



# Multivariate Monitoring – Outlier Detection

## Introduction

Drug manufacturing in the modern pharmaceutical industry has become increasingly challenging to control, especially after the introduction of live organisms in the development process since critical process parameters and critical factors inherently present high variability. This increase in process complexity entails unexpected outcomes potentially resulting in significant production inefficiencies.

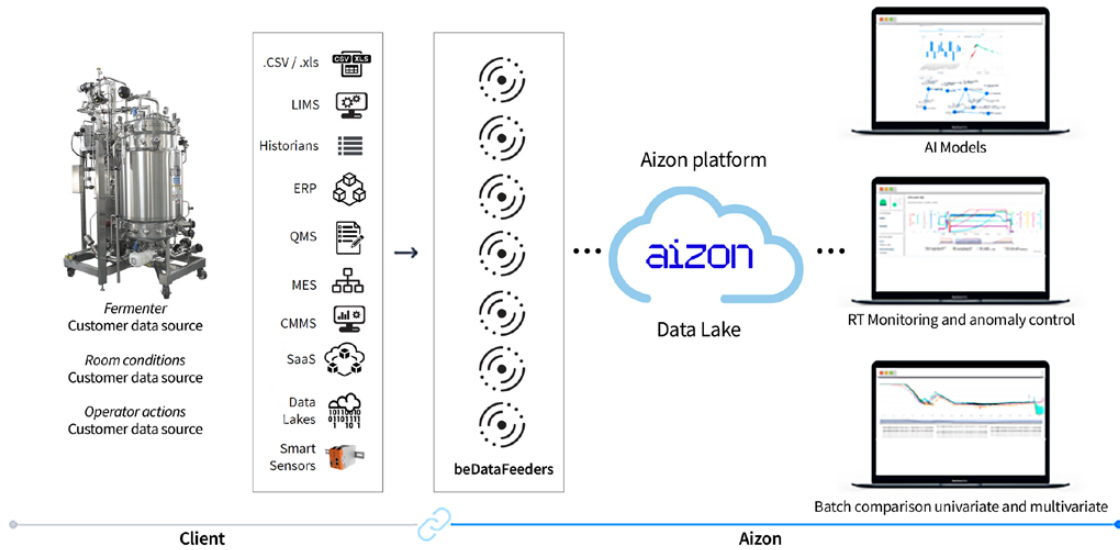
The obtention of multivariate real-time knowledge and the adoption of Industry 4.0 technologies in pharmaceutical manufacturing are increasingly necessary in continuous manufacturing to avoid process deviations which could lead to low efficiency or rejected batches. As ICH guideline Q8 on pharmaceutical development (2017) recommends, monitoring and analyzing the data from just one data source is no longer an option.

The benefits of using Industry 4.0 technologies can be extremely positive, not only from an economic standpoint but also from a Quality Assurance aspect. Being able to fully control the state of a process ensures the capability of the manufacturing team to avoid variability and ensure every batch is exactly right.

## Multivariate monitoring

Pharmaceutical companies require anomaly detection tools for their manufacturing processes. The use of classical alarms monitoring single variables still is a common way of controlling the limits of key process parameters to maintain the process under control. However, process knowledge is limited when the parameters are studied individually and the dependencies between all variables are unknown. For such reasons, multivariate analysis of process data may help to detect anomalies when all the process parameters are studied in the same analysis.

The control of these multivariate operations must be managed under advanced analytics capable of interpreting complex reactions with multiple factors. The variety of information to be managed and the need to understand the sensitivity of the biosystems suggest that manufacturing in this area could benefit from artificial intelligence (AI).



The use of state-of-the-art technologies in process monitoring can have a huge impact on any pharmaceutical manufacturing operation. In this specific situation, outlier detection and multivariate monitoring allows process experts and manufacturing teams to control in real time combination of variables and get alerted when the process, even if within specifications, is behaving unexpectedly.

Among Aizon’s multivariate functionalities is the Outlier Detection widget. This widget uses the Isolation Forest algorithm to study the combination of values from all the relevant variables and alerts the user when the relationship between values has deviated from the trained pattern.

The Outlier Detection widget is used to detect, in real time, early deviations in the manufacturing processes by analyzing the combination of variables using machine learning. The AI model compares the Principal Component Analysis (PCA) results from the current batch with values from the reference batch, warning customers if abnormal situations occur.

The screenshot displays the Aizon Outlier Detection widget interface. It includes a sidebar with batch information, a main panel for outlier detection, and a real-time monitoring section.

**Batch information**

- Run ID: FE01Batch\_0060
- Start date: 2020-04-28 06:17:30
- End date: --
- Other specifications: Other specifications
- Settings changed: No
- Process/Phase name: Not defined

**Outlier detection**

- Model ID: OutlierDetection\_CPPs\_0055\_0056\_v01
- Entities: FE01\_AirFlow, FE01\_CellGrowth, FE01\_DissolvedOxygen, FE01\_GlucoseFeed, FE01\_pH, FE01\_Stirrer
- Last outlier: Value: 0.899, Time: 2020-04-28 10:24:32

**Outliers log**

| Time                | Score |
|---------------------|-------|
| 2020-04-28 10:24:32 | 0.899 |
| 2020-04-28 10:24:03 | 0.901 |
| 2020-04-28 10:23:33 | 0.914 |
| 2020-04-28 10:23:02 | 0.914 |
| 2020-04-28 10:22:33 | 0.914 |
| 2020-04-28 10:22:02 | 0.92  |
| 2020-04-28 10:21:32 | 0.906 |
| 2020-04-28 10:21:02 | 0.899 |

**Real time**

- Batch total count: 494

**Outlier Detection**

- Model ID: OutlierDetection\_CPPs\_0055\_0056\_v01
- Outlier Percentage: 0.05

**Outliers summary**

- Count: 42
- Last value: 0.9
- Last outlier: 12 minutes ago

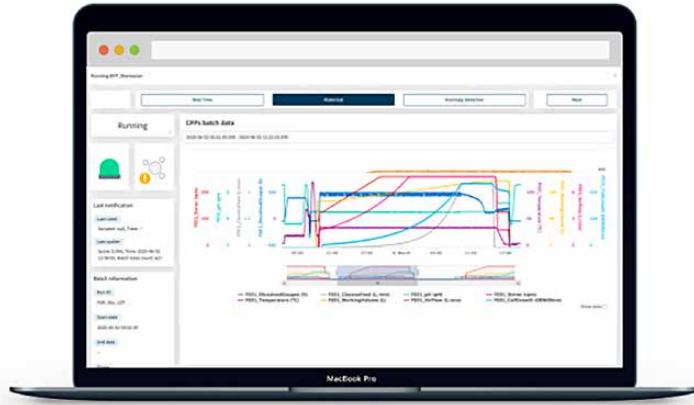
**Real time graph**

The graph shows a real-time score fluctuating around a mean value of 0.5, with a threshold line at 0.5. A red line indicates a recent spike in the score, reaching approximately 1.25.

## Benefits of multivariate monitoring with the Aizon platform

Aizon's AI-powered, GxP-qualified platform offers a range of functionalities that allow for the creation of fully adaptable, real-time solutions to help production teams anticipate process deviations and, as a result, achieve higher process control, less variability and ultimately a higher product quality with reduced production costs.

The Outlier Detection widget uses artificial intelligence to identify changes in the process parameters that the human eye alone cannot possibly detect and performs a multivariate monitoring of the process to predict deviations even when within specifications.



Users can receive an email notification or visualise an alert at the precise moment a deviation is detected, giving enough time for operators to react and ensure the process is maintained inside specifications ensuring quality and preventing an eventual batch rejection.

## Conclusion

Aizon's multivariate monitoring, and especially the Outlier Detection widget, provides manufacturers with real-time feedback when their process is deviating from the expected behavior, even before individual variables are out of control. This is due to the multivariate analysis performed on the combination of the most relevant parameters.

It gives manufacturers time to react and correct the process before any major issues occur and thus can prevent both batch rejections, which could cost millions of dollars, or delays in getting the drug to market.

This can enable pharmaceutical companies to significantly improve yield output and drastically reduce manufacturing costs for any given process. Being able to control the state of a process and minimise variability can have a huge positive impact for any manufacturing operation and not only from an economic standpoint but also from a Quality Assurance situation.

**About Aizon:** Aizon is a software provider that transforms manufacturing operations with the use of IoT, cloud, advanced analytics, artificial intelligence, and pharma 4.0 technologies focused on optimizing pharmaceutical and biotech companies. The Aizon analytics platform seamlessly integrates unlimited sources of structured and unstructured data to deliver actionable insights across all manufacturing sites. Aizon offers an intuitive way to gain meaningful operational intelligence with data by enabling real-time visibility and predictive insights in a GxP compliant manner with end-to-end data integrity. Founded in 2014, the company is based in San Francisco, California and also has a European office in Barcelona, Spain.