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TRENDING AND PATTERN RECOGNITION FOR ANNEX 1

Digital Contamination Control Strategy
Data Use To Meet Regulatory Requirements

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INITIALLY
- FDA - 21 CFR Part 11, Electronic Records; Electronic Signatures - Scope and Application
- EMA - Annex 11, Computerised Systems

RECENTLY
- FDA - Data Integrity and Compliance With CGMP Guidance for Industry
- EMA – Data Integrity Q & A
- PIC/S GUIDANCE - Good Practices For Data Management And Integrity In Regulated GMP/GDP Environments
- Others…

CURRENT
- EU Annex 1
- PDA TR 13
- FDA - Sterile Drug Products Produced by Aseptic Processing
- USP 1116
- ICH Q9 Revision on Quality Risk Management

INITIALLY
- The regulations evolved to account for the ever-increasing use of computerized system in the late 90s and early 2000s. Both US and EU set forth regulations to govern the use of system when managing GMP data on which quality and batch release decision are made. These regulations have been revised and most recently Annex 11 concept paper is being circulated for the latest changes

RECENTLY
- Between 2010 and 2020 the industry focus on electronic records related to the integrity of the data. FDA, EMA, and other regulatory agencies set forth regulations and guidance documents relating to data integrity to ensure the records being collected and used for quality decisions were reliable.
- ALCOA originated from the FDA's Office of Enforcement in the 1990s., it is used in regulated industries as a framework for ensuring data integrity for both paper and electronic records.

CURRENT
- The industry collects significant electronic records, the next logical step is to make use of the records to improve the processes that are related to the data being collected.
- In the new Annex 1, the word 'Trend' occurs 23 times. The latest evolution in the regulations for EMA, and FDA now encourages companies to use the records being collected to enhance product quality and patient safety.

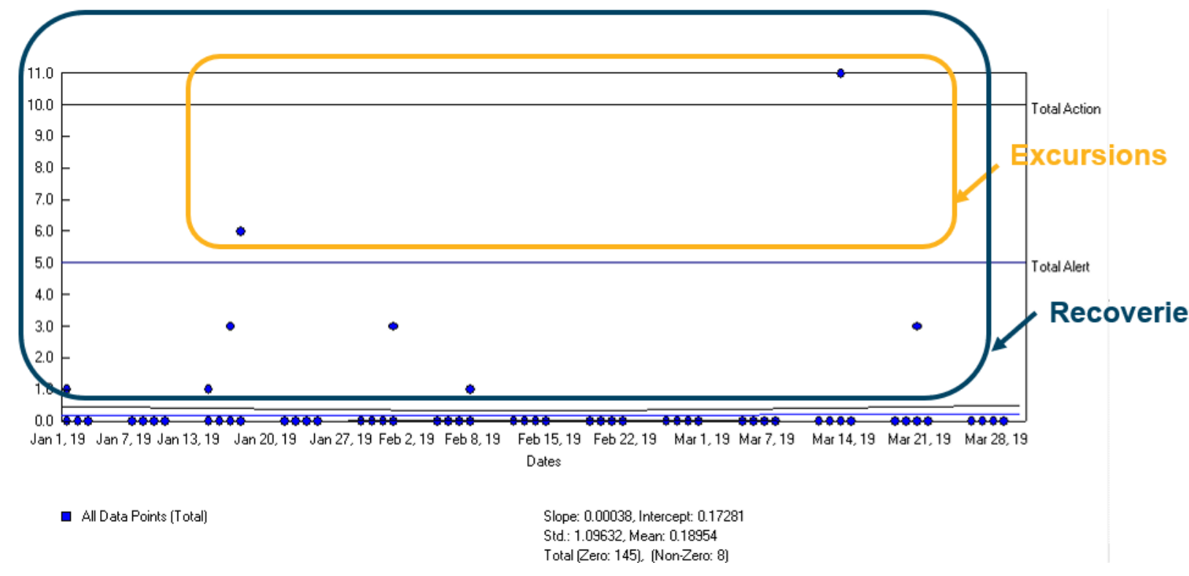
HUMANS PROCESS VISUAL DATA BETTER
Published on September 15, 2014
https://www.t-sciences.com/news/humans-process-visual-data-better

- The human brain processes images 60,000 times faster than text.
- 90 percent of information transmitted to the brain is visual.
- Because humans are so good at looking at images, visual trending tools allow scientists to recognize patterns in the data and identify data sets, data groupings, and process anomalies.

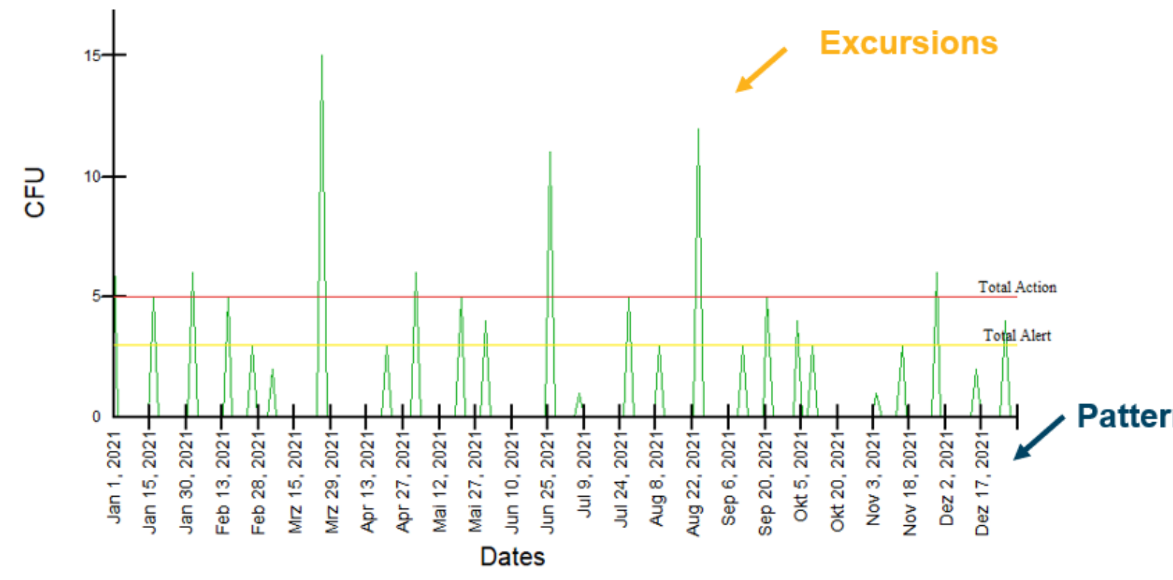
PATTERN RECOGNITION & GENERALISATION

•Patterns are the same within a problem and between problems.
•Pattern recognition is based on the 5 key steps of:
1. Identifying common elements in problems or systems
2. Identifying and Interpreting common differences in problems or systems
3. Identifying individual elements within problems
4. Describing patterns that have been identified
5. Making predictions based on identified patterns.

Selecting chart types should be based on the data and what the reviewer is looking for.



Visual representation which allows a reviewer to quickly see both Alert level and Action limit excursions.



A line chart is a good option to look at patterns over time, this chart shows a clear quarterly pattern based on Action limit excursions.

What is Critical data, which data fields should be tracked when collecting samples for contamination control?

Critical Data is the data you do not have when investigation!

Monitoring Data Fields

Sample Type	Taken By	Media	Exposure Time
Test Disposition	Handled By	Media Lot Number	Exposure Amount
Group	Read By	Media Type	Incubation Duration
Operator (Gowning Monitoring)	Equipment ID	Microorganism identification	Incubator (20-22 C°)
Date Test Taken	Equipment Name	Genus	Temperature
Date Test Entered	Eq. Calibration Date	Species	Time / Unit
Location / Port	Sample Start Time	Strain	Inc. Calibration Date
Location Description	Sample End Time	Gram Stain	Incubator (30-32 C°)
Room	Shift	Reference	Temperature
Classification	Comments	Storage	Time / Unit
Operational/Routine	Protocol ID Code	Product Lot Number	Inc. Calibration Date
Loop	Surface Type	Safety Margin	Sample Collection Date

Critical Notifications are indicators an investigation and CAPA is required!
- Alert level excursion
- Action limit excursion
- On personnel – two action limit excursions in a row
- At a sample point – three alert level excursions within the last ten samples collected
- In a room – five alert level excursions in within the last two weeks
- In a department – the same microorganism was found in three different rooms.

Notifications must be configured based on the state of control, being more or less sensitive in time and count as needed.

Process automation to collect electronic records has never been more important, FDA regulations call for auto saving data at each step, and steps are executed contemporaneously.

Real time data collection and sample collection with the latest technology in automated systems.

Complete electronic data capture and management from sample collection, to result input, approvals and trending and reporting is now a must have. According to PDA technical report 13, "Based on the large number of samples tested by a given facility, a computer-based data-tracking system is essential."

Regulatory Evolution Data Integrity & Record Use

REGULATIONS ~ EU Annex 1:
Prevention – **trending**, investigation, corrective and preventive actions (CAPA), root cause determination and the need for more comprehensive **investigational tools.**

Process and equipment alarm events should be reviewed and approved and evaluated for trends. The frequency at which alarms are assessed should be based on their criticality (with critical alarms reviewed immediately).

Results for critical parameters and critical quality attributes of high-risk utilities should be subject **to regular trend analysis** to ensure that system capabilities remain appropriate.

Alert levels should be based on the qualification or a **review of ongoing monitoring data that will identify an adverse trend in system performance**.

Breaches of alert levels should be documented and reviewed and **include investigation of system trends** to determine whether the breach is a single (isolated) event or if results are indicative of loss of control or system deterioration.

Each breach of action limits should be investigated to determine the root cause of the issue and any impact on the quality of products ….

There should be systems in place for disqualification of personnel from entry into cleanrooms based on aspects including ongoing **assessment and/or identification of an adverse trend** from the personnel monitoring program…

Monitoring procedures should **define the approach to trending**. Trends can include but are not limited to:
a) Increasing numbers of action or alert limit breaches
b) Consecutive breaches or alert limits
c) Regular but isolated breaches of limits that may have a common cause, for example single excursions that always follow planned preventative maintenance
d) Changes in flora type and numbers

Trends in the Data Review Frequency

TRENDING AND REVIEW REQUIREMENTS
How often should Contamination Control data be reviewed?
What statistical tools should be used to review the data?

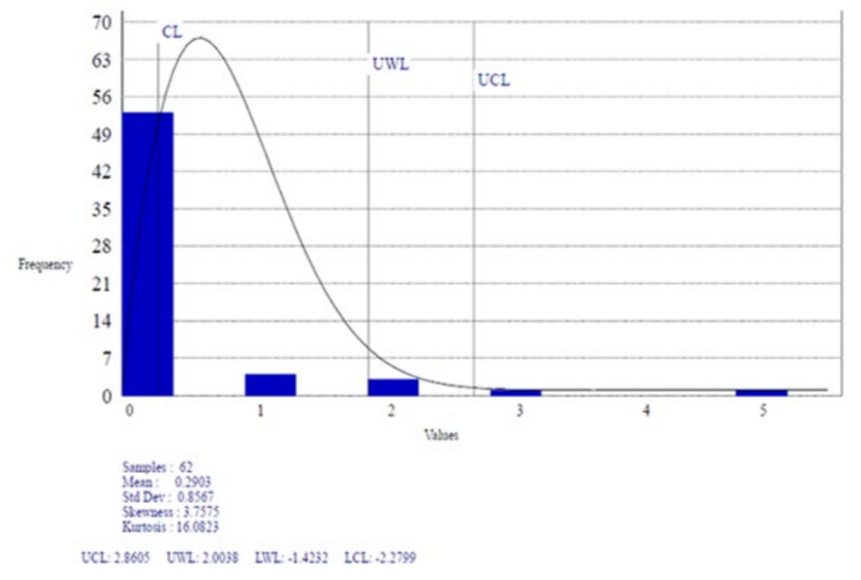
Statistical Tools:
- Recovery Rate Reports
- Excursion Count and Rate Reports
- Control Charts (Shewhart, Weibull, Percentiles, Quantiles)
- Line/Bar Charts/Pie Charts
- Others …

Frequency of data review using trending tools:

Monthly:
- Excursion reports, filtered by Grade and Test Types while grouping by sampling locations.
- Recovery Rate reports for all Sample Types and Grade / ISO Classification.
- Recovery Rate for Personnel (Glove and Gown samples)

Quarterly:
- Regression Analysis, Cleaning Process – Analytical Methods
- Line/Bar chart to trend Safety Margin for cleaning validation samples
- Pie Charts for Genus & Species filtered and grouped by Grade and Test Type
- Propagation (Heat) maps – show the path of the organisms through the facility over time

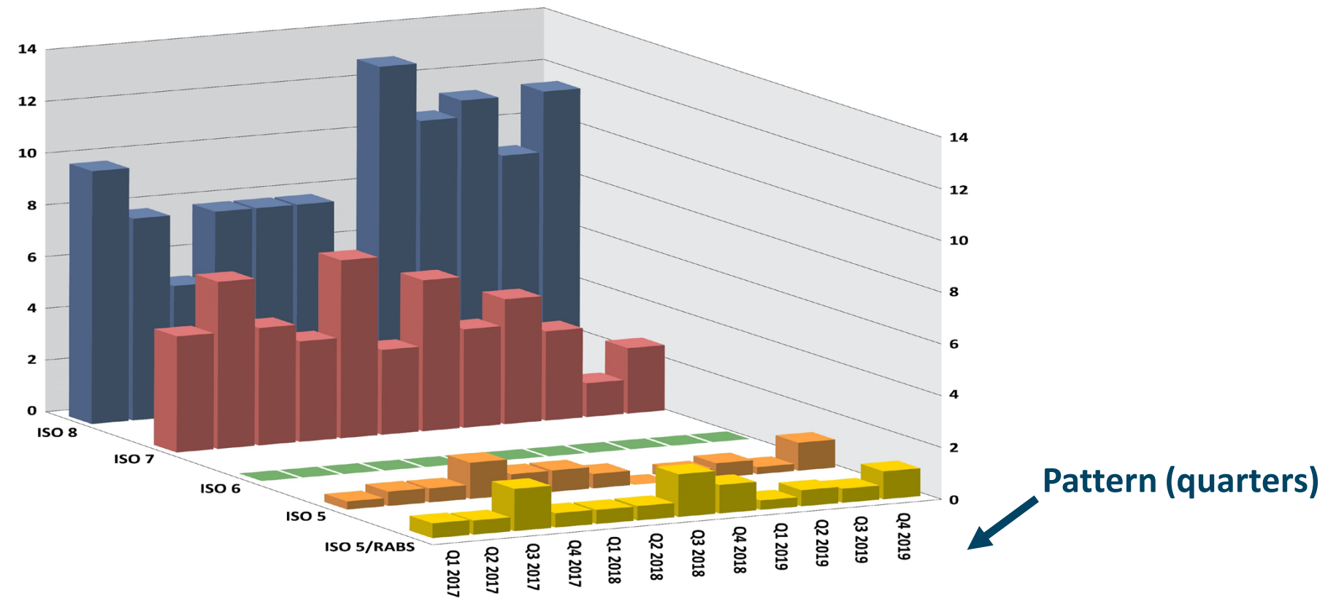
Annually:
- A Weibull Distribution or Percentile or Quantile graph to review and recalculate alert levels and action limits.



Weibull Graph displays the alert level and action limit calculation based on historical data.

Visual Trends & Pattern Recognition

Considering recovery rates, USP 1116, different chart types can be applied to review the data.



A quarterly 3D bar chart, data is compared across quarters and across the ISO classifications for four years in one chart.

Quarterly Recovery Rate Report

2017	Q1 (%)				Q2 (%)				Q3 (%)				Q4 (%)				Annual Rate
Classification	JAN	FEB	MAR	Total	APR	MAY	JUN	Total	JUL	AUG	SEP	Total	OCT	NOV	DEC	Total	
ISO 5/RABS	0.00	0.00	1.61	0.70	0.00	1.61	0.00	0.55	3.23	1.61	0.00	1.63	0.00	1.67	0.00	0.54	0.87
ISO 5	0.00	0.89	0.00	0.35	0.83	0.81	0.00	0.55	0.81	0.81	0.00	0.54	0.00	2.50	1.67	1.37	0.72
ISO 7	5.56	6.25	1.85	4.17	8.33	7.02	3.92	6.41	5.88	3.51	4.17	4.49	1.85	5.56	4.17	3.85	4.76
ISO 8	0.00	16.67	6.67	10.00	8.33	6.67	8.33	7.69	0.00	6.67	8.33	5.13	8.33	6.67	8.33	7.69	7.48

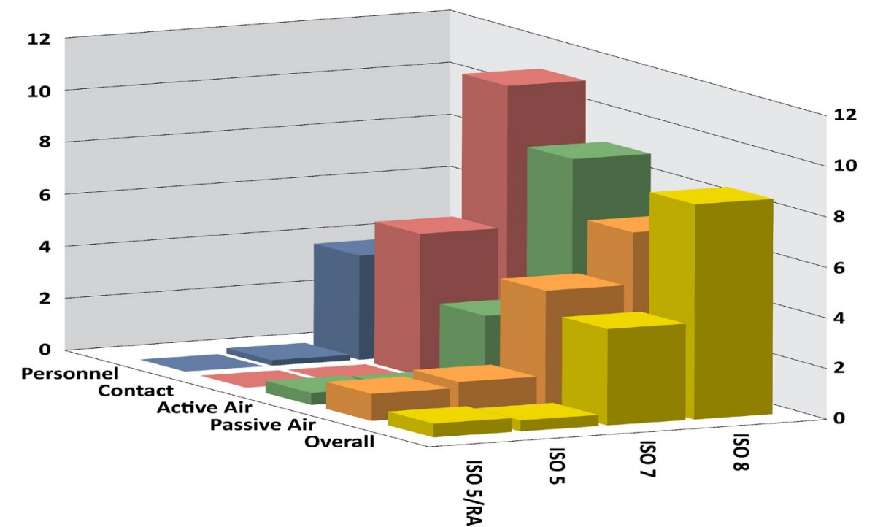
2018	Q1 (%)				Q2 (%)				Q3 (%)				Q4 (%)				Annual Rate
Classification	JAN	FEB	MAR	Total	APR	MAY	JUN	Total	JUL	AUG	SEP	Total	OCT	NOV	DEC	Total	
ISO 5/RABS	1.61	0.00	0.00	0.56	1.67	0.00	0.00	0.55	1.61	0.00	3.33	1.63	0.00	1.67	1.61	1.09	0.96
ISO 5	1.61	0.00	0.81	0.83	0.83	0.81	0.83	0.82	0.81	0.00	0.83	0.54	0.00	0.00	0.00	0.00	0.55
ISO 7	10.53	0.00	9.80	7.05	3.92	1.75	4.17	3.21	5.56	5.56	2.08	4.49	5.26	3.92	2.08	3.85	4.65
ISO 8	6.67	0.00	16.67	7.69	16.67	0.00	8.33	7.69	8.33	0.00	0.00	2.56	13.33	16.67	8.33	12.82	7.69

2019	Q1 (%)				Q2 (%)				Q3 (%)				Q4 (%)				Annual Rate
Classification	JAN	FEB	MAR	Total	APR	MAY	JUN	Total	JUL	AUG	SEP	Total	OCT	NOV	DEC	Total	
ISO 5/RABS	1.08	0.00	0.00	0.37	0.00	0.00	1.67	0.80	0.00	1.61	0.00	0.54	1.61	0.00	1.61	1.09	0.66
ISO 5	0.54	0.40	0.18	0.37	0.83	0.00	0.83	0.55	0.81	0.00	0.00	0.27	1.61	0.00	1.61	1.09	0.48
ISO 7	7.02	3.13	4.17	4.90	NR	8.33	2.08	3.33	0.00	1.96	1.96	1.26	1.75	2.08	3.70	2.52	3.84
ISO 8	14.00	10.00	7.50	10.77	8.33	16.67	8.33	11.54	11.11	7.41	8.33	8.97	12.90	8.33	12.50	11.39	10.68

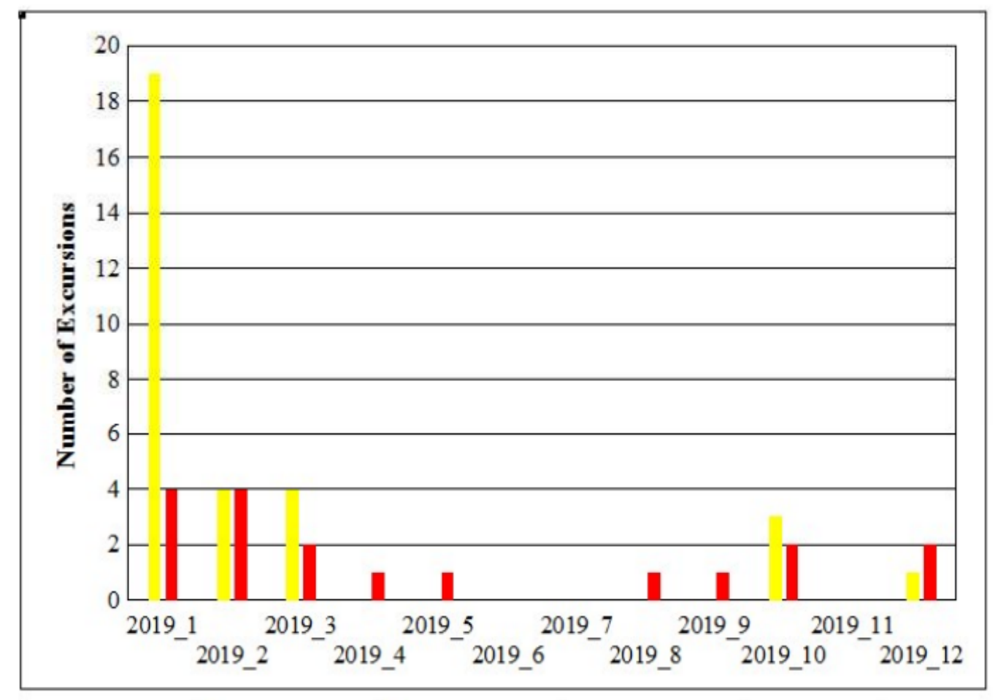
Well formatted and data rich tabular reports can be used to check seasonal changes in recovery rates. This chart displays monthly, quarterly, and annual rates across three years making season patterns very easy for a reviewer to detect.

Investigation & Root Cause Analysis

Snapshot of the recovery rates for all classifications and all sample types. Displays on overall summary of viable samples in any area of the facility.



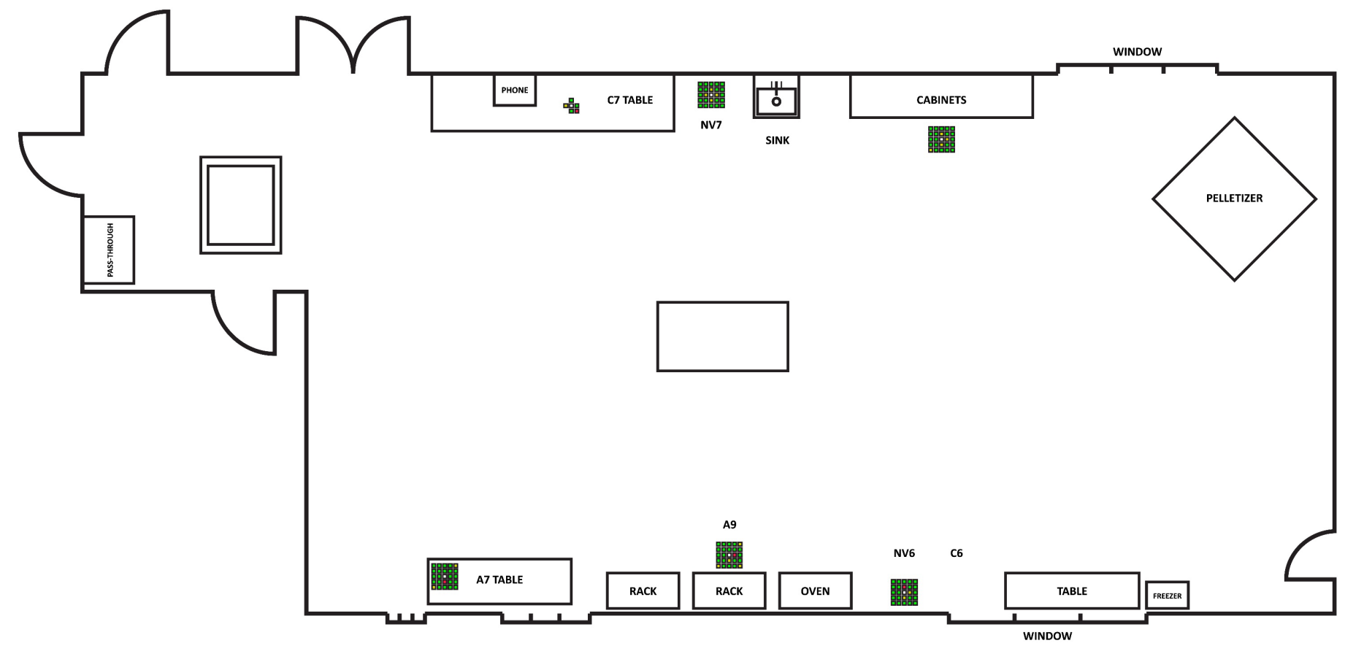
Grade	Active Air (%)	Passive Air (%)	Contact (%)	Personnel (%)	Overall (%)
ISO 5/RABS	0.49	1.10	NR	NR	0.56
ISO 5	0.44	1.34	0.00	0.22	0.45
ISO 7	3.14	4.81	5.77	4.23	3.92
ISO 8	9.27	6.94	11.54	NR	8.75



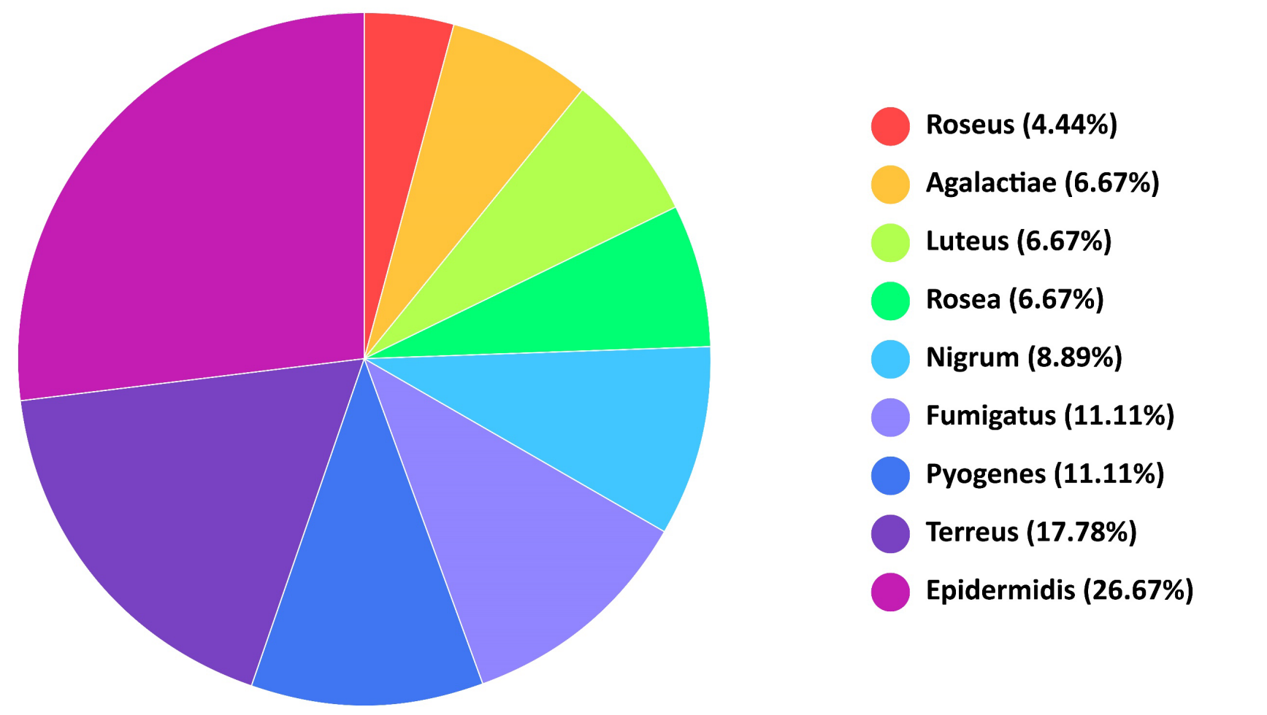
Date test done	🟨 Alerts	🟥 Actions	Total Samples No.	Alert %	Action %
Jan 2019	19	4	1,516	1.25	0.26
Feb 2019	4	4	1,216	0.33	0.33

Excursion reports to investigate into the number of Alert level and Action limit excursion. Count is not enough; the excursion rate should be considered. Display shows both count and rate monthly over a one-year period.

Intra Results Patterns & Automated Notifications



Heat map showing positive, alert, action recoveries. Maps can potentially indicate where the initial contamination was found and assist in investigation and root cause analysis.



Pie chart showing a percentage distribution of the top microorganisms found. Charts like this are used to investigate changes in the flora found across different months, quarters, or years as possible root cause.

Process Manual vs Automation & Continuous Improvement

MANUAL PROCESSES
- Manual auditing is difficult and subject to human error
    - "Spot auditing" is often done
    - Errors and omissions are difficult to detect
- Manual systems are difficult to validate and maintain
- Data storage requires a lot of space
- Subject to damage or loss, cannot be easily be replicated or replaced
- Trending is performed at a delay
- Trending and analysis is often not complete
- Root Cause analysis is more time consuming

COMPUTERIZED / DIGITALIZED SYSTEMS AND PROCESSES
- Large volume of data is easily managed and is accessible
- Less / No vulnerability to human error
- System can be validated, along with calculations and statistical formulas, data point counts
- Data analysis and trending can be performed with efficiency and accuracy
    - Large amounts of data can be accessed and processed in seconds
    - Data can be easily manipulated to analyze different aspects
    - Analysis can be performed in real time
- Audit trails document each and every change or correction
- Errors and omissions are automatically detected
- Data storage requires very little space
- Data can be replicated and recovered
- Cost effective

You can fix processes. **You can fix systems.** **You can fix procedures.**

CAN YOU FIX PEOPLE'S HABITS WITHOUT AUTOMATION?
CAN YOU ACHIEVE PROCESS INTEGRITY WITHOUT AUTOMATION?

Learn About Digital Contamination Control Strategy Solutions

Learn About Automation in Environmental Monitoring

Understand the Process to Electronically Manage the Cleaning Validation Process

Learn About Automation in Utility Monitoring

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