Case Study #1

- Description of the Process
- Problem Definition
- Root Cause Identification
- Solution Development
- Corrective Action Implementation

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“Causes and effects are often not closely related in time and space.”

This was one of my earliest problems I help solve using my new problem solving process. This problem came to me without notice at a time when I was finalizing a new approach to problem solving methodology.

It was a trial by fire “so to speak” which prove to be both enlightening and exciting!
Donated blood has a shelf life. It does not last for ever. Have you ever wondered what organizations like the Red Cross do with all of their dated stores of blood donations? Well, what they do is sell it to companies who make therapeutic products from it.

This slide shows some of the products that can be developed from blood plasma. Remember, blood plasma is whole blood that no longer contains red blood cells. The red blood cells or RBCs have already been harvested and used prior to the company receiving the plasma.

Here we show pictorially how a company might separate the components of plasma to extract the saleable products. At the end of the run is Albumin. 80% of our blood consists of Albumin which has trace amounts of stay protein in it. Albumin is used as a blood expander when someone has lost a lot of blood. It’s primary use is to keep the fluid volume up in your arterial system.
The Observed Problem

QC Test Sample

Heat Stability Testing @ QC

Particulates in Solution After QC Testing

Reqm’t: No Observable Particulates are Allowed in Solution
Describe the Problem

Structured Problem Solving Process

1. Describe the Problem
2. Identify Related Concepts
3. Describe Critical Concepts
4. Collect Additional Data to Identify Root Cause
5. Derive Corrective Actions
6. Validate, Implement, and Operationalize

We start our problem solving effort by providing a complete description of the observed issue that all team members agree on.
Problem Statement

In the last month, 3 consecutive batches of Human Albumin show excessive levels of an unknown precipitate after heat stability testing in QC causing them to be placed into a quarantined state. Loss of all three batches is expected based on past experience.
The total production cost of these 3 batches is $185,000, and the expected sales value is $350,000. This problem has occurred three times in the past without adequate solution rendering a total business loss to date of $1.4M
Goal Statement

Identify the cause of excessive product precipitation at heat stability testing within 2 weeks. Determine if the quarantined lots can be recovered without adverse risks. Develop a corrective action plan within 3 weeks, and implement a solution plan within 4 weeks.

Establish agreement with Management Team upfront...
This is a guide used by the team to prepare the Is vs Is Not matrix supporting the problem or issue.
### Example: Is vs. Is Not Matrix

**Problem:** Precipitates of an unspecified protein found in sample bottles after the QCA heat stability testing of human albumin.

<table>
<thead>
<tr>
<th>WHAT</th>
<th>IS</th>
<th>IS NOT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Large, (&gt;10mm), of unspecified protein with &gt;20% conc samples and small, (&lt;5mm), with 5% conc samples (most likely Human Albumin)</td>
<td>- Is not aluminum or paper.</td>
</tr>
<tr>
<td></td>
<td>- Transparent sheet-like appearance in &gt;20% samples.</td>
<td>- Thin fibers, or large clusters.</td>
</tr>
<tr>
<td></td>
<td>- Sample containers with concentration &gt;20% Human Albumin.</td>
<td>- In the ≤5% final product containers. (up to AUJ03600)</td>
</tr>
</tbody>
</table>
Step 2a. Identify:
Identify Potential Causes

Structured Problem Solving Process

1. Describe the Problem
   - Define the problem
   - Identify key characteristics
   - Set goals and objectives

2. Identify Potential Causes
   - Brainstorm possible causes
   - Use tools such as fishbone diagrams

3. Define, Organize, and Analyze Data
   - Collect data
   - Analyze data using statistical tools

4. Collect Additional Data to Identify Root Cause
   - Conduct experiments
   - Conduct additional data collection

5. Determine Corrective Actions
   - Develop potential solutions
   - Select the best solution

6. Verify, Implement, and Evaluate Results
   - Implement the selected solution
   - Evaluate results and make necessary adjustments

Structured Problem Solving
A Fishbone diagram used to mine potential causes for use on the Contradiction Matrix. The team did not come up with theories during this evaluation period—only possibilities where the problem may exist.
### Example: Distinction and Changes

**Problem:** Precipitates of an unspecified protein found in sample bottles after the OCA heat stability testing of human albumin.

<table>
<thead>
<tr>
<th>IS</th>
<th>IS NOT</th>
<th>DISTINCTIONS</th>
<th>CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Large, (&gt;10mm) of unspecified protein with 20% conc. samples and small, (&lt;5mm), with 5% conc. samples. (most likely human albumin)</td>
<td>- Is not aluminum or paper.</td>
<td>- Precipitate vs. contaminant</td>
<td>- In the past, the observed defects were foreign material such as aluminum or paper:</td>
</tr>
<tr>
<td>- Sample contains with concentration &gt;30% human Albumin.</td>
<td>- Thin fibers, or large clusters.</td>
<td>- Surface area of defect.</td>
<td>- Small precipitates in lab 03200 and 03100, 04100, and 04200, (04100 and 04200, with 5% conc.)</td>
</tr>
<tr>
<td>- In the 5% final product containers, up to AUF 03500</td>
<td>- Protein concentration, 0% vs. &gt;20%</td>
<td></td>
<td>- Sample containers selected from production line vs. prepared manually.</td>
</tr>
<tr>
<td>A siliconized container has a thin film of silicone deposited on the inner walls of the glass bottle to keep the contents from contacting the glass walls. Why is this needed? And, why are some sample bottles siliconized while others are not?</td>
<td></td>
<td></td>
<td>- Sample containers are now siliconized to the same as product containers using the same bottle pre-treatment process.</td>
</tr>
</tbody>
</table>

Did you notice in this very limited display of the Is vs. Is Not Matrix some possible clues about the problem?

Did you observe that not all test samples are prepared the same way?

As it turns out, test samples may be selected from the actual batch or prepared separately…

One might ask how representative a given test sample is of the original group if it is prepared uniquely from the production units.
Notice at this point in time we do not have any “hypothesis” or “theories” about the cause(s) supporting the observed problem-symptoms.

This lack of action is by design. We will not have a reasonable clue to the possible causes until we finish Step 3. Stay tuned!
When I joined the team and asked them for their data I was not too surprised to see this chart. Everyone in this particular industry is focused on specifications.

Never mind where the specs come from to begin with as that is another very challenging discussion. But when running these data through Change-Point Analyzer I did not find any signals to work with. The only signals in these data are the values that exceed the upper control limit. Other than that we are at a loss to go any further with our understanding.

So, I asked the team to get me the “raw” data. The raw data are the actual measurements made using analytical equipment. In the next slide I explain how the “raw” data are obtained…
Illustration:
Optical Density Measurement

- A sample free of coagulated particulates has a transmitted light ~100%.
- With coagulated particulates, scattering reduces transmitted light to <100%.
- OD test method is highly variable, but can be use as a rough guide.
This slide shows the run history for relative %Optical Density over a 3 year period. What do you see? Is it what you expected? We have signals of change clearly shown. But, these signals are not the beginning of the change… They are at the end of the change…

- Evaluated base %Optical Density measures for clues.
- Plotted data on an Individuals SPC chart—a pattern emerged!
Using a method called Change Point Analysis we were able to determine the confidence bounds for the timing changes.

This plot includes a background produced by a method called Change-Point Analysis. We demonstrated its use during the talk.

Change Point Analysis is a method of assessing changes in a trend of data that is more robust and sensitive than typical trend analysis approaches such as the Western Electric rules. A change point is determined by summing successive differences between each data value and the mean of the entire set of data. Using what are called Bootstrap or Re-sampling methods the software is able to determine the statistical significance for each observed change point.

The down arrows in the plot identify the points in time where there was a statistically significant decline in the relative percent optical density. These are the points in time that identify the changes in the process we are interested in understanding.
One real challenge today is having too much data! Much of this extra data is noise, or as Sherlock puts it “incidental.” All of this extra data is confusing and unnecessary. The trick is figuring out which is which...

In this slide we show a table of significant changes determined using the Change-Point Analyzer. This table mirrors the earlier plot of data having the cyan background sections.

We are only interested in the timing points where the %Relative OD declined. Any other entrees are of little use. Therefore, we have covered up the data entrees that do not provide us any utility.

What do you see in this table? Do you see repeat timing points or durations that are consistent? Does this table give you any clues about the timing of the problem?
Step 3. Evaluate the Data:
Comparing Causes to the Facts

Structured Problem Solving Process

1. Describe the Problem
2. Identify Related Causes
3. Compare Causes to Facts
4. Collect Additional Data to Identify Root Cause
5. Determine Corrective Actions
6. Validate, Implement, and Evaluate Results

Evaluate
### C-Matrix Example:
**Narrowing the Causal Possibilities**

This is the example C-Matrix shown earlier for illustration purposes. Notice the cyan regions in the slide illustration. These are the regions where the causes were consistent with all of the facts supporting the problem. Therefore, we consider these causes more likely than the ones closed out with the “Xs.” This is how our method works. It is designed to first eliminate the unlikely causes from consideration.

Once all of the unlikely causes are eliminated, what remains are the likely causes.

Usually, when subject matter experts clearly see only the likely causes they are more able to develop sound theories of cause that are useful. This is the way the process should work.
So, now we are closing in on the final stages of the contradiction work. Most causes have been eliminated. Only a few remain. Notice the two causes that remain. Does it appear these two causes may be related?
Step 3. Evaluate the Data:
Initial Conclusions

- The Contradiction Matrix identified two areas that could affect particle generation at heat QC stability testing:
  - Bottle Pre-treatment process
  - Quality of the Bottle from Supplier

- Six other areas, which contained 50-60 possibilities, were excluded as possible causes of the observed problem.
Step 4. Evaluate the Data:
Collect Additional Data
Structured Problem Solving

Step 4. Collect New Data: Verifying the Potential Causes

What factors within the bottle pre-treatment process could contribute to the problem?

Our goal in conducting these DoEs is to elicit the problem symptoms, and also eliminate the problem symptom within the framework of the design. We are not really interested in modeling the process characteristics, but rather interested in producing them and turning them off. In doing so, we can set new boundaries for the operation of the process.
Evaluate New Data:
Achieving Understanding

Effects Table for Particle Count, Categorical (ea)

<table>
<thead>
<tr>
<th>Term</th>
<th>Log[Average]</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average, AS^2, HC^2, AS*HC</td>
<td>0.22204 **</td>
<td>0.26245 ***</td>
</tr>
<tr>
<td>CP</td>
<td>-0.045081</td>
<td>0.047859</td>
</tr>
<tr>
<td>AS</td>
<td>0.1995</td>
<td>0.27638 ***</td>
</tr>
<tr>
<td>HC</td>
<td>0.24458 *</td>
<td>0.22852 **</td>
</tr>
<tr>
<td>CP<em>AS, AS</em>HC</td>
<td>0.1995</td>
<td>0.27638 ***</td>
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<tr>
<td>CP<em>HC, AS</em>HC</td>
<td>-0.24458 *</td>
<td>-0.22852 **</td>
</tr>
</tbody>
</table>

* = Significant (* = 0.1, ** = 0.05, *** = 0.01)

Effects Plots for Particle Count

PS - Avg

Effects Plots for Particle Count

PS - CV

0 percent 20 percent

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Observations and Results

- Initial experiments identified the likely inputs affecting particle generation during heat stability testing to be:
  - **Protein Concentration** (*trivial factor*)
  - **Bottle Siliconization Process** (*a key factor*)
  - **Foam and Bubbles in Test Sample** (*observation*)
  - **Environmental controls in filling and test areas** (*a key factor*)
Causal Mechanism:
Evaluating Container Passivation

Entire process was pushed forward by changes in area temp and humidity...

Open areas in silicone passivation can cause Albumin to nucleate

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Determine Corrective Actions

Structured Problem Solving Process:

1. Describe the Problem
   - Define the problem
   - Identify key factors

2. Identify Related Causes
   - Conduct Root Cause Analysis
   - Develop Hypotheses

3. Develop and Analyze Deficient Data
   - Collect Data
   - Analyze Data

4. Develop Additional Data to Identify Root Cause
   - Conduct Further Analysis
   - Make Adjustments

5. Determine Corrective Actions
   - Develop Action Plan
   - Implement Corrective Actions

6. Validate, Implement, and Evaluate
   - Monitor Performance
   - Evaluate Results
Step 5. Corrective Actions:
Required Action Items

- Observed the bottle siliconization process.
- Reviewed the process validation.
- Significant areas in the process validation were incomplete.
- Increased coating thickness, key cause.
- Reworked siliconization process validation.
- Improved process consistency.
Establish New Controls

Structured Problem Solving Process

1. Describe the Problem
   - Define the problem clearly.
   - Identify the key issues.

2. Identify Related Causes
   - Analyze the root causes of the problem.
   - Use tools like 5 Whys or Fishbone Diagrams.

3. Develop Solutions
   - Brainstorm potential solutions.
   - Evaluate each solution for feasibility.

4. Implement Solutions
   - Plan the implementation steps.
   - Monitor the outcomes and adjust as necessary.

5. Review and Adjust
   - Assess the effectiveness of the solutions.
   - Make adjustments if necessary.

Control

Process

Inputs

Outputs
Step 6. Control:
Establish Process Controls

- Developed a test for passivating coating viscosity.
- Included viscosity test into process control and monitoring schema.
- Established requirements for viscosity, bake temperature, and time.
- Encoded requirements into automated equipment operation.
- Particle generation at heat stability testing no longer exists.
### What was the Process?

#### Roadmap for Problem Resolution

1. Describe the problem dimension with IS/IS Not Matrix.
2. Develop an extensive list of potential causes.
3. Organize and analyze the existing data.
4. Use the *Contradiction Matrix* to rule out unlikely causes.
5. Identify unknowns and assumptions – follow-up.
6. Construct an interim action plan based on unknowns and assumptions from the C-Matrix.
7. Determine *causal* mechanism for the problem.
8. Prepare a action plan to eliminate and control problem.
Some Closing Comments:
Learning from Structured Methods

- Focuses on Facts and data instead of Perceptions.
- Managed by eliminating the unlikely causes first—what remains is likely...
- Allows everyone to participate.
- Uses time and limited resources efficiently.
- Method is a Natural Team Building Activity.

Using this approach, the team members focused on the facts rather than perceptions or unguided experiences.

Using this approach, all possible causes were filtered through the Contradiction Matrix leaving only those causes that supported all the facts.

At each step of the process deliverables were required. Having these deliverables focuses the problem solving team on the requirements for building a sound strategic investigation.

In combination, the disciplined methods used to conduct the problem solving process results in the lowest investment of time and resources.

--- It provides an ability to achieve consensus among team members quickly and effectively.
--- It uses a common approach that all team members can support, regardless which area each member supports.