



ILONA ENDISCH
ASSOC. DIR. PRODUCT INNOVATIONS
NOVATEK INTERNATIONAL

**Achieving Both:
Contamination Control as per Annex 1 and
Digitalization of the Environmental
Monitoring Process**

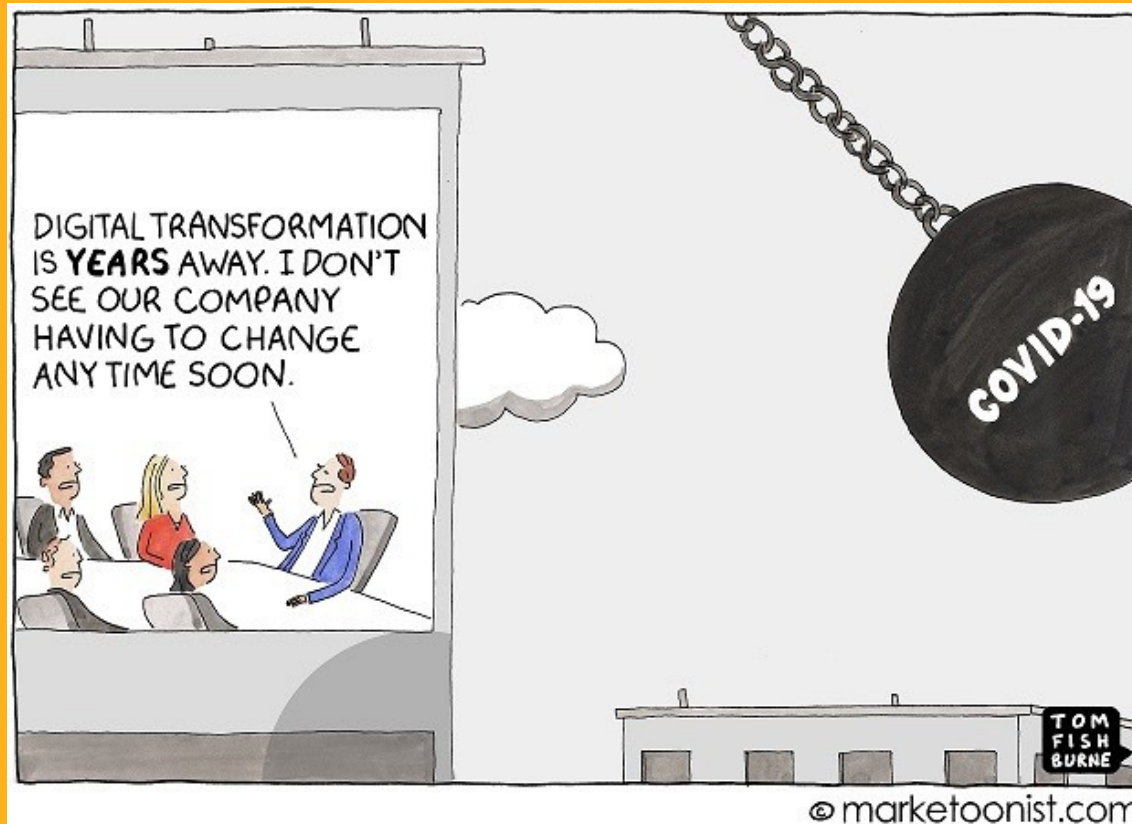
Agenda

Achieving Both: Contamination Control as per Annex 1 and Digitalization of the Environmental Monitoring Process

- Digital Transformation
 - Cloud, IoT, AI, EM software
 - Sampling in Real-Time
 - Integrating with different systems and technologies
- Annex 1 and the importance of trending your data
- How an EM Trending software can help to meet Annex 1 regulations
 - Setting alert levels
 - Personnel Monitoring
 - Identification of Microorganisms
 - Batch Related Reporting
 - Trends and adverse trends
 - Utility Monitoring



Digital Transformation



“Digital innovation has been accelerated by 10 years by what has happened over the course of the last 18 months.”

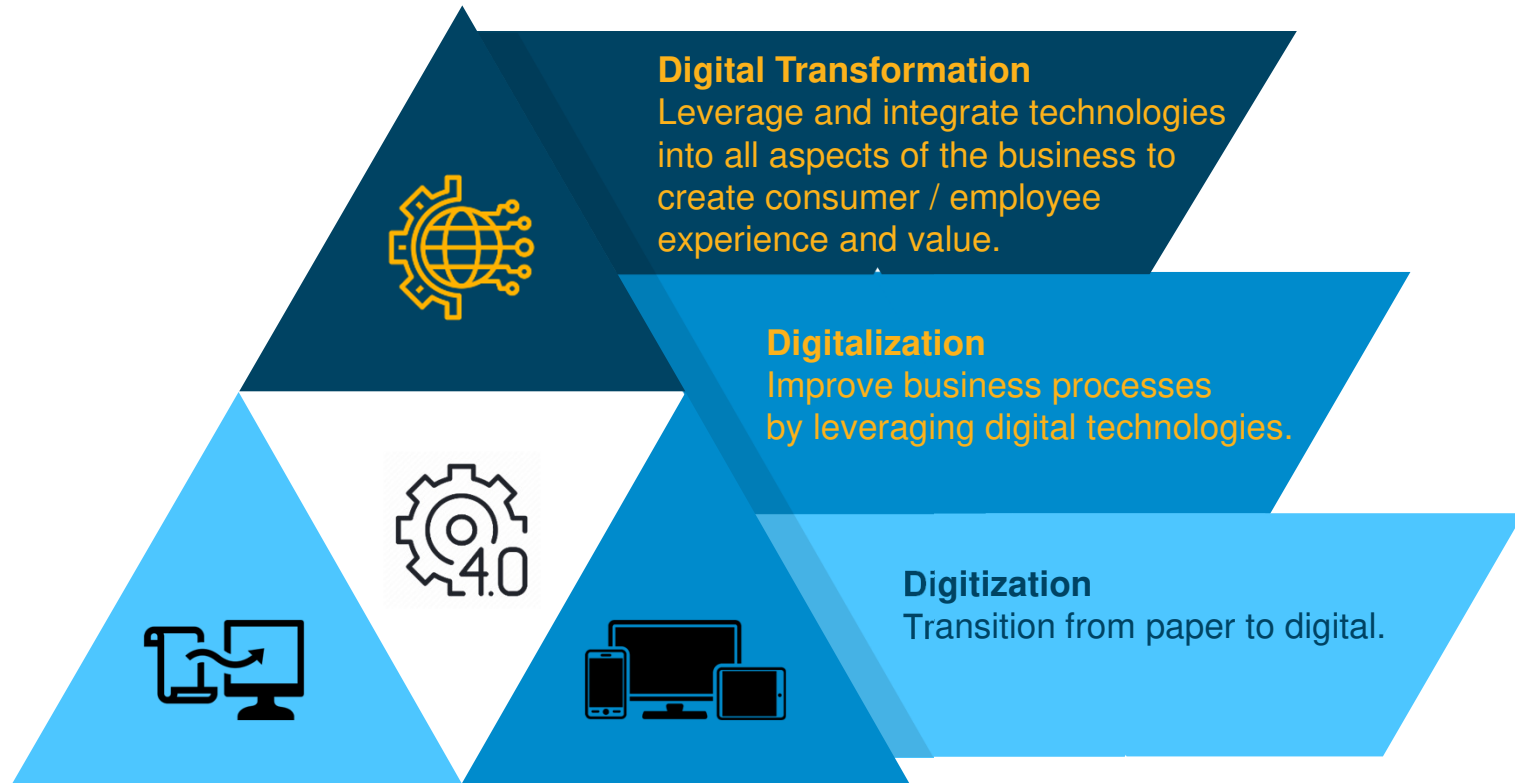
—Manoj Raghunandan, president, global self-care and consumer experience, Johnson & Johnson - 2021

Reference: Article 8 Dec. 2021 - <https://www2.deloitte.com/us/en/insights/industry/life-sciences/biopharma-digital-transformation.html>

What is Digital Transformation / Innovation

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



Digital Transformation in Pharma Environmental Monitoring

- Improves the efficiency and accuracy of the process
 - Improves compliance to regulations
 - Data is at your fingertips in real-time
 - Analyzes large amounts of data in a short amount of time
 - Traces a problem to its root cause
 - Faster and more accurate corrective and preventive actions
 - Reduces the risk of contamination
 - Faster product release
-

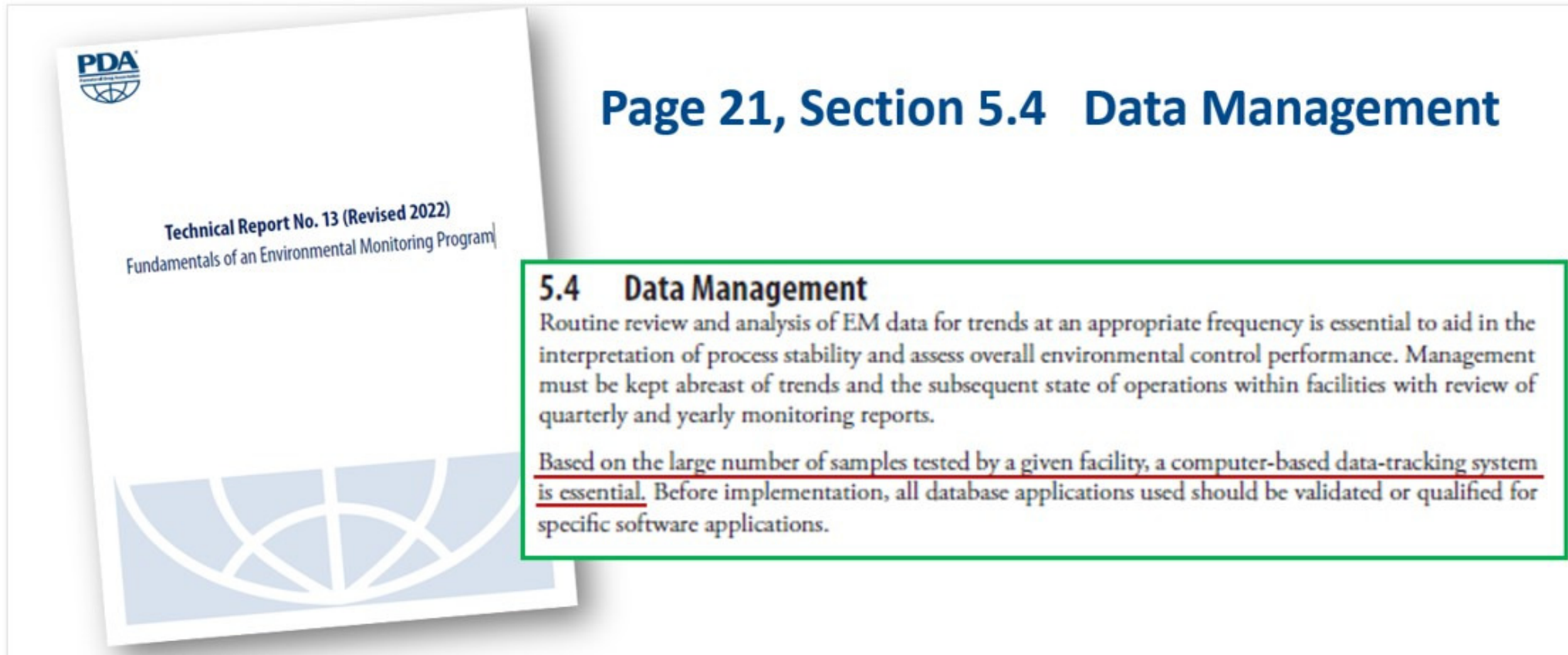
Examples of Digital Transformation Technologies in Use

- **Internet of Things (IoT):** Integration to devices and equipment through their sensors to track readings in real-time. This identifies potential issues before they become problems and improves overall efficiency.
 - **Artificial Intelligence (AI):** AI can be used to analyze large amounts of data and identify patterns that humans may not be able to detect, assisting in preventive measures while improving the accuracy of data analysis that leads to better decision-making.
-

Examples of Digital Transformation Technologies in Use

- **Cloud:** The cloud has provided scalability and agility for organizations to enable employees to work collaboratively and flexibly from home, securely store and share data and reduce the IT maintenance and resources needed.
 - **Environmental Monitoring Software:** that can tie many of these technologies together seamlessly, through instrument connectivity pulling the data from source points and using AI or other means to correlate and evaluate large datasets. The FDA has always believed that computer trending for pattern recognition is the most efficient and effective way to handle such large quantities of data.
-

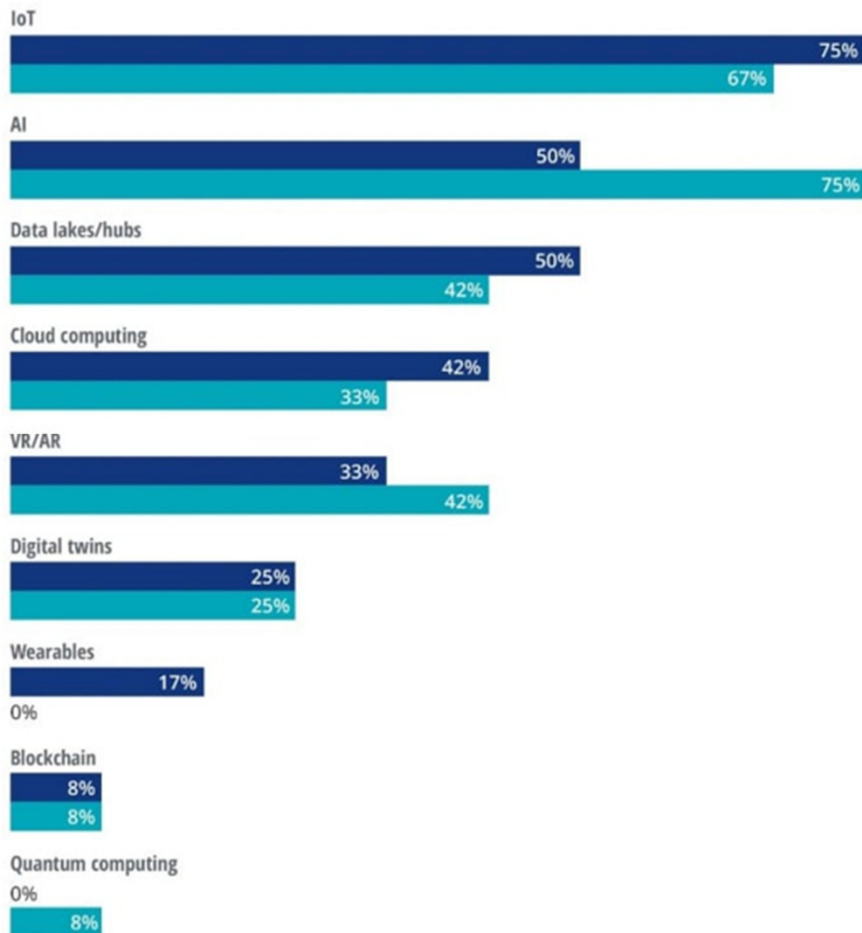
PDA Technical Report 13



Manufacturing: Current and planned investments in digital technologies

Respondents were asked to rank the most innovative technologies in which their function is currently investing and plans to invest in the next five years.

■ Current investment priorities ■ Investment priorities over the next 5 years



Note: Percentages indicate options ranked among the top 3 by survey respondents.

Source: Deloitte's Biopharma Digital Innovation Survey 2021.

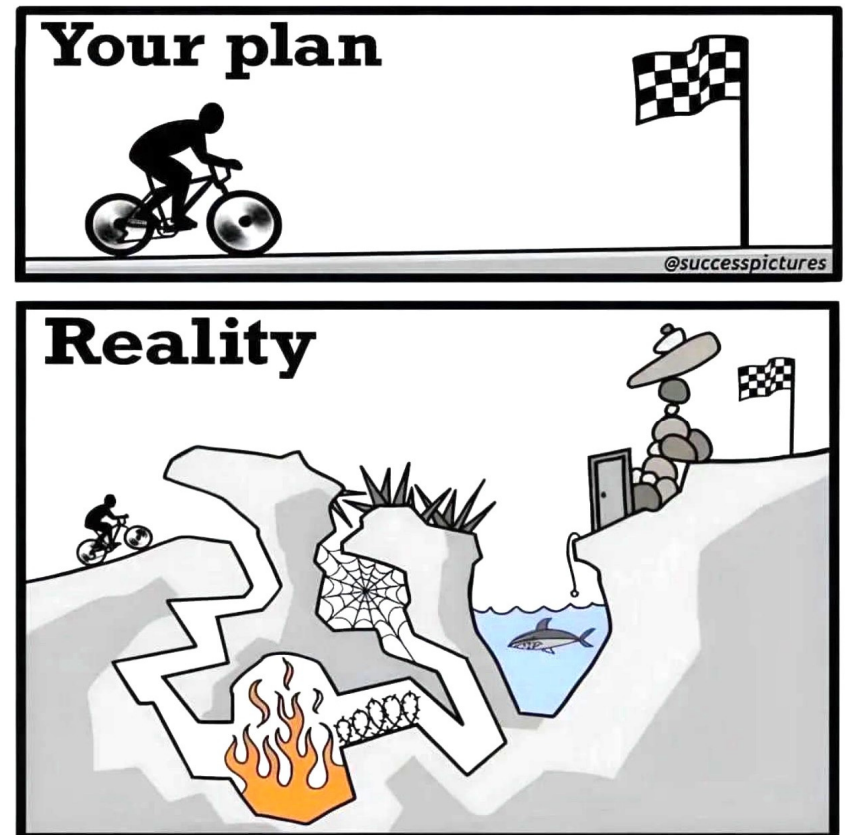
“Digital innovation is a burning strategic priority. 77% of respondents say their organization views digital innovation as a competitive differentiator.”

- Survey of 150 Biopharma companies
- 2021

DIGITAL TRANSFORMATION

is moving away from isolated scientific instruments, manual data collection, and siloed databases, to create an interconnected manufacturing ecosystem for fluid data tracking, sharing, review and analysis.

MANUAL PROCESS

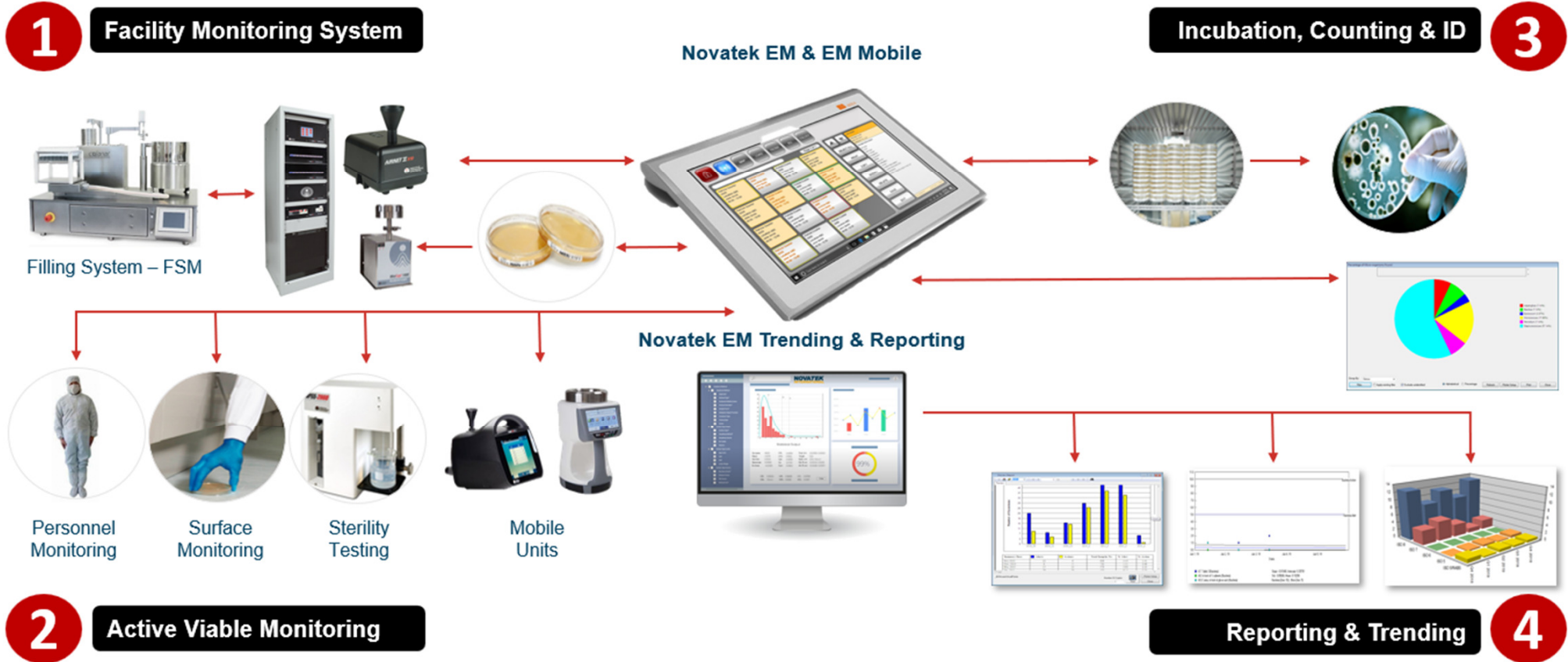


Digital Transformation in Pharma Environmental Monitoring

BEFORE SAMPLE IS TAKEN

EM DATAFLOW

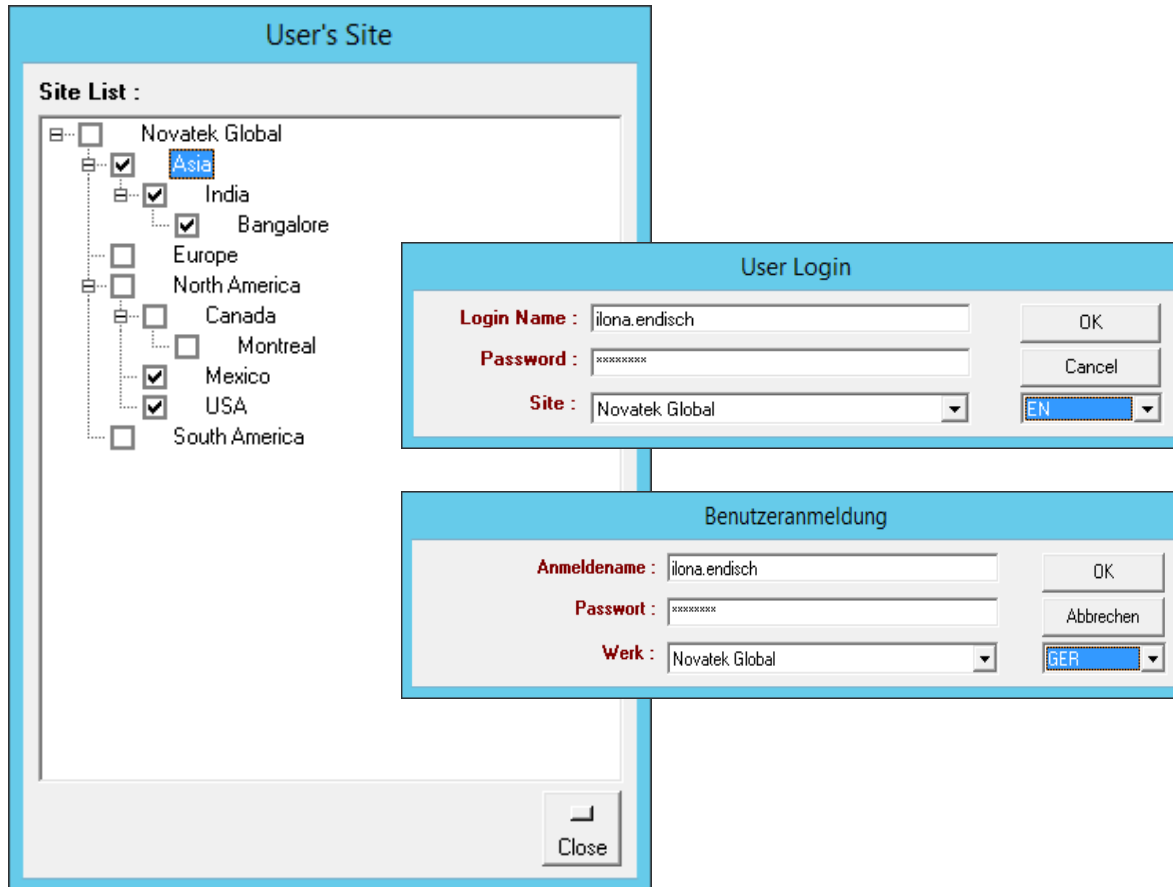
AFTER SAMPLE IS TAKEN



Examples of Digitalization in the EM Process

- Cloud, Data segregation and Visibility
- Digitalize the complete EM process (not have missing parts)
- Workload Distribution and Dissemination
- Media Management
- Sampling in Real-Time
- Sample Reconciliation (No Missed Samples)
- Automated data entry: Integration to Particle counters, Air samplers, Continuous monitoring devices (IoT), instruments for water analysis (TOC analyzer, etc.)
- Incubation in Real-Time
- Integration to Micro ID systems and Colony Counters
- Trending and Reporting for Pattern Recognition (AI)
- Ad-hoc Reporting

Cloud, Data Segregation and Visibility



Various options for system setup (On-Premise, Cloud vendor hosted or other, SaaS, Citrix or Terminal Server etc.

Deploy the system across sites and provide visibility across all areas

Identify best practices and share across sites and in different languages

Segregate data based on user roles, sites and other categories

Digitalize the Complete EM Process

- Viable testing
- Non-viable testing
- Utility monitoring: clean steam, compressed gas, water
- HVAC qualification and monitoring
- Media and media fills
- Growth promotion testing
- Personnel monitoring
- Aseptic gowning qualifications
- Sampling process
- Incubation process
- Continuous monitoring and connectivity to devices
- Trending and analysis

Sampling in Real-Time



Manual RISKS:

- Errors in sampling
- Introducing contamination
- Missed samples

Ability to scan media plate during sampling

Sampling in Real-time through the use of 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 and Barcode Labels



Loop B
Appearance
00:00:00
Manufacturing
MET-022

Loop B
TOC
00:00:00
Manufacturing
MET-011

Loop B
Nitrates ≤ 0.1 PPM
00:00:00
Manufacturing
MET-012

Loop B
Nitrates ≤ 0.2 PPM
00:00:00
Manufacturing
MET-012

Loop B
Oxidizable Substances ≤ 0.01 M 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 pre-labeled 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 bulk 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: automatically short lists, loads the sample list without having to touch to scroll

Preset Media and Preset Default Equipment: no need to enter media / equipment by hand / no need to print labels

Offline Feature: work without WIFI

Notification to avoid Missed Samples

Group Barcode: Scan one barcode to manipulate a large set of samples for bulk operations

Autosave: Enter only one Save at the end of the session eliminating the need to enter multiple signatures. Data is protected throughout the process.

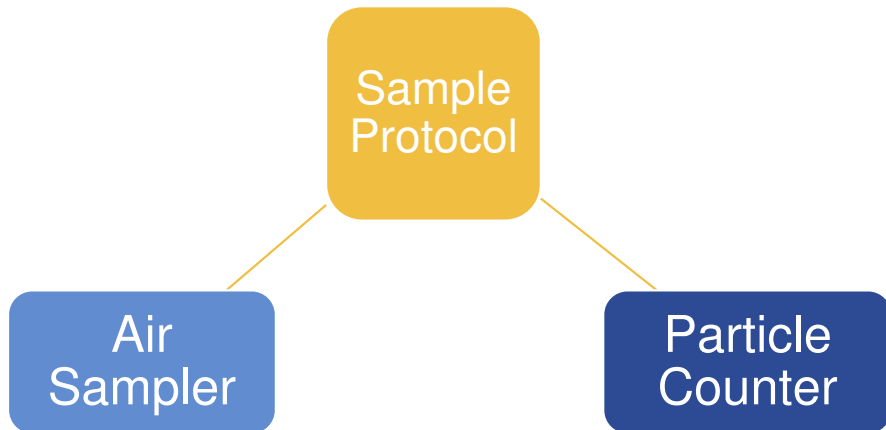
Failsafe to Protect Data: to sign the data electronically from outside of the tablet

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

Integration to Instruments and IoT



Integration Example: Air / Particle Sampler



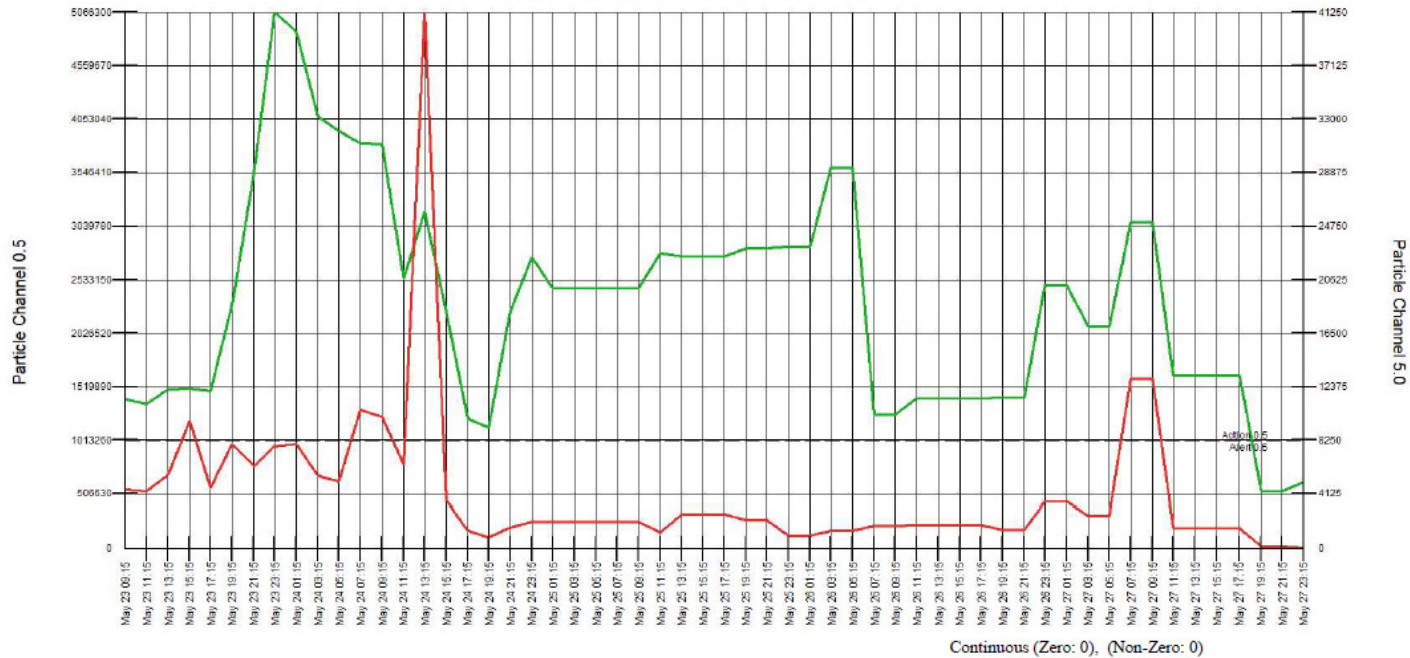
Transfer your scheduled protocol to your sampling device...

- 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)

Integration Example (IoT): Continuous Monitoring Systems

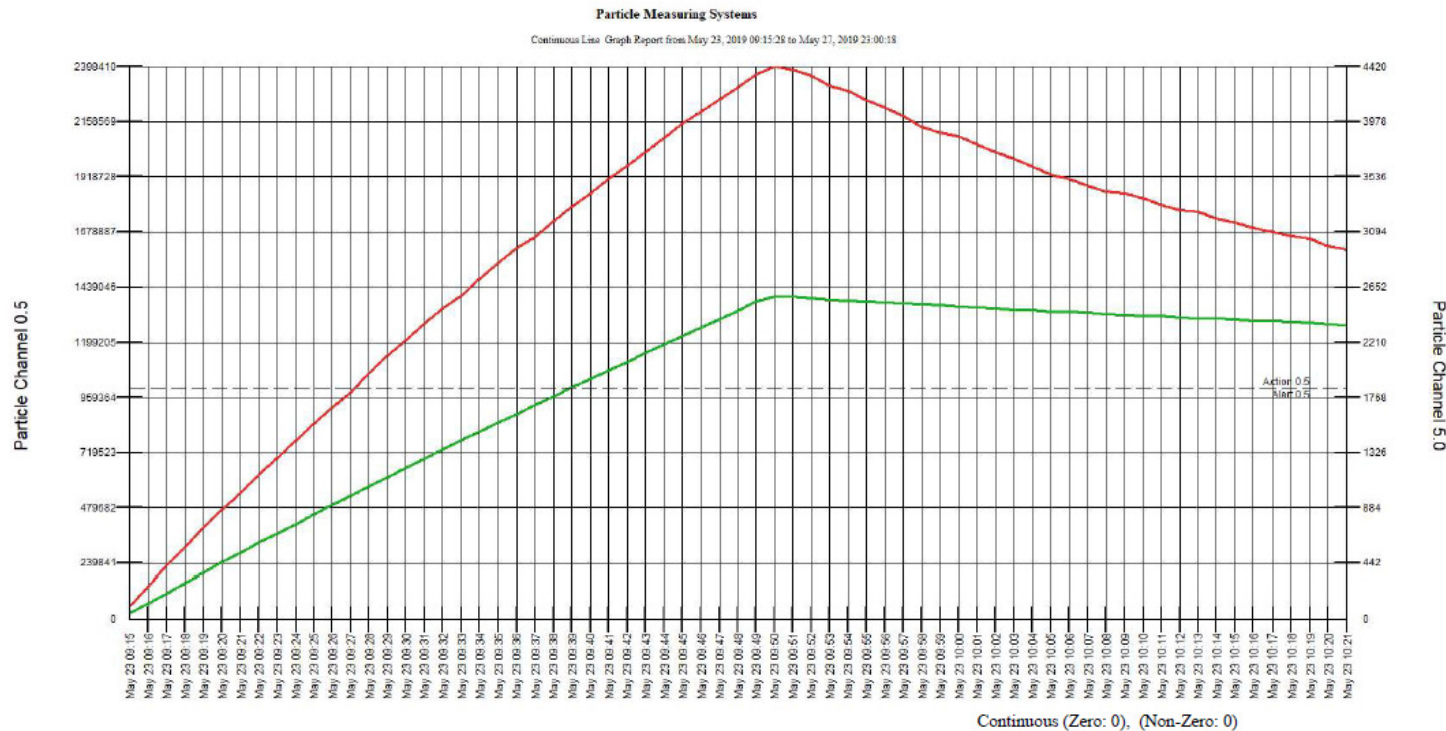
Particle Measuring Systems

Continuous Line Graph Report from May 23, 2019 09:15:28 to May 27, 2019 23:00:18



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

Integration Example (IoT): Continuous Monitoring Systems

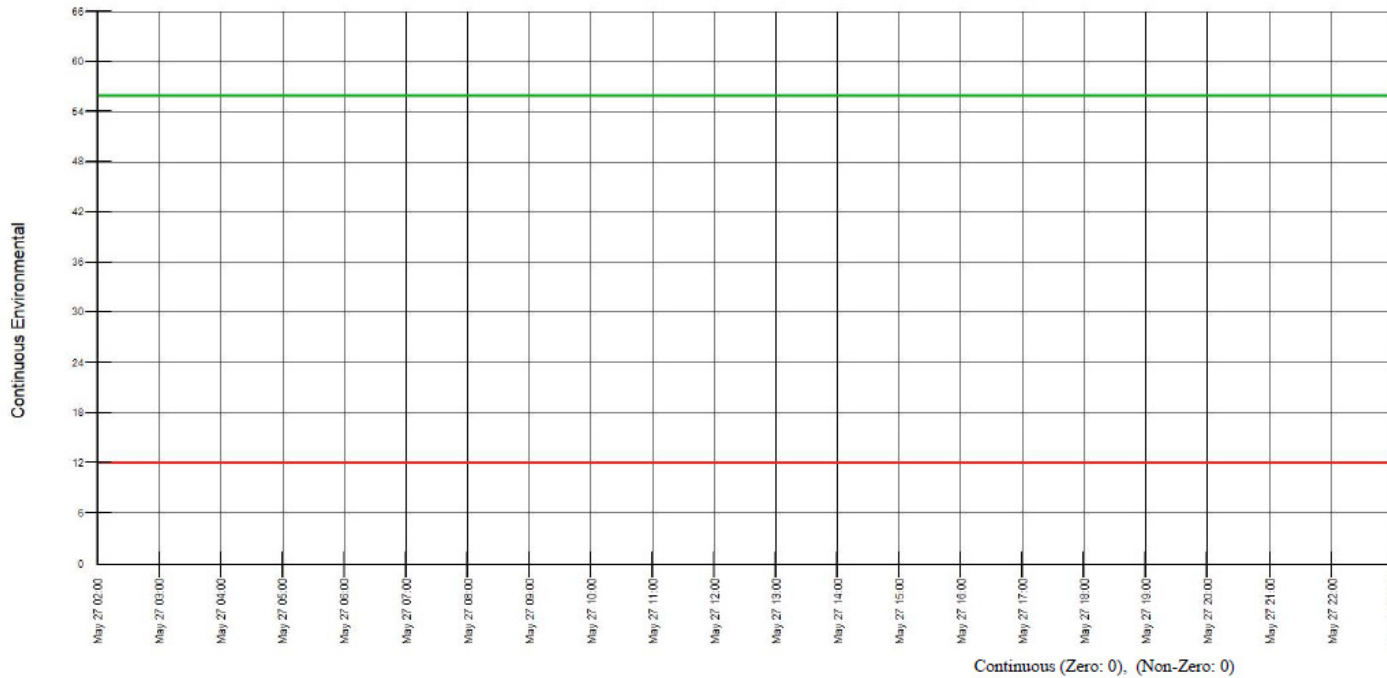


- ✓ Continuous monitoring of 0.5 (green) and 5.0 (red) microns
- ✓ Trending across 3 days
- ✓ Trending across 1 min

Integration Example (IoT): Continuous Monitoring Systems

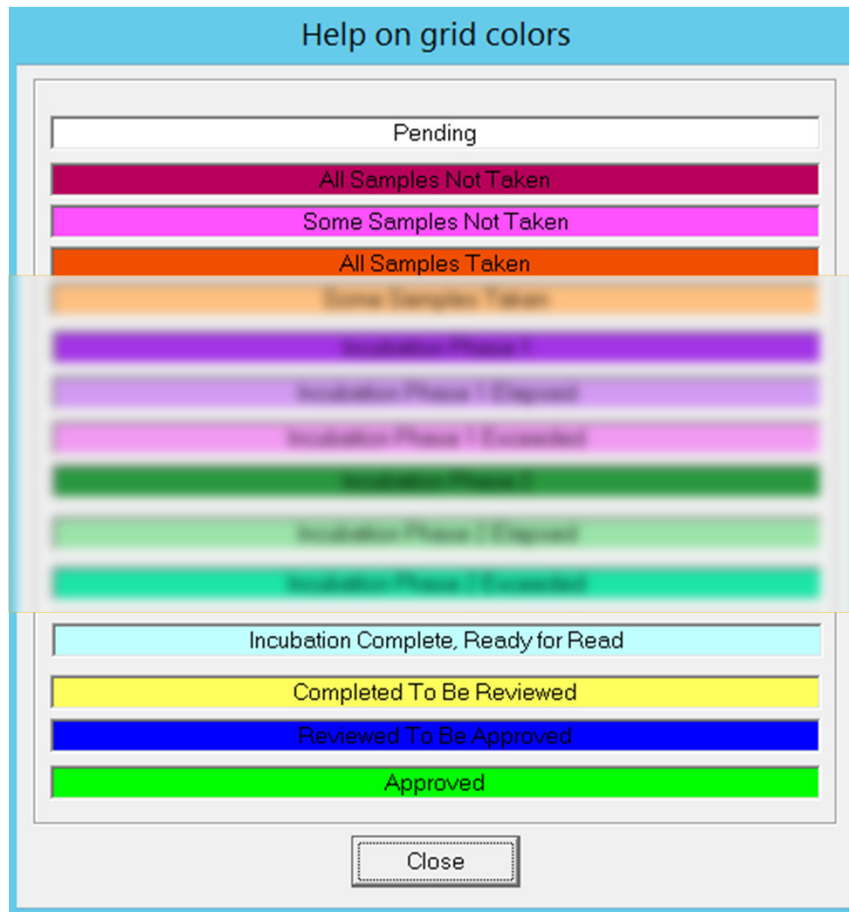
Particle Measuring Systems

Continuous Line Graph Report from May 27, 2019 02:00:00 to May 27, 2019 23:44:53 - Location 1, Location 2, Location 3, Location 4, Location 5, Location 6



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

Sample Reconciliation



Status notifications for:

- Sampling process
- Incubation process
- Approval process

Ability to provide notification for missed samples here and on the shop floor

Ability to provide sample reconciliation reporting

Avoid missed samples

Digital Transformation Liberates the Most Precious Commodity...Time!










REGULATIONS

EU GMP Annex 1

9.1 The site's environmental and process monitoring programme forms part of the overall CCS and is used to monitor the controls designed to **minimize the risk of microbial and particle contamination.**

10.10 Environmental monitoring data and **trend data** generated for classified areas should be reviewed as part of **product batch certification/release.** A written procedure should be available that describes the actions to be taken when data from environmental monitoring are found **out of trend or exceeding the established limits.**

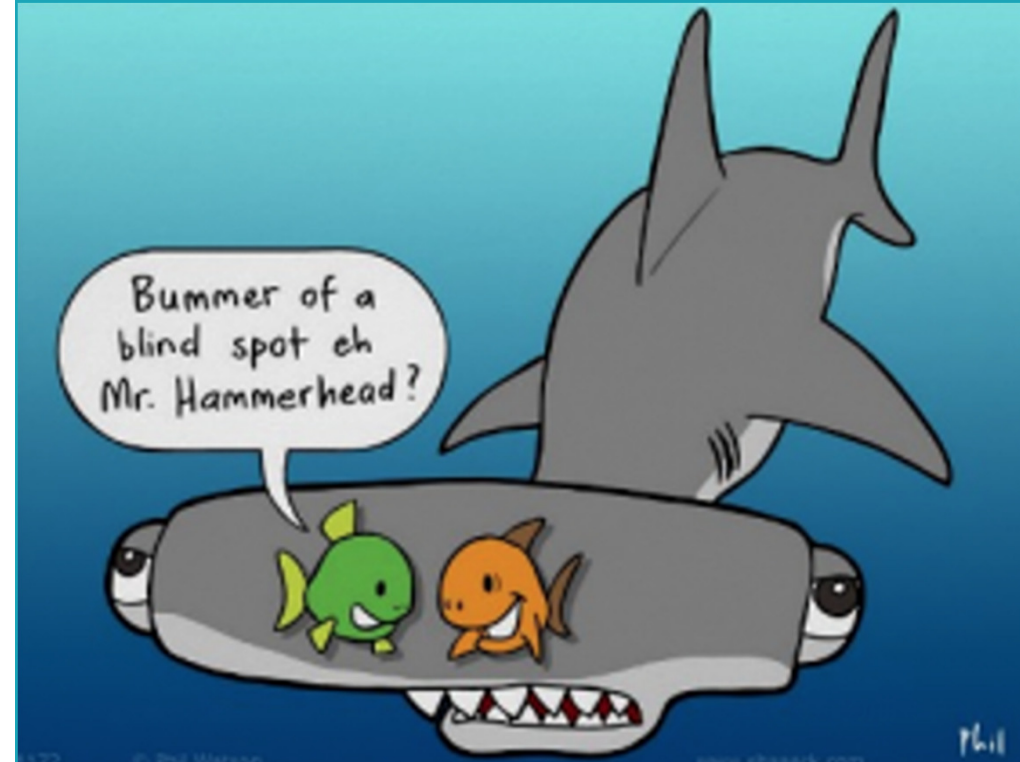
Considerations for Contamination

<p>LOCATION </p> <p>Location (site) Location Description Room Room Classification Room Status Group Protocol ID Code Department Plant</p>	<p>EQUIPMENT </p> <p>Equipment ID Equipment Name Eq. Calibration Date</p>	<p>SAMPLE </p> <p>Sample Start Time Sample End Time Date Test Taken Date Test Entered Taken By Handled By Read By Type of Test</p>	<p>PRODUCT </p> <p>Product Name Lot Number</p>	<p>INCUBATION </p> <p>Exposure Time Exposure Amount Incubation Duration Incubators Temperature Time / Unit Inc. Calibration Date</p>
<p>MICROORGANISM</p> <p>Microorganism identification Genus</p>	<p></p> <p>Species Strain Gram Stain Reference Storage</p>	<p>MEDIA</p> <p>Media Media Lot Number Media Type</p>	<p></p> <p>Storage Expiration Quantity in Stock Quantity Used Supplier</p>	

Ways to Use Trending

- Preventive trending across all elements
- Routine trending for product release and state of control
- Investigational Trending
- Post Corrective Trending

Trend Across all Parameters to Avoid Blind Spots



WHAT IS AN ADVERSE TREND?

- **EU GMP Annex 1** gave an example:

9.10 Alert levels for grade A (total particle only) grade B, grade C and grade D should be set such that **adverse trends (e.g. a numbers of events or individual events that indicate a deterioration of environmental control)** are detected and addressed.

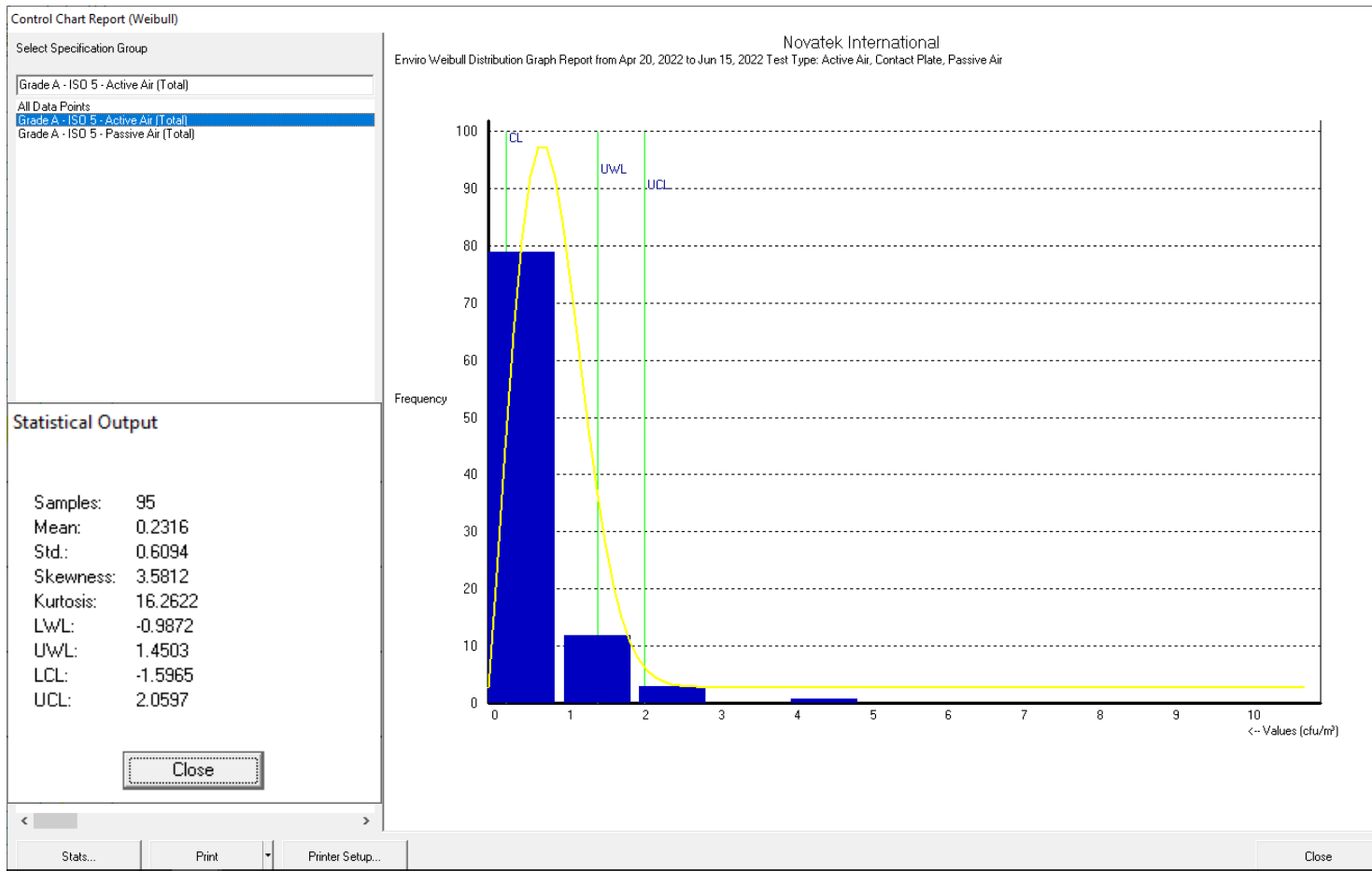
- **Client Definition:** a series of alert level or action level excursions, or an increase in contamination incidents that indicates that the environment is drifting out of control and may potentially affect product quality.
- **Client Definition:** three or more consecutive points, drifts or pattern, or three or more clusters of recoveries in one day in one room above the alert level signals an adverse trend. Alternatively, an increase in frequency of recovery in a short period is considered an adverse trend

REGULATIONS

EU GMP Annex 1

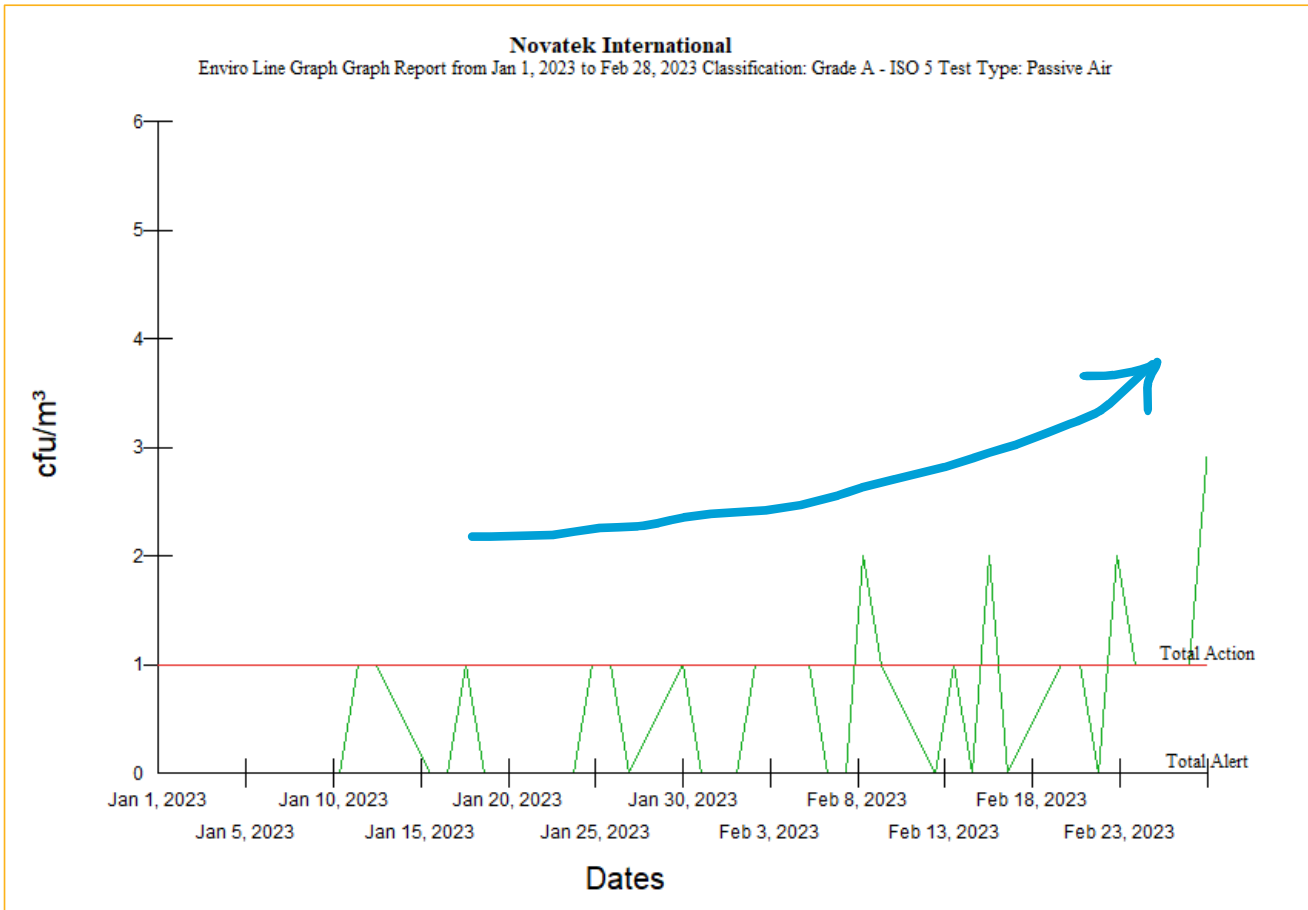
9.9 Both viable and total particle **alert levels** should be established based on results of cleanroom qualification tests and **periodically reviewed based on ongoing trend data.**

Setting Your Alert Limits – Normal / Weibull Distribution



- Types of distribution charts: Poisson, Normal, Weibull, Negative binomial, 99% Quantile, etc.)
- Clean room data is typically not normally distributed:
- The microbial data in clean rooms are mostly zero
- Non-normal distribution is defined based on random distribution (such as Weibull)
- Use the method chart that best represents your data

Exceeding Levels - Excursions



Regulation EU GMP Annex 1:

9.11 Monitoring procedures should define the approach to trending. Trends should include, but are not limited to:

i. **Increasing numbers of excursions** from action limits or alert levels.

- Trending becomes a powerful visual tool to see if counts are increasing

Exceeding Levels - Excursions

The screenshot shows a configuration window for a specification. At the bottom, there is a section with a checked checkbox labeled 'Promote alert to action on'. Below this checkbox are two input fields: 'Alerts, From' and 'Results', both containing the value '3'. A red rectangular box highlights this entire section.

Regulation EU GMP Annex 1:

9.11 Monitoring procedures should define the approach to trending. Trends should include, but are not limited to:

- ii. **Consecutive excursions** from alert levels
- A software can include a helpful built-in rule for rolling specifications

Exceeding Levels - Excursions

Department Map: B1 / Oncology Suite Version: 1

File Print

Building: B1 Department: Oncology Suite Filter by Building

Legend

- Actions
- Alerts
- In Spec
- Promote alert to action

Show Results
 Show Micro-IDs
 Show Personnel
 Show Equipment

Legend Filter... Cancel

Approved By: Sheba Zaman May 24, 2022

- Based on the built-in rolling specification rule, a tool for viewing your excursions on a map is helpful
- Capabilities can include to view a heat map by room or suite / department
- Ability to filter and view the map excursions and other information. Include a detailed report

Exceeding Levels - Excursions

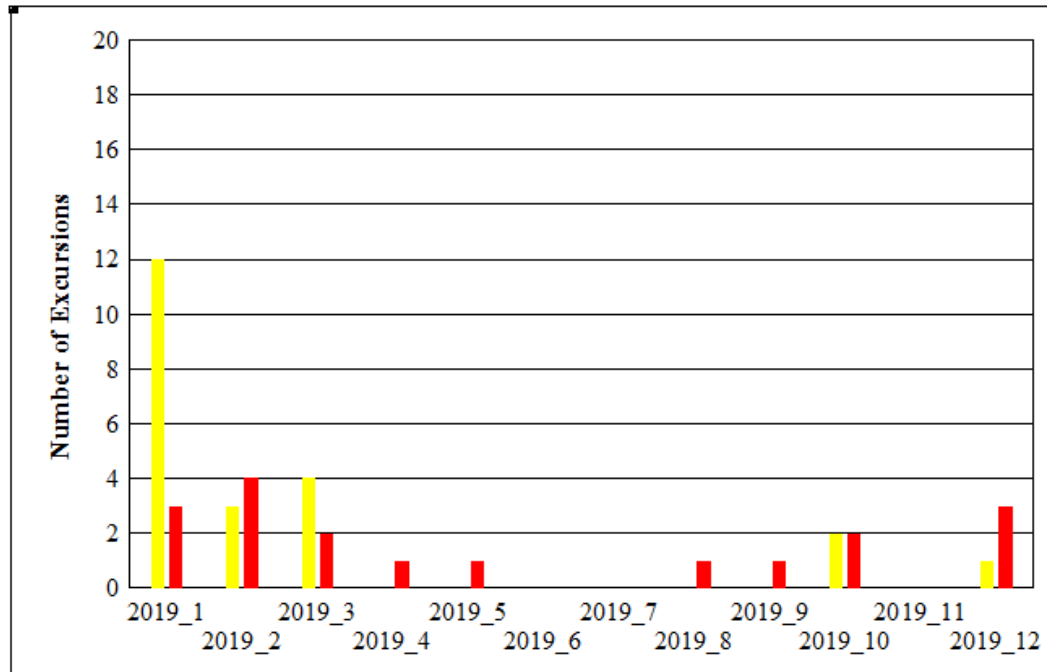
Summary Excursion Report

Filter by:

(For Total) Date test done = From Jan 1, 2019 To Dec 31, 2019

Room = 105, 147, 180, 254, 305

Site = Novatek Global



Date test done	Alerts	Actions	Total Samples No.	Alert %	Action %
Jan 2019	12	3	1,071	1.12	0.28
Feb 2019	3	4	840	0.36	0.48
Mar 2019	4	2	1,028	0.39	0.19
Apr 2019	0	1	135	0.00	0.74
May 2019	0	1	208	0.00	0.48

- Ability to view a list of excursions by area, date range, type of sampling, type of microorganisms found, separately for personnel, etc.
- Ability to have a calculated 'alert rate'.

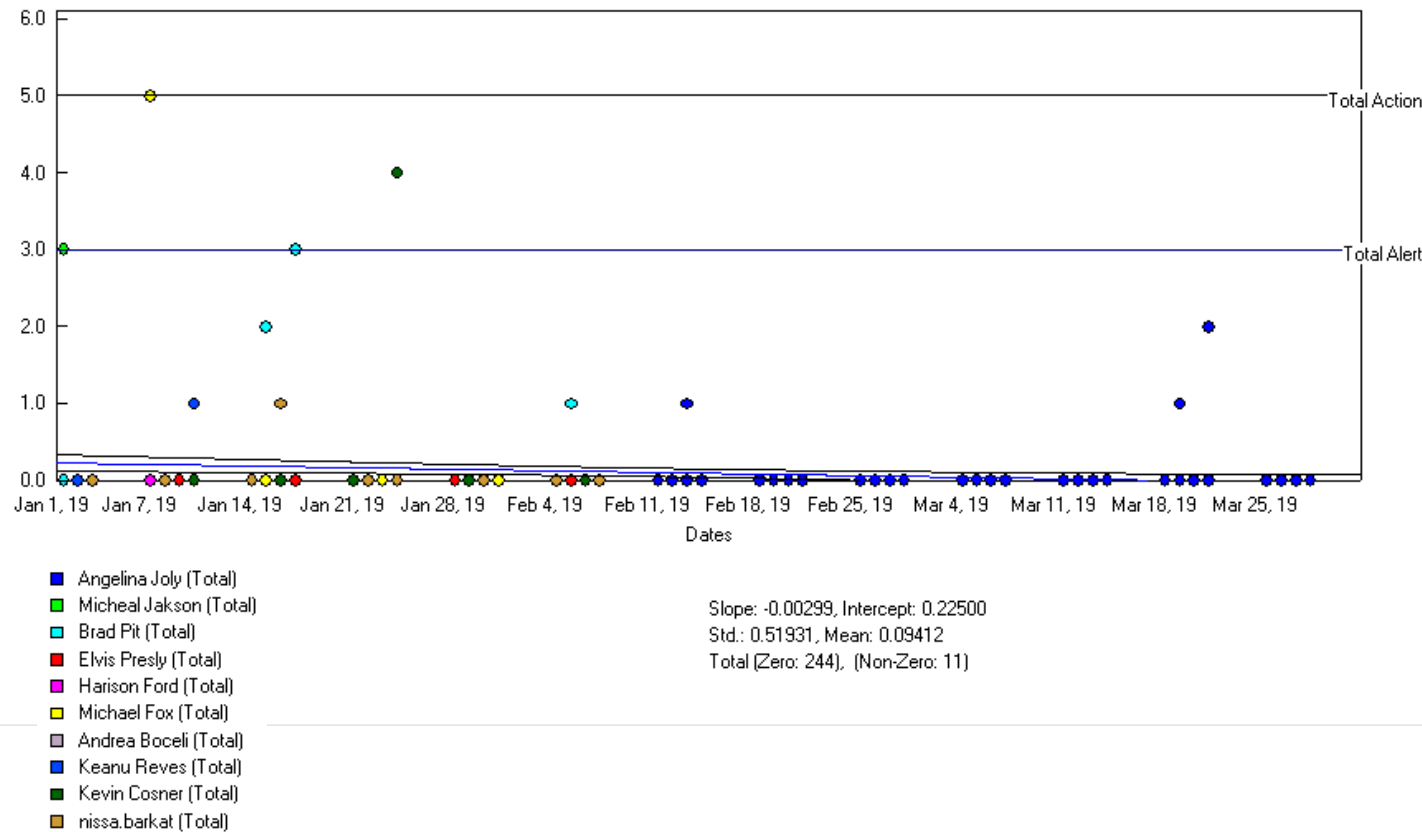
REGULATIONS

EU GMP Annex 1

7.6 There should be systems in place for the disqualification of personnel from working in or given unsupervised entry into cleanrooms that is based on aspects including ongoing assessment and/or **identification of an adverse trend from the personnel monitoring programme** and/or after being implicated in a failed APS.

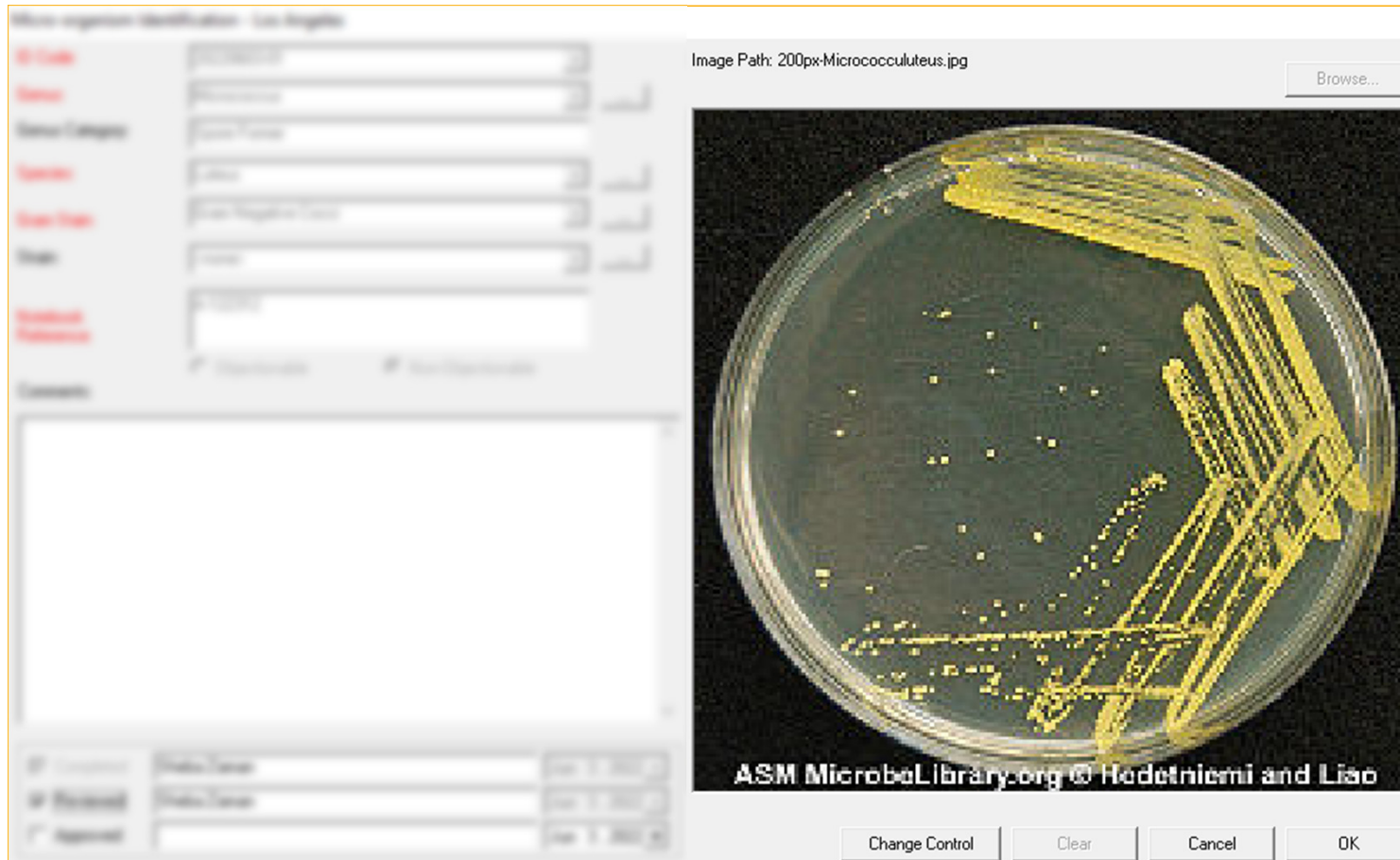
Personnel Monitoring and Pattern Recognition

Enviro Trend Graph Report from Jan 1, 2019 to Mar 31, 2019 H1- Room
 147 And Finger Dabs, Personnel Glove, Personnel Gown, Gowning
 Monitoring



- In the same way that we want to evaluate contamination in a room, we need to perform this on personnel that is accessing these rooms
- If we find higher counts, this may indicate a training or gowning material quality issue
- This information can be correlated with when and where was the person performing other monitoring (handling samples) and seeing if there were also increased counts there

Identification and Trending of Microorganisms

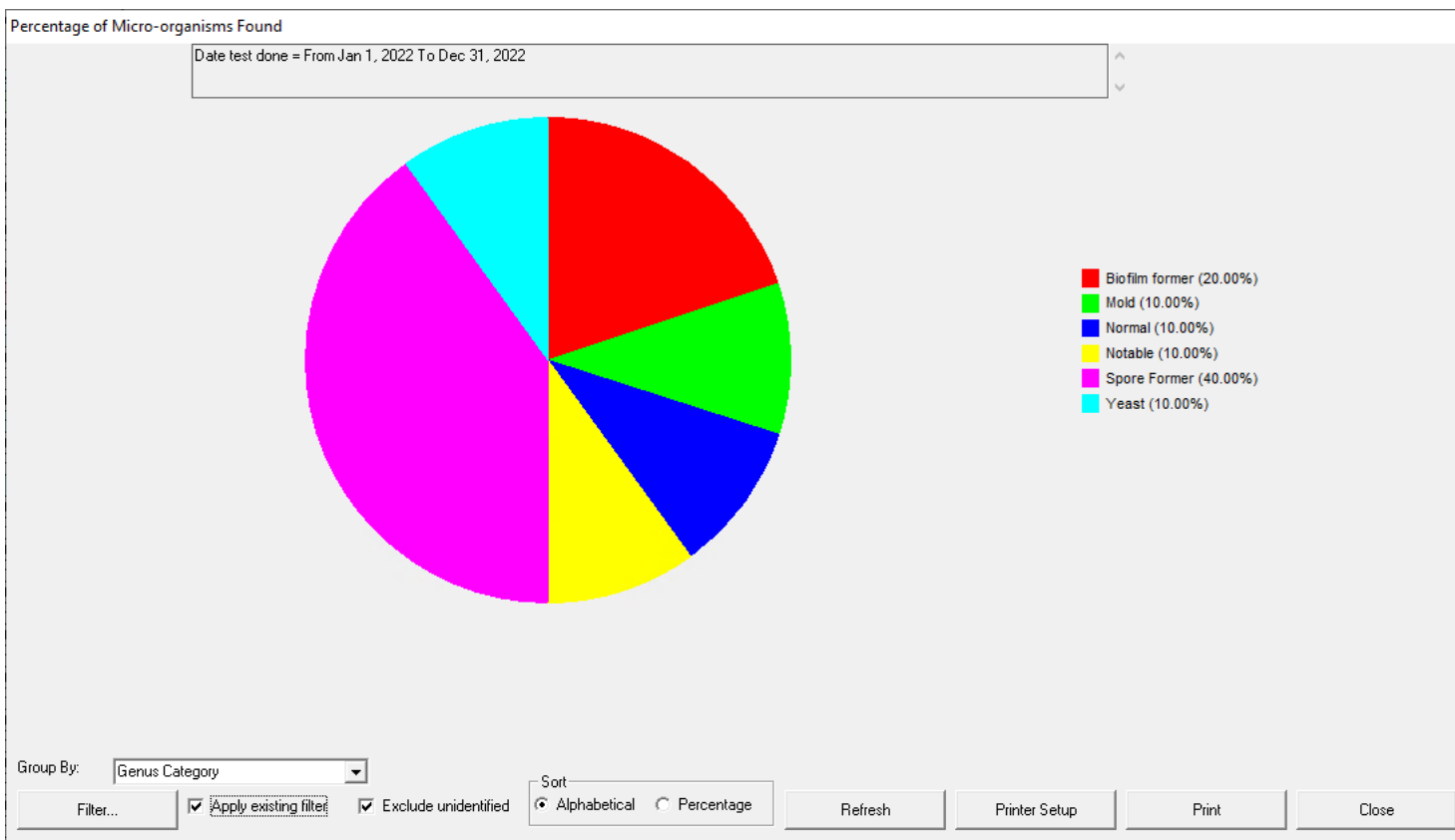


Regulation EU GMP Annex 1:

9.31 Microorganisms detected in the grade A and grade B areas should be identified to **species** level. Consideration should also be given to the identification of microorganisms that may be difficult to control such as **spore-forming** microorganisms and **moulds**.

- Ability to categorize the microorganism

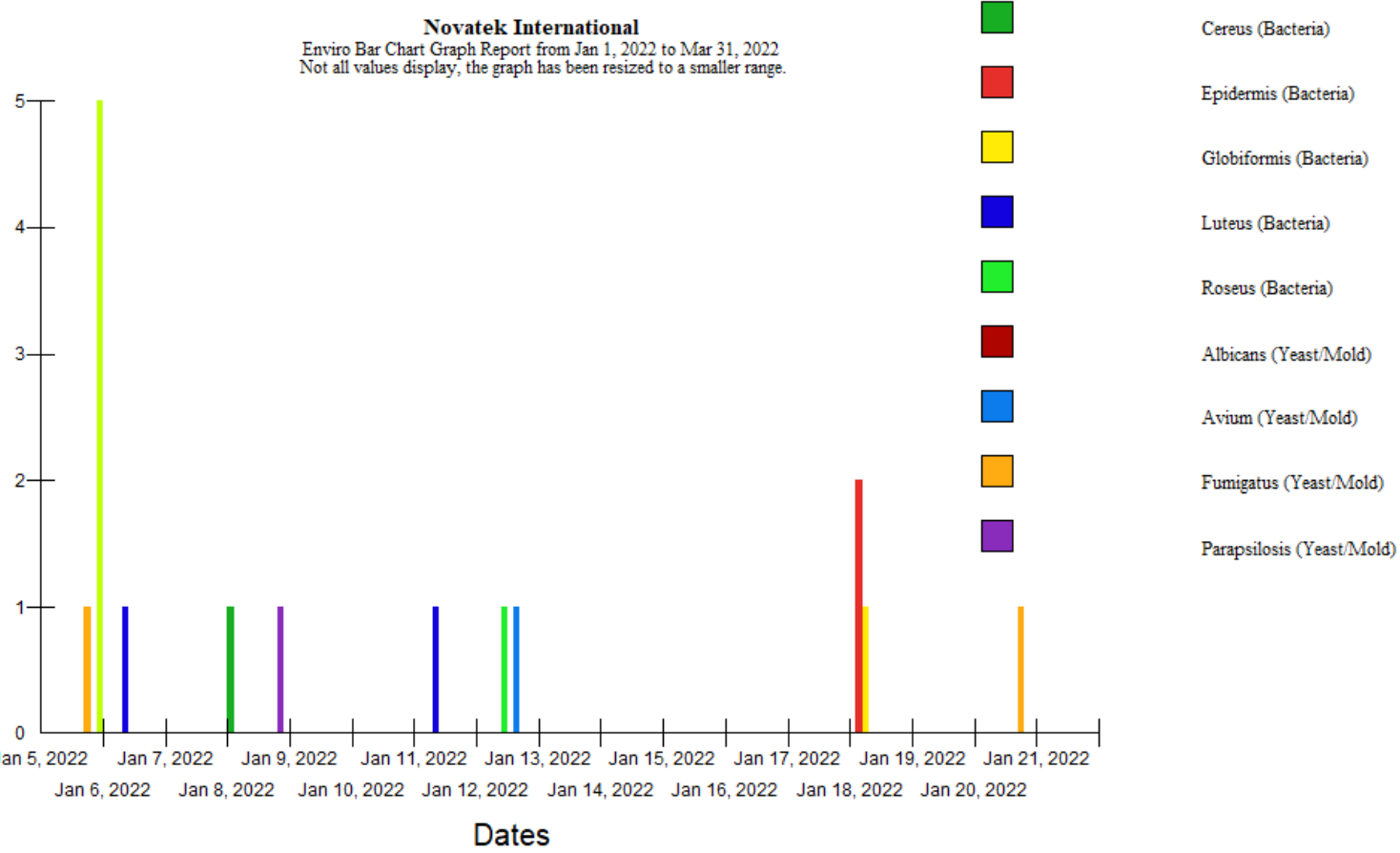
Identification and Trending of Microorganisms



- Ability to receive alerts if a specific microorganism is high risk
- What are the top 10 bugs found in your facilities
- Ability to view other types of distributions to gain an understanding where they are concentrated, under which conditions

Identification and Trending of Microorganisms

Novatek International
 Enviro Bar Chart Graph Report from Jan 1, 2022 to Mar 31, 2022
 Not all values display, the graph has been resized to a smaller range.



Regulation EU GMP 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 class Grade B in the months of April to June.

Batch Release Reporting



Novatek International

Table Batch Report

Filter: Date test done: Apr 1, 2022-Oct 6, 2022
Lot Number: LT108

Approved By	Date test done	Classification	ID Code
Ilona Endisch	May 13, 2022	Grade A - ISO 5	B1 - Room 105
Ilona Endisch	May 13, 2022	Grade A - ISO 5	B1 - Room 105

Summary of Tests

Zeros		Positives		Alerts	
Count	%	Count	%	Count	
31	83.78	5	13.51	0	

ALL DATA IN THIS REPORT IS APPROVED .

* Alert, ** Action, *** Invalid.

Requestor: (ilona.endisch) Ilona Endisch
Print Date: Sep 29, 2022
Print Time: 16:12:17
Time Zone: UTC - 05:00

Regulation EU GMP Annex 1:

9.3 The information from these systems should be used for routine **batch certification/release** and for periodic assessment during process review or investigation.

REGULATIONS

EU GMP Annex 1

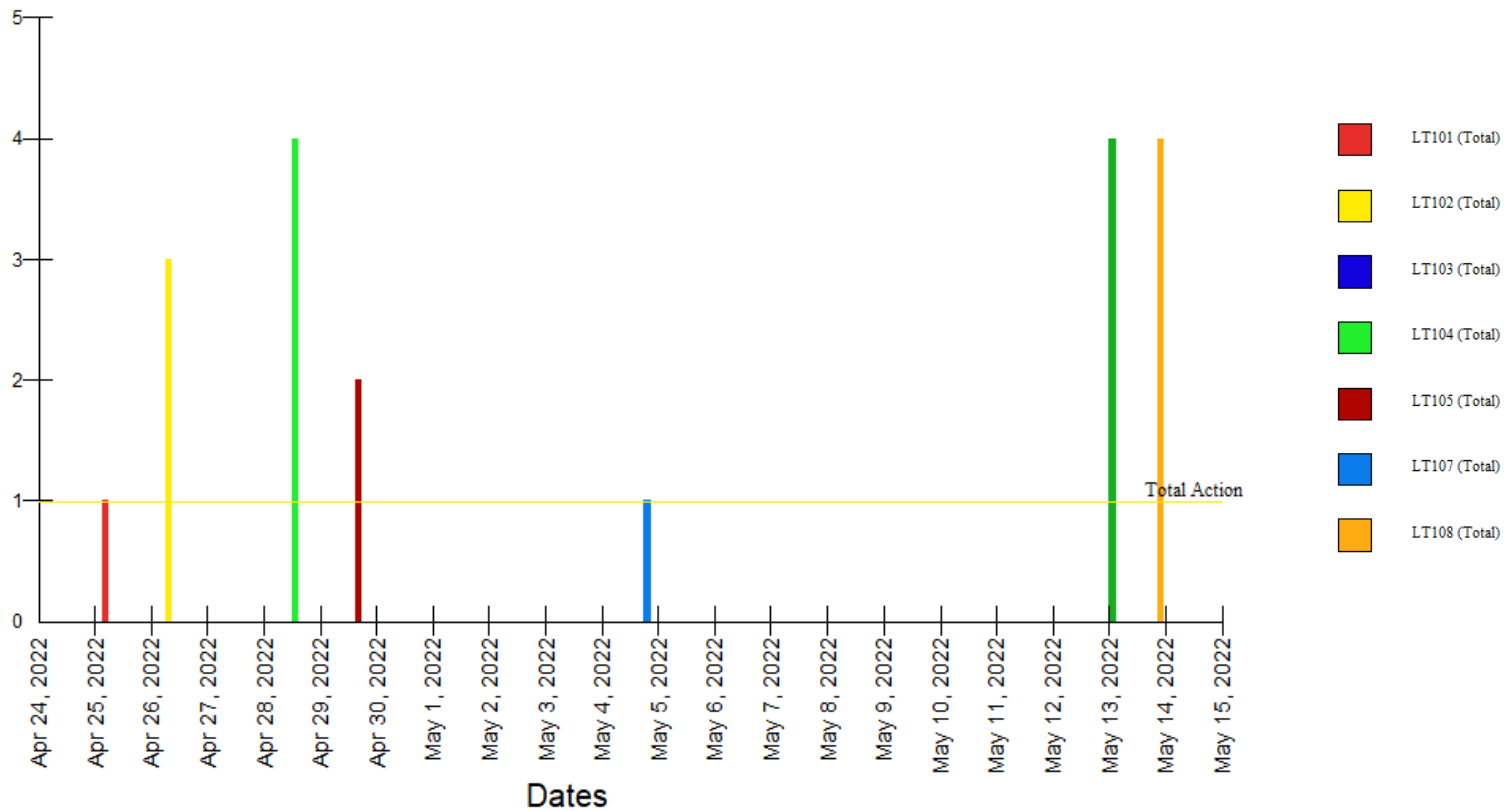
3.2 All non-conformities, such as sterility test failures, environmental monitoring excursions or deviations from established procedures should be adequately **investigated before certification/release of the batch.**

3.2 The investigation should determine the potential impact upon process and product quality and whether any other processes or **batches are potentially impacted.**

Batch Release Reporting

Novatek International

Enviro Bar Chart Graph Report from Apr 24, 2022 to May 15, 2022 Classification: Grade A - ISO 5 Test Type: Active Air, Contact Plate, Passive Air



- Timely notifications for excursions and objectionable organisms
- Tracking excursions
- Investigation tracking tool
- Root Cause and pattern analysis to trace the source of contamination
- Trending to view if other batches were impacted

REGULATIONS

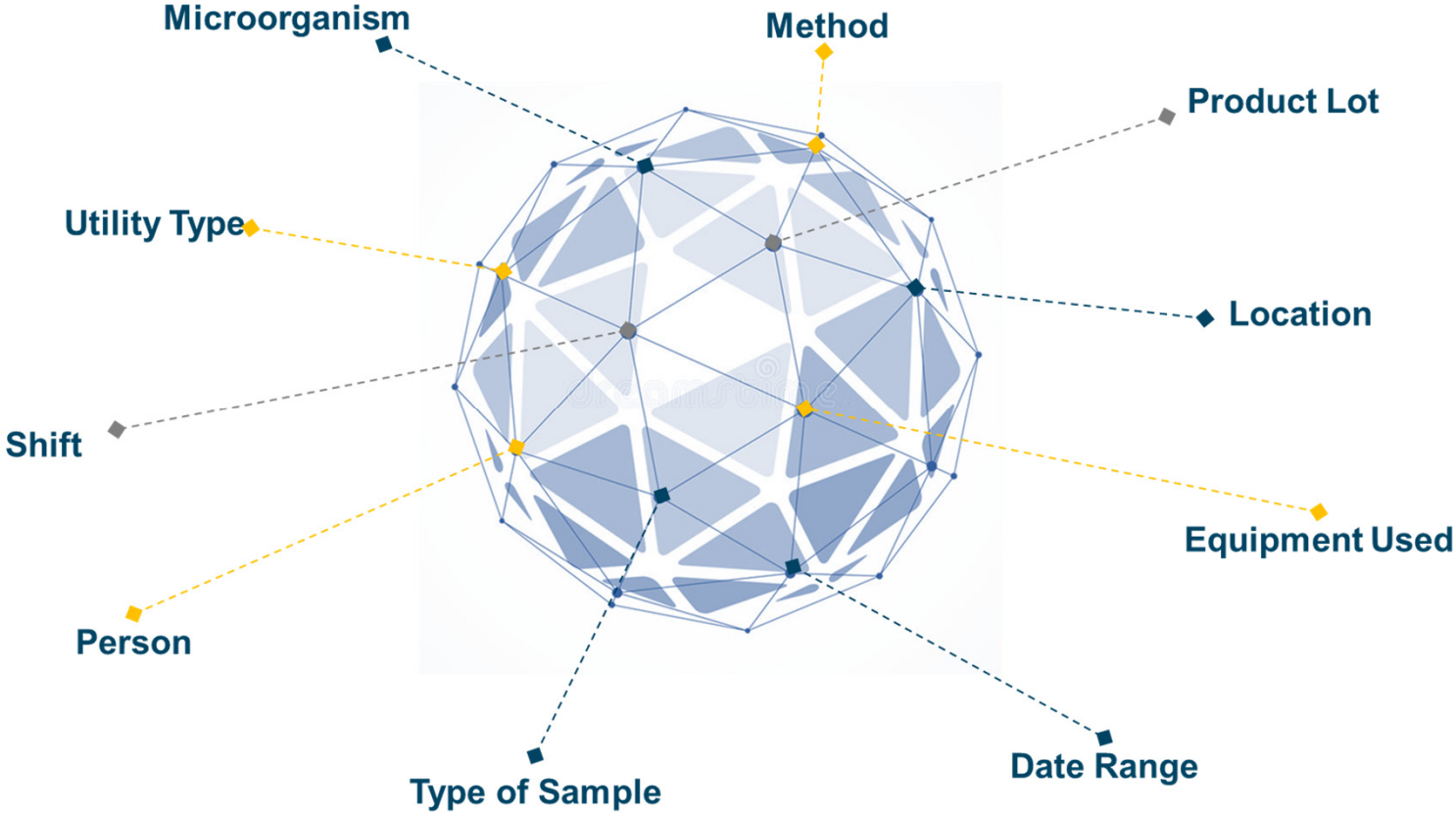
EU GMP Annex 1

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

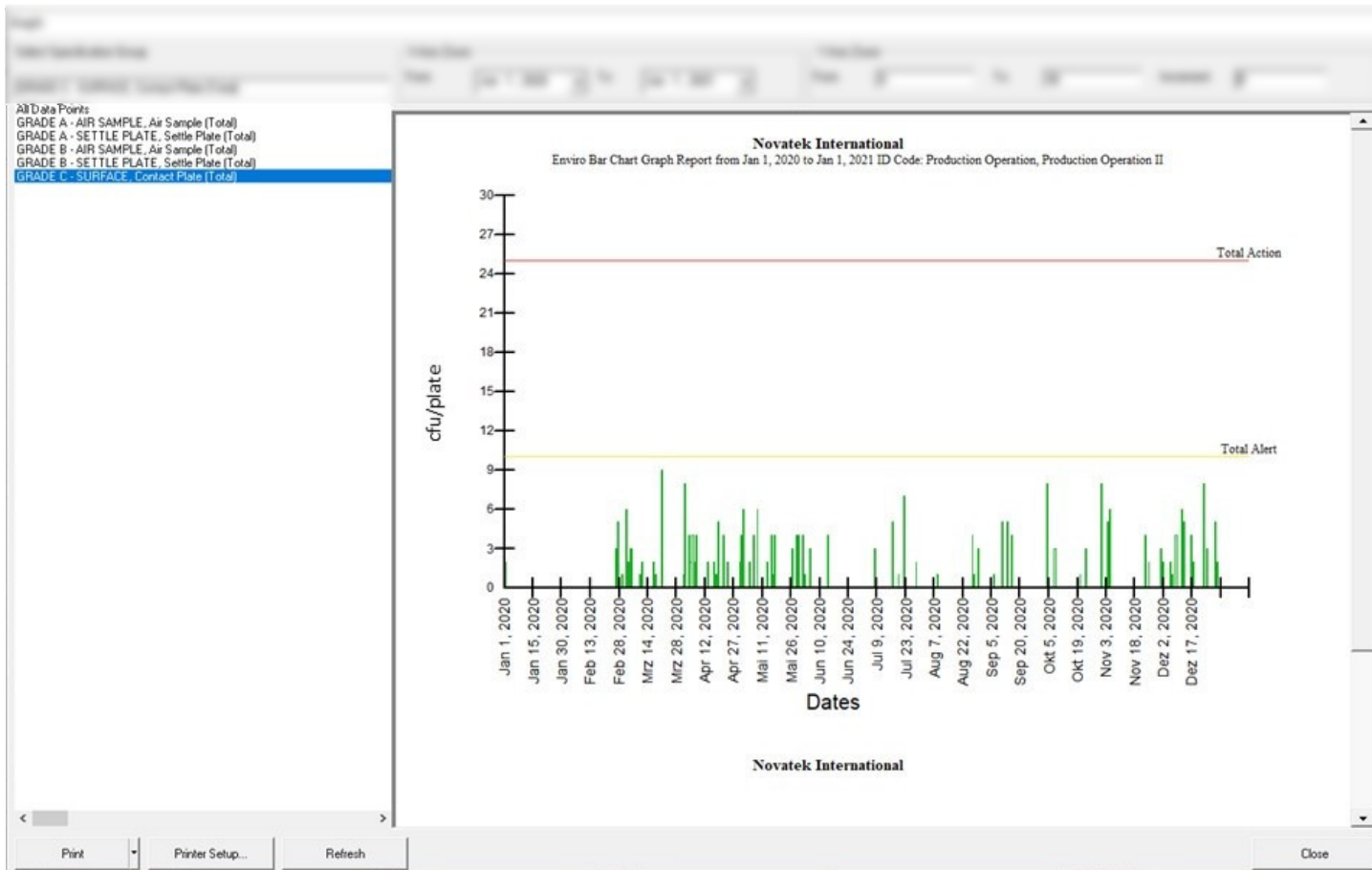
xv. Prevention mechanisms – **trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA)** and the need for comprehensive investigational tools.

xvi. **Continuous improvement** based on information derived from the above

Contamination Control Multifaceted Trending



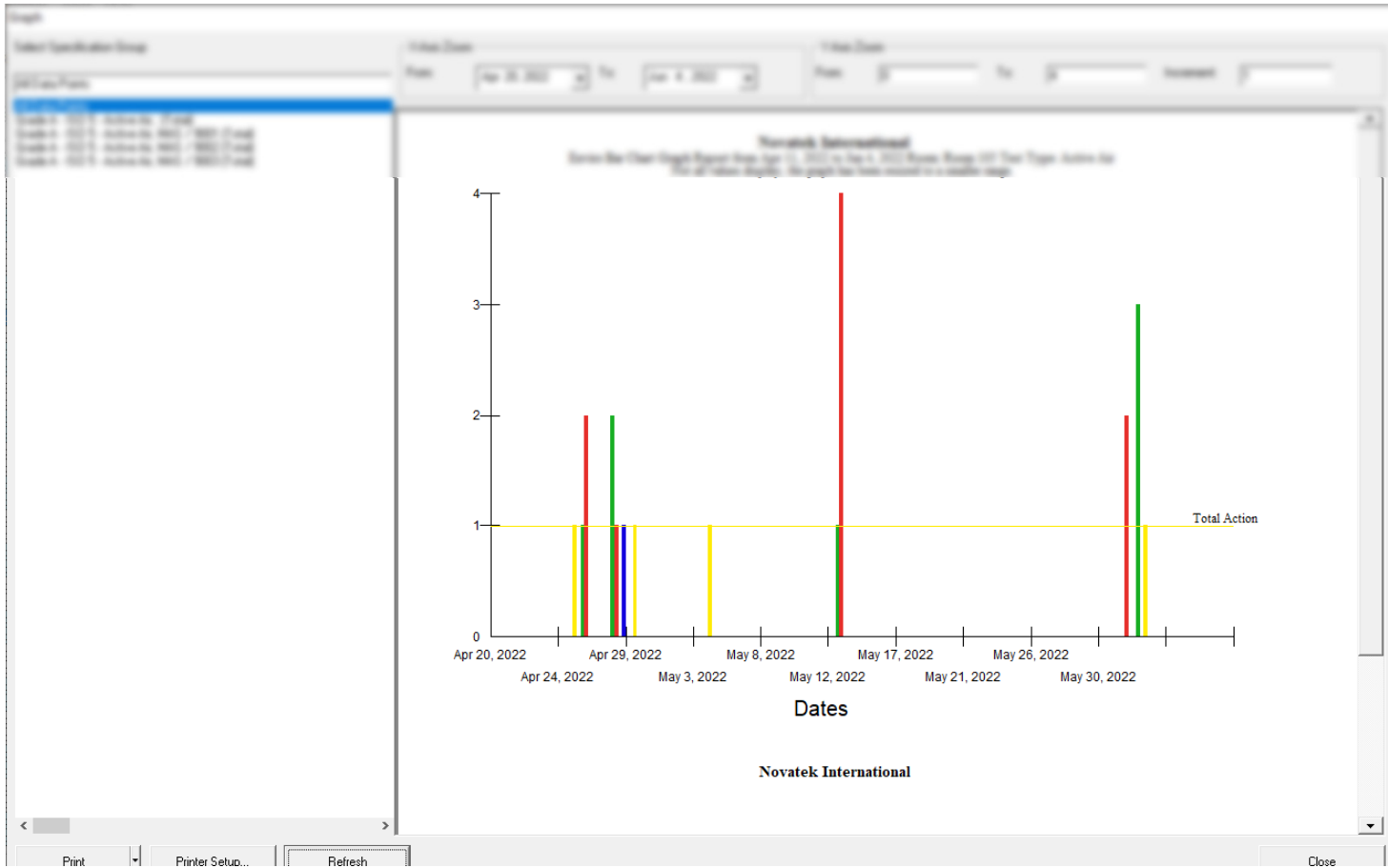
Importance of Rapid Access to Your Trends



Here the interesting part is how you can group the dataset by a category (i.e. classification, sample type, room, etc.) and then click to view them all on the graph in separate colors, or click to view them one by one for a very rapid comparison without having to keep re-filtering the dataset.

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

Importance of Filtering: Trend by Equipment

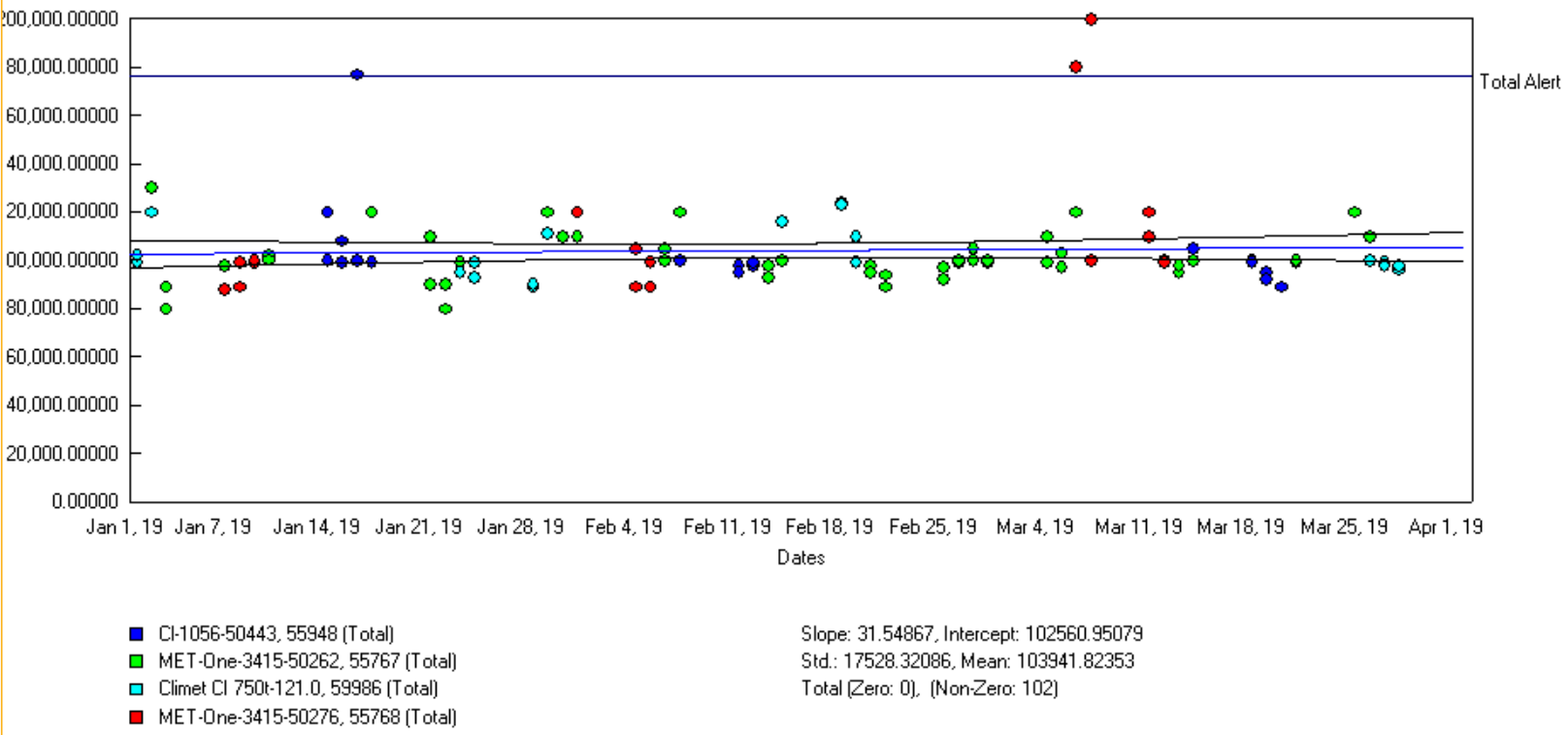


Similar example here where we are trending by equipment

Example: trending air sampling equipment for Grade A

Types of Graphs

Enviro Trend Graph Report from Jan 1, 2019 to Apr 1, 2019 147 And Particle Count 0.5µ
 Not all values display, the graph has been resized to a smaller range.



There are different types of graphs needed for different purposes.

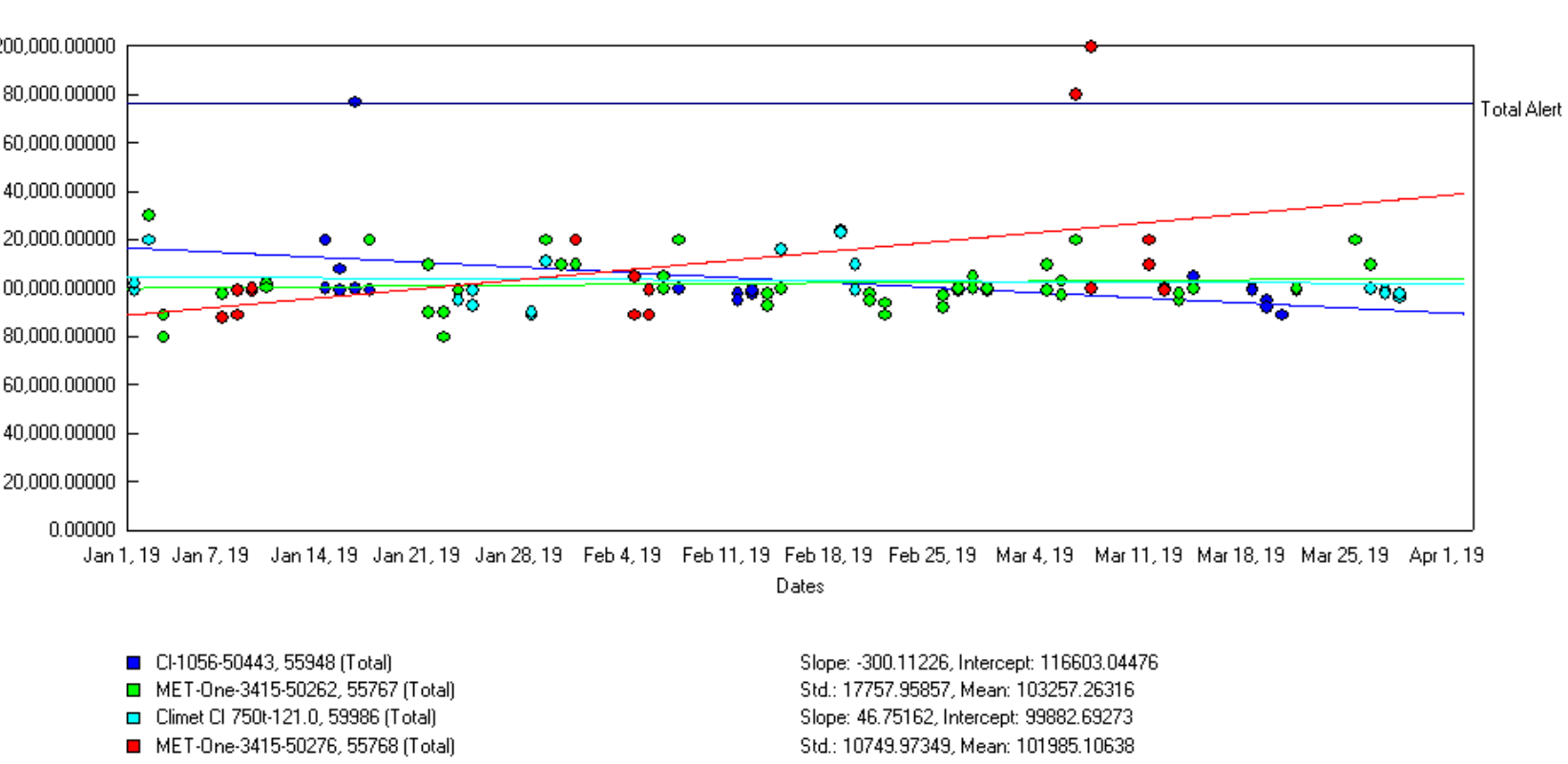
Line charts are useful for trending continuous data and for long-term trending

Bar charts are useful for shorter term trending or for sparse or categorized data

Linear regression are useful for non-zero data (particle counts, utility monitoring, etc.)

Types of Graphs

Enviro Trend Graph Report from Jan 1, 2019 to Apr 1, 2019 147 And Particle Count 0.5μ
 Not all values display, the graph has been resized to a smaller range.



The previous graph pooled the data

This example splits the data and we can see if a line is approaching a level for separate equipment

REGULATIONS

EU GMP 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.

6.13 Regular ongoing **chemical and microbial monitoring of water systems** should be performed to ensure that the water continues to meet compendial expectations.

6.14 **Alert level** excursions should be documented and reviewed, and include an investigation to determine whether the excursion is a single (isolated) event or **if results are indicative of an adverse trend** or system deterioration. Each **action limit** excursion should be investigated to determine the probable **root causes** and any potential impact on the quality of products and manufacturing processes as a result of the use of the water.

6.19 When gases are used in the process, **microbial monitoring of the gas should be performed** periodically at the point of use.

Track the Complete Utility Monitoring Process

NOVATEK
INTERNATIONAL

Novatek International

Print Date: Nov 10, 2022

Print Time: 16:13:56

Certificate of Compliance

REM - Purified Water - Chemical tests EP

Date: Jan 25, 2022

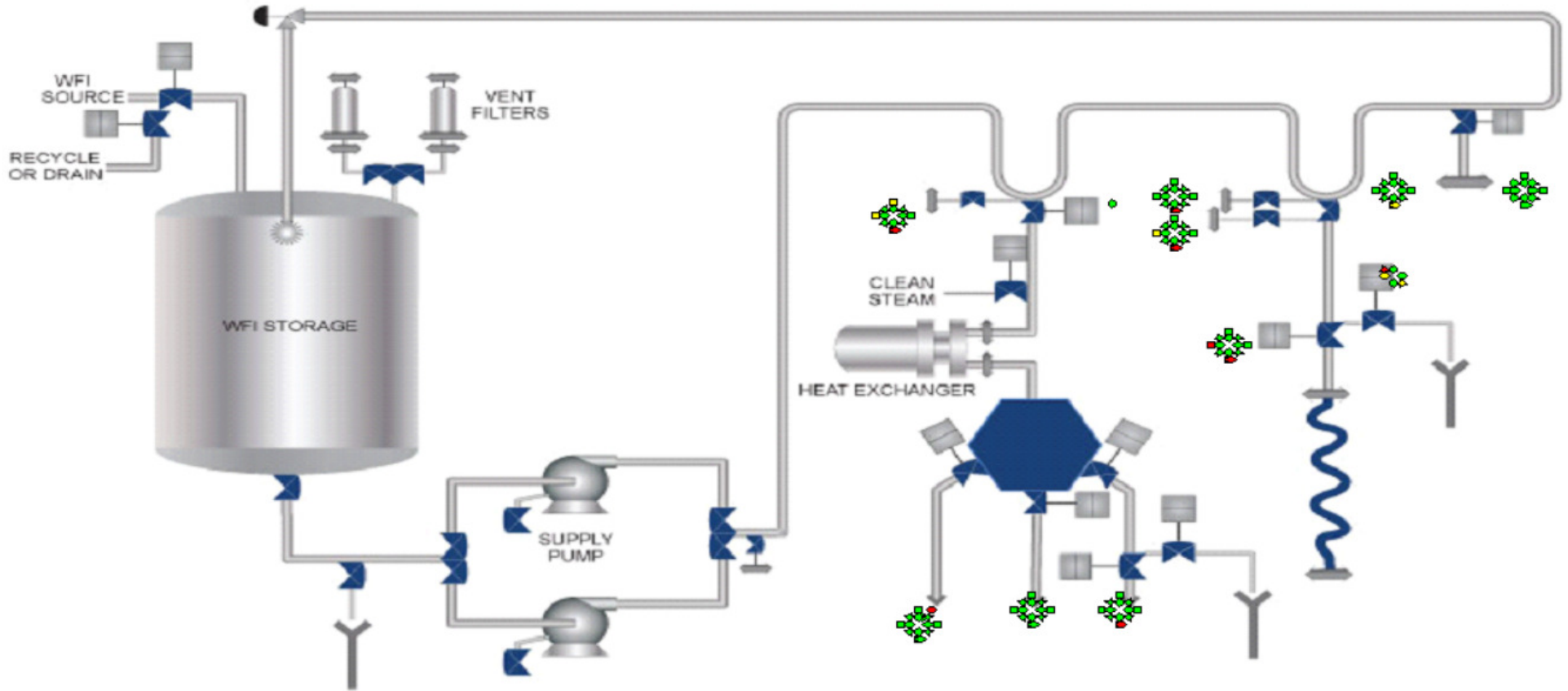
Expires: 28-Jan-2022

Version: 1

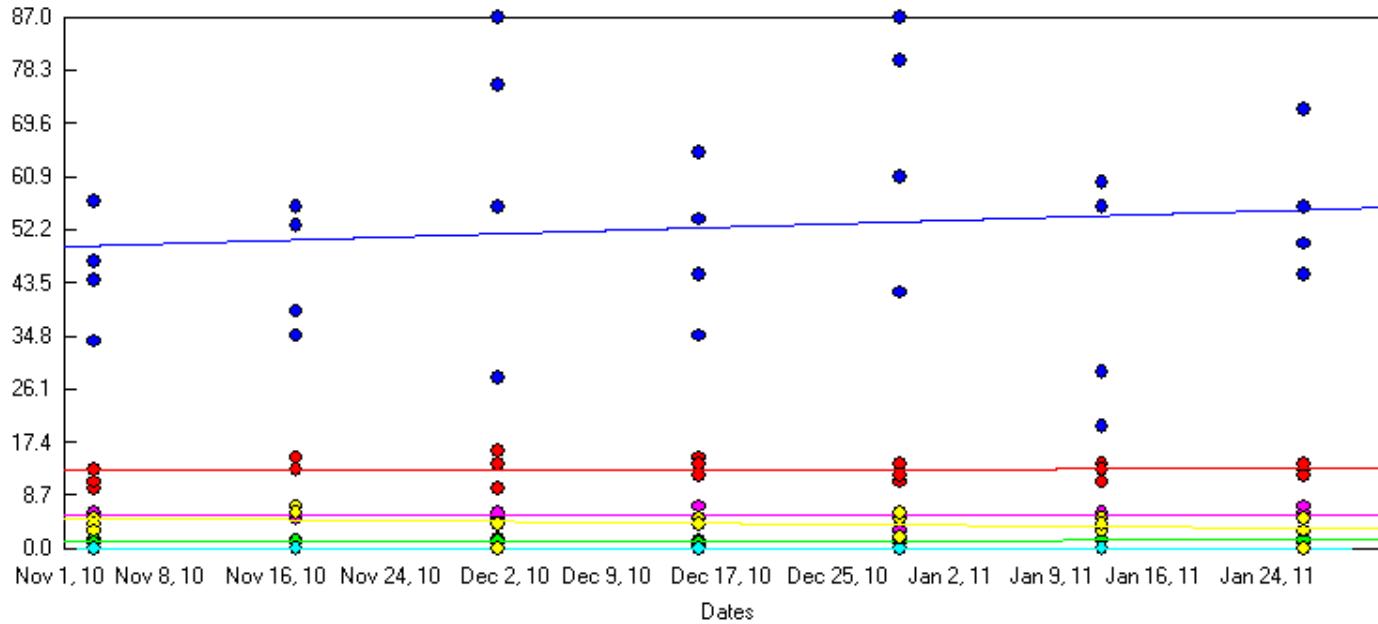
Test Type	Specification	Result	Method Number
Appearance	Clear and Colorless	Conductivity PW - EP	MET-022
Conductivity	Alert: $\leq 1.0 \mu\text{S}/\text{Cm}$ Action: $\leq 4.3 \mu\text{S}/\text{Cm}$	1.3	MET-010
Nitrates $\leq 0.1\text{PPM}$	Alert: $\leq 0.1\text{PPM}$ Action: $\leq 0.2\text{PPM}$	0.1	MET-012
Oxidizable Substances $\leq 0.01\text{M KMnO}_4$	Conforms with 0.02M KMnO_4	Conforms	MET-043
Microbiological monitoring	Alert: $< 100\text{cfu}/\text{mL}$ Action: $< 100\text{cfu}/\text{mL}$	24	MET-023

- Water, Clean Steam, Compressed gas,
- HVAC qualification testing
- Include in your periodic reports and Batch Release reporting

Dispersion Mapping

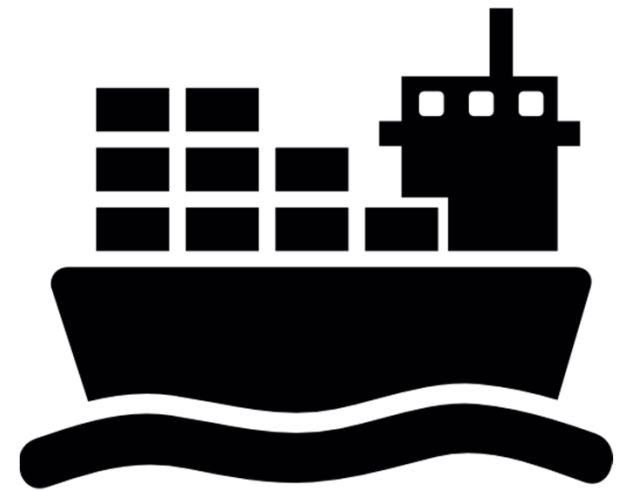
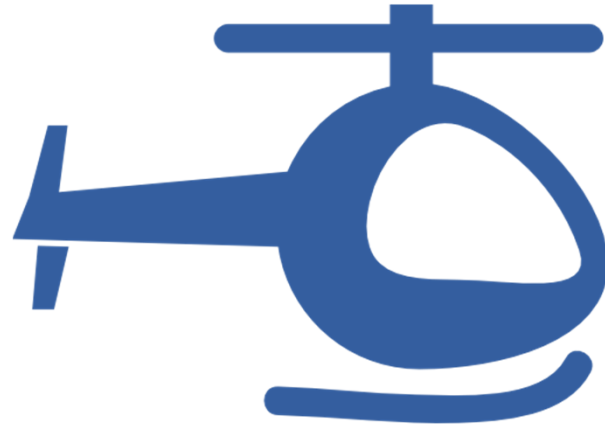


Utility Monitoring Trending



■ TOC (Value)	Slope: 0.07015, Intercept: 49.37755, SD: 17.53560, Mean: 52.46429
■ Conductivity (Value)	Slope: 0.00083, Intercept: 1.26352, SD: 0.24999, Mean: 1.30000
■ LAL (Value)	Slope: -0.00047, Intercept: 0.04219, SD: 0.03886, Mean: 0.02143
■ Temperature (Value)	Slope: 0.00170, Intercept: 12.87755, SD: 1.76075, Mean: 12.95238
■ pH (Value)	Slope: 0.00000, Intercept: 5.61905, SD: 1.05012, Mean: 5.61905
■ Bioburden (Value)	Slope: -0.01956, Intercept: 5.00340, SD: 1.83925, Mean: 4.14286

- Apply similar tools and reasoning as for environmental monitoring
- Trend periodically to have visibility across your process
- Trend to prevent and predict contamination risk
- Trend for investigation, for root cause analysis and pattern recognition



FIT TO PURPOSE

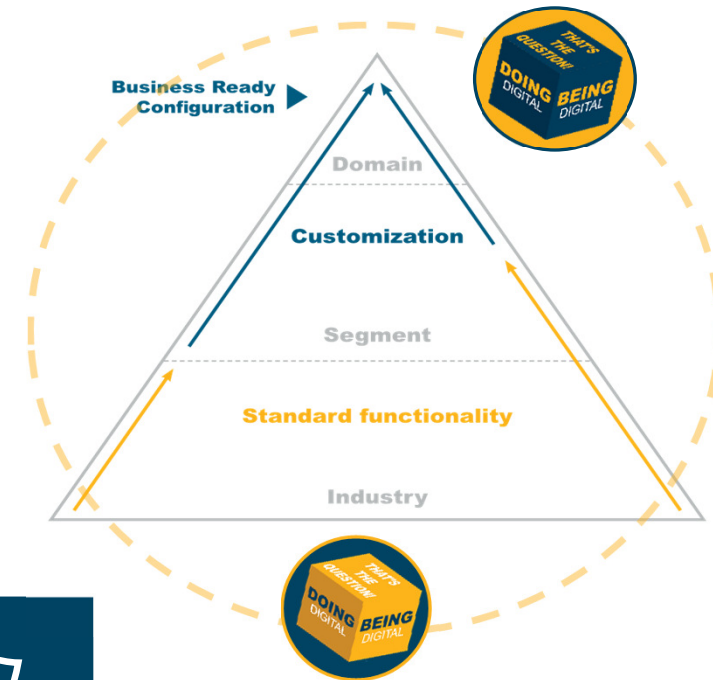


CUSTOMIZATIONS THAT DON'T FIT THE NEED

Process-Based OTS Applications Provide Benefits in Digital Transformation of Pharma Manufacturing & Quality Operations

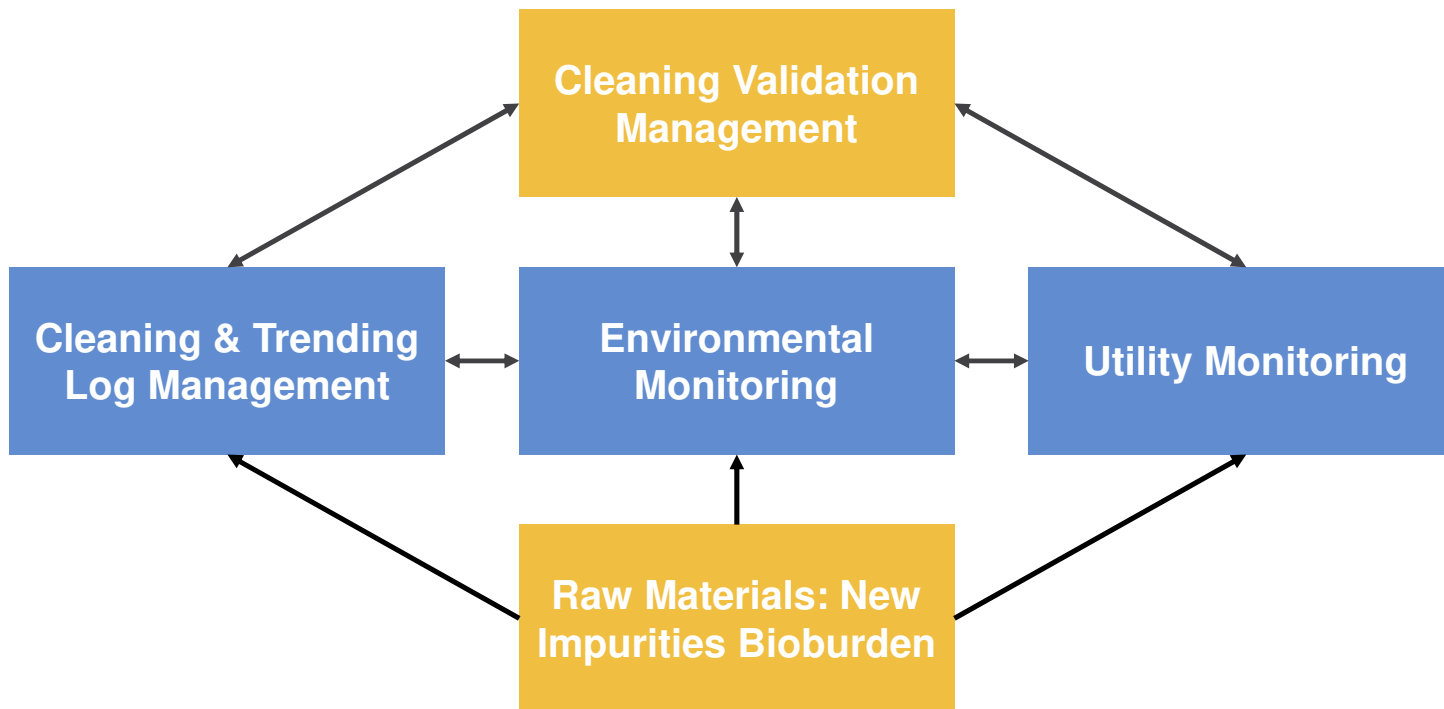
- Reduces data integrity issues
- Does not require a costly and complex introduction into a company.
- Ready for businesses and built to service a realistic and fast return on investment (ROI).
- Does not lock a business into the proprietary technology of a particular system.
- Are easy to integrate with the existing information infrastructure
- Vendor is abreast of industry needs and regulations and updates the system to meet best practices.
- Can be updated quickly
- Provides visibility across the process with a great trending tool
- Is by far the most flexible and cost effective one.

Process-based applications saves you from hammering a triangle in a square!



Total Contamination Control Strategy

Not an Isolated process!



Regulation

EU GMP 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.**

Thank you for your time today!



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Ilona Endisch, BCompSc., is the Associate Director of Product Innovations at Novatek International, with over 20 years of experience in regulated industries. Ilona works with clients, partners, regulatory agencies, consultants, and other experts world-wide to assist in improving quality processes. Ilona is involved with industry training, developing user requirements, performing process mapping, and identifying and managing new product innovations for quality control software. Ilona is active in the industry, giving presentations and performing trainings in topics related to digitalization, contamination control, quality management, cleaning validation, risk assessment, and other areas. Ilona was a trainer at PDA-TRI for many years.