Six Sigma Applied to the Pharmaceutical and Medical Device Industries

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T E

Evolution of Quality

- Six Sigma is the next step in the evolution of management and quality practices
- It builds on previous stages: TQM, Deming, SPC and much more
- While much will be familiar, it has new elements:

"What accounts for the clearly superior performance these companies have achieved?"

TE

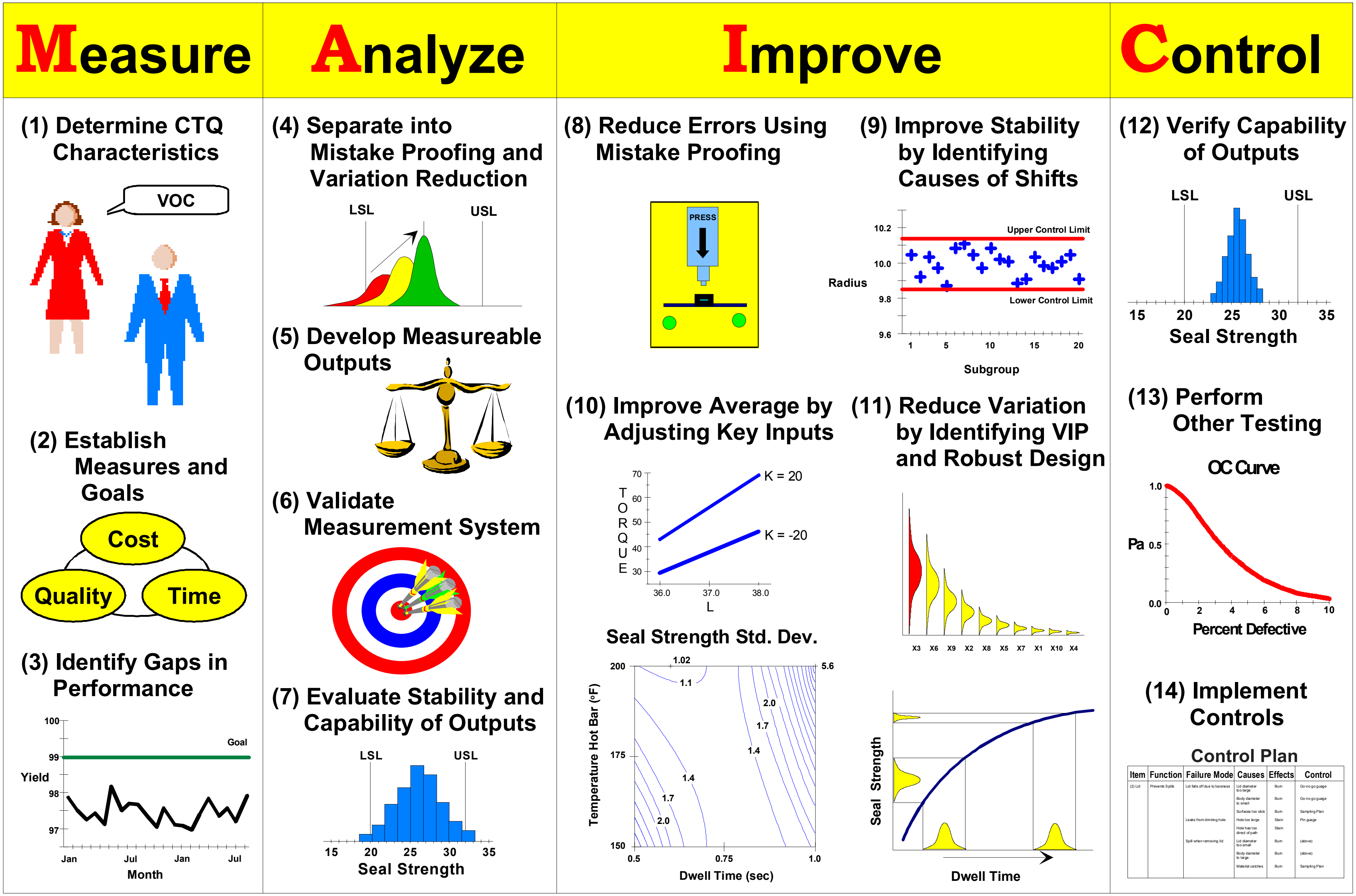
Lessons of Six Sigma

1. Tie to Business Goal (Six Sigma Quality, Reduce Cost, Regulatory Compliant …)
2. Not Just Tools but Processes for Achieving Results:
   - Six Sigma Improvement Process
   - Six Sigma Design Process
3. Dedicated Resources
4. Not Just Training but a Deployment Strategy

Six Sigma

- Six Sigma is about the rapid **deployment** of the Six Sigma tools and processes into an organization and the effective **use** of these tools to **achieve key business initiatives:**
    - Scrap and cost reduction
    - Quality improvements (Six Sigma Quality)
    - Time to market and cycle time reductions

Six Sigma Improvement - MAIC



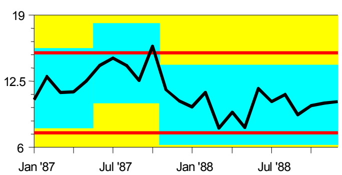
Six Sigma Problem Solving - MAIC

Measure

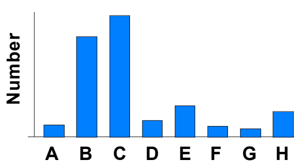
(1) Describe the Problem

	IS	IS NOT
What		
Where		
When		
Extent		

(2) Determine When Problem Started

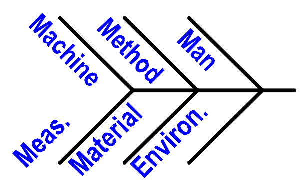


(3) Measure Problem Magnitude

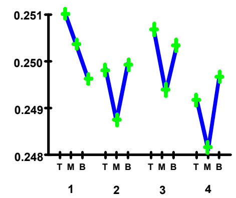


Analyze

(4) Identify Potential Causes



(5) Analyze Existing Data



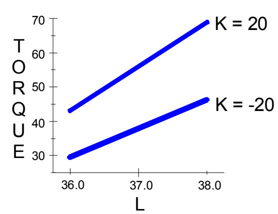
(6) Construct List of Verified Facts

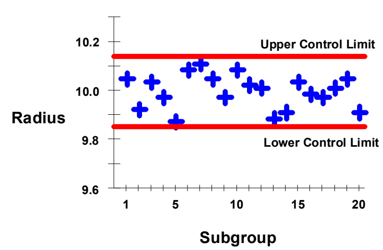
FACTS
(1) All Machines
(2) Second Shift
(3) Certain Codes
(4) Started 8/22
(5) Steadily Worse
(6) All Operators

(7) Compare Causes to Facts

	Fact 1	Fact 2	Fact 3	Fact 4	Fact 5
Cause 1	O	X	X	O	A
Cause 2	X	O	A	A	O
Cause 3	O	O	A	A	O
Cause 4	X	A	X	O	O
Cause 5	O	O	O	O	X

(8) Collect Additional Data Until Root Cause Identified



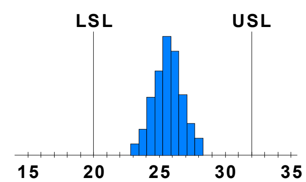


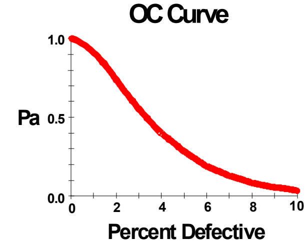
Improve

(9) Determine Best Solution

(10) Pilot Solution

(11) Verify Solution Works





Control

(12) Implement Solution

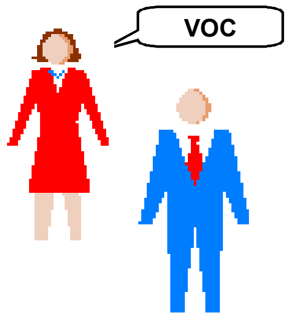
Control Plan

Item	Function	Failure Mode	Causes	Effects	Control
(2) Lid	Prevents Spills	Lid falls off due to looseness	Lid diameter too large	Burn	Go-no go gauge
			Body diameter to small	Burn	Go-no go gauge
			Surfaces too slick	Burn	Sampling Plan
		Leaks from drinking hole	Hole too large	Stain	Pin gauge
			Hole has too direct of path	Stain	
		Spill when removing lid	Lid diameter too small	Burn	(above)
			Body diameter to large	Burn	(above)
			Material catches	Burn	Sampling Plan

Design for Six Sigma - IDOV

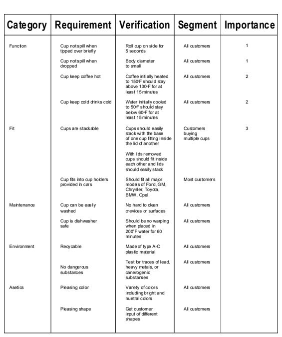
Identify

(1) Define Customer Requirements



(2) Establish Measures and Standards

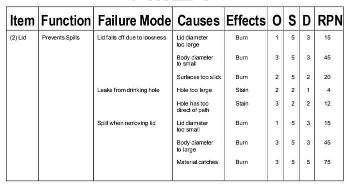
Requirements Definition



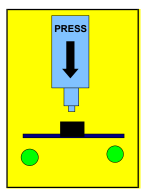
Design

(3) Identify Potential Failure Modes

FMEA

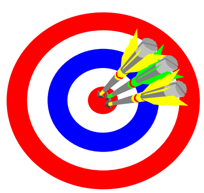


(4) Mistake Proof



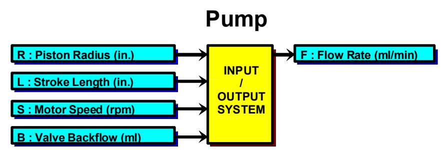
(5) Develop Measureable Outputs

(6) Validate Measurement System

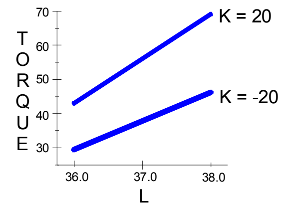


Optimize

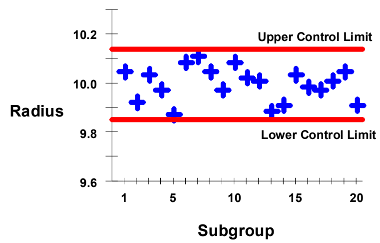
(7) Candidate Inputs

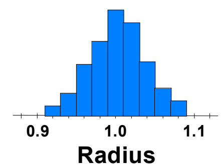


(8) Key Inputs



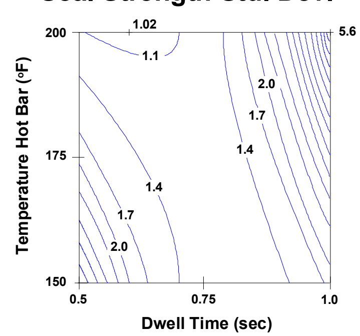
(9) Characterize Behaviors of Key Inputs



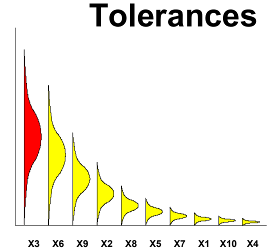


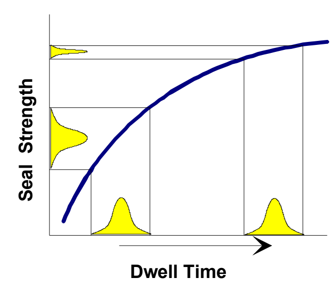
(10) Discover Variable Relationships

Seal Strength Std. Dev.



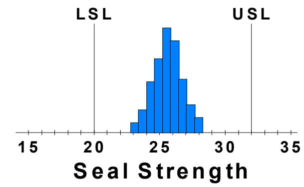
(11) Set Targets and Tolerances



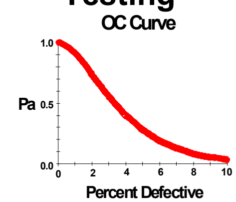


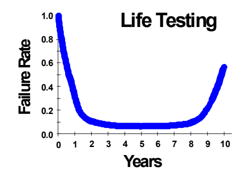
Validate

(12) Verify Capability of Outputs



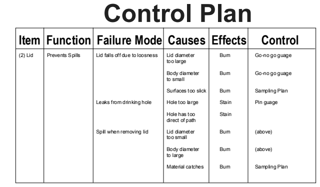
(13) Perform Other Testing





(14) Implement Controls

Control Plan



Validation / Six Sigma Tools

- GHTF Annex A (pages 12-20) describe the tools useful for validation and their roles:
  - Statistical Process Control (SPC)
  - Acceptance Sampling
  - Designed Experiments
  - Mistake Proofing
  - FMEA
  - Robust Design and Tolerance Analysis
  - Statistical Methods (confidence intervals, hypothesis testing, ANOVA, regression)

Validation Tools

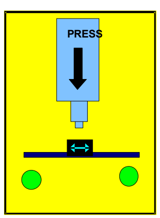
IQ

(1) Risk Assessment

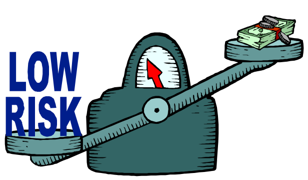
FMEA

Item	Function	Failure Mode	Causes	Effects	O	S	D	RPN
(2) Lid	Prevents Spills	Lid falls off due to looseness	Lid diameter too large	Burn	1	5	3	15
			Body diameter to small	Burn	3	5	3	45
			Surfaces too slick	Burn	2	5	2	20
		Leaks from drinking hole	Hole too large	Stain	2	2	1	4
			Hole has too direct of path	Stain	3	2	2	12
		Spill when removing lid	Lid diameter too small	Burn	1	5	3	15
			Body diameter to large	Burn	3	5	3	45
			Material catches	Burn	3	5	5	75

(2) Mistake Proof

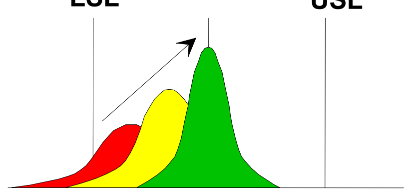


(3) EquipmentChallenge Testing

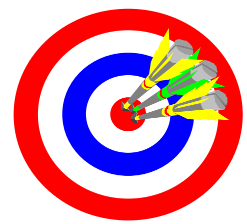


OQ

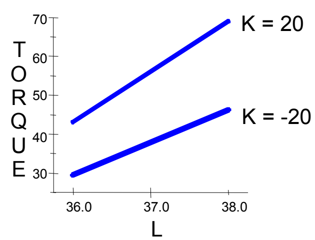
(4) Develop Measurable Outputs



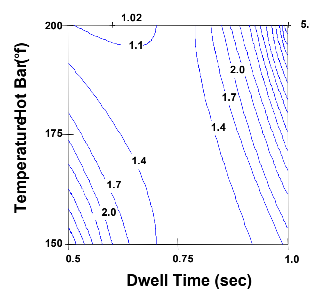
(5) Validate Measurement System



(6) Determine and Characterize Key Inputs



(7) Determine Variable Relationships

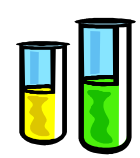


(8) Finalize Control Plan

Control Plan

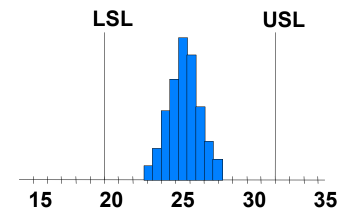
Item	Function	Failure Mode	Causes	Effects	Control
(2) Lid	Prevents Spills	Lid falls off due to looseness	Lid diameter too large	Burn	Go-no go gauge
			Body diameter to small	Burn	Go-no go gauge
			Surfaces too slick	Burn	Sampling Plan
		Leaks from drinking hole	Hole too large	Stain	
			Hole has too direct of path	Stain	Pin gauge
		Spill when removing lid	Lid diameter too small	Burn	(above)
			Body diameter to large	Burn	(above)
			Material catches	Burn	Sampling Plan

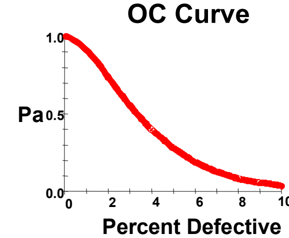
(9) Determine and Test Worst-Case Conditions



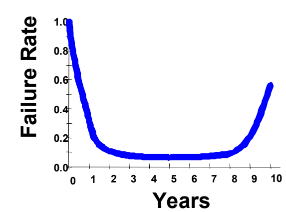
PQ

(10) Process PQ Testing





(11) Product PQ Testing



Control Plan

- In GHTF Guidance Document:
  - "One output of process validation is a control plan."
  - "The final phase of validation requires demonstrating that this control plan works."
- We will learn about the elements that make up a control plan
- Control Plan to be completed prior to OQ Limit Testing

FMEA

- Evaluates risks associated with the process and its control plan – column on FMEA form
- Helps identify where improvements are needed
- Used to determine if the process is ready for the final phase of validation
- We will briefly outline what an FMEA is and how it fits into the validation process

Process FMEA Form

FAILURE MODES AND EFFECTS ANALYSIS

Product or Process: Hot / Cold Cup   Division or Dept.: TE

Team Leader: Wayne Taylor   Date Completed: 10/3/00

Item or Step	Function	Potential Failure Mode	Potential Effect(s) of Failure	S	Potential Root Cause(s) of Failure	O	Current Controls	D	RPN	C/A Required?
Body	Holds 12 ounces	Small	Some customers may complain doesn't hold enough	6	Diameter, Cpk = 1.5	2	Set-up check	5	60	
					Height, Cpk = 1.1	5	Control chart	3	90	
		Large	Customer may complain cup is too large or heavy	5	Diameter, Cpk = 1.5	2	Set-up check	5	50	
					Height, Cpk = 1.1	5	Control chart	3	75	
	Insulates	Thin	Drink gets cold too fast	7	Thickness, Cpk = 1.3	4	Mold qualification, Sampling plan	4	112	
		Too conductive a material	Drink gets cold too fast	7	Property of material not subject to change	1	None	10	70	
	Withstands being dropped	Thin	Burns customer, stains carpet, must replace cup	10	Thickness, Cpk = 1.3	4	Mold qualification, Sampling plan	4	160	
		Brittle	Burns customer, stains carpet, must replace cup	10	Material property makes subject to cracking or shattering	6	none	10	600	Yes

Statistical Requirements

Part 820-Quality Systems Regulations

Subpart 0, 820.250 Statistical Techniques

(a) Where appropriate, each manufactures shall establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characterization.

(b) Sampling plans, when used, shall be written and based on a valid statistical rationale. Each manufacturer shall establish and maintain procedures to ensure that sampling methods are adequete for their intended use and to ensure that when changes occur the sampling plans are reviewed. These activities shall be documented.

Valid Statistical Techniques

- **Recognized Technique**
- **Properly Applied**
- **Assumptions are Met**

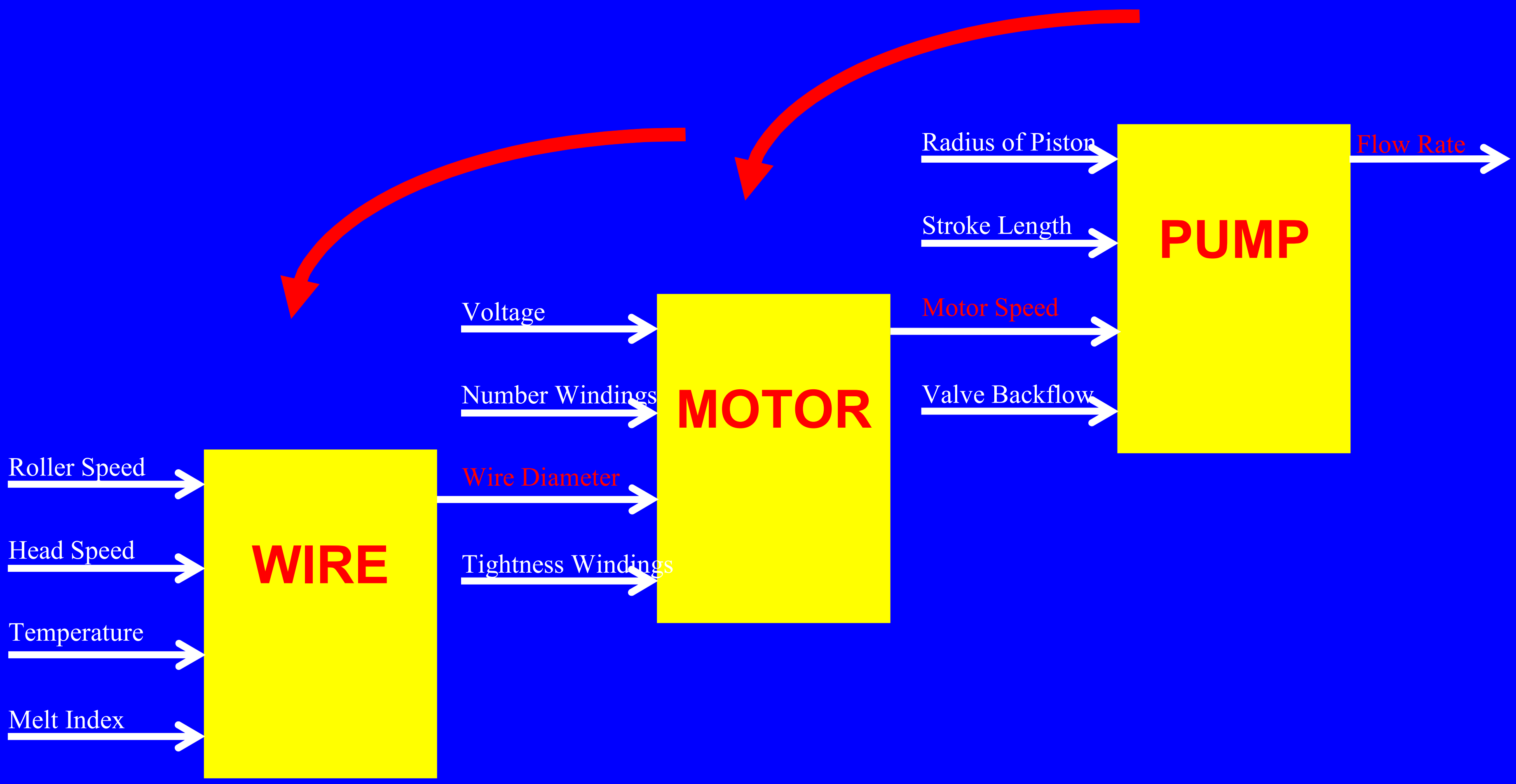
Areas of Application

- **Establish – Tools for identifying and understanding key variables, for reducing variation and**
  - **Designed Experiments (Screening Experiment, Response Surface Study, Taguchi Methods)**
  - **Capability Studies, Analysis of Variance, Variance Components**
  - **Robust Design Methods, Tolerance Analysis**
- **Control – control plan for**
  - **Statistical Process Control (Control Charts)**
  - **Manufacturing Sampling Plans**
- **Verify –**
  - **Validation/Verification Sampling Plans (Capability Studies)**
  - **Gauge R&R**

Establish – Setting Specs

- **Translate Customer Requirements into Product, Process and Material Requirements**
  - **Assumes customer requirements are identified and translated into verifiable specifications**
  - **Must identify key product/process/material parameters that must be controlled**
  - **Must understand the effect these key parameters have**
  - **Must understand ability to control these key parameters**
  - **Use all this to establish targets and tolerances on these parameters**

Establish – Setting Specs



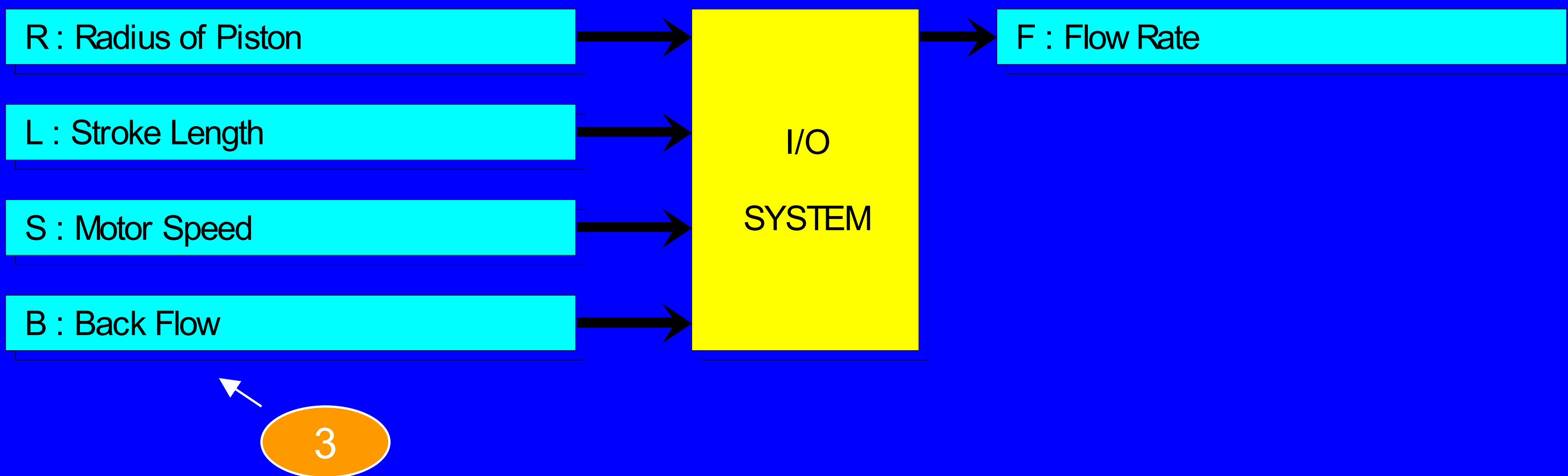
Pump Case Study

- **The Requirement:**
  - **Flow Rate of 10 ± 1 ml/min**

1 2

- **The Concept:**
  - **Piston and Valves**

Identify Key Parameters



- **DOE – Screening Experiment**

Effect of Key Parameters

$$F = (16.388\,\pi\,R^2\,L - B)\,S$$

4

- **DOE – Response Surface Study**

Control of Key Parameters

Inputs	Initial Targets	Standard Deviation
Piston Radius (R)	---	0.0005”
Stroke Length (L)	---	0.0017”
Motor Speed (S)	---	0.17 rpm
Back Flow (B)	0.05	0.005 ml

5

- Capability Studies

TE

Initial Design

- **Designer has freedom to select targets for R, L and S.**

Inputs	Initial Targets	Standard Deviation
Piston Radius (R)	0.1	0.0005”
Stroke Length (L)	0.5	0.0017”
Motor Speed (S)	48.2	0.17 rpm
Back Flow (B)	0.05	0.005 ml

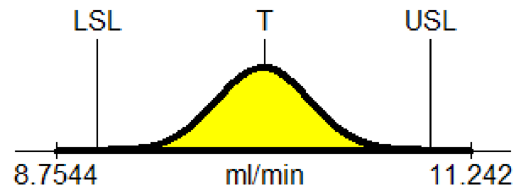
Tolerance Stack-up

Predicted Performance Initial Design ➜

Capability Study - F

Flow Rate - (F)

Statistical Tolerance



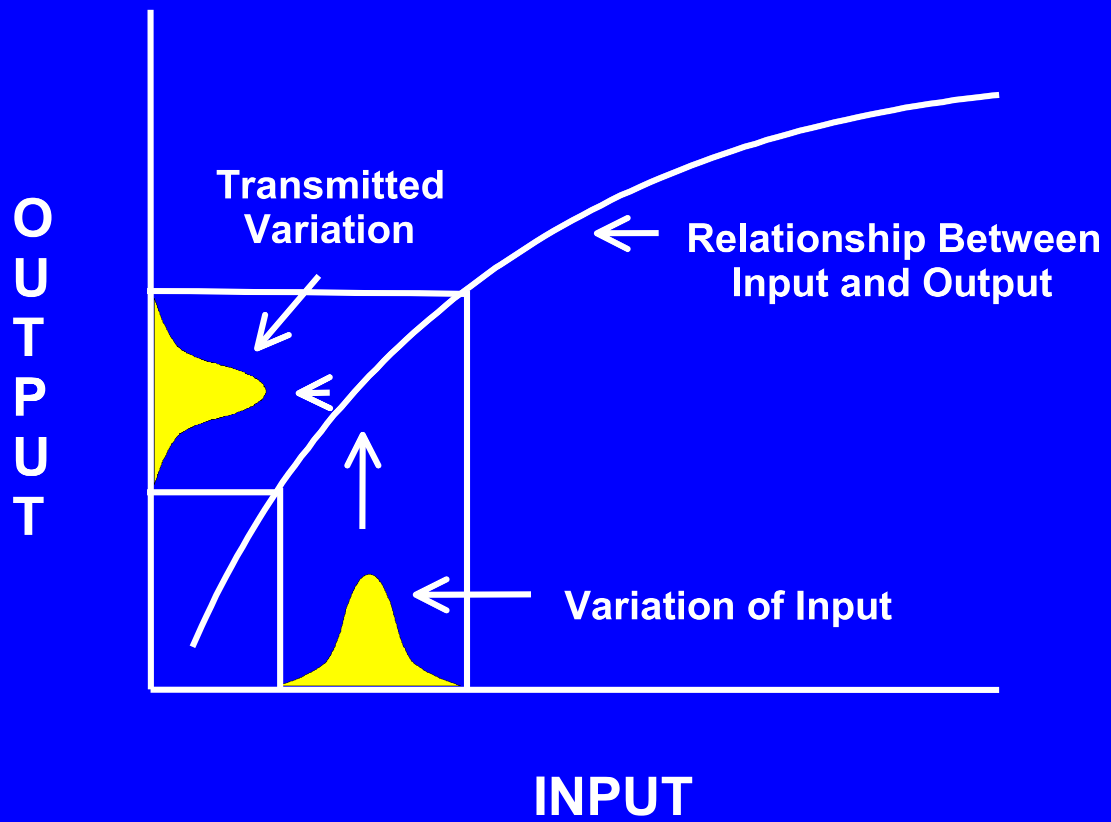
Characteristic	Value
Average:	9.9981
Standard Deviation:	0.27638
Cp:	1.21
Cc:	0.00
Cpk:	1.20
Def. Rate (normal):	297 dpm
Z-Score (short-term):	3.43
Sigma Level:	3.43

Interval for Values = (8.7544, 11.242) +/-4.5SD

Calculated | Simulated | Worst-Case Conditions

Options | Print | Copy | Help | Lock

Tolerance Stack-up



- **One way of predicting the variation is by performing a simulation**

Optimal/Robust Design

- **There are many ways to achieve a 10 ml/min flow rate. One minimizes the variation. The design minimizing the defect rate is:**

Inputs	Initial Targets	Standard Deviation
Piston Radius (R)	0.1737	0.0005”
Stroke Length (L)	0.4094	0.0017”
Motor Speed (S)	17.06	0.17 rpm
Back Flow (B)	0.05	0.005 ml

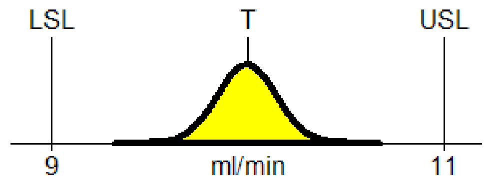
Optimal/Robust Design

Predicted Performance Robust Design →

Capability Study - F

Flow Rate - (F)

Statistical Tolerance



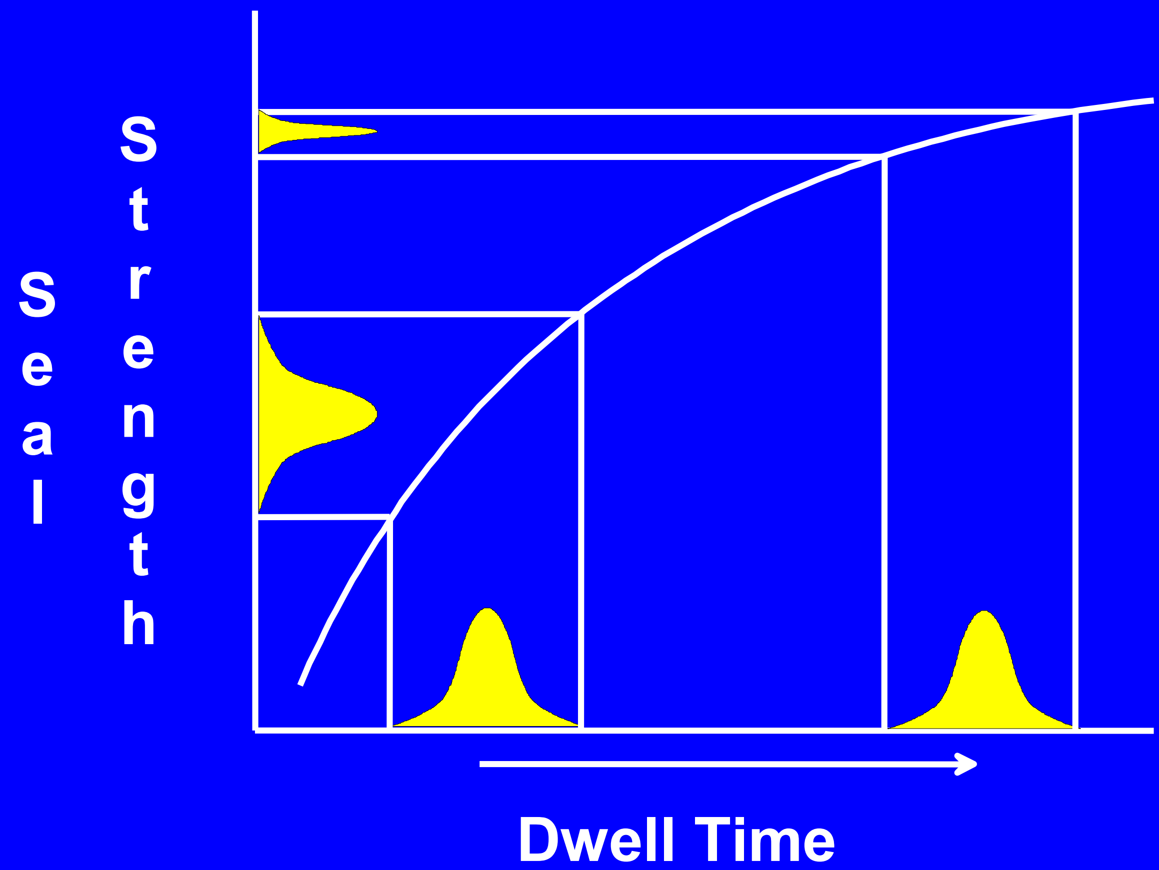
Characteristic	Value
Average:	9.9964
Standard Deviation:	0.15055
Cp:	2.21
Cc:	0.00
Cpk:	2.21
Def. Rate (normal):	0.0000313 dpm
Z-Score (short-term):	6.54
Sigma Level:	6.54

Interval for Values = (9.3189, 10.674) +/-4.5SD

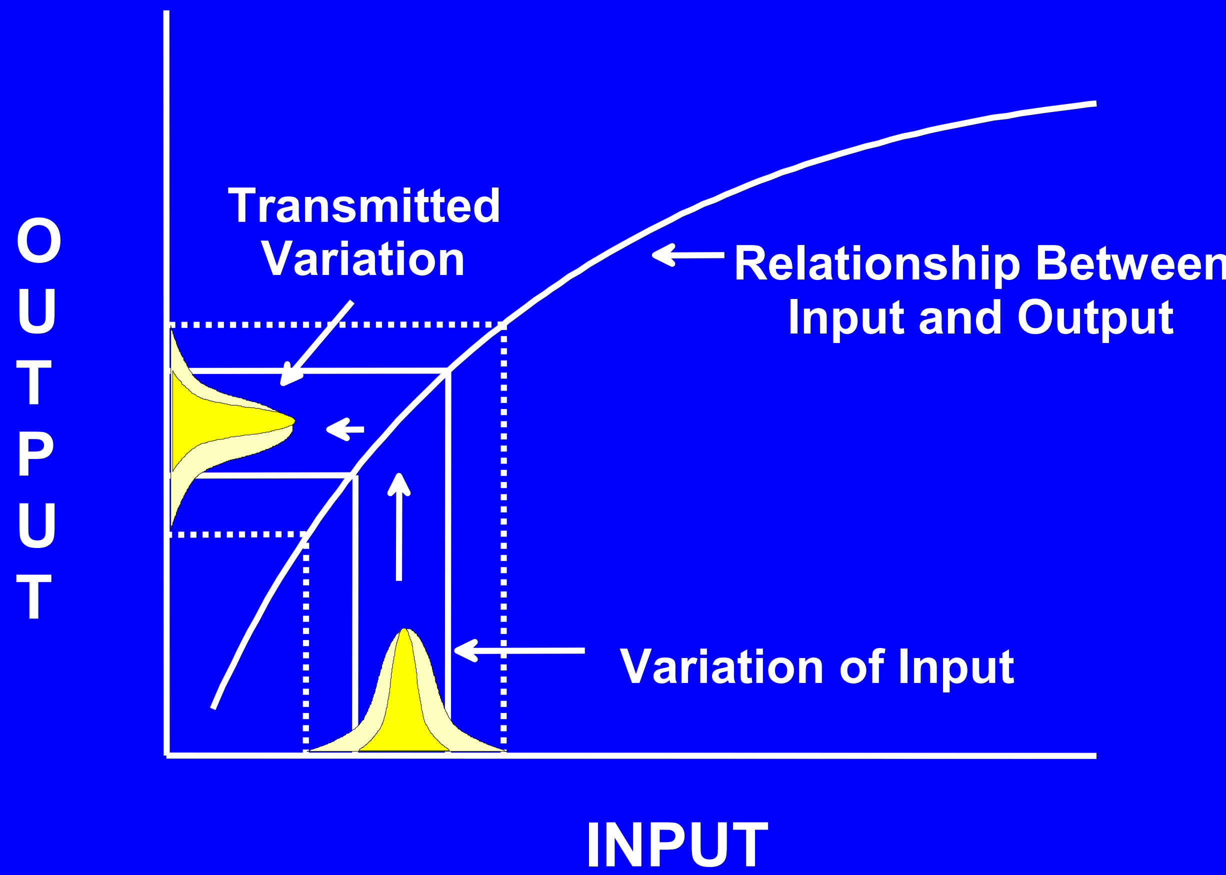
Calculated | Simulated | Worst-Case Conditions

Options | Print | Copy | Help | Lock

Robust Design - Adjust Targets

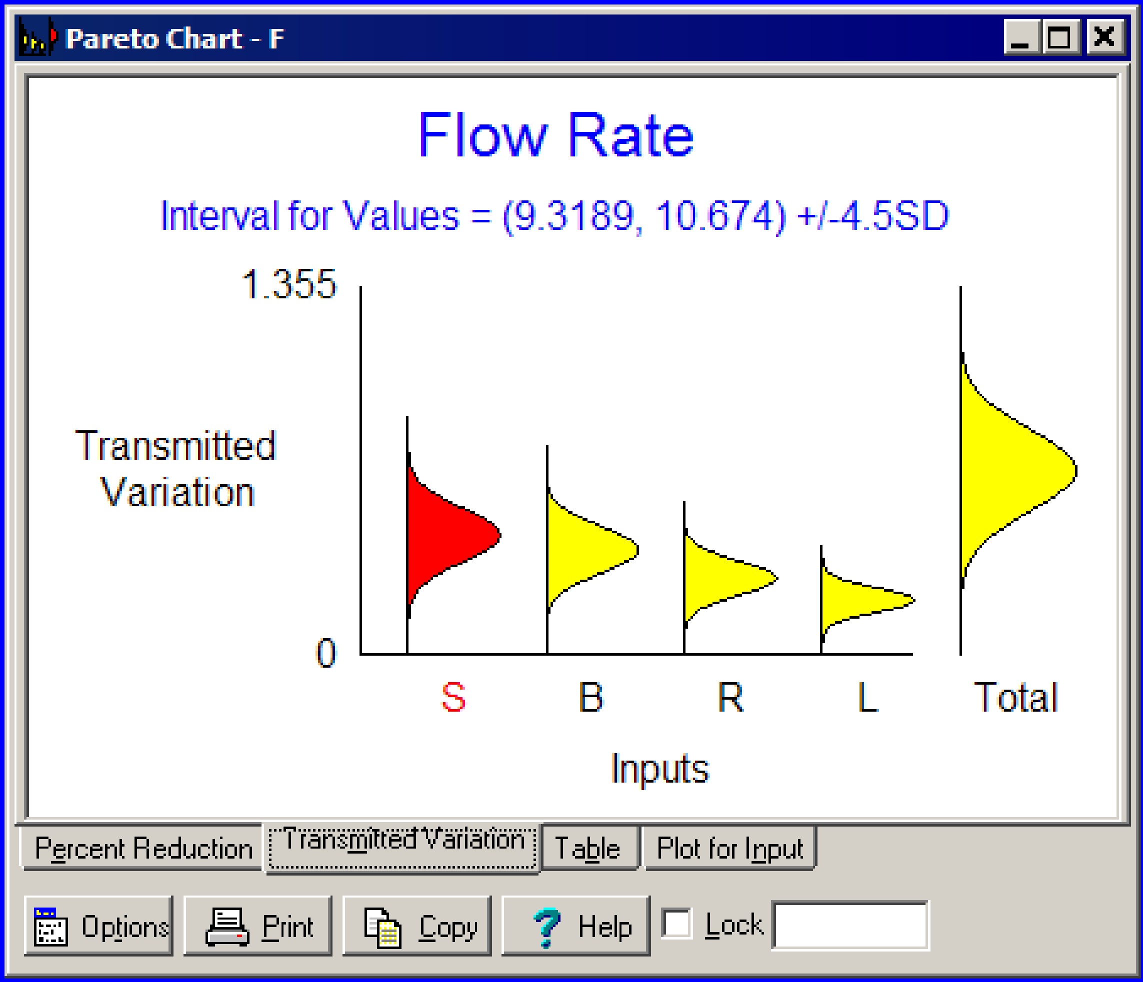


Tighten Tolerances



TE

Tolerance Sensitivity Analysis



Review: Establish – Setting Specs

- **Collect 5 Key Pieces of Information:**
  1. **Identify customer requirements**
  2. **Translate into verifiable specifications**
  3. **Key product/process/material parameters that must be controlled (screening experiment)**
  4. **Understand effect these key parameters have (response surface study)**
  5. **Understand ability to control these key parameters (capability studies on parameters)**
- **Establish targets and tolerances on these parameters (tolerance stack-ups, robust design, tolerance sensitivity analysis)**

Control – Maintaining Specs

- **Statistical Process Control (Control Charts)**
- **Manufacturing Sampling Plans**
- **100% Inspections**
- **Mistake Proofing**
- **Close Loop Feedback**

Verify – Demonstrating Specs Met

- **Validation/Verification Sampling Plans (Capability Studies)**
- **Gauge R&R**

Validation Tools

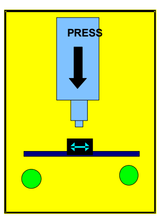
IQ

(1) Risk Assessment

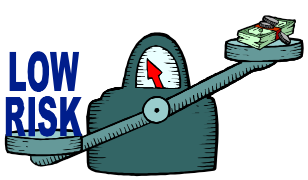
FMEA

Item	Function	Failure Mode	Causes	Effects	O	S	D	RPN
(2) Lid	Prevents Spills	Lid falls off due to looseness	Lid diameter too large	Burn	1	5	3	15
			Body diameter to small	Burn	3	5	3	45
			Surfaces too slick	Burn	2	5	2	20
		Leaks from drinking hole	Hole too large	Stain	2	2	1	4
			Hole has too direct of path	Stain	3	2	2	12
		Spill when removing lid	Lid diameter too small	Burn	1	5	3	15
			Body diameter to large	Burn	3	5	3	45
			Material catches	Burn	3	5	5	75

(2) Mistake Proof

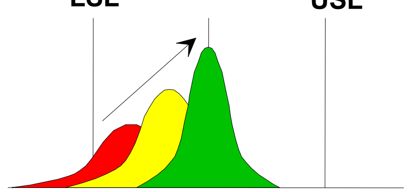


(3) EquipmentChallenge Testing

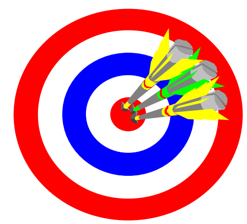


OQ

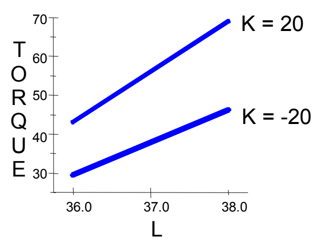
(4) Develop Measurable Outputs



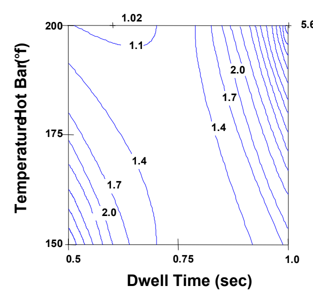
(5) Validate Measurement System



(6) Determine and Characterize Key Inputs



(7) Determine Variable Relationships

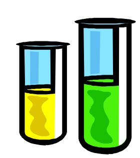


(8) Finalize Control Plan

Control Plan

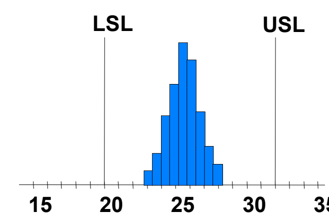
Item	Function	Failure Mode	Causes	Effects	Control
(2) Lid	Prevents Spills	Lid falls off due to looseness	Lid diameter too large	Burn	Go-no go gauge
			Body diameter to small	Burn	Go-no go gauge
			Surfaces too slick	Burn	Sampling Plan
		Leaks from drinking hole	Hole too large	Stain	Pin gauge
			Hole has too direct of path	Stain	
		Spill when removing lid	Lid diameter too small	Burn	(above)
			Body diameter to large	Burn	(above)
			Material catches	Burn	Sampling Plan

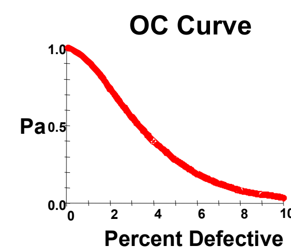
(9) Determine and Test Worst-Case Conditions



PQ

(10) Process PQ Testing





(11) Product PQ Testing