



Unscrambler[®] X Process Pulse II for Advanced Multivariate Process Monitoring: Enabling a Data Driven Culture of Quality throughout the Pharmaceutical Organization

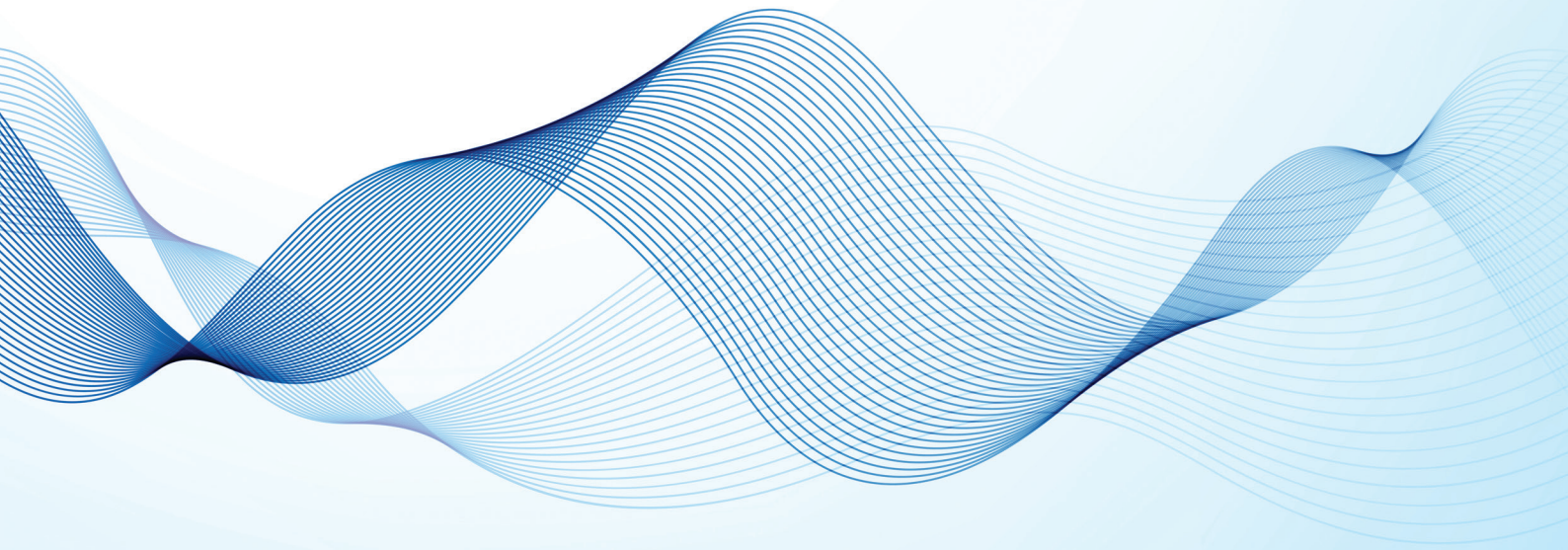


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PROCESS ANALYTICAL TECHNOLOGY

In 2004 the FDA issued the Process Analytical Technology (PAT) framework guidance in order to support innovation and efficiency in pharmaceutical development, manufacturing and quality assurance [1]. This framework has been defined by the agency as “a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality”. The PAT framework propounds process scientific understanding in order to facilitate sound innovation and risk-based decision making. The tools and approaches described within the PAT guidance are expected to promote a pharmaceutical cultural change and to encourage the development of more efficient pharmaceutical manufacturing processes. This in turn, should increase the effectiveness of the health care system (from the patient’s perspective). Besides innovation and process understanding, the PAT framework (and tools) can be used in support of post approval changes and to justify flexible regulatory routes such as demonstrating process validation through continuous quality assurance [1, 2].

Two of the most important principles advocated by the PAT initiative are timely measurements (to obtain process knowledge) and the characterization of the multivariable relationship between formulation properties, process variables and quality attributes.

Process knowledge and multivariate models can be used to design and implement science based process improvements throughout the product lifecycle and to de-risk the process by means of real-time measurement/control strategies. Real-time multivariate process monitoring can be achieved by evaluating data from the following sources:

- Physical advanced process analyzers – NIR, Raman, etc.
- Process equipment – variables measured by traditional sensors (temperature, humidity, vibrations, pressures, etc.)
- Inferential sensors (soft sensors) – variable estimates from fundamental or empirical models

Real-time measurement strategies allow identifying process faults and undesired trends during production facilitating preventive/corrective actions to be taken before product quality is compromised. These actions could be automated (closed control system) or defined in a work instructions document (operator control). Preventive actions should reduce the number of costly quality assurance investigations.

The aforementioned principles and benefits of real-time process measurement and control strategies should not be limited to pilot plants and manufacturing/operations groups. They should rather be embraced by the different stakeholders within the organization as they can bring significant value and agility to different departments. Unfortunately, the complexity of PAT engineering terminology, real-time data management and scientific novelty (a new way of doing things) has not allowed a speedy adoption by the different organization groups and roles. In many cases, PAT as a mission lies on the shoulders of relatively small technology teams rather than embedded throughout the organization.

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In this paper, CAMO aims to reiterate the value of the PAT framework throughout the Pharmaceutical organization and to describe how our new product, Unscrambler® X Process Pulse II, can bring significant value to the different departments by simplifying real-time data modeling, access and management which in turn enables a data driven culture of quality.

THE UNSCRAMBLER® X AND UNSCRAMBLER® X PROCESS PULSE II

For over 30 years, CAMO has been an industrial leader in multivariate data analysis, developing intuitive, robust and powerful multivariate data analysis and Design of Experiments (DoE) software. **The Unscrambler® X** provides a comprehensive multivariate software package for the PAT scientist since it incorporates traditional and advanced multivariate algorithms into one complete package, figure 1. Our new plug-in, **Unscrambler® X Batch Modeling Module**, also allows empirical batch process modeling and multivariate statistical process monitoring of time-depending processes. This and other capabilities and add-ons position **The Unscrambler® X** as the most complete and flexible multivariate data analysis package in the market. In order to take the fullest advantage of the powerful **Unscrambler® X** modeling engines at the manufacturing floor, CAMO has developed **Unscrambler® X Process Pulse II**, an easy to use multivariate process monitoring solution for on-line and at-line applications, figures 2-3. **Unscrambler® X Process Pulse II** can be used to model data (in-real time) from multiple process analyzers and process variables. It allows a user to:

- Directly import and align data from multiple data sources (accept multiple proprietary and standard communication formats)
- Apply regression, classification, projection, batch or hierarchical multivariate models to new data from advanced process analyzers and/or traditional sensors
- Assess the state of the process with respect to an established Design Space and/or good operation conditions.
- Detect trends, process shifts and process instability in a multivariate and univariate manner (univariate SPC capability also included)

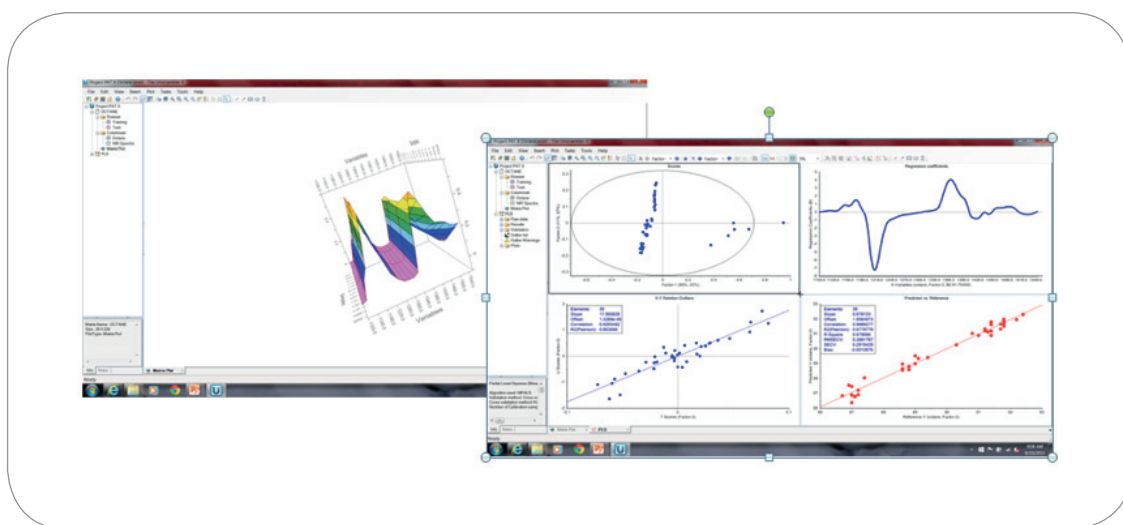


Figure 1. The Unscrambler® X is a comprehensive multivariate software package which incorporates traditional and advanced multivariate algorithms in one complete package. It offers superb graphic capabilities for thorough multivariate data visualization and analysis.

Unscrambler® X Process Pulse II also offers simple to set alarm capability, compliant data and model storage, interactive graphics for data visualization, audit trail, network access and reporting.

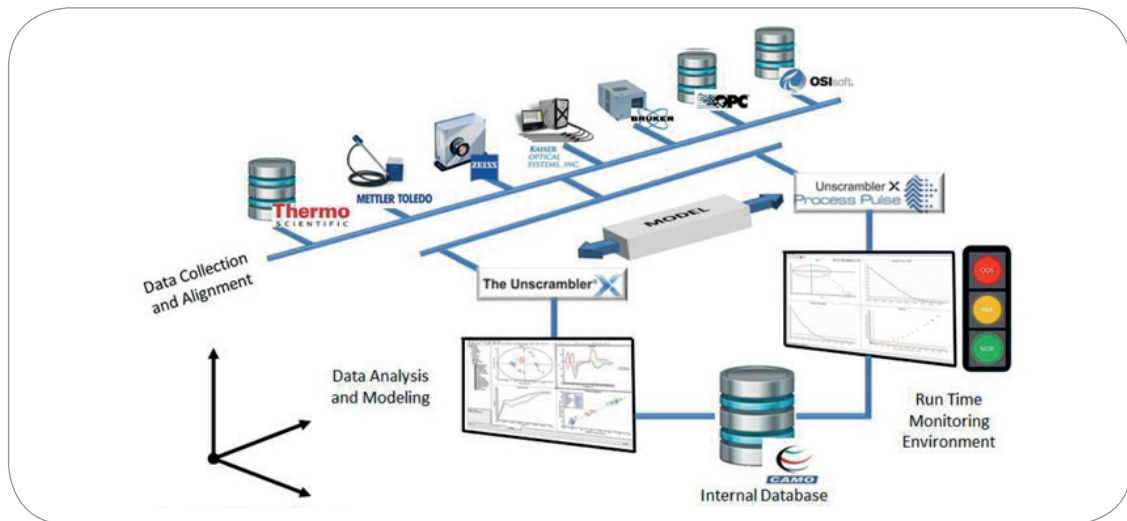


Figure 2. Unscrambler® X Process Pulse II Architecture Schematic with some of the many supported data sources.

UNSCRAMBLER® X PROCESS PULSE II FOR YOUR MANUFACTURING ORGANIZATION

Quality and Regulators

Advanced multivariate process monitoring's final goal is to ensure consistent manufacturing processes and high quality products. For quality departments and regulatory agencies **Unscrambler® X Process Pulse II** can bring tremendous value since it can significantly improve and simplify data revision and inspection processes. Moreover, the implementation of representative multivariate process monitoring as a modern quality system demonstrates plant commitment to the development of a culture of quality and could even be incorporated as a factor when generating production quality metrics [3]. Representative multivariate process monitoring paired with process control can also minimize risk based regulatory inspections, critical drug shortages and more importantly, quality defects.

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Figure 3. From laboratory measurements to real-time process control and optimization, The Unscrambler® X and Unscrambler® X Process Pulse II are designed to enable and promote a data driven culture of quality and to improve your plant quality metrics.

Operational Excellence

Multivariate data analysis and real-time process monitoring can strengthen Operational Excellence, OpEx, organizations particularly when adding multivariate analysis as a tool within the Define Measure Analyze Implement Control (DMAIC) methodology [4]. Also, the use of real-time process measurements, inferential variable estimation and multivariable Process Condition Monitoring (PCM) are all well aligned with the Six Sigma discipline, particularly with the Measure, Improve and Control stages. Given the wealth of process representative information that can be generated when using advanced multivariate process monitoring strategies, data driven and scientifically based continuous improvement strategies can also be seamlessly developed and implemented. With this in mind, CAMO has designed **Unscrambler® X Process Pulse II** to be a great ally of OpEx organizations as it can consolidate information from multiple data sources into a single dashboard with real-time multivariate and univariate SPC charts and time series plots. These powerful graphical tools can be revised in real-time and/or reported out along with process capability indexes for DMAIC process improvement projects and/or Annual Product Reviews. **Unscrambler® X Process Pulse II** can also play a fundamental role enabling Lean Manufacturing since it:

- Consolidates real-time process information in the same compliant historian (this minimizes the data collating time or “data digging time” and “searching for correlations”)
- Enables PAT implementation and model based automation
- Has a central role in process error proofing and risk mitigation.

The gained process understanding and predictability can also support a more effective, and efficient, supply chain.

Technical Services

CAMO's **Unscrambler® X Process Pulse II** could enable a more efficient and intelligent Technical Service organization. For process investigations and validations, accessing networked representative data, multivariate batch model trajectories, time series plots, control charts and associated quality metrics can bring agility to the organization. This could be achieved especially when process critical data (determined by proper risk assessment) is stored within the same **Unscrambler® X Process Pulse II** compliant data historian. Representative batch data, from process analyzers, model estimations and process equipment, can be also used to isolate the nature of undesirable trends and/or non-conformities. Representative data extraction/analysis is of paramount importance to establish effective Corrective Action/Preventive Actions (CAPAs), generate change request justifications and design corrective work status measurement strategies. **Unscrambler® X Process Pulse II** offers the capability of retrieving, analyzing and reporting historical data within the same platform bringing significant flexibility to the organization.

Manufacturing

Unscrambler® X Process Pulse II is a powerful yet simple solution designed to allow manufacturing groups to achieve two of their most important metrics: manufacturing consistency and acceptable product quality. Real-time process monitoring allows identifying process abnormalities (trends, special causes, atypical variations etc.) in real-time by the use of alarms and taking remedial action before product quality is compromised or before the process needs to be stopped. This maximizes the probability of operating within validated working limits and without interruptions once process startup has been approved. When atypical trends are detected, **Unscrambler® X Process Pulse II** offers the capability of drilling down into specific data and process time points. This enables time specific troubleshooting and allows for possible product segregation, if needed. **Unscrambler® X Process Pulse II** reporting capabilities can also be used by operators and/or supervisors to consolidate and report out relevant process data in one report which can be appended to the batch record along with important batch quality metrics. The availability of representative and dynamic historical data along with associated statistics can be used to justify flexible regulatory paths when devising postapproval changes [1, 5].

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Engineering Reliability

Unscrambler® X Process Pulse II and the **Unscrambler® X Batch Modeling Module** can be used by Engineering Reliability departments to develop PCM platforms. PCM platforms can help to proactively prevent defects and equipment downtime and to generate knowledge based preventive maintenance best practices and protocols. Multivariate batch PCM can be achieved by monitoring the process trajectory in-real time and ensuring that it performs within acceptable pre-defined dynamic limits in a Multivariate Statistical Process Control (MSPC) setting [6, 7]. Deviating from an acceptable process hyperplane can be used to indicate process instability and to activate equipment maintenance protocols on-demand.

OTHER IMPORTANT APPLICATIONS

Research and Development and Laboratory

CAMO's **Unscrambler® X Process Pulse II** solution is a powerful tool for R&D departments. **The Unscrambler® X** and **Unscrambler® X Process Pulse II** can play a fundamental role during process development and process characterization by enabling the use of Quality by Design (QbD) principles throughout the developmental stage [8]. **The Unscrambler® X** and **Unscrambler® X Process Pulse II** can also be used during process scale ups to ensure that the chemical and physical process signatures obtained by using process analyzers at the pilot plant and commercial scales match [1]. A match in process signatures reduces the risk of poor commercial product quality. **Unscrambler® X Process Pulse II** is also a viable alternative to instrument vendor software that has limited modeling/prediction options as it is a cost-effective solution for single instruments or multiple instruments, figure 4.

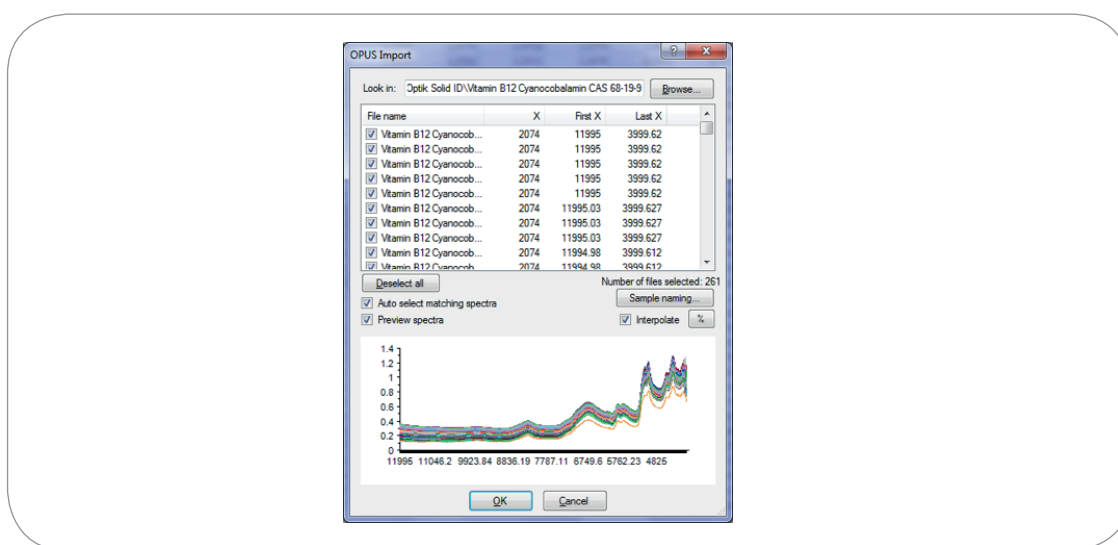


Figure 4. *Unscrambler® X Process Pulse II* is also alternative to instrument vendor software that has limited options.

CONCLUSIONS

As described in this note CAMO's **Unscrambler® X Process Pulse II** has been designed to bring value to the entire manufacturing organization. For the pharmaceutical industry, **Unscrambler® X Process Pulse II** can be regarded as powerful investigative and monitoring tool capable of supporting the development and implementation of cost effective innovative approaches for more efficient product/process development, transfer, manufacturing and quality assurance. **Unscrambler® X Process Pulse II**, like other CAMO products, is a powerful yet simple to implement solution that promises to promote a data driven culture of quality throughout your entire organization.

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