Data Analysis for an Online Water Bioburden Analyzer

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Evaluation of an Alternative Microbiological Method

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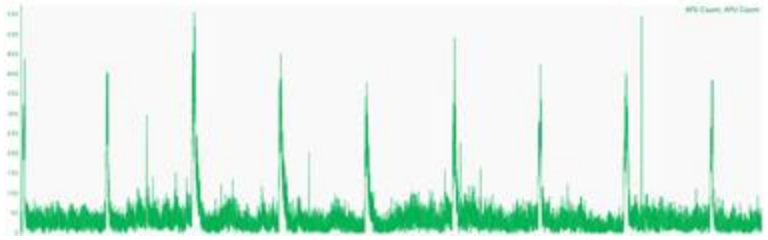
Data Analysis for an Online Water Bioburden Analyzer using the Seeq Data Analytics Platform

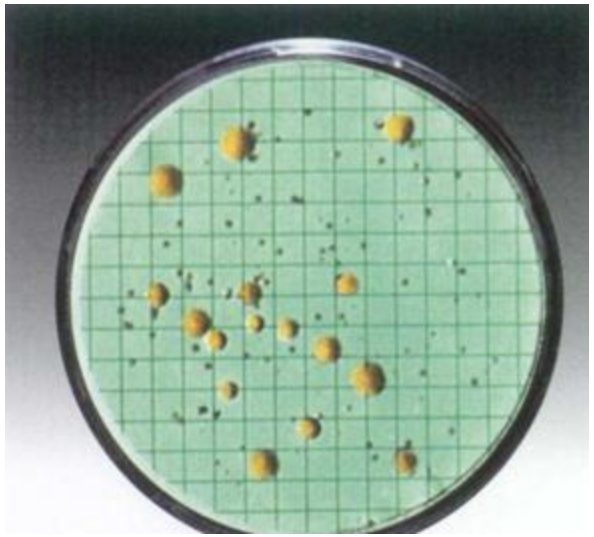
Background

- **Importance of real time data in Drug Substance Manufacturing**
  - Current Microbiology methods are growth based and deliver results for utility water monitoring in 5-7 days
    - Need to get results faster in order to reduce risk to processing and release product faster
  - Solution is Bio-fluorescent Particle Counters (BFPC)generally and specifically for analysis of water a Online Water Bioburden Analyzer (OWBA)
    - Delivers results real time



Challenge of Implementing OWBA

- **Current method reports results in Colony Forming Units (CFU) (ex. 3 CFU/100mL)**
- **OWBA reports out in Auto Fluorescent Units (AFU) (ex. 100 AFU/100ml)**
  - CFU and AFU are not comparable as a CFU is a colony of cell vs. an AFU which could be a single cell



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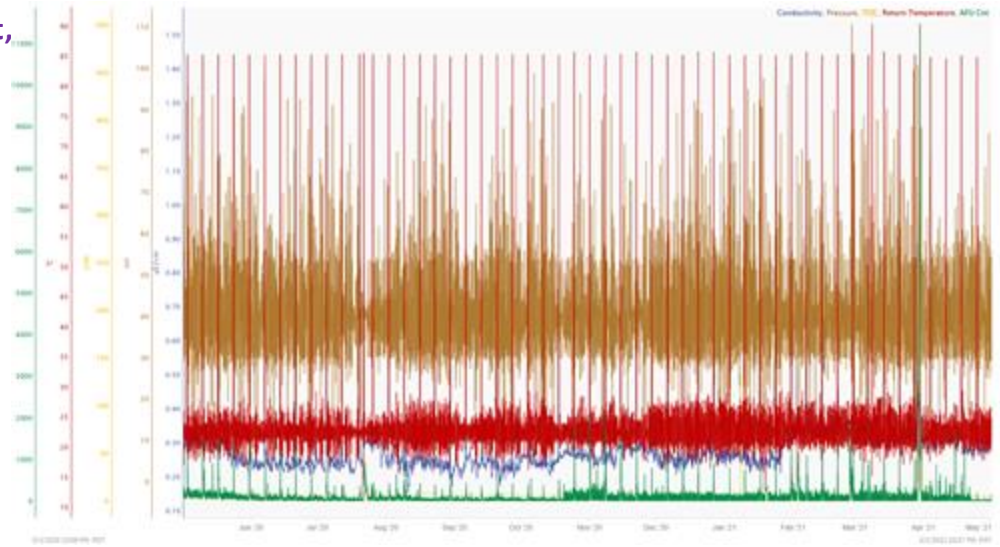
CHALLENGE

- **Bio-fluorescent particle counters generate data in significantly higher volumes than the traditional growth-based methods** currently used to monitor viable microorganisms in regulated utility water systems.
- **In addition to the volume of data, the unit of measure is also different, with the current method reporting results in Colony Forming Units (CFU) while the (OWBA) technologies measure in auto-fluorescence units (AFU).**

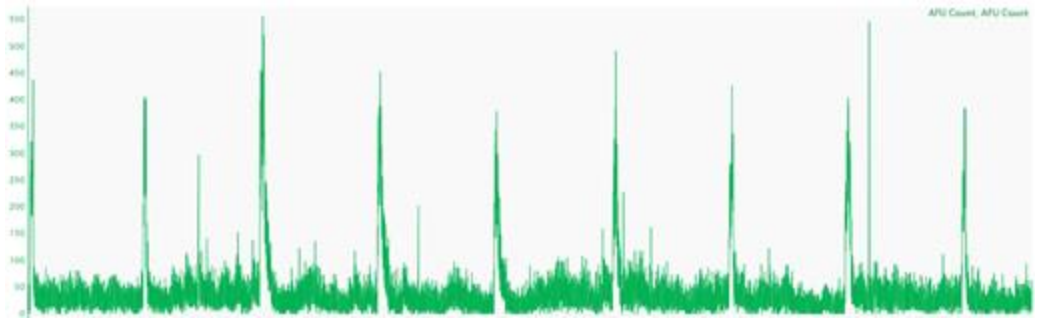


SOLUTION

- **New ways of analyzing data are needed to evaluate complex data sets in real time**

RESULTS

1) **Greater understanding of sensitivity of OWBA unit and its relationship to CFU**
2) **Loop sanitization efficacy which may lead to operational and environmental benefits (increased manufacturing time and reduction in Carbon footprint)**
3) **Sanitization peak characterization leading to better understanding of process impact to AFU counts**



Genentech
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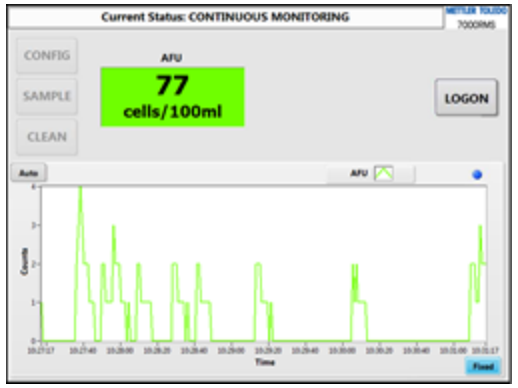
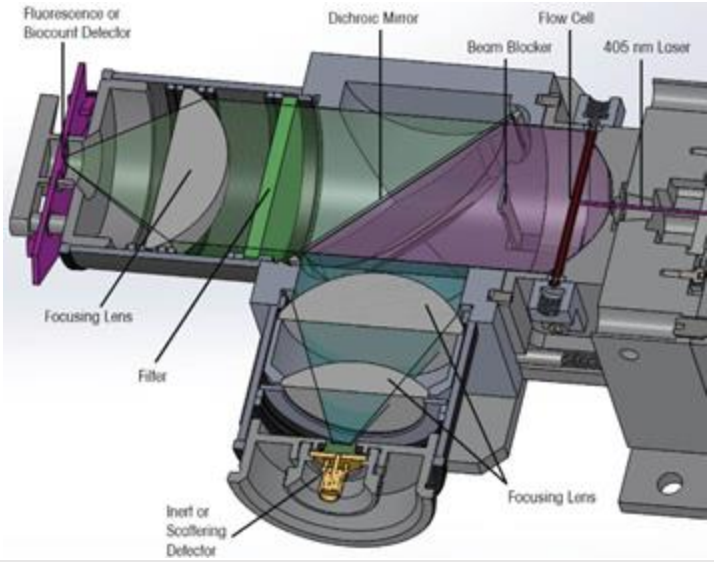
METTLER TOLEDO

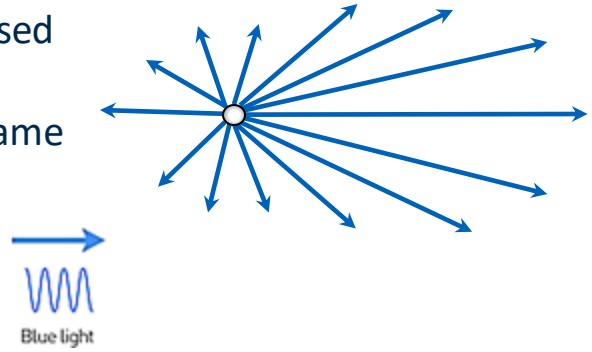
METTLER TOLEDO 7000RMS Leverages Optical Phenomena





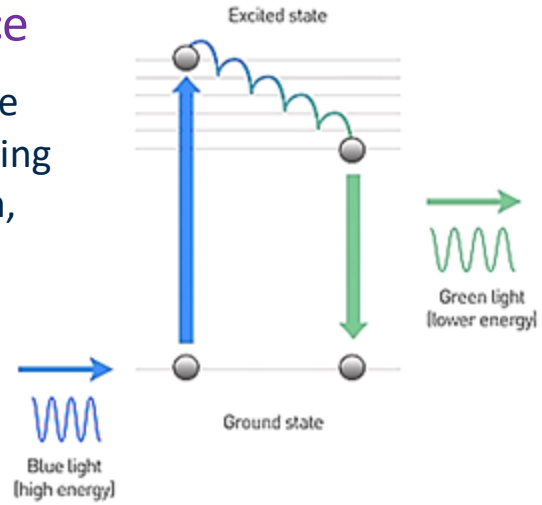
Mie Scattering

Scattering photons at different distances, based on particle size. The scattered light is the same wavelength as the excitation source



Laser Induced Fluorescence

Absorbing photons from the excitation source and emitting light at a longer wavelength, producing fluorescence



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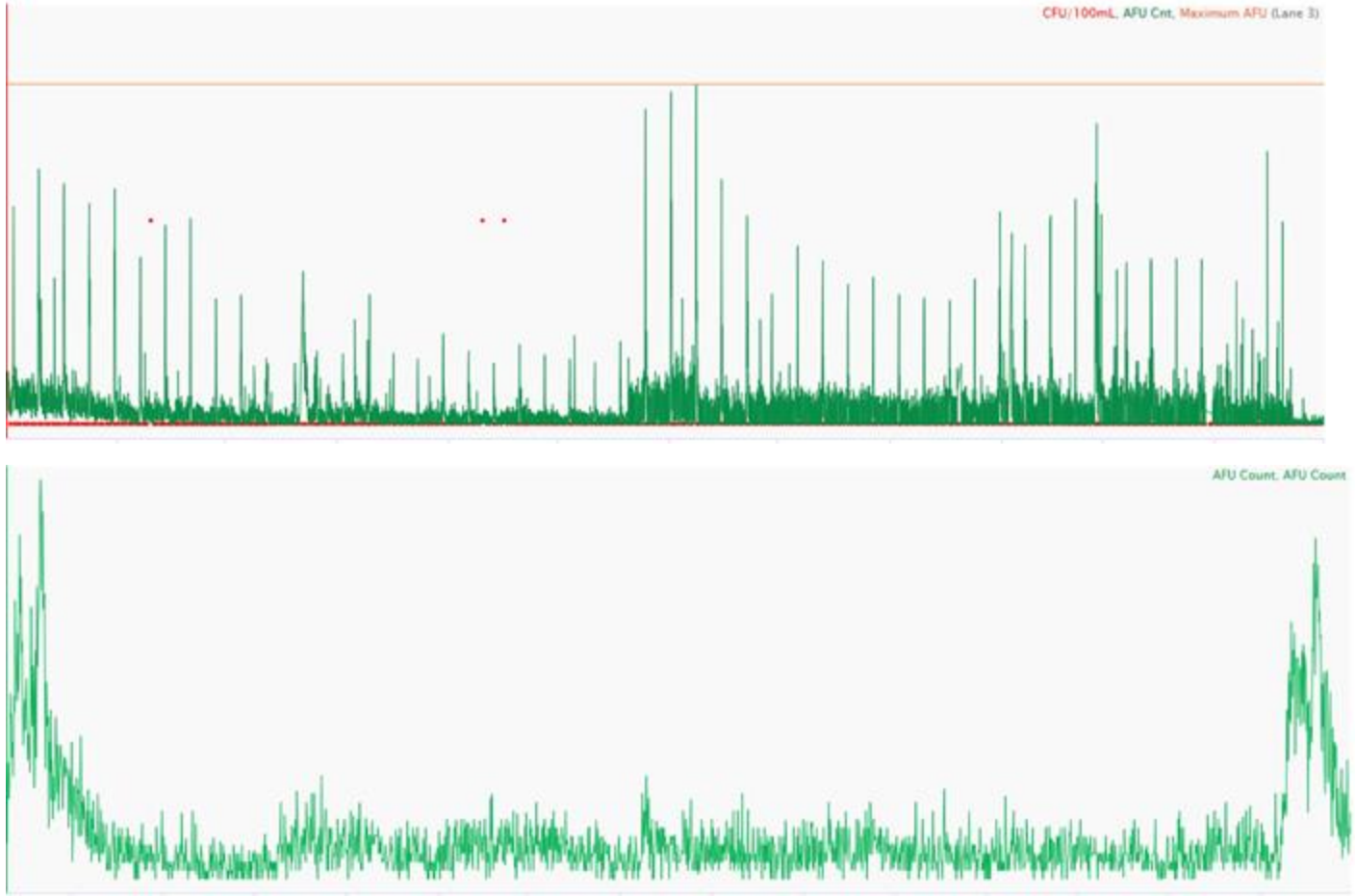
Analysis Using Seeq

- **Evaluated three aspects of the data**
    1. **AFU Peak with CFU overlay**
        a. looking for any trends between AFU and CFU data as well as provided information on the lower AFU limit
    2. **Sanitization of loop evaluation**- Looking for trends from immediately after sanitization to just prior to next sanitization
    3. **Sanitization characterization-** Looking for trends which can be used to profile the sanitization



Methodology and Findings

Samir Mukhida

Data Acquisition

METTLER TOLEDO 7000RMS

- Using Modbus TCP, the AFU data is fed to an Gateway device linked to Emerson DeltaV Distributed Control System (DCS).
  - The 7000RMS is configured to send data for every 100mL being processed.
  - With the a fixed flow rate of 30mL/min, new data is sent every 3m20s.

Conventional CFU Plate Counts

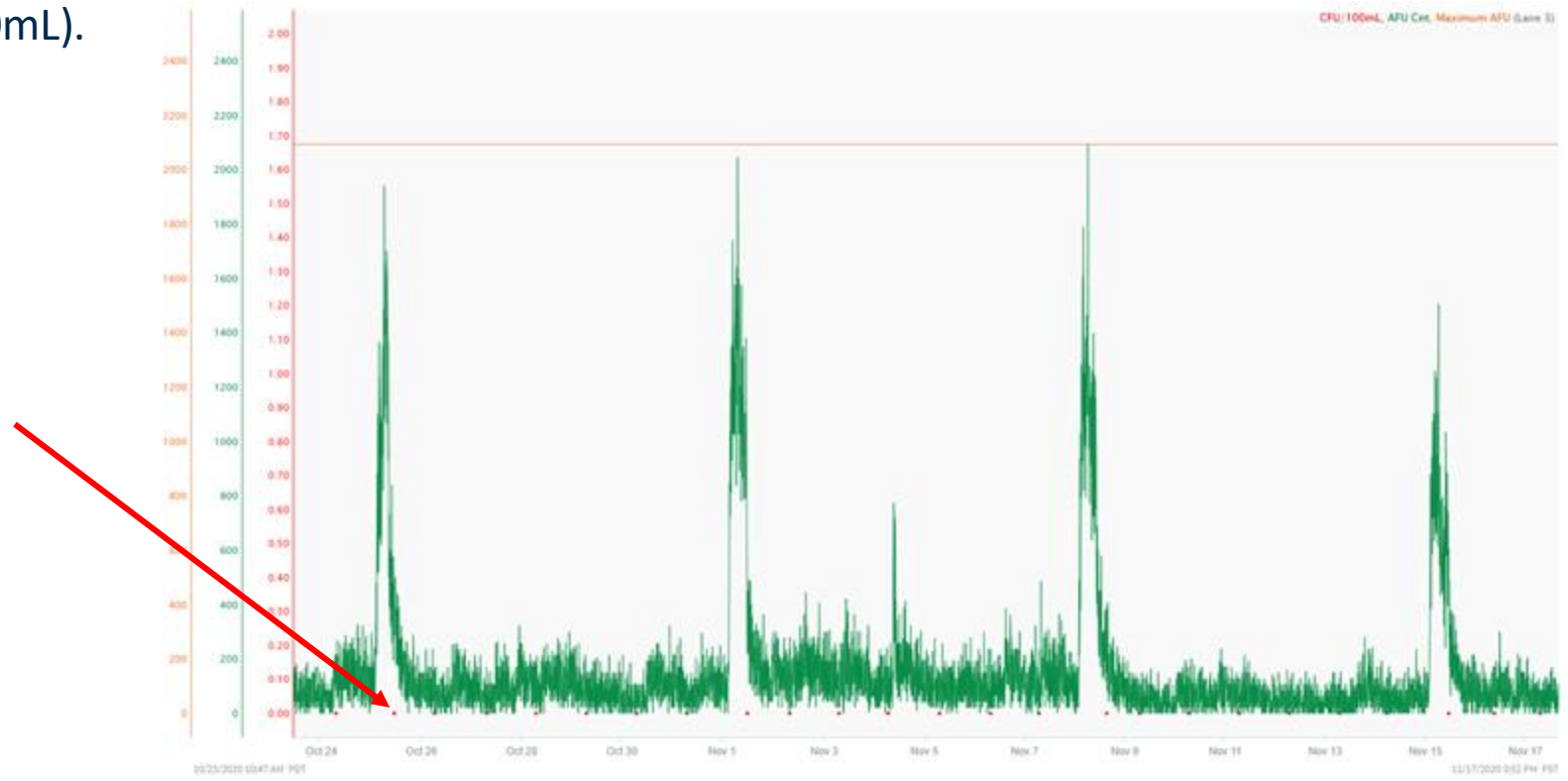
- Water samples are collected manually and tested by QC Analysts.
  - CFU data is recorded by the lab after colony growth.
  - Historical CFU records are exported to an Excel format, which can be pre-processed and manually imported into Seeq.

Other Process Parameters

- Other process parameters measured by a variety of analytical instruments and sensors communicating to the DCS.
  - TOC (Total Organic Carbon)
  - Conductivity
  - Temperature
  - Pressure
- DCS data is recorded to OSIsoft PI Historian
- The Historian is connected to the Seeq application, feeding live data into Workbench and Organizer dashboards.

Sensitivity of Real Time Monitoring Platform

- While the plant routinely recovers 0 CFU during daily discrete sampling events, shown by the red dots, continuous AFU data can yield enhanced status of the water system.
  - This highlights the limitations of the existing growth-based detection method. The samples represent our current knowledge of the system.
  - Seeq was used to find the maximum AFU level at which CFU counts remained in specification (<10 CFU/100mL).

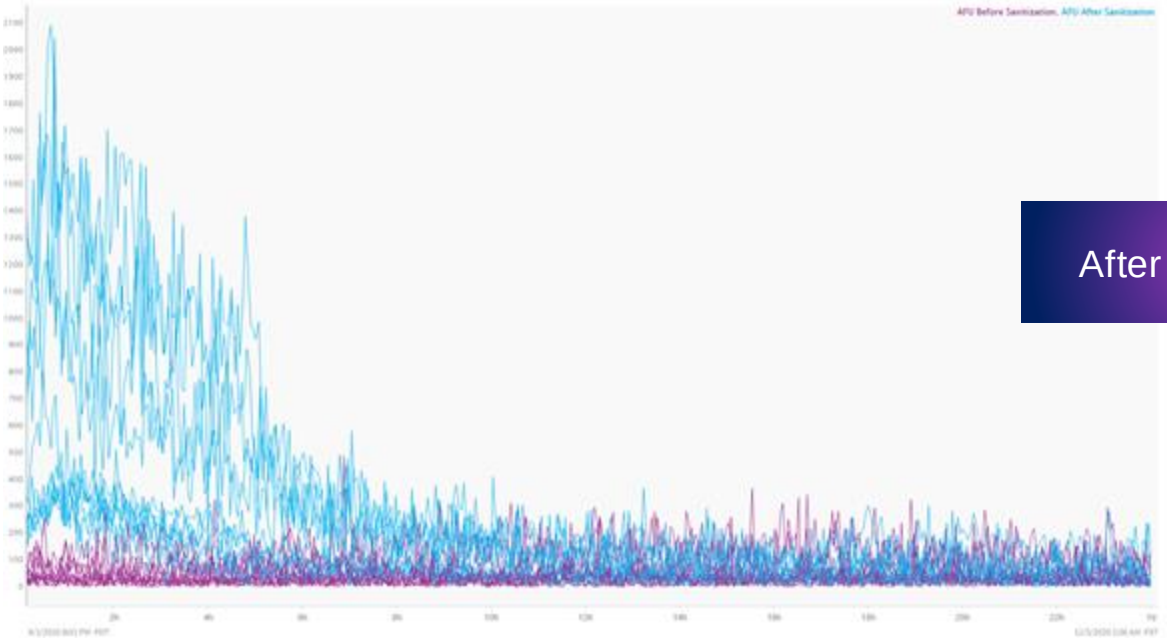


Extending Time Between Sanitization

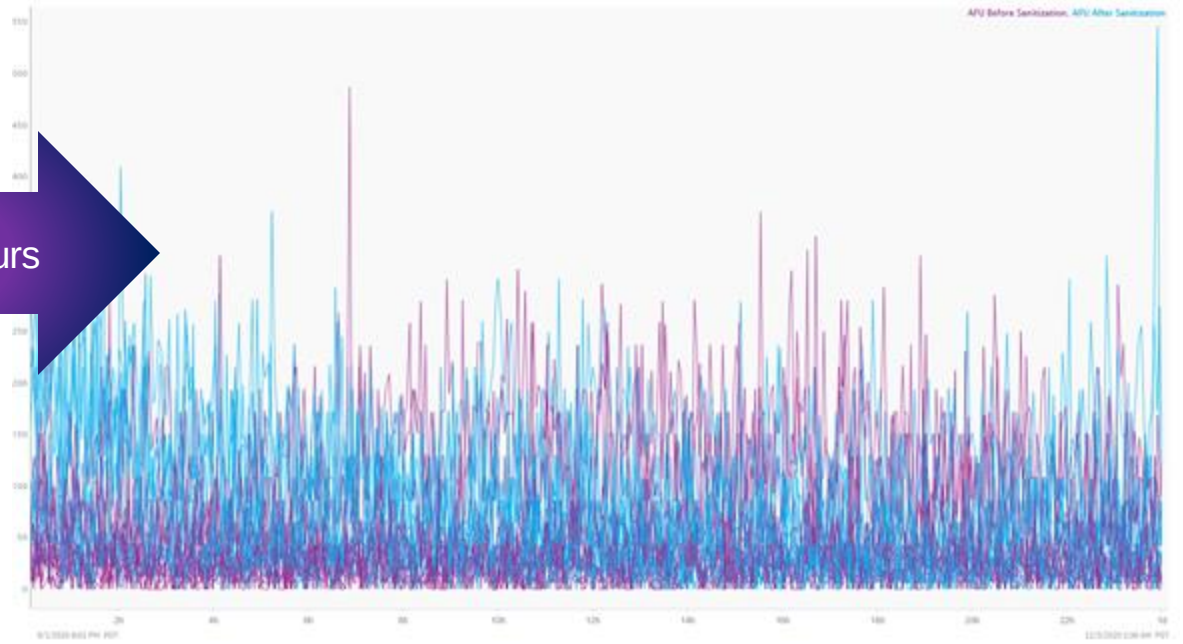
- Using capsules targeting the day immediately **after** and **before** the next sanitization, the AFU levels can be shown to regress back to a baseline.
  - Since there is no discernable increase in counts prior to sanitization, justification can be provided to extend the time between sanitizations.
  - This results in significant increases in production throughput, and decreases in energy consumption.

Production Throughput

Energy Consumption

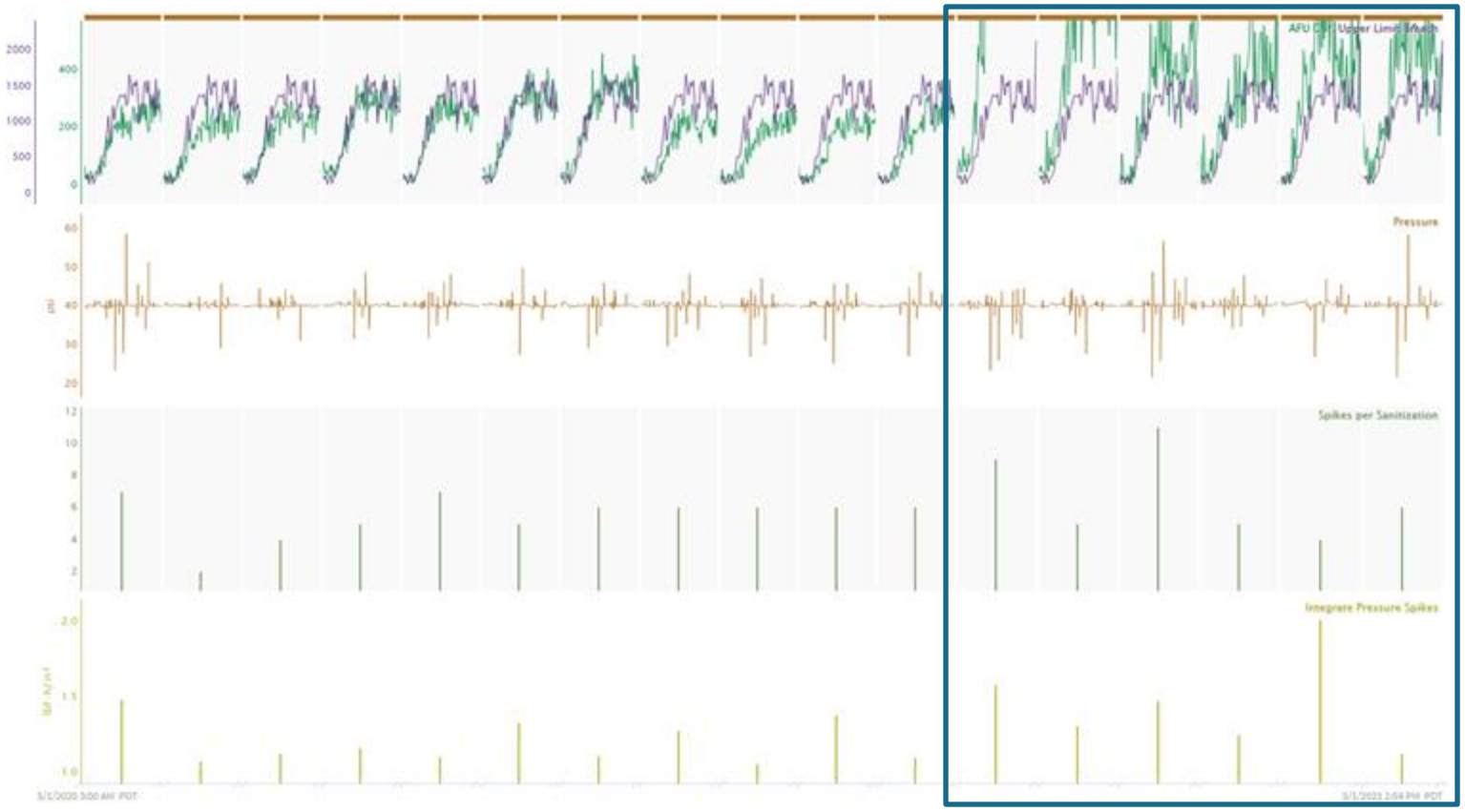


After 8 Hours



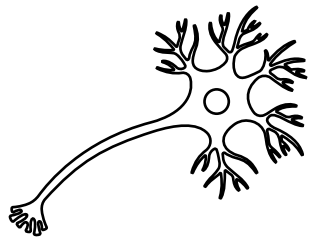
Characterizing Sanitizations

- An AFU model profile for sanitization was calculated using Seeq Reference Profile (5σ).
  - Periods of higher than normal AFU activity were correlated to Pressure changes.
  - Pressure spikes 3PSI above or below the setpoint were counted.
  - Area under/below the pressure curve was also integrated.
  - This relationship corroborates the mechanism of action of the sanitization process, inducing biofilm liberation from pipe walls.

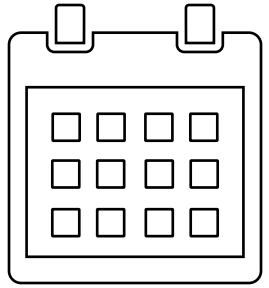


Next Steps

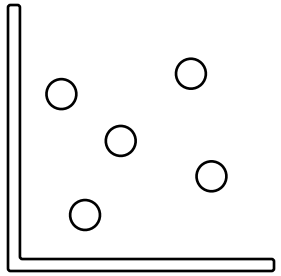
- Establish a predictive measure of water quality.

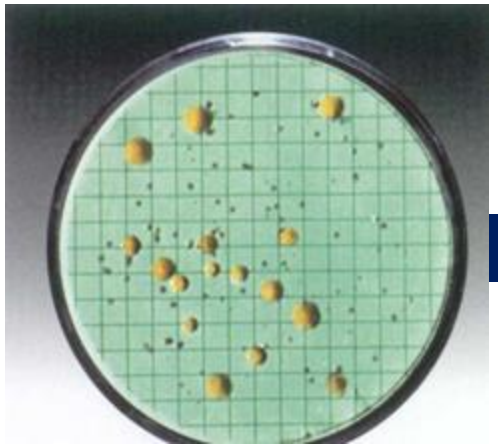


- Finalize alert/action limits and allow the system to be used for GMP.



- Further explore the relationship between other parameters.
  - TOC
  - Conductivity
  - Temperature





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