NOVATEK INTERNATIONAL

Today's Presenter:

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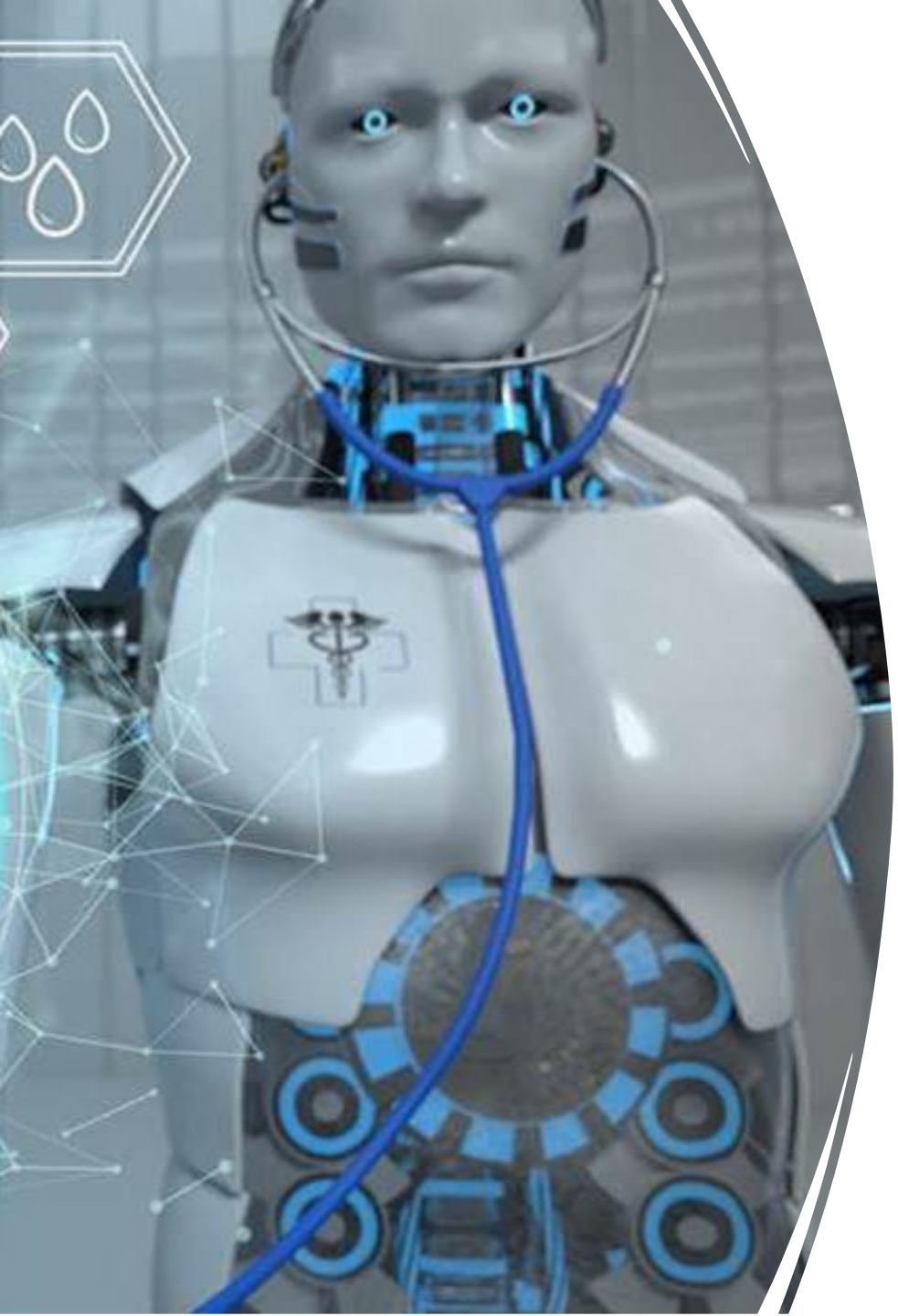
Over 20 years experience defining requirements for Pharmaceutical and Biotech



Agenda - Roadmap to a Digitalized CCS

- A Word on Annex 1 & CCS
- Let’s talk about Digitalization!
- Is our Industry Digitalized?
- Hybrid states versus Digitalized States
- Steps to Digital Transformations
- Elements of Contamination Control and Digitalization
- Continuous Monitoring
- Pulling it All Together: Digital Transformation

REGULATIONS

EU Annex 1 Examples

2.3 A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the CCS should establish robust assurance of contamination prevention.

2.5 Elements to be considered within a CCS (Contamination Control Strategy) should include (but are not limited to):

xv. Prevention mechanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA) and the need for comprehensive investigational tools.

xvi. Continuous improvement based on information derived from the above

Annex 1 Revision & Digital Solutions

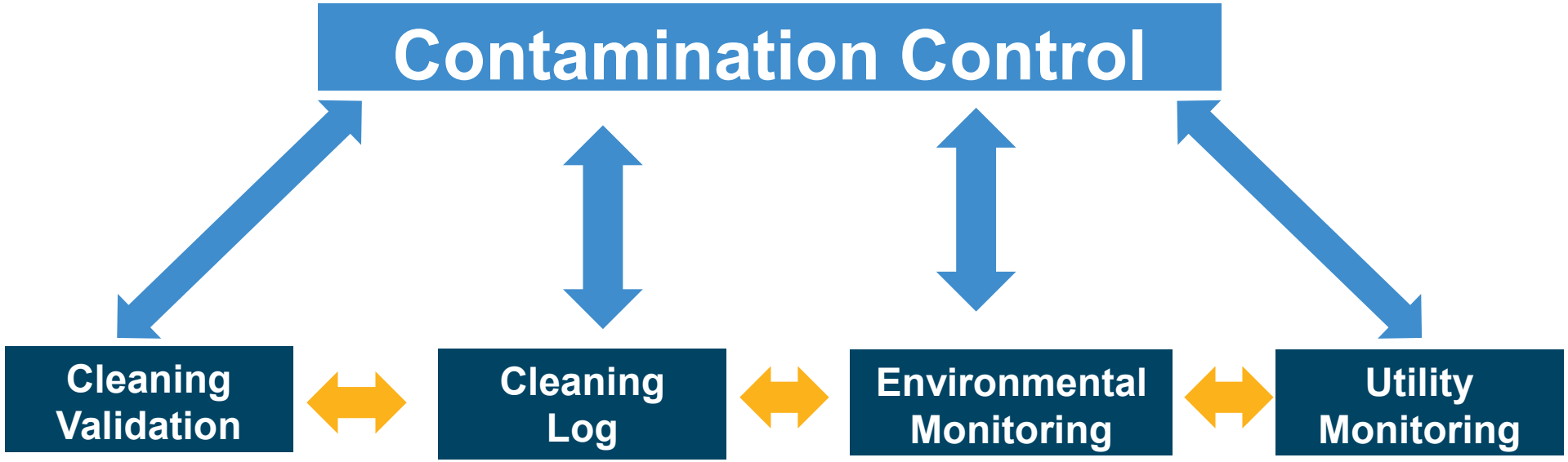
- Focus on risk-based approaches to contamination control
- Holistic approach to CCS
- Focus on Data Integrity
- Guidance on the use of Advanced Technologies, including automated monitoring and control systems

Total Contamination Control Strategy (CCS)

Not an isolated process!

Regulations EU Annex 1:

2.4 Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources includes a series of interrelated events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered together.



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Digitized vs Digitalized Data

- Digitization:
    - conversion of paper-based records to digital records

- Digitalization:
    - digitalization uses advanced analytics to analyze large volumes of contamination control relevant data, the adoption of blockchain technology for secure data sharing and tracking, and the use of artificial intelligence (AI) and robotics to improve manufacturing and supply chain operations

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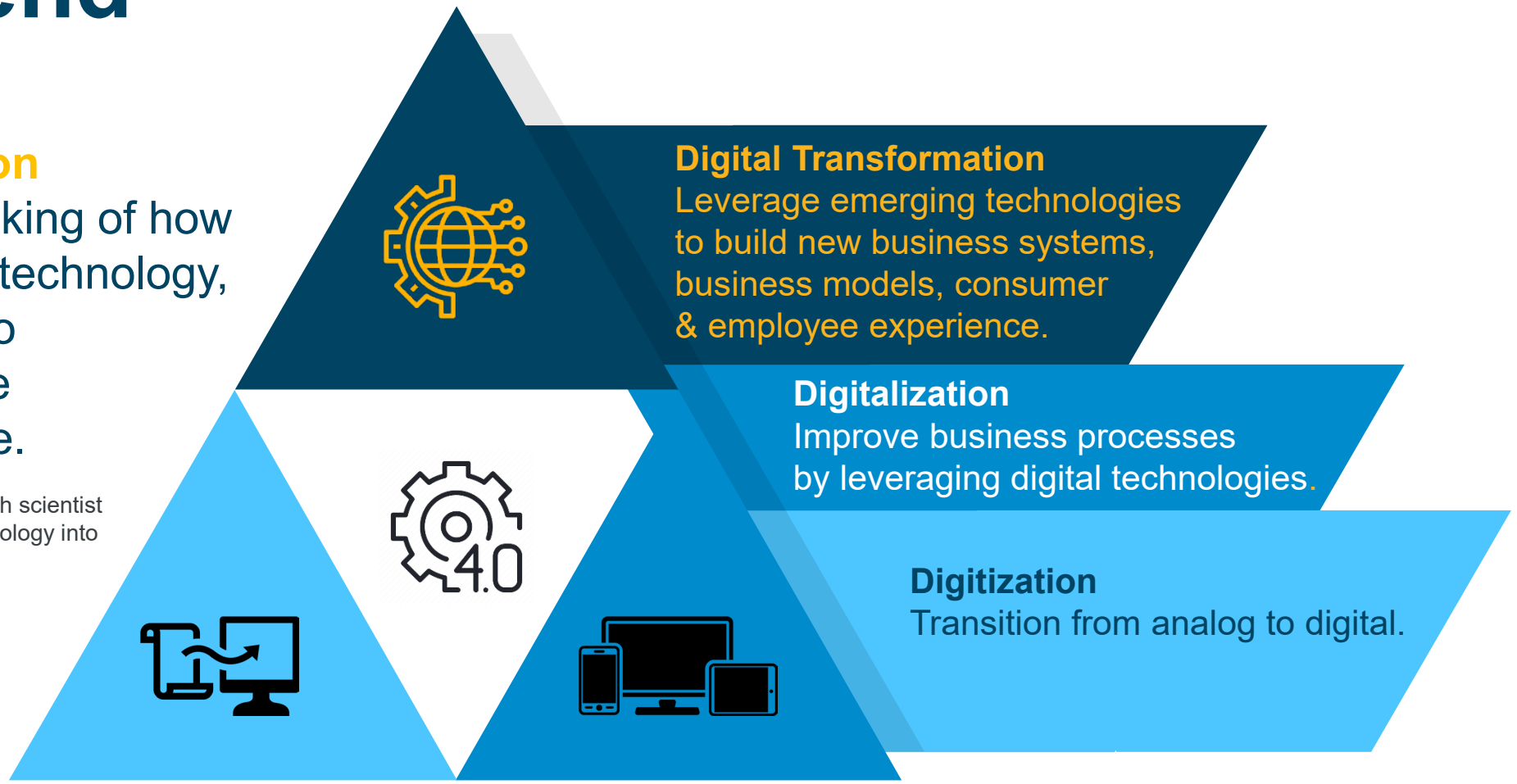
Market Trend

Digital transformation
marks a radical rethinking of how an organization uses technology, people & processes to fundamentally change business performance.

George Westerman, MIT Principal research scientist and author of leading digital: Turning technology into business transformation



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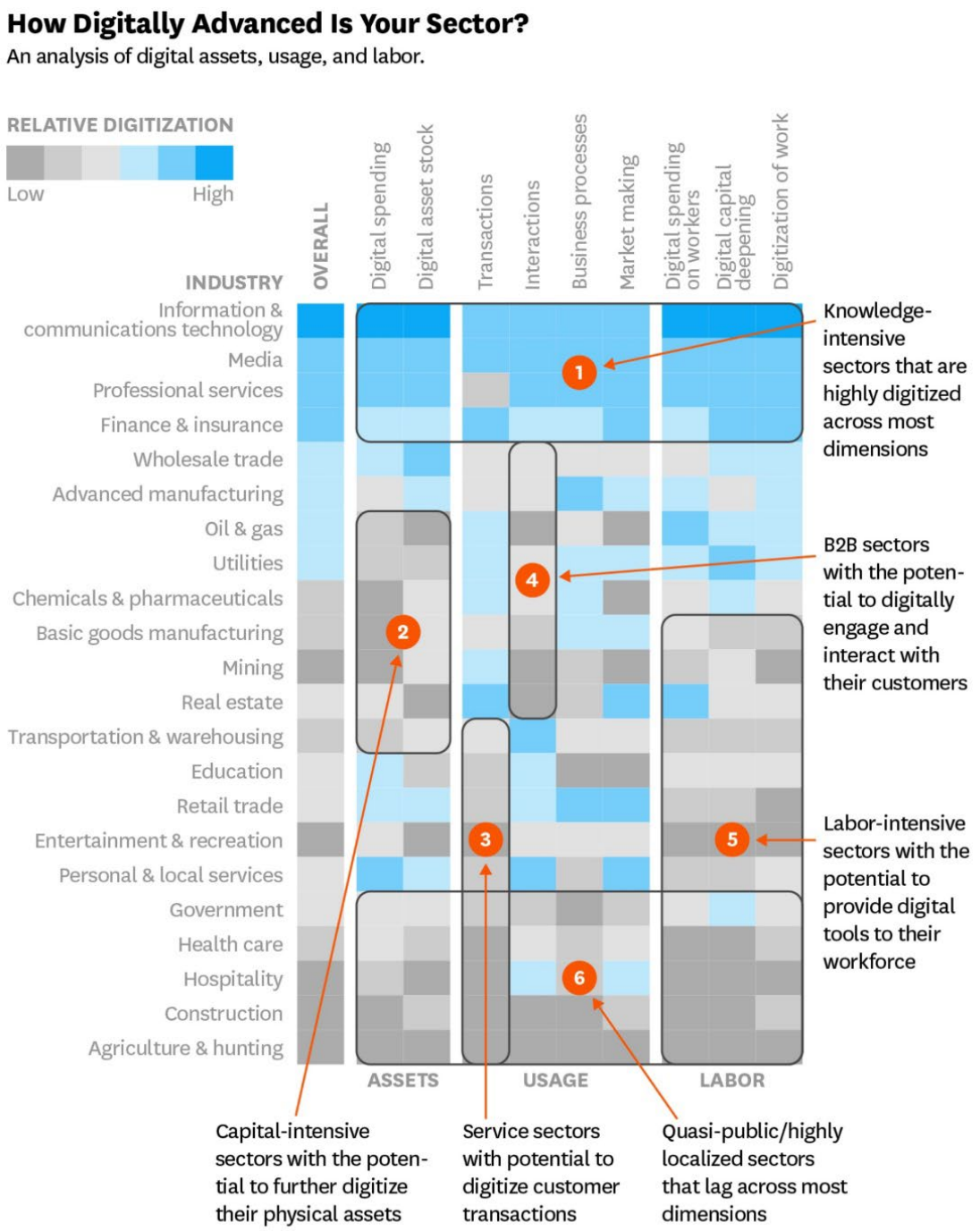
Is our Industry Digitalized?

Some of the most common organizational barriers to digital transformation are:

- unclear vision and objective of digital transformation.
- lack of management understanding, knowledge and experience.
- lack of leadership skills.
- lack of organizational agility, rewards and incentives that are not aligned to digital transformation.
- unclear measurement and rewarding system.
- lack of employee' involvement and engagement
- employee' resistance to change.



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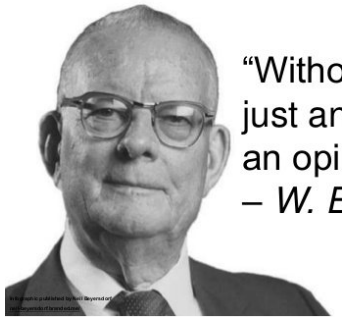
Your Data is more than just a Number

It has the power to drive compliancy and improve your business



"Without data you're just another person with an opinion."
– *W. Edwards Deming*

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Digital Transformation in Contamination Control

Differences between digitized and digitalized:

- Centralized access to all contamination control data
- Correlation between elements of contamination control for risk-based approach
- Efficiency of data management and operations
- Improves compliance considerations
- Real time monitoring and immediate detection of contamination events
- Rapid, powerful and flexible data analysis
- Preventive measures with adverse trend recognition
- Pattern recognition to assist in root cause analysis
- Faster product release with reduced risk

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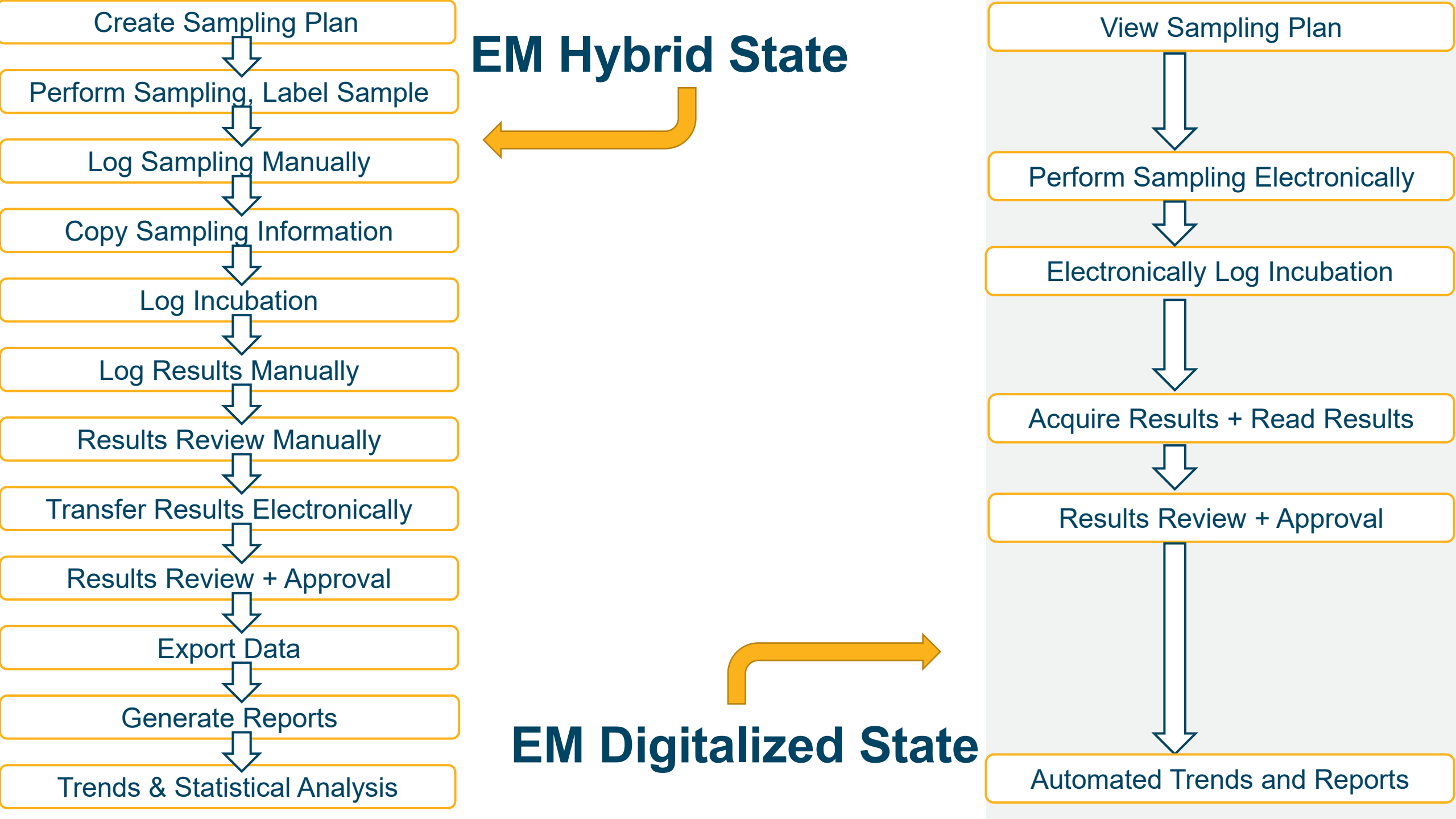
HYBRID vs DIGITALIZED

- Manual auditing is difficult and subject to human error
  - “Spot auditing” is often done
  - Errors and omissions are difficult to detect
- Hybrid systems are difficult to validate and maintain
- Data storage requires a lot of space
- Data linking is labor intensive
- Data is 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
- Additional time for manual and electronic verification
- Redundancy in Data Storage
- Multiple access points for data

- Large volume of data is easily managed and is accessible
  - Utilizes far less employee hours
- Less vulnerable to human error
- System can be validated
  - 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 and accession
  - 100% audited
  - Errors and omissions are easier to detect
- Data storage requires very little space
- Data can be replicated and recovered
- Cost effective


Create Sampling Plan
Perform Sampling, Label Sample
Log Sampling Manually
Copy Sampling Information
Log Incubation
Log Results Manually
Results Review Manually
Transfer Results Electronically
Results Review + Approval
Export Data
Generate Reports
Trends & Statistical Analysis
EM Hybrid State
EM Digitalized State
View Sampling Plan
Perform Sampling Electronically
Electronically Log Incubation
Acquire Results + Read Results
Results Review + Approval
Automated Trends and Reports

DIGITALIZED

- All the benefits of computerized systems
- Centralized data access
- Correlated elements of quality control
- Intelligent, purposeful trending & data analysis
- Built in pattern recognition & predictive trending

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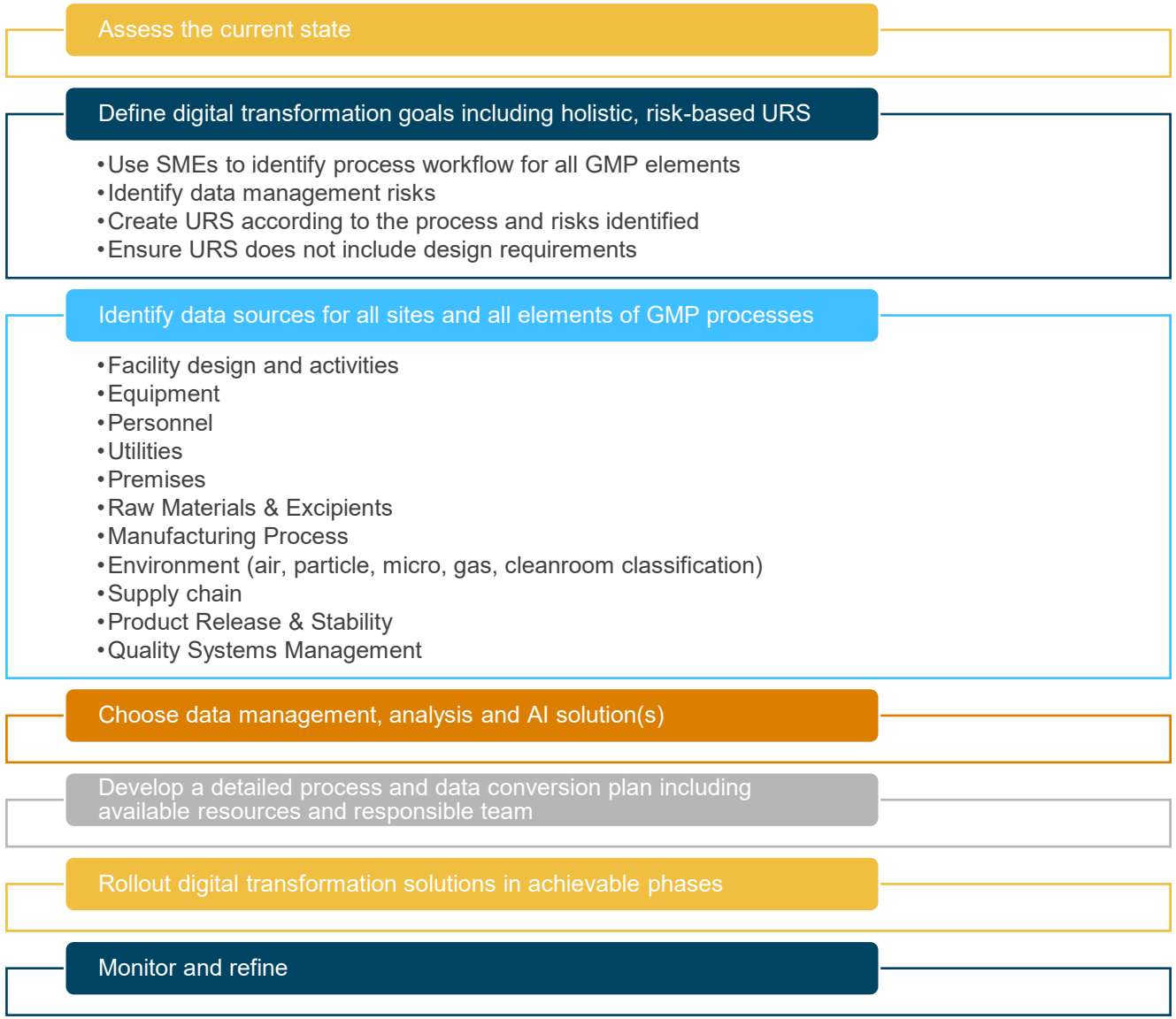
Steps to a True Digital Transformation



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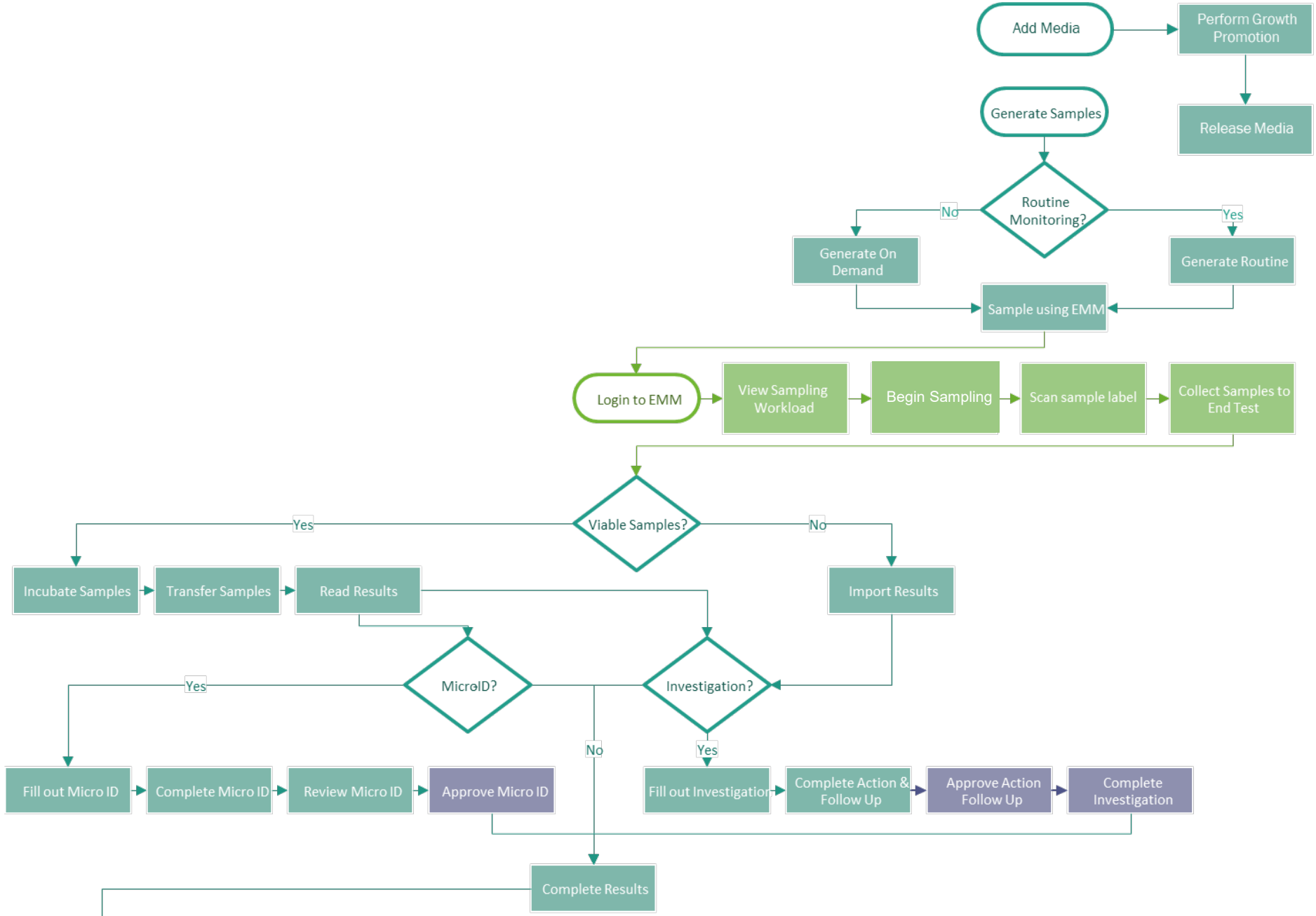

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Environmental Monitoring Mapping Example

Create both *current and future workflows* for all contamination control relevant processes. For each workflow step that includes data management, identify the data source, responsible group, and other relevant parameters such as correlation parameters and time spent managing the data.

For example:

Current State: EM sampling:
Responsible Department: *QC Micro* Data Source: *Paper Form in QMS*
Responsible Group: *Micro supervisors* Time Spent: *1 min/sample site*

Future State: EM sampling :
Responsible Department: *QC Micro* Data Source: *Automated CC solution software*
Responsible Group: *Micro supervisors* Time Spent: *0.5 min/sample site*
Data Correlation: LIMS release data and QMS investigation
Data Integrity Considerations: ALCOA++

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Elements of Contamination Control and Digitalization

- Environmental Monitoring
- Utility Monitoring
- Cleaning Validation
- Sampling in Real-Time
- Raw Material Bioburden
- Integration with equipment
- Continuous Monitoring

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Trending and Data Analysis

- A well-designed, trending program is **powerful.**
- CC data must be analyzed; not simply reported:
  - What information does the data provide?
  - What conclusions can be drawn?
  - Are new risks identified?
  - Does any action need to be taken?
- Critical and detailed data analysis can greatly facilitate:
  - Effectiveness of the CCS
  - Root cause analyses
  - Batch impact assessments
  - Continuous improvement of CCS
  - Continuous improvement of the processes monitored

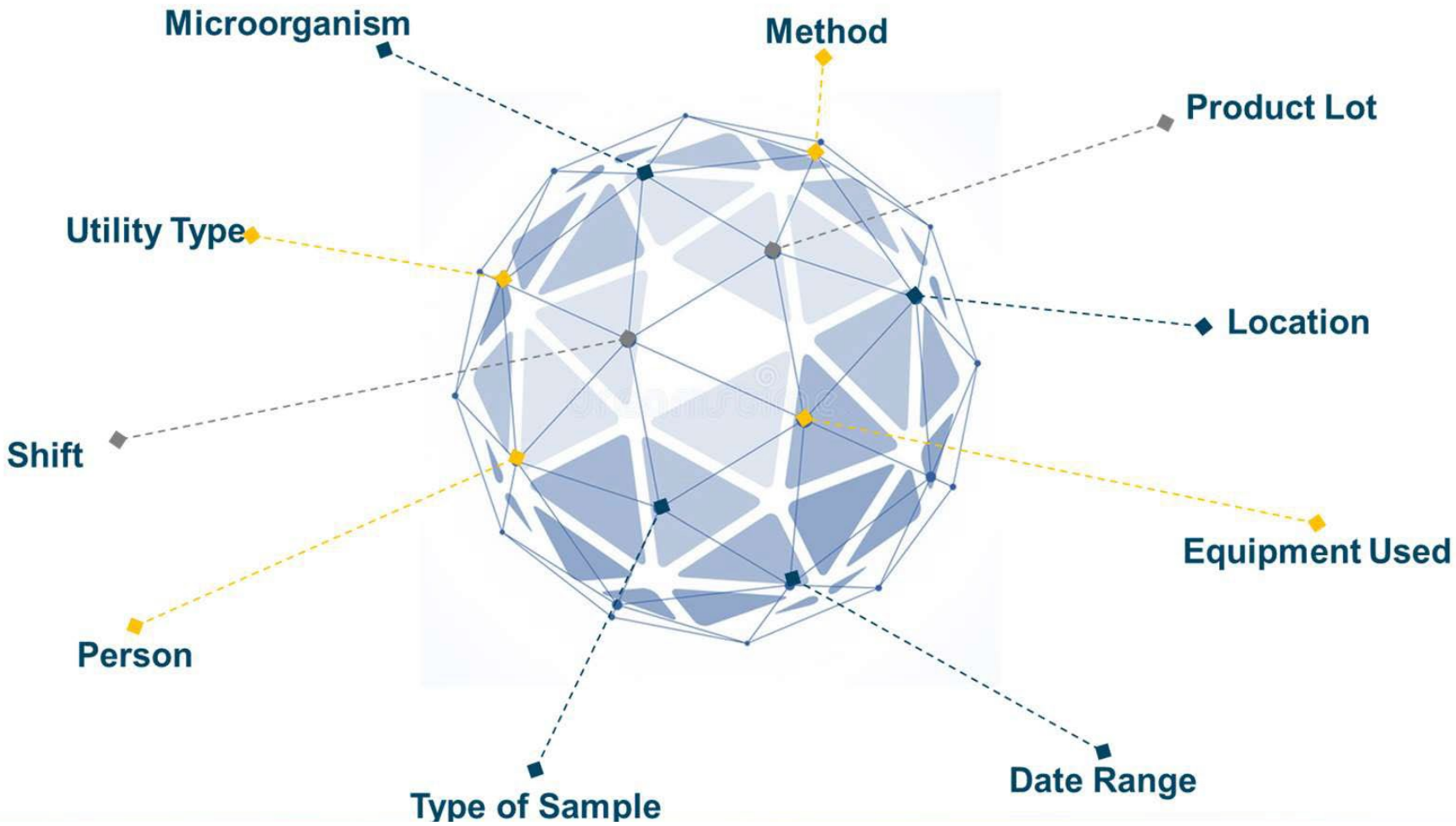
Analyzing
Reporting

Trending

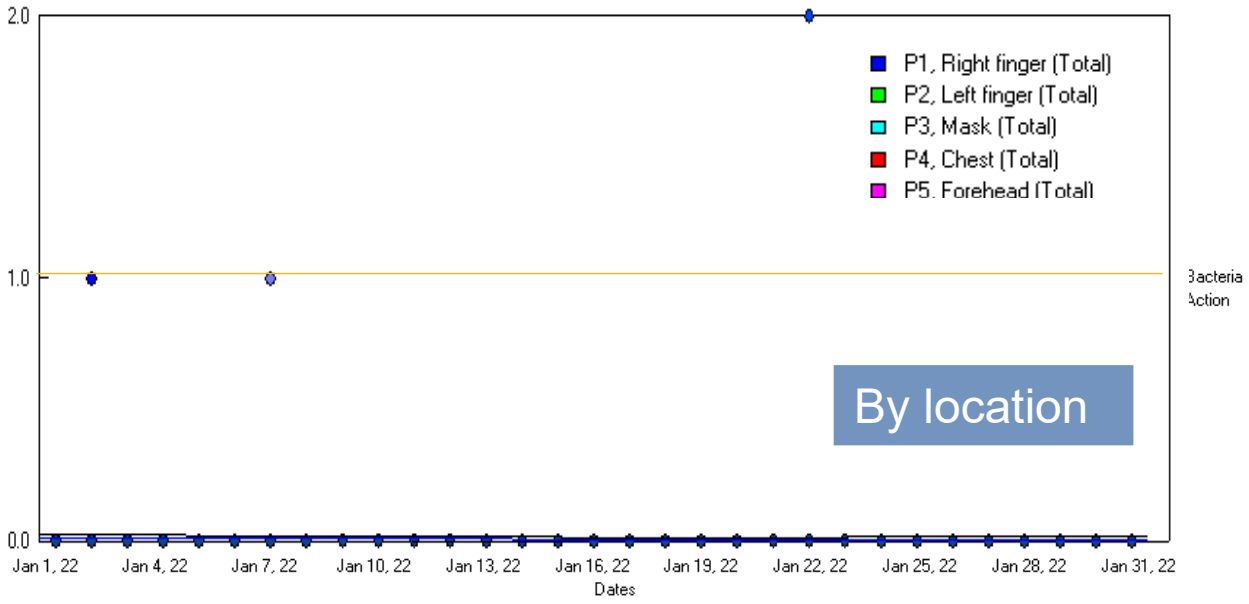
Pattern Recognition

Root Cause Analysis

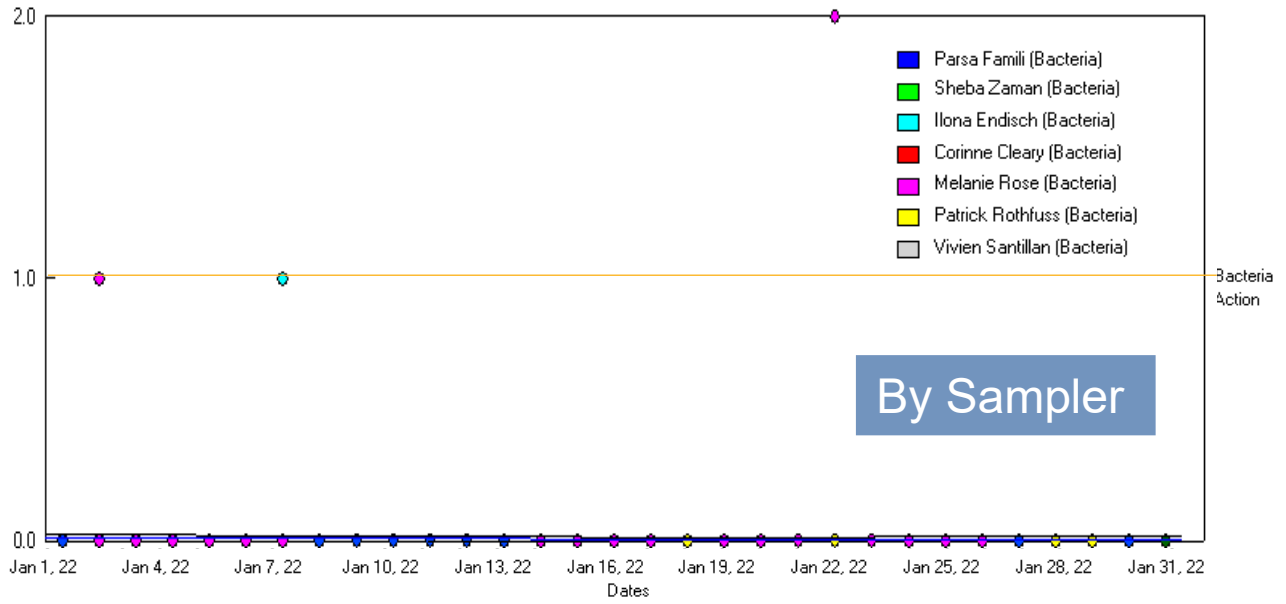
Contamination Control Multifaceted Trending



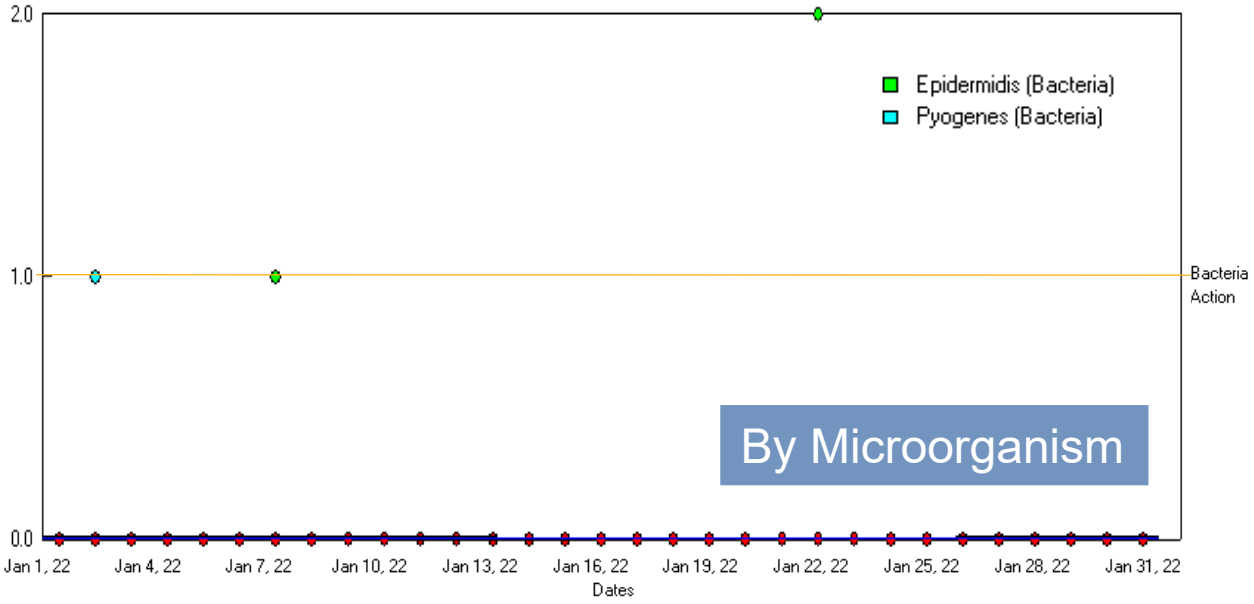
Trending And Pattern Recognition Examples



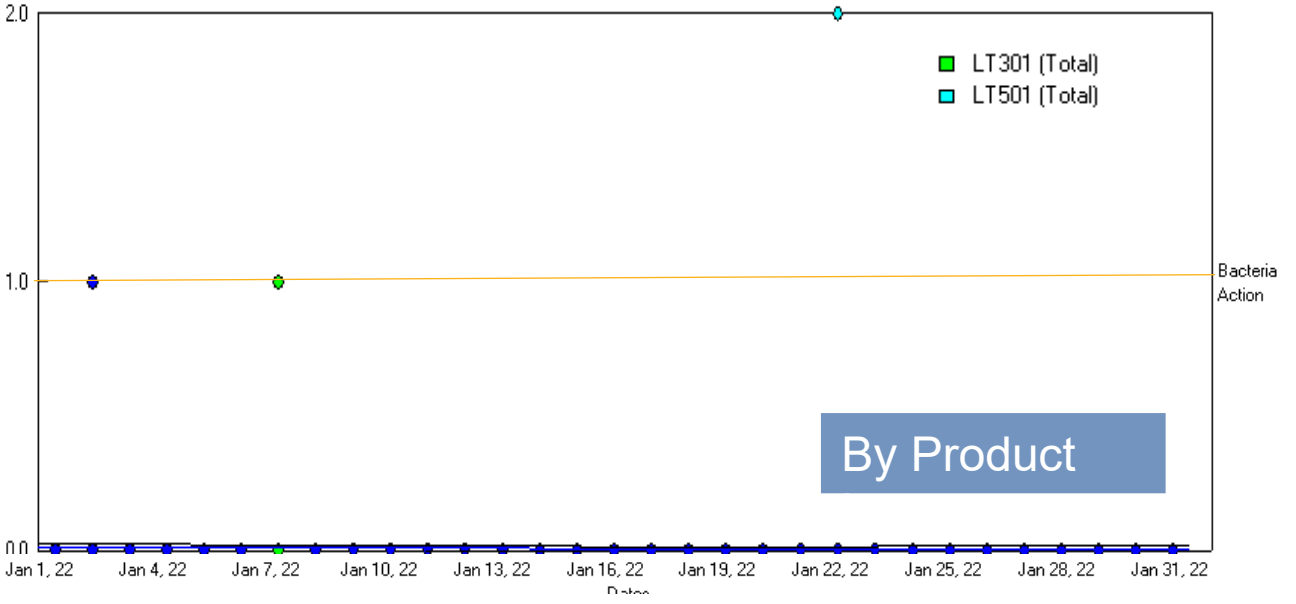
By location



By Sampler

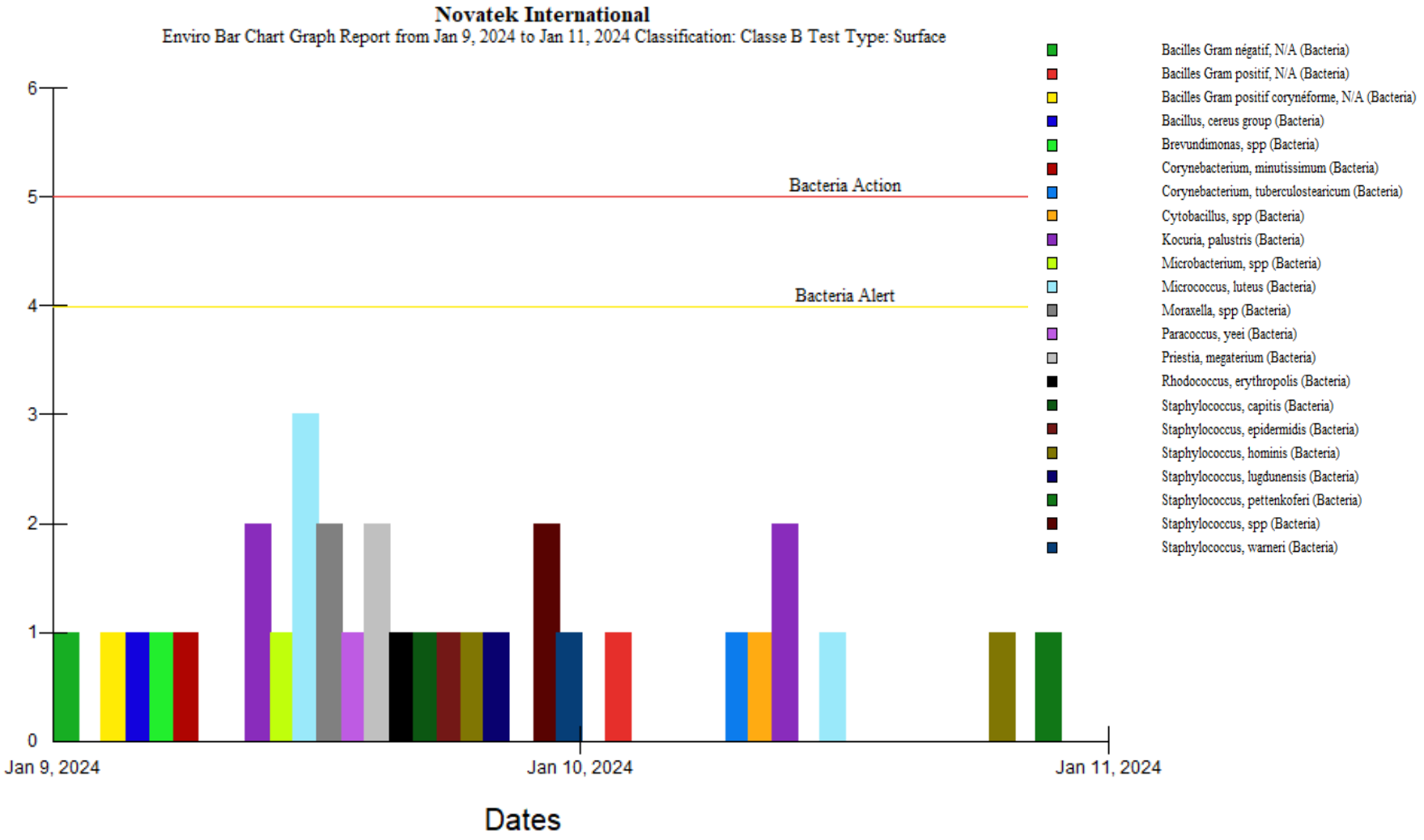


By Microorganism



By Product

Root Cause Analysis: Trend by Microorganisms



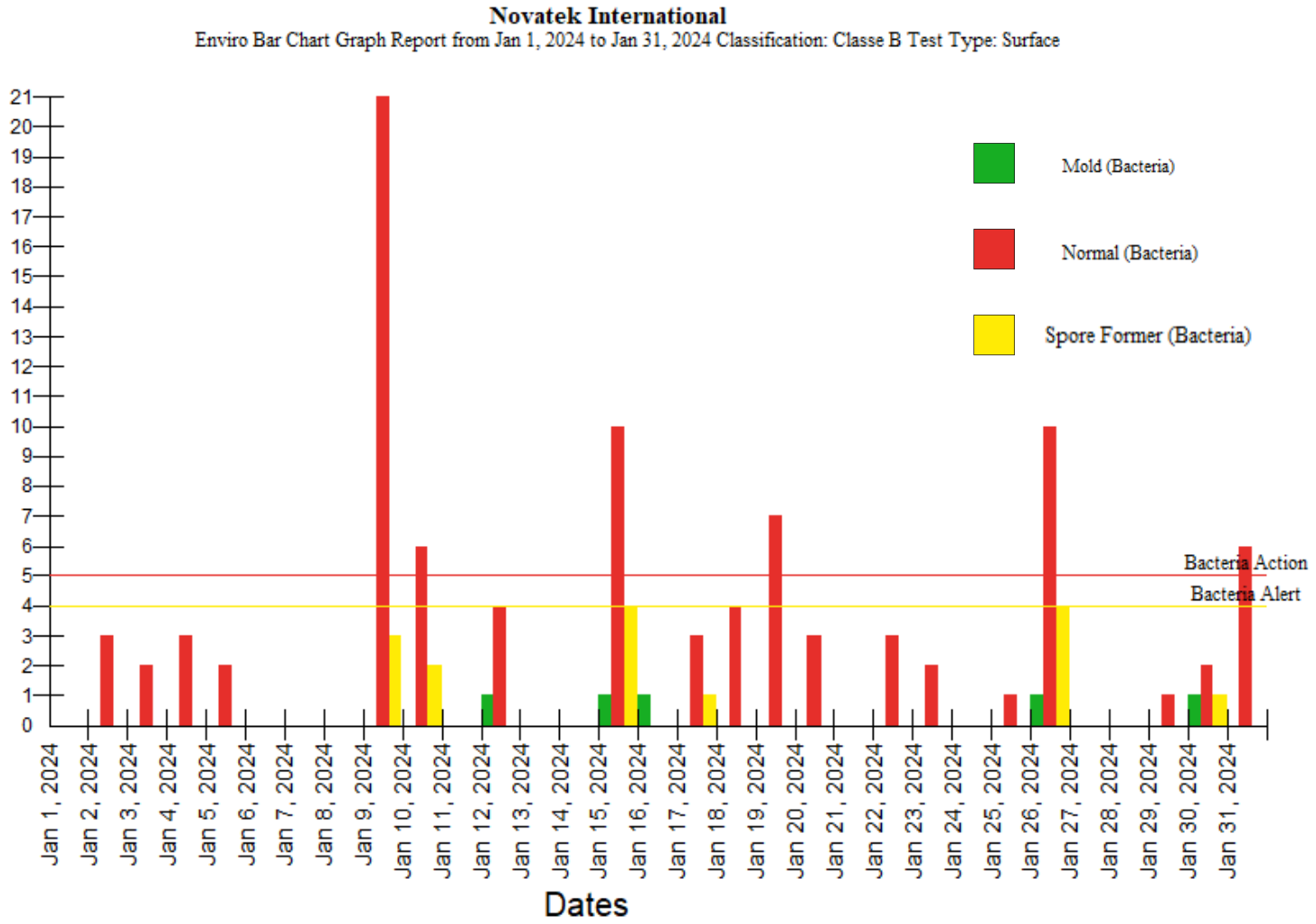
Regulation EU Annex 1:

9.11 Trends should include, but are not limited to:

iv. Changes in microbial flora type and numbers and predominance of specific organisms.

Example: various species found in Grade B surface test in the month of January.

Root Cause Analysis: Trend by Microorganisms



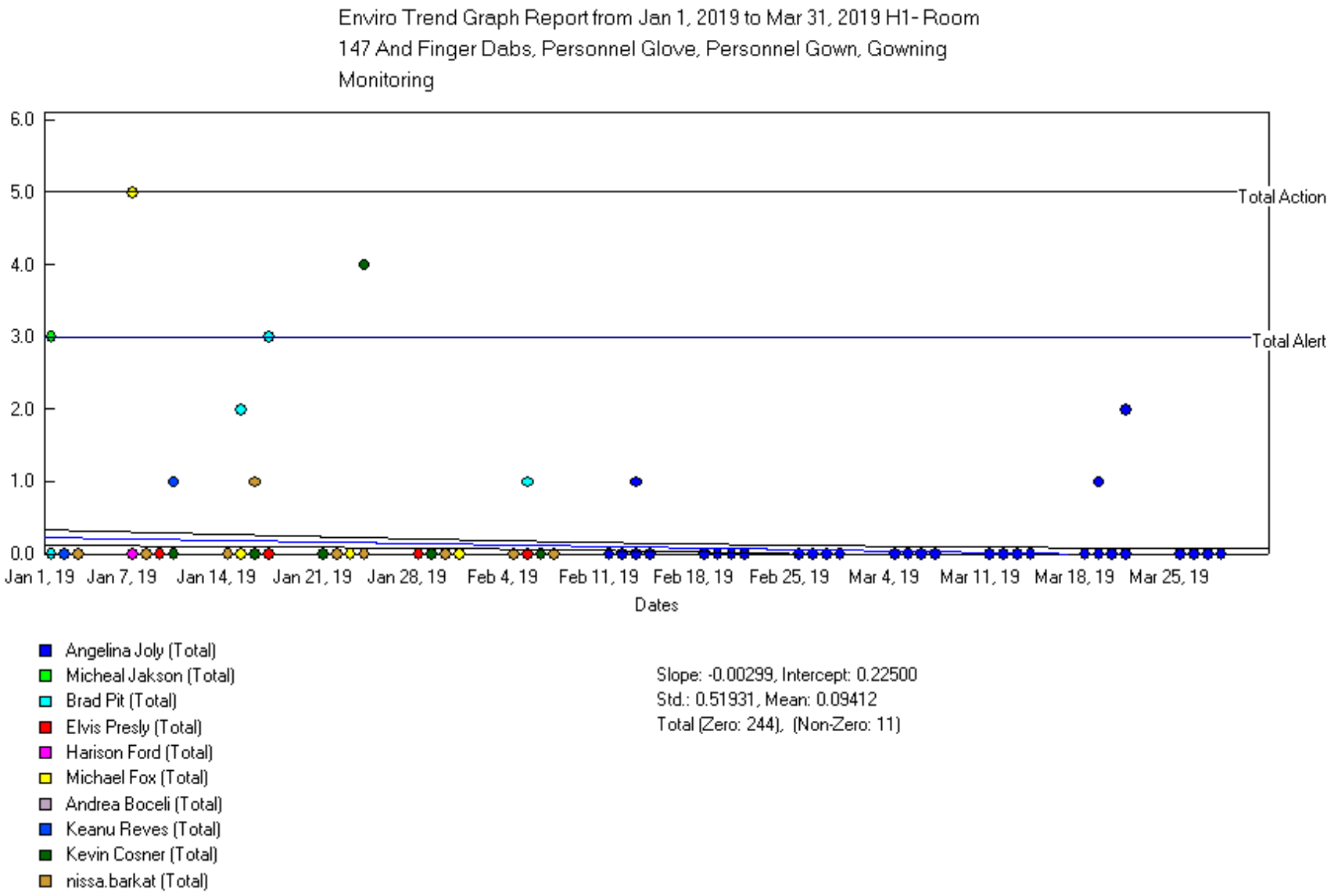
Regulation EU Annex 1:

9.11 Trends should include, but are not limited to:

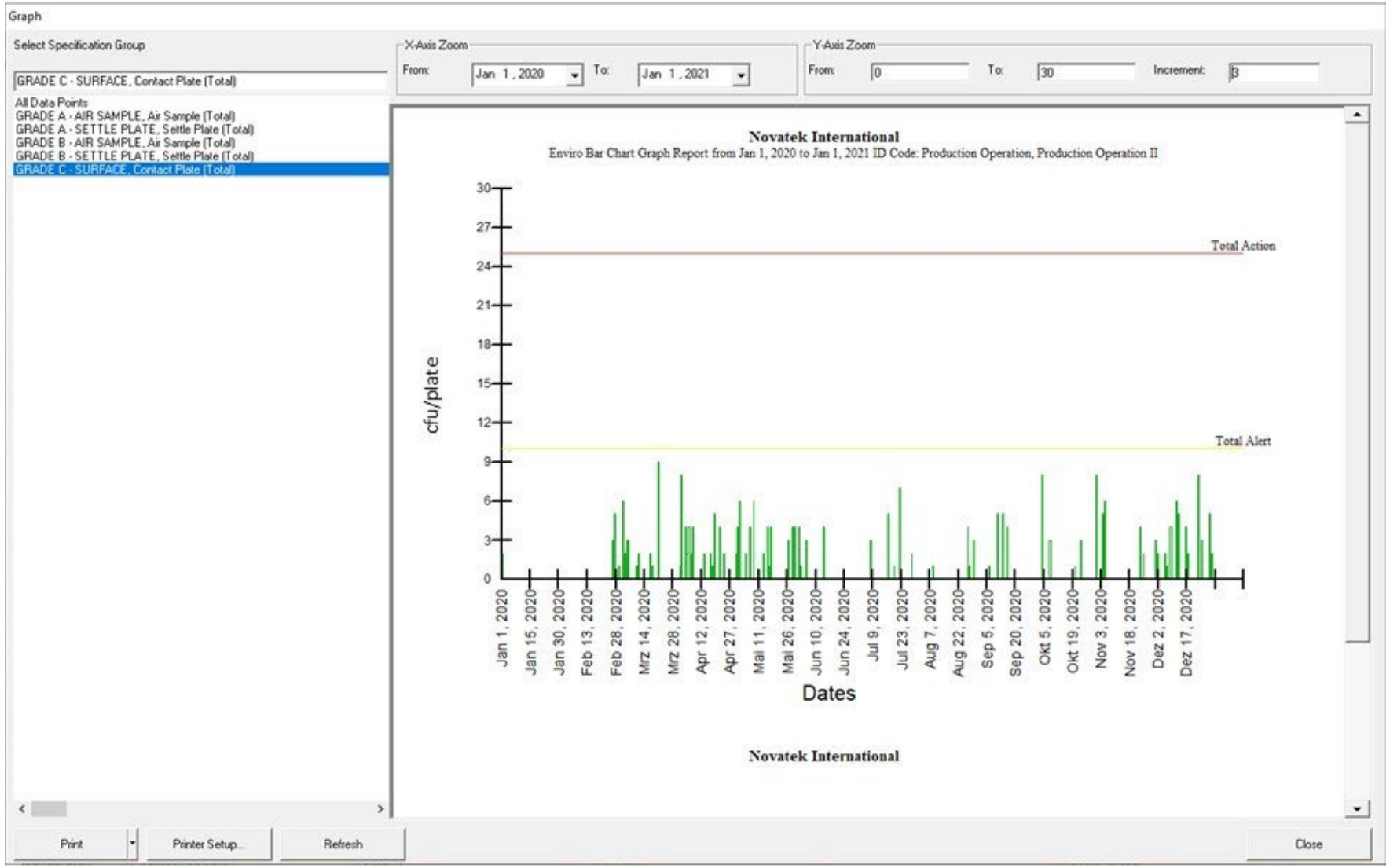
iv. Changes in microbial flora type and numbers and predominance of specific organisms.

Example: Microorganism categories in Grade B surface test in the month of January.

Personnel Monitoring and Pattern Recognition



Importance of Rapid Access to Your Trends



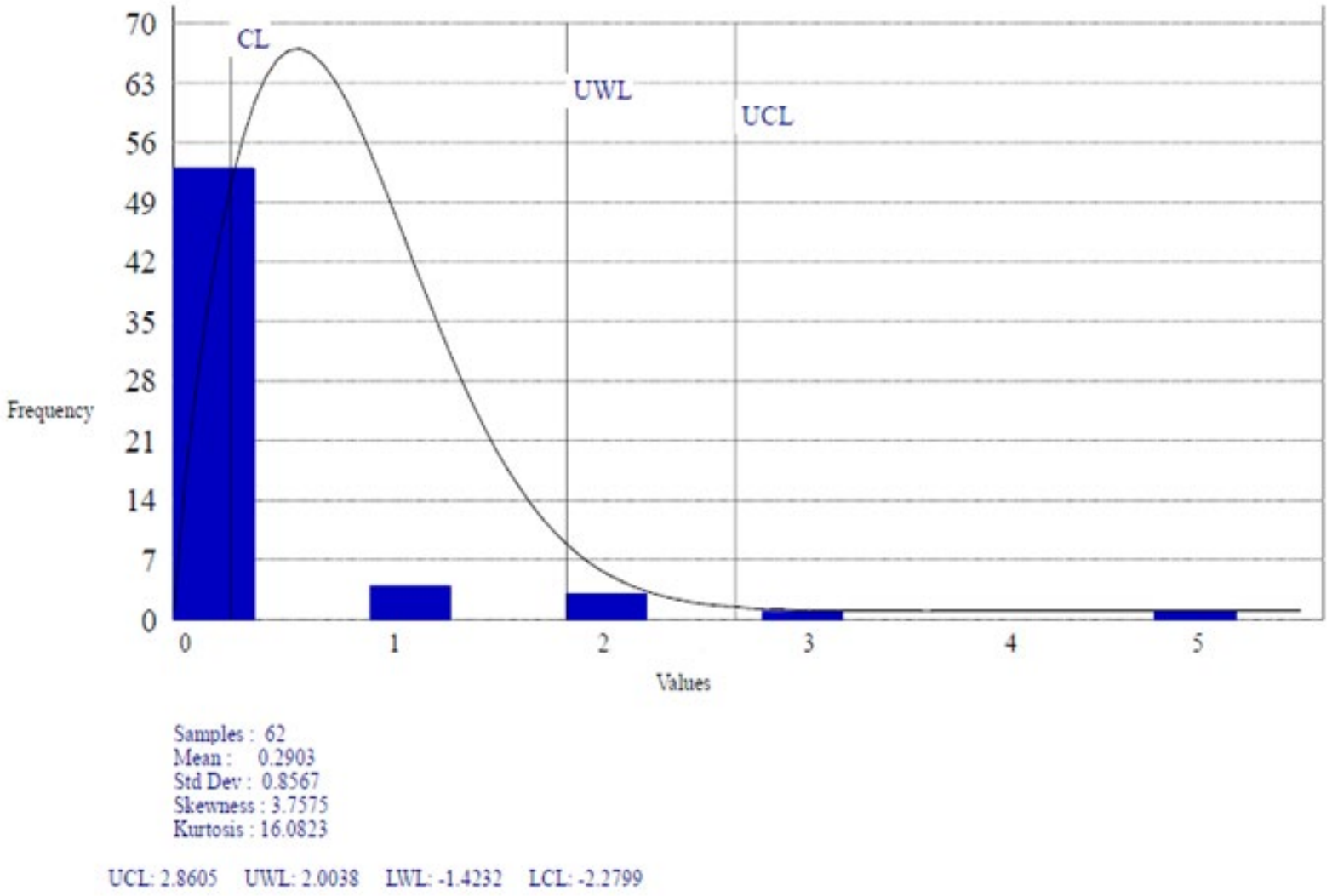
- Ability to group the dataset by category (i.e. classification, sample type, room, etc.)
- View all groups on the graph in separate colors,
- Or click through the list to review them separately
- Avoids having to re-filter for a dataset each time.

Example: Viable testing results across various Grades. Grade C Contact Plate results graph is selected

RISK:

Not setting Alert Levels and Action Limits based on company's historic data

Alert Level Recalculation



RISKS:

- Using outdated levels that don't represent your data can lead to **missed adverse trend** identification

MITIGATION:

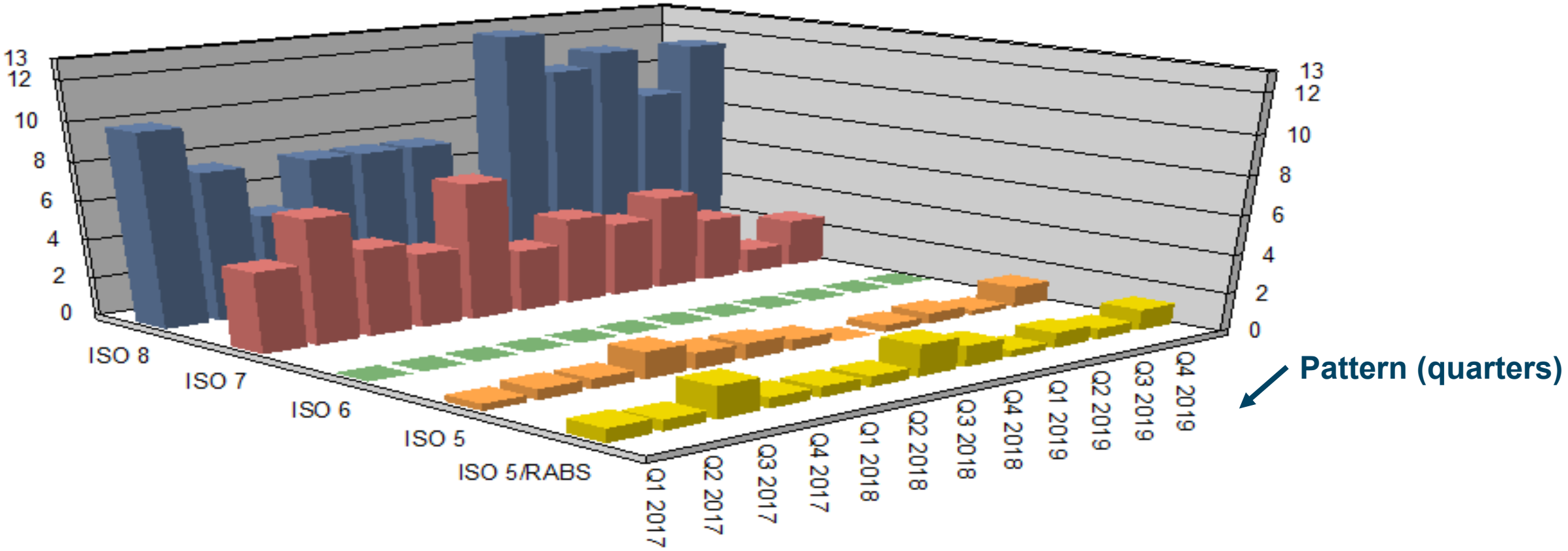
- ✓ **Normal, Weibull or Quantile Distribution chart can assist in setting alert/action levels**
- ✓ Use the chart that best represents your data and adjust your levels with the 95th and 99th percentile.

ROUTINE ENVIRONMENTAL MONITORING REPORTING

Why Recovery Rate Reports?

What information is provided by Recovery Rate Reports?

Recovery Rate Reporting



Recovery Rate Reporting

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

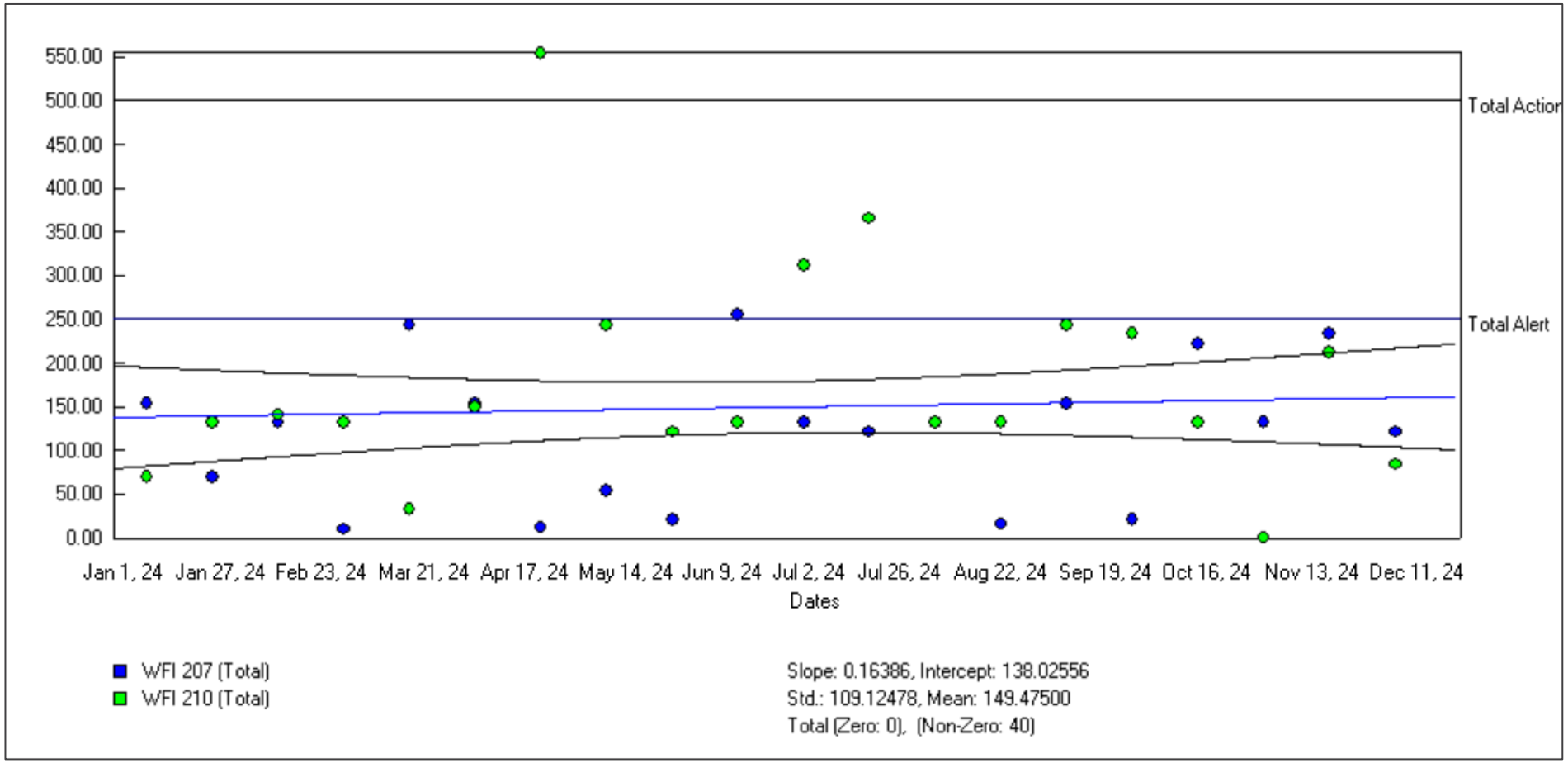
2018	Q1 (%)				Q2 (%)				Q3 (%)				Q4 (%)				Annual Rate
Classification	JAN	FEB	MAR	Total	APR	MAY	JUN	Total	JUL	AUG	SEP	Total	OCT	NOV	DEC	Total	
ISO 5/RABS	1.61	0.00	0.00	0.56	1.67	0.00	0.00	0.55	1.61	0.00	3.33	1.63	0.00	1.67	1.61	1.09	0.96
ISO 5	1.61	0.00	0.81	0.83	0.83	0.81	0.83	0.82	0.81	0.00	0.83	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

Elements of Contamination Control and Digitalization

- Environmental Monitoring
- **Utility Monitoring**
- Cleaning Validation
- Sampling in Real-Time
- Raw Material Bioburden
- Integration with equipment
- Continuous Monitoring

Utility Monitoring – TOC by WFI port



Regulation EU Annex 1:

6.4 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.

Novatek BENEFITS

- Manage utility monitoring: clean steam, compressed gas, water, etc.
- Define levels as ranges
- Be able to filter by loop, valve, utility type, and other criteria

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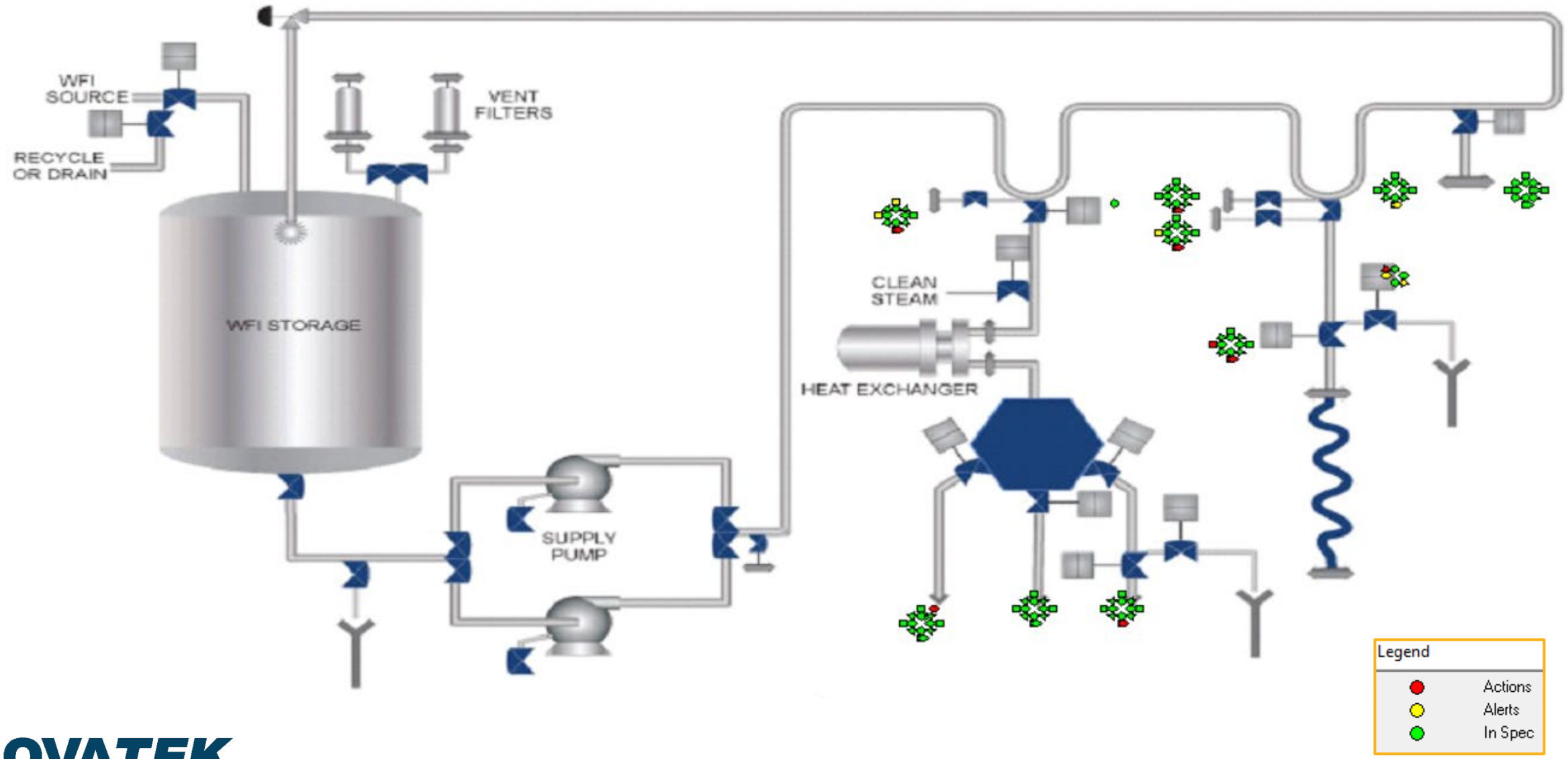
31

Utility Monitoring: Dispersion Mapping



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Elements of Contamination Control and Digitalization

- Environmental Monitoring
- Utility Monitoring
- **Cleaning Validation**
- Sampling in Real-Time
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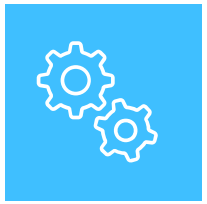
Benefits of a Computerized Cleaning Validation Software System

Master Data (equipment, product, API, Method, CA, validation train, etc.)

Automated Worst-Case determination



Automated MAC / MSC limit calculation

Real-Time Tracking of Cleaning Activities with the CL Mobile Tablet / Scanner system

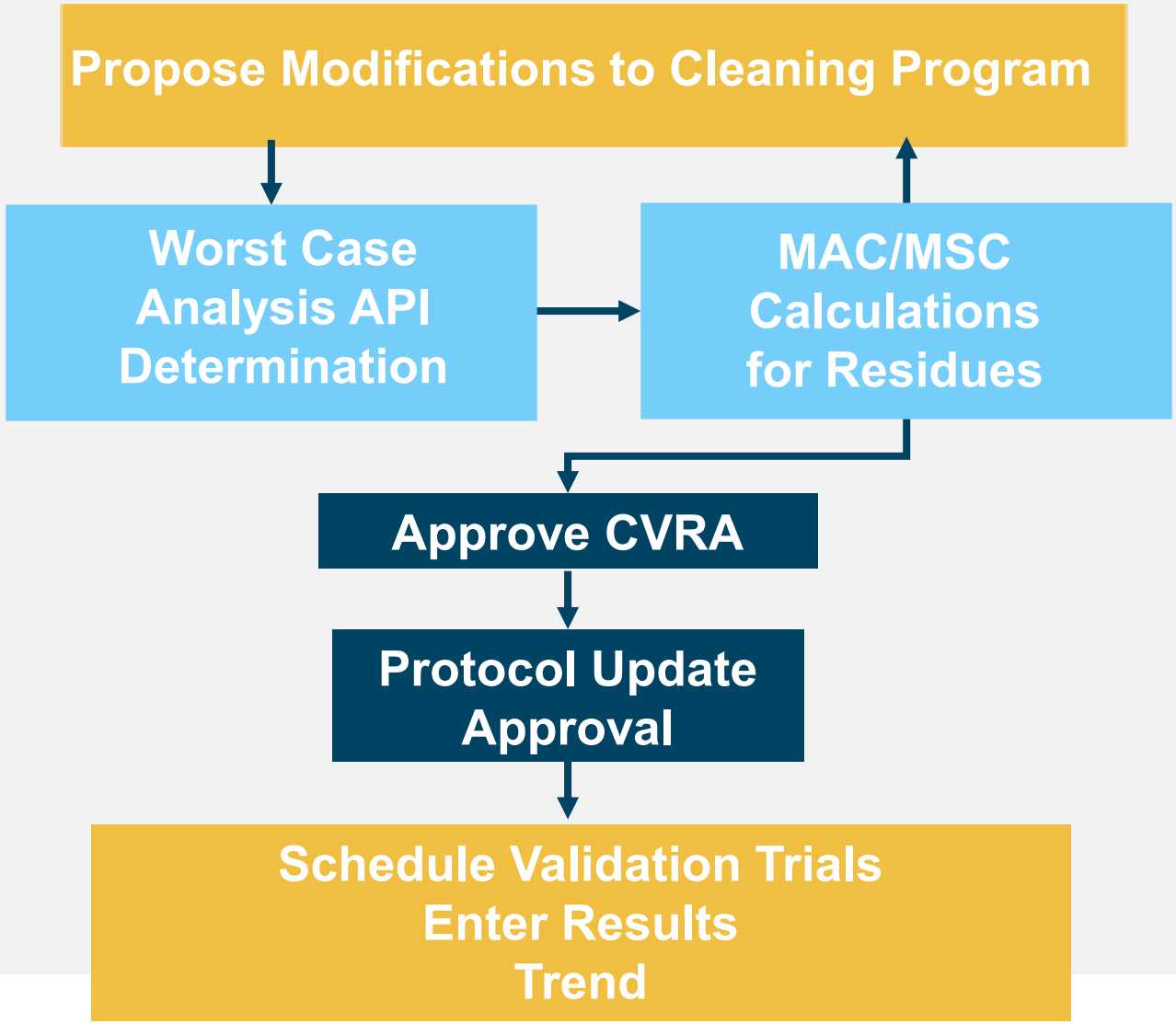
Trending and Reporting of Cleaning and of Cleaning Validation Samples

Investigation of OOS/OOT (results and safety thresholds)

Data integrity and security

Regulatory compliance: No 483s/Citations

Cleaning Validation Risk Assessment



- Correlates all the master table data together
- Identifies the worst product and calculates all MAC/MSCs
- 'Test out' changes in the sandbox and view MAC/MSCs – easily roll back or approve.

Elements of Contamination Control and Digitalization

- Environmental Monitoring
- Utility Monitoring
- Cleaning Validation
- **Sampling in Real-Time**
- Raw Material Bioburden
- Integration with equipment
- Continuous Monitoring

Sampling in Real-Time

Manual RISKS:

- Errors in sampling
- Introducing contamination
- Missed samples

Ability to scan media plate during sampling

Sampling in Real-time using tablets and scanners

Touchless sampling- use scanning for most operations – minimum touch needed for the rest

Data protection to maintain data integrity

Go paperless

Sampling in Real-Time: Information Read in

By scanning the media plate, the EM software will track the chain of custody of the sample throughout its sampling process

- media
- equipment used
- sample status
- person setting out plates
- person collecting plates
- comments
- sampling start time
- sampling end time
- product Lot number
- Incubation status
- other data

Sampling in Real-Time Scanning

Loop B
Appearance
00:00:00
Manufacturing

MET-022

Loop B
TOC
00:00:00
Manufacturing

MET-011

Loop B
Nitrates <= 0.1PPM
00:00:00
Manufacturing

MET-012

Loop B
Nitrates <= 0.2PPM
00:00:00
Manufacturing

MET-012

Loop B
Oxidizable Substances <=0.01M KMnO4
00:00:00
Manufacturing

MET-043

- Ability to track and update media inventory – quantities and status
- Ability to track growth promotion
- Ability to print barcodes or to scan prelabeled manufacturer media plate barcodes
- Ability to recognize the sample that matches the media, to notify if media is expired, quarantined, or in use already and prevent use accordingly
- Ability to scan a group barcode for incubation operations
- Use high performant and quality hardware for cleanroom use

Sampling in Real-Time: Significantly Reduce Physical Interaction with Devices

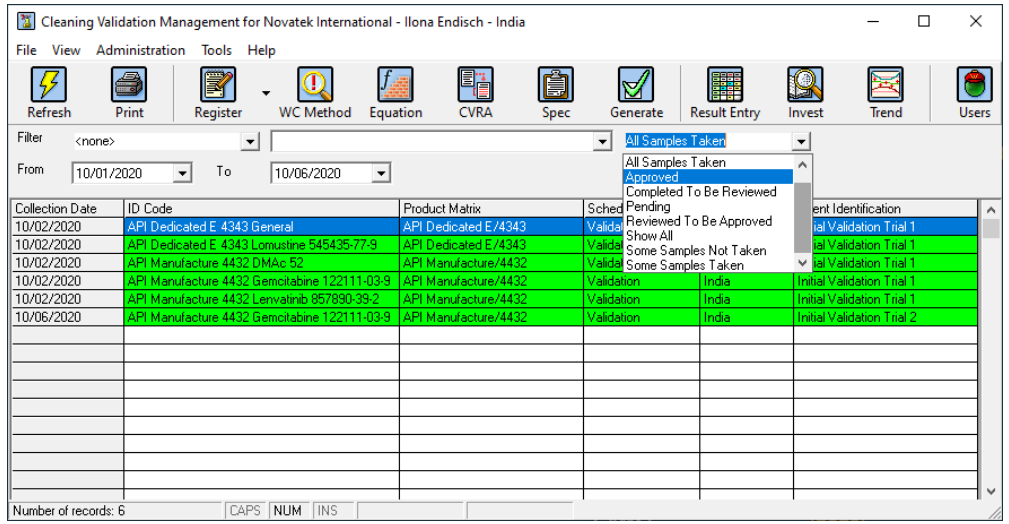
Minimal physical interaction with the tablet should be needed reducing the amount of cleaning and contamination risk during a session.

- **Smart Filter**
- **Preset Media and Preset Default Equipment**
- **Offline Feature**
- **Notification to avoid Missed Samples**
- **Sample Group Barcode**
- **Autosave for Data Integrity**
- **Failsafe to Protect Data**

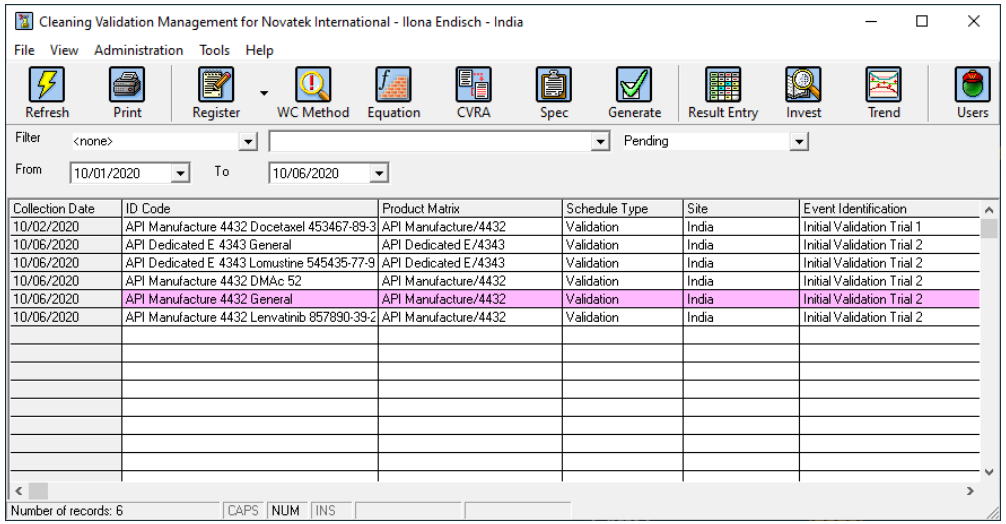
For a more touchless experience, users can install the scanner in one designated area and scan samples without having to touch it

Sample Reconciliation: First Week of October

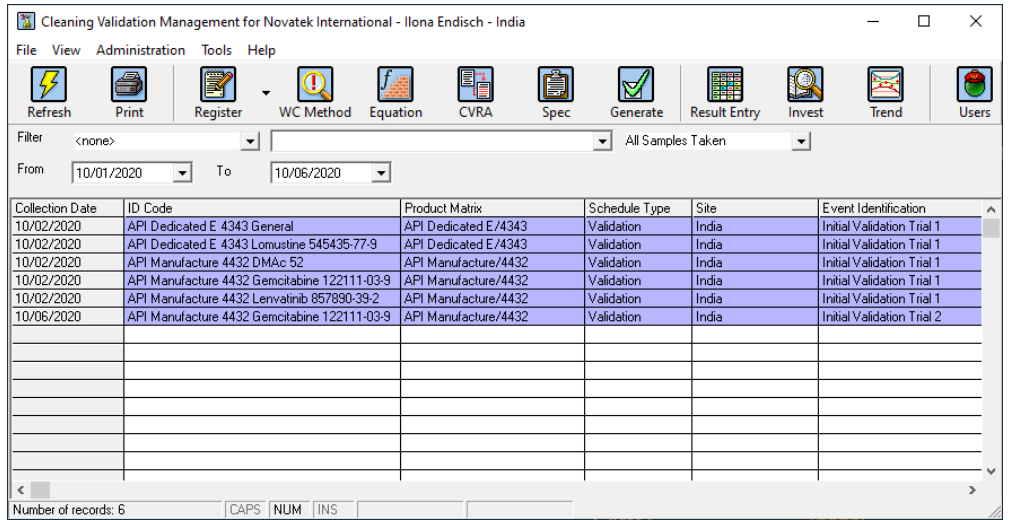
SAMPLES COMPLETED and APPROVED



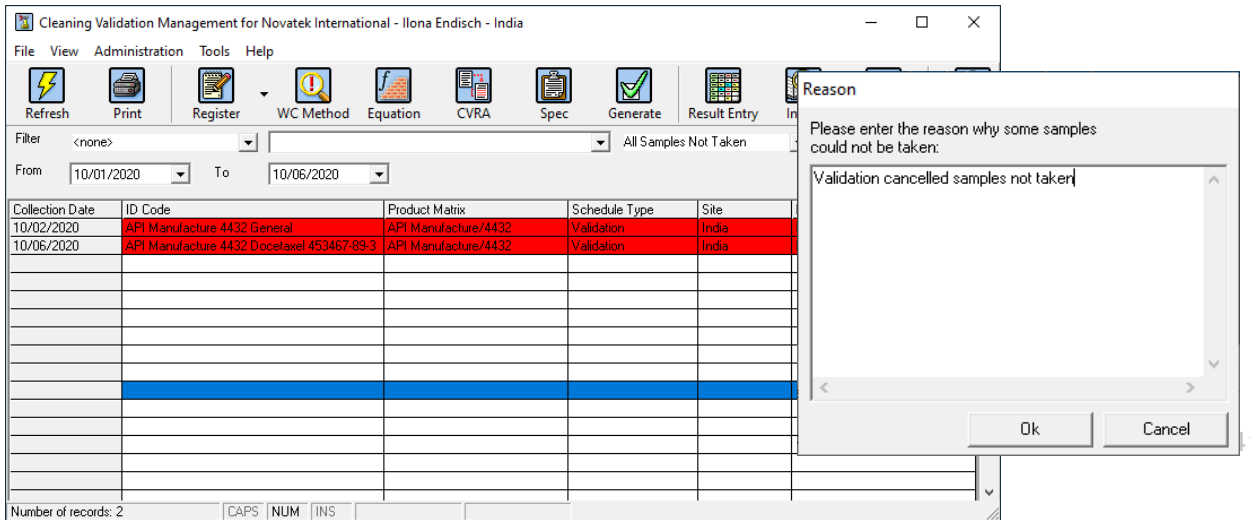
SAMPLES PENDING



SAMPLES TAKEN



SAMPLES NOT TAKEN and REASON

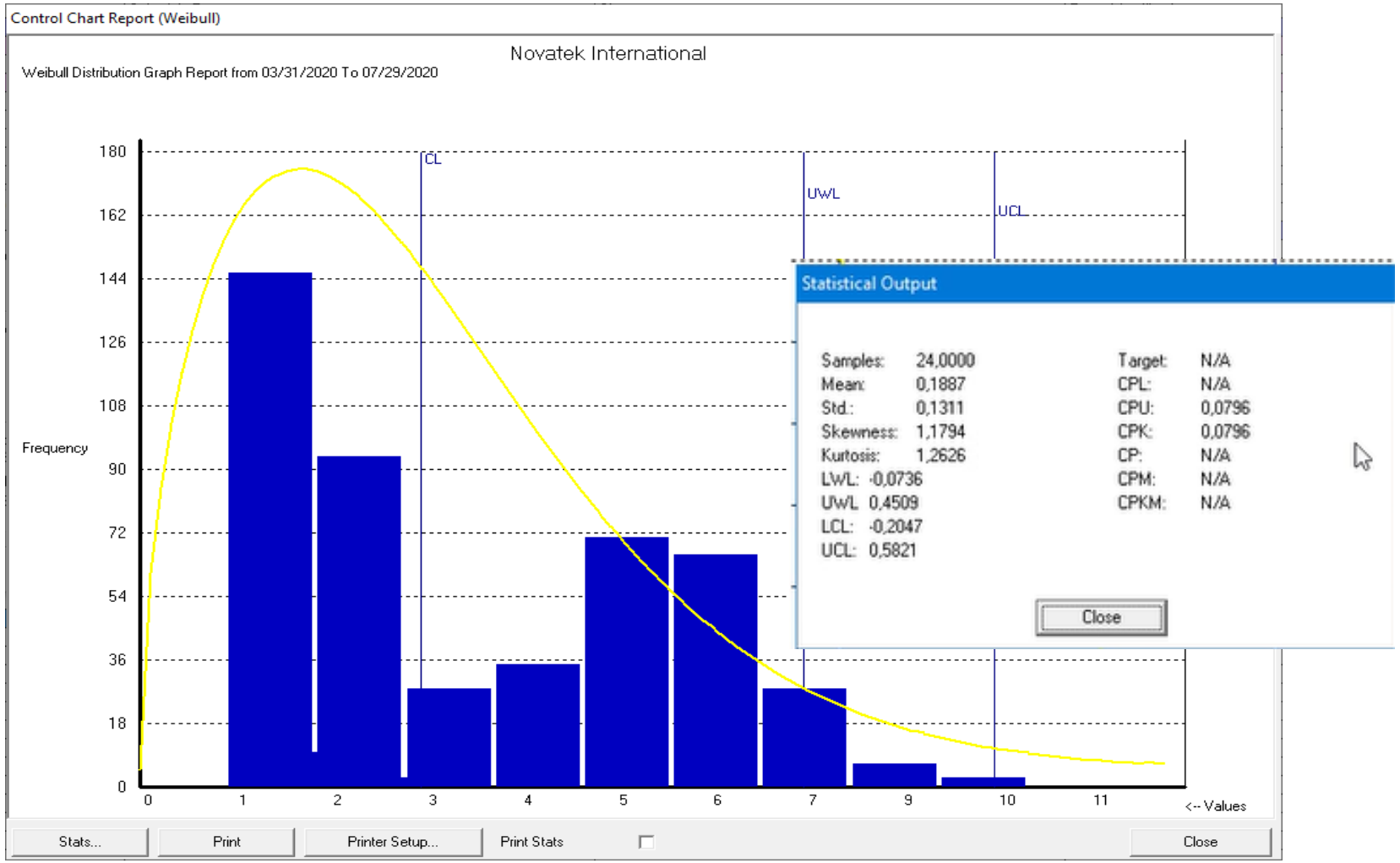


Elements of Contamination Control and Digitalization

- Environmental Monitoring
- Utility Monitoring
- Cleaning Validation
- Sampling in Real-Time
- **Raw Material Bioburden**
- Integration with equipment
- Continuous Monitoring

Raw Materials: New Impurities & Bioburden

Statistical Analysis/Reporting



Regulation –

EU Annex 1

2.5 Elements to be considered within a CCS should include :

xv. Prevention mechanisms – trend analysis, root cause determination, CAPA and the need for comprehensive investigational tools.

xvi. Continuous improvement

- Graph: distribution graph, **Cpk, Cp, CPL, CPU Cpm** Indices

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Elements of Contamination Control and Digitalization

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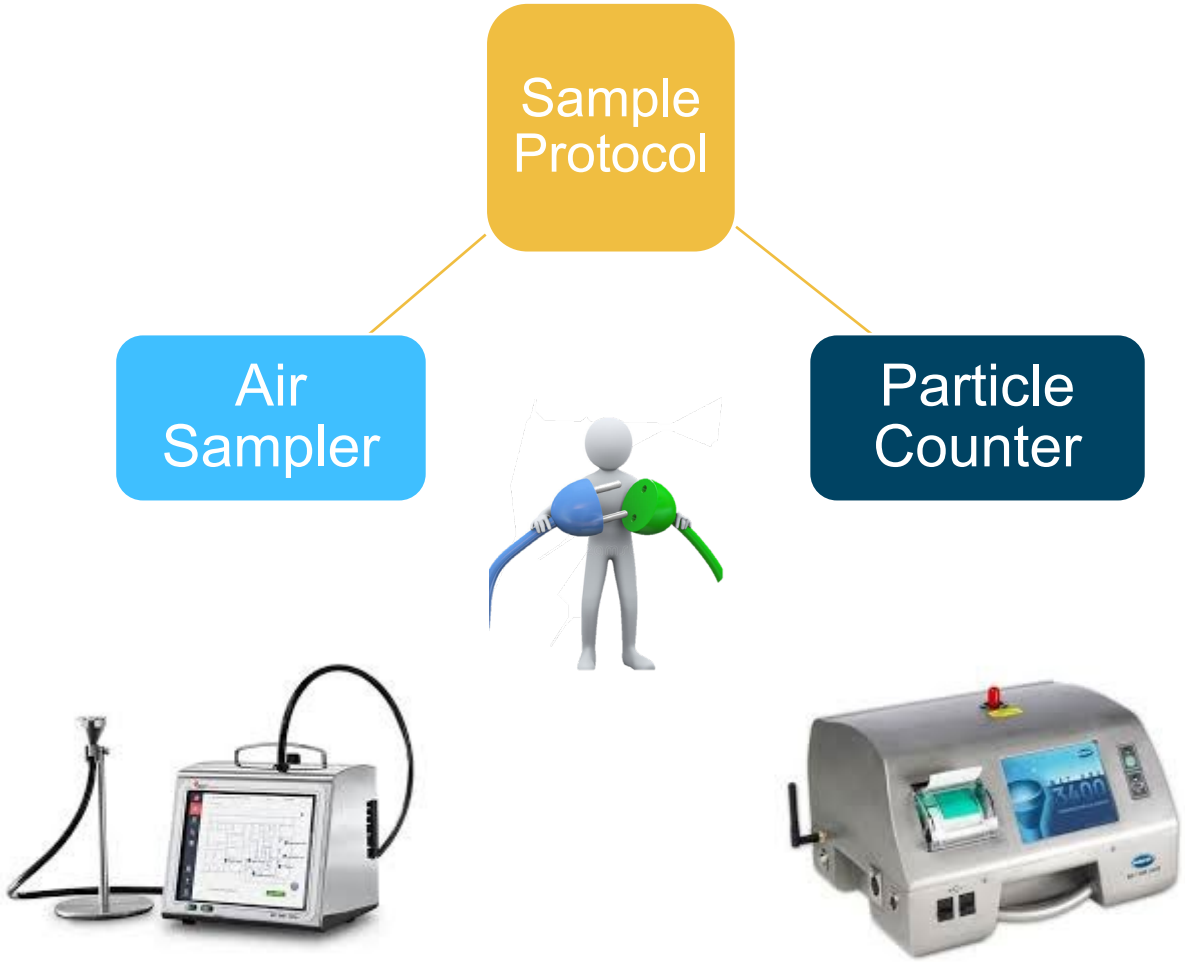
Integration Example: Air / Particle Sampler



Transfer your scheduled protocol to your sampling device…

- Downloads data from the device and auto links to the EM software protocols
- Provides a validated data transfer
- Compliant to 21 CFR Part 11
- Meeting data integrity: data is recorded contemporaneously
- For particle counters, results are ready for trending once transferred
- Reduced human error
- More efficient process
- Prevents the use of non-calibrated instruments
- Helps to prevent missed or double taken samples
- Correctly tracks interrupted runs
- Visibility across devices and chain of custody (data is attributable)

Benefits of Particle Counter Integration

Real-Time Monitoring and Rapid Response

Comprehensive Environmental Control

Data Centralization and Trend Analysis

Compliance with Regulatory Standards

Improved Data Accuracy and Integrity

Continuous Improvement and Optimization

Facilitates Risk-Based Environmental Monitoring

No Device Setup Required

Transfer Large Volumes of Data Instantl

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Elements of Contamination Control and Digitalization

- Environmental Monitoring
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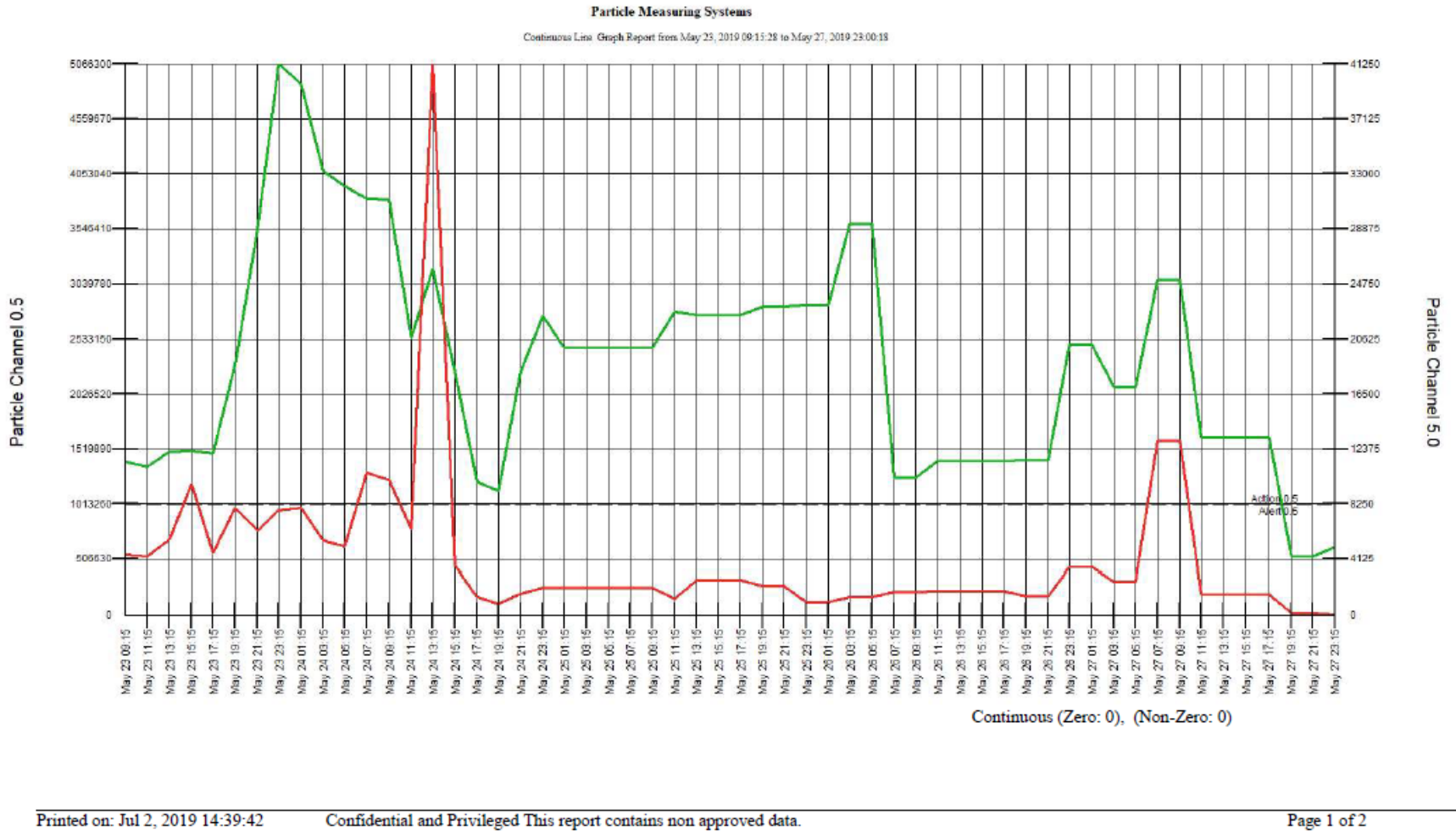
- Integration with equipment
- Continuous Monitoring

Integration Example (IoT): Continuous Monitoring Systems



- ✓ Continuous monitoring of 0.5 (green) and 5.0 (red) microns
- ✓ Trending across 3 days

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Integration Example (IoT): Continuous Monitoring Systems

- ✓ Continuous monitoring of 0.5 (green) and 5.0 (red) microns
- ✓ Trending across 3 days
- ✓ Trending across 1 min

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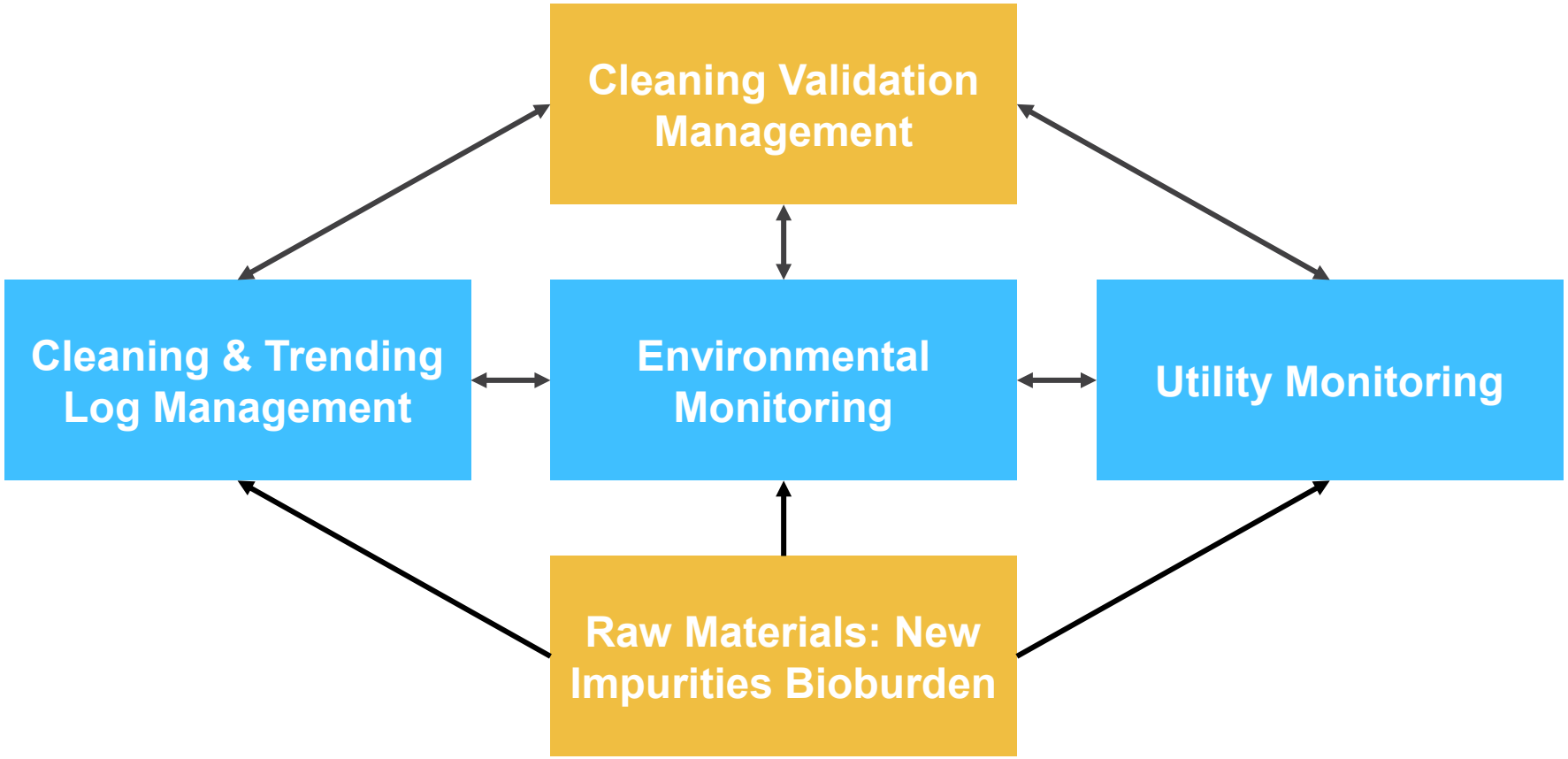
PULLING IT ALL TOGETHER

Total Contamination Control Strategy

Not an Isolated process!



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Sourcing Tech Tools

Conduct research of available tools and technologies	Online forums Conferences
Work with technology vendors	Partner with your tech vendors
Leverage industry organizations such as KenX & PDA	Consult for trusted industry tools as well as up and coming technologies
Consider regulatory guidance	E.g., special considerations for data integrity compliance
Consider scope of resources available	E.g., out of the box or configurable systems

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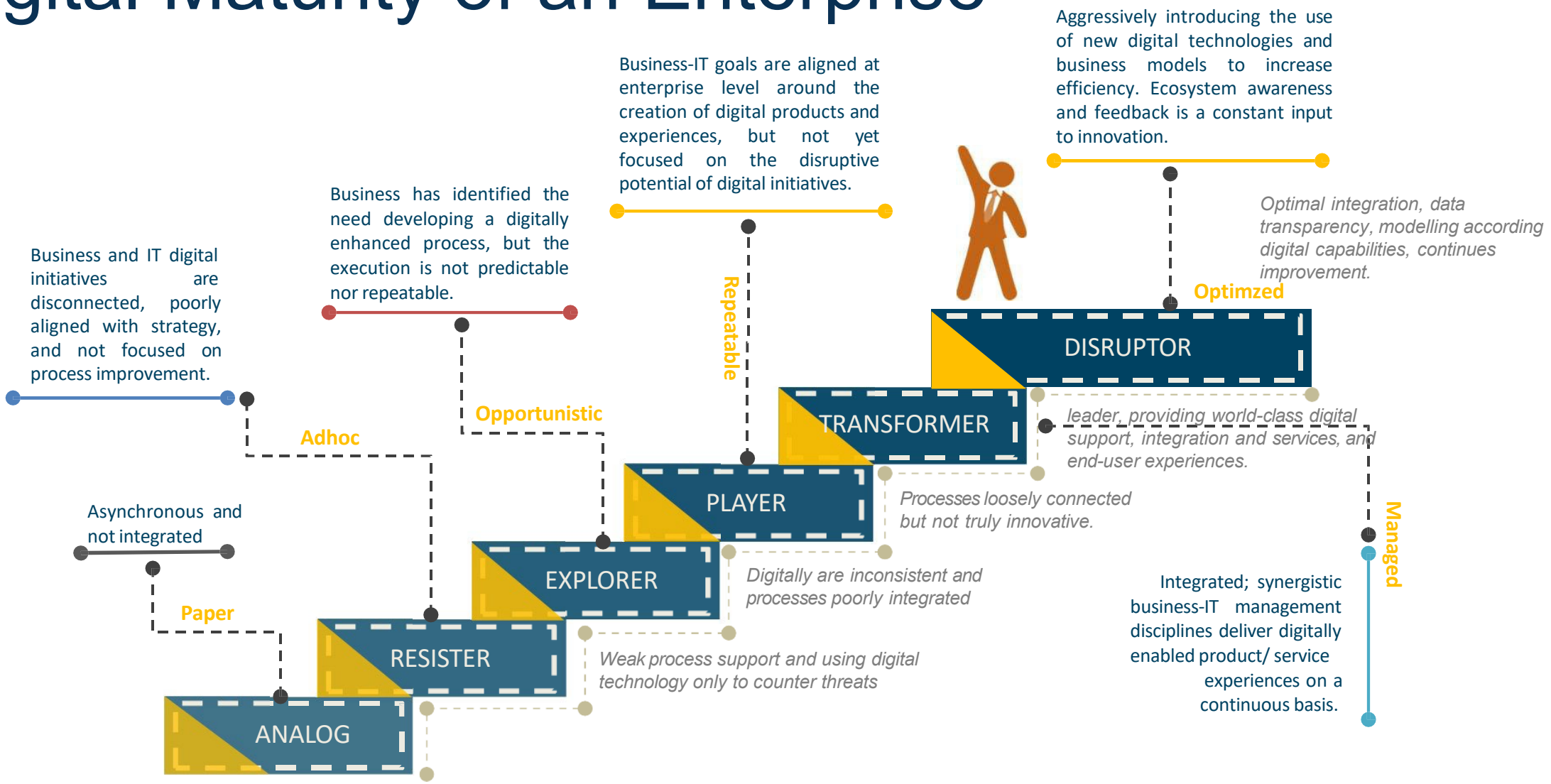
Manage Digitalization Risks

- Data integrity & Compliance risks
  - Identify all compliance requirements and manage compliance at the workflow step level
  - Consider all ALCOA+ elements as well as corresponding verification and validation activities
- Cybersecurity risks
  - Implement robust security measures, such as firewalls, intrusion detection systems, and encryption, as well as training employees on cybersecurity best practices
- Technical challenges
- Cultural challenges
  - Employees may be resistant to changes in the way they collect, manage, and analyze data, which can impact the success of the digital transformation.
  - Involve employees in the planning and implementation process, providing training and support to ensure they are comfortable with the new system, and communicating the benefits of the digital transformation to build buy-in and support.
- System Downtime
  - Perform testing and validation of the new system prior to implementation, as well as having backup systems and contingency plans in place to minimize the impact of any disruptions.
- Cost
  - Identify Business Ready Solutions as much as possible
  - Perform cost-benefit analysis to identify potential cost savings and return on investment

Digital Maturity of an Enterprise



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Your data is not just a collection of data !

It’s a collection of built-for purpose information that supports your operations with value-adding insights, that are to-the-point and accurate.

Built for purpose, “business ready” regulatory compliant quality- process management applications should provide holistic, global contamination control analysis.

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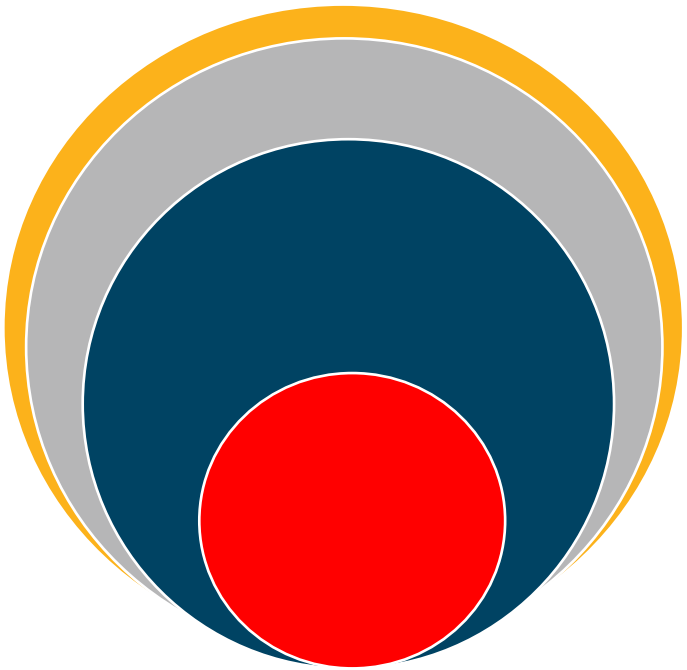
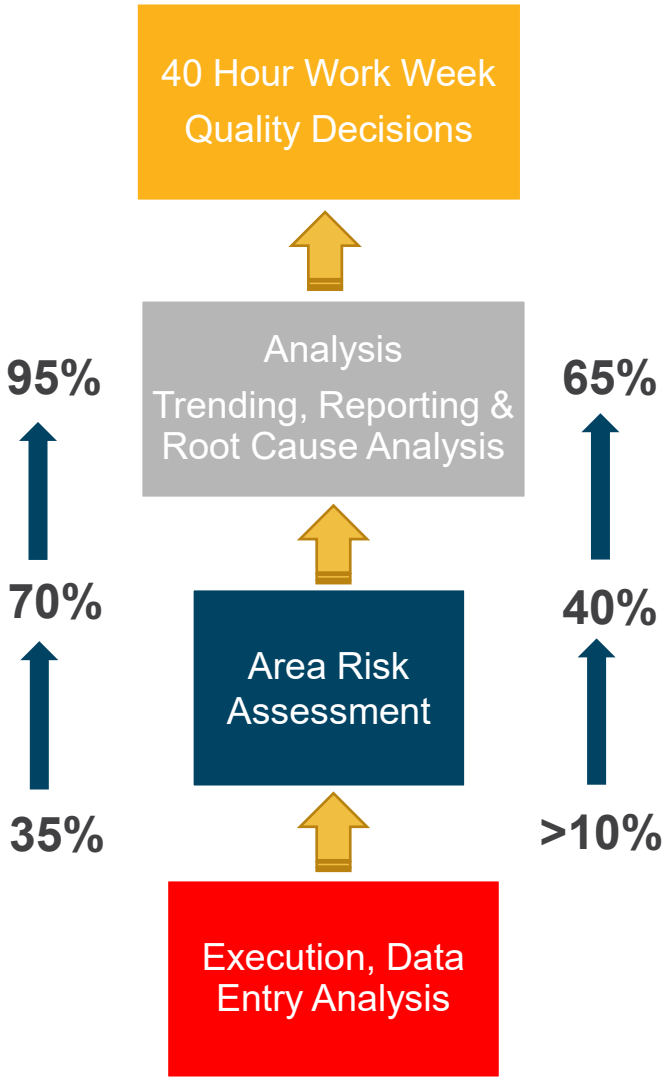
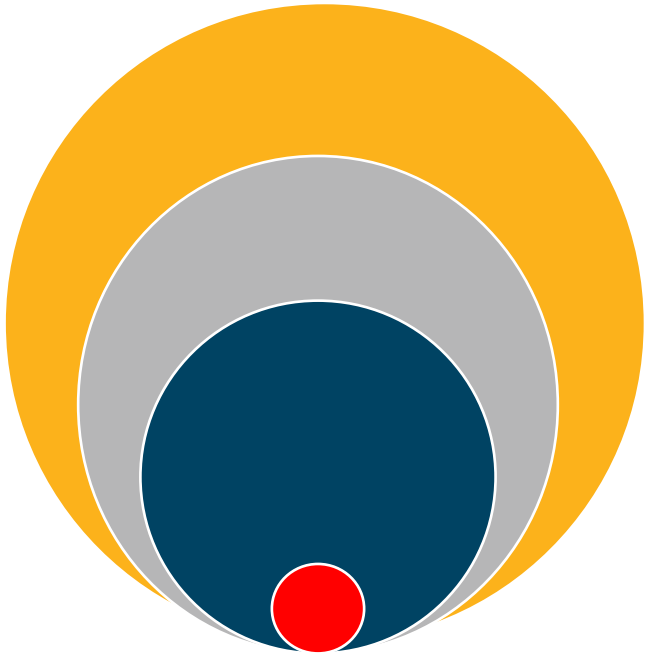
Proactive not Reactive

PAPER-BASED





ELECTRONIC SYSTEM



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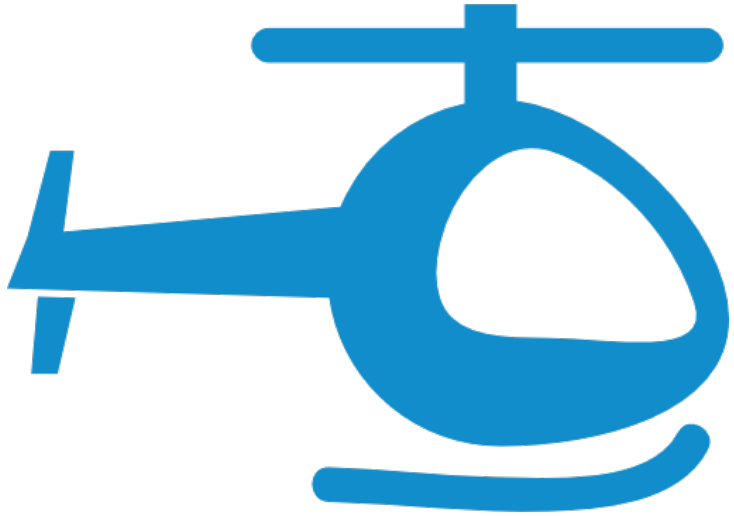

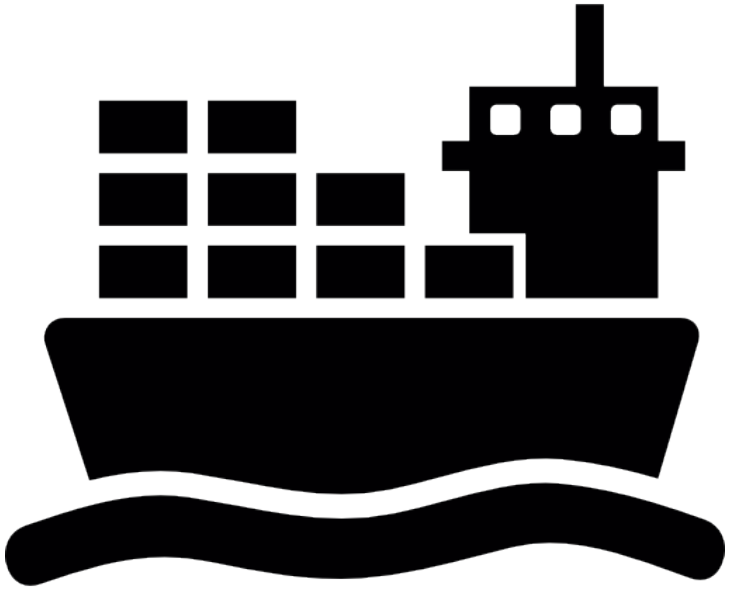

FIT FOR PURPOSE

CUSTOMIZATIONS THAT DON’T FIT THE NEED

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Thank You for your time today. Contact me for a Live Demo!

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Over 20 years experience defining Requirements for Pharmaceutical and Biotech