Six Sigma in BioPharma

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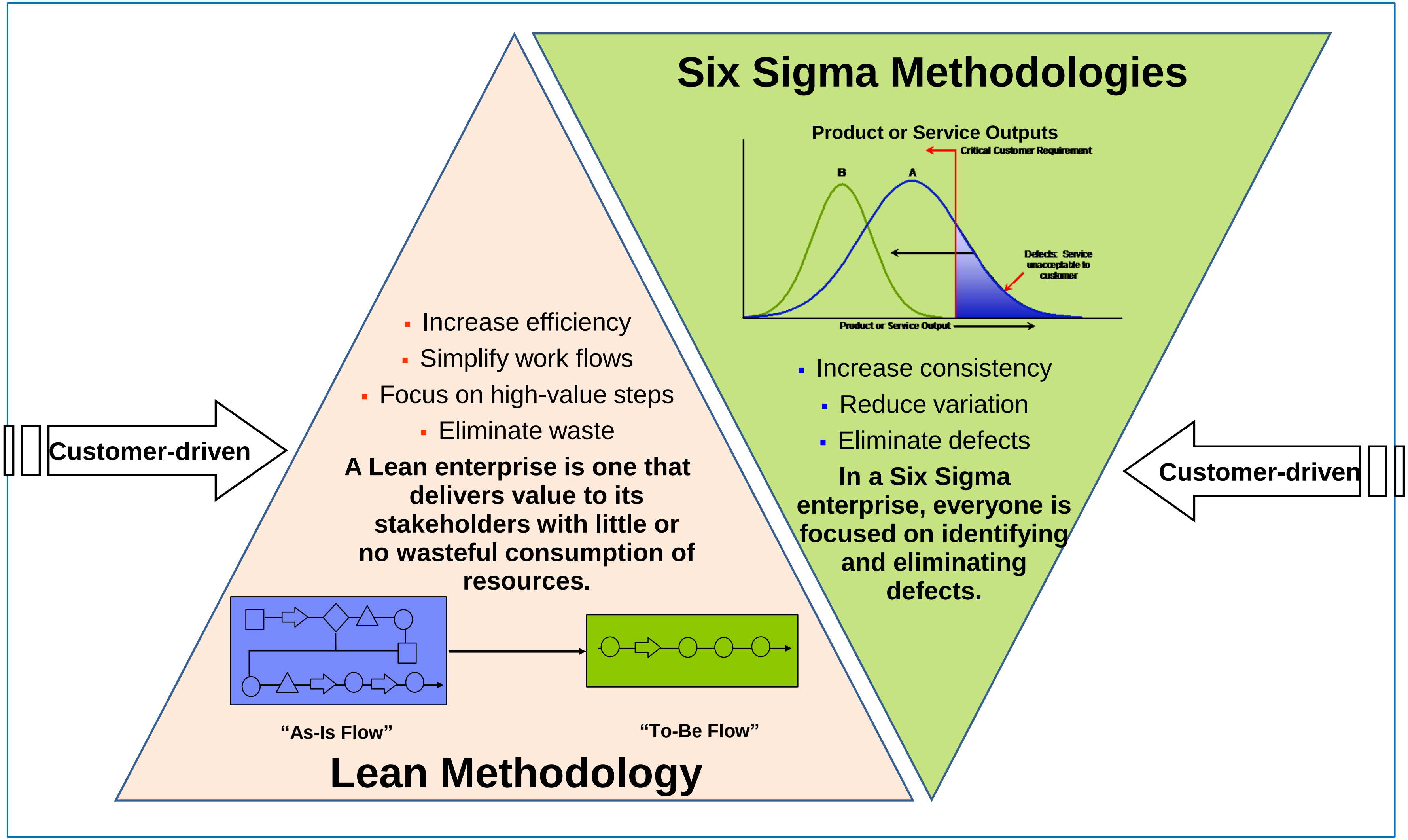
Agenda

- Introduction to Six Sigma
- Categorizing Six Sigma Techniques
- Take-Away

Lean and Six Sigma



Introduction to Six Sigma

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Introduction to Six Sigma

- Sigma (σ) – Standard deviation

Philosophy

- Control the process, control the output
- Y = f(Xs)

Methodology

- DMAIC
- DMADV
- DFSS

Metrics

- 3.4 DPMO
- C_p, C_{pk}

Set of Tools

- Control charts
- FMEA
- DOEs
- Etc.

Variation & Defect Reduction →

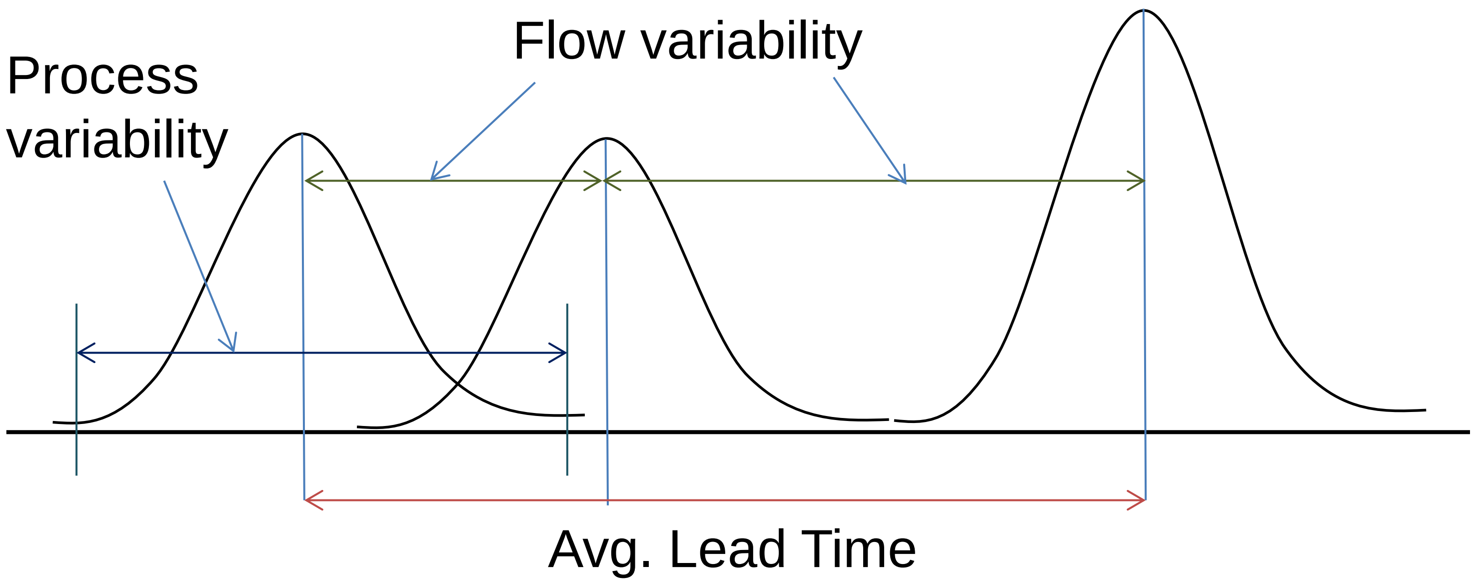
Kubiak and Benbow, 2009

Introduction to Six Sigma (cont'd)

- Types of variability
  - Temporal
  - Material
  - Measurement
  - Spatial
  - Behavior

Introduction to Six Sigma (cont'd)

- Process variability vs. flow variability



Introduction to Six Sigma (cont'd)

- Increased variability increases effective cycle time

$$CT_e = V \times U \times T_p + \sum T_o$$

- Higher variability degrades system performance

$$WIP = TH \times CT_e$$

- Systems with variability have to be buffered (Hopp and Spearman, 2011)
  - Time
  - Capacity
  - Inventory

Categorizing Six Sigma Techniques

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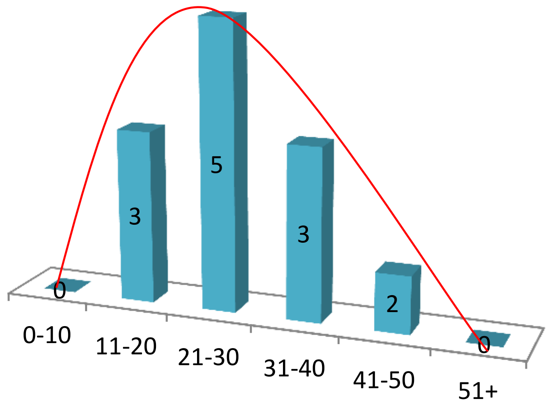
Six Sigma Techniques

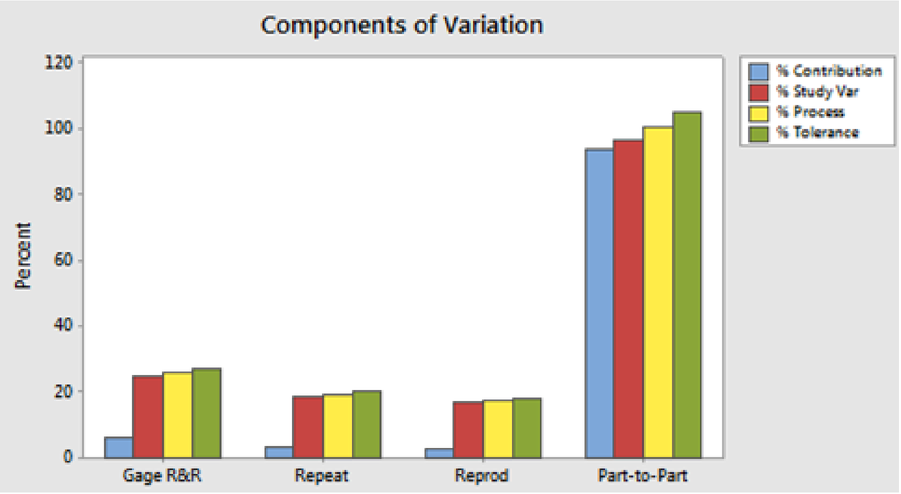
- Six Sigma techniques can enable various degrees of understanding variability at following levels:
  - Descriptive
  - Quantifying / Predictive
  - Control
  - Behavioral

Descriptive Techniques

- Histogram
- Stem & Leaf plot
- Box plots
- Gage R&R
- Etc.

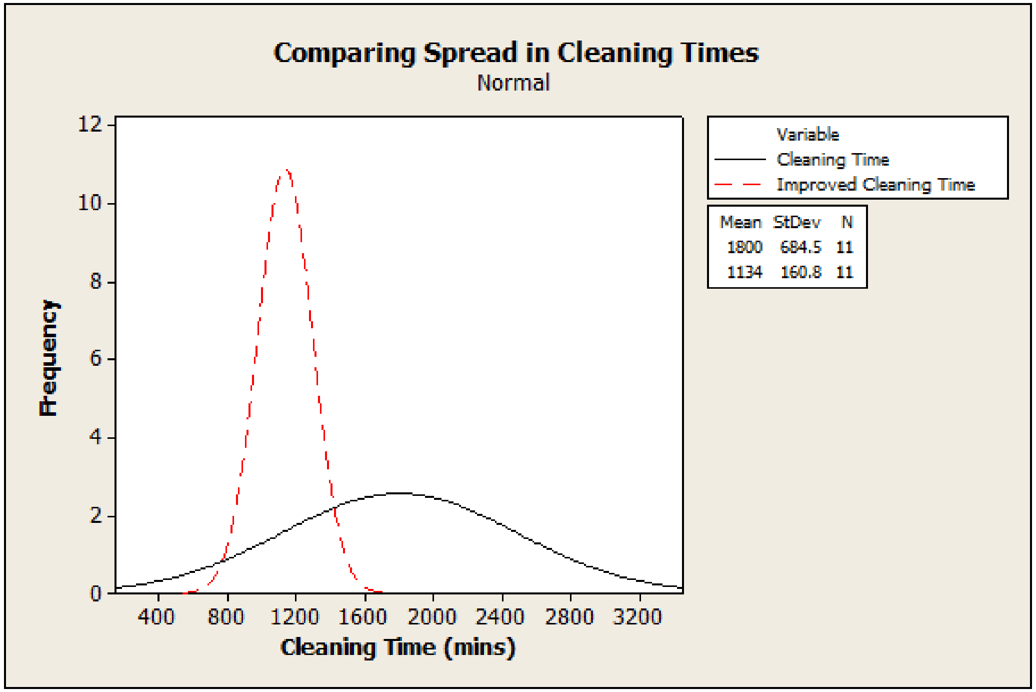


Stem	Leaf
1	2, 3, 7
2	1, 3, 3, 4, 7
3	0, 3, 9
4	5, 6
5	0



Case Study – Descriptive Techniques

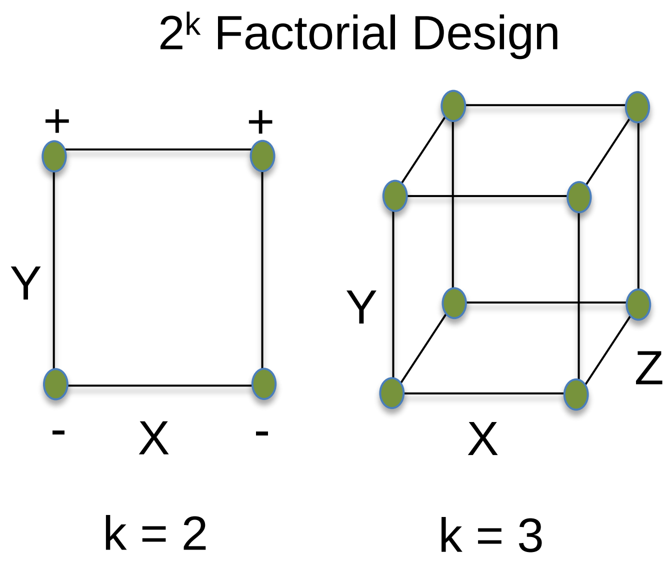
- Lengthy and highly variable changeover time impacted throughput

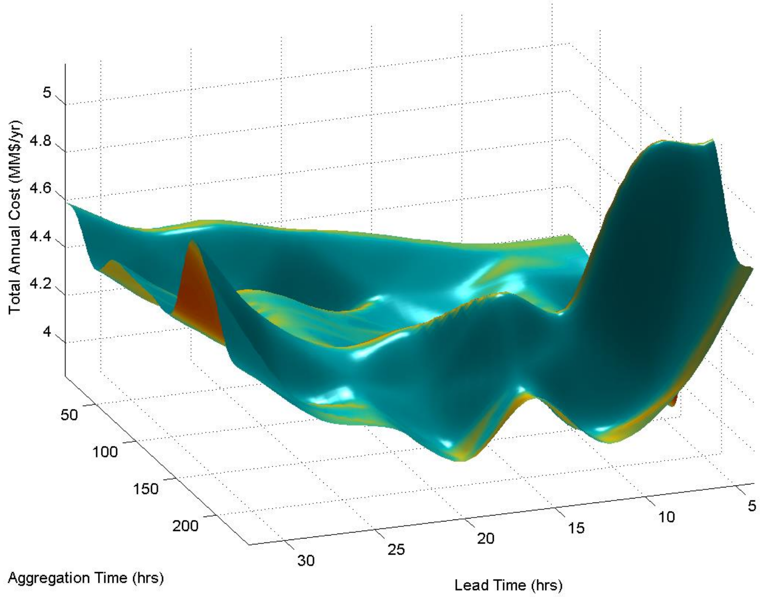


- 35% reduction in changeover times

Quantifying / Predictive Techniques

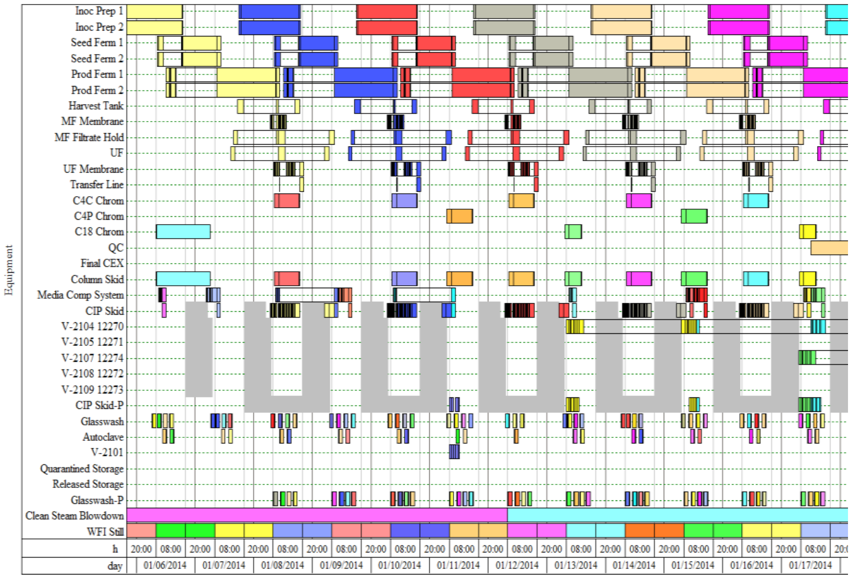
- Design of Experiments
- Simulations
- Statistical and Probabilistic approaches



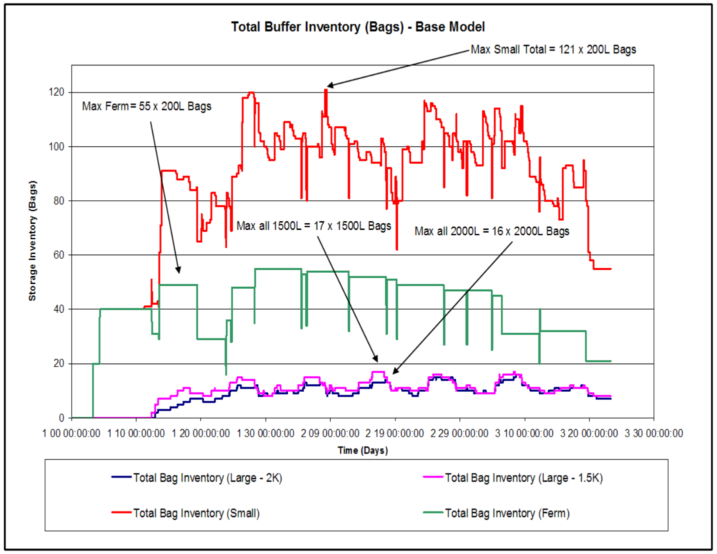


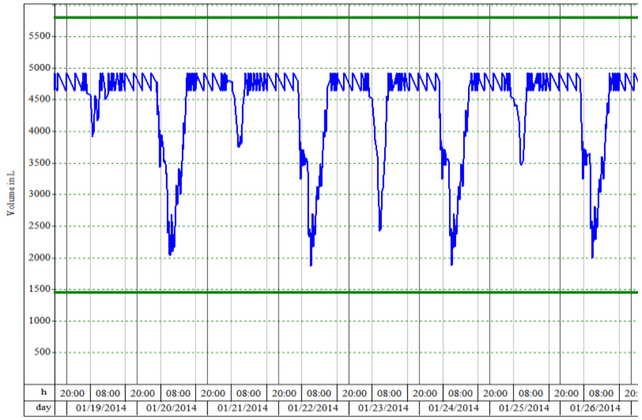
Typical Process Simulation Outputs

Feasible Schedule



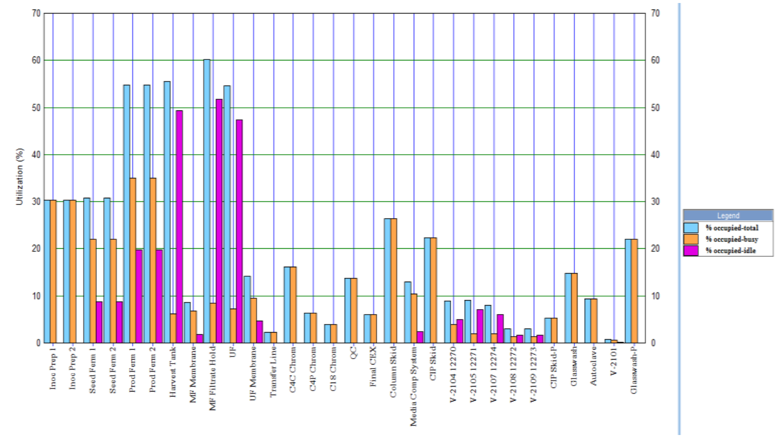
Inventory Sizing





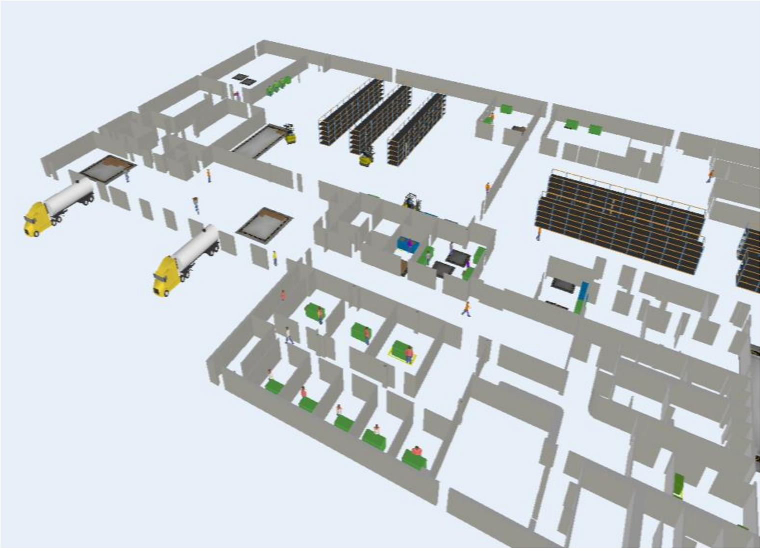
Utilities Consumption

Equipment Utilization

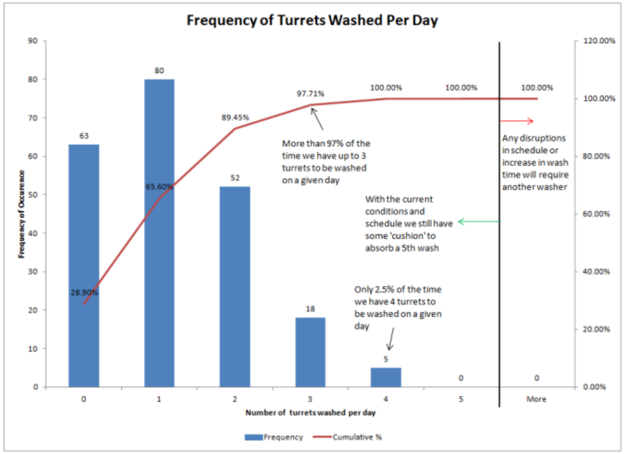


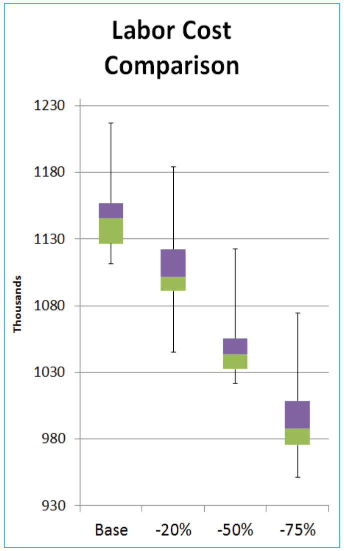
Typical DES Outputs

DES Model Snapshot

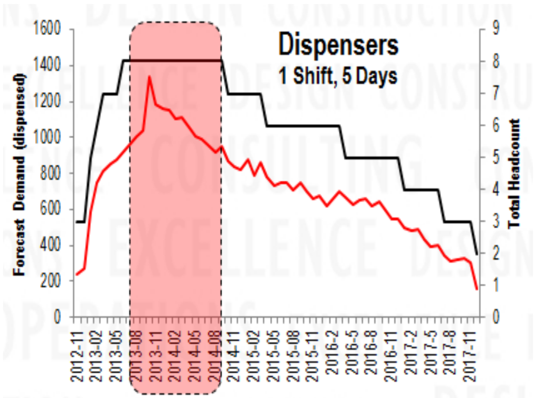


Pareto Analysis to Understand Utilization

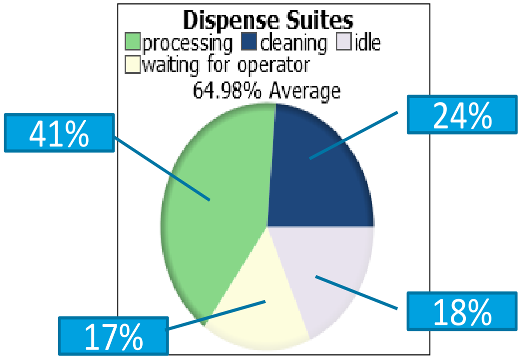


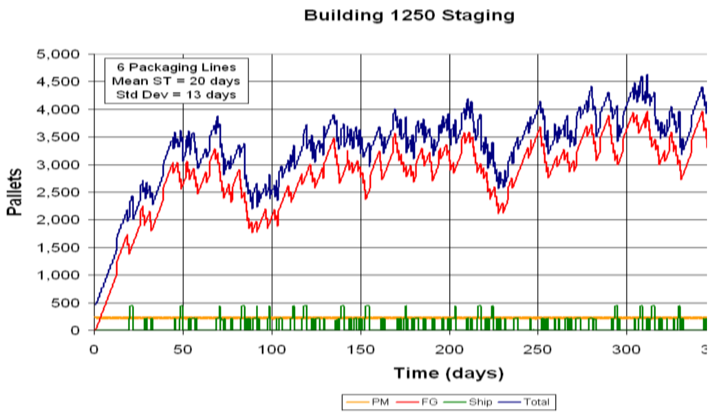


Headcount Requirements for Changing Demands



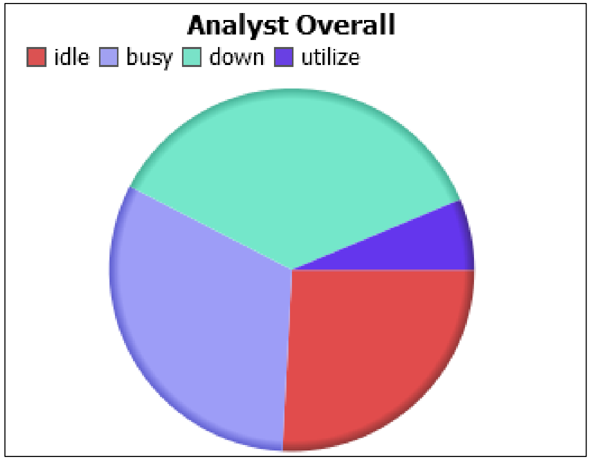
Utilization Charts Capturing Different States



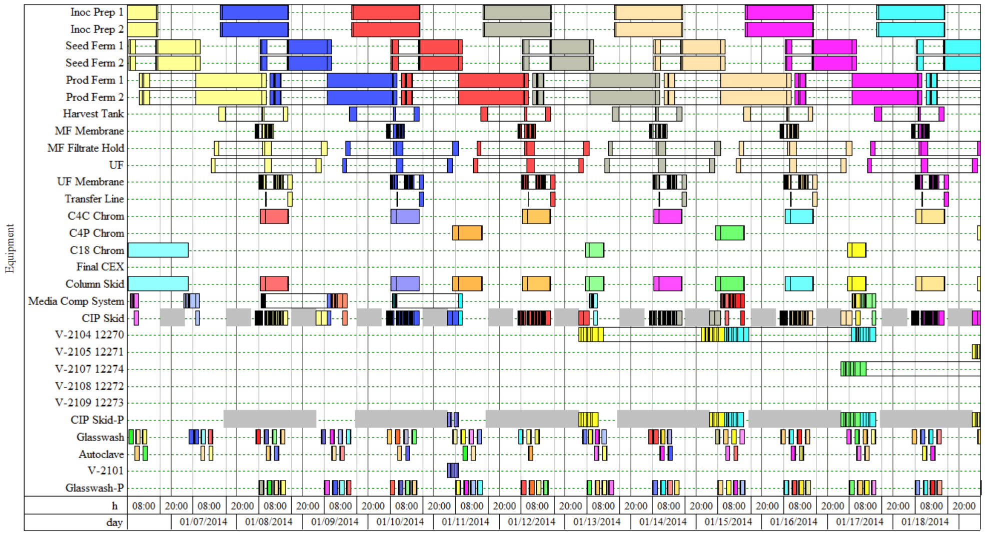


Case Study 1 – Quantifying Techniques

- Given the constraints, recommend strategies to improve efficiency and throughput
- Increase in throughput
  - Manufacturing (# Batches) by 60%
  - QC Labs (# Tests) by 43%

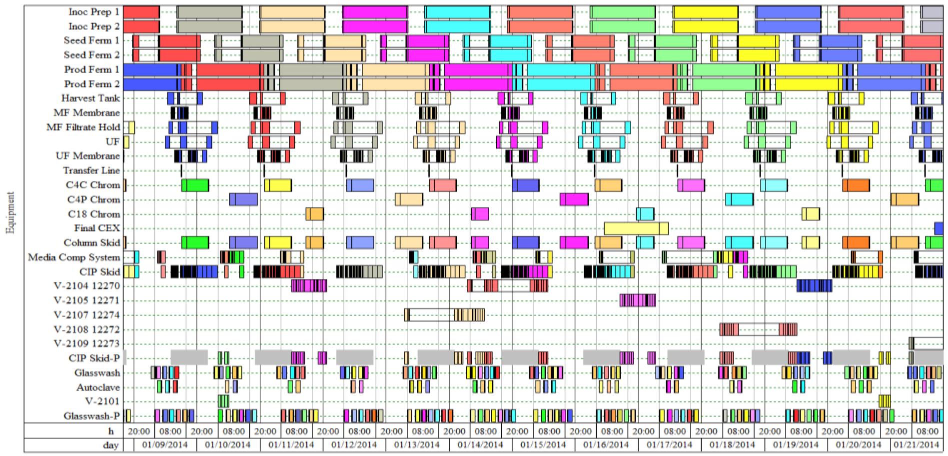


Case Study 1 – Quantifying Techniques



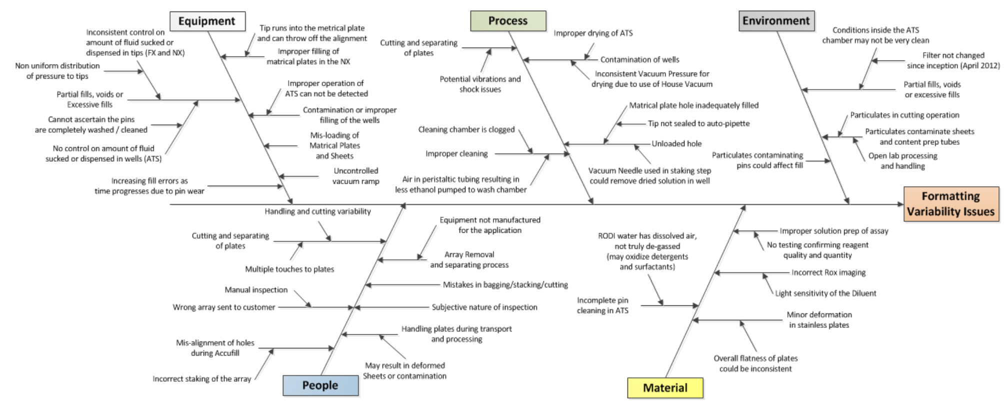
Scenario – Base case

Scenario – Increased throughput

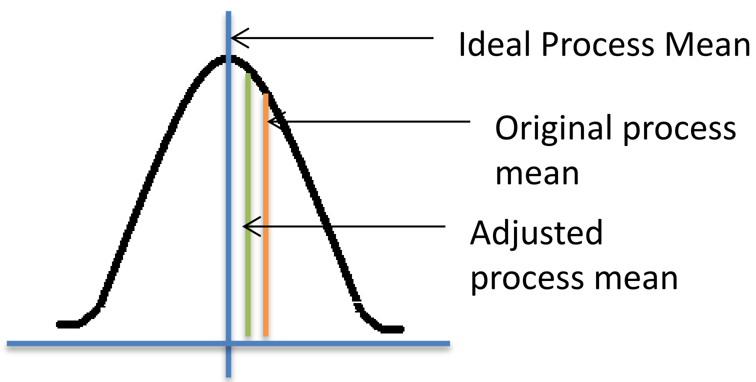


Case Study 2 – Predictive Techniques

- Identify variability inducing processes affecting quality of finished product
- Predictive model
  - Capture probability of conformance
  - Helped readjust process mean and develop sampling plan

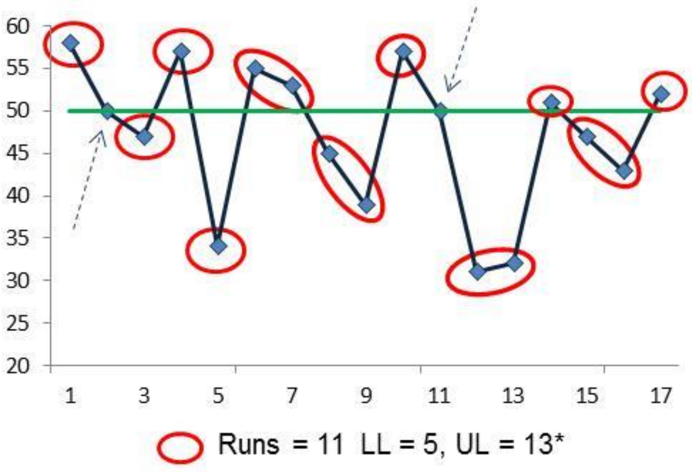


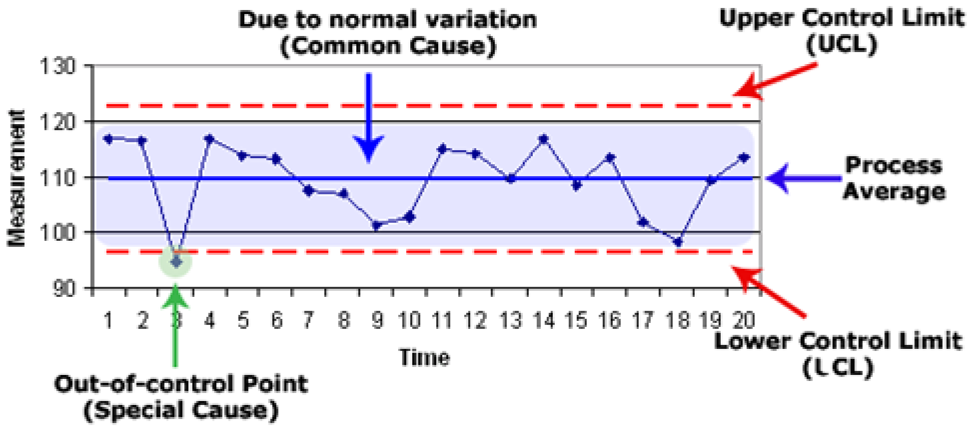
$$P\{a \le x \le b\} = \Phi\left(\frac{b-\mu}{\sigma}\right) - \Phi\left(\frac{a-\mu}{\sigma}\right)$$



Control Techniques

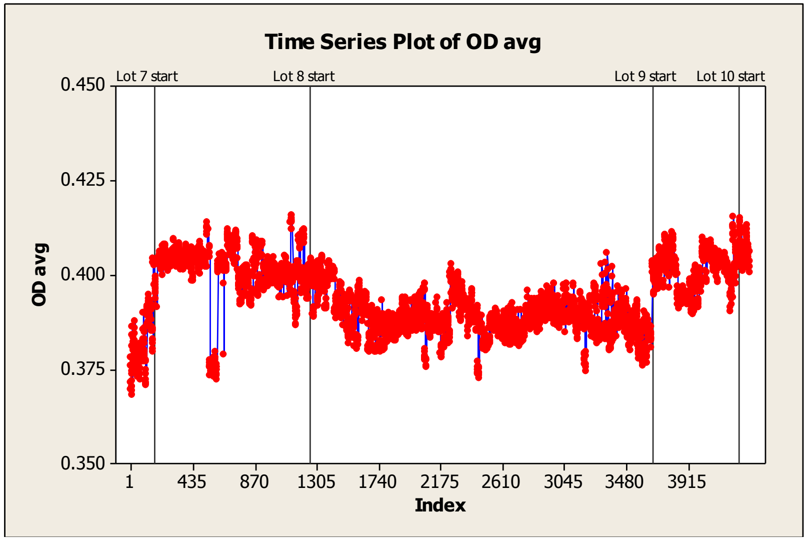
- Process monitoring and control charts
- Process capability indices

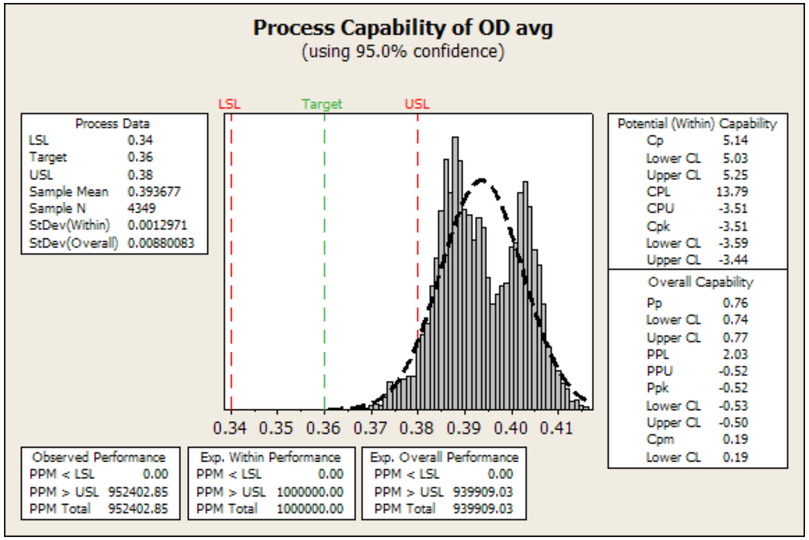




Case Study – Control Techniques

- High fallout rate observed when raw material lot changed
- Raw material variability suspected
- Control charting to understand between lots OD variation
- Poor process capability revealed
- Adjustments initiated at supplier's end





Behavioral Techniques

- Behavior characteristics
  - Behavior is an erratic, dynamic, continuous phenomenon
  - Behavioral variability is a result of intrinsic / extrinsic environmental influence
  - Individual’s behavior may (or may not) be different than the group’s behavior

Behavioral Techniques (cont'd)

- Averaging responses of individual subjects within large groups not recommended – random nature of variability is cancelled out

- Capturing behavioral variability
  - Three main concepts
    - » Basic Probability Assignment
    - » Belief (b)
    - » Plausibility (p)
  - Providing imprecise probability of an event

$$P(A) = [b, p]$$

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Case Study – Behavioral Techniques

- FMEA for NPI
- Based on expert opinions only
- Combining responses
- Ranking failures modes

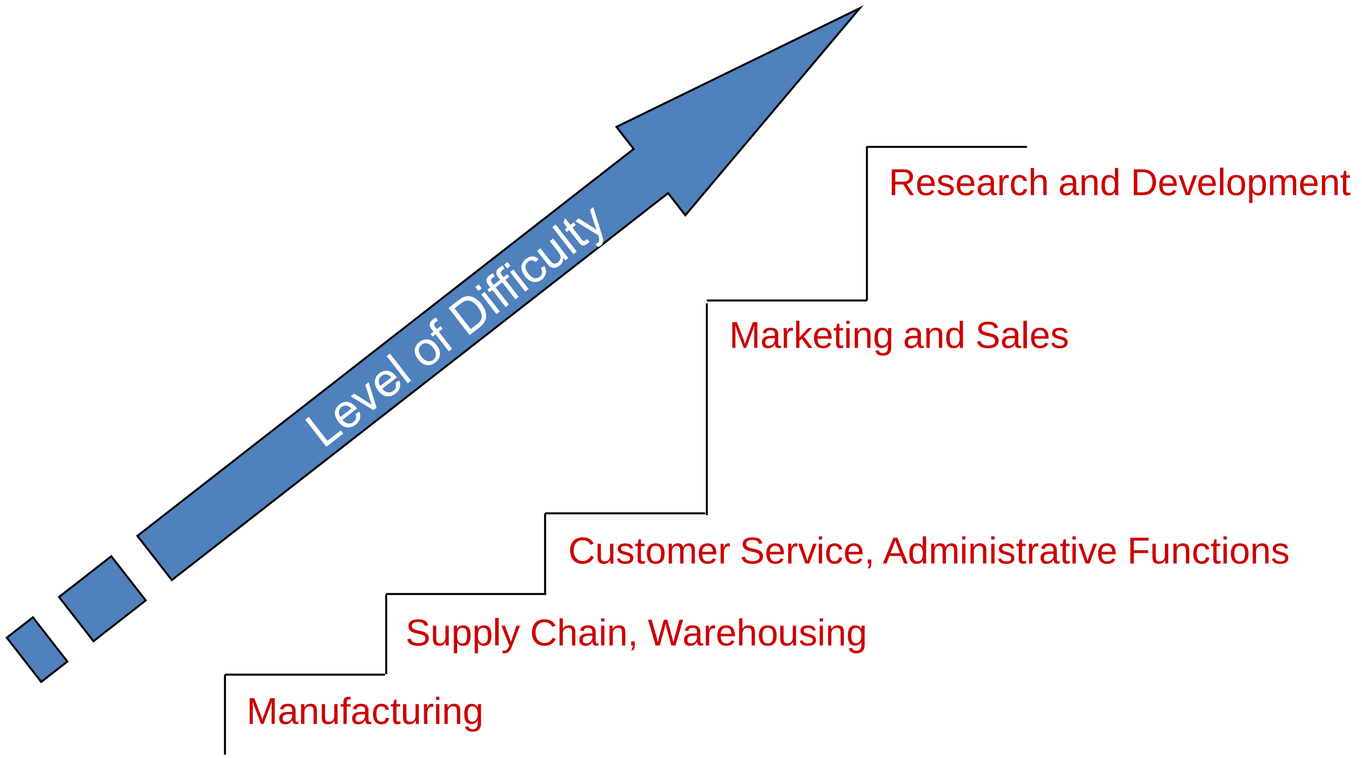
(F)	Expert 1		Expert 2		Combined Evidence		
	Rating	$\mathfrak{B}_1$	Rating	$\mathfrak{B}_2$	$\mathfrak{B}_{1,2}$	$\mathfrak{b}_{1,2}$	$\mathfrak{p}_{1,2}$
$\varnothing$	-	0.00	-	0.00	0.00	0.00	0.00
A	-	0.45	-	0.30	0.40	0.40	0.42
B	-	0.05	-	0.05	0.03	0.03	0.07
C	-	0.30	-	0.40	0.52	0.52	0.57
$A \cup B$	-	0.00	-	0.00	0.00	0.43	0.48
$A \cup C$	-	0.11	-	0.00	0.01	0.93	0.97
$B \cup C$	-	0.00	-	0.18	0.03	0.58	0.60
$A \cup B \cup C$	-	0.09	-	0.07	0.01	1.00	1.00
					c = 0.429		

(F)	O		S		D		$O \times S \times D \times 1000$		RPN
	$\mathfrak{b}(F)$	$\mathfrak{p}(F)$	$\mathfrak{b}(F)$	$\mathfrak{p}(F)$	$\mathfrak{b}(F)$	$\mathfrak{p}(F)$	$\mathfrak{b}(F)$	$\mathfrak{p}(F)$	
A	0.40	0.42	0.12	0.17	0.08	0.08	3.900	6.203	2
B	0.03	0.07	0.43	0.56	0.01	0.01	0.098	0.597	3
C	0.52	0.57	0.30	0.41	0.04	0.05	5.509	10.693	1

Kulkarni and Johnson, 2012

Take-Away

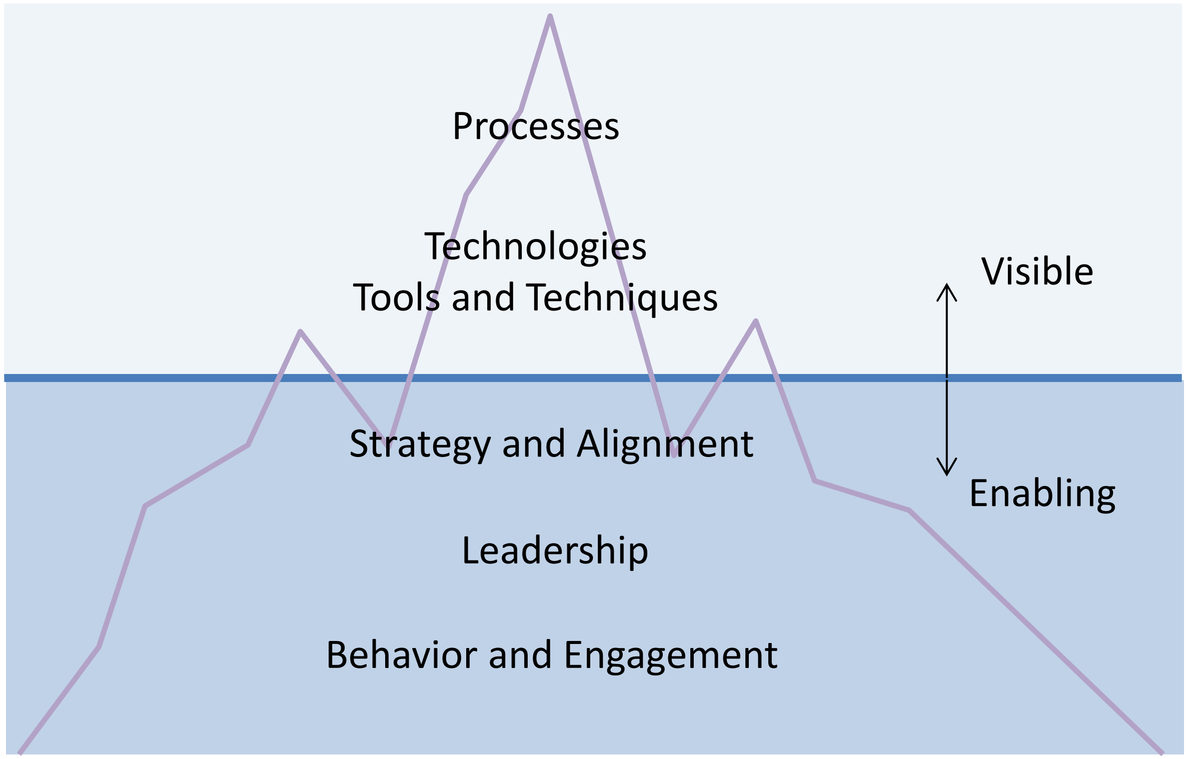
Let's use Six Sigma for everything!?!



The reason: DMAIC is not well suited for some parts of the organization

Ramakrishnan, et al., 2007

We Touched Just The Surface…



Hines, et al., 2008

- We just discussed the 'visible' things
- Improving operations may necessitate cultural changes

Don’t Forget the Human Element!

Thank You

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