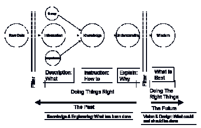
# API Development

- 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

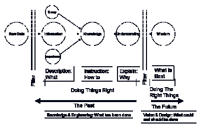
$$\frac{d}{dt}\mathbf{P} = -\Delta\left(\frac{\langle\upsilon^2\rangle}{\langle\upsilon\rangle}\mathbf{w} + p\mathbf{S}\right) + \mathbf{F}^{(m)} - \mathbf{F} + m_{tot}\mathbf{g}$$

## Macroscopic Energy Balance

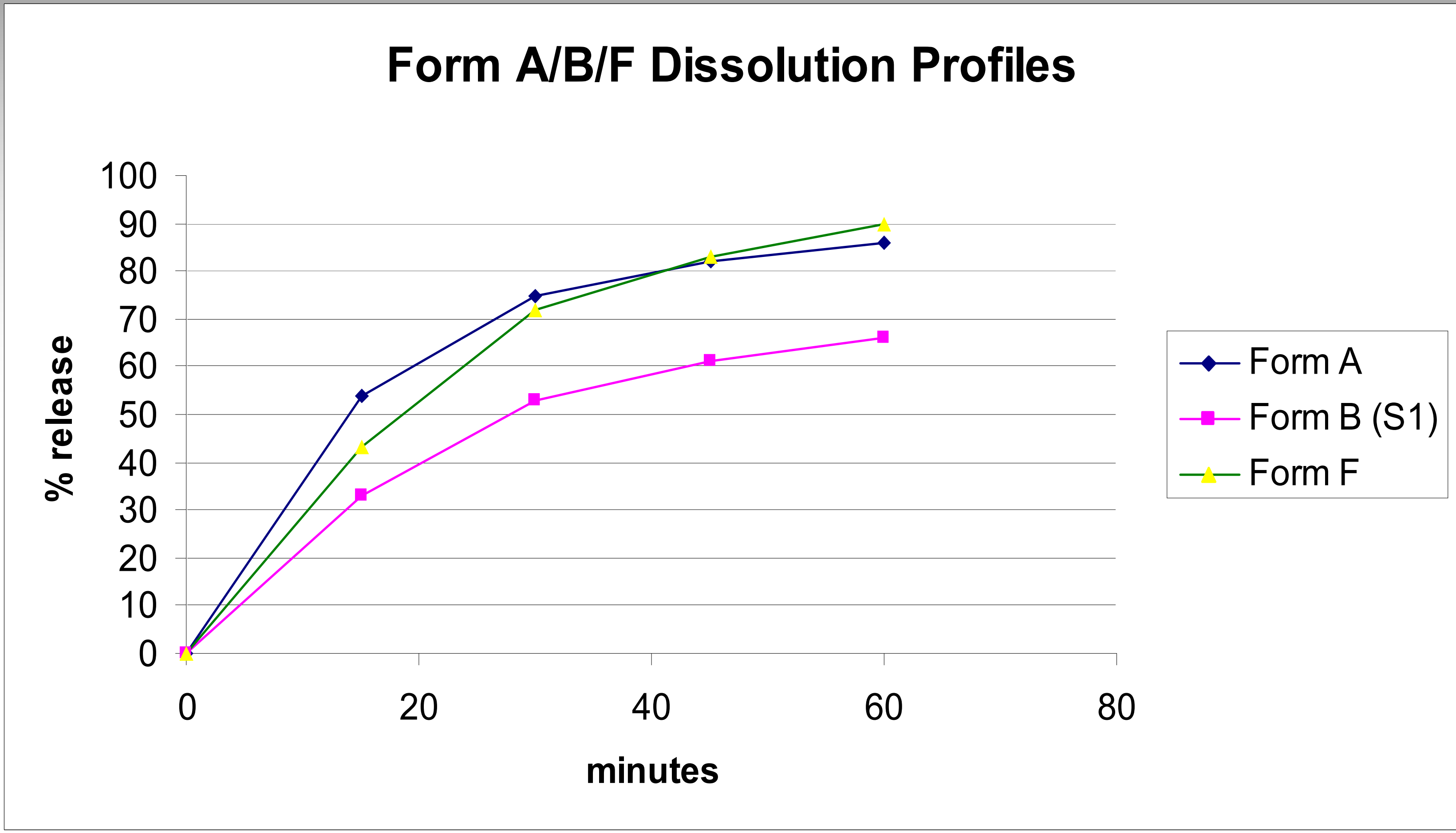
$$\frac{d}{dt}E_{tot} = -\Delta\left[\left(U + pV + \frac{1}{2}\frac{\langle\upsilon^3\rangle}{\langle\upsilon\rangle} + \Phi\right)w\right] + Q^{(m)} + Q - W$$

## Macroscopic Mechanical Energy Balance

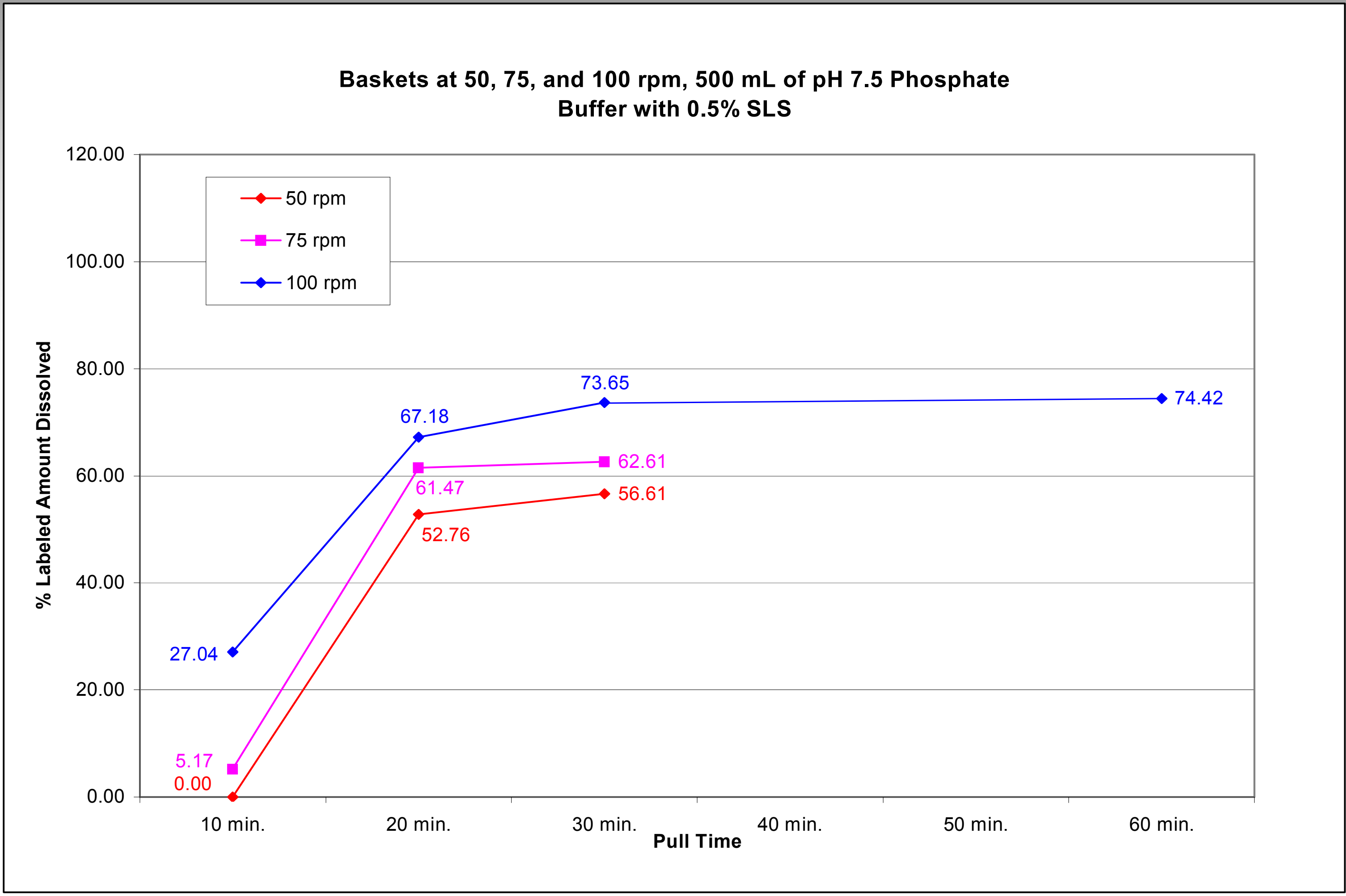
$$\frac{d}{dt}\left(K_{tot} + \Phi_{tot}\right) = -\Delta\left[\left(\frac{1}{2}\frac{\langle\upsilon^3\rangle}{\langle\upsilon\rangle} + \Phi + \frac{p}{\rho}\right)w\right] + B^{(m)} - W - E_{\upsilon}$$

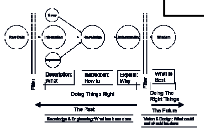


# Tablet Dissolution (Forms A/B/F)



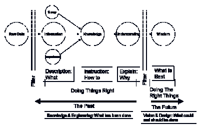
# API Form X Tablet Dissolution



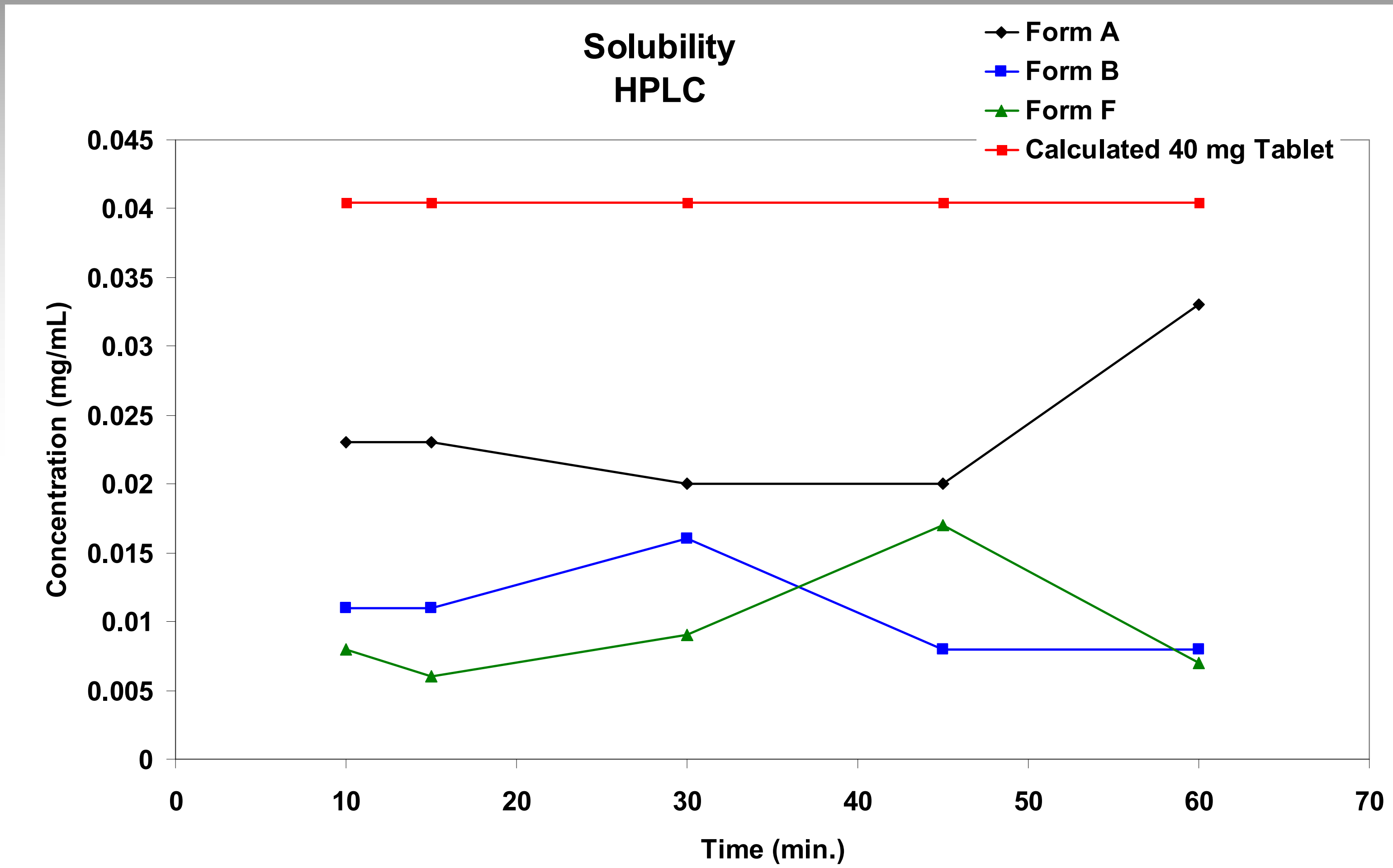



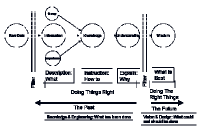
# Polymorph Solubility Study Metrics

- ~ 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



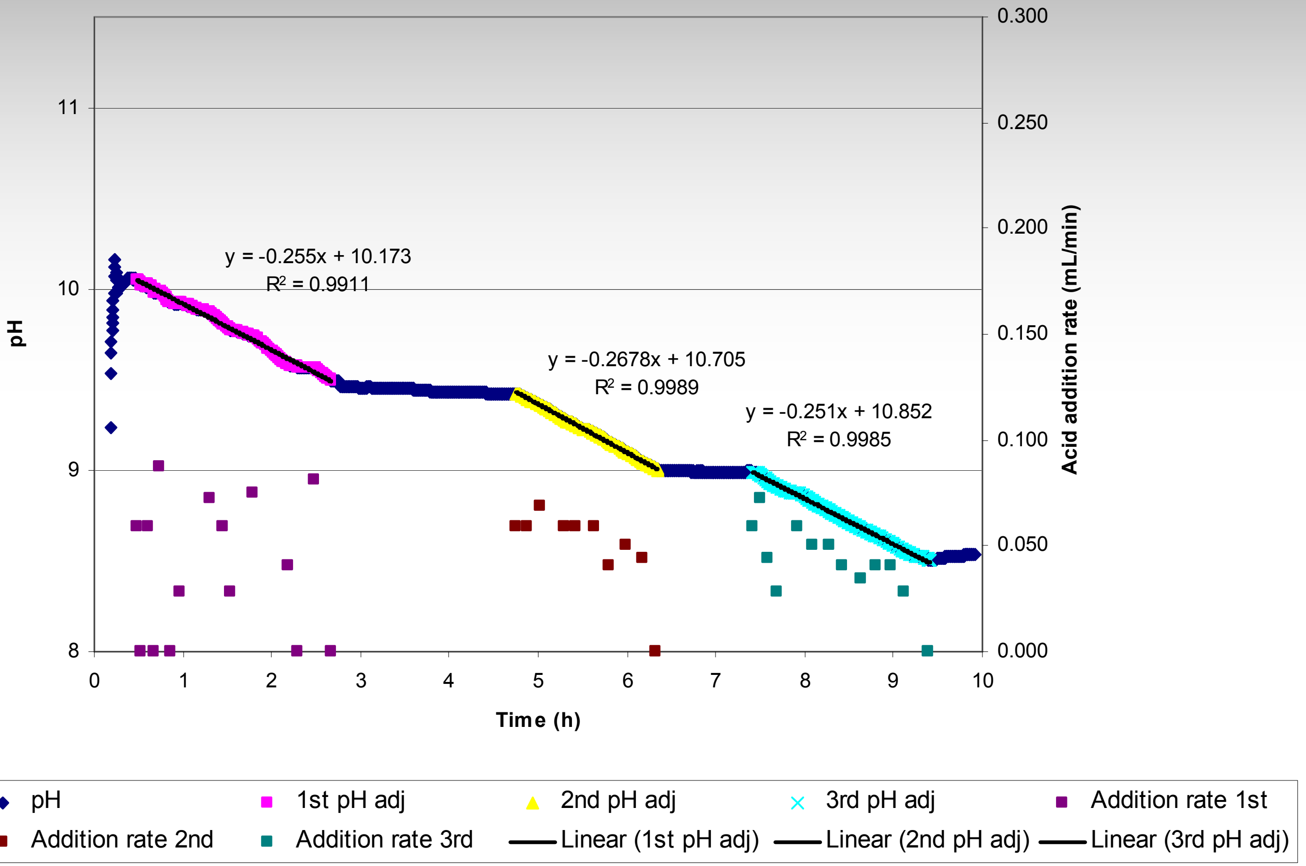
# Solubility Study

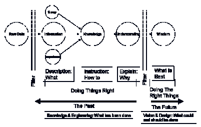


# API Particle Engineering:
# Control of API Polymorphic Form

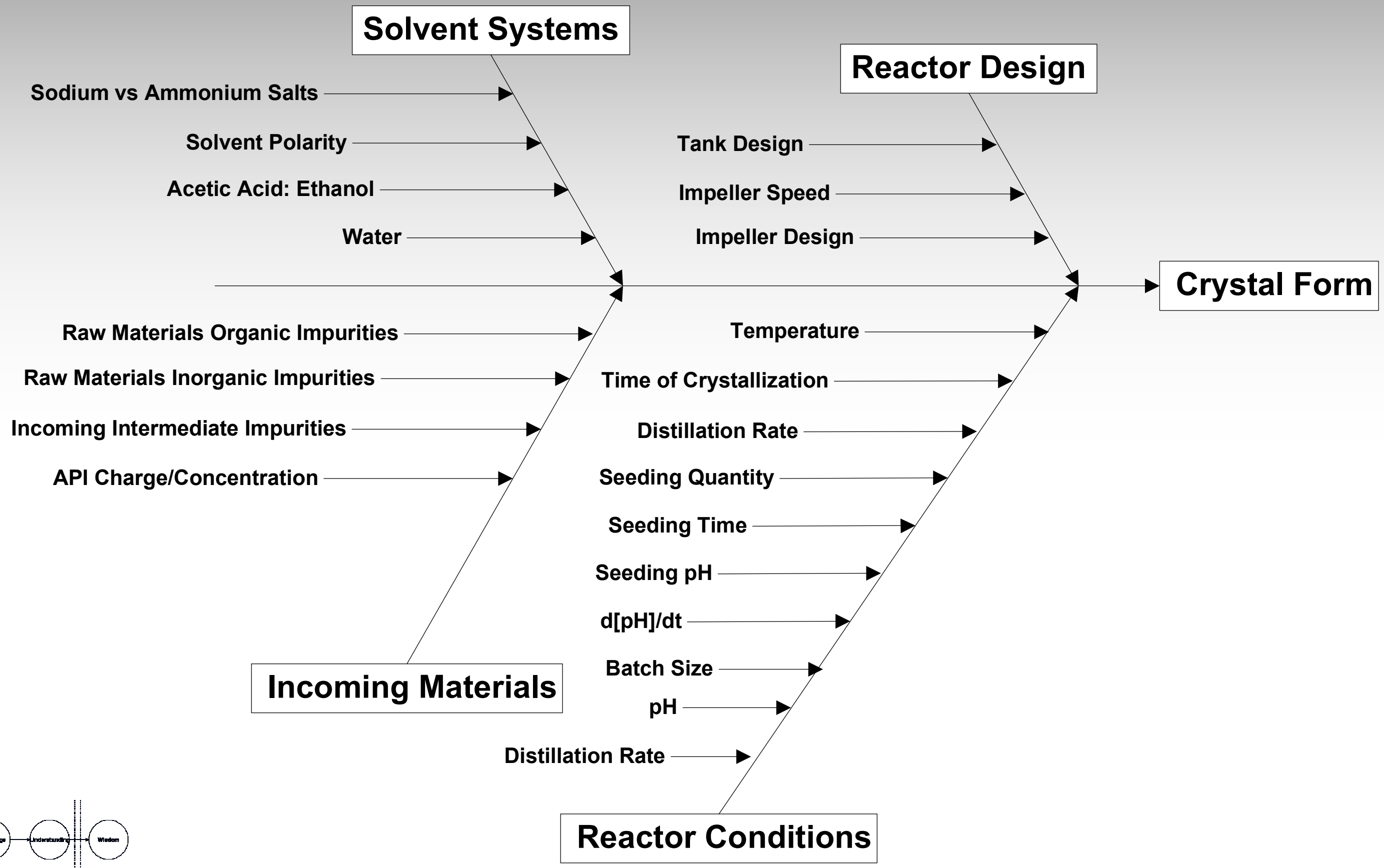
## Basic Process

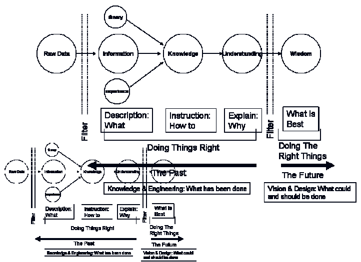


# API Particle Engineering: Control of API Polymorphic Form

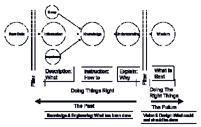
## Step 1. Identification of Potential Critical Variables



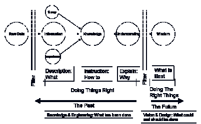
# API Particle Engineering:
# Control of API Polymorphic Form

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



# API Particle Engineering: Control of API Polymorphic Form

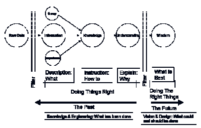
- **3. Initial Experimental Design**
  - Evaluated important, critical parameters
  - Set conditions for future experimentation
  - Developed preliminary models to determine initial manufacturing plant equipment requirements



# 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**

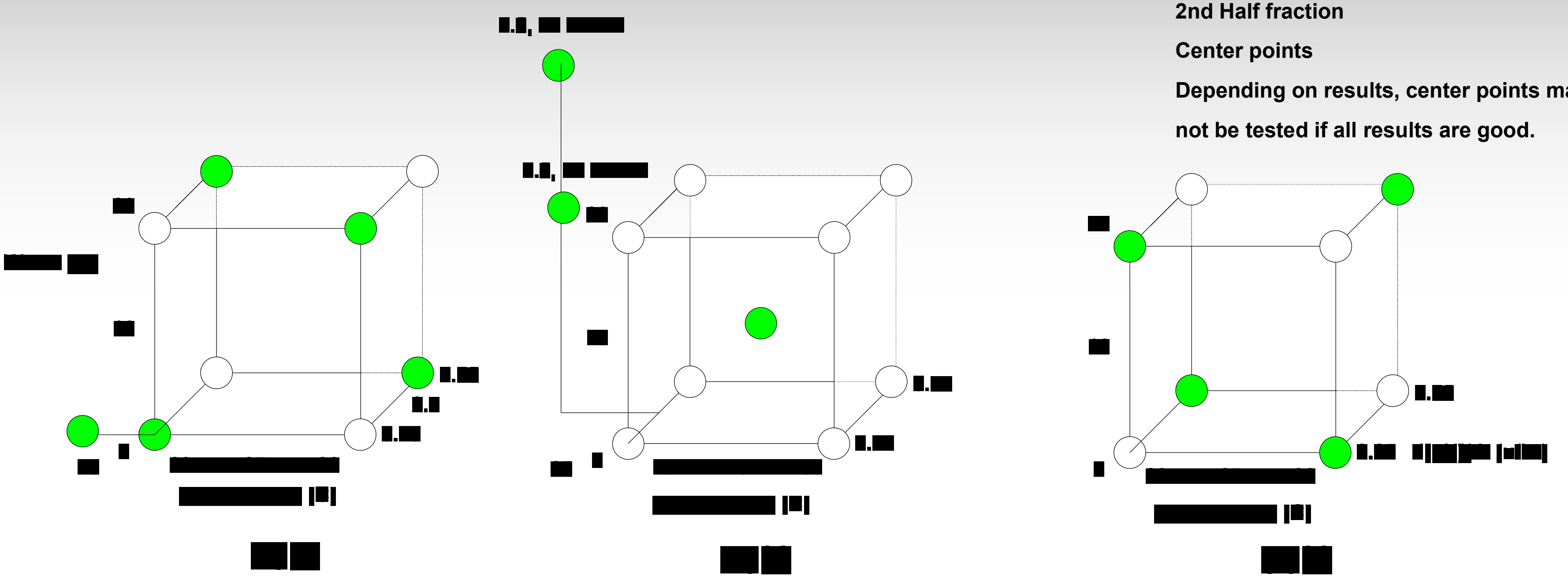
**Conducted in 3 Phases**

**1st Half fraction**

**2nd Half fraction**

**Center points**

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



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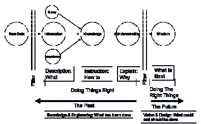

# API Particle Engineering:
# Control of API Polymorphic Form

## Step 4. Analysis of Data

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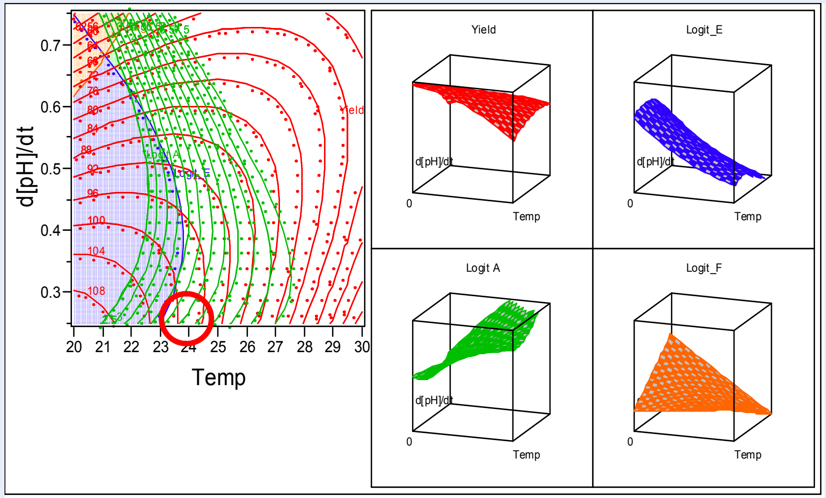
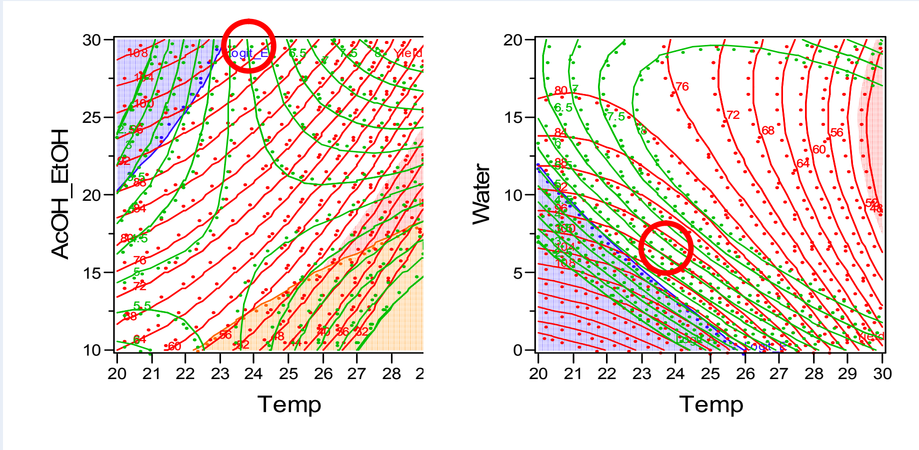
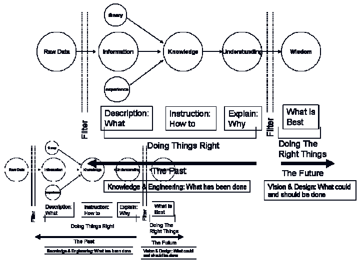
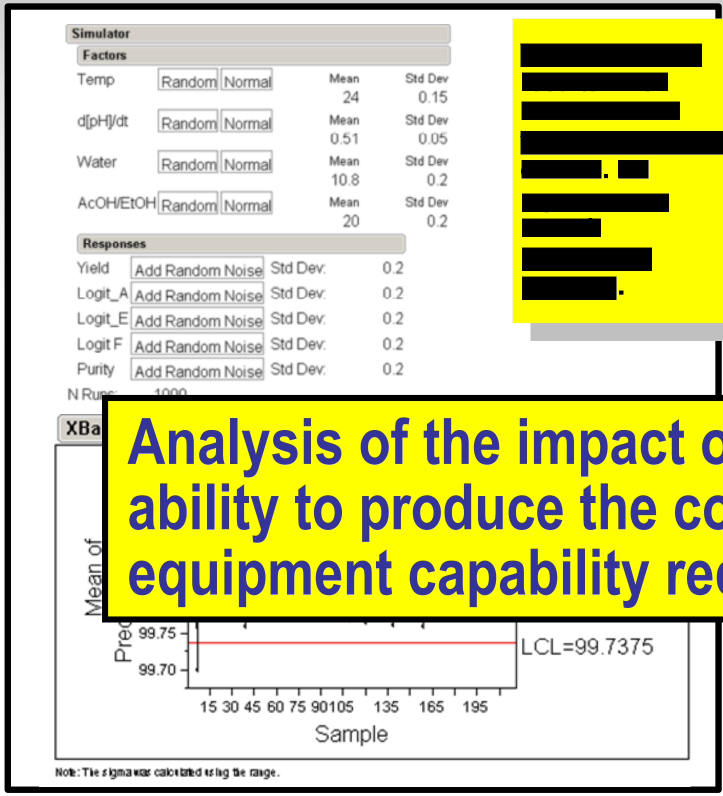


# API Particle Engineering: Control of API Polymorphic Form

## Step 5. Monte Carlo Simulations of Future Events

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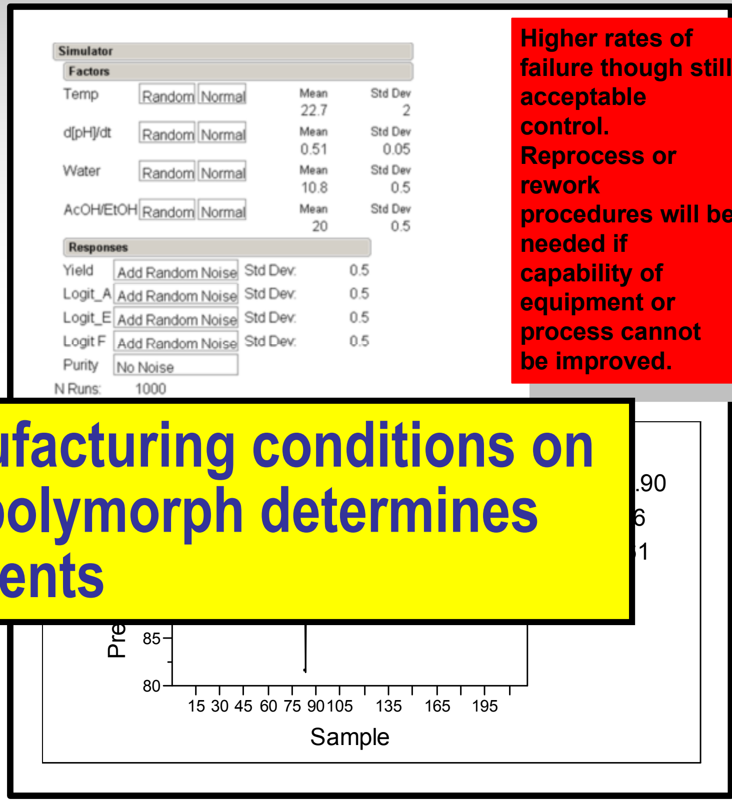
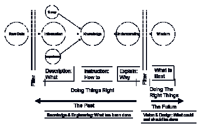



**Higher rates of failure though still acceptable control. Reprocess or rework procedures will be needed if capability of equipment or process cannot be improved.**

**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?