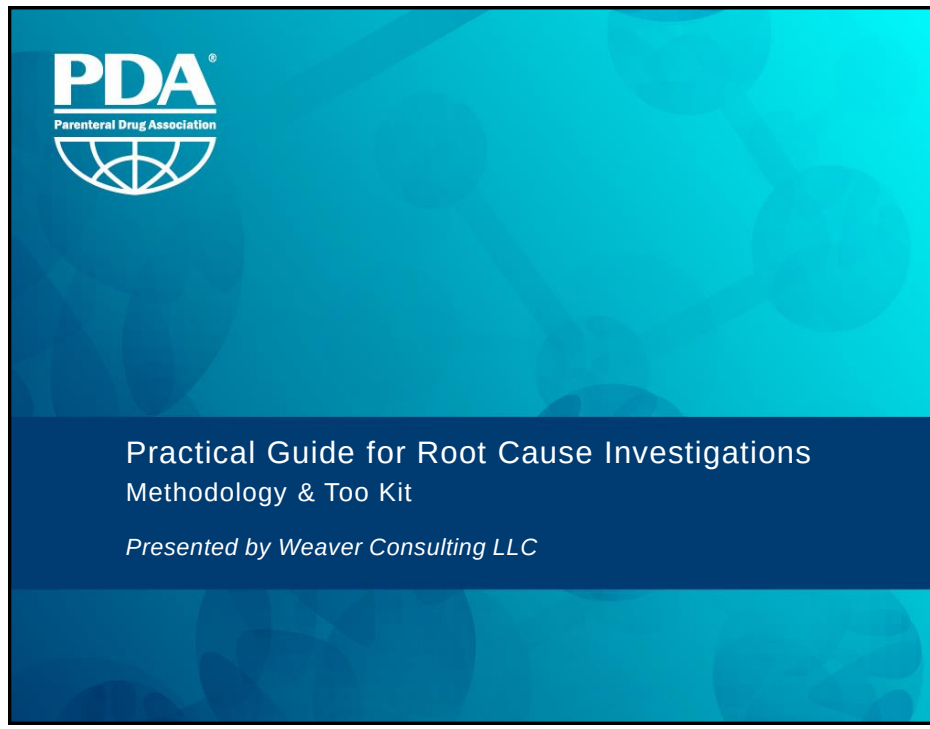


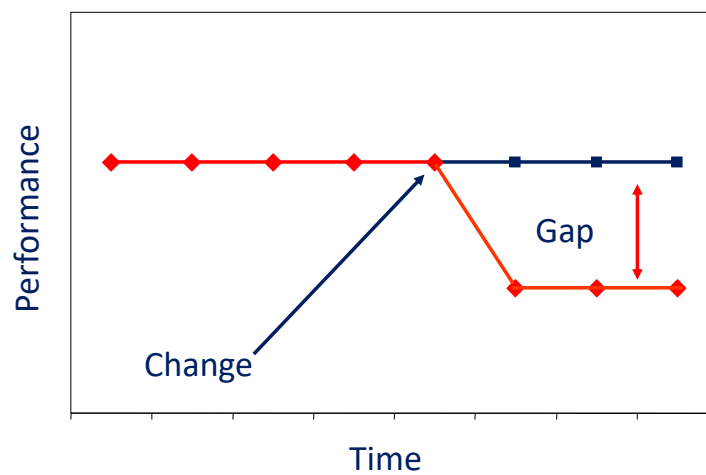
Table of Contents

2

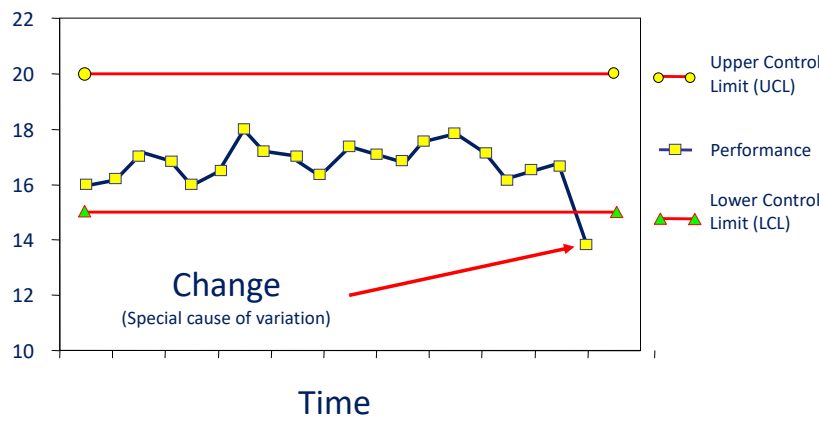
Connecting People, Science and Regulation®

Introduction

Simplified Investigation



Realistic Investigation



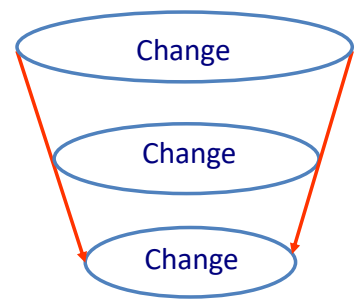
Examples

- Manufacturing
  - Surge in the defect rate
- Laboratory
  - Incidence of false positives in a micro lab
- Process
  - Increased transaction time
- Customer
  - Rise in complaints
- Regulatory
  - Spike in noncompliance issues

Common Investigation Mistakes

- Focus on possible causes from beginning of investigation
- Inconsistent approach to investigations
- Unnecessary experiments & studies
- Neglect to identify and address systemic root causes
- Weeks or months without resolution

Focus: Fact Based Investigation



Learning Objectives

- Apply a 7 step investigation methodology to determine the root cause(s) of a technical problem: technical root cause or the change
- Identify any systemic root causes: system or detection failures that allowed the change to occur and/or go undetected
- Implement appropriate corrective/preventive actions to restore performance
- Implement a control plan to monitor future performance

Documentation

21 CFR 820(b) requires documentation of all investigation activities, as well as the results of those activities

Electronic templates are provided to assist documenting the investigation

Critical Terms

Correction

Corrective action

Preventive action

Correction

- Action taken to eliminate a detected nonconformity
- Containment to stabilize problem
- Examples
  - Scrap
  - Repairs or modifications
  - Recalls
- Investigation has not been conducted
- Nonconformities continue
- Additional work + expense

Corrective Action……..vs Preventive Action

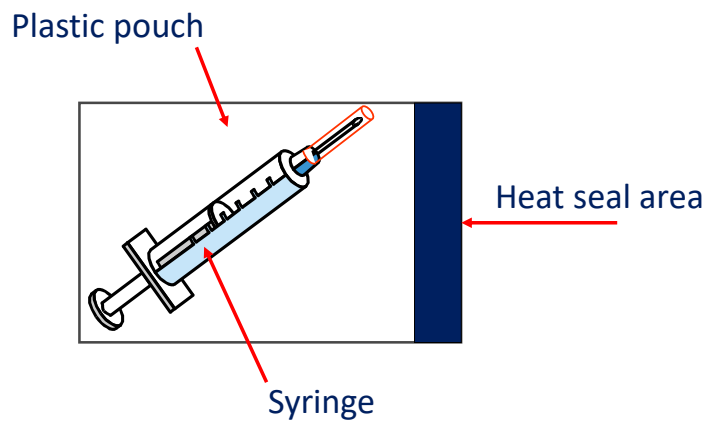
- Action taken to eliminate the cause of a detected nonconformity
- Requires investigation and identification of root cause
- Action taken to stop or minimize recurrence
- Action taken to eliminate the cause of a potential nonconformity
- Often impractical to prevent all possible nonconformities
- Some, perhaps most can be prevented

Step 1: Define the Performance Problem

Define the Performance Problem

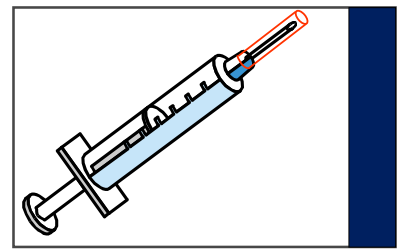
Input	Process	Output
Performance gap	State the problem	Problem statement
	Describe the problem	Is/Is Not diagram
	Describe the process	Process flow diagrams
	Identify the inputs	Input/output diagrams
	Timeline of events	Timeline of events
	Team charter	Team charter

Case of the Unsealed Pouch



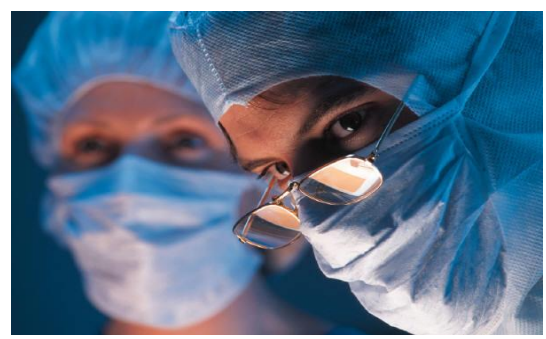
Case of the Unsealed Pouch

- Seal requirements
  - Withstand a 10 lb (44 n) pull test
  - Open with a 20 lb (88 n) pull test



Case of the Unsealed Pouch

Customers are reporting some seals are open upon receipt…



…sterility has been compromised

State the Problem

What specific object has the defect?

Syringe pouch seals…

What is the specific defect?

…are open

…or failing the 10 lb pull test

For your case study…

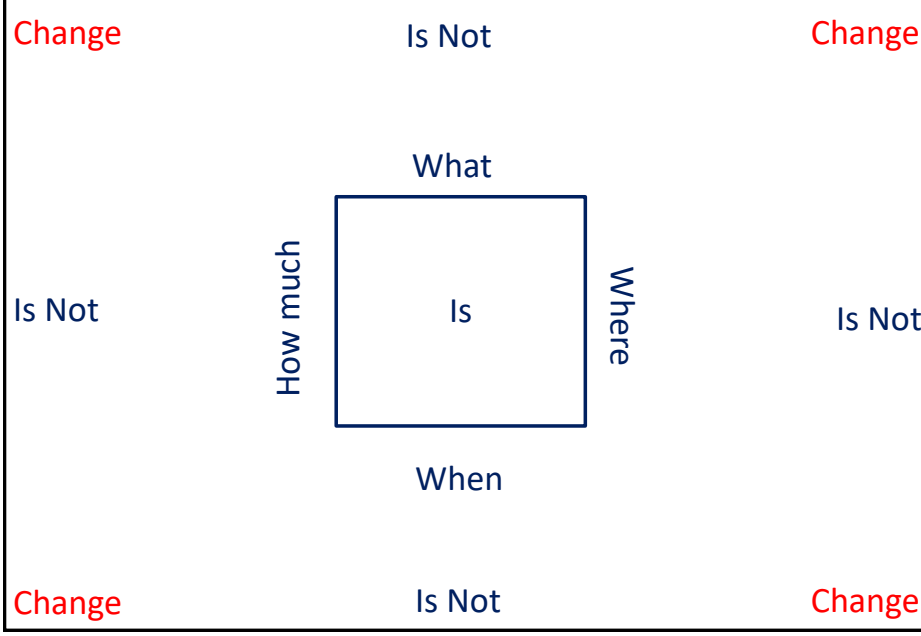
What specific object has the defect?

What is the specific defect?

Define the Performance Problem

1. State the problem
2. Describe the problem

Describe the Problem



Is/Is Not Diagram

	Is	Is Not
What	What specific object has the defect?	What similar objects could have the defect but don't?
	What is the specific defect?	What other defects could be seen but aren't?
	What are the defect characteristics?	*What could the characteristics be but aren't?*
	What product lots have the defect?	What product lots could have the defect but don't?
	What part lots are linked with the defect?	What part lots could be linked with the defect but aren't?
	What patterns are in the "What" answers?	What patterns aren't seen in the "What" answers?
Where	Where is the defective object observed geographically?	Where could the defective object be observed geographically but isn't?
	Where is the defect on the object?	Where could the defect be on the object but isn't?
	Where is the defect 1st seen in the process?	*Where could the defect 1st be seen in the process but isn't?*
	Where else is the defect?	Where else could the defect be but isn't?
	What patterns are in the "Where" answers?	What patterns aren't seen in the "Where" answers?
When	*When was the defective object 1st seen (date/time)?*	*When could the defective object 1st been seen but wasn't?*
	When since the 1st time has the defective object been seen (date/time)?	When since the 1st time could the defective objective have been seen but wasn't?
	What patterns are in the "When" answers?	What patterns aren't seen in the "When" answers?
How Much	How many objects have the defect?	How many objects could have the defect but don't?
	How big or small is the defect?	How big or small could the defect be but isn't?
	How many defects are on the object?	How many defects could be on the object but aren't?
	What is the trend (stable, better, worse)?	What could the trend be but isn't?
	What patterns are in the "How Much" answers?	What patterns aren't seen in the "How Much" answers?

Is/Is Not Diagram: What Questions

Is	Is Not
Syringe pouch seals	Surgeon glove pouch seals
Seals are open or failing pull test	Tears, holes, product in seals, etc
Failing 10 lb pull test	Failing 20 lb pull test
SY217, SY218…SY235	SY216 and earlier product lots
Part/component lots?	Part/component lots?
Patterns?	Patterns?

Is/Is Not Diagram: Where Questions

Is	Is Not
Customers from all NA sales regions	Some sales regions
Johnsville facility	Janesville facility
Final seal (1)	Supplier's seals (3)
Final inspection & release?	Before final inspection & release?
Production line 3 (Johnsville)	Production lines 1,2,4 (Johnsville)
Patterns?	Patterns?

Is/Is Not Diagram: When Questions

Is	Is Not
June 1st (two weeks ago)?	Before June 1st?
Continuously every day since June 1st	Sporadically or other pattern
Patterns?	Patterns?

Is/Is Not Diagram: How Much Questions

Is	Is Not
Avg 5% of daily production	Historical avg .01%
Avg defect is 9.3 lbs force (41 newtons)	More or less than avg
1 defective seal (final)	2,3,4 (supplier)
Stable	Climbing, falling, sporadic
Patterns?	Patterns?

Is/Is Not Diagram: Key Points

- Ask every question, understanding not all will be applicable
- Ask each Is and corresponding Is Not question together
- There will always be an Is Not answer for every Is recorded
- Record multiple answers to the same question separately
- Record disagreements to questions
- Answers at this step are opinions…nothing more

Is/Is Not Diagram: Key Points

- The defective object can be anything: widgets, people, software, physical/virtual processes, systems, etc
- The Where questions are attempting to identify location related patterns: geographically, on the object, in a process, etc
- The When questions are attempting to identify time related patterns: time of day/week/month/year, shift, season, etc
- The How Much questions are attempting to identify numerically related patterns, specific or general

Is/Is Not Diagram: Key Points

- The most critical question: What are the defect characteristics?
- May need to conduct a technical analysis to better characterize the defect
- A sensory description may be beneficial…how does the defect…
  - Feel: rough surface
  - Smell: burnt
  - Sound: hiss
  - Look: blackened material
  - Taste: bitter

Is/Is Not Diagram: Key Points

- The 3 most important questions to describe the problem:
  - What are the defect characteristics?
  - Where is the defect 1st seen in the process?
  - When was the defect 1st seen (date and time)?
- More detail = tighter fence

Is/Is Not Diagram: Key Points

- This is the problem description
- The team must understand the problem in this level of detail
- Places limits on the investigation
- Helps identify critical patterns

	Is	Is Not
What		
Where		
When		
How Much		

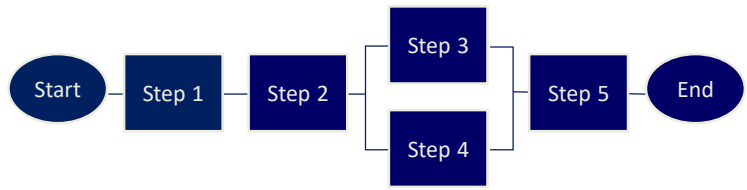
Define the Performance Problem

1. State the problem
2. Describe the problem
3. Describe the process(es) under investigation

Describe the Process(es)

Develop process flow diagram of work being conducted

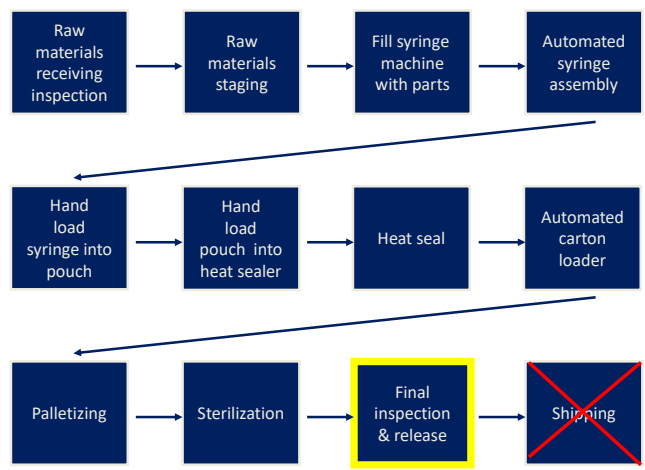
- Product development
- Manufacturing
- Sterilization
- Release
- Distribution
- Laboratory
- Customer usage
- Disposal
- Repair/service



Technical root causes often result from a process change

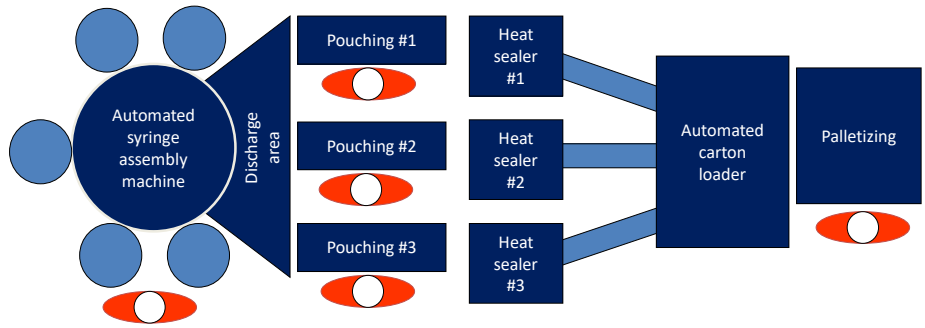
Describe the Process(es)

Syringe production process flow diagram



Describe the Process(es)

Other techniques such as a schematic diagram can be leveraged to supplement the process flow diagram



Part feeder bowl

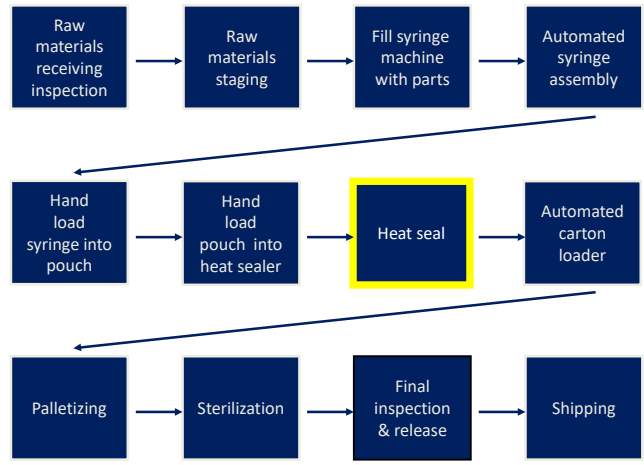
Production operator

Define the Performance Problem

1. State the problem
2. Describe the problem
3. Describe the process(es) under investigation
4. Identify the inputs

Identify the Inputs

Syringe production process flow diagram



Identify the Inputs

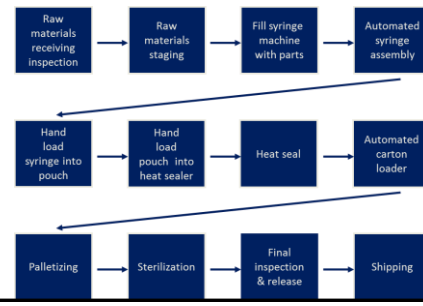
Key

Input	Process	Output
Hot bar temp Cold bar temp Pressure Dwell time Pouch temp Pouch thickness Room temp Cooling air pressure	Heat seal	Sealed pouch

Technical root causes often result from an input change

Flow Diagram with Inputs: Key Points

- Assures team understands the process being investigated
- Develop with the experts: individuals executing process regularly
- Will be leveraged in step #3 to identify possible causes

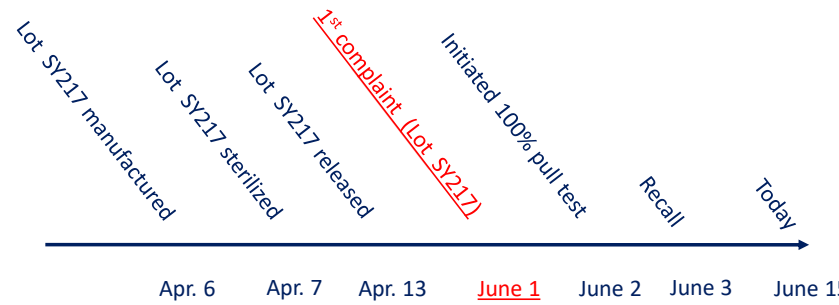


Define the Performance Problem

1. State the problem ✓
2. Describe the problem ✓
3. Describe the process(es) under investigation ✓
4. Identify the inputs ✓
5. Timeline of events
6. Team charter

Timeline of Events

List known relevant events in chronological order



Provides clarification when many events have occurred

Team Charter

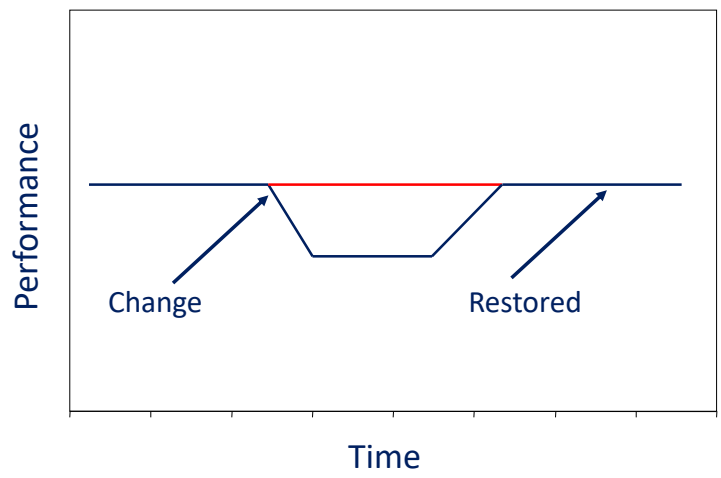
- High level statement describing the who, what and why of the investigation
- Used selectively to capture senior management's attention to convey importance of the investigation

Team Charter

- Purpose of the investigation
  - Problem statement
  - Performance goal
  - Cost savings goal
- Identify the investigation team & leader
- Identify the member(s) of management sponsoring the investigation
- Everyone signs the charter to:
  - Verify what the team is working toward
  - Identify any concerns of the team, management, or sponsors
  - Identify key issues where the team will need help

Team Charter: Performance Goal

Restore performance to previous level or requirement



Team Charter: Cost Savings Goals

Estimate monetary expenses associated with problem if unaddressed for 1 year:

- Inspections
- Scrap
- Rework
- Complaints
- Recalls
- Legal actions
- Regulatory actions
- Lost sales

Team Charter: Examples of Goals

- Performance goal:

  Return defective seal rate from 5% to historical average of .01%

- Cost savings goal

  Eliminate $350,000 of additional annualized cost caused by the defective seals

Documentation

- Problem statement
- Is/Is Not diagram
- Process flow diagrams
- Input/output diagrams

Strongly recommended

- Timeline of events
- Team charter

As needed

Step 2: Collect Data

Collect Data

Input	Process	Output
Opinions		Facts
Is/Is Not diagram	Data collection plan	Is/Is Not diagram
Flow diagrams		Flow diagrams
Inputs		Inputs

Data Needed

- Verify answers in the initial opinion based Is/Is Not diagram

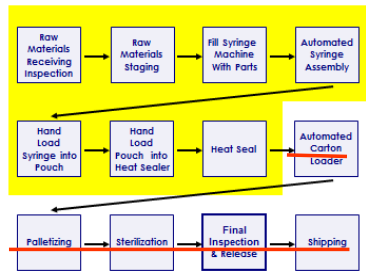
	Is	Is Not
What	Syringe pouches	Surgeon glove pouches
	Seals open or failing a pull test	Cuts, tears, sealing over product, etc.
	Failing 10 lb pull test	Failing 20 lb pull test

- Determine additional data needed

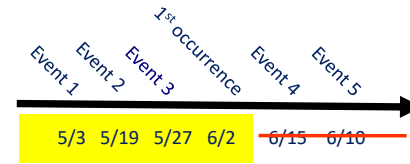
Data Needed

Leverage data to “tighten fence”

- Product System
  - ~~Hardware~~
  - ~~Software~~
  - Disposable
- Geography
  - ~~Facility A~~
  - Facility B
  - ~~Facility C~~
- Process



- Time

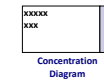


Data Location

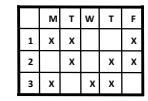
- Some already exists
  - Batch records
  - Lab notebooks
  - Previous experiments/studies
- Some can be captured on a go forward basis as it is generated during the investigation
  - Limited experiments to better characterize the problem
  - Not to test a possible cause

Data Analysis

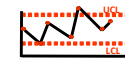
- Format data so it can be interpreted:
  - Check sheets/spreadsheets
  - Pivot tables
  - Pareto analysis
  - Concentration diagrams
  - Control charts
  - ANOM (analysis of mean)
  - Multi-variable charts
  - Capability studies
  - Histograms
  - Summary reports
  - Pie charts
  - Scatter diagrams



Concentration Diagram



Checksheet



Control Chart


Capability Study


Multi-Vari Chart

Analysis of Mean

Data Collection Plan: Additional Data Needed

Determine data needed to better characterize the answers to:

- 3 most important questions from Is/Is Not Diagram (red)
- Patterns
- Anything else deemed important

Additional Data Needed & Analysis Tools

Is	Is Not	Data Needed	Data Location	Analysis Tool
How many objects have the defect?	**How many objects could have the defect but don't?**			
5% of daily production	Historical average of .01% ✓	**Additional Data** Is the defect rate consistently 5% throughout a production shift?	Begin tracking defective pouches back to time of day they were sealed	✓ sheet

Checksheet

Used to collect What, Where, When, & How Much data

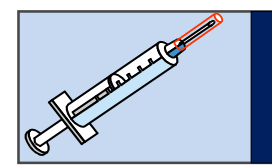
Hour	1	2	3	4	5	6	7	8
Defect count	卌卌卌卌卌 卌卌卌卌卌 卌卌卌卌 II	卌卌卌卌卌 卌卌卌卌卌 卌卌 I	卌卌卌卌卌 卌卌卌卌卌 卌卌卌卌 III	卌卌卌卌卌 卌卌卌卌卌 卌卌卌 IIII	卌卌卌卌卌 卌卌卌卌卌 卌卌卌卌卌 IIII	卌卌卌卌卌 卌卌卌卌卌 卌卌卌卌卌	卌卌卌卌卌 卌卌卌卌卌 卌卌卌 III	卌卌卌卌卌 卌卌卌卌卌 卌卌卌卌卌 II
Total defects	72	61	73	69	79	75	68	77
Product produced	1412	1298	1431	1380	1519	1470	1388	1481
Hourly defect %	5.1%	4.7%	5.1%	5.0%	5.2%	5.1%	4.9%	5.2%

Additional Data Needed & Analysis Tools

Is	Is Not	Data Needed	Data Location	Analysis Tool
Where is the defect on the object?	**Where else could it be on the object, but is not?**			
Final seal (1)	Supplier's seals (3) ✓	**Additional Data** Can the issue be narrowed down to a particular section of the final seal?	Begin collecting	Concentration diagram of a syringe pouch

Concentration Diagram

Used to collect Where and How Much data

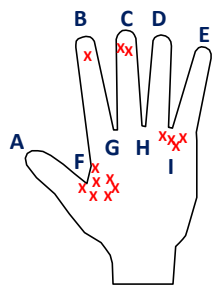


Section 1	xxxxxx xxxxxx x
Section 2	xxxxxx xxxxxx xxxxxx
Section 3	xxxxxx xxxxxx xx
Section 4	xxxxxx xxxxxx xxxx
Section 5	xxxxxx xxxxxx xxx

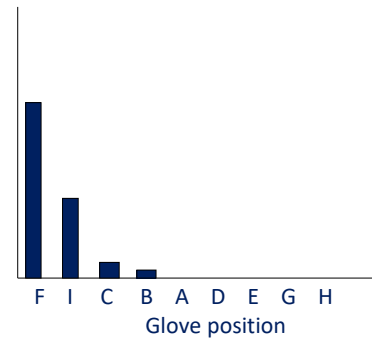
Defective area of seal

Concentration Diagram

Concentration diagram



Pareto analysis

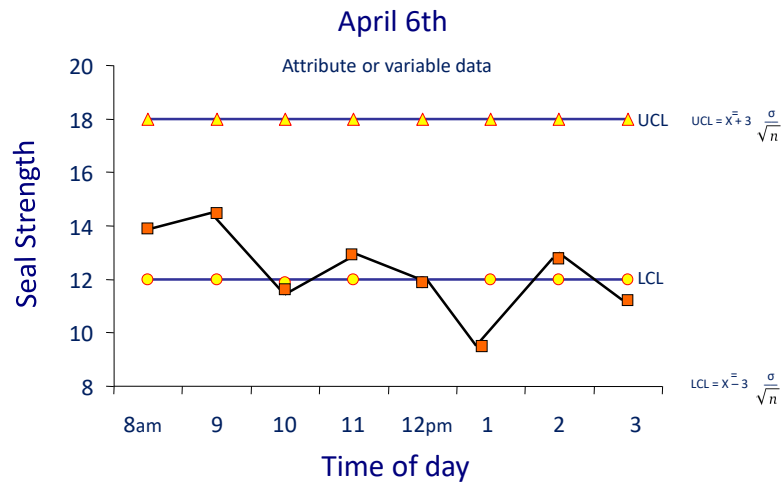


Additional Data Needed & Analysis Tools

Is	Is Not	Data Needed	Data Location	Analysis Tool
When was the defective object 1st seen (date/time)?	***When could the defective objective 1st been seen but wasn't?***			
June 1st?	Before June 1st? ✓	**Additional Data** Can this issue be identified before June 1st?	QC records for production line 3	Control chart measuring seal strength

Control Charts

Used to collect When data

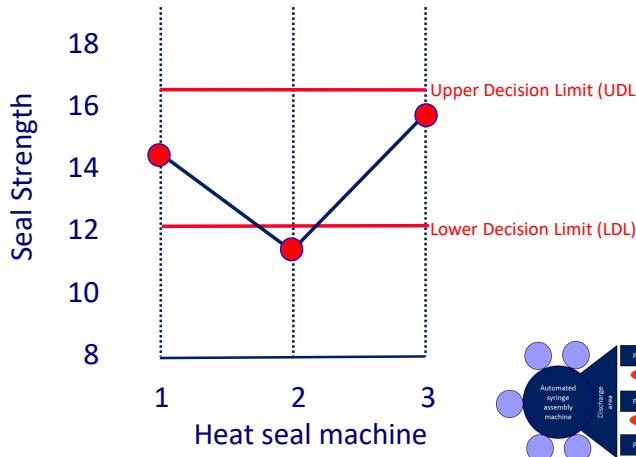


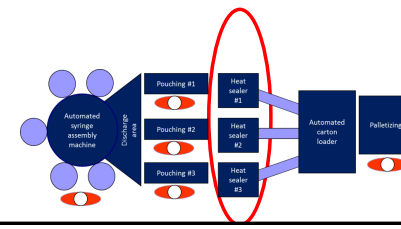
Additional Data Needed & Analysis Tools

Is	Is Not	Data Needed	Data Location	Analysis Tool
Where else is the defect?	**Where else could the defect be but is not?**			
Production line 3	Production lines 1,2,4	**Additional Data** Can the issue be narrowed down to a particular heat seal machine on production line 3?	Begin collecting samples from each heat seal machine	ANOM Multi-vari chart Capability study

Analysis of Mean (ANOM)

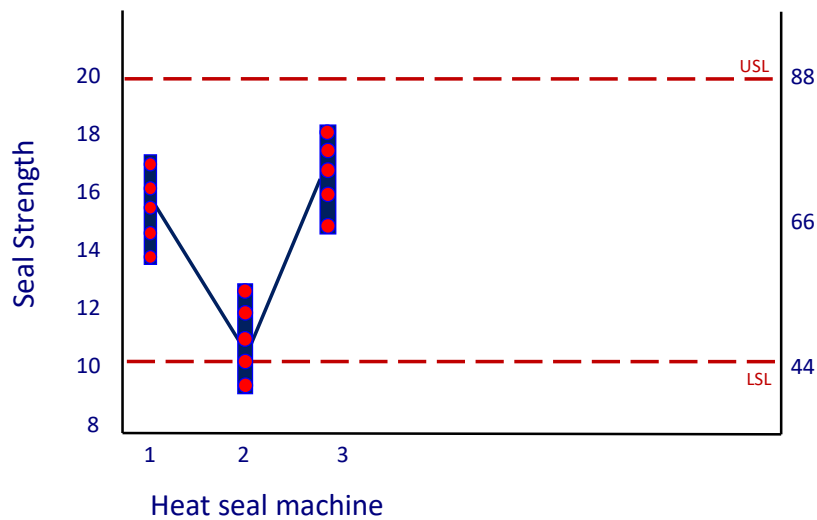
Detecting differences between similar entities
(people, work streams, machines, products, etc)





Multi-Variable Chart

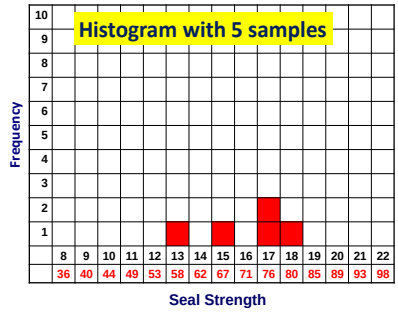
Detecting variation within and between similar entities

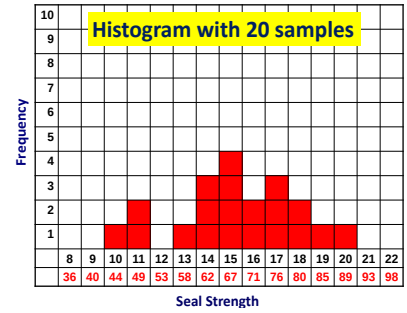


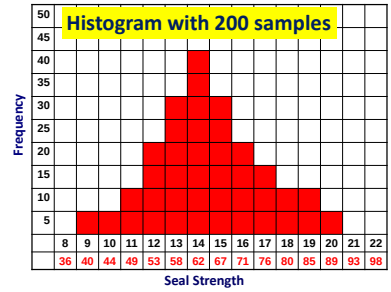
Capability Study

- Describes the performance of the product, process, machine, system, etc
  - Is there too much variation?
  - Is the variation properly targeted?
- How capable is the entity of meeting requirements?

Capability Study

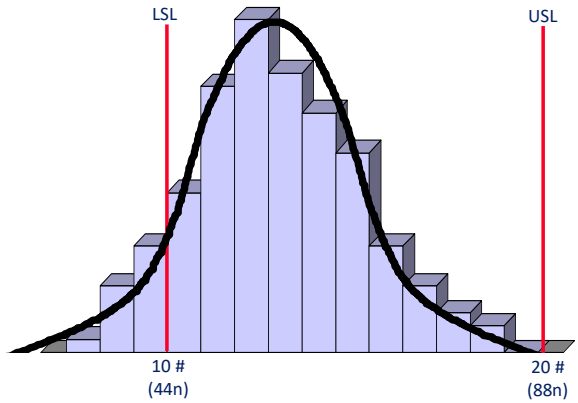






Capability Study

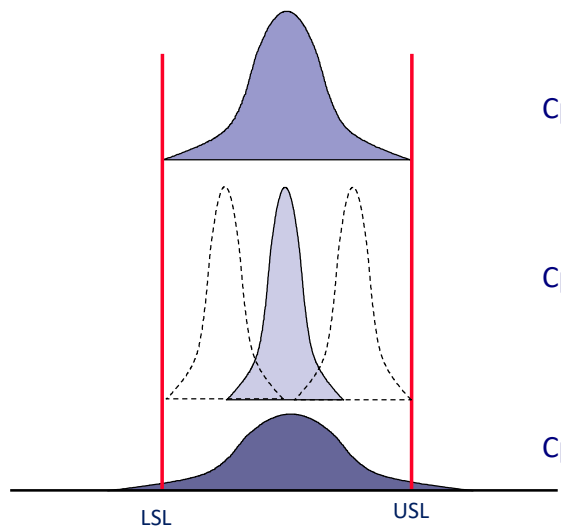
Heat seal machine #2 actual results



Is the problem one of:

- Too much variation?
- Incorrect targeting?
- Both? ✓

Capability Study



Cpk = 1

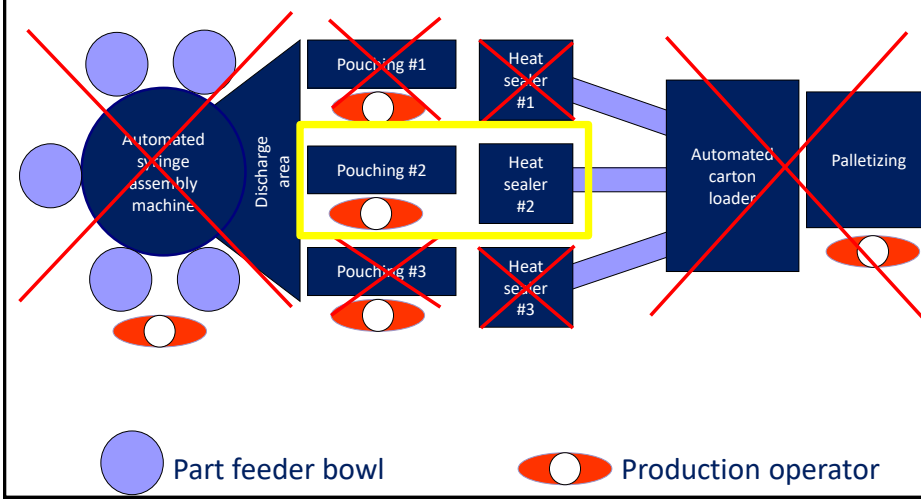
Cpk = 2

Cpk = .8

Recommended minimum Cpk $\geq$ 1.33

Leverage Data to "Tighten Fence"

Defects are in or around heat seal machine #2…

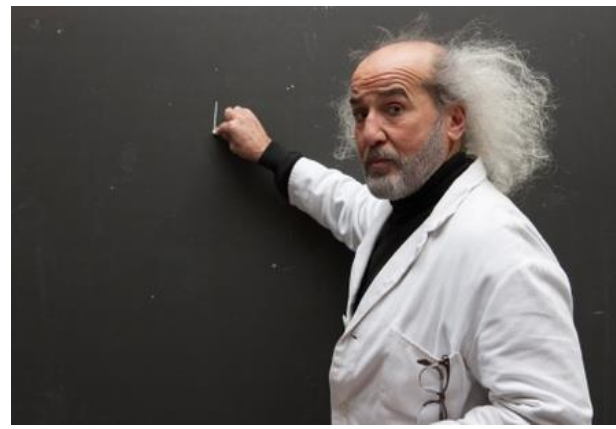


Output: Factual Is/Is Not Diagram

	Is	Is Not
What	* Syringe pouch seal	* Surgeon glove pouch seal
	Fails pull test on lower limit	Failing pull test on upper limit
	Excessive variation	Acceptable variation
	* SY217…SY235	* SY216 and earlier
Where	* Customers from all NA regions	* Some NA regions
	* Johnsville facility	* Janesville facility
	Entire final heat seal area	Part of final heat seal area
	After heat seal	Before heat seal
	* Production line 3	* Production lines 1, 2, 4
	* Heat seal machine #2	* Heat seal machine #1 or #3
When	Customer 1st reported June 1	Earlier
	Seal strength changed April 6, 10 a.m.	Earlier
	* Occurring continuously since June 1	* Sporadic
How Much	~ 5% of daily production	Historical avg .01%
	Avg defect size: 9.3#	More or less than avg
	* 1 defect seal	* 2-4 defect seals
	* Trend stable	* Trend not climbing or falling

Collect Data: Key Points

Leverage subject matter experts from outside the investigation team to help determine information needed, analyze data, identify patterns, etc



Collect Data: Key Points

- Whenever possible, collect data from:
  - Actual place where the work is being conducted
  - Actual people executing the work
  - Real time as the problem is occurring
- Critical thinking to determine additional data needed

Documentation

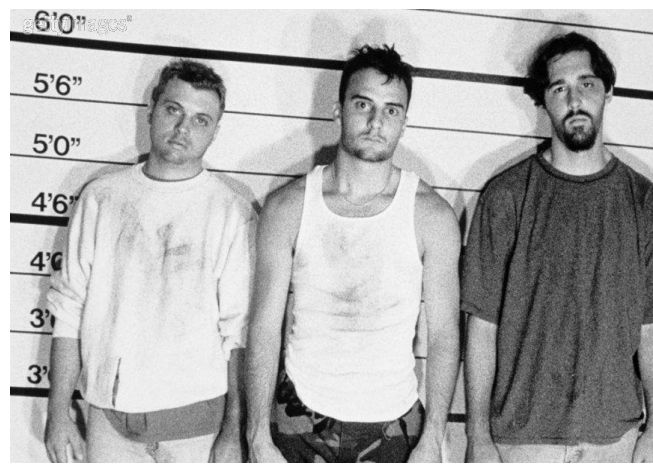
- Data collection plan
- Factual Is/Is Not diagram

Strongly recommended

- Data analysis tools

Leverage whatever is appropriate

Step 3: Identify Possible Causes



Identify Possible Causes

Input	Process	Output
Factual Is/Is Not diagram Flow diagram with inputs	Timeline of changes Differences & changes Review risk analysis Cause & effect diagram Brainstorming techniques	Possible causes

Identify Possible Causes: Key Points

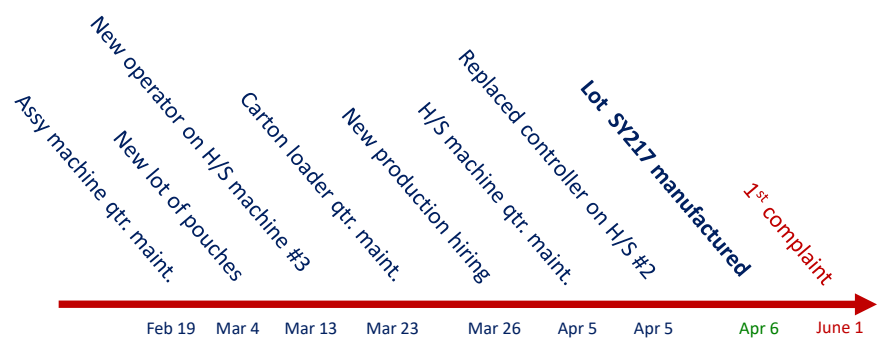
- The investigation will fail if the real root cause isn't identified
- Develop a robust list of possible causes to ensure success

Identify Possible Causes: Key Points

- Knowledge gained from Steps 1 and 2 will generate possible cause ideas
- Past experiences of investigation team members will generate possible cause ideas
- More strategies should be leveraged to ensure success

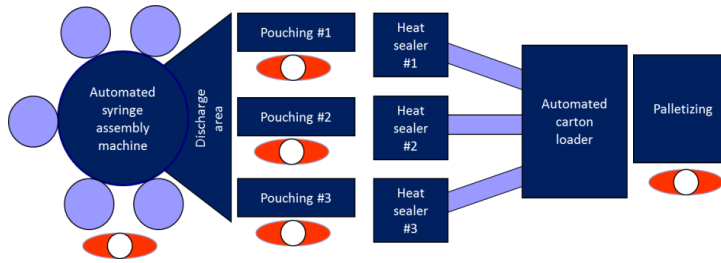
Timeline of Changes

- The problem was caused by 1 or more changes….
- List all known relevant changes in chronological order: each change identified becomes a possible cause



Differences Between Is and Is Not Facts

What is different about the Is fact compared to the corresponding Is Not fact?



	Is	Is Not	Differences
	Heat seal machine #2	Machine #1 or #3	Operator Location 71B controller

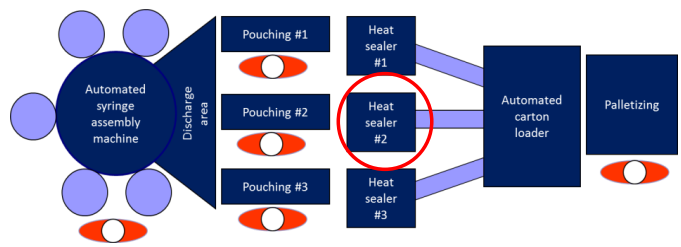
Factual Is/Is Not Diagram

	Is	Is Not
What	* Syringe pouch seal	* Surgeon glove pouch seal
	Fails pull test on lower limit	Failing pull test on upper limit
	Excessive variation	Acceptable variation
	* SY217…SY235	* SY216 and earlier
Where	* Customers from all NA regions	* Some NA regions
	* Johnsville facility	* Janesville facility
	Entire final heat seal area	Part of final heat seal area
	After heat seal	Before heat seal
	* Production line 3	* Production lines 1, 2, 4
	* Heat seal machine #2	* Heat seal machine #1 or #3
When	Customer 1st reported June 1	Earlier
	Seal strength changed April 6, 10 a.m.	Earlier
	* Occurring continuously since June 1	* Sporadic
How Much	~ 5% of daily production	Historical avg .01%
	Avg defect size: 9.3#	More or less than avg
	* 1 defect seal	* 2-4 defect seals
	* Trend stable	* Trend not climbing or falling

Differences Between Is and Is Not Facts

	Is	Is Not	Differences
What	Syringe pouch seal	Glove pouch seal	Material composition
	Fails lower limit	Fail upper limit	
	Excessive variation	Acceptable variation	
	Lots SY217 - SY235	Lots SY216 or earlier	
Where	All NA regions	Some NA regions	
	Johnsville facility	Janesville facility	Highly automated
	Entire heat seal area	Part of heat seal area	
	After heat seal	Before heat seal	
	Production line 3	Lines 1, 2, or 4	Training line
	Heat seal #2	Heat seal #1 or #3	Operator, 71B controller, location

Changes Made to Identified Differences



Changes Made to Identified Differences

	Is	Is Not	Differences	Changes
What	Syringe pouch seal	Glove pouch seal	Material composition	Changed materials Feb 25
Where	Johnsville facility	Janesville facility	Highly automated	
	Production line 3	Lines 1, 2, 4	Training line	New hiring Mar 26
	H/S machine #2	#1 or #3	Operator 71B controller Location	Assigned Mar 28 Installed Apr 5

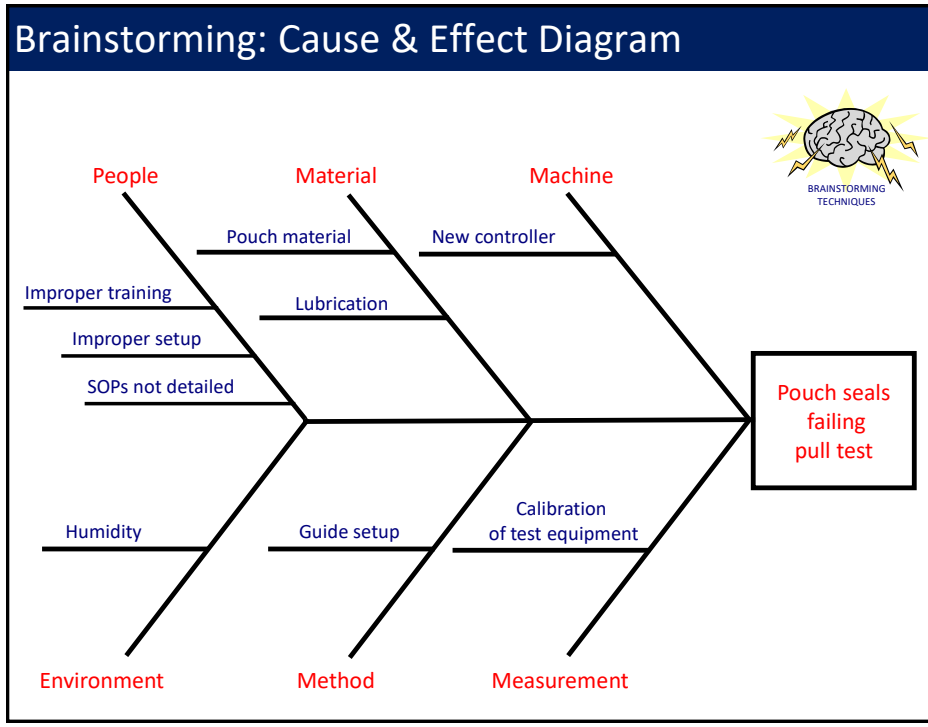
Review Risk Analysis

- Risk analysis may reveal a problem similar to the one being investigated, in which case potential failure modes and/or causes would have been identified

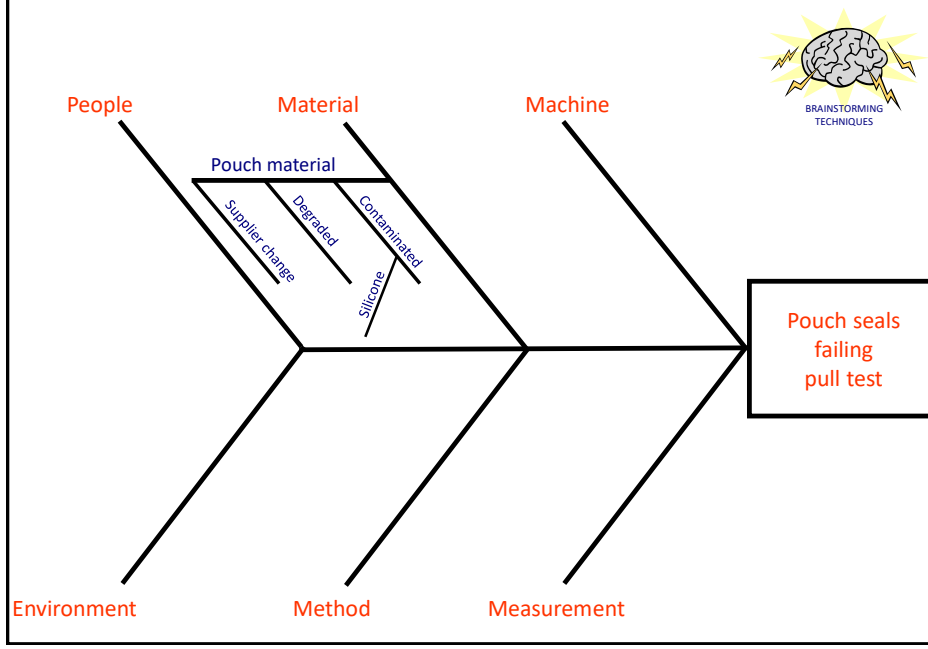
Example: Failure Mode and Effects Analysis (FMEA)

Item or Process Step	Item or Step Function	Potential Failure Mode	Potential effect	Potential Cause of Failure
- Load pouch into heat seal machine	- Proper orientation of pouch into heat seal machine	- Incorrect pouch orientation	- Seal incorrect area - Product damage - **Incomplete seal across pouch**	- Improper training - Improper guide setup

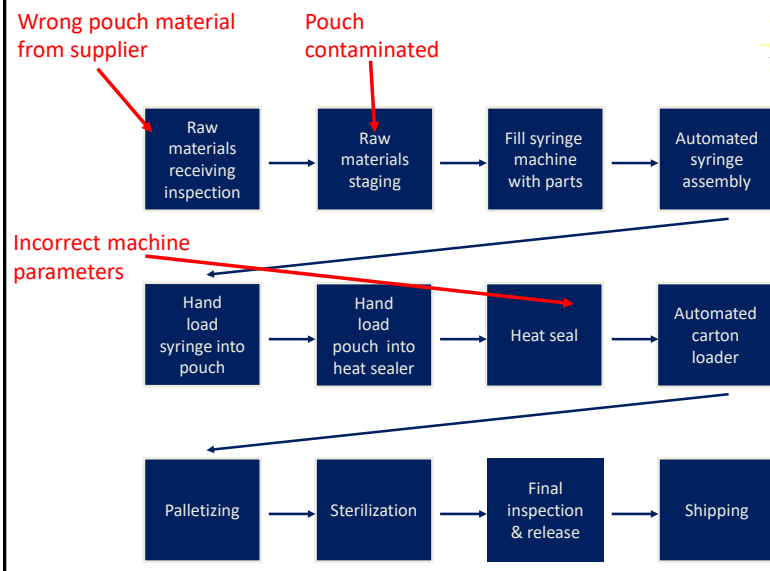
Brainstorming: Cause & Effect Diagram



Brainstorming: Cause & Effect Diagram



Brainstorm: Process Flow Diagram(s)



Brainstorming: Other Techniques

Technique

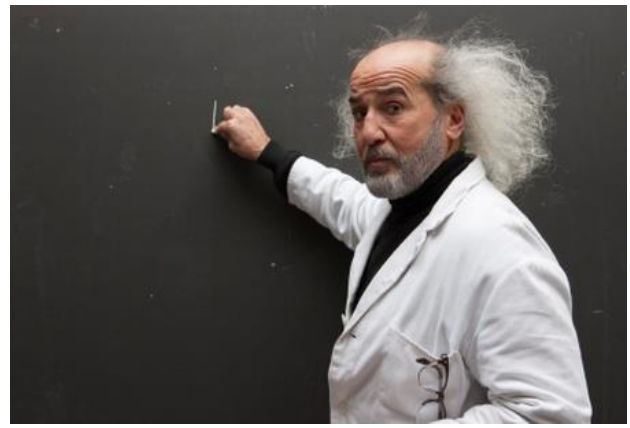
- Share ideas out loud with group
- Share ideas anonymously with group

Brainstorming rules, regardless of technique:

- Determine which method of brainstorming is most appropriate
- Record all ideas
- Do not debate ideas

Identify Possible Causes: Key Points

Leverage subject matter experts from outside the investigation team to help identify possible causes



Documentation

- Timeline of changes
- Differences and changes
- Risk analysis review
- Master list of possible causes

Strongly recommended

- Brainstorming techniques

Leverage whatever is appropriate

Step 4: Test Possible Causes

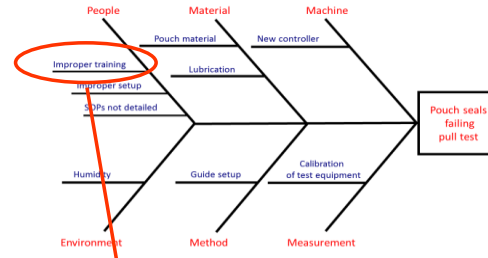
Test Possible Causes

Input	Process	Output
Factual Is/Is Not diagram Robust list of possible causes	Test possible causes against facts	Reduced list of probable causes

Test Possible Causes

Test each possible cause…

…against each set of facts in the Is/Is Not diagram



	Is	Is Not
What	* Syringe pouch seal	* Surgeon glove pouch seal
	Fails pull test on lower limit	Failing pull test on upper limit
	Excessive variation	Acceptable variation
	* SY217…SY235	* SY216 and earlier
	Manufacturing process	Earlier or later processes
Where	* Customers from all NA regions	* Some NA regions
	* Johnsville facility	* Janesville facility
	Entire final heat seal area	Part of final heat seal area
	After heat seal	Before heat seal
	* Production line 3	* Production lines 1, 2, 4
	* Heat seal machine #2	* Heat seal machine #1 or #3
When	Customer 1st reported June 1	Earlier
	Seal strength changed April 6, 10 a.m.	Earlier
	* Occurring continuously since June 1	* Sporadic
How Much	~ 5% of daily production	Historical avg .01%
	Avg defect size: 9.3#	More or less than avg
	* 1 defect seal	* 2-4 defect seals
	* Trend stable	* Trend not climbing or falling

Test Possible Causes

Testing formula:

If x is the cause, how does it explain each set of Is and Is Not facts?

Example:

If the new 71B controller installed on heat seal machine #2 the evening of April 5 is causing the pouch seal failures, how does it explain…

Factual Is/Is Not Diagram

	Is	Is Not
What	* Syringe pouch seal	* Surgeon glove pouch seal
	Fails pull test on lower limit	Failing pull test on upper limit
	Excessive variation	Acceptable variation
	* SY217…SY235	* SY216 and earlier
Where	* Customers from all NA regions	* Some NA regions
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	Entire final heat seal area	Part of final heat seal area
	After heat seal	Before heat seal
	* Production line 3	* Production lines 1, 2, 4
	* Heat seal machine #2	* Heat seal machine #1 or #3
When	Customer 1st reported June 1	Earlier
	Seal strength changed April 6, 10 a.m.	Earlier
	* Occurring continuously since June 1	* Sporadic
How Much	~ 5% of daily production	Historical avg .01%
	Avg defect size: 9.3#	More or less than avg
	* 1 defect seal	* 2-4 defect seals
	* Trend stable	* Trend not climbing or falling

Test Possible Causes

If the new 71B controller installed on heat seal machine #2 the evening of April 5 is causing the pouch seal failures, how does it explain…

Test Sheet

Is	Is Not	Facts not explained	Assumptions
Control chart showed seal strength changed at 10 am on April 6	Earlier	Seal strength changed at 10 am	Sample size too small (see multi vari chart)

Test Possible Causes

Possible causes	Facts not explained	Assumptions
New 71B controller installed April 5	Seal strength changed at 10 AM on April 6	Sample size too small
~~Change in sterilization process~~	~~Defect 1st seen after heat seal~~	~~None~~
Inadequate operator training	Only machine #2 No problem until April 6	Operator #2 has different learning needs Less supervision starting April 6

Contradiction Matrix

Causes \ Facts	Entire seal vs partial	10 AM vs 8AM on 6/1	Machine #2 vs #1 & #3	After sealing vs later	6/1 vs later or earlier	Continuous vs sporadic	5% vs more or less
71B controller	O	A	O	O	O	O	O
~~Sterilization~~	~~O~~	~~O~~	~~X~~				
Inadequate training	O	A	A	O	O	A	O
~~Humidity~~	~~O~~	~~O~~	~~X~~				
~~Test equipment calibration~~	~~O~~	~~A~~	~~X~~				

O - Facts support cause X - Facts contradict cause A - Assumptions

Test Possible Causes: Key Points

- Possible causes must only be ruled out using facts
- Assumptions must be based on real life experiences

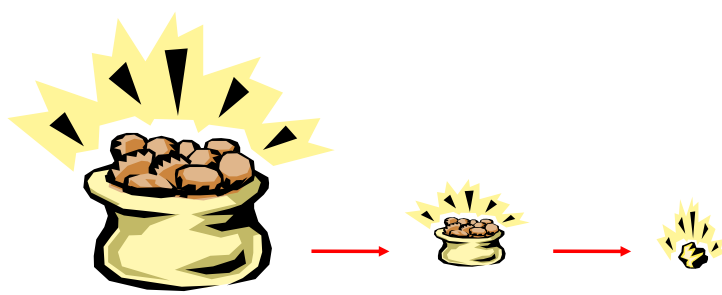
Documentation

- Test sheet for each possible cause — Strongly recommended
- Contradiction matrix — Optional

Step 5: Identify Technical & Systemic Root Causes

Identify Technical & Systemic Root Causes

- A large list of possible causes has been reduced to a smaller list of probable causes
- What needs to be done to identify the technical root cause(s)?



Identify Technical & Systemic Root Causes

Input	Process	Output
Probable causes	Verify assumptions Conduct experiments	Technical root cause(s)
	3 Legged 5 Why	Systemic root cause(s)

Identify Technical Root Cause(s)

Assumptions

Collect data to verify assumptions made to help a probable cause explain the Is/Is Not facts

Identify Technical Root Cause(s)

Causes \ Facts	Entire seal vs partial	10 AM vs 8AM on 6/1	Machine #2 vs #1 & #3	After sealing vs later	6/1 vs later or earlier	Continuous vs sporadic	5% vs more or less
71B controller	O	A	O	O	O	O	O
~~Sterilization~~	~~O~~	~~O~~	~~X~~				
Inadequate training	O	A	A	O	O	A	O
~~Humidity~~	~~O~~	~~O~~	~~X~~				
~~Test equipment calibration~~	~~O~~	~~A~~	~~X~~				

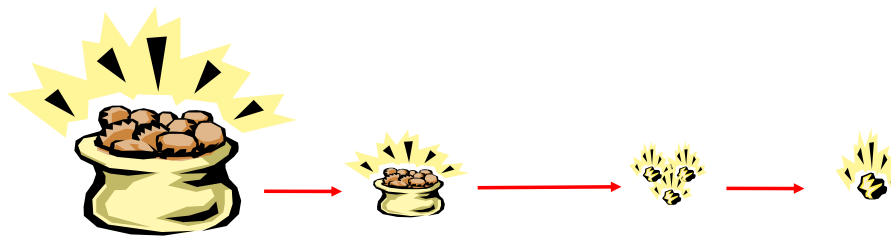
O - Facts support cause X - Facts contradict cause A - Assumptions

Identify Technical Root Cause(s)

Possible causes	Facts not explained	Assumptions
New 71B controller installed April 5	Seal strength changed at 10 AM on April 6 ✓	Sample size too small
~~Inadequate operator training~~	~~Only machine #2~~ ~~No problem until April 6~~	~~Operator #2 has different learning needs~~ ~~Less supervision starting April 6~~

Identify Technical Root Cause(s)

- A large list of possible causes has been reduced to a smaller list of probable causes
- Verifying assumptions may further reduce the list of probable causes
- Leverage experiments to find the technical root cause(s)



Identify Technical Root Cause(s)

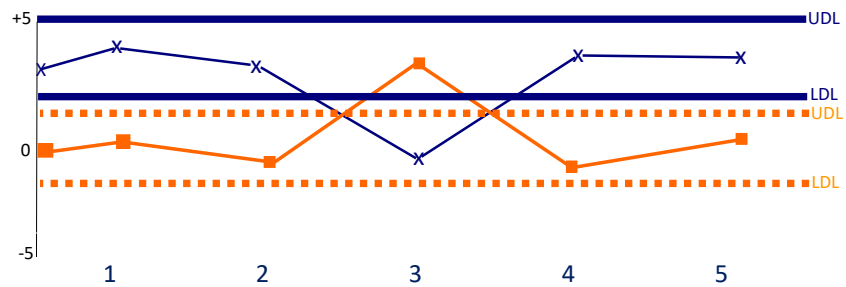
Examples of experiments

Input	Process	Output
Probable causes	Component swapping study Screening experiment Response surface studies Robust tolerance analysis	Technical root cause(s)

Component Swapping Study

Determine if a part, component, input, person, etc is responsible for differences in performance between similar entities

Component Swapping Study

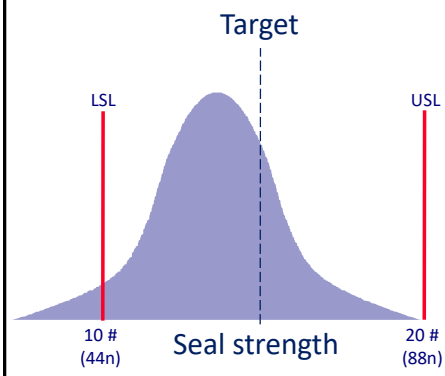


Swap	Description	Resulting change
1	Battery	None
2	Hands	None
3	Gear box	Full reversal
4	Drive motor	None
5	Confirmation	None

X Blue watch

■ Orange watch

Causes for Excessive Variation



- Excessive variation
- Improper targeting

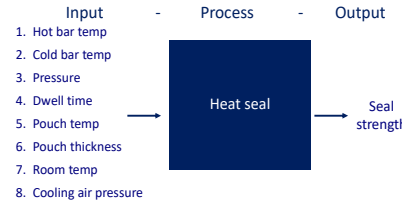
Causes for Excessive Variation

Input	Process	Output
Hot bar temp Cold bar temp Pressure Dwell time Pouch temp Pouch thickness Room temp Cooling air pressure	→ Heat seal →	Sealed pouch

Excessive variation and/or improper targeting of 1 or more inputs may cause excessive variation and/or improper targeting of the output

Screening Experiment

- Identifies the key inputs that affect the output
- Used when there are numerous inputs (≥ 6) to dramatically reduce the amount of effort needed with a follow up response surface study



This type of experiment involves changing one or more inputs and measuring the resulting effect on one or more outputs

Screening Experiment

Results

Some input variables have little or no effect on pouch seal strength

1. ~~Cold bar temperature~~
2. ~~Cooling air pressure~~
3. ~~Pouch thickness~~
4. ~~Room temperature~~

Other input variables do have an effect on pouch seal strength

1. Hot bar temperature
2. Pressure
3. Dwell time
4. Pouch temperature

Response Surface Studies

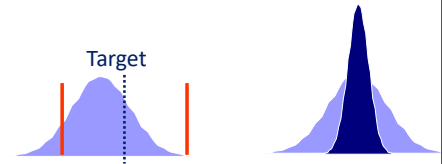
- Builds on the data from a screening experiment
- Determines the equation relating the inputs to the outputs
- Identifies the best set points of the inputs

Response Surface Studies

Results

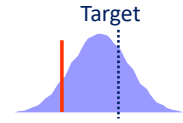
2 input variables affect both the seal strength average and the amount of variation

- Hot bar temperature
- Dwell time



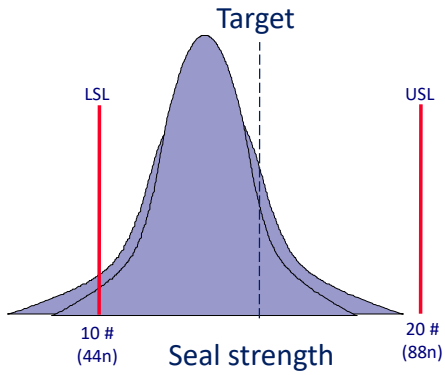
2 other input variables affect only the seal strength average

- Pressure
- Pouch temperature



Response Surface Studies

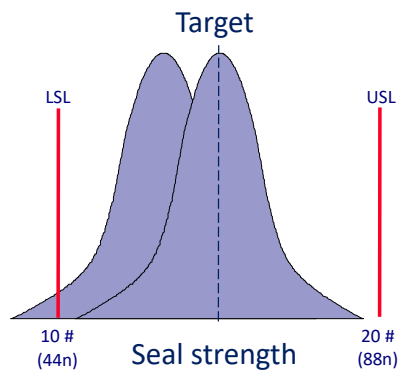
First, reduce variation…



1. Set hot bar temperature to 200°F (93°C)
2. Set dwell time to .75 seconds

Response Surface Studies

Second, optimize variation…



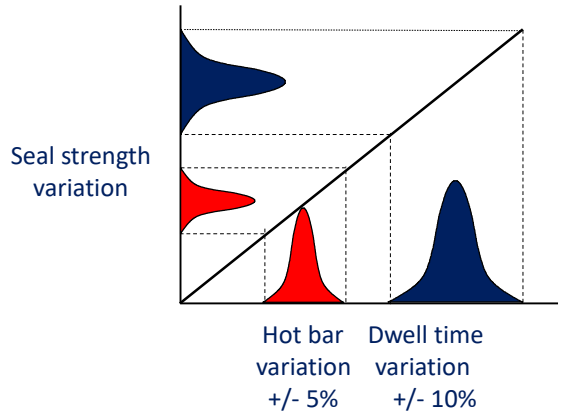
Options

- Adjust the pressure setting to 80 psi (550 kPa)

or

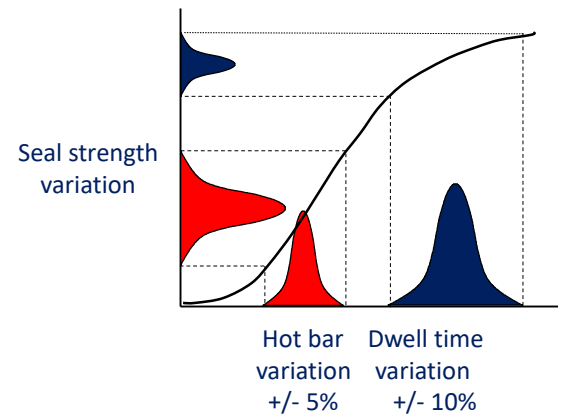
- Maintain the pouch temperature at 95º F (35ºC) to center the process on the target

Robust Tolerance Analysis



Effects of input variation on output variation

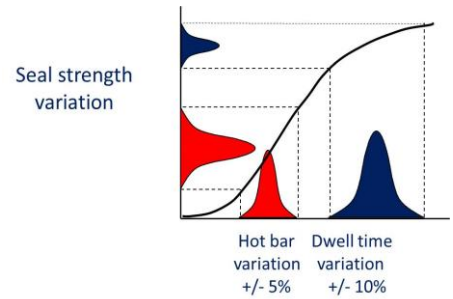
Robust Tolerance Analysis



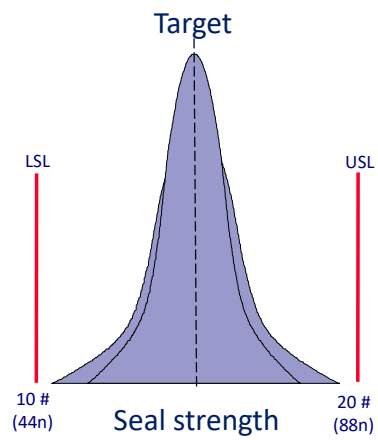
Effects of input variation on output variation

Robust Tolerance Analysis

- The hot bar setting contributed more variation to seal strength than dwell time
- Reduce hot bar variation further by investing in a more capable controller



Robust Tolerance Analysis



Purchase a controller capable of holding temperature at 200°F ± 2% (93°C ± 2%)

Identify Technical Root Cause(s)

Causes \ Facts	Entire seal vs partial	10 AM vs 8AM on 6/1	Machine #2 vs #1 & #3	After sealing vs later	6/1 vs later or earlier	Continuous vs sporadic	5% vs more or less
71B controller	O	A	O	O	O	O	O
~~Sterilization~~	O	O	X				
~~Inadequate training~~	O	A	A	O	O	A	O
~~Humidity~~	O	O	X				
~~Test equipment calibration~~	O	A	X				

O - Facts support cause X - Facts contradict cause A - Assumptions

Identify Technical Root Cause(s): Key Points

When, through experiments, the problem can be controlled, moved, manipulated, etc…the technical root cause has been identified

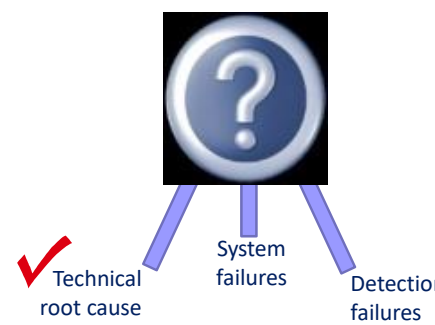
Identify Technical & Systemic Root Causes

Input	Process	Output
Probable causes	Verify assumptions Conduct experiments	✓ Technical root cause(s)
	3 Legged 5 Why	Systemic root cause(s)

Identify Systemic Root Cause(s)

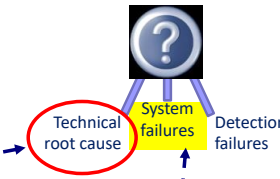
Asking "why" may uncover systemic root causes that:

- Allowed the change to occur
- Failed to detect the change



3L5WHY
(3 Legged 5 Why's)

Identify Systemic Root Cause(s)



Why did this change occur?

The 71B controller was not capable of meeting process requirements

Why was a controller selected that wasn't capable?

Process needs weren't reviewed before a replacement was selected

Why weren't process needs reviewed?

Focus was on cost, 71B was less expensive

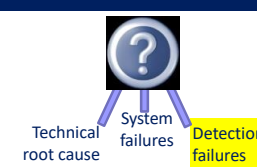
Why was focus on cost?

Communication systems allowed people to overreact to management stressing cost control

Why did the system allow this to happen?

???

Identify Systemic Root Cause(s)



Why didn't we detect the controller wasn't capable?

Process validation wasn't conducted

Why wasn't process validation conducted?

Validation department was unaware the control had been changed

Why was the Validation Department unaware?

Systems allowed for to Mechanic forgot to communicate

Why did the systems allow this to happen?

???

Documentation

- Test sheet with verification of assumptions
- Experiments & results
- 3L5Why detailing technical & systemic root cause(s)

Strongly recommended

Step 6: Determine Corrective & Preventive Actions

Determine Corrective & Preventive Actions

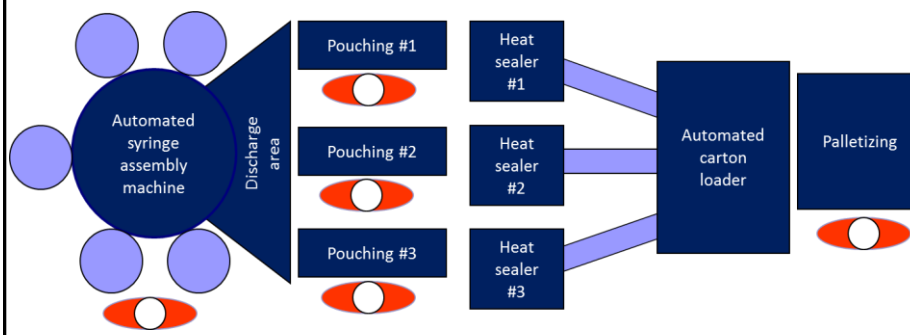
Input	Process	Output
Technical & systemic root causes	Mistake proofing vs. optimization & variation reduction (OVR)	Corrective/preventive action(s)
	FMEA Design verification Process validation	Risk mitigation
	Future monitoring	Control plan

Documentation

21 CFR 820.100(a)(3) Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems

Determine Corrective & Preventive Actions

How are technical problems such as pouch seals failing a pull test resolved?



Determine Corrective & Preventive Actions

All root causes will result from:

Human error

Mistake proofing

Too much variation

Optimization & variation reduction (OVR)

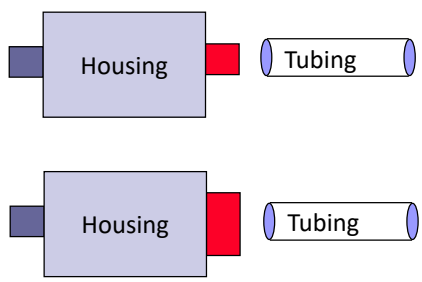
Mistake Proofing

Ensuring the problem…

- cannot occur again
- cannot get through our systems undetected

Mistake Proofing

Eliminate: Make it impossible for the defect to occur



Example: Designing components so they can only be assembled the correct way

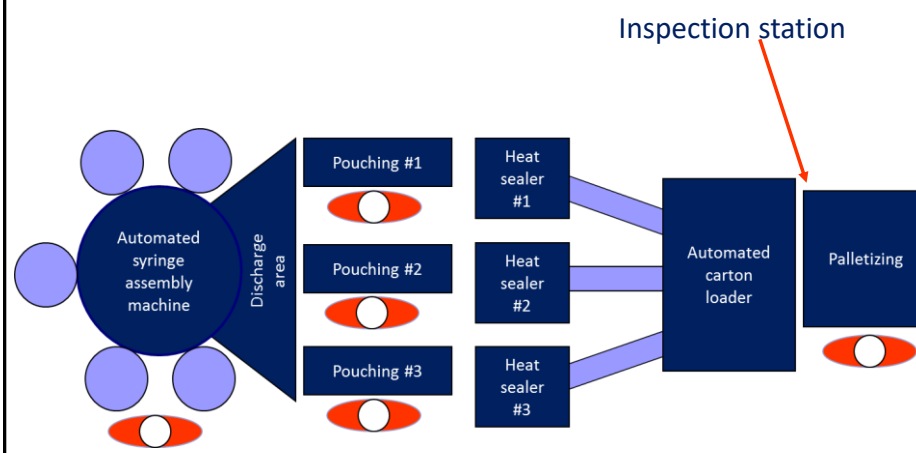
Mistake Proofing

Facilitate: Reduce the probability of the defect occurring

Example: Double entries when establishing a new password to reduce the probability of a typing error

Mistake Proofing

Flag: Implementing an inspection

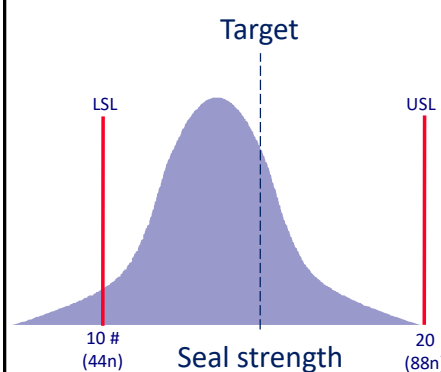


Mistake Proofing

Mitigiation: Reduce the consequences of defect as it's occurring

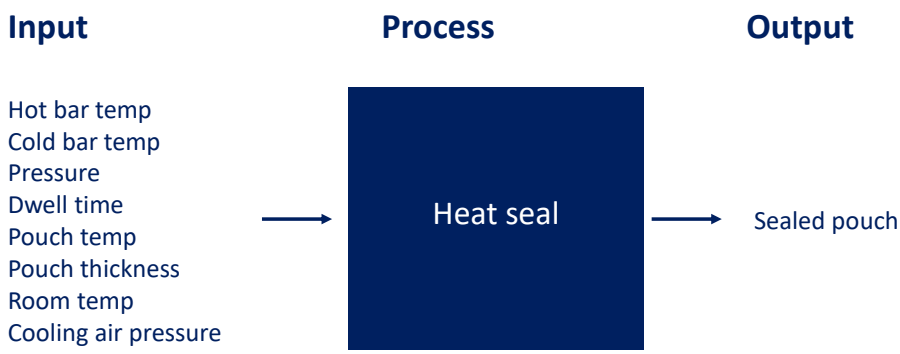
Used when the defect cannot be controlled

Optimization & Variation Reduction (OVR)



- Excessive variation
- Improper targeting

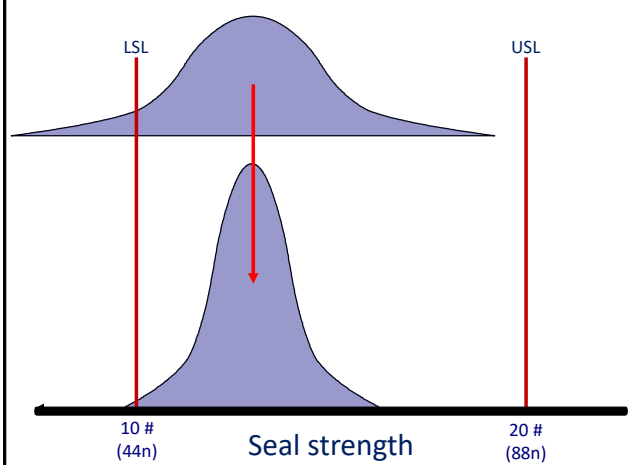
Optimization & Variation Reduction (OVR)



Excessive variation and/or improper targeting of 1 or more inputs may cause excessive variation and/or improper targeting of the output

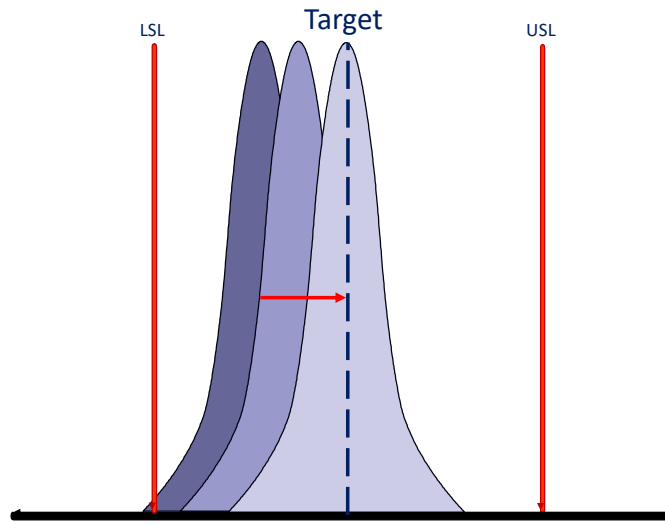
Optimization & Variation Reduction (OVR)

1st reduce performance variation…



Optimization & Variation Reduction (OVR)

2nd move performance as close to target as possible



Corrective & Preventive Action Plan (3L5Why)

Root Cause	Corrective Action	Risk Mitigation	Control Plan	Acceptance Criteria
Technical: Change to 71B controller	Replace with standard model controller historically leveraged			1. Capability study ≥1.33 Cpk 2. Defect rate returns to <.01% for 3 straight days
System: People overreacting to management stressing cost control	1. Mgmt to address balancing cost and quality at next all employee meeting 2. Topic at each management review of QS for next year			1. Conduct by 8/31 2. No recurring issues for next year
Detection: Mechanic forgot to communicate to Validation Dept	Revise maintenance electronic system to not allow mechanic to close out WO without sending change notice to Validation Dept			1. No communication failure in next 6 months

Risk Mitigation

21 CFR 820.100(a)(4) Procedures for verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device

Risk Mitigation

Consider unintended consequences of the correction/preventive actions…

- Review risk analysis
  - FMEA, fault tree analysis, etc
- Repeat design verification studies
- Repeat process validation studies

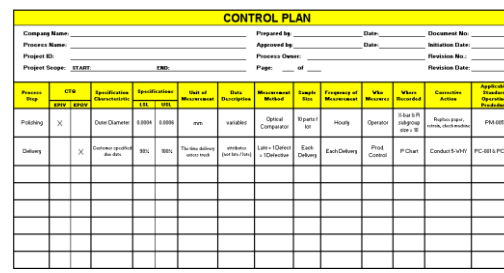
Corrective & Preventive Action Plan (3L5Why)

Root Cause	Corrective Action	Risk Mitigation	Control Plan	Acceptance Criteria
Technical: Change to 71B controller	Replace with standard model controller historically leveraged	Validate heat seal process		1. Capability study ≥1.33 Cpk 2. Defect rate returns to <.01% for 3 straight days
System: People overreacting to management stressing cost control	1. Mgmt to address balancing cost and quality at next all employee meeting 2. Topic at each management review of QS for next year	Front line mgrs stress importance at next team meeting		1. Conduct by 8/31 2. No recurring issues for next year
Detection: Mechanic forgot to communicate to Validation Dept	Revise maintenance electronic system to not allow mechanic to close out WO without sending change notice to Validation Dept	Validate electronic system		1. No communication failure in next 6 months

Control Plan

Ensure the problem remains fixed…

- Before & after measurements
- Monitoring performance
- Quality process checks
- Standardization


CONTROL PLAN

Company Name: _____ Prepared by: _____ Date: _____ Document No: _____

Process Name: _____ Approved by: _____ Date: _____ Initiation Date: _____

Project ID: _____ Process Owner: _____ Revision No.: _____

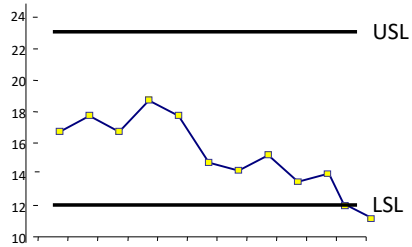
Project Scope: START: _____ END: _____ Page: ___ of ___ Revision Date: _____

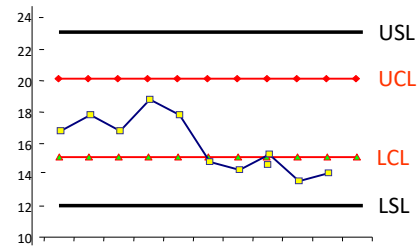
Process Step	CTQ		Specification Characteristic	Specifications		Unit of Measurement	Data Description	Measurement Method	Sample Size	Frequency of Measurement	Who Measures	Where Recorded	Corrective Action	Applicable Standard Operating Procedure
	EPIV	EPDV		LSL	USL									
Polishing	X		Bore Diameter	0.0004	0.0006	mm	variables	Optical Comparator	10 parts / lot	Hourly	Operator	8 Bad & Rt subgroup size = 10	Replace paper, retrain, check machine	PM-005
Delivery		X	Customer specified due date	95%	100%	The time delivery truck	Late = 1/Defect 0 = 0/Defective	Late = 1/Defect 0 = 0/Defective	Each Delivery	Each Delivery	Prod. Control	P Chart	Conduct 5-WHY	PC-001 & PC-002

Control Plan

Monitor performance

- Early warning to minimize recurrence

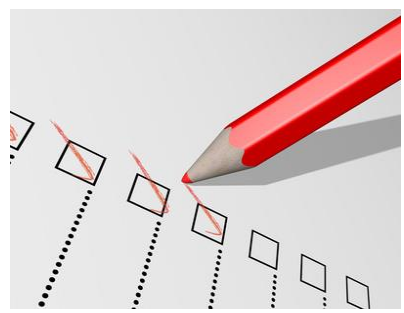




Control Plan

Quality process checks (audits)…

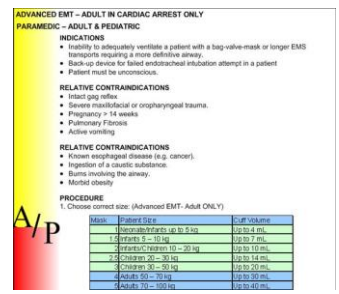
- Checking process inputs to minimize non conformances



Control Plan

Standardization

- Ensuring important elements of a process are performed consistently
- Developing procedures:
  - Specify tasks and how they need to be executed
  - Provide direction when and how inputs are to be adjusted
  - Training



Corrective & Preventive Action Plan (3L5Why)

Root Cause	Corrective Action	Risk Mitigation	Control Plan	Acceptance Criteria
Technical: Change to 71B controller	Replace with standard model controller historically leveraged	Validate heat seal process	1. Control chart each machine 2. Same for all lines	1. Capability study ≥1.33 Cpk 2. Defect rate returns to <.01% for 3 straight days
System: People overreacting to management stressing cost control	1. Mgmt to address balancing cost and quality at next all employee meeting 2. Topic at each management review of QS for next year	Front line mgrs stress importance at next team meeting	Electronic tracking of front line mgrs	1. Conduct by 8/31 2. No recurring issues for next year
Detection: Mechanic forgot to communicate to Validation Dept	Revise maintenance electronic system to not allow mechanic to close out WO without sending change notice to Validation Dept	Validate electronic system	Verify during internal audits	1. No communication failure in next 6 months

Documentation

Leverage the 3L5Why to document:

- Corrective/preventive actions plans for technical, systemic, and detection failures
- Risk mitigation for unintended consequences (leveraging appropriate techniques)
- Control plan to monitor corrective/preventive action plan performance
- Acceptance criteria to determine success

Strongly recommended

Step 7: Verify Corrective & Preventive Actions

Verify Corrective & Preventive Actions

Input	Process	Output
Corrective/preventive actions	Implement Measure effectiveness Ensure control plan is working Share the knowledge	Technical problem disappears No new problems arise Problem stays corrected

Verify Corrective & Preventive Actions

21 CFR 820.100(a)(5) Procedures for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems

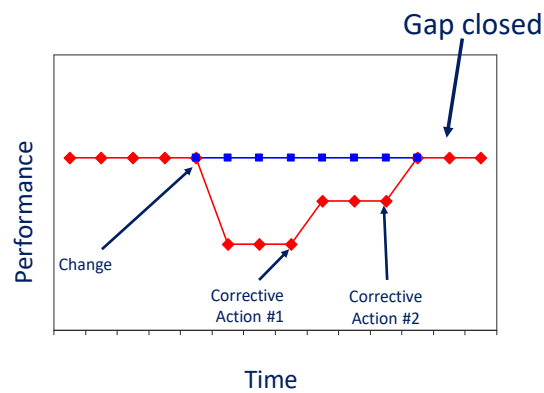
21 CFR 820.100(a)(4) Procedures verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device

Verifying Corrective & Preventive Actions

Documenting that the corrective/preventive actions have been implemented

Validating Corrective & Preventive Actions

Demonstrating with data that the previous level of performance has been restored or the requirement is now being met (effectiveness checks)



Validating Corrective & Preventive Actions

If the performance gap persists…

- The corrective action may not have been completely effective
  - How was corrective action implemented?
  - How were effectiveness measures taken?
  - Does more need to be done?

If the performance gap still persists…

- There must be more than 1 technical root cause
  - Assumptions may need to be reviewed to flush out a 2nd technical root cause
  - Go back to Step 3 to identify more possible causes and continue to follow the process

Root Cause	Corrective/Preventive Action	Risk Mitigation	Control Plan	Acceptance Criteria	Actual Measure
Technical: Change to 71B controller	Replace with standard model controller historically leveraged	Validate heat seal process	1. Control chart at each machine 2. Same on all lines	1. Capability study ≥1.3Cpk 2. Defect rate returns to <.01% for 3 days	1. 1.8 Cpk 2. Defect rate = .01%
System: People overreacting to management stressing cost control	1. Mgt to address at next all employee meeting 2. Topic at each management review of QS for next year	Dept. managers stress at following dept meeting	Electronic tracking of front line mgrs	1. Conduct by 8/31 2. No recurring issues	1. Done on 8/27 2. No issues recurred
Detection: Mechanic forgot to communicate to Validation Dept	Revise maint. system to not allow mechanic to close out WO without sending change notice to Validation Dept	Validate system	Verify during internal audits	1. No communication failure in next 6 months	1. No Failures

Capture the Knowledge

- Update risk analysis to reflect knowledge gained during the investigation
- If problem occurs again in the future, new investigation team should be able to resolve much more quickly

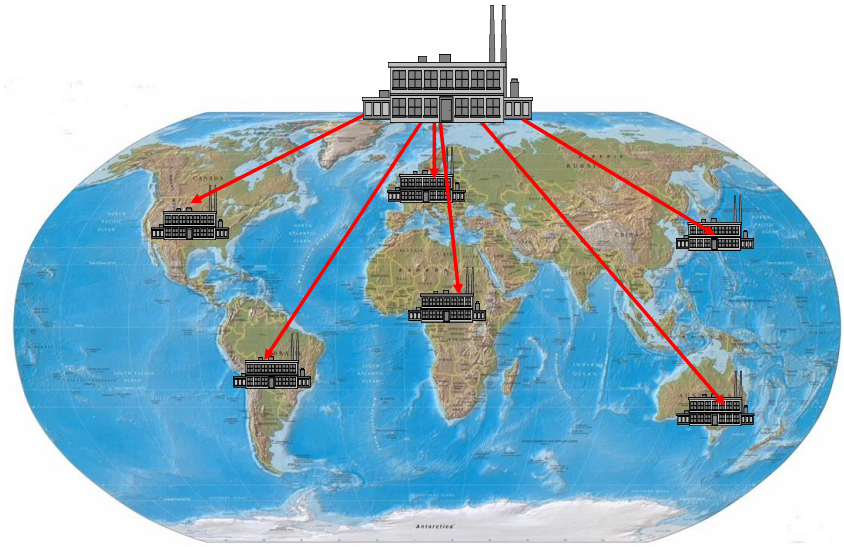
Failure Mode & Effects Analysis (FMEA)

Item or process step	Item/step function	Potential failure mode	Potential effect	Potential causes of failure
Stencil "For Demo Only" on flotation device	Identify flotation device to be used for demo	Incorrect paint	• Red sweat • Itching / burning sensation	• Improper training • Forgets

Preventive Actions

21 CFR 820.100(a)(6) Procedures for ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems

Preventive Actions



Communicate lessons learned to appropriate parties

Root Cause	Corr. / Prev. Action	Acceptance Criteria	Actual Measure	Additional Prev. Actions
Technical: Change to 71B controller	Replace with standard model controller historically leveraged	1. Capability study ≥1.3Cpk 2. Defect rate <.01% for 3 days	1. 1.8 Cpk 2. Defect rate = .01%	1. Control chart at all heat seal stations 2. Review with Janesville
System: People overreacting to management stressing cost control	1. Mgt to address at next all employee meeting 2. Topic at each mgt. review of QS for next year	1. Conduct by 8/31 2. No repeat issues	1. Done on 8/27 2. No repeat issues	Review with Janesville facility
Detection: Mechanic forgot to transmit change notice to Validation Dept	Revise maint system so WO can't be closed out without sending change notice to Validation Dept	1. No communication failure in next 6 months	1. No Failures	Review with Janesville facility

Documentation

Leverage the 3L5Why to document:

- Verify the corrective/preventive actions have been implemented & documented
- Validate with data (effectiveness checks) that performance has been restored

Strongly recommended

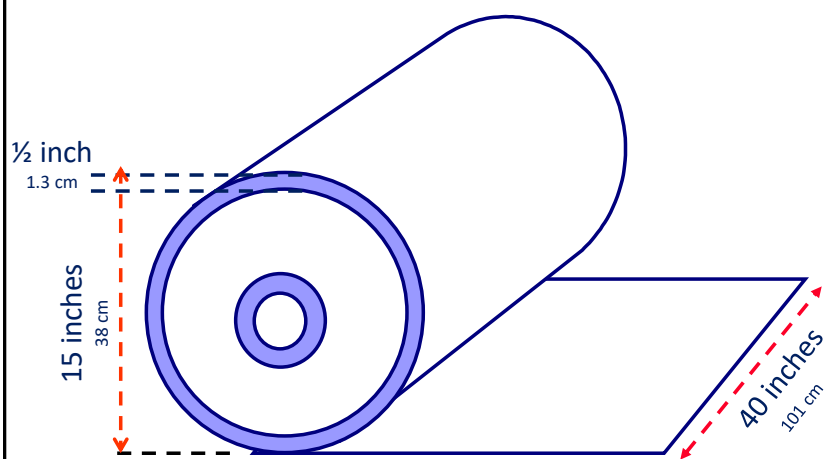
Verify Corrective & Preventive Actions

If the corrective/preventive actions were successful…

- The technical problem disappears
- No new problems arise
- Problem stays corrected

The Orange Company Case

Film Dimensions

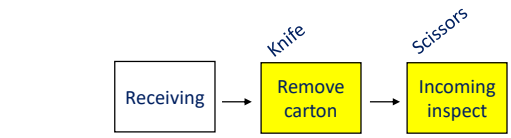


Process Flow

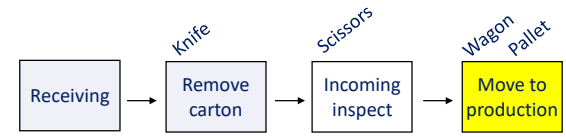
Receiving

Each film shipment = 1 supplier/part lot = 5 pallets with 9 cartons/pallet

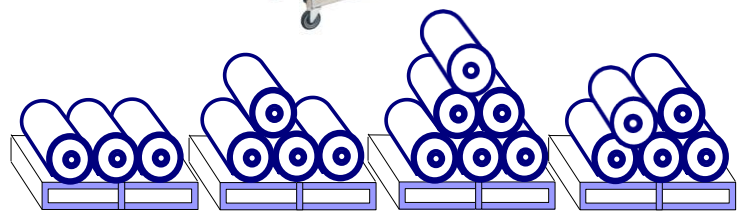
Process Flow



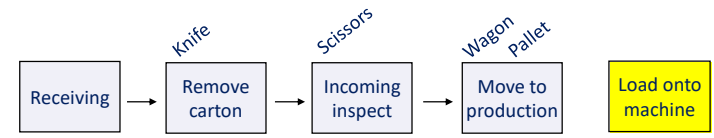
Process Flow



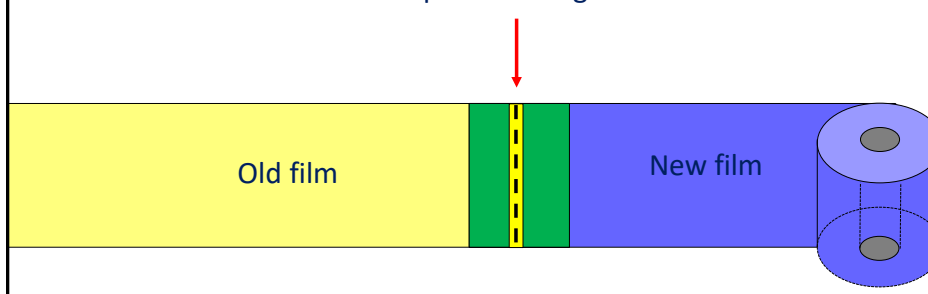
Film still in polybag



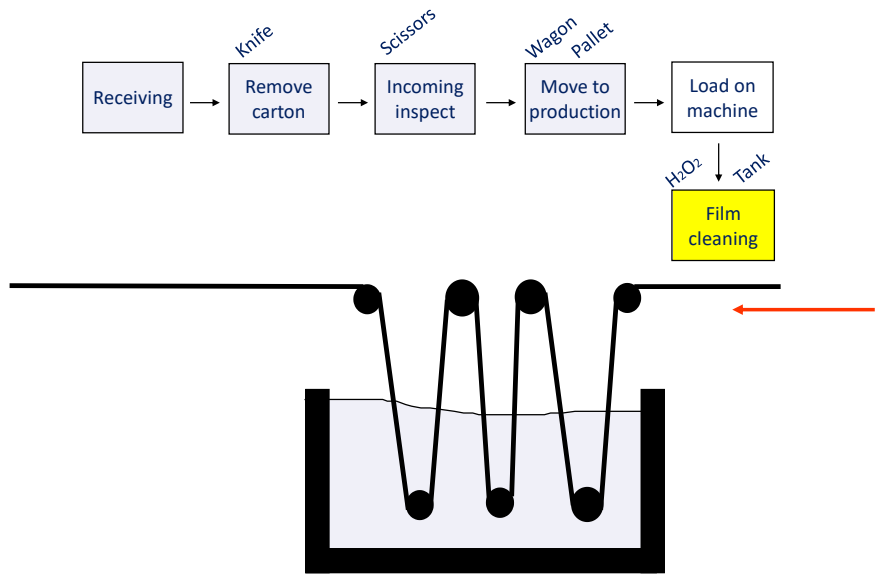
Process Flow



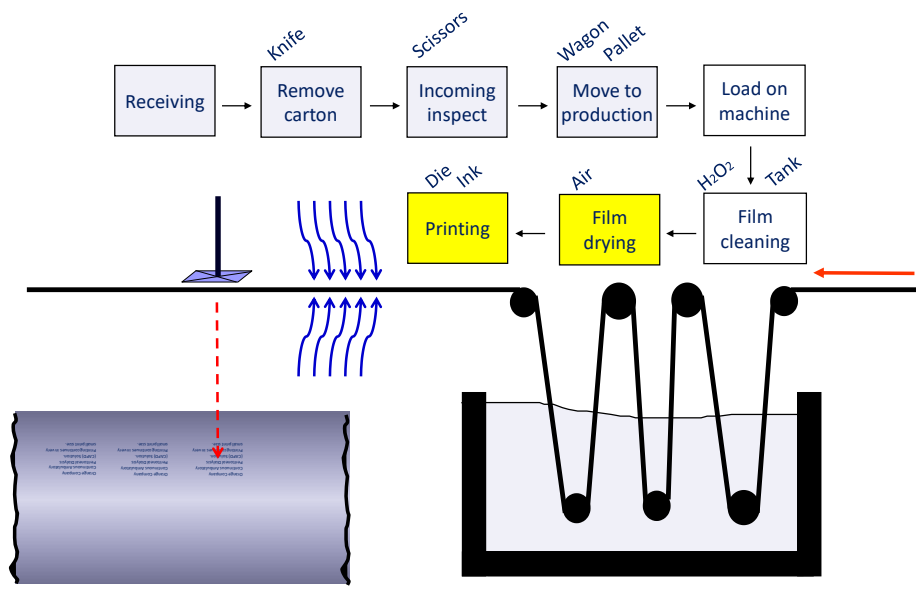
Heat seal the overlap to splice film together



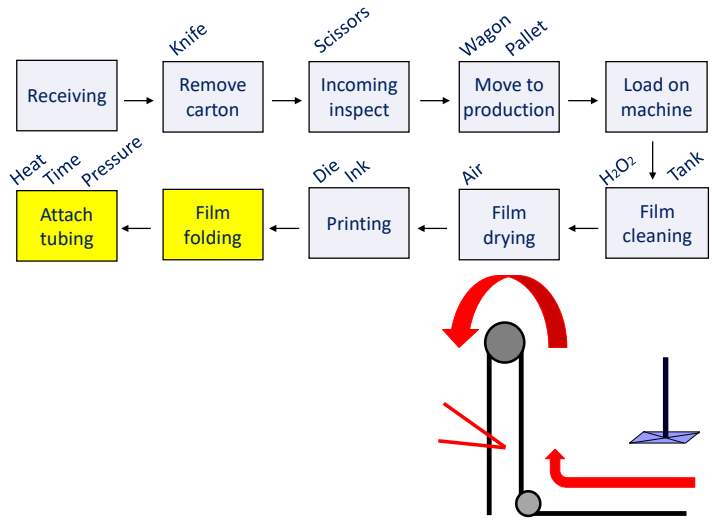
Process Flow

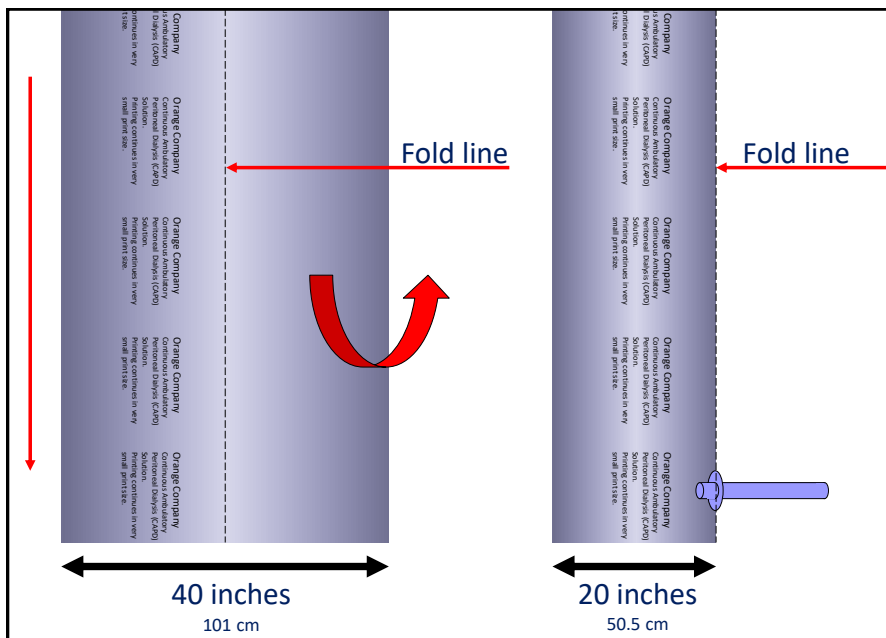


Process Flow



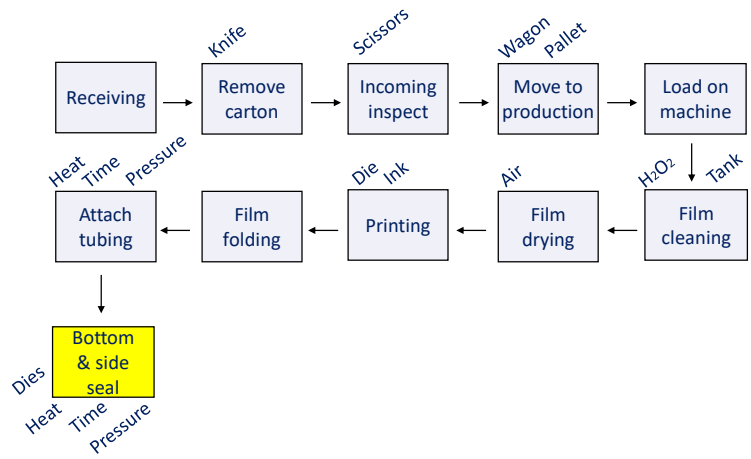
Process Flow



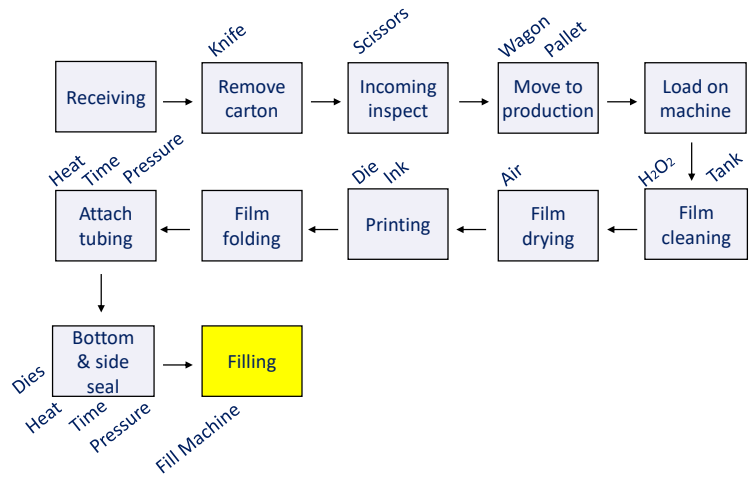


Folding film & attaching tube

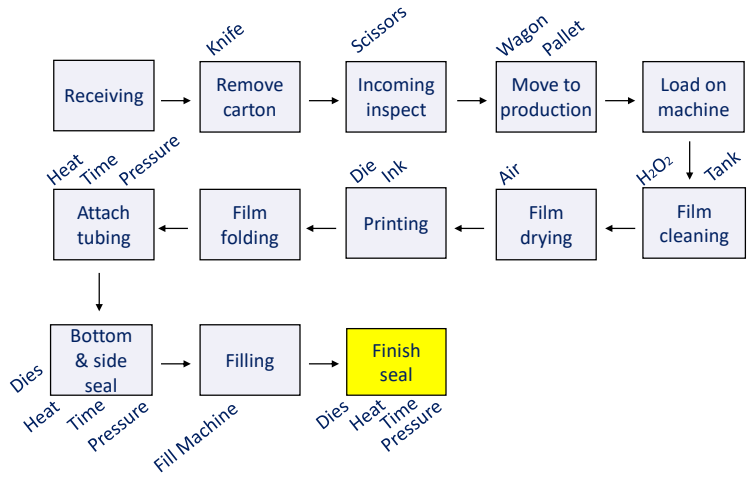
Process Flow

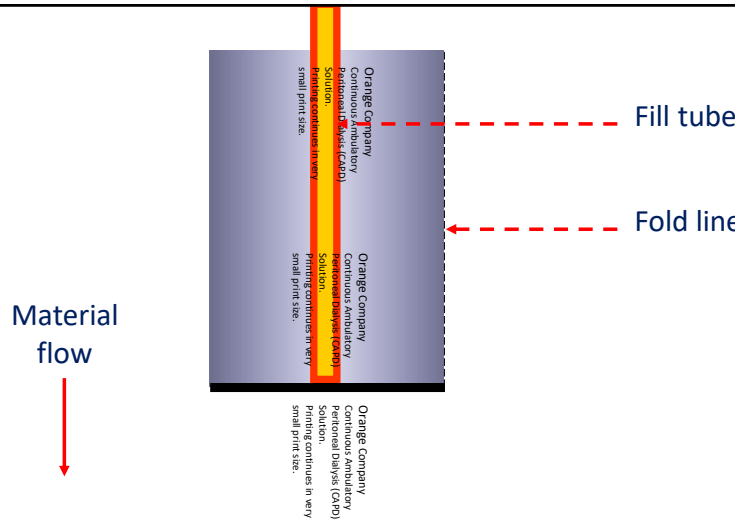


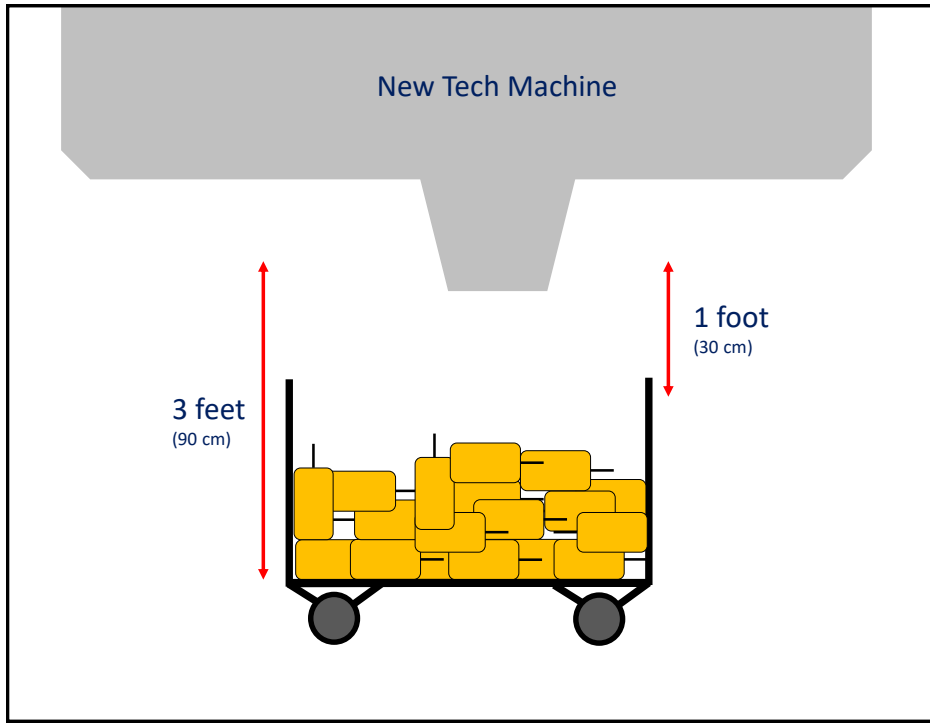
Process Flow



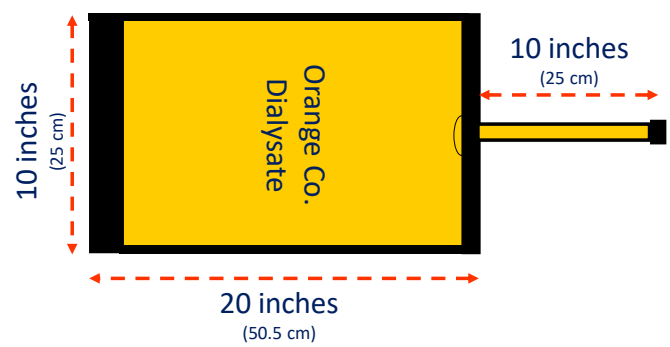
Process Flow



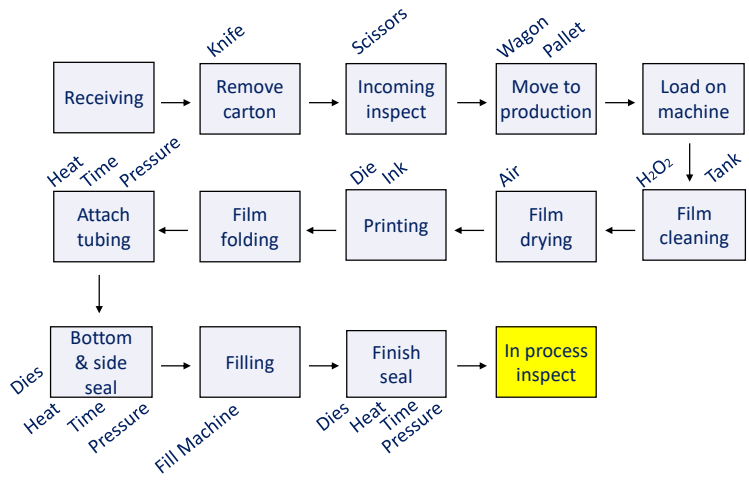




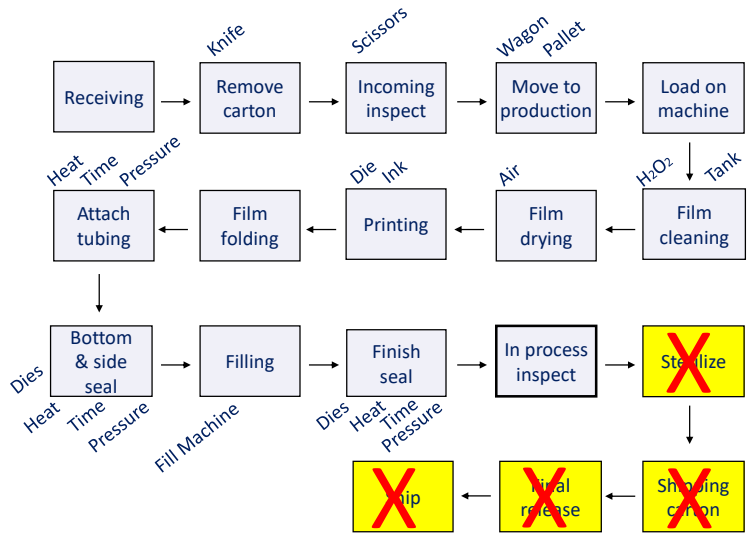
Product Dimensions



Process Flow



Process Flow



New Tech Vs. Old Tech

New Tech Production

- Australian film supplier
- 1st shift – bag fabrication & filling
- 2nd shift – cleaning & sanitizing
- 3rd shift – mixing pharmaceutical for use the next day
- 1 day's production = 1 product (finished goods) lot

Old Tech Production

- Different film material
- U.S. film supplier
- Different fabrication method
  - Fabricate bag in one production room
  - Fill bag in a second production room

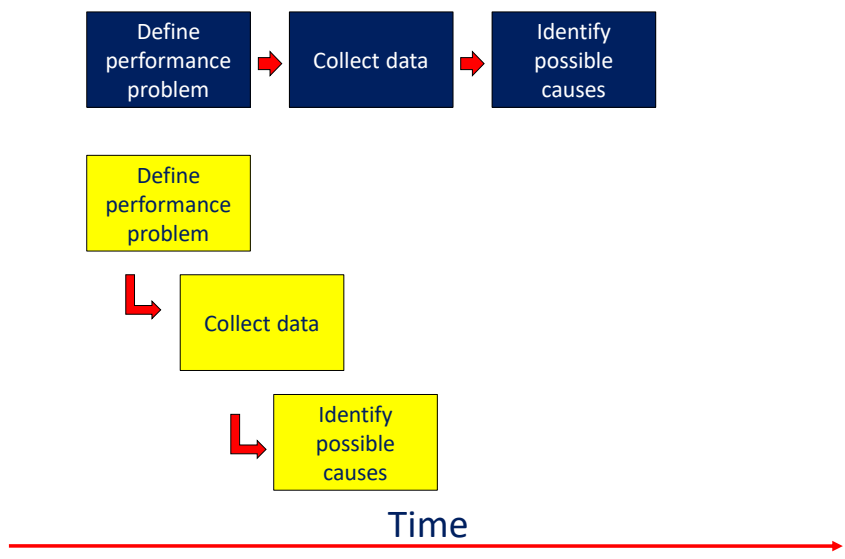
Finale

Finale

- Shortcuts
- Simple investigations
- Difficult investigations
- Investigation report
- Return on investment

Shortcuts

Steps 1, 2, & 3 can overlap



Shortcuts

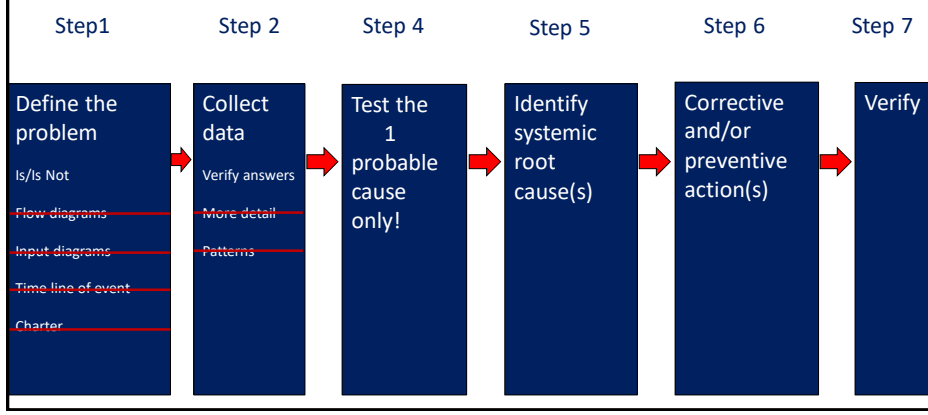
Develop “pretest” leveraging the strongest patterns

	Is	Is Not
What	*Attendants	*Pilots, passengers, etc.
	“Red sweat”	Flu, common cold, allergies, etc.
	*Red pigment in sweat/spots	*Other color pigment in sweat/spots
	Both genders, young & old	1 gender, only young or old
Where	*Flights b/w LGA-MIA, both ways	*Flights b/w LGA-DFW, LGA-LAX
	* Exposed skin on face, neck, arms, hands	*Other exposed body parts or covered skin
	* Symptoms 1st seen during trolley prep	*Earlier
	*All 5 A300s	*< 5 A300s, other aircraft
When	January 3 1980	Earlier
	*Increasing frequency each wk	*Sporadic, decreasing
How Much	69 attendants	More or less
	127 incidences	More or less
	*”pin prick” size spots	*Larger than “pin prick” size spots
	*Many spots	*A few

	Is	Is Not
What	*Attendants	*Pilots, passengers, etc.
Where	*Flights b/w LGA-MIA, both ways	*Flights b/w LGA-DFW, LGA-LAX
	*All 5 A300s	*< 5 A300s, other aircraft

Simple Investigations

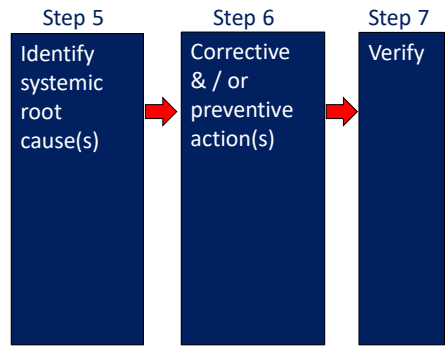
Sometimes the root cause is already known



Simple Investigations

Sometimes there hasn't been a change…

Example: An internal audit reveals a regulatory requirement is not being met



Difficult Investigations

Worse case scenarios…

- Can't get data
- One time events
- Out of box failures

How to handle…

- Follow the methodology
- Carefully document what's opinion & what's fact
- Carefully document actions taken to obtain the facts
- May need to rely more on experiments
- May need to take corrective action on many more possible causes

Investigation Report

Investigation leveraged the 7 step methodology as per our internal procedure…

- Step 1
  - Defined the problem using an Is/Is Not Diagram (Attachment A)
  - Flow charted processes under investigation & identified inputs (Attachments B, C, & D)
  - Constructed timeline of events (Attachment E)
- Step 2
  - Developed a measurement plan (Attachment F)
  - Restated problem in fact based Is/Is Not diagram (Attachment G)
- Etc

Return on Investment

- Training
  - Train a critical mass of investigators
  - Educate management
- Implementation
  - Ask investigators to use the methodology
  - Have investigators show you how they used methodology
  - Develop and issue a procedure
- Measure
  - Average investigation time
  - # of investigations over time
  - Audit investigations
- Celebrate
  - Recognize & publicize success