Baxter

Contamination Recovery Rate Using Statistical Process Control

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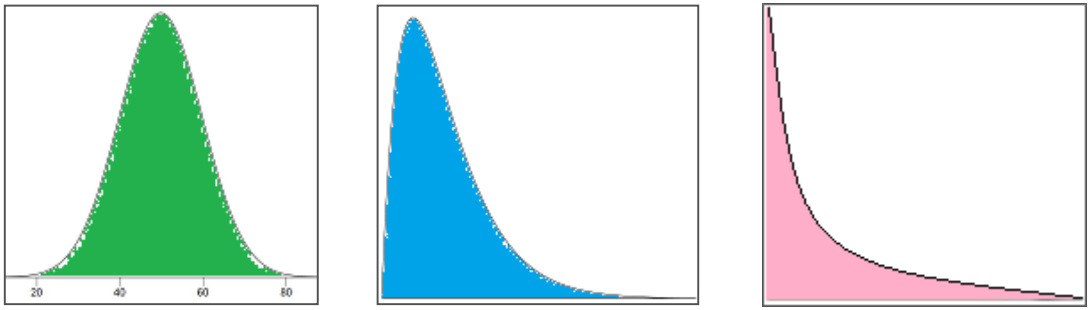
Statisitics and Microbiology Challenges

On Data Sets

- Cleanroom microbiology testing results have a majority of samples with results of 0 CFU.



On Test Assays

- Different tests have different recovery abilities.

On Personnel

- Statistical knowledge among microbiologists varies person to person.

Resource Constraints

- Tools need to be flexible to allow use for multiple sample types.

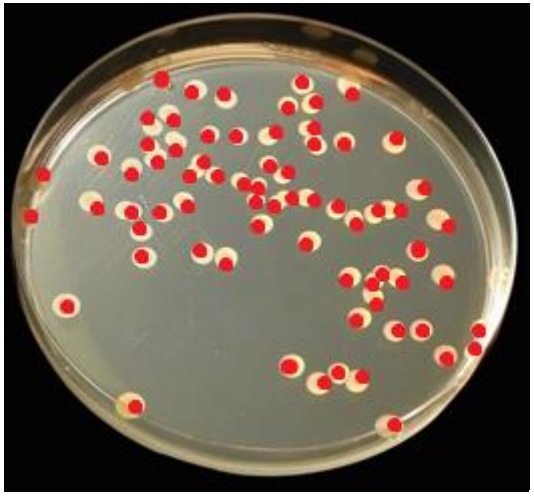
What is Contamination Recovery Rate?

Enumeration

Individual results (Count / Plate)

Compare magnitude to existing Limits

React when limits exceeded



70 CFU/Plate

Contamination Recovery Rate

By Sample Site / Type (%)

Regardless of count magnitude (1=70CFU)

Samples over time (e.g. monthly, weekly)

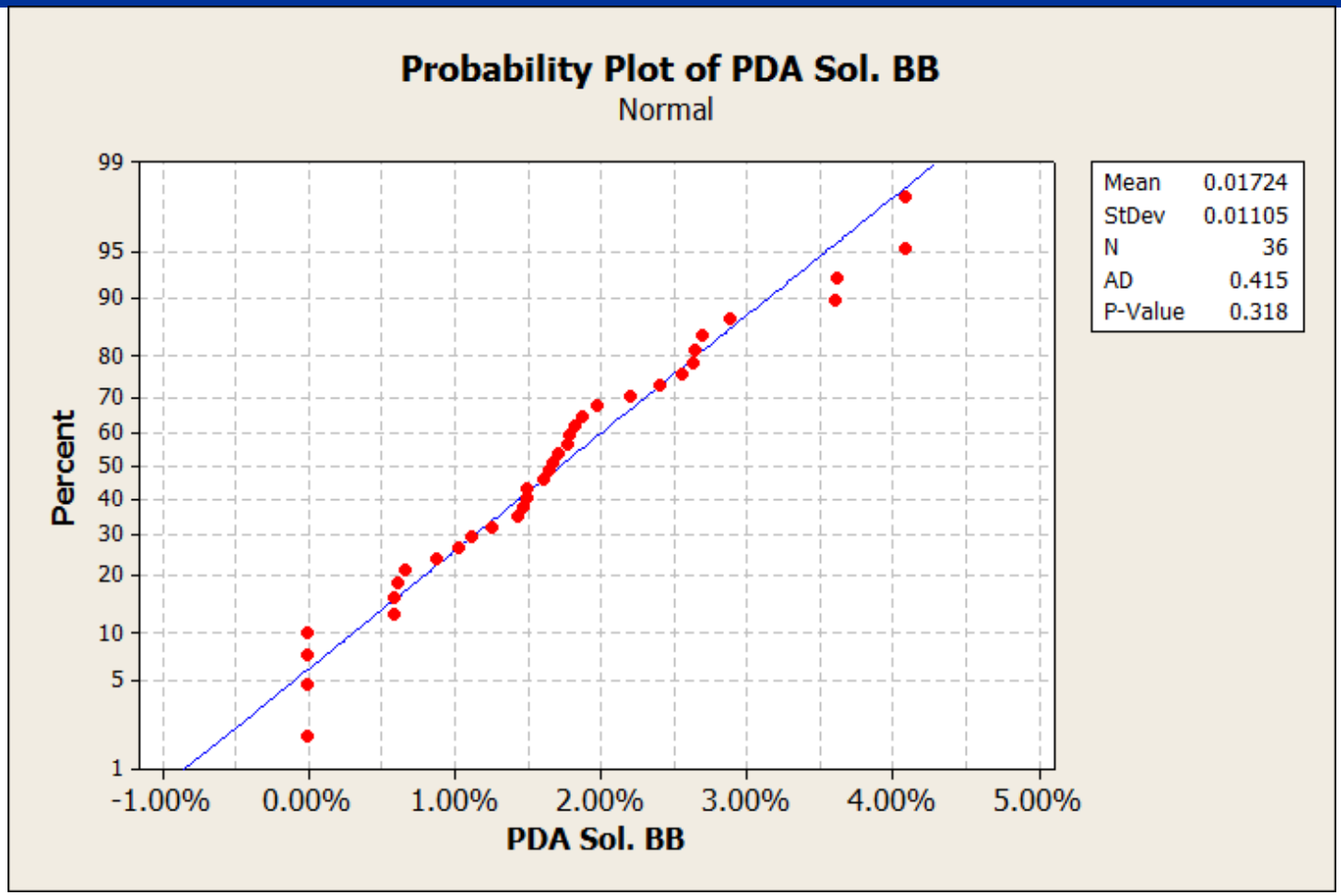
11% Recovery Rate

Why Contamination Recovery Rate?

Microorganisms may be in a clump when recovery assay occurs.

- Can lead to colony growth that makes it difficult to count/compare results to Action/Alert Limits

Why Contamination Recovery Rate?



Here is a normality test of the presterilization bioburden example used later on in this presentation

a. Normally distributed data allows use of more statistical tools

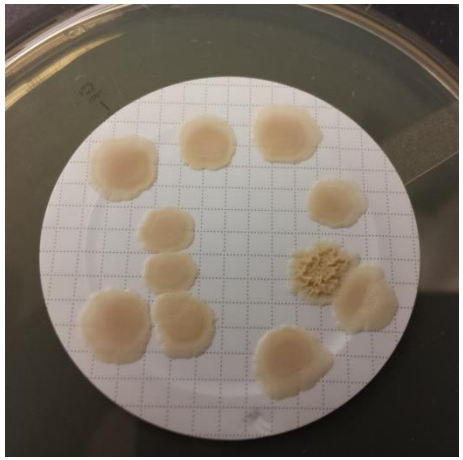
b. Trend Analysis much easier to technically justify with normal distribution

Why Contamination Recovery Rate?

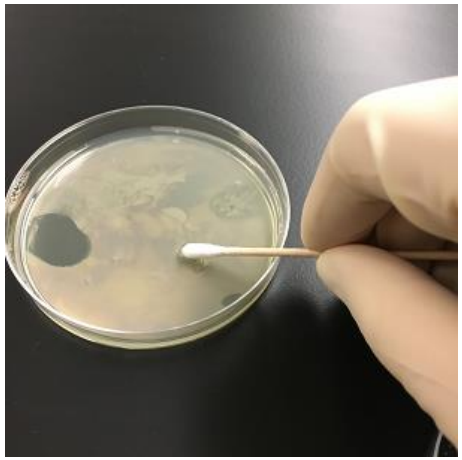
Different recovery methods have different recovery percentages:

a. Example: Surface Sampling
   - Difference in recovery ability
   - Inherent differences in personnel technique

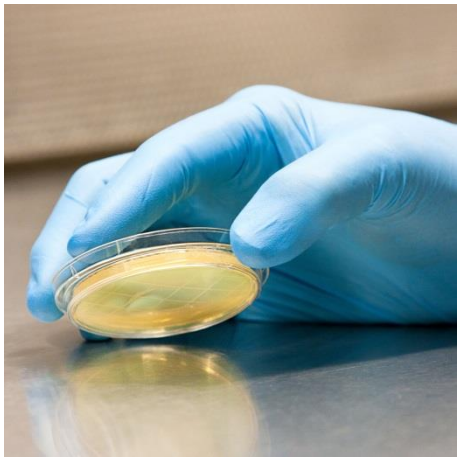
Membrane Filtration



Direct Swab



Contact Plate



Flexibility: Can be used on any non-sterile assay:

a. Product BB, EM, WFI
b. Especially useful in Grade C/D environments (more likely to recover)
c. We strive for no growth, so a grow/no grow monitoring system is desirable/useful.

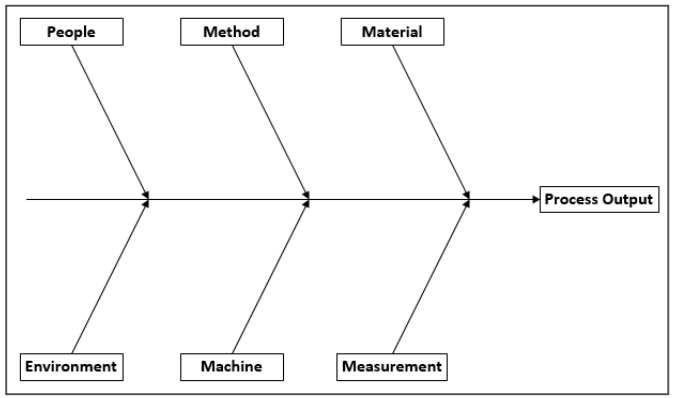
What is Statistical Process Control?

Definition

- Statistical process control involves getting a process to consistently operate to its full potential and **continually improving** in performance through the use of control chart tools.

About Data Sets

- **Variation** always exists. Even identical processes using the same equipment, personnel, product, etc. will experience variation.
- Variation can be **routine** or **exceptional**.



Process Behavior Charts

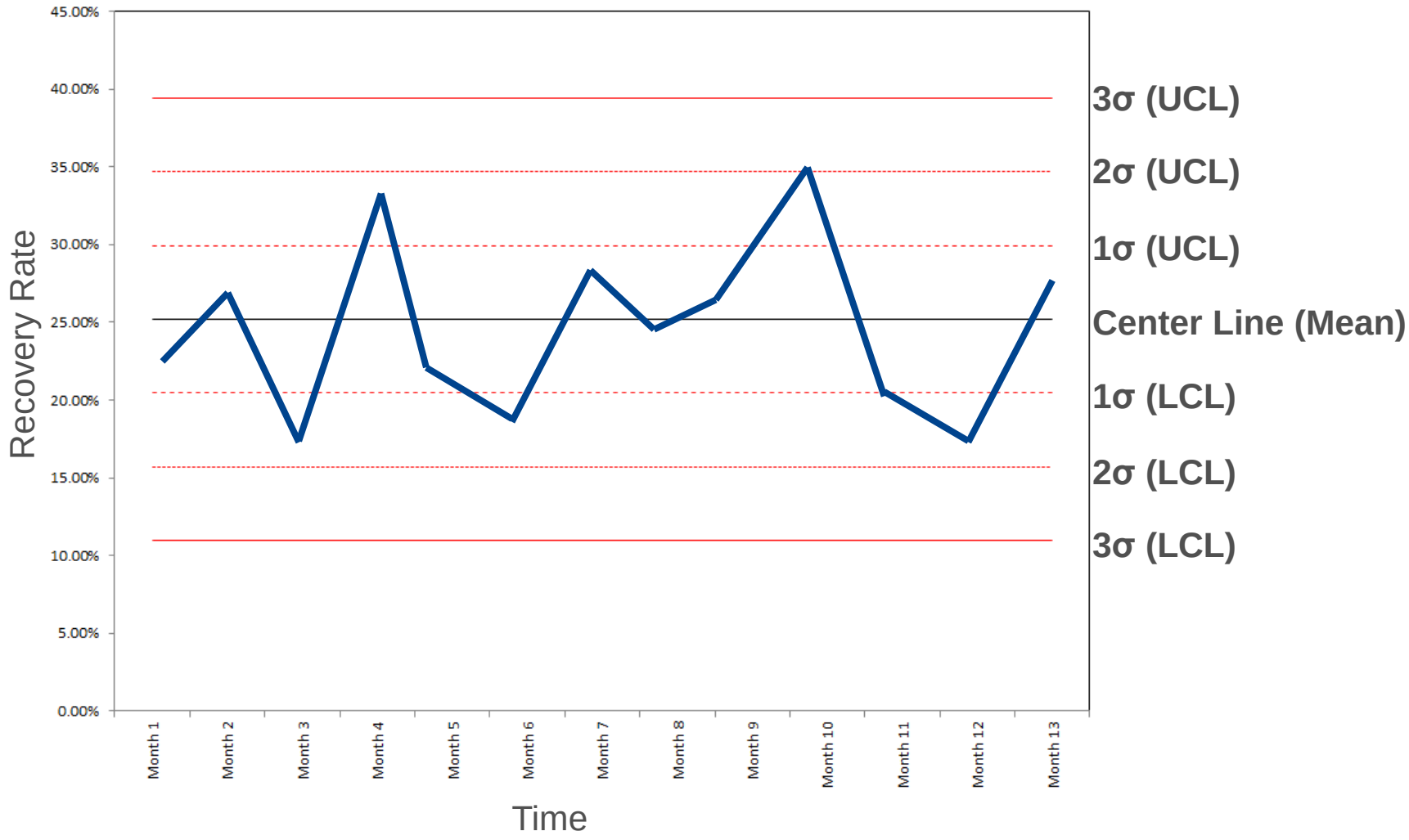
- Data points plotted in a time series.
- Central Line (Mean) plotted.
- **3σ limits** plotted for upper control and lower control.

Contamination Recovery Rate

- **Individual Values charts** are utilized when subgroup n=1.

Statistical Process Control

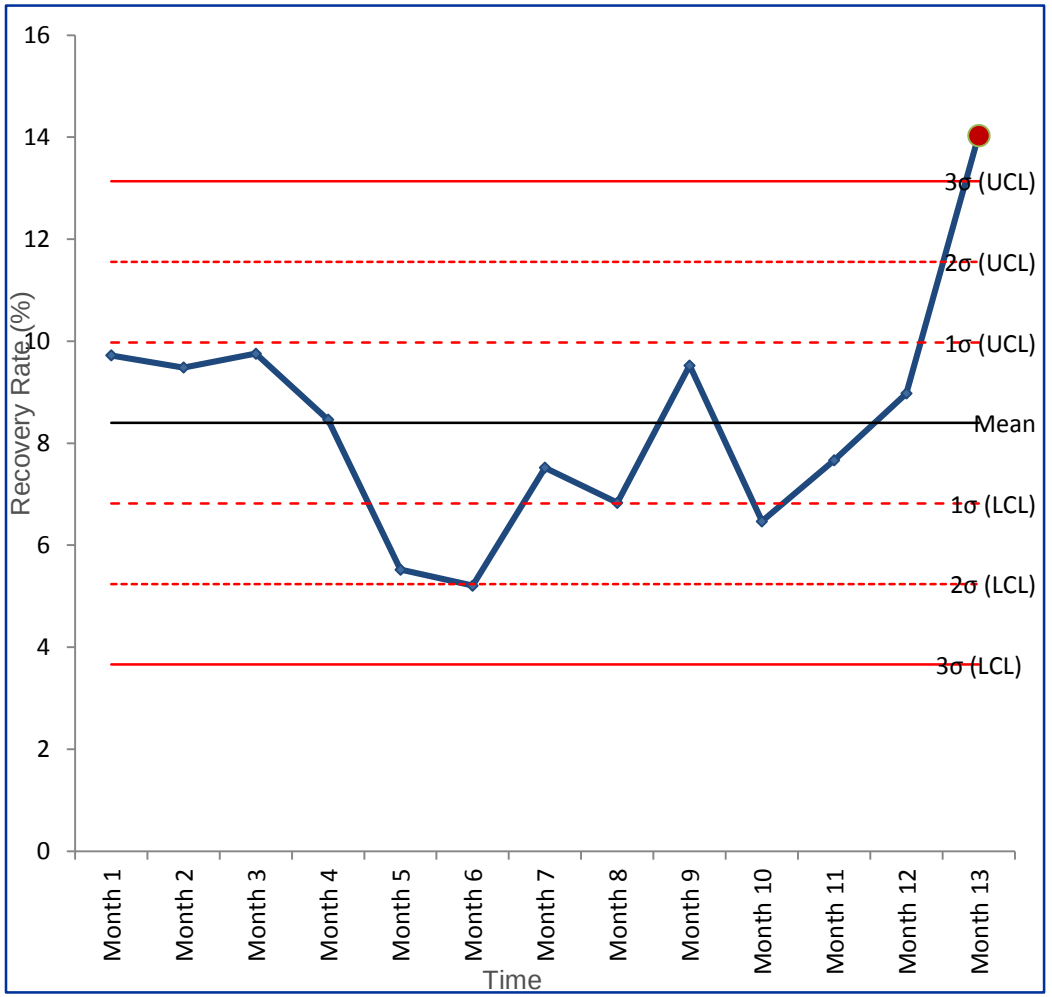
Analyzing Data Set via Individual Values Control Charts



How to Identify Exceptional Variation – Rule 1

Rule 1:

One data point that is greater than the 3σ UCL.

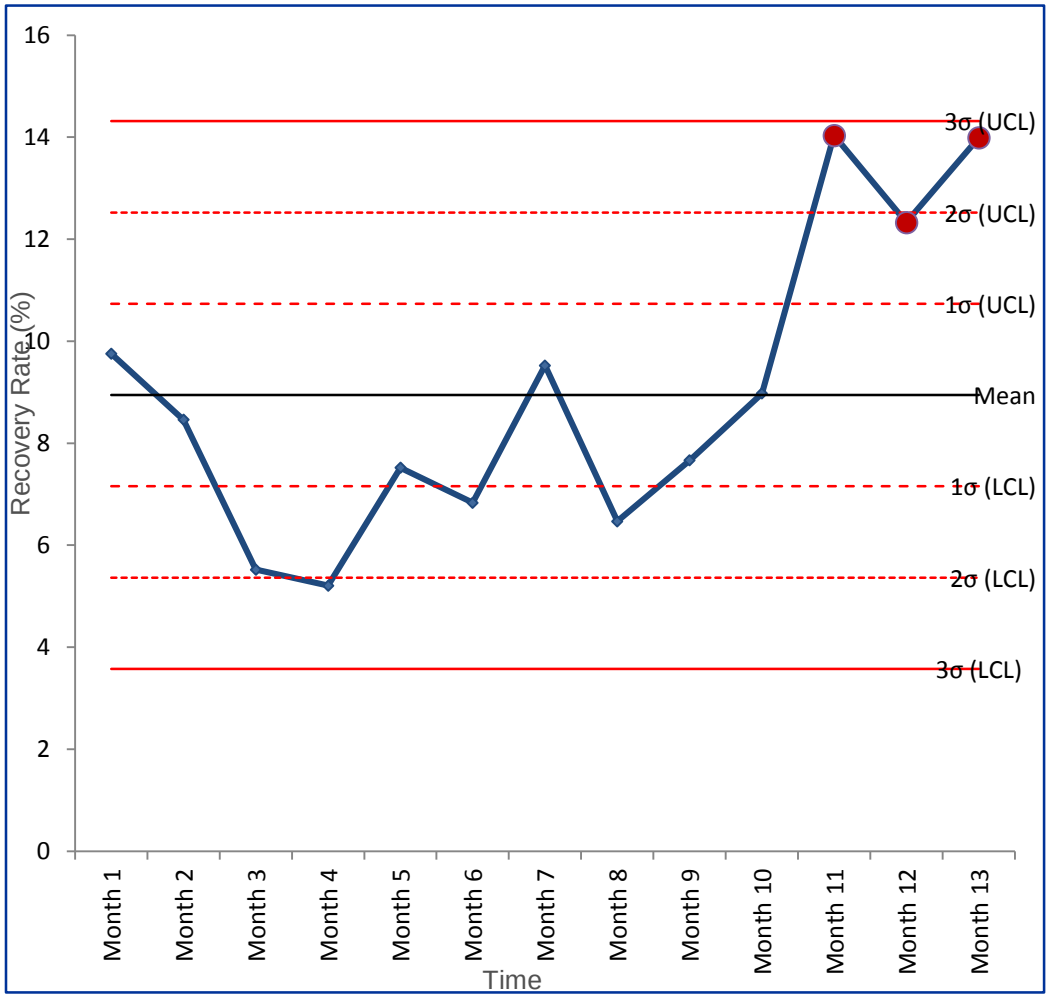


Based on Nelson's Rules. We have highlighted 4 rules most useful for our recovery rate analysis.

How to Identify Exceptional Variation – Rule 2

Rule 2:

Two out of three consecutive data points that are greater than the 2σ UCL.

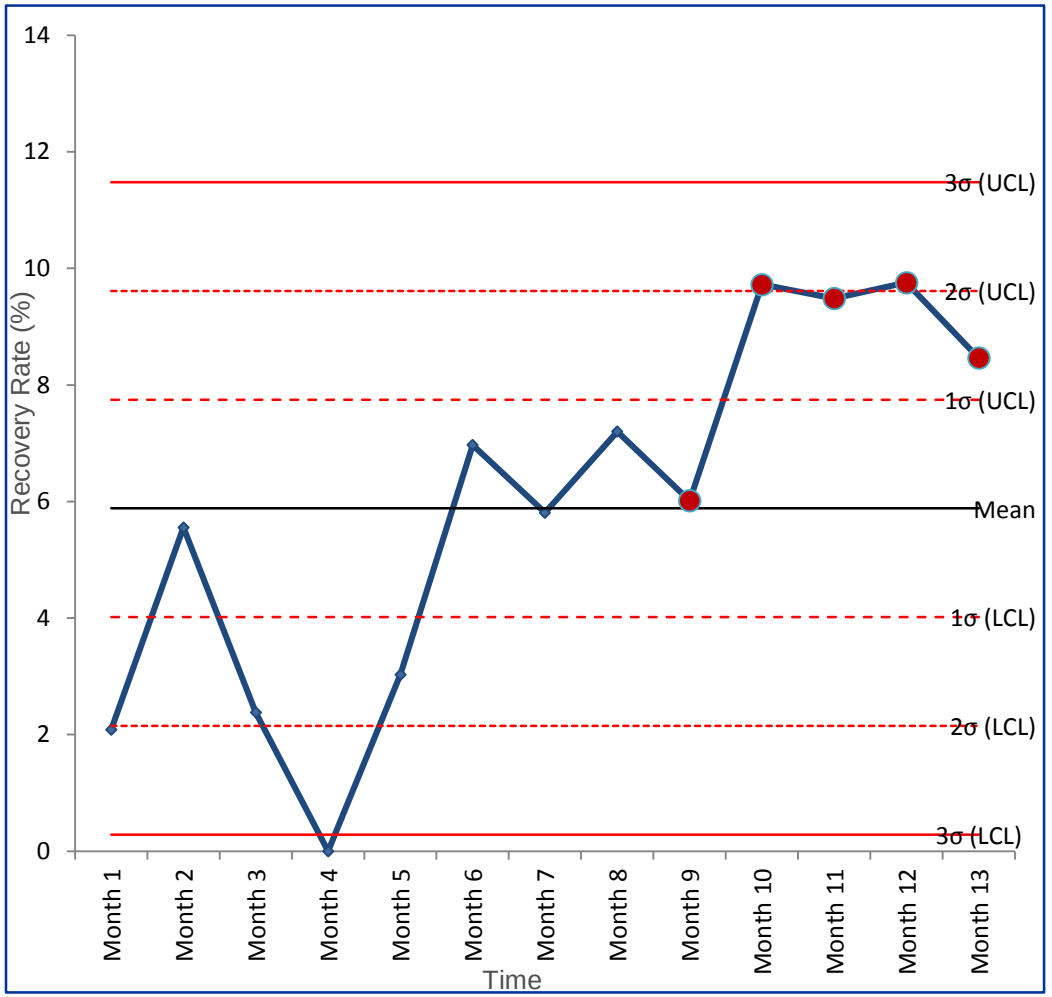


Based on Nelson's Rules. We have highlighted 4 rules most useful for our recovery rate analysis.

How to Identify Exceptional Variation – Rule 3

Rule 3:

Four out of five consecutive data points that are greater than the 1σ UCL.

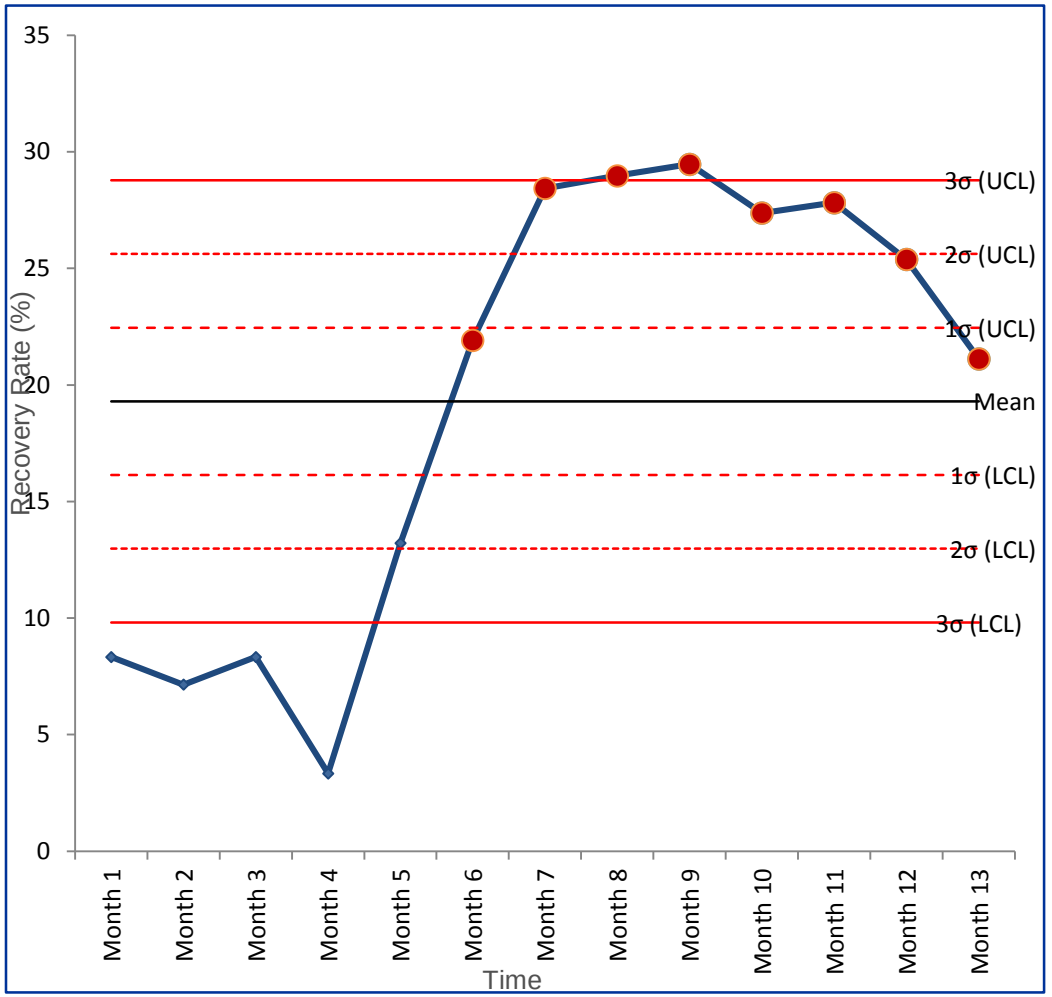


Based on Nelson's Rules. We have highlighted 4 rules most useful for our recovery rate analysis.

How to Identify Exceptional Variation – Rule 4

Rule 4:

Eight consecutive data points that are greater than the mean.

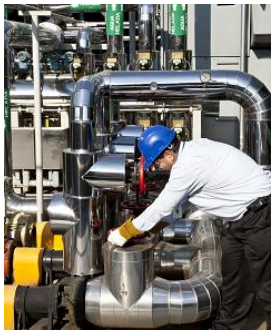


Based on Nelson's Rules. We have highlighted 4 rules most useful for our recovery rate analysis.

Responses to Process Instability (Exceptional Variation)

Justifiable to Look for Assignable Cause:

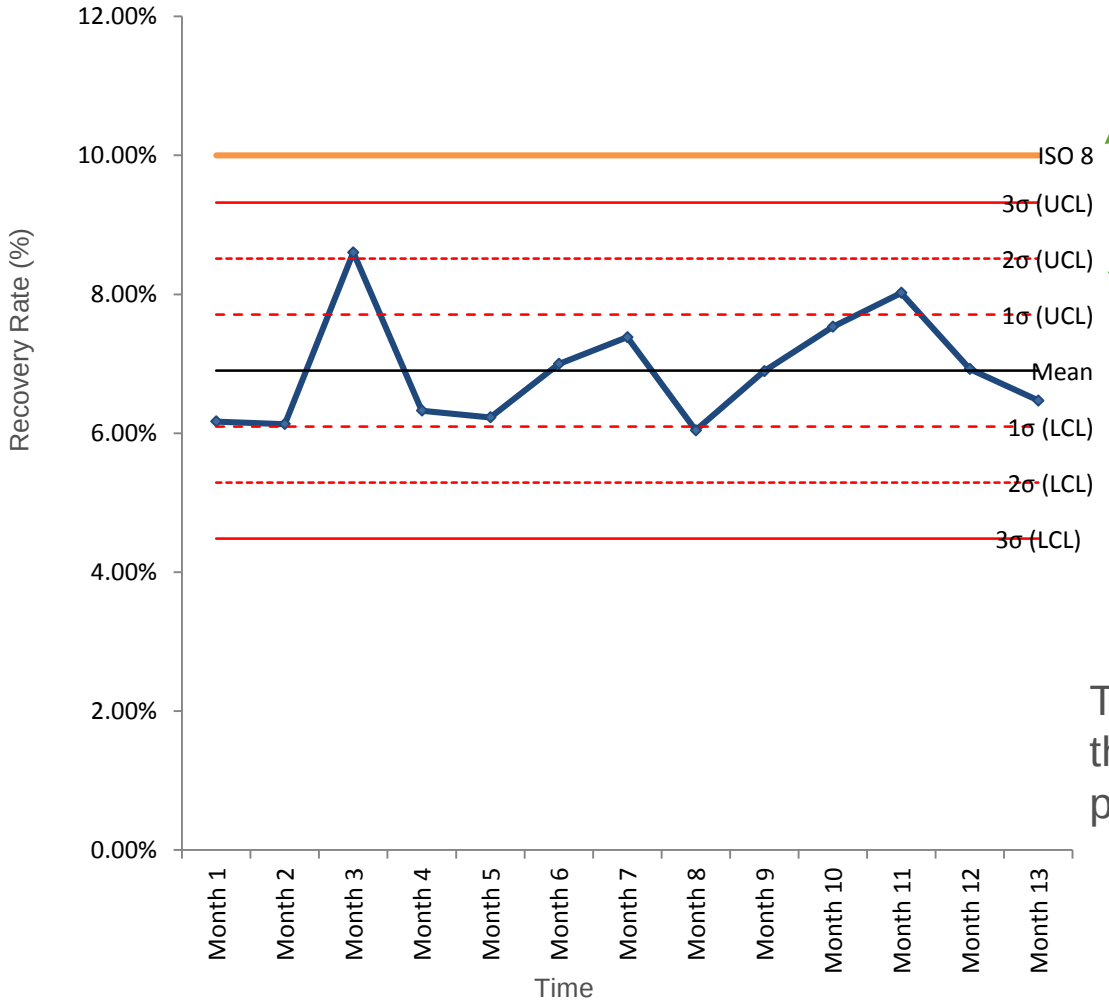
When Cause Is Identified, Act:



If Assignable Cause Is Not Immediately Identifiable, Keep Track:

Special Project / Initiative may be required

Voice of the Process vs. Voice of the Customer



Voice of the Customer

- Requirements that the product / process must meet

Voice of the Process

- How the process is actually performing

The Voice of the Process will be within the Voice of the Customer range for a process within control.

Important!

- **Never confuse the control chart limits with specification limits.**
- **Control Chart limits are calculated each time from the process data and represents “Voice of the Process”**
- **Guide for predicting behavior and/or preemptively act when variation in data exists.**
- **Specification limits represent “Voice of the Customer” – requirements product must meet.**

Case Study Data Disclaimer

All data shared throughout the presentation has been developed to illustrate the concepts of the SPC approach.

Intro to Case Study #1

Background

The following slides contain information on viable surface samples (EM) collected on a monthly basis at facility with product that is Aseptically Processed.

Scope

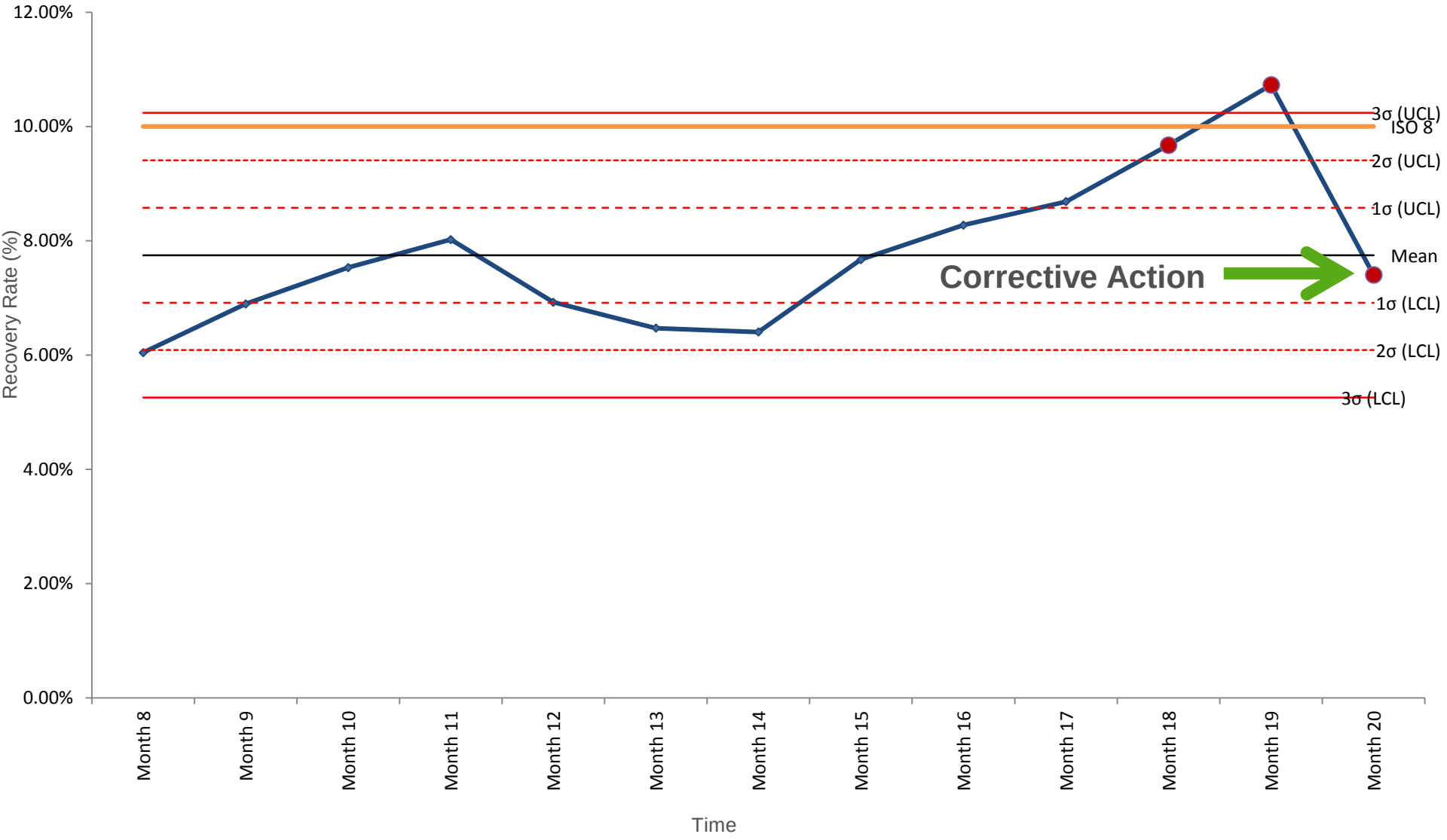
All surface samples in scope were collected in an ISO Class 8 environment.

For each month, an average of ~250 surfaces samples were collected.

Specific Case Details

- At the time of the data collection, statistical process control was not in use to analyze the data (this is a retroactive review).
- The facility has a specification contamination recovery rate limit of 10% (USP <1116>)

Environmental Monitoring Surfaces - Case Study #1



Summary of Case Study #1

What Happened?

Starting in Month 14, the facility would have seen an uptick in recovery rate that would have led up to an Exceptional Variation rule violation (Rule 1-one point above the 3σ limit) in Month 18; however, at this time no Preventative Action took place because the facility was not using SPC.

The Month 19 data showed that data was above the USP <1116> guidance limit for contamination recovery rate when it exceeded 10%. The reaction led to a Corrective Action which drove the recovery rate back down to the mean in Month 20.

Significance

- If using SPC and contamination recovery rate, the out of specification condition could have been potentially avoided because the previous month signaled Exceptional Variation, which would lead to a Preventative Action.
- SPC offers proactive response driven by data.

Intro to Case Study #2

Background

The following slides contain mix tank product solution bioburden samples collected on a monthly basis at a facility with product that is Terminally Sterilized via moist heat.

Scope

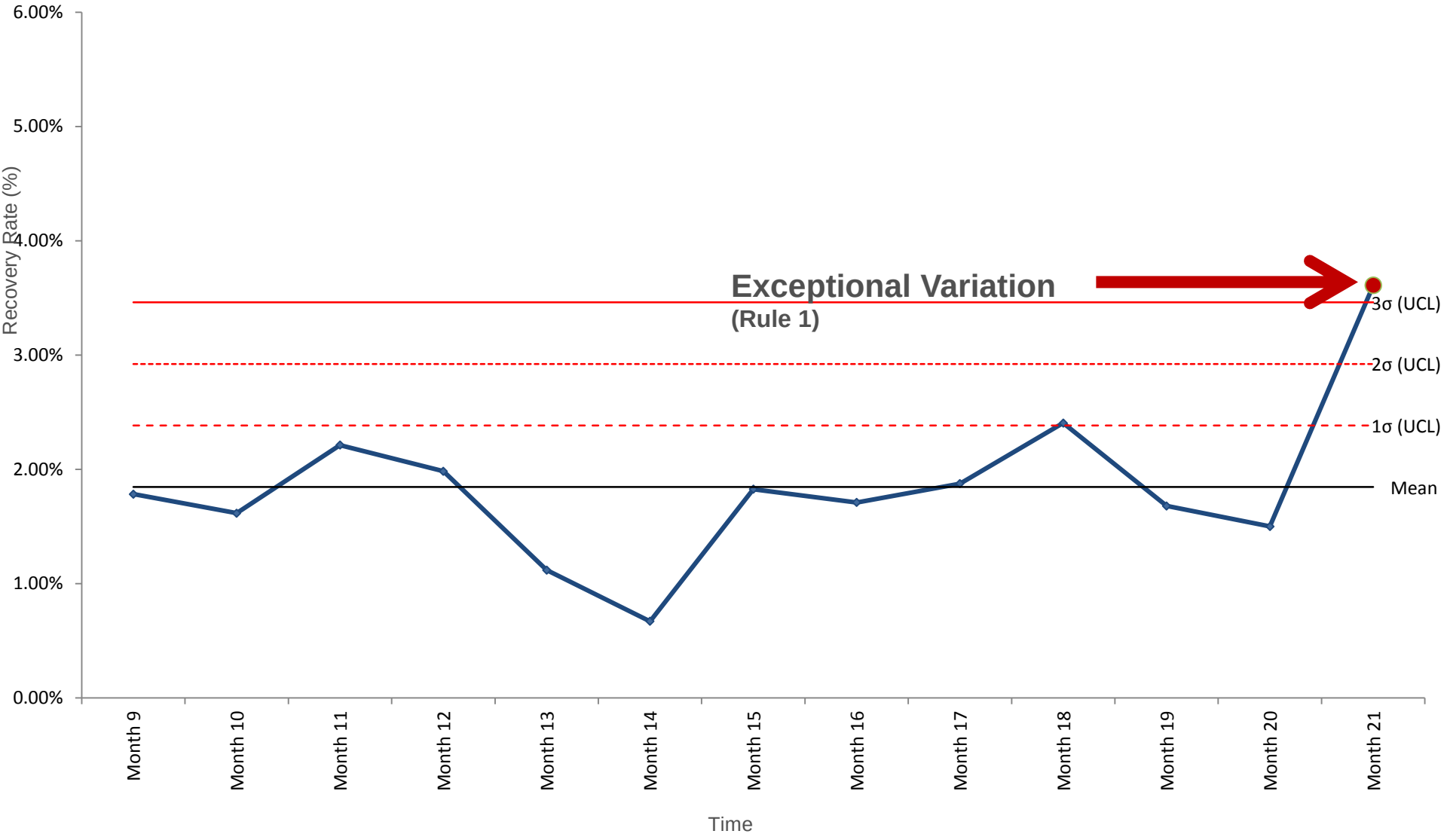
All bioburden samples in scope were collected in a Grade D environment from one mix tank.

For each month, an average of ~125 samples were collected from the specific mix tank.

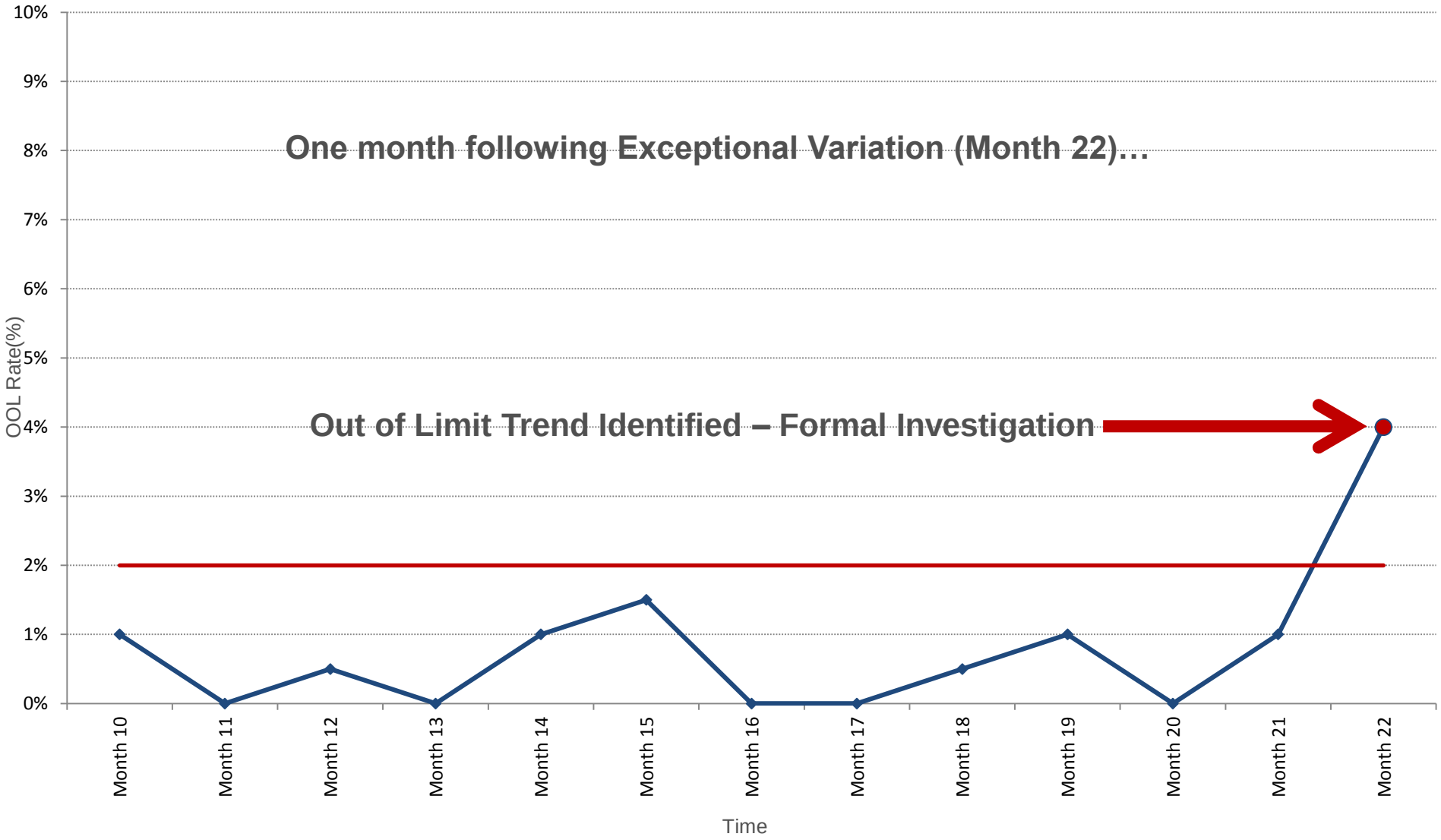
Specific Case Details

- At the time of the data collection, statistical process control was not in use to analyze the data (this is a retroactive review).
- This facility uses a P-chart to determine the monthly limit for ratio of samples that are above alert limits for trend analysis.

Mix Tank Bioburden SPC Trend Analysis - Case Study #2



Mix Tank Bioburden SPC Trend Analysis - Case Study #2



Summary of Case Study #2

What Happened?

In Month 21, the facility would have identified an Exceptional Variation rule violation (Rule 1- one point above the 3σ limit); however, at this time no Preventative Action took place because the facility was not using SPC.

The traditional trending tool (comparing # samples over Alert Limit to trend limit) did not signal an investigation for Month 21. The following month's data (Month 22) did signal an investigation due to an elevated number of samples over the Alert Limit.

Significance

- If using SPC and contamination recovery rate, the out of trend condition could have been potentially avoided because the previous month signaled Exceptional Variation, which would lead to a Preventative Action.
- SPC offers a more sensitive monitor of system quality.
- If SPC is detecting drifts, but Alert/Action Levels do not, perhaps these levels should be assessed.

Intro to Case Study #3

Background

The following slides contain WFI bioburden samples collected on a monthly basis at two (2) facility locations (A and B).

Scope

All WFI samples in scope collected at the respective facilities.

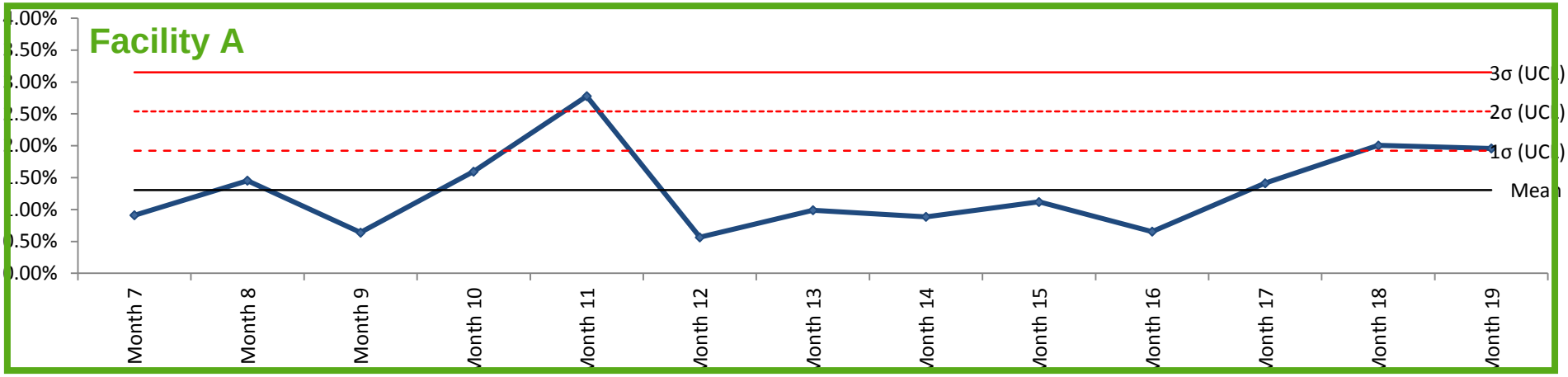
Each facility collects >40 samples per month.

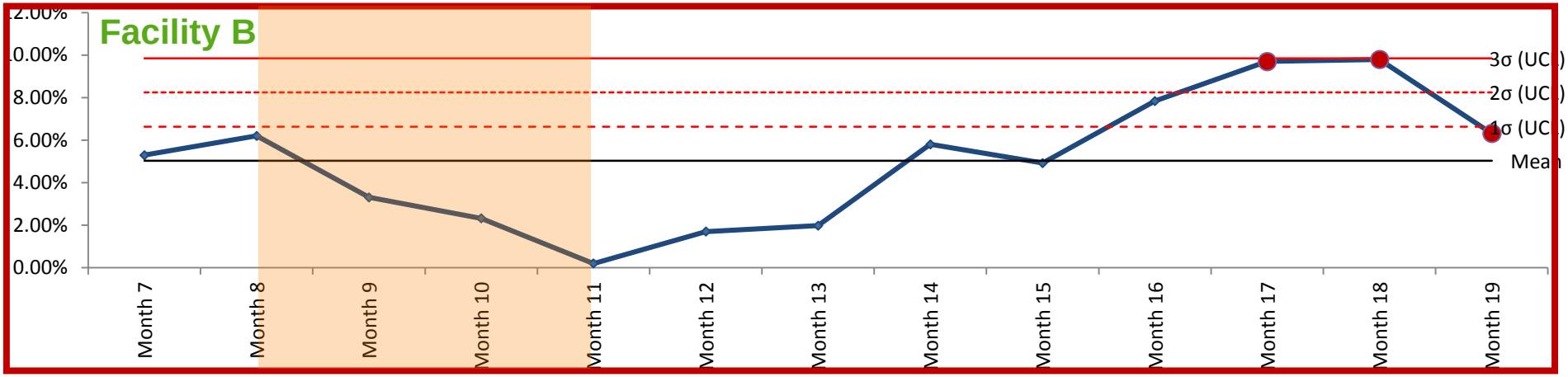
Both systems utilized different combinations of equipment/processes to produce WFI.

Specific Case Details

- At the time of the data collection, statistical process control was not in use to analyze the data in either facility (this is a retroactive review).
- The following slide shows a side-by-side comparison of two (2) facilities.

Multiple Facility WFI Comparison - Case Study #3





Summary of Case Study #3

What Happened?

In Month 17, Facility B would have identified an Exceptional Variation rule violation, Facility B also experienced Exceptional Variation data sets for the following two (2) months. Over the same time period, Facility A experienced only Routine Variation.

From Month 8 through Month 11, Facility B experienced a sustained downtrend in recovery. What was going on during this time period to account for the increased control? Can that be duplicated?

Facility A had a mean of ~1% and Facility B had a mean of ~5%. What can account for these differences?

Significance

- Production of WFI is not standardized for each facility (different combinations of equipment can produce WFI as necessary for the product).
- The Exceptional Variations in the data set would intiate Preventative Actions in Facility B that could potentially improve quality to match Facility A.
- Comparing the SPC allows the corporate functions to monitor the differences between facility systems and standardize those which have better data sets, which can lead to continuous improvement through harmonization and collaboration.

Why Statistical Process Control w/ Recovery Rate?

Advantages

- Data sets follow a **normal distribution**.
- Statistical Process Control (SPC) is an **established mechanism** for Quality Control in industry (easy to learn, use and maintain).
- **Flexibility**
- The tool can be **"Plug and Play"**.
  - Combination of validated tool and guidance can lead to easy to follow stats training/knowledge for local microbiologists.
  - Can be used retrospectively to compare past with present.
- More Sensitive monitor that can **preemptively** identify signals compared to Action/Alert excursions.
  - Investigations signaled before system is "off the rails."
  - Ratio of Preventative to Corrective Actions (health of CAPA).
  - Greater confidence in data analysis.
  - Data driven **Preventative Actions**.
- **Harmonization** of facility systems for companies with multiple locations producing similar products/materials.

References

1. United States Pharmacopeia. USP 40–NF 35, Microbiological Control and Monitoring of Aseptic Processing Environments <1116> Rockville, MD: USP; 2017:1430-1443.

Acknowledgements / Thank You-s

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