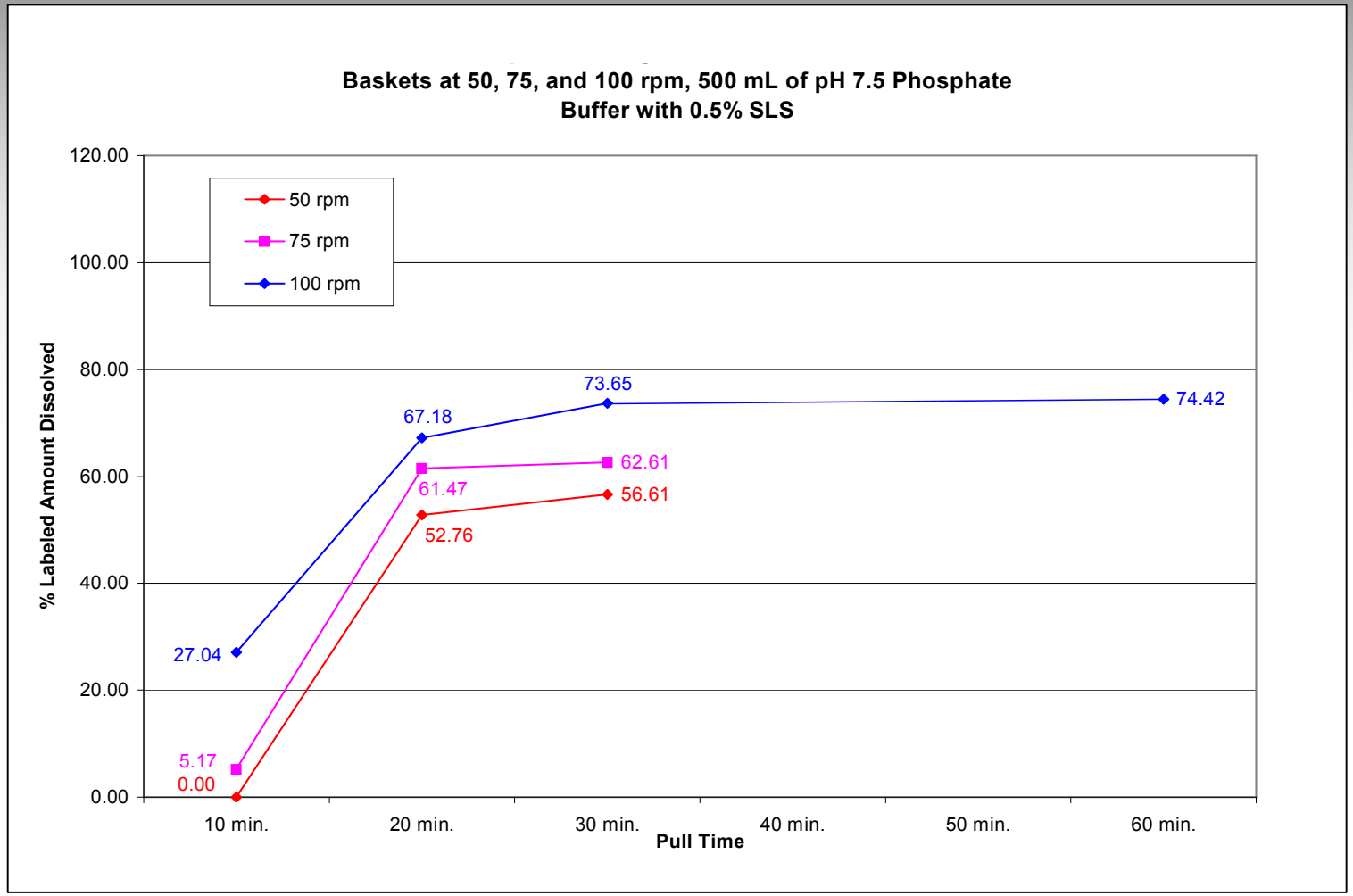
$$\frac{d}{dt}\left(K_{tot} + \Phi_{tot}\right) = -\Delta\left[\left(\frac{1}{2}\frac{\langle \upsilon^3 \rangle}{\langle \upsilon \rangle} + \Phi + \frac{p}{\rho}\right)w\right] + B^{(m)} - W - E_\upsilon$$



Tablet Dissolution (Forms A/B/F)

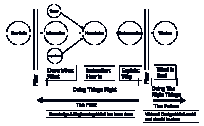


API Form X Tablet Dissolution

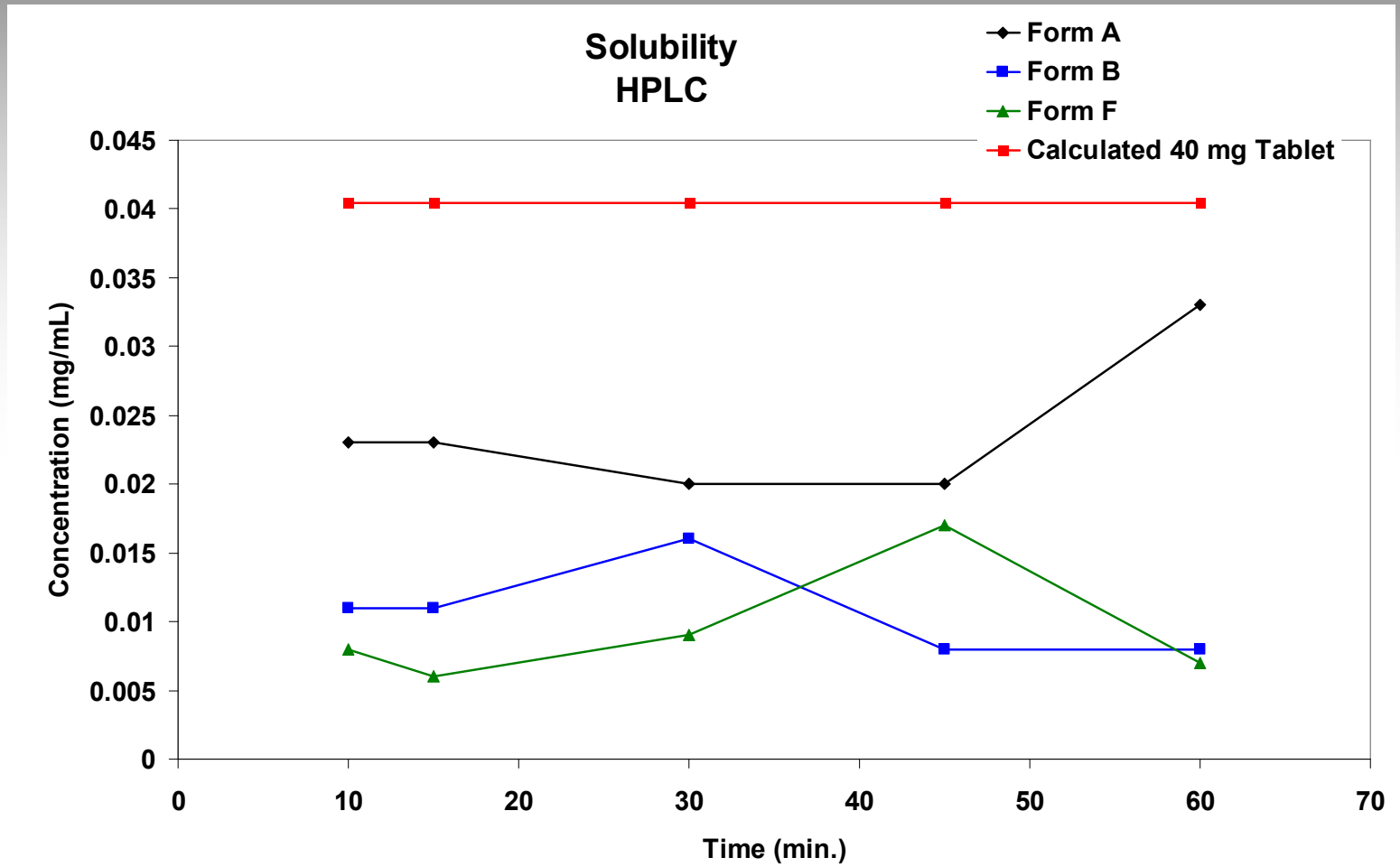


Polymorph Solubility Study Metrics

- ~ 400 mg API – create a slurry to wet the particles and transfer to disso bath
- Disso conditions – buffer, SDS, 37°C
- Centrifuge sample and analyze supernatant via HPLC

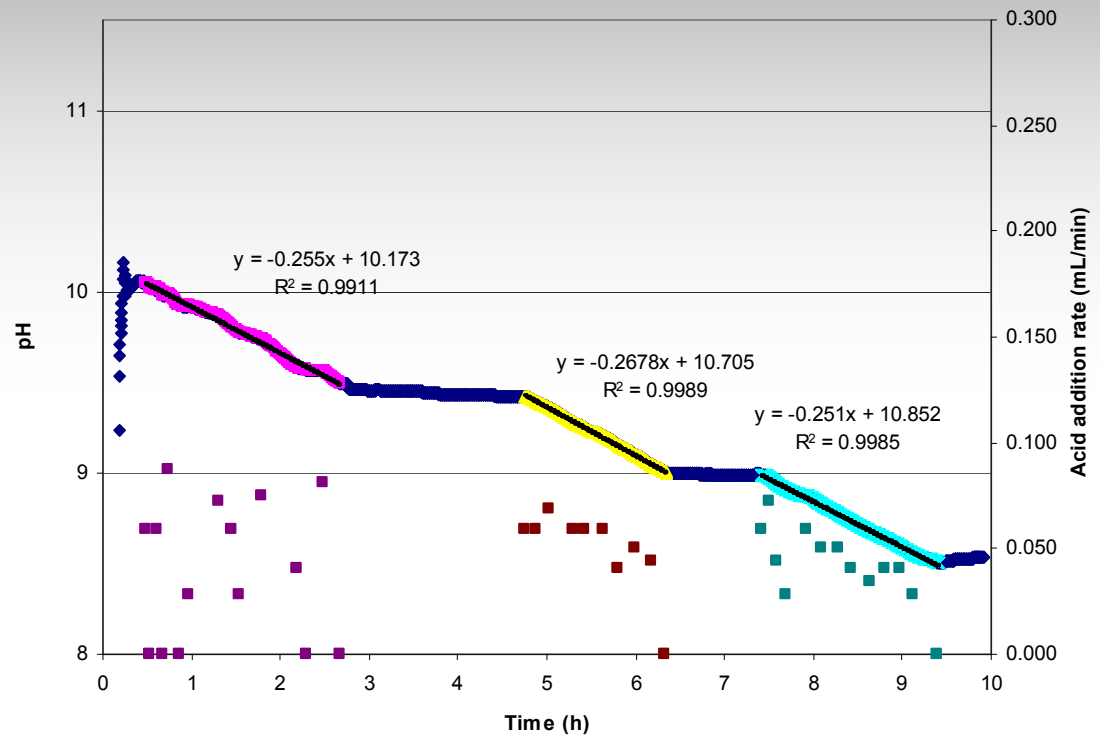


Solubility Study



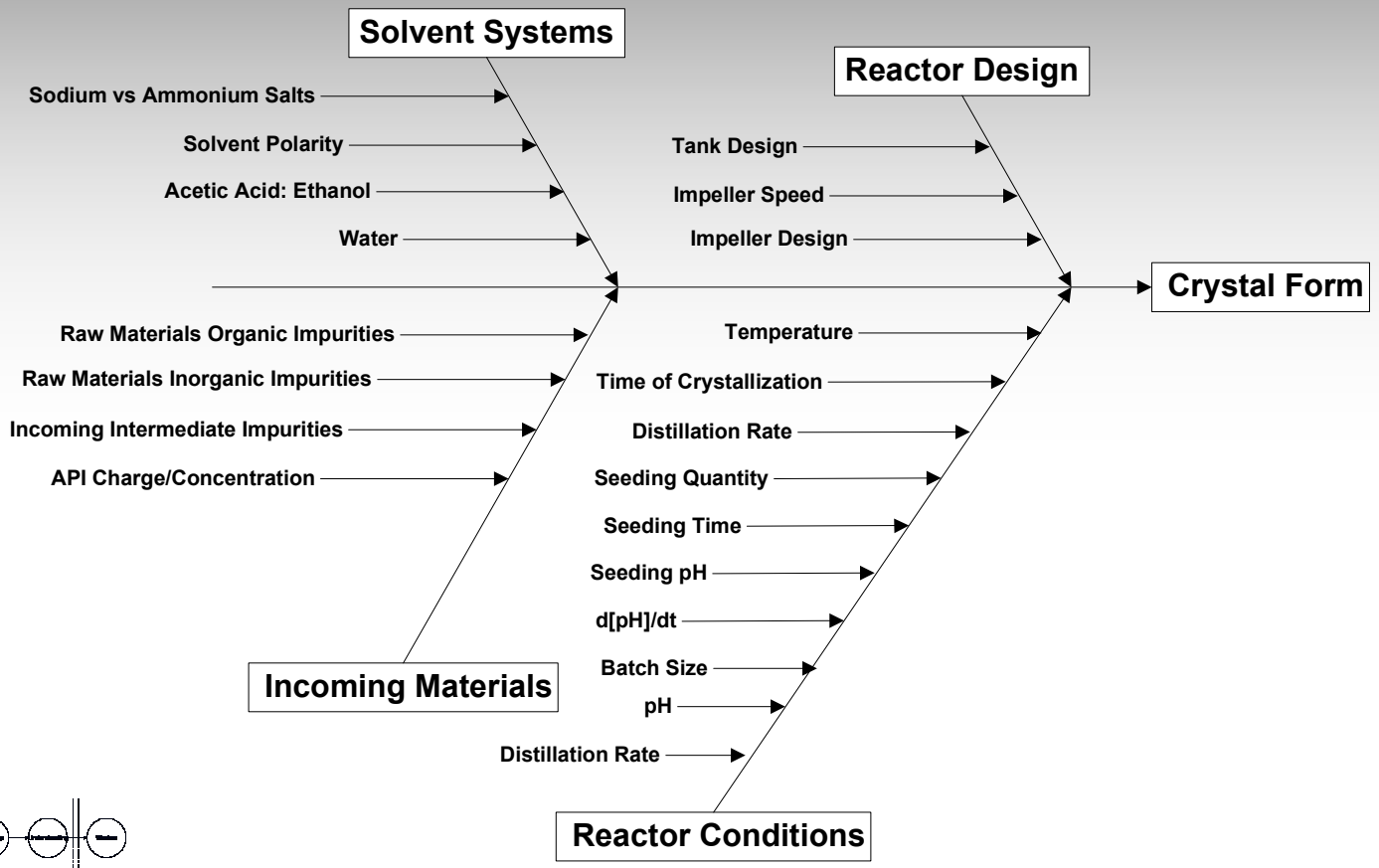
API Particle Engineering: Control of API Polymorphic Form

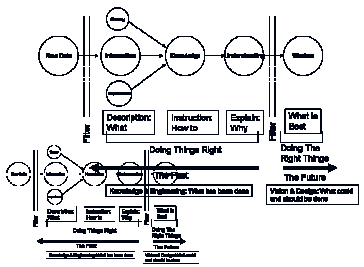
Basic Process



API Particle Engineering: Control of API Polymorphic Form

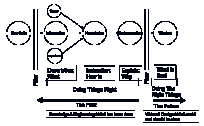
Step 1. Identification of Potential Critical Variables





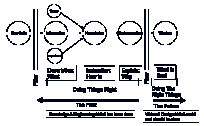
API Particle Engineering: Control of API Polymorphic Form

- **2. Screening Experiments**
  - **Evaluated important but not critical parameters**
  - **Set conditions for future experimentation**



API Particle Engineering: Control of API Polymorphic Form

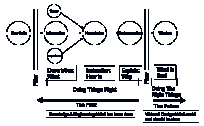
- 3. Initial Experimental Design
  - Evaluated important, critical parameters
  - Set conditions for future experimentation
  - Developed preliminary models to determine initial manufacturing plant equipment requirements



API Particle Engineering: Control of API Polymorphic Form

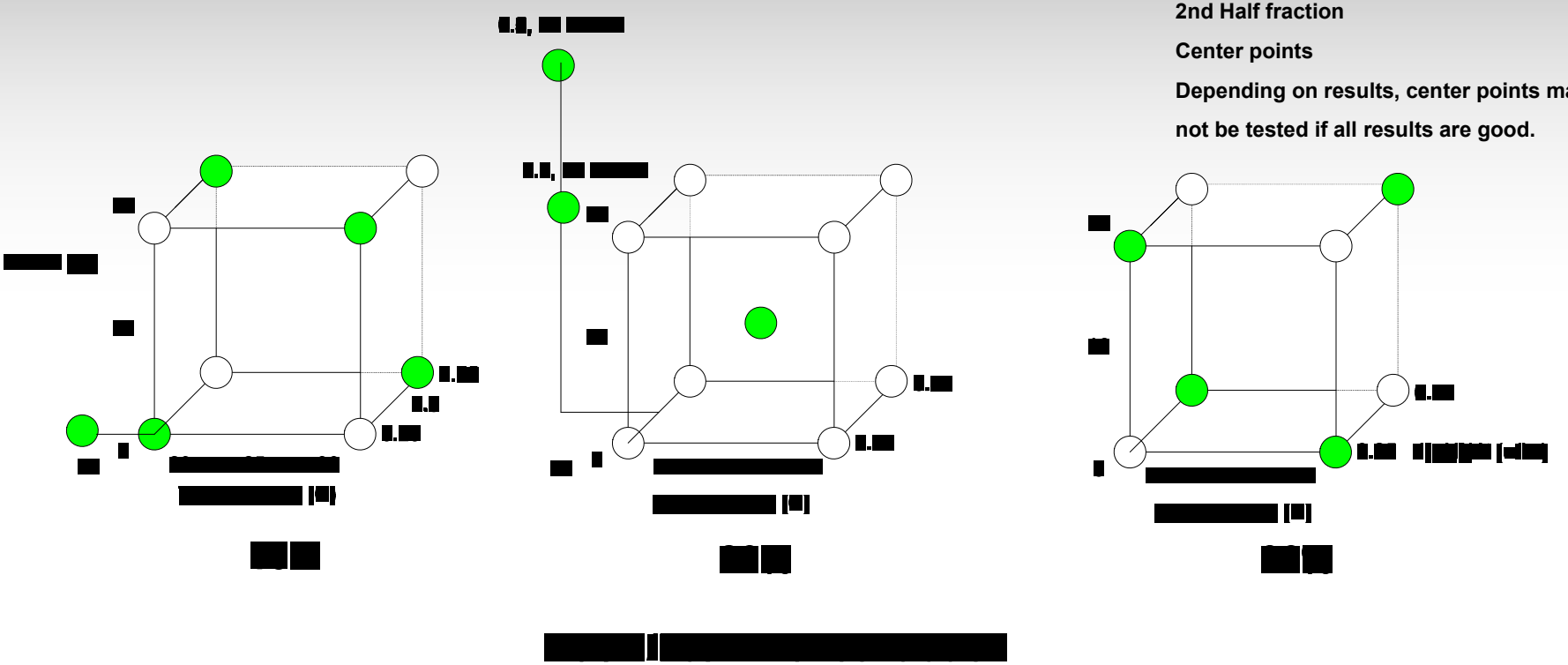
Step 3.Initial Experimental Design

Variables			Responses				
Temp	d[pH]/dt	Water	Yield	% Form X	% Form Y	% Form Z	HPLC
000 25	0.5	10					
000 25	0.5	10					
++− 30	0.75	0					
−−+ 20	0.25	20					
+++ 30	0.75	20					
+−+ 30	0.25	20					
000 25	0.5	10					
−+− 20	0.75	0					
−−− 20	0.25	0					
+−− 30	0.25	0					
−++ 20	0.75	20					
15	0.25	0					



API Particle Engineering: Control of API Polymorphic Form

Step 3. Final (Executed) Experimental Design



Original DOE Design,
Central Composite Design

Conducted in 3 Phases

1st Half fraction

2nd Half fraction

Center points

Depending on results, center points may not be tested if all results are good.

API Particle Engineering: Control of API Polymorphic Form

Step 4. Analysis of Data

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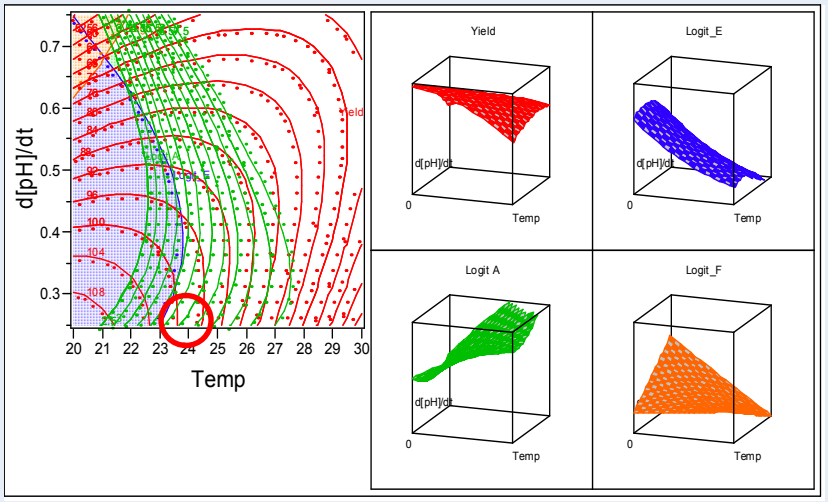
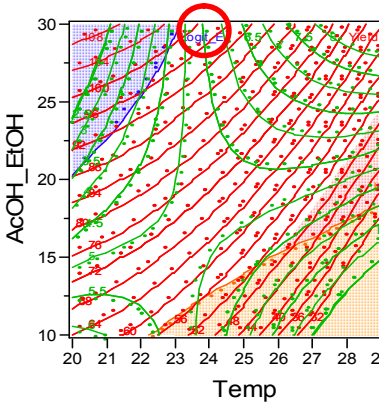
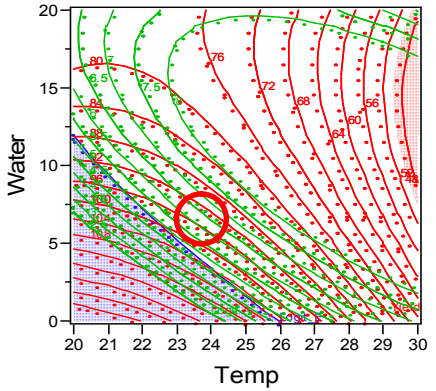
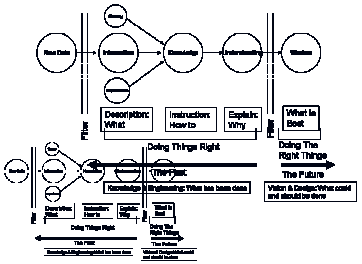


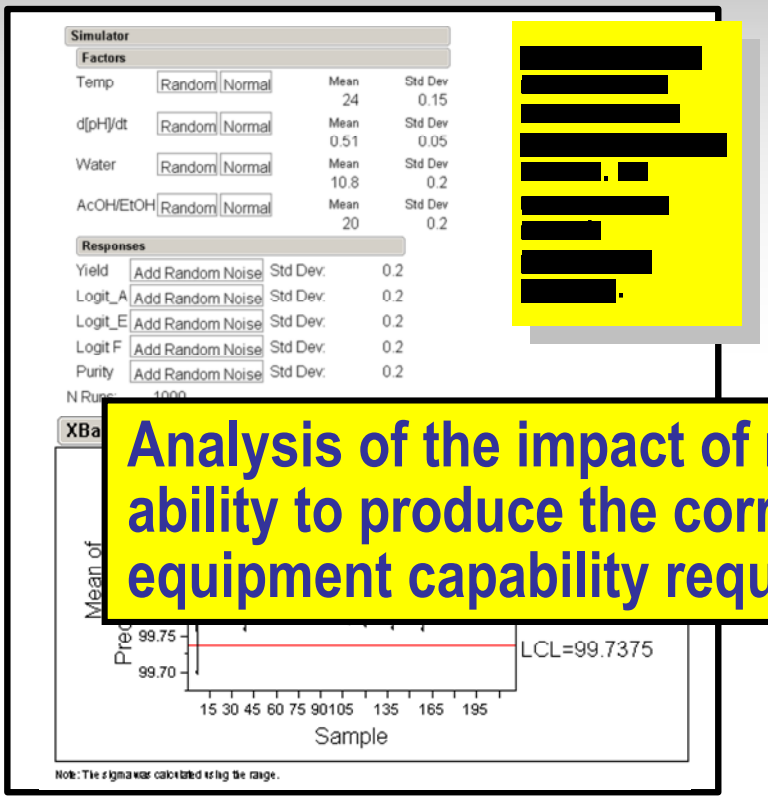


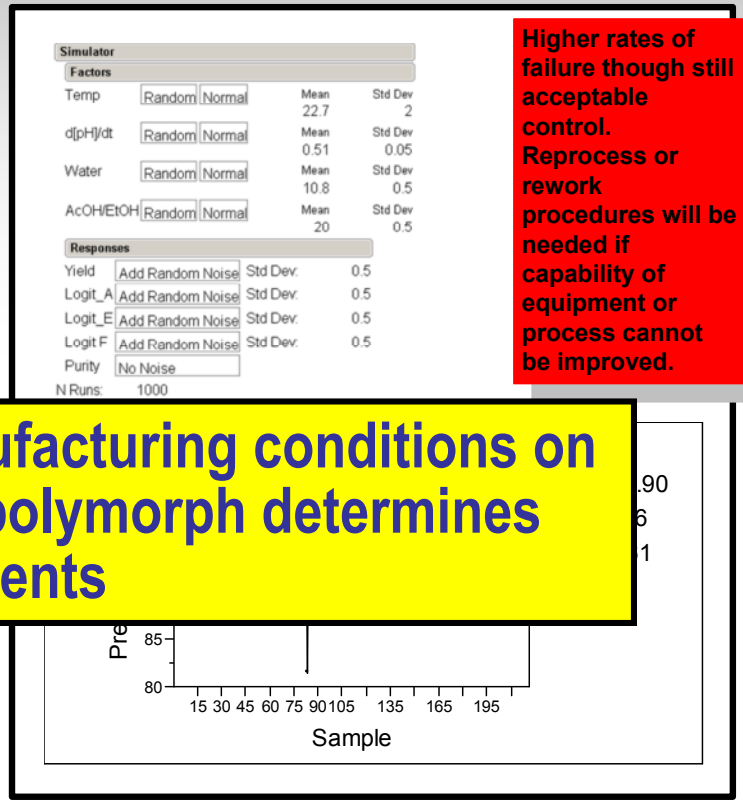




API Particle Engineering: Control of API Polymorphic Form

Step 5. Monte Carlo Simulations of Future Events





Higher rates of failure though still acceptable control. Reprocess or rework procedures will be needed if capability of equipment or process cannot be improved.

Analysis of the impact of manufacturing conditions on ability to produce the correct polymorph determines equipment capability requirements

API Particle Engineering: Control of API Polymorphic Form

- Process Design and Control
  - Define from DOE experimentation on polymorphic form
  - Adds a dimension of predictability relative to uncertainty
    - Am I confident in this process or not if I run it under these conditions?