Turnkey Process Control Solutions for Continuous Manufacturing Plants

ContinuousPlant® Software Suite
Software, Services, and Integrated Solutions

CONTINUA
PROCESS SYSTEMS

Continuous Manufacturing for the Pharmaceutical and Biotech Industries

Today most pharmaceutical and biotech manufacturers utilize batch processes to produce drug products. Batch processes are inherently less efficient, more time consuming, and more costly than continuous. This inefficiency is primarily due to the "start-stop-inspect" sequence of batch operations required to ensure the drug product is in compliance with its quality specifications.

Continua Process Systems' software products, services, and integrated solutions are designed to enable pharmaceutical and biotech manufacturers to consistently produce drug products to pre-defined and measured Critical Quality Attributes (CQA) in real-time utilizing a continuous manufacturing process. This concept is consistent with the Food and Drug Administration's Quality by Design (QbD) and Process Analytical Technology (PAT) initiatives, which suggest that quality should be "built-in" to your process control strategies and manufacturing processes.
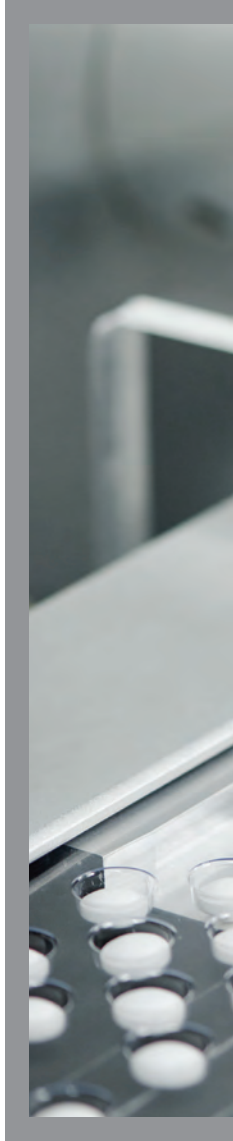
ContinuousPlant® Software Suite Solutions for Continuous Manufacturing

A Flexible Manufacturing Platform for Oral Solid Dosage (OSD)

ContinuousPlant® Software Suite is a powerful advanced process control (APC) and data management software solution that can be configured to be the supervisory controller of any number of process units and processes such as direct compression, dry granulation, and wet granulation. This modular flexible software platform allows multiple equipment suppliers to be integrated into one system, giving you the ability to pick and choose your preferred process equipment vendors best suited for the drug products you manufacture.

The ContinuousPlant® Software Suite is designed to permit the interchangeability of unit operations through S88 batch recipes. The number, type, and order of the process units is dictated by a single recipe without requiring any additional programming or validation. This functionality gives you the ability to create the recipe in a drag-and-drop process similar to creating a Visio diagram and configure the units within the recipe via simple drop-down menus.

With ContinuousPlant® Software Suite you can now run multiple products with different processes on a single CM line through its recipe control feature. For example, you can make a product using dry granulation on one day and a make a different product using wet granulation on the next. This unique flexibility is at the core of ContinuousPlant® Software Suite and validated as a part of the system.

ContinuousPlant® Software Suite enables pharmaceutical and biotech manufacturers to produce drug products more efficiently, reliably, and of better quality than traditional batch manufacturing methods

Built-in flexibility enables you to create and manage a variety of recipes and products with total control throughout the entire manufacturing process.

Flexible Batch
ANSI/ISA-88 (S88)

- S88 standard adapted for continuous manufacturing (CM) processes
- Enables flexible manufacturing – mix and match unit operations without re-validation
- Recipe driven process/product
- Multiple vendor systems integration
- Multiple vendor turnkey approach
- PAT integration

Materials Tracing
Residence Time Distribution (RTD)

- One RTD per unit
- 30 Inputs/30 Outputs per sec
- Multiple RTD model types to match non-ideal behavior of products
- Each RTD regressed to specific unit make, model, and product formula
- Custom RTD models can be developed
- Client RTD models can be integrated into the system

Materials Tracking
C-MES (Continuous-MES)

- Barcodes of material lots of each component are scanned into the system
- Materials compositions and lots are tracked through the system from dispensing to final product
- Batch reports with lot and material composition data printed automatically at end-of-batch
- Labels with barcodes printed and attached to final product packages
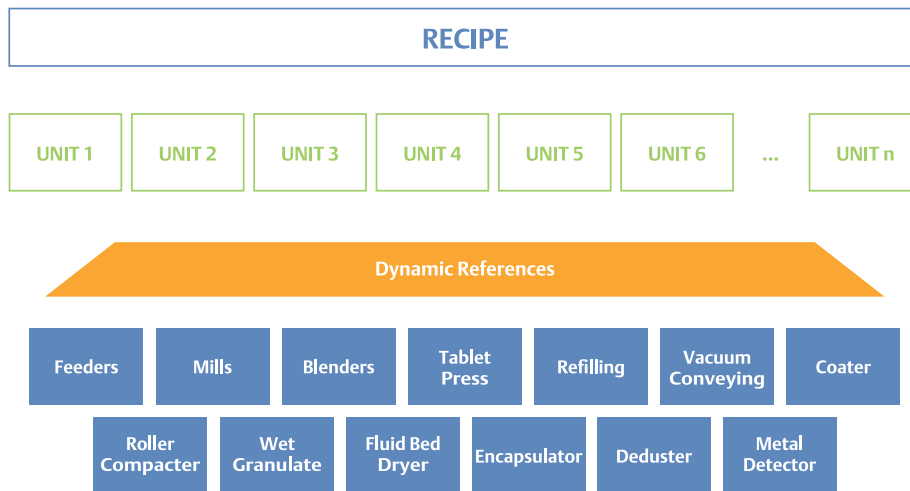- Labels printed for samples based on IPC schedule

ContinuousPlant® Flexible Batch

Built-in Flexibility Compliant with S88 & S95 Standards

ContinuousPlant® Flexible Batch enables a batch management system to be applied to continuous manufacturing. This is the core of the ContinuousPlant® Software Suite, which is built upon object-oriented design principles and established batch industry process control standards such as S88 and S95. Continua Process Systems developed this software to uniquely adapt the S88 batch standard to make continuous manufacturing more flexible.

ContinuousPlant® Flexible Batch allows the user to build multiple product recipes and configure multiple continuous manufacturing processes through visually oriented software. The required units are dragged-and-dropped into a recipe window and the recipe parameters are added through drop down menus. Once the recipe is created for the desired product and CM process, it is saved and downloaded. The recipe is then initiated and controlled by an operator through the Emerson DeltaV™ Batch Operator Interface.

Multiple recipes can be created by a recipe author to allow you to manufacture multiple products using multiple CM processes such as direct compression, dry granulation, wet granulation, and custom processes. ContinuousPlant® Flexible Batch is also ideal for running DOEs.

RECIPE

UNIT 1	UNIT 2	UNIT 3	UNIT 4	UNIT 5	UNIT 6	...	UNIT n

Dynamic References

Feeders	Mills	Blenders	Tablet Press	Refilling	Vacuum Conveying	Coater

Roller Compacter	Wet Granulate	Fluid Bed Dryer	Encapsulator	Deduster	Metal Detector

DeltaV is a trademark of the Emerson Automation Solutions family of companies.

ContinuousPlant® software uniquely adapts the S88 batch standard to make your continuous manufacturing more flexible.
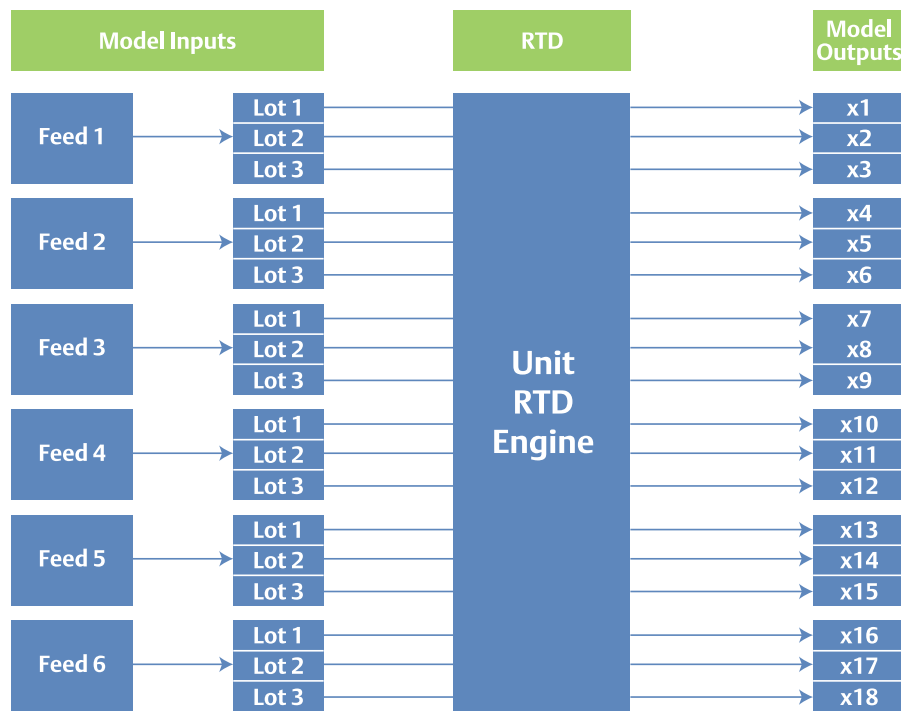
ContinuousPlant® Materials Traceability

The ContinuousPlant® Materials Traceability model utilizes a statistical equation called Residence Time Distribution (RTD) that estimates the time a particle will spend in a vessel to trace material from the tablet drum back to the raw material drum. Each RTD model is fit to the process or the product being produced to optimize accuracy.

Each ContinuousPlant® unit contains a control module that runs an RTD model in real-time. Each unit RTD can have up to thirty (30) inputs and predicts up to thirty (30) outputs. The inputs and outputs are objects that contain the mass flowrate, the composition, and the lot number of each component and the thirty (30) inputs and outputs can be comprised of up to ten (10) components with three (3) lots each.

The RTDs can be linked together in parallel or in series to match the process. The inputs of one RTD are the outputs of the previous upstream process. For example, three (3) feeders in parallel might each have one output going to a blender, which is the next unit in line. The blender RTD would then have three (3) inputs, one for each feeder. The blender would then process the three (3) inputs in its RTD engine and pass the single output to the next unit in line, which could be a tablet press.

The structure of the process, either parallel or serial paths, is defined through a single parameter in the recipe design. Once the structure of the process is built through the recipe, the RTDs are automatically linked together and automatically run when the process is started. There are various RTD model types that can be supplied with the system or the user can apply their own models, which can be integrated into the system to match the characteristics of unique products.

| Model Inputs		RTD	Model Outputs
Feed 1	Lot 1		x1
	Lot 2		x2
	Lot 3		x3
Feed 2	Lot 1		x4
	Lot 2		x5
	Lot 3		x6
Feed 3	Lot 1		x7
	Lot 2	Unit RTD Engine	x8
	Lot 3		x9
Feed 4	Lot 1		x10
	Lot 2		x11
	Lot 3		x12
Feed 5	Lot 1		x13
	Lot 2		x14
	Lot 3		x15
Feed 6	Lot 1		x16
	Lot 2		x17
	Lot 3		x18

Feeder Algorithm – Kalman Filter

Feeder loss-in-weight (LOI) algorithms are known to be problematic. Since the feeder is mounted on top of a weigh scale, the rotation of the feeder and mixer shafts transmit a significant amount of noise to the weigh scale. The weigh scale needs to be highly sensitive to pick up the change in weight and accurately predict the mass feed rate out of the hopper. The combination of the sensitive signal and physical vibration creates noise in the weight signal.

To dampen the noise, the feeder weight data needs to be filtered. However, if the data is over-filtered, the mass rate prediction is not representative of the true mass weight. The method in which the data is filtered is also critical to obtain an accurate representative of the mass rate.

Continua Process Systems developed the ContinuousPlant® Kalman Filter, a powerful algorithm that uses the weighted average of raw data and a predicted value from a physical model to determine the most accurate estimate. The Kalman filter algorithm is commonly used in GPS, missile guidance, economics and signal processing applications, and is the de facto standard in aerospace and robotics. It is considered to be the optimal estimator for applications where there is statistical noise and a priori knowledge. This makes the Kalman filter algorithm ideally suited for CM feeder applications to combine the noisy feeder data with a feeder model to estimate the mass rate.

Our ContinuousPlant® Kalman Filter Feeder Algorithm utilizes a feeder model that estimates the powder density to predict the expected mass rate. The Kalman filter then uses the expected mass rate along with the raw LOI data to statistically estimate the optimal mass rate.

- readings from the sensor
- Kalman filtering
- simplified Kalman filtering
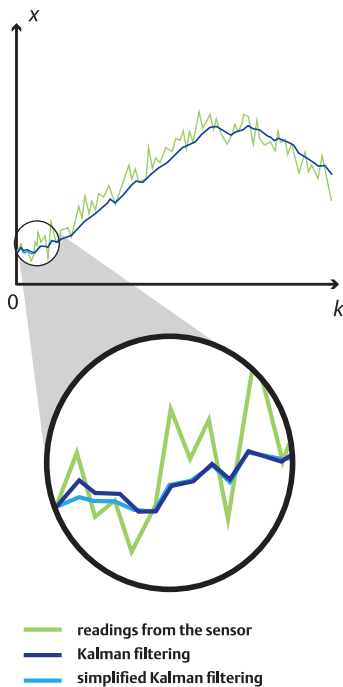
RTD Models in Real-time

The closed form RTD equation E(t) = 1/tc * e(-t/tc) is valid for ideal constant volume tanks. To compute the RTDs in real-time for variable mass and non-ideal conditions, the mass balance equations are computed instead of using the closed-form equation above. The differential equation for the mass balance is computed and solved in real-time for each component every second. The differential equation is solved in real-time using the ContinuousPlant® Process Solver - a unique method and software product developed by Continua Process Systems.

Every second the RTD model for each unit reads the new mass rates and compositions, solves the differential equations, computes the new exit mass and compositions, and writes them to the next process unit. The last unit in the process (tablet press, encapsulator etc.) contains the compositions and lot information for each tablet. The RTD and tablet data is stored in a database to satisfy cGMP requirements for Data Integrity and the data is used to generate batch reports and product labels.
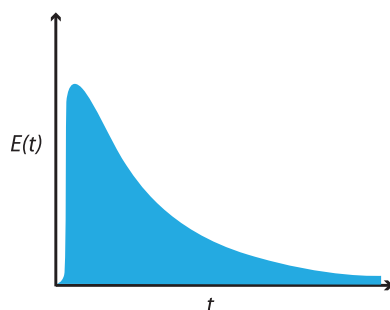
Ideal CSTR has an exponential residence time distribution:)

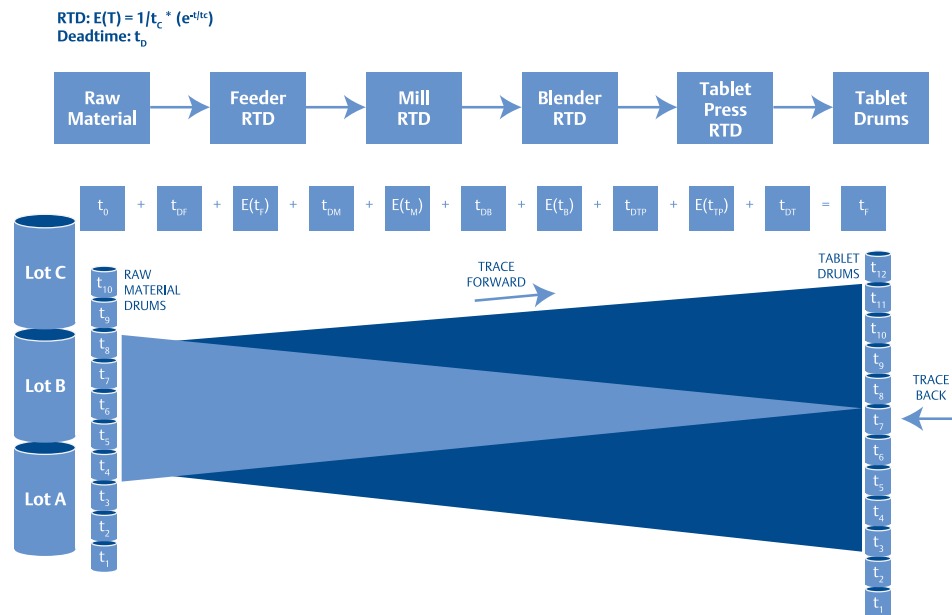Residence Time (t_c)

$E(t) = 1/t_c * (e^{-t/bc})$

ContinuousPlant® Materials Tracking

Continuous Manufacturing Execution System (C-MES)

The ContinuousPlant® Materials Tracking system uses the data from the Materials Traceability model to provide several functions of a typical batch Manufacturing Execution System (MES). The Materials Tracking application constitutes Continuous Manufacturing Execution System (C-MES).

Material is tracked from the time it enters the system through raw material drums to the time it exits the system as packages of tablets. The raw materials drum barcodes are scanned into the Materials Tracking system as soon as they are loaded into the dispensing bay bins. The barcode is stored with the drum weight, material ID, and lot number. This lot and material data are propagated through the system of unit operations via the RTDs.
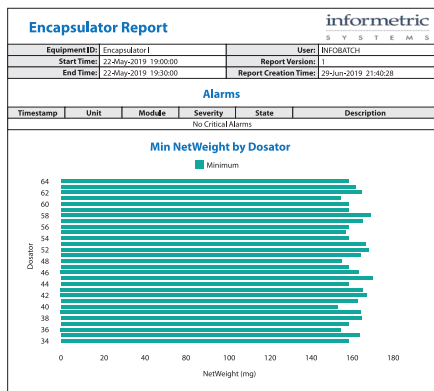
The material compositions and lot numbers of the tablets are stored along with a barcode that is generated for each package of tablets. The barcode is printed on a label that is attached to the final package of tablets including the package weight.

RTD: $E(T) = 1/t_c * (e^{-t/tc})$
Deadtime: t_D

$$t_0 + t_{DF} + E(t_F) + t_{DM} + E(t_M) + t_{DB} + E(t_B) + t_{DTP} + E(t_{TP}) + t_{DT} = t_T$$

Traceability is assured from incoming materials, through intermediate steps, to final product.

Encapsulator Report

Equipment ID:	Encapsulator I	**User:**	INFOBATCH
Start Time:	22-May-2019 19:00:00	**Report Version:**	1
End Time:	22-May-2019 19:30:00	**Report Creation Time:**	29-Jun-2019 21:40:28

Alarms

Timestamp	Unit	Module	Severity	State	Description
			No Critical Alarms		

Min NetWeight by Dosator

■ Minimum

Batch Reports – InfoBatch™

InfoBatch provides comprehensive reporting by aggregating data from the Materials Traceability and Materials Tracking systems. InfoBatch incorporates ContinuousPlant® batch context based on a specified number of tablets, material quantity or run time. The batch context enables traceability from incoming materials through intermediate process steps to final product containers.

Batch reports can include active and excipient ingredient lot information, intermediate process conditions, alarms and events, and final tablet summary data and statistics. Reports can be generated automatically with InfoBatch AutoGen™ or interactively through the InfoBatch Web Server. InfoBatch can also print barcode labels in a configurable format.

InfoBatch and AutoGen are trademarks of Informetric Systems Inc.

8

ContinuousPlant® Software Suite Modules

ContinuousPlant® Nonlinear Process Optimizer

- Embedded advanced process control (APC) algorithm that either maximizes or minimizes a convex or concave parabolic process value in real-time for nonlinear applications
- Unlike a linear process controller, there is no predetermined or fixed setpoint because the process is designed to continuously control within its optimal minimum or maximum specified value limits, which are variable
- Can be applied in CM for optimizing blend uniformity of a continuous blender by varying the rotational speed to minimize Relative Standard Deviation (RSD). The process controller running the Nonlinear Process Optimizer algorithm looks at the current RSD, then semi-continuously adjusts the blender speed in real-time to maintain the RSD at its minimum/optimum control point to prevent over-mixing and under-mixing

ContinuousPlant® Process Solver

- Embedded advanced process control (APC) algorithm that continuously solves nonlinear differential equations in real-time using numerical methods for closed loop process control
- Can be applied in CM to solve a nonlinear equation for tablet press feed rate to optimize tablet hardness and weight

ContinuousPlant® Process Modeler

- Embedded advanced process control (APC) algorithm that fits a nonlinear equation to real-time data, solving for multiple coefficients
- Predicts future trajectory of multiple time variant, nonlinear processes like bioreactors and chromatography systems and the optimization of wet granulation processes for incorporating extruder and fluid bed dryers into CM processes in real-time
- Calculates the coefficients dynamically in real-time as opposed to using theoretical coefficients developed offline where variations in historical process data may be inaccurate when run in real-time
- The algorithm runs continuously producing a new curve with every scan and then predicts a new set of coefficients based upon the new process data inputted from each scan
- Fuses the theoretical model with real-time process data to predict the optimal state

ContinuousPlant® Nonlinear Kalman Filter

- This algorithm combines measurement data and model prediction to find the statistically optimal estimate of the system state
- Model performs a regression of a nonlinear model in real-time for each new measurement
- Model coefficients are updated with the adaptive regression for each iteration of the filter
- Model can be a customer supplied mechanistic or empirical equation
- Applications include chromatography elution endpoint detection, bioreactor glucose control, and API crystallization

Enterprise Features of the ContinuousPlant® Software Suite

Tech Transfer
- S88 enabled recipe management system and standardization platform facilitates highly efficient tech transfer

Data Contextualization
- Meta data is built into the software standards enabling data contextualization for efficient data analysis:
    - Regulatory control modules are contextualized with the unit, process area, batch ID, etc.
    - All batch steps and actions are logged to the Events Database

Design of Experiments (DOE)
- Automated start-up, shutdown, and condition transitions
- Data collected in uniform fashion with synchronized time stamps

Data Integrity
- Emerson's DeltaV™ distributed control system (DCS) is a commercial off-the-shelf (COTS) product that supports Part 11 and Annex 11 compliance with standard features such as:
    - Version Control and Audit Trail (VCAT)
    - Recipe Authorization
    - Operator Actions with Confirm/Verify
    - Batch Historian
    - Continuous Historian
    - Operator Electronic Logbooks
    - Electronic Signatures

Your Single-Source, Turnkey Solution

Continua Process Systems Process Automation & Data Management Services

At a minimum, project team members should include a project manager and systems engineers from Continua Process Systems and the user's process automation project team lead, process equipment suppliers (i.e. tablet presses, feeders, etc.) and engineering firm. This model emphasizes close collaboration and direct communication between project team members starting with the initial front-end engineering and design (FEED) phase through project scoping, implementation, startup and system commissioning.

At the front end, it is essential the project team mutually review the User Requirements Specification (URS) to agree upon the scope of work, the optimal system architecture, control network communication protocols, and process control and data management strategy for monitoring and controlling the critical product quality and process performance parameters defined in the URS.

Our experience shows that deploying an integrated project team model from project conception to completion enables key project stakeholders to stay focused on assuring the intent of the URS is clearly understood and met.

Our integrated CM solution enables you to produce drug products more efficiently, reliably, and of better quality than traditional batch manufacturing methods.

Our Continuous Manufacturing Partners

Emerson | Emerson is the leading supplier of automation solutions to the Life Sciences Industry, with automation expertise and technologies to solve your greatest cGMP manufacturing challenges. Emerson has effective technology solutions for improving your real-time product quality, reliability, and operating costs. From design to implementation, and start-up to on-going optimization, you can rely on Emerson to stay competitive in a global economy.

Emerson's DeltaV™ distributed control system (DCS) is an easy-to-use automation system that simplifies operational complexity and lowers project risk. The state-of-the-art suite of products and services increases continuous manufacturing performance with intelligent control that is easy to operate and maintain. The DeltaV DCS adapts to meet your needs, scaling easily without adding complexity.

www.emerson.com/en-us/industries/automation/life-sciences-medical
www.emerson.com/en-us/automation/deltav

C-SOPS | Founded in 2006, the Center for Structured Organic Particulate Systems (C-SOPS) brings together a cross-disciplinary team of researchers from major universities to work closely with industry leaders and regulatory authorities to improve the way pharmaceuticals, foods and agriculture products are manufactured. C-SOPS focuses on advancing the scientific foundation for the optimal design of SOPS with advanced functionality while developing the methodologies for their active control and manufacturing.

Headquartered at Rutgers University, C-SOPS partners include the New Jersey Institute of Technology, Purdue University, the University of Puerto Rico at Mayaguez, and more than 40 industrial consortium member companies including Continua Process Systems and Emerson.

www.csops.org | www.csops.org/our-industry-program

Integra Continuous Manufacturing Systems | Integra CMS is the leading provider of comprehensive scientific and technical support to manufacturers who seek to formulate, implement, or optimize continuously manufactured products. Their top network of global universities, industrial partners, and technology suppliers are here to deliver tailored, effective continuous manufacturing solutions. Integra applies a step-by-step approach to help pharmaceutical manufacturers create efficient systems through effective integration of multiple methods and tools to meet key objectives, including maximum process understanding and maximum product quality at minimal cost.

www.integracms-pharma.com

Informetric Systems Inc. | Informetric Systems Inc. develops software applications that enable manufacturers to improve quality and increase productivity. Informetric software provides data acquisition and reporting for critical product release activities in batch and continuous GMP manufacturing facilities.

www.informetric.com

Continua Process Systems
20 Commerce Drive
Allendale, NJ 07401
Phone: (844) 828-6823

www.ContinuaPS.com