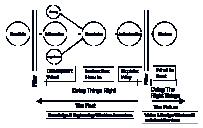
Drug Product

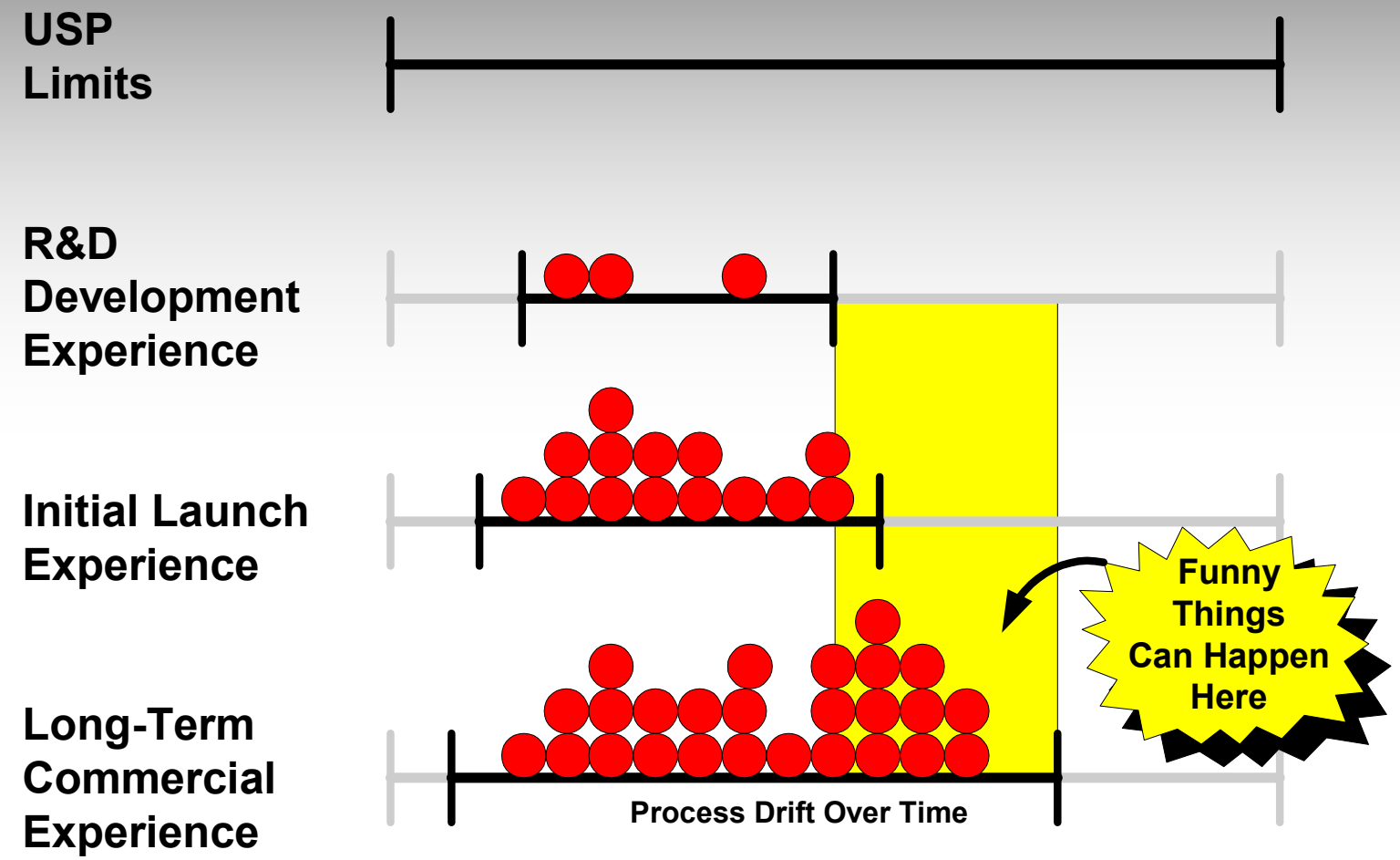
Raw Materials Design Space

- Usually very limited data available from R&D
- Difficult to obtain raw materials for R&D evaluation that have varying physicochemical properties
- Define which excipients are critical and why
- Characterize materials, as best possible
- Work extensively with vendors to source materials and investigate range of material properties (design space) as efficiently as possible (DOE if possible)
- Baseline/Characterize properties of raw materials so that commercial operations can evaluate any potential shifts



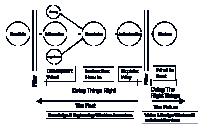
Range of Excipient Critical Properties Over Time

e.g. HPMC Wyeth Example Case Study #3



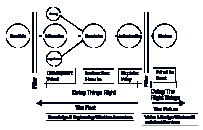
Case Study 1: Qualifying a 2nd Manufacturing Site

- Can we transfer this product to a 2nd manufacturing site?
  - Political
  - Financial
  - Reputation of Division/Department/Company
  - QbD principles applied



Use of DOEs During Site Transfer to Further Understand Manufacturing Behavior in Originating Site

- Site transfer of product initiated
  - "Standard" wet granulation process
  - Granulation process switched from Collette Gral 600L to Fielder 600L
  - All other process parameters were "the same"
  - Raw Materials "same"
- Objectives
  - Needed to optimize process for granulation endpoint
  - Nested experimental design for compressing studies

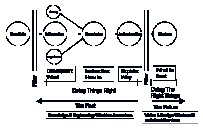


Granulation Design DOE

Run	Power (KW)	Water (kg)	Vacuum	Time (min)
1	20.5	37	On	≤ 3
2	22.5	36	Off	≤ 3
3	18.5	38	On	≤ 3
4	20.5	36	Off	≤ 3
5	22.5	37	On	≤ 3
6	18.5	37	Off	≤ 3
7	18.5	36	On	≤ 3
8	22.5	38	Off	≤ 3
9	20.5	37	On	≤ 3

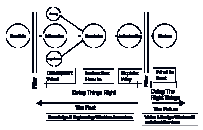
Political Variable

Run 1 and Run 9 are identical, to estimate “clean bowl effect”

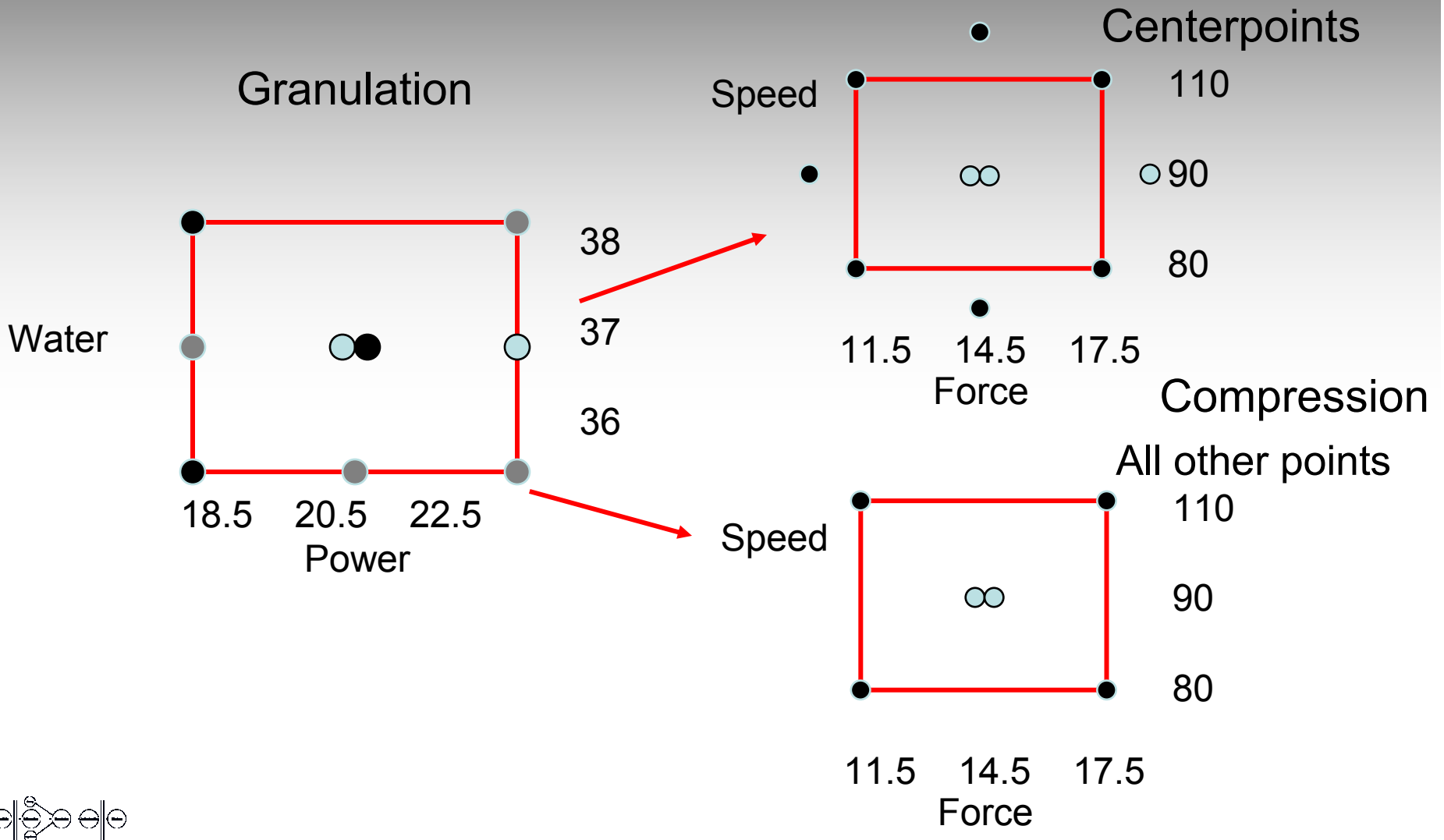


Compressing Study DOE

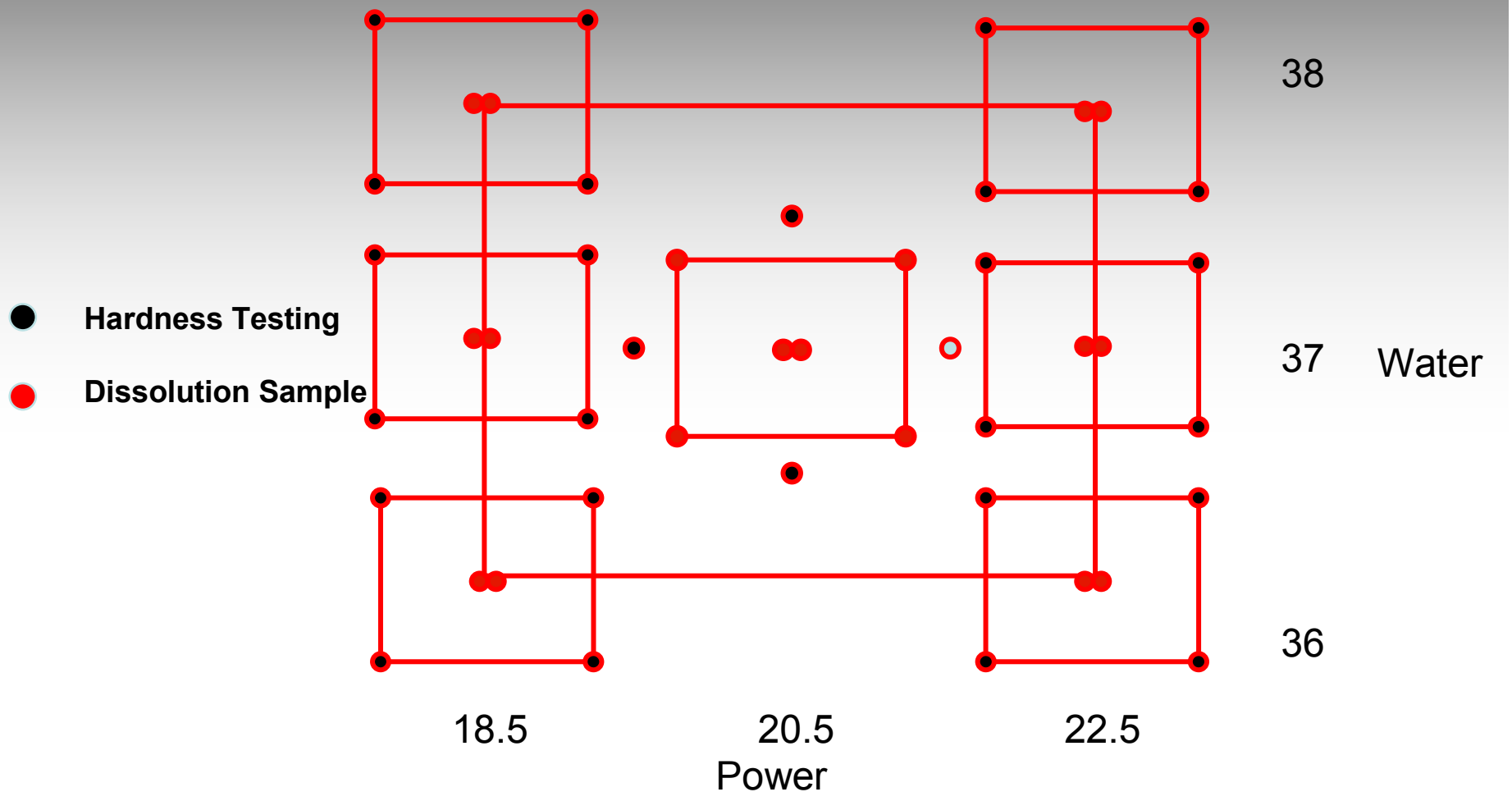
- Compressing study DOEs are nested in granulation study DOE.
- At the center runs of the granulation study (run 1 and run 9), central composite design (CCD) was used for the compressing study.
- For the other 7 granulation runs, minimum design should be used for the compressing study.
- Two compressing process variables
  - Compressing force: 11.5 ~ 17.5 kN
  - Press speed: 70,000 ~ 110,000 tph
- Central composite design with 2 center runs, total of 10 runs
- Minimum design 6 runs



Compressing Study DOE



Tablet Hardness & Dissolution Sampling (n=6)



Dissolution Model

- Full model:

  Release = Loading WC PC WC*PC WC^2 PC^2 FC SC FC*SC FC^2

  R^2 = 0.97

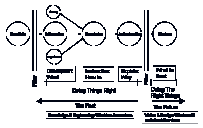
- Final model:

  Release = 68.36-1.35(Water-37)-1.464(Power-20.5)+2.44$(Water-37)^2$ –2.99(Force-14.5)

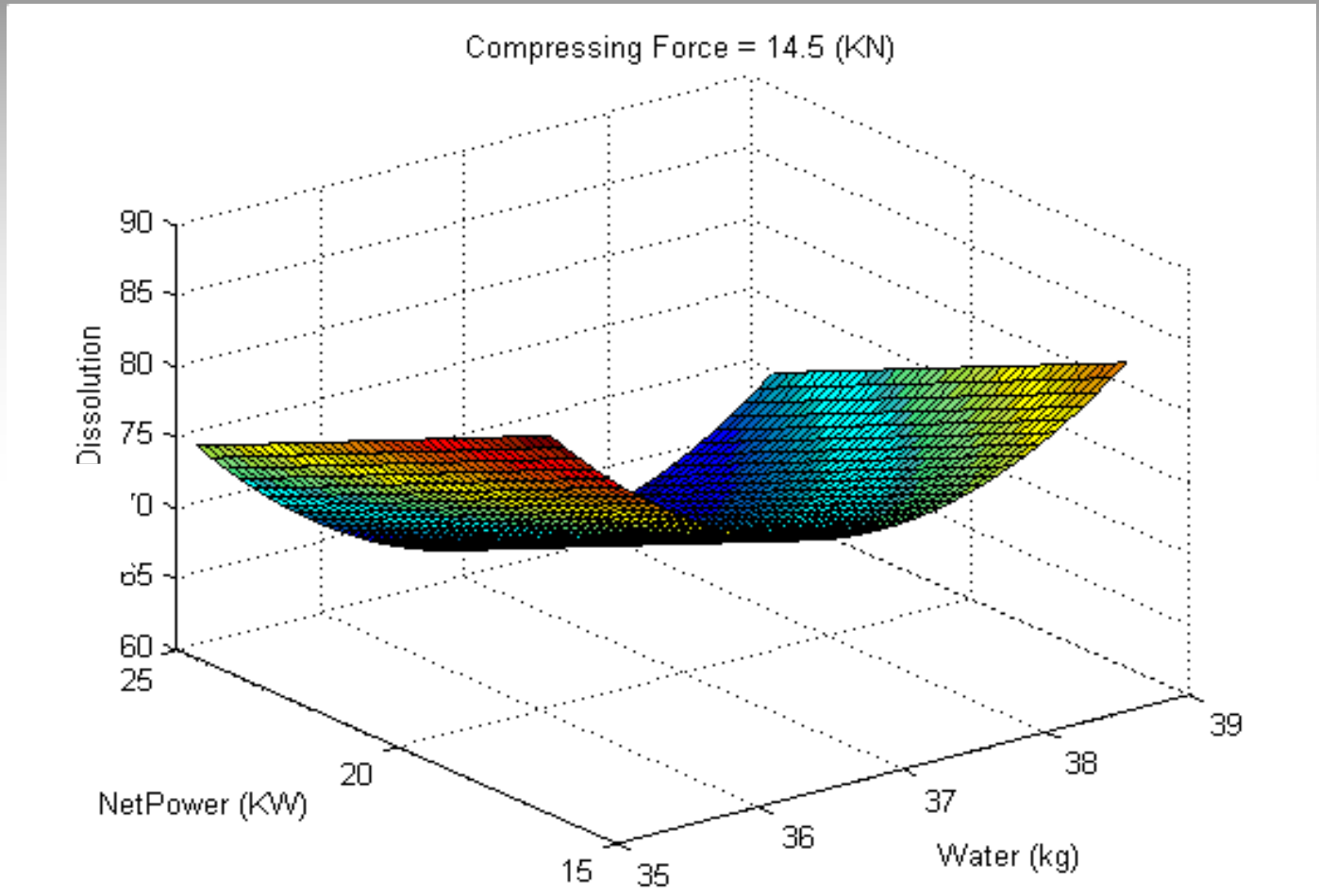
  R^2=0.91

  Water = 37.3 → Release minimum

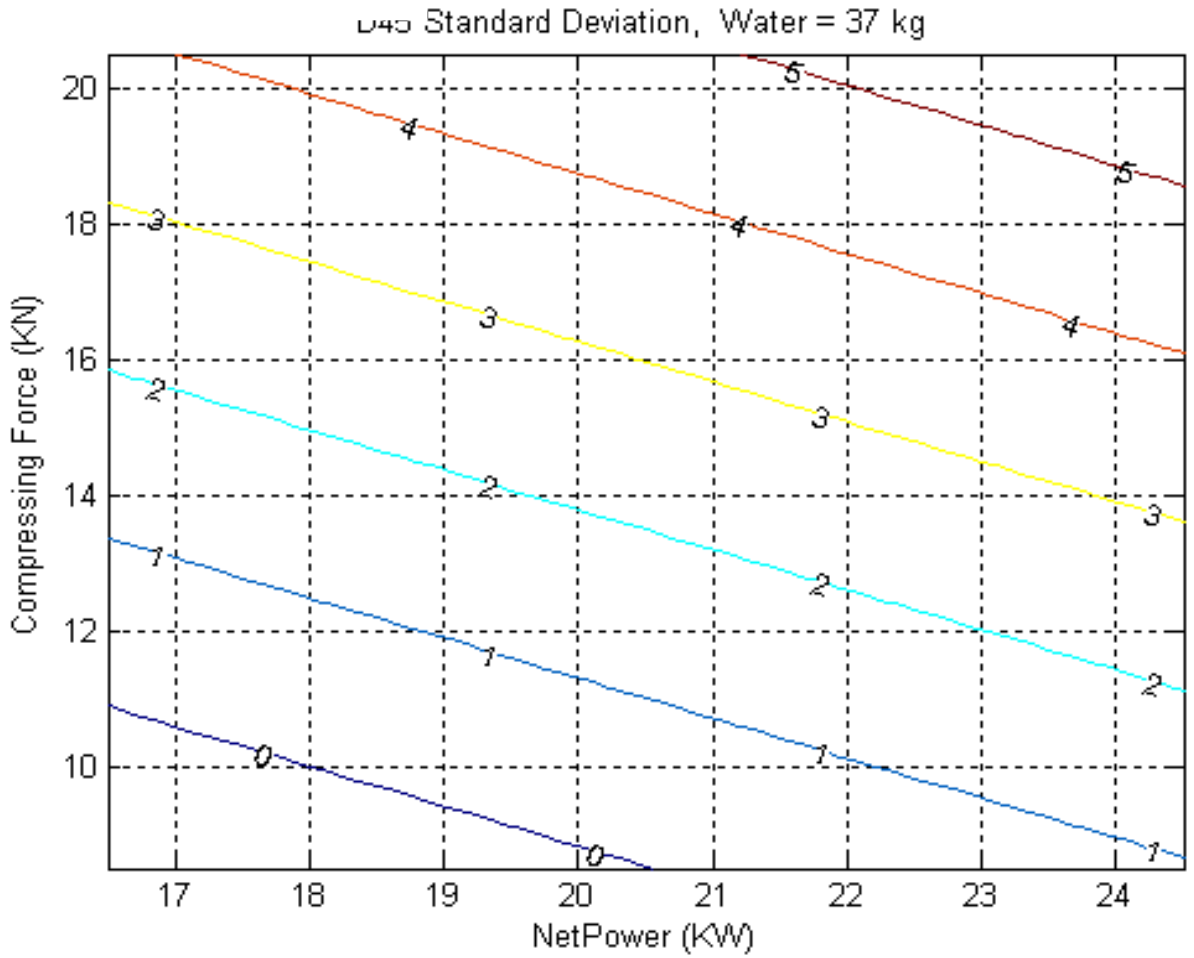
- Standard Deviation of Release Rate:
  - Release St Dev = 2.41+0.50(Water-37)+0.24(Power-20.5)-0.34(Water-37)*(Power-20.5)+0.43(Force-14.5)
  - R^2 = 0.69
  - All linear effects



Response Surface of Dissolution Rate vs Granulating Power and Water Quantity

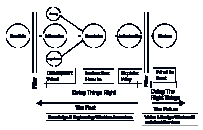


Release Rate Standard Deviation

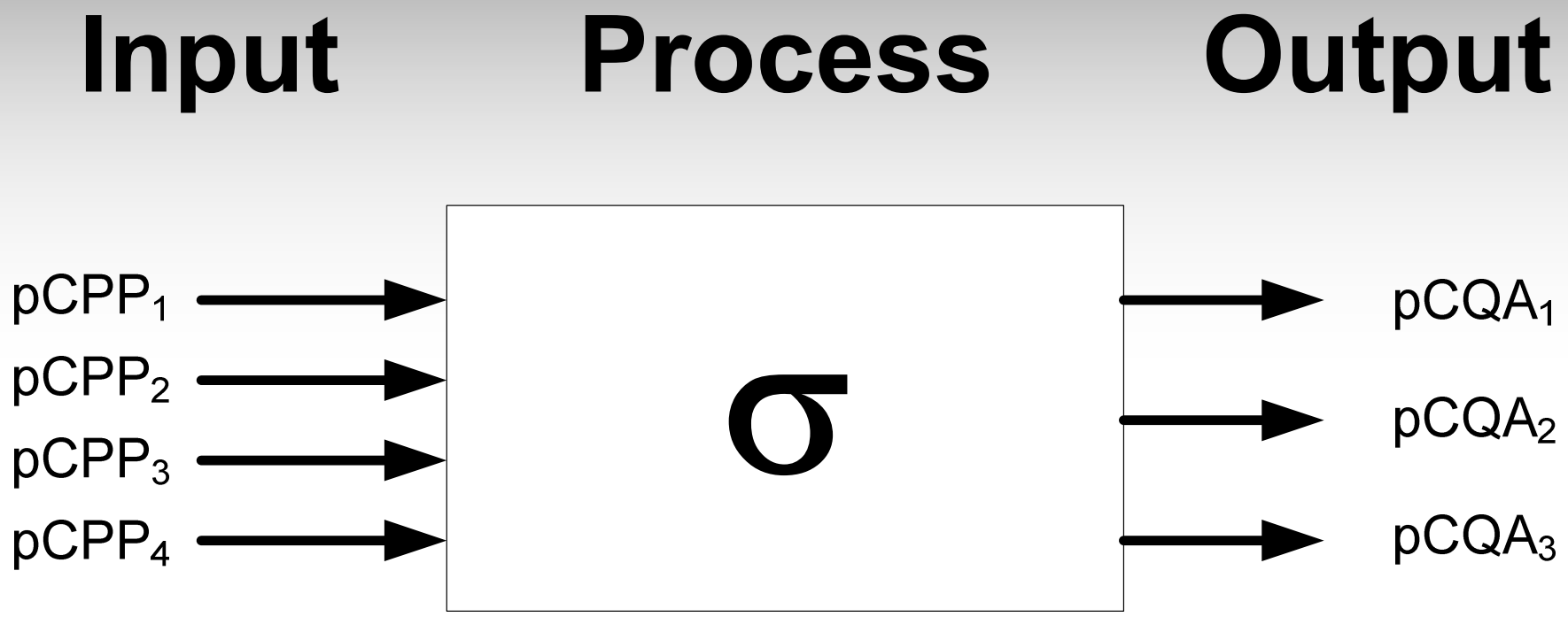


Case Study #2

- Process Overview
  - Fluid-Bed Granulation Process
    - Granulate
    - Dry
  - Mill Dried Granules
  - Blend
  - Compress
- Input Parameters
  - Incoming Raw Materials
    - Particle size fraction >355 μm
  - Blending Time
  - Tableting
    - Compression Force
    - Press Speed



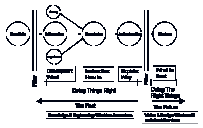
Design of Experiments



Design of Experiments
Outcomes of Experimentation

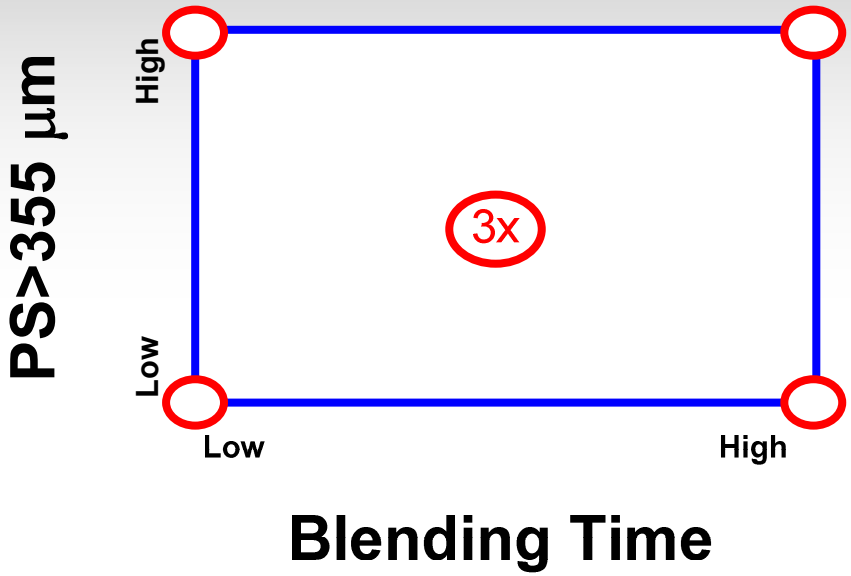
Design of Experiments
SIPOC

Input	Process	Output
PS >355 mm	Granulation	
	Milling	Particle Size (Sieve)
Blending Time	Blending	
Compression Force Press Speed	Compressing	Tablet Hardness Dissolution Friability Content Uniformity



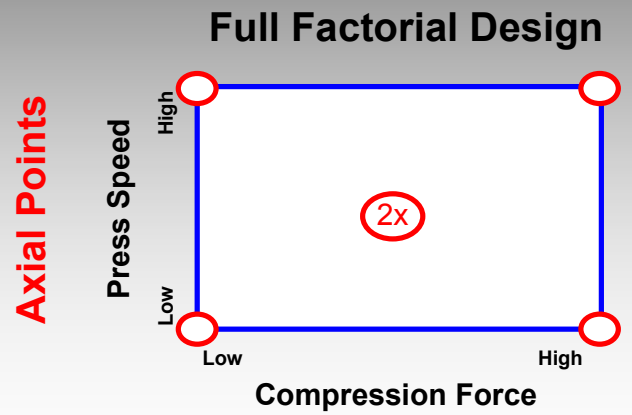
Design of Experiments
Granulations

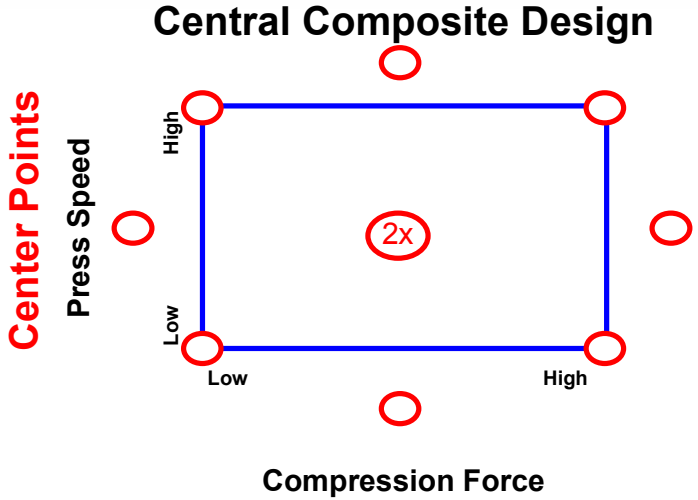
- 7 Granulations Manufactured
  - Full-Factorial Design
  - Three replicated centerpoints



Design of Experiments
Compression Phase

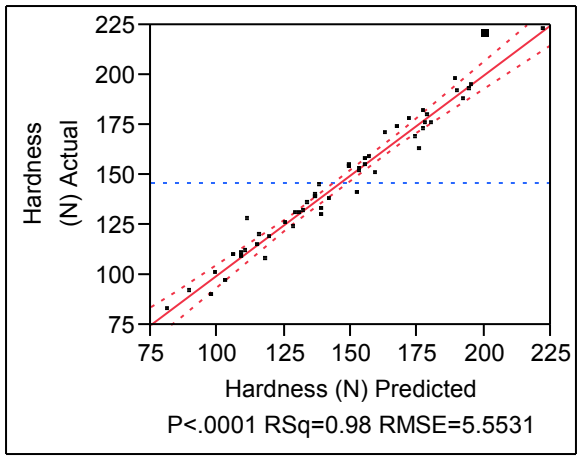
- Full Factorial for All Four Granulation Axial Points
- Central Composite Design for All Three Centerpoints





Analysis
Impact on Tablet Hardness & Friability (Traditional Analysis)

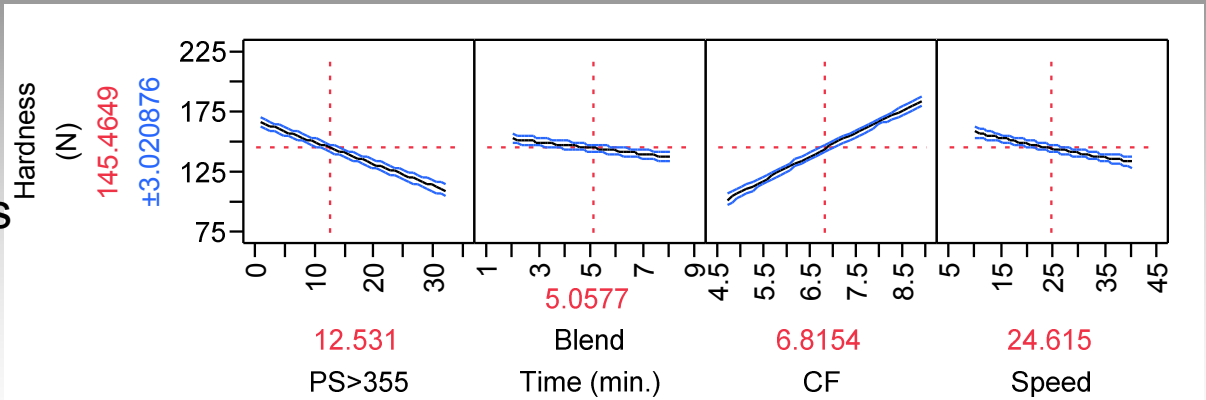
- Good model developed
  - 2 outlier points
  - R^2=0.98
- Statistically Significant Parameters
  - Compression Force (CF)
  - PS>355μm (PS)
  - Press Speed (RPM)
  - Blend Time (BT)
  - PS*BT
  - PS*CF



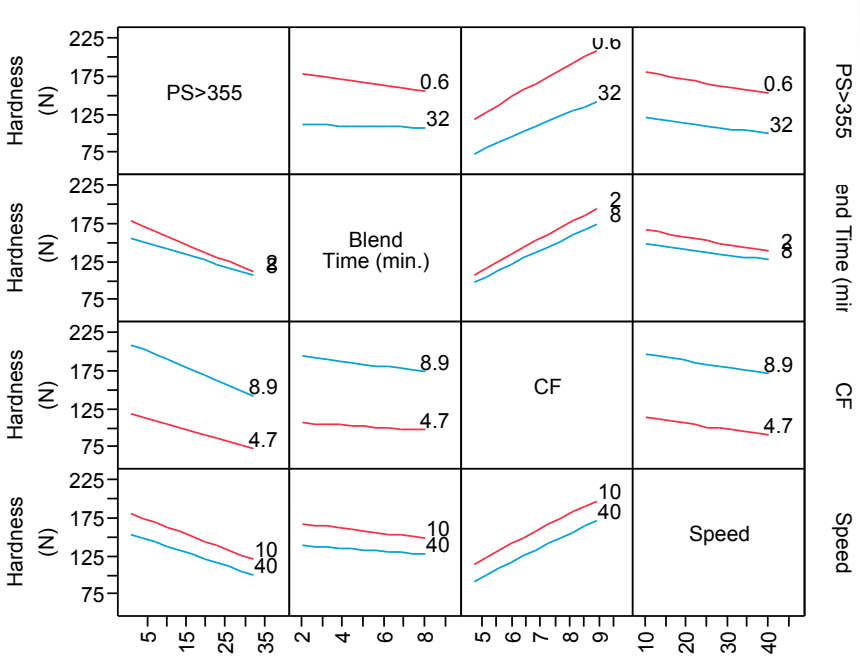
There was no change in friability
Therefore entire design space is within the Proven Acceptable Range

Analysis
Main Effects & Interaction Plots

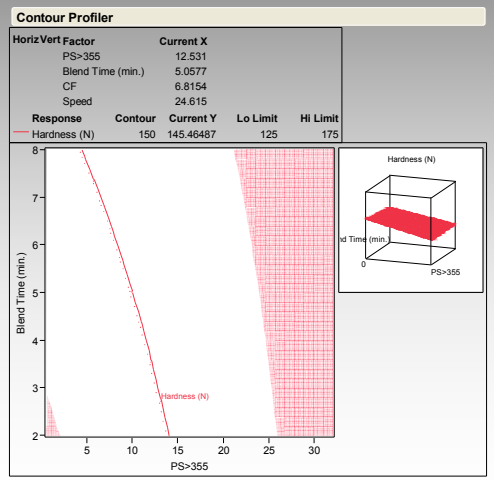
Main Effects

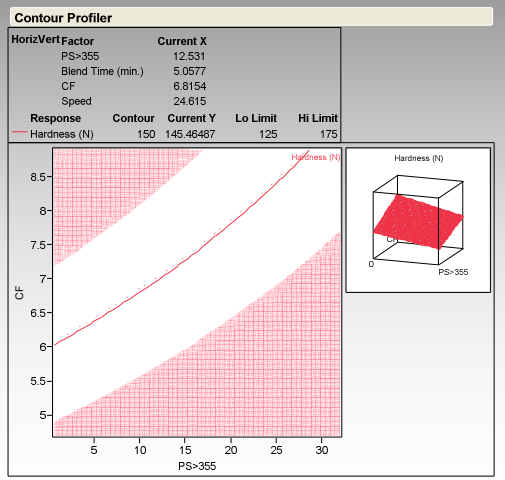


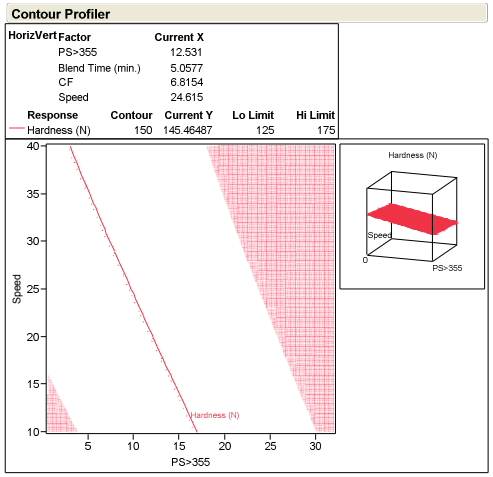
Interaction Effects

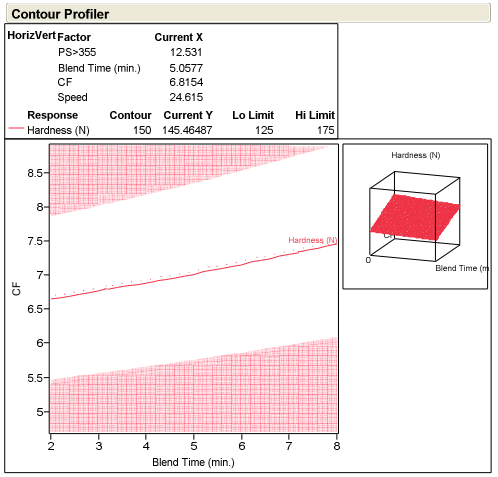


Analysis
Contour Plots





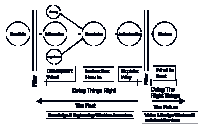




Concluding Remarks

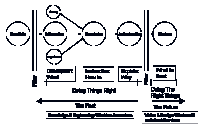
Additional Industry Pressures in 2009

- Significantly reduced pipeline throughput
- Biotech options significantly below expectation
- Driving significantly more complex line extensions
- Resulting in higher risk
- Increased generic competition
- Dramatic increase in counterfeiting
- Major patent expiry cash flow issues
- No significant reduction in the cost of quality
- Are current business and regulatory models sustainable?

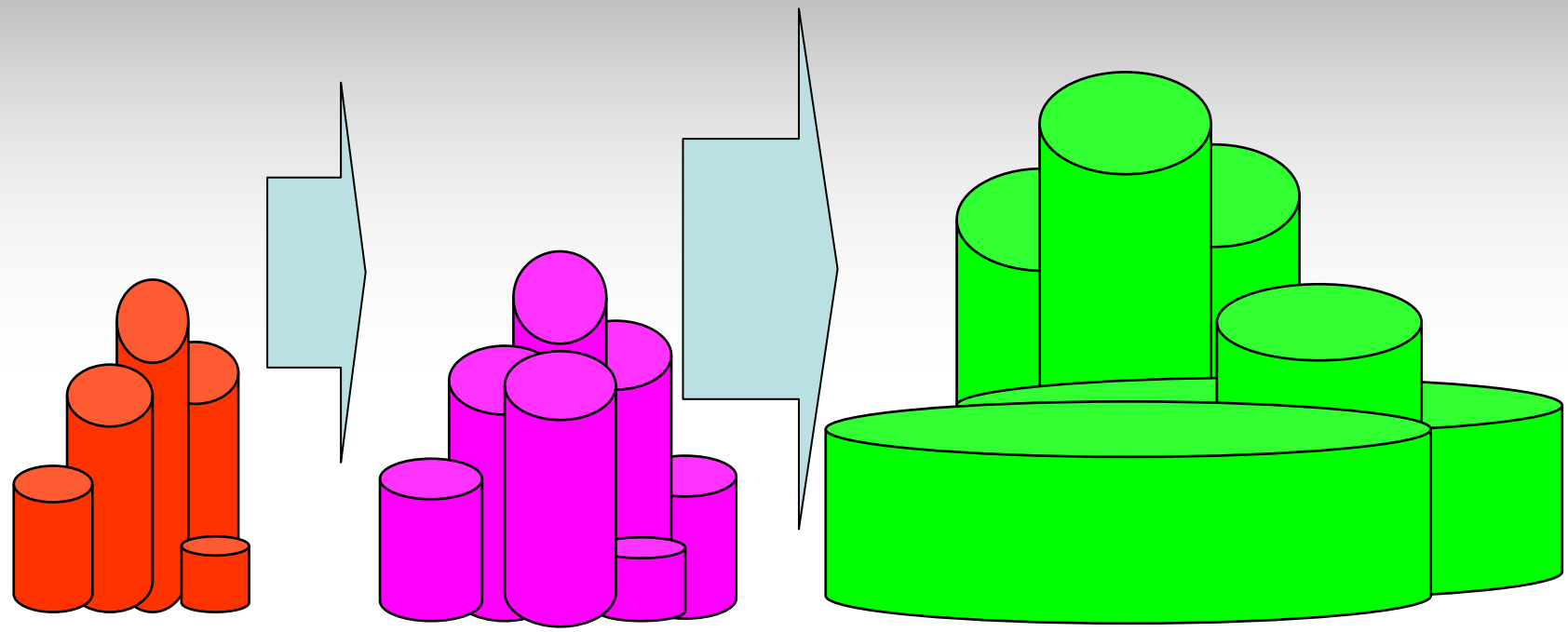


Today's Environment and Challenges

- Far more intimidating
- Expanding patient expectation and cost awareness
- Globalisation
- Must understand the linkage between process and product specifications and therapeutic performance
- Question the relevance of current manufacturing assets
- Need to establish a continuum between Research, Development and Manufacture to facilitate cost effective technology transfer
- Need to bridge the physical gap between API and Formulated product using particle engineering
- Continuous processing of API's and Drug Product are both on the agenda
- Downsizing and Outsourcing
- Far bigger challenges and opportunities

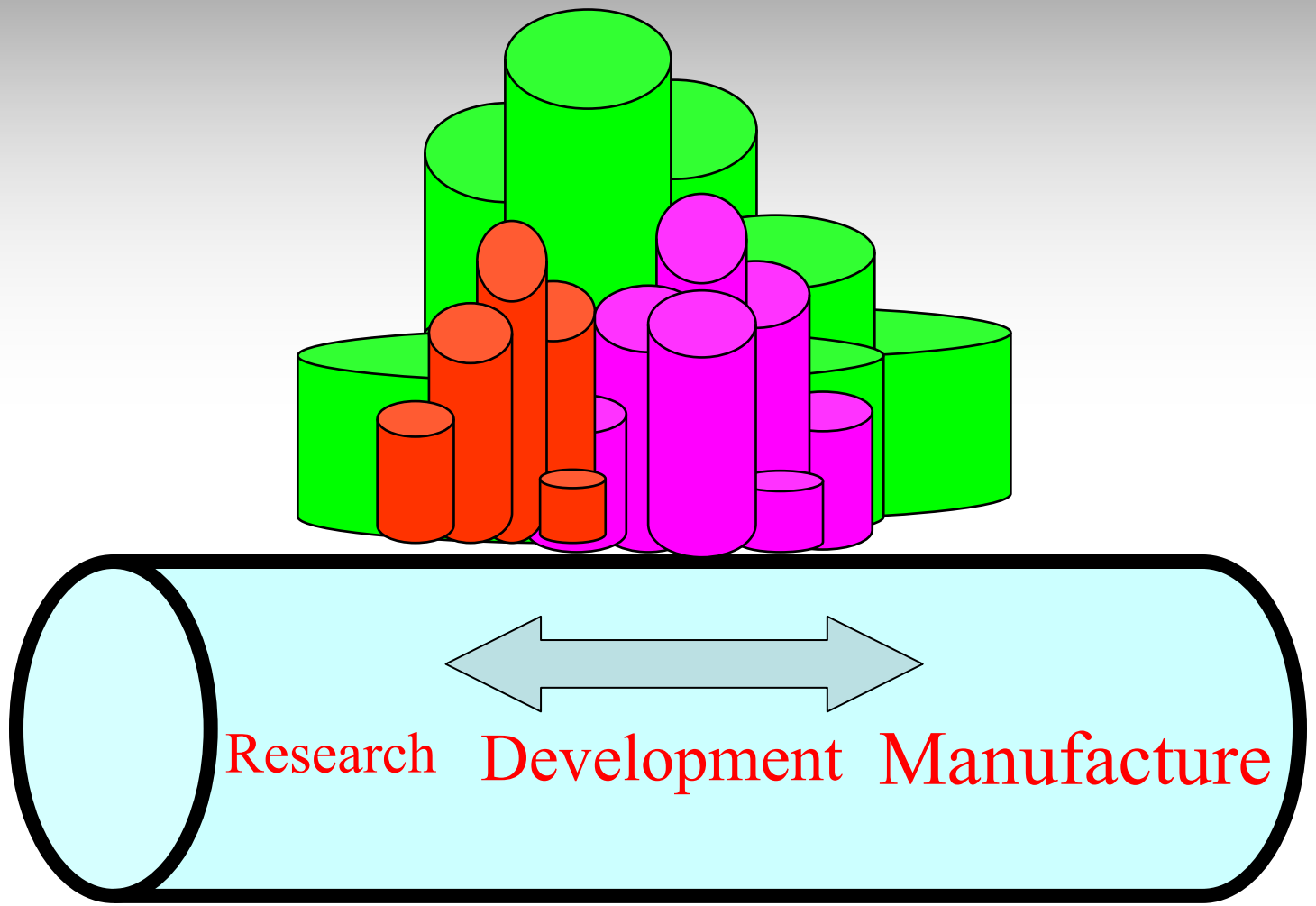


The Silo Business Model



Research Development Manufacture

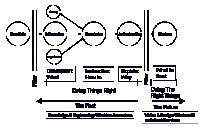
The Desired Business Model



Don't Underestimate the Cultural Issues

Why Transforming Efforts Fail?

- Not establishing a great enough sense of urgency
- Not creating a powerful enough guiding coalition
- Lacking a vision
- Under communicating the vision by a factor of ten
- Not removing obstacles to the new vision
- Not systematically planning for and creating short-term wins
- Declaring victory too soon
- Not anchoring changes in the corporation's culture



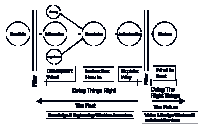
Leading Change by John Kotter

“In theory there is no difference between theory and practice.”

“But in practice there is!”

Jan L.A van de Snepscheut

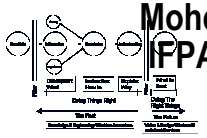
Courtesy Ken Lieper



Quality by Design

QbD is:

- Scientific, risk-based, holistic and proactive approach to pharmaceutical development
- Deliberate design effort from product conception through commercialization
- Full understanding of how product attributes and process relate to product performance (safety, efficacy)



Moheb Nasr, "FDA's Pharmaceutical Quality Initiative," IFPAC 2007, Baltimore, MD (USA)


Thank
You!