

Troubleshooting in Drug Product Development and Technology Transfer: Root Cause Analysis

By Scott Herbig

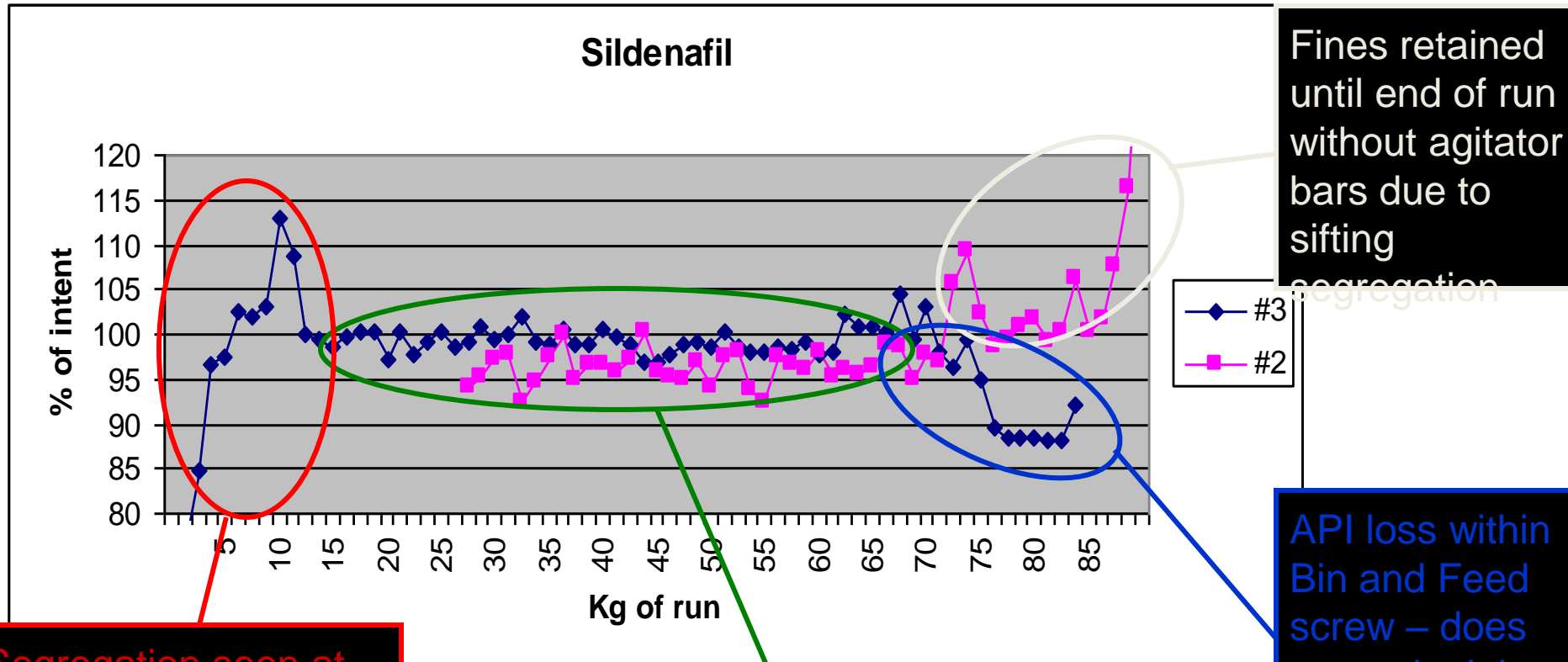
February 27, 2014



The “Always” factor in Drug Product Development

- **Always #1:**
 - You will **always** encounter problems and issues during Dosage Form Design and Development – no matter how “simple” the project is.
- **Always #2:**
 - When you encounter a problem or issue someone will **always** have a quick solution that should be implemented immediately
- **Always #3:**
 - It is always best to conduct a root cause analysis – both to understand the problem so the solution addresses the underlying problem and to explain why the solution really have resolved the problem or issue (and why the problem or issue is under control)

Evaluation of May (#2) and July (#3) Manufacturing Runs



Fines retained until end of run without agitator bars due to sifting segregation

Segregation seen at beginning of run - self corrects with agitator bar in place
Sifting or fluidization segregation?

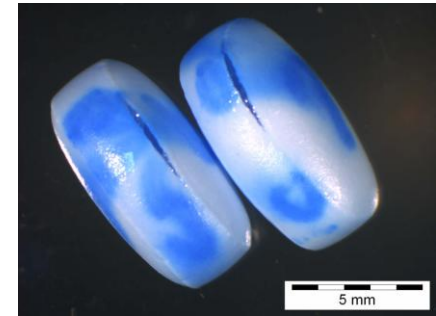
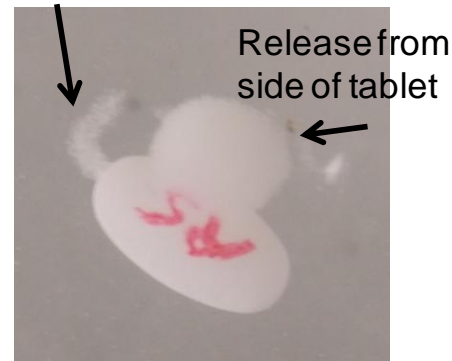
Middle portion of run shows acceptable homogeneity
Low potency for May batch without agitator bars – corrected for July batch

API loss within Bin and Feed screw – does not make it into Hopper
Mechanism unknown

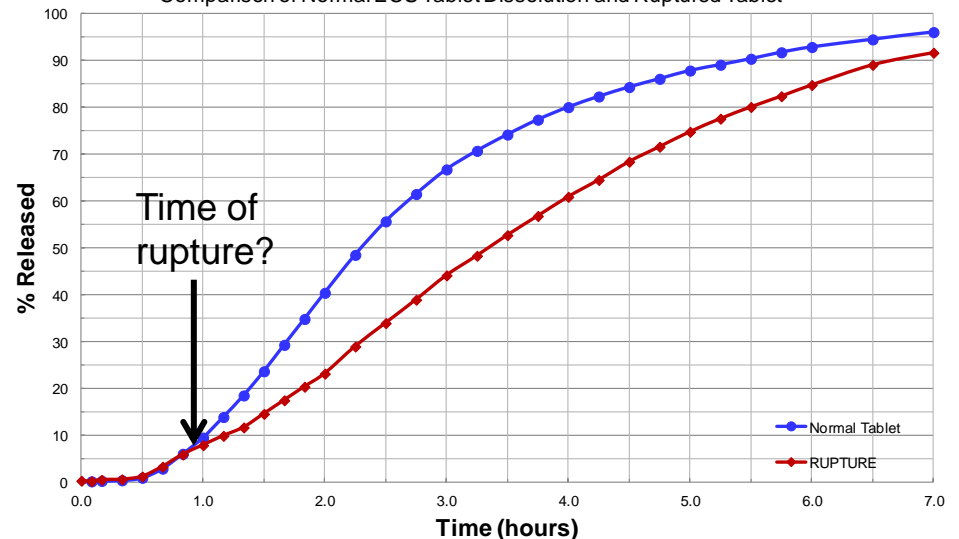
Tablet Rupture Observations

- 1 of 24 tablet ruptured during 1163 clinical release testing.
- Rupture occurs along edge of tablet band and land.
- No visual indication of membrane defects.
- Event occurs ~1 hour into in vitro dissolution testing.
- Additional testing of demo lots suggested rupture rate of ~2% in dissolution release test.

Extrudate from release port

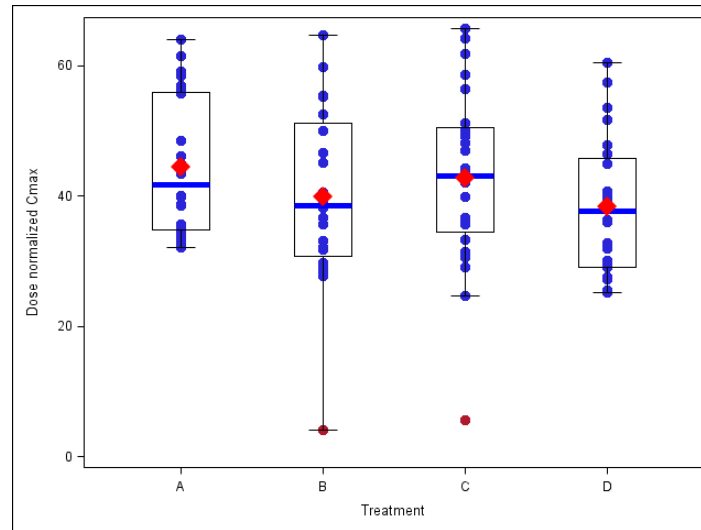


Comparison of Normal ECS Tablet Dissolution and Ruptured Tablet

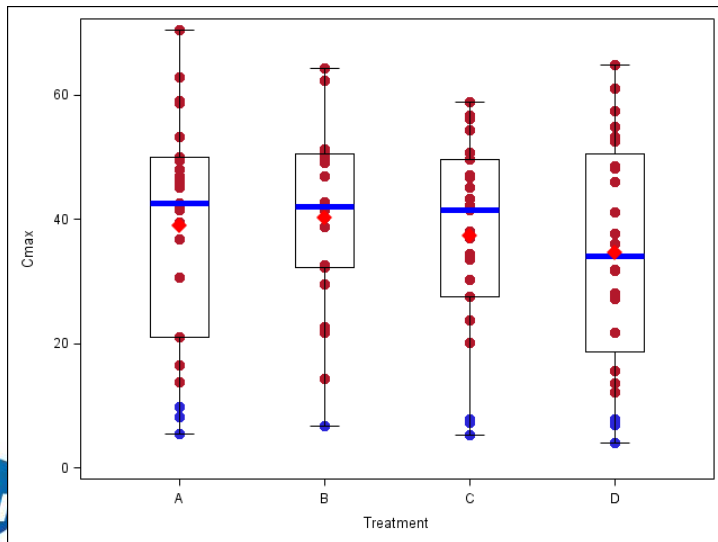


Comparison of Inter-subject variability in C_{max}

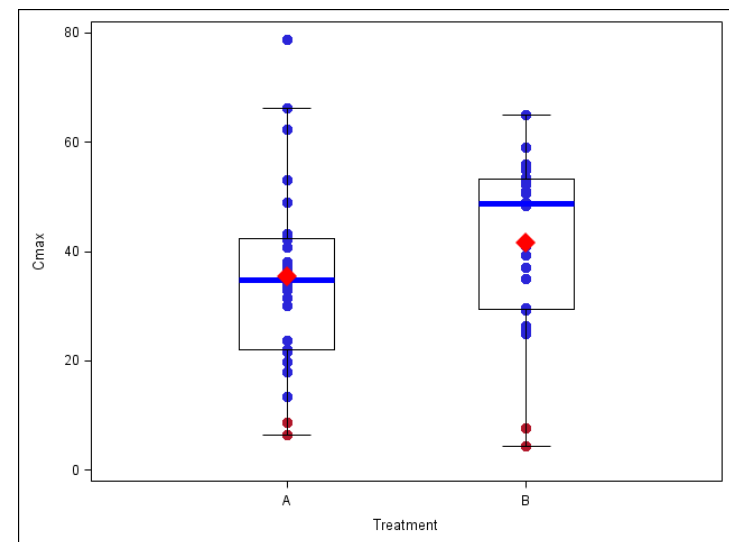
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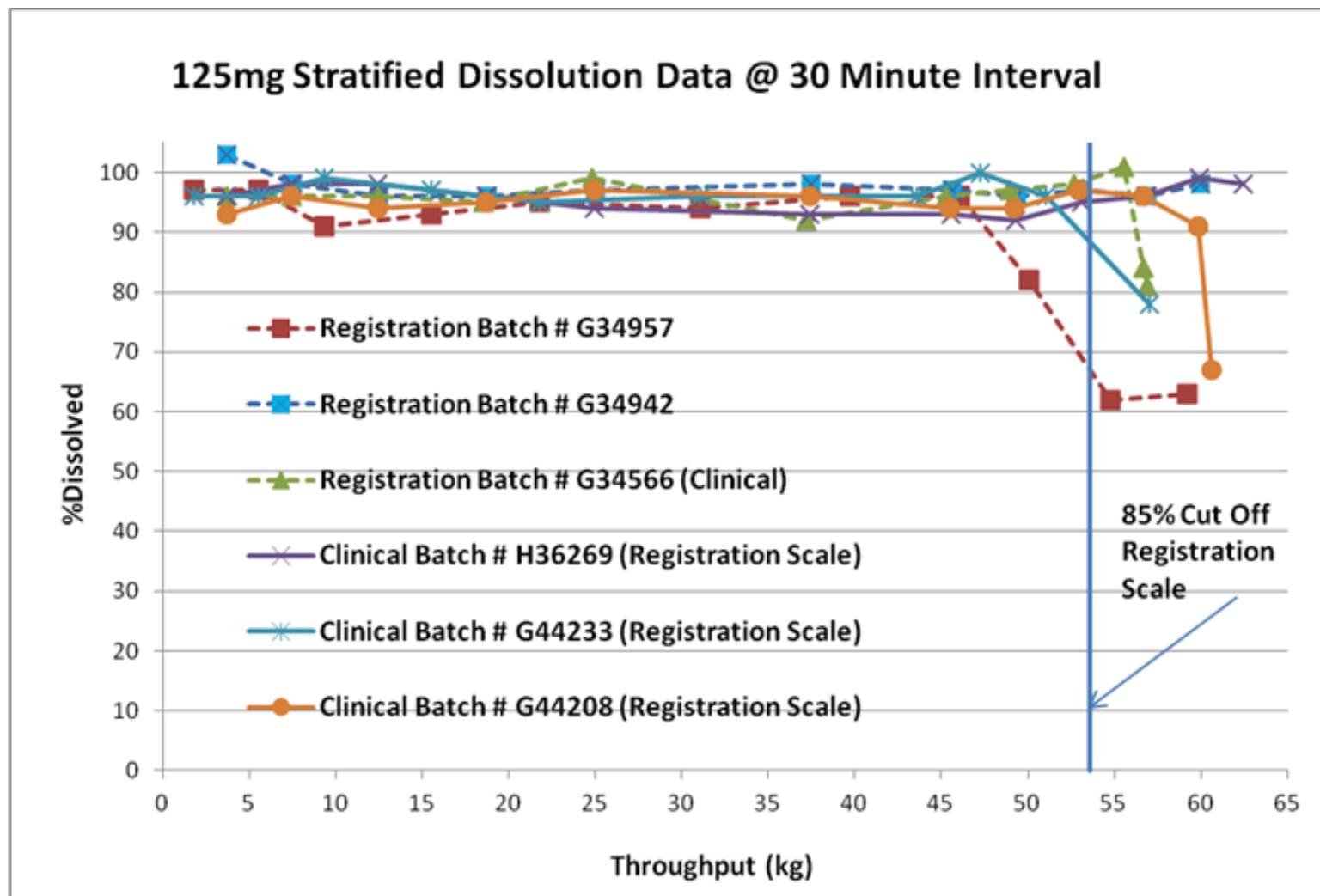
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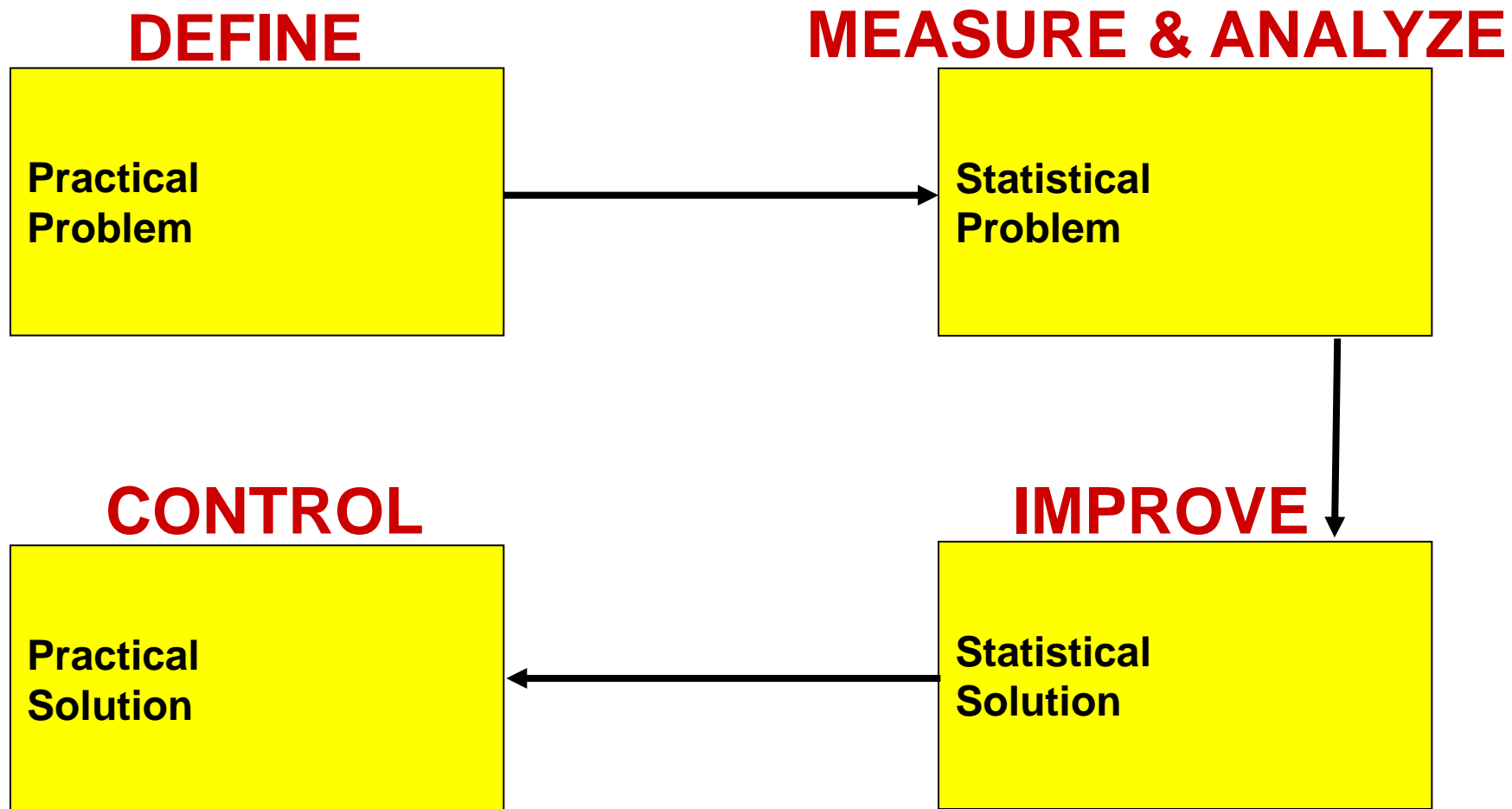
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Issues with Product made at end of ICH runs

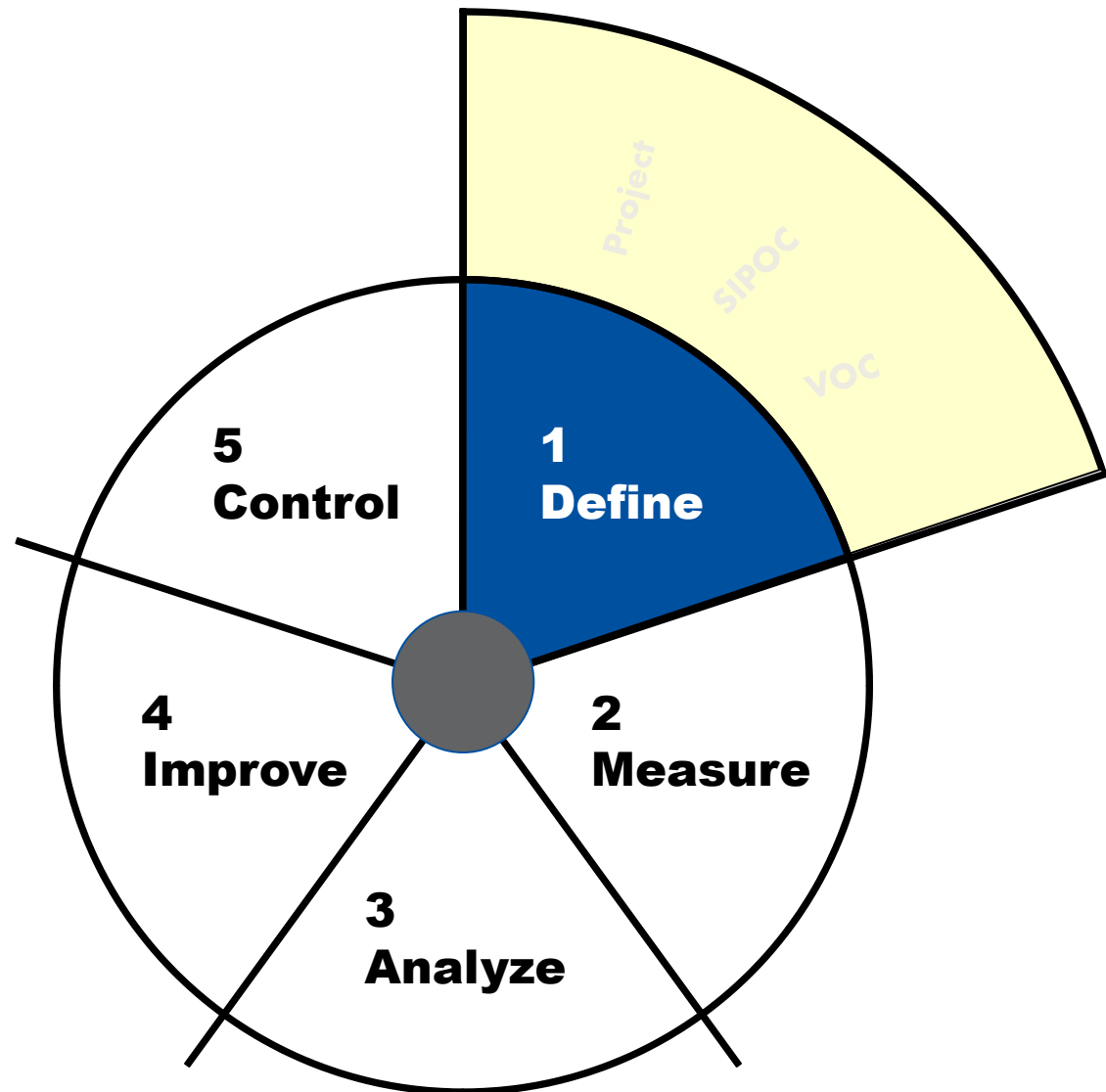


Six Sigma – DMAIC process

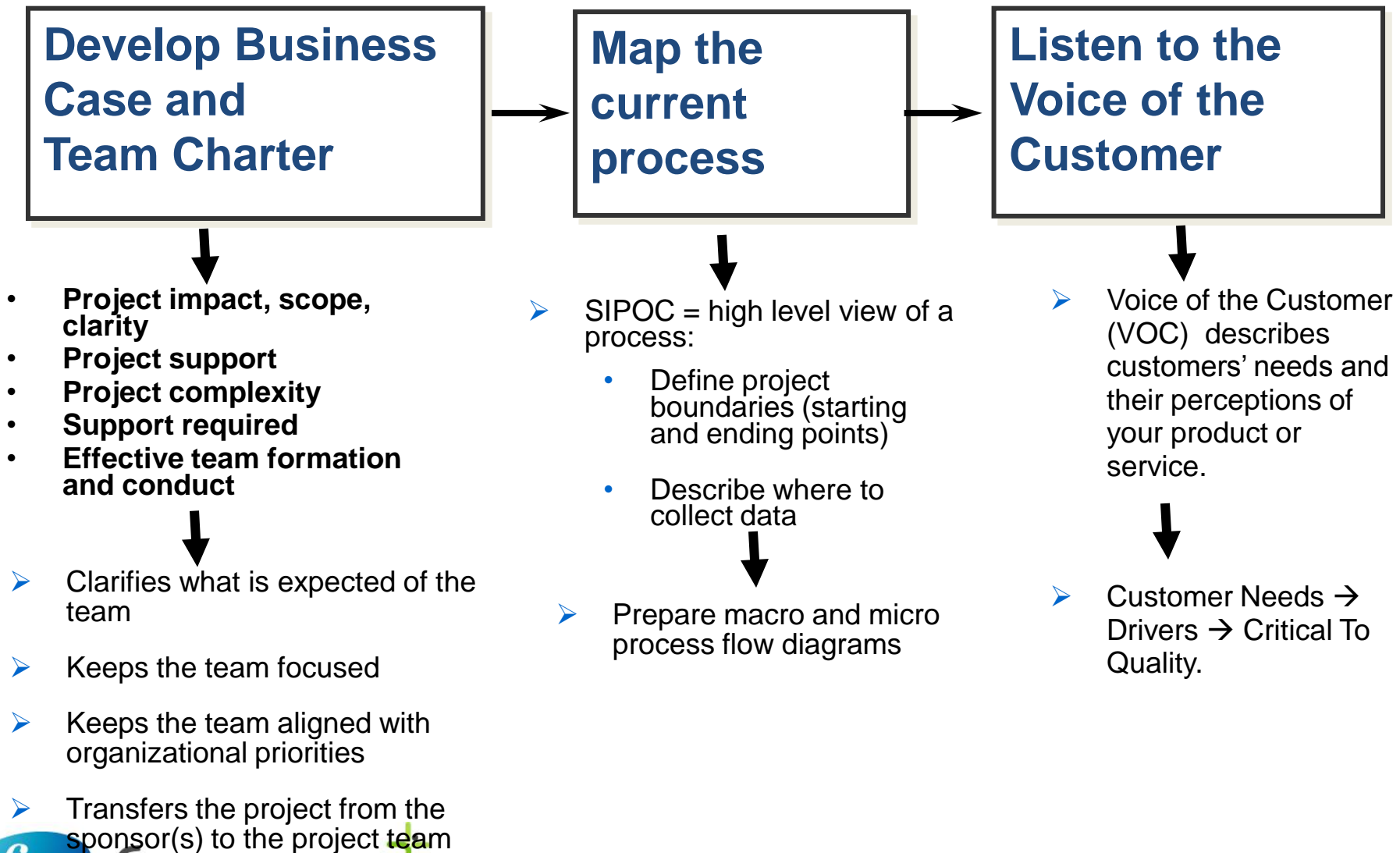


Step 1: DEFINE

- **Goal**
 - Define the project's **purpose** and **scope** and get **background** on the **process** and **customer**
- **Output**
 - A clear statement of the intended improvement and how it is to be measured
 - A high-level map of the process
 - A list of what is important to the client



You Are Here at Define

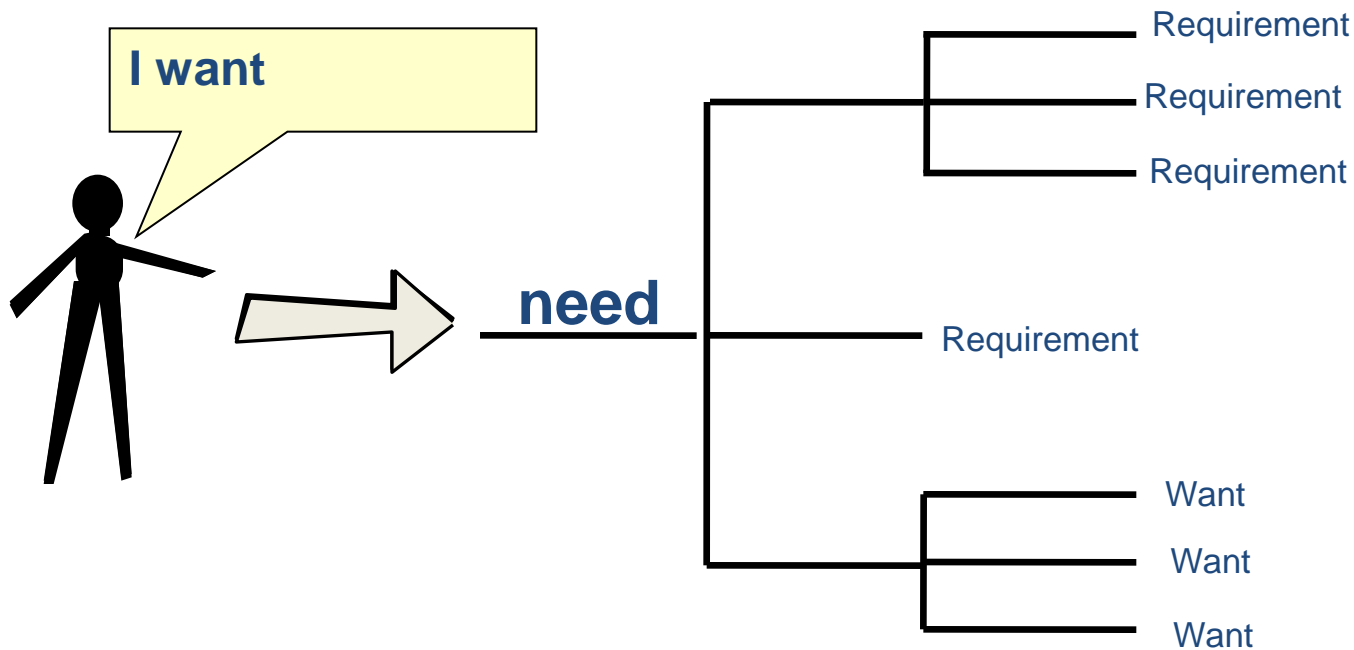


Translating Customer Comments into Customer Requirements

Critical to Quality

Customer Comment

Customer Requirements

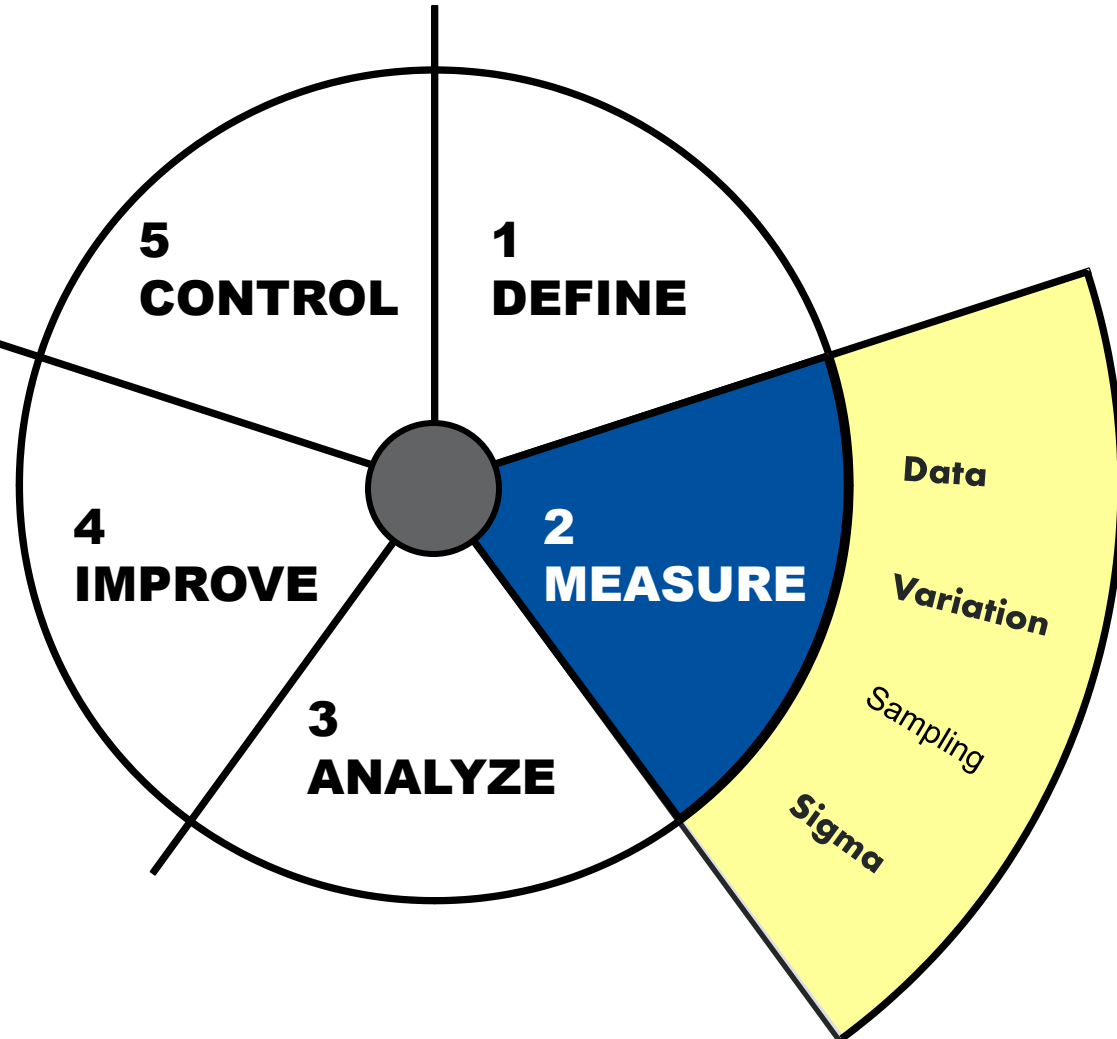


Define Completion Checklist

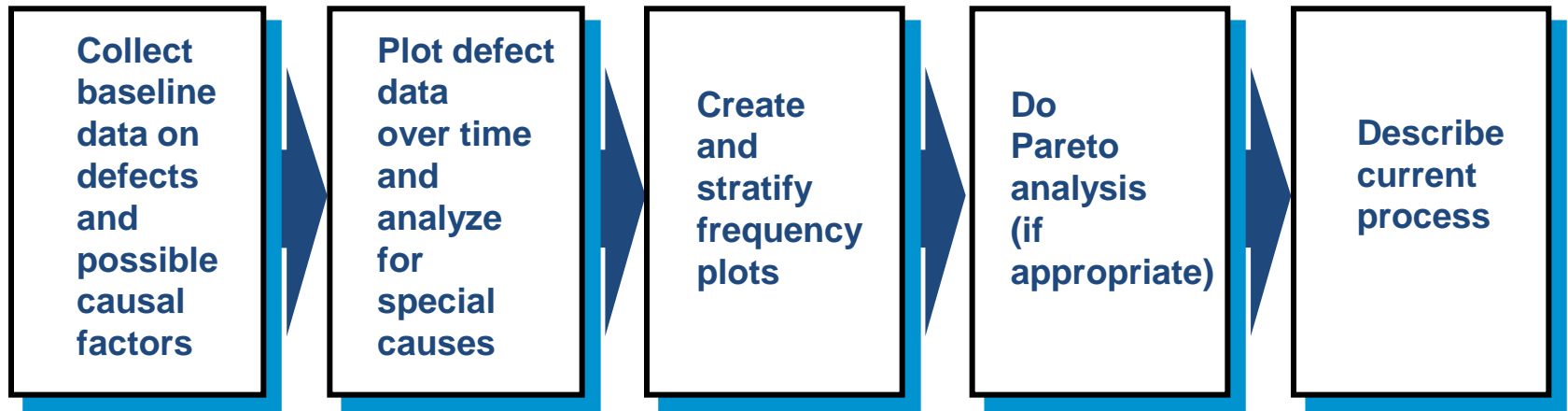
- **By the end of Define, you should be able to describe for your sponsor:**
 - What key process is involved (including its Suppliers, Input, Outputs, and Customers) → SIPOC
 - What about the process output is important to customers → CTQ Tree Diagram
 - What customers currently think of the process and its output
 - Why this project is important to your organization and what business goals the project must achieve to be considered successful → Project Objectives need to be clear
 - Who the players are on the project (sponsors, advisors, team leader, team members) → Stake Holders Analysis Form
 - What limitations (budget, time, resources) have been placed on this project → Project Charter

Step 2: MEASURE

- **Goal**
 - Focus the improvement effort by gathering information on the current situation
- **Output**
 - Data that pinpoints problem location or occurrence
 - Baseline data on current process sigma
 - A more focused problem statement



You Are Here at Measure



Data Collection Plan

Data Collection Plan

Project _____

What questions do you want to answer?

Being clear about your question will help you make sure you collect the right data.

Data		Operational Definition and Procedures			
What	Measure type/ Data type	How measured ¹	Related conditions to record ²	Sampling notes	How/where recorded (attach form)

Recording what data you are going to collect reminds you what you want to accomplish. Noting the type of data helps you decide how you should analyze the data.

An operational definition defines exactly how you will go about collecting and recording the data.

Sampling

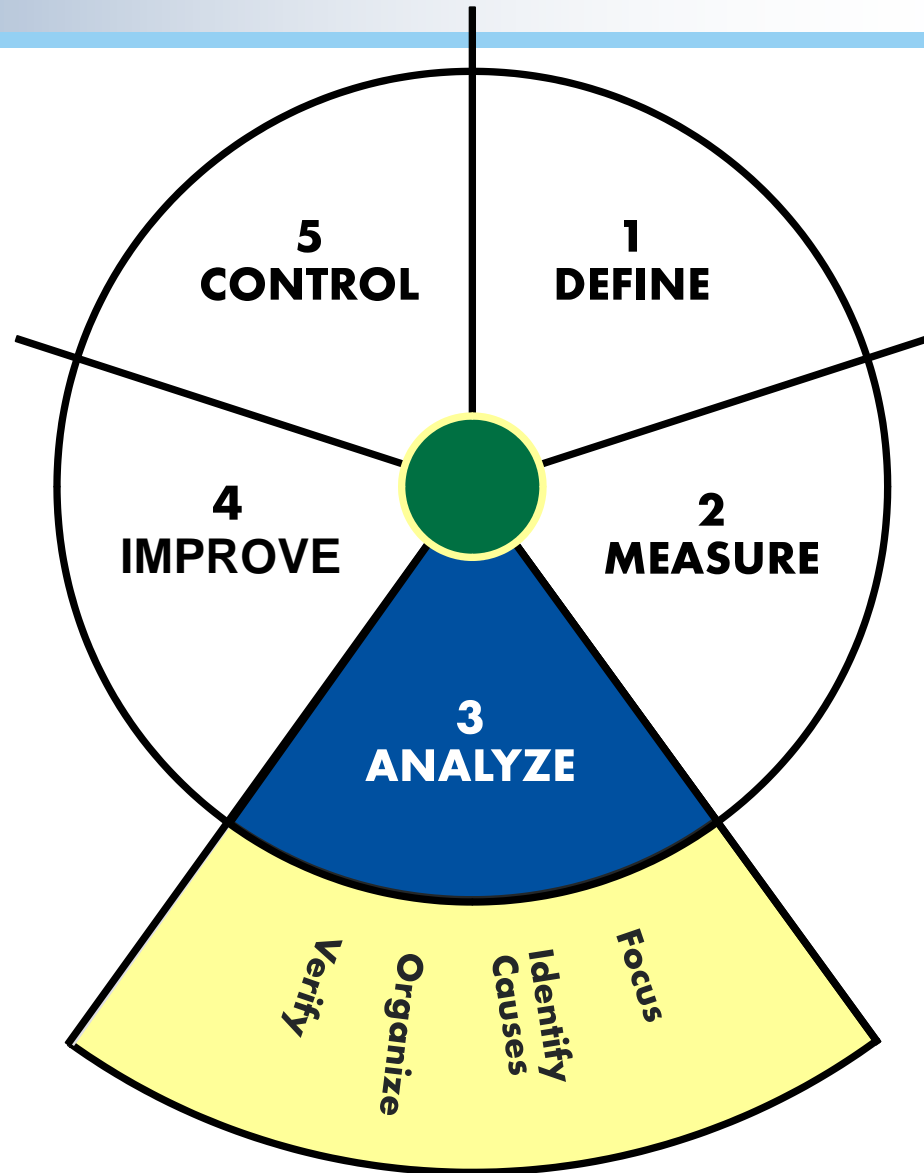
- **There are many times when collecting all the data from a process isn't possible.**
 - There may be too much data, and it would be impractical, too costly, or too time consuming to collect and analyze it all
 - Collecting the data may be destructive (e.g., taste testing) and you need to minimize product loss
- **Sampling means collecting only some of the data.**
 - Statistical methods allow us to make sound conclusions about a process even from a relatively small sample (this is called “statistical inference”)

Measure Completion Checklist

- **Before moving on to Step 3: Analyze, you should be able to precisely define what problems are occurring and under what conditions they are likely to appear.**
 - What specifically is the main problem or problems
 - What patterns related to time are exhibited → Time series and Control Charts
 - What special causes of variation were uncovered – any patterns? Any clear cause and effect?

Step 3: ANALYZE

- **Goal**
 - Identify deep causes and confirm them with data
- **Output**
 - A theory that has been tested and confirmed



You Are Here at Analyze



Brainstorming Potential Causes

- **Purpose**

- Brainstorming is a method of generating lots of ideas quickly.

- Encourage creativity
- Involve everyone
- Generate excitement and energy
- Separate people from ideas they suggest



- **Uses in Analyze**

- Use brainstorming to generate a lot of potential causes of the problem you defined in Measure

- Use “5 Whys” to push for root causes
- Key question is “why does that happen?”

5 Whys

- **To push for root causes, start with your focused problem and then ask WHY five times.**

Why does this problem happen?

Backup operators take longer to connect callers.

Why does it take backup operators longer?

Backup operators don't know the job as well as the regular operator/receptionists do.

Why don't operators know the job as well?

There is no special training, no job aids to make up for the gap in experience and on-the-job learning for the backups.

Why don't they have special training or job aids?

In the past, the organization has not recognized this need.

Why hasn't the organization recognized the need?

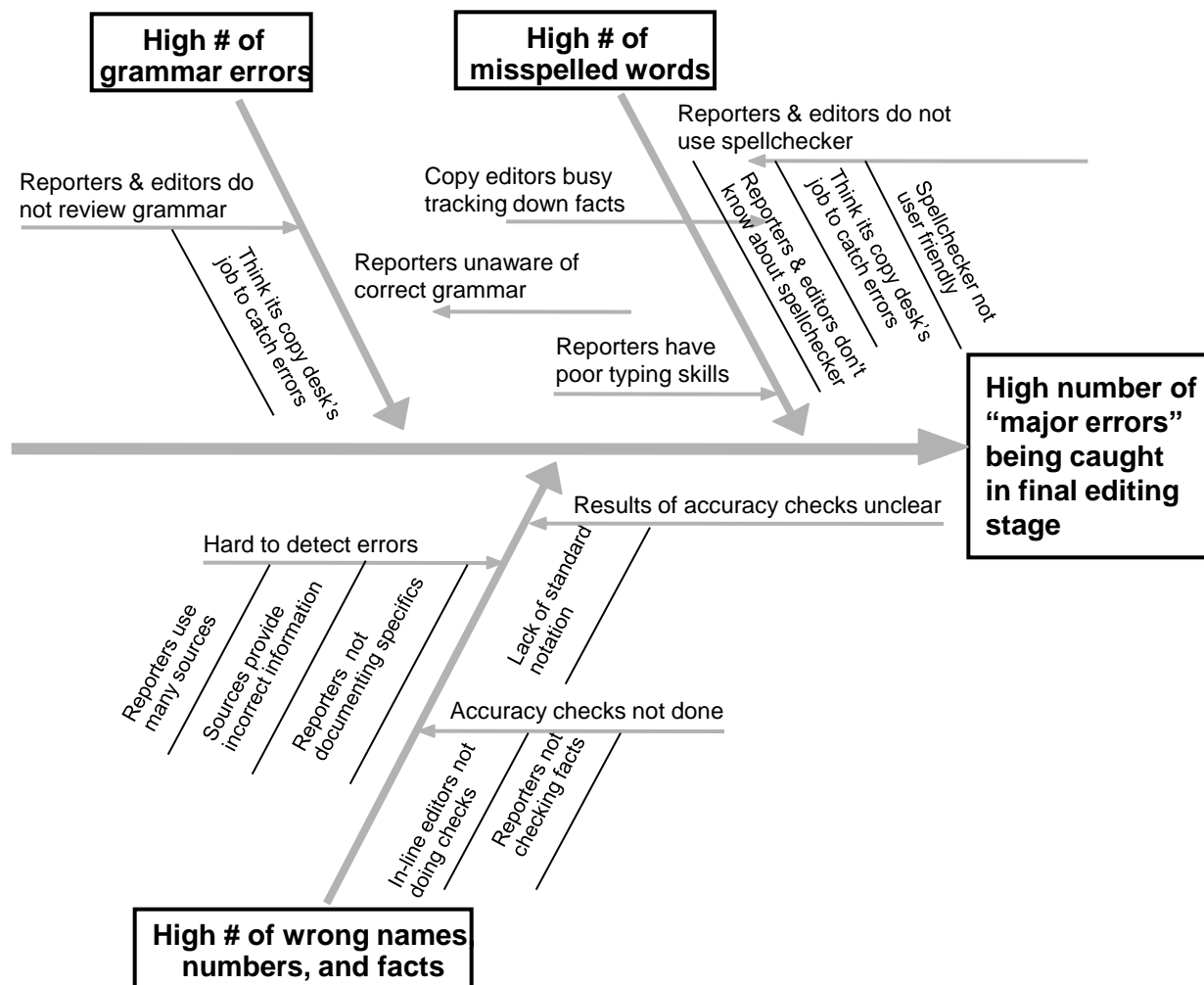
The organization has no system to identify training needs.

- **Example:**
- **Focused Problem**
— **Customers complain about waiting too long to get connected to staff during lunch hours.**



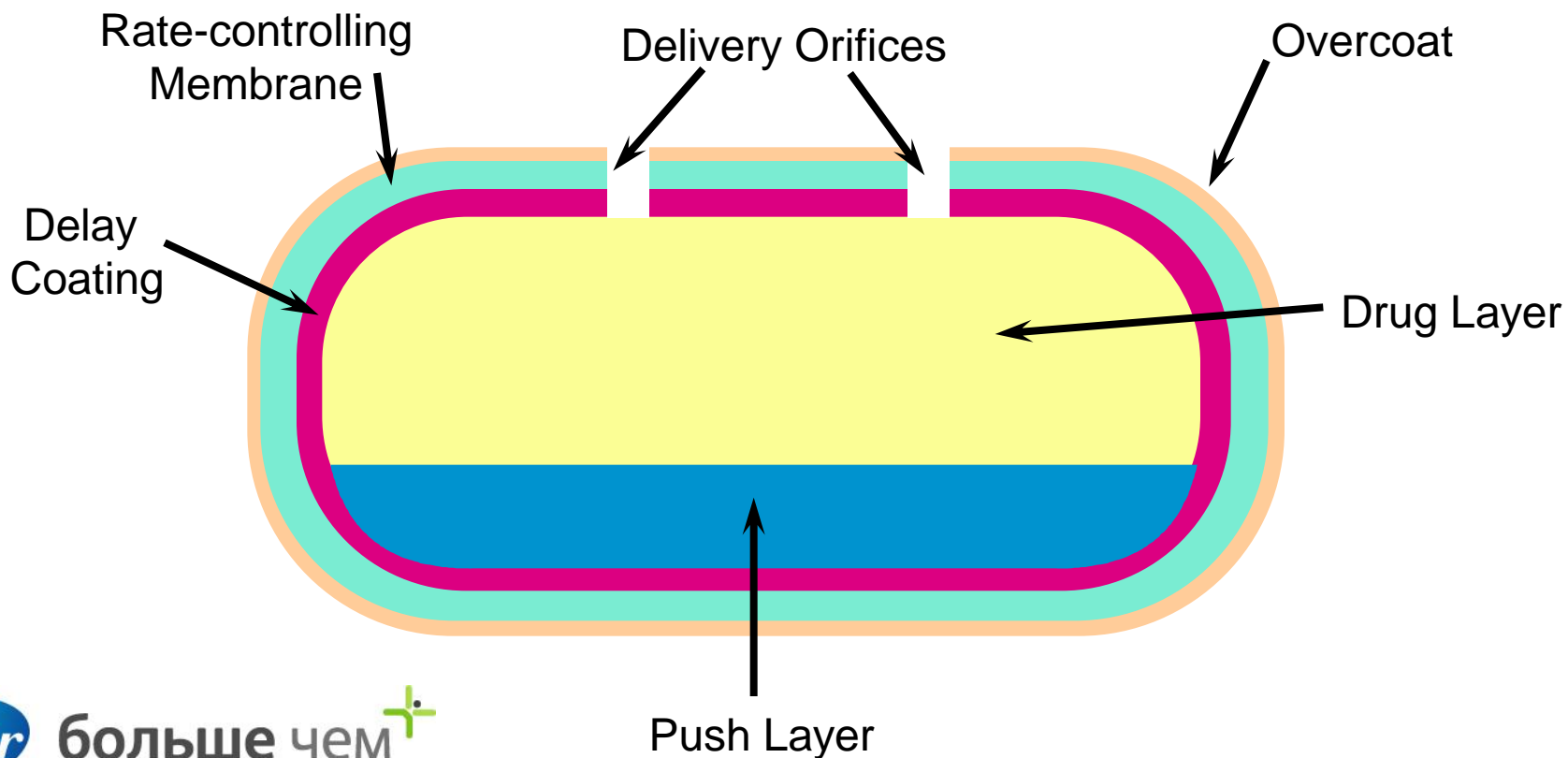
Cause-and-Effect Diagram Definition

- Cause-and-effect diagrams graphically display potential causes of a problem. The layout shows cause-and-effect relationships between the potential causes.



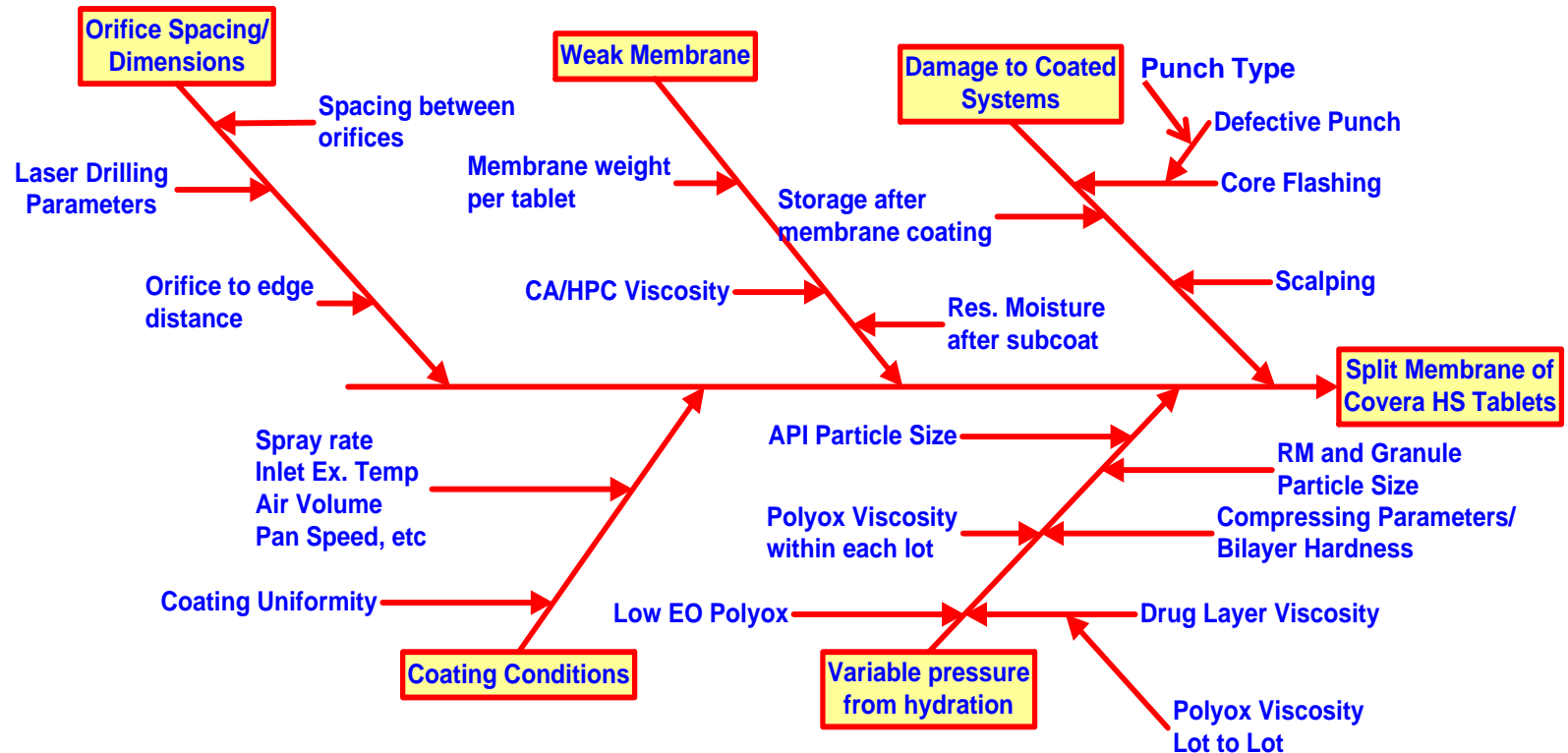
Background

Covera HS OROS™ Technology



Problem Analysis: Identify Sources of Split Membrane

Ishikawa Diagram (C&E Analysis)



Above factors extracted from 41 potential influencing factors

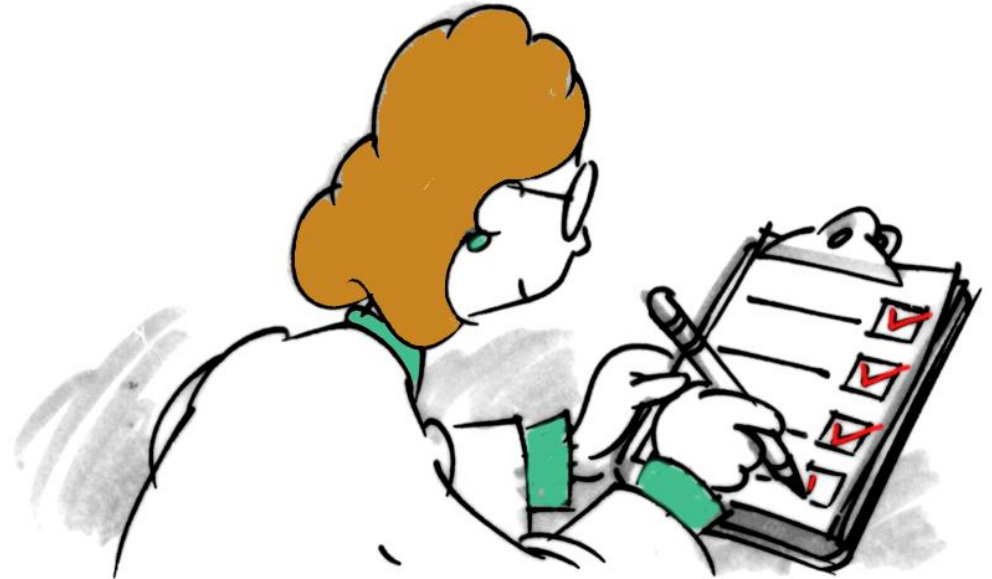
Cause-and-Effect Diagram Uses

- To stimulate thinking during a brainstorm of potential causes
- To understand relationships between potential causes
- To track which potential causes have been investigated, and which proved to contribute significantly to the problem



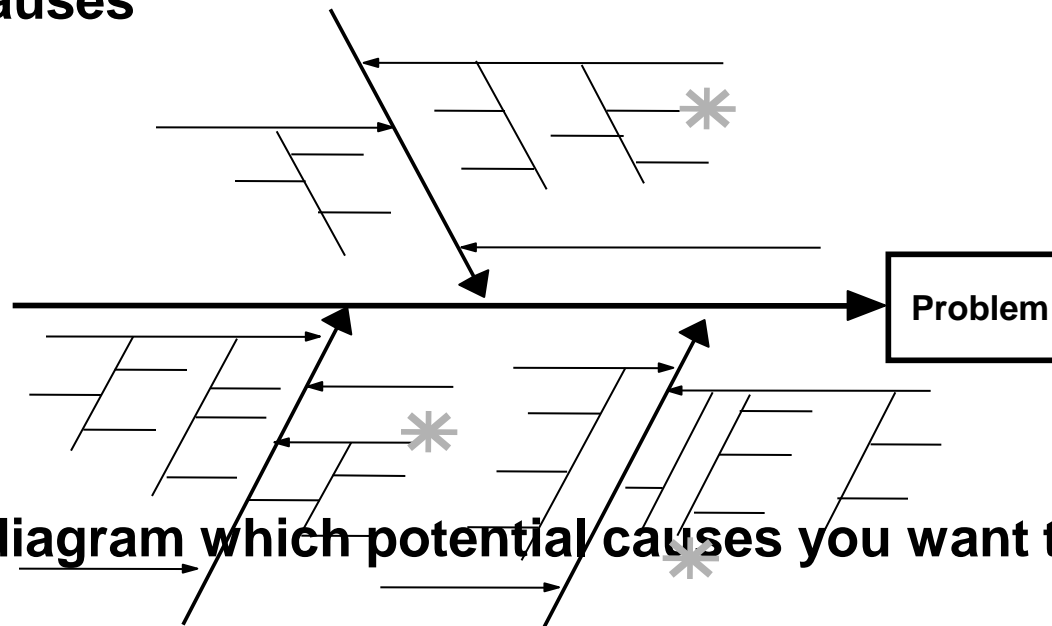
Verifying Causes

- **A lot of thinking and effort goes into constructing a cause-and-effect diagram or tree diagram**
 - But those diagrams only identify potential causes
 - You need to collect data to confirm which potential causes actually contribute to the problem



Which Causes to Verify

- You likely identified many potential causes on your cause-and-effect diagram or other tool
- Now you need to set priorities and collect data on only the most likely causes



- Mark on the diagram which potential causes you want to verify

Design of Experiments

- **Design of Experiments is an approach for effectively and efficiently exploring the cause-and-effect relationship between numerous process variables (Xs) and the output or process performance variable (Y).**
 - Identifies the “vital few” sources of variation (Xs)
 - Those that have the biggest impact on results
 - Quantifies the effects of the important Xs, including their interactions
 - Produces an equation that quantifies the relationship between the Xs and Y
 - You can predict how much gain or loss will result from changes in process conditions

Approaches to Root Cause Analysis

- **Observe the process**
- **Observe the process “as is” using historical data or special studies**
 - Time plots, control charts, stratification
 - Correlation studies using regression analysis
- **Experiment with the process**
 - Change the process in a planned way and measure the results
 - Use Design of Experiments (for more than 1 factor)

“To determine what happens with a process when you interfere with it, you have to interfere with it, not passively observe it.”

— George Box

Analyze Completion Checklist

- **By the end of Analyze, you should be able to describe which causes you will focus on in the Improve Step by describing:**
 - Which potential causes you identified
 - Which potential causes you decided to investigate and why
 - What data you collected to verify those causes
 - What the data showed
 - Root cause must be identified and verified

The People Side

- **Too often we spend all our time on the “technical” side of a change—what has to happen by when, etc.**
- **We ignore the people side of the change—how to help those who will have to change make the transition**
- **There are three elements of the people side:**
 - Communication: the exchange of information both from you to others and from others to you
 - Participation: involving people in the planning and execution of a change so they can develop shared ownership and commitment
 - Education: providing people with what they will need to know before they successfully implement the desired changes



Six Sigma – DMAIC process

