Upgrading from Pharmaceutical Net to FacilityPro®

Abstract

Now is the time to improve older automated industrial architecture and meet regulatory guidelines with the FacilityPro® Environmental Monitoring System. Beneficial impact encompasses QA/QC, production, IT and operator functions, with expansion to microbial collection integration, report and audit trail capability, and the option for system redundancy. The upgrade is a streamlined process made easy by FacilityPro's user requirement specifications (URSs) of data integrity, automation, simplicity, integration, service and support.

Why Should I Upgrade?

The primary reasons you should upgrade to the FacilityPro Environmental Monitoring System:

1. **Data Integrity** - *Ensures accurate, unaltered data collection records*
2. **Design Simplicity** - *Organizes numerous components (sensors, vacuum lines, clients, etc.) into a straightforward and manageable network for personnel*
3. **Ease of Integration** - *Facilitates cleanroom protocol and procedure generation*
4. **Automation Improvement** - *Improved gathering, storing and reporting of data, and remote access expansion via WiFi*

Aseptic Manufacturing Requirements

Environmental Monitoring System (EMS) design changes based on needs of the area being monitored. EU Annex 1 establishes four grades for cleanrooms:

- Grade A: Local zones for high risk operations (filling, closing, etc.)
- Grade B: The background environment of the Grade A zone
- Grade C and D: Clean areas for less critical stages

> *"Classification should be clearly differentiated from operational process monitoring."*
>
> EU Annex 1

The FDA defines two types of clean areas:

- Critical areas: Areas where the drug product, sterilized containers and sterilized closures are exposed
- Supporting clean areas: Where non-sterile components and materials are prepared, held or transferred

> *"Routine particle monitoring is useful in rapidly detecting significant deviations in air cleanliness."*
>
> FDA Aseptic Guidelines

The European Medicines Agency (EMA) and the Food and Drug Association (FDA) both require that a cleanroom is classified and then monitored. Classification denotes the proof that a cleanroom meets the required ISO class (ISO 14644-1), while monitoring is the continued, ongoing verification that a cleanroom has not shifted from standard conditions.

To certify that a cleanroom (or clean area) meets a defined class of the ISO 14644-1 standard, a routine evaluation is performed every 6 or 12 months, as required in ISO 14644-1. The purpose of certification is to verify that a cleanroom meets certain requirements and can be used for a certain function.

	EMA	FDA
Number of locations	Follow ISO 14644-1 per table	Follow ISO 14644-1 per table
Sample volume per location	Follow ISO 14644-1 (V_S = (20/C) * 1000) (except Grade A = 1 m^3)	Follow ISO 14644-1 (V_S = (20/C) * 1000)
Cleanroom state during classification	At Rest and In Operation	In Operation
Particle size	0.5 and 5 µm	0.5 µm

Table 1. Cleanroom elements by regulatory body

Monitoring Location and Frequency

EU Annex 1

To meet the regulations specified by EU Annex 1, certain actions must be performed in cleanrooms based on their certified grade. In Grade A, "all interventions and transient events" must be detected, meaning continuous monitoring must be performed. In Grade B, the recommendation is the same as Grade A, but monitoring frequency can be reduced. For Grade C and D, the standard specifies frequency should be "in accordance with the principles of quality risk management."

> *"Monitoring locations based on a **formal risk analysis study** and the results obtained during classification."*
>
> EU Annex 1

> *"Measurements [should be] taken at sites where there is the **most potential risk** to the exposed sterilized product, containers, and closures."*
>
> FDA Aseptic Guidelines

FDA Aseptic Guidelines

In critical areas, the FDA Aseptic Guidelines recommend "...conducting nonviable particle monitoring with a remote counting system", due to its capability of "collecting more comprehensive data than portable counters". In supporting clean areas, the frequency of sampling depends on the nature of cleanroom activities.

Sample Volume

It is specified in EU Annex 1 that the monitored sample volume does not need to be the same as the volume used in the formal classification of cleanrooms. Cubic meter samples are not required during continuous monitoring, with 1-minute sample periods being the most common.

Microbial or "Viable" Monitoring

In an aseptic manufacturing environment, both particle and microbial monitoring is required. Collection points for each type are often adjacently placed, with the locations chosen based on risk assessment. Batch records must include both sets of data, alarms, any other measurements, etc.

EU Annex 1 recommends the use of settle plates, volumetric air and surface sampling, while FDA Aseptic Guidelines specify that the use of settling plates is optional when used with active air samplers (required for this standard). The evaluation of each single sample result should be performed, which deters unacceptable localized conditions becoming masked by averaging.

Pharmaceutical Net does not perform microbial monitoring, limiting old systems to just particle counts. With growing importance placed on both types of sampling, FacilityPro is the preferred choice for a modern EMS.

Figure 1. Viable and nonviable sampling points (BioCapt® Single-Use and Airnet® II Particle Sensor)

	EMA	FDA
Monitoring locations	Risk-based	Risk-based
Monitoring frequency in critical areas (Grade A/B)	Continuous (Grade B: Continuous recommended)	Continuous
Monitoring frequency in support areas (Grade C/D)	Routine	Routine
Microbial and particle monitoring	Yes	Yes
Compressed gas monitoring	Yes	Yes

Table 2. Recommended types of monitoring according to EMA and FDA

Pharmaceutical Monitoring Applications

Positioning the Sample Inlet

When deciding where to place the collection point, look for an area adjacent to the critical location. FDA guidance specifies the point must be within one foot (0.3 m) of the critical location. It is recommended that sampling occur just above the critical point, which allows verification that clean air is being supplied to the critical area. This cannot be verified by collecting directly from filtered air vents. Collecting directly above the critical point is also not advised, as airflow is potentially disturbed and may create turbulence.

Filling Lines

There are at least three monitoring locations within a typical filling line operation, including the vial entry point (Accumulator), point-of-fill (Fill Needle) and stopper area (Stopper Bowl). When Lyophilization is used, the transfer from the filler to the freeze dryer must also be monitored as a critical point.

Grade B Areas

There are multiple choices for sensor mounting locations in Grade B, with a direct mount to the wall or machine, a flush mount with an inside wall enclosure and running tubing through walls being potential options.

For isolators, tubing is restricted to internal areas of the unit, with ports built-in for sampling point access. Sensors should be mounted below or on the side of the isolator. For systems that use vaporized hydrogen peroxide (VHP), sensors with VHP resistance are necessary.

For Biosafety Cabinets, the number of sampling points depends on the size of the cabinet. Per cabinet, there is typically one particle counter and one microbial sampler. Sensor mounting can be below or on the side of the cabinet. Tubing running flush through a barrier wall is also an option.

Environmental Monitoring Solutions

Particle Measuring Systems portable products are organized below depending on their application. The following can be used in mobile applications.

Particle Counting

Lasair® III

DataAnalyst

Microbial Sampling

MiniCapt® Mobile

The following products can be applied to continuous applications.

Particle Counting

Airnet® II

IsoAir® 310P

Microbial Sampling

MiniCapt® Remote

BioCapt®
Stainless Steel

System Software and Control

FacilityPro® Processor
and Rack

FacilityPro® Software

FacilityPro® SMART

Project Services

Validation and
Compliance

Design and
Documentation

Installation

In the next section, the solutions shown are integrated into a complete monitoring system using industrial automation design, and compared to an older system.

Automated System Design and Benefits

The below schematic displays a ***typical, computer-based*** implementation of automated system design.

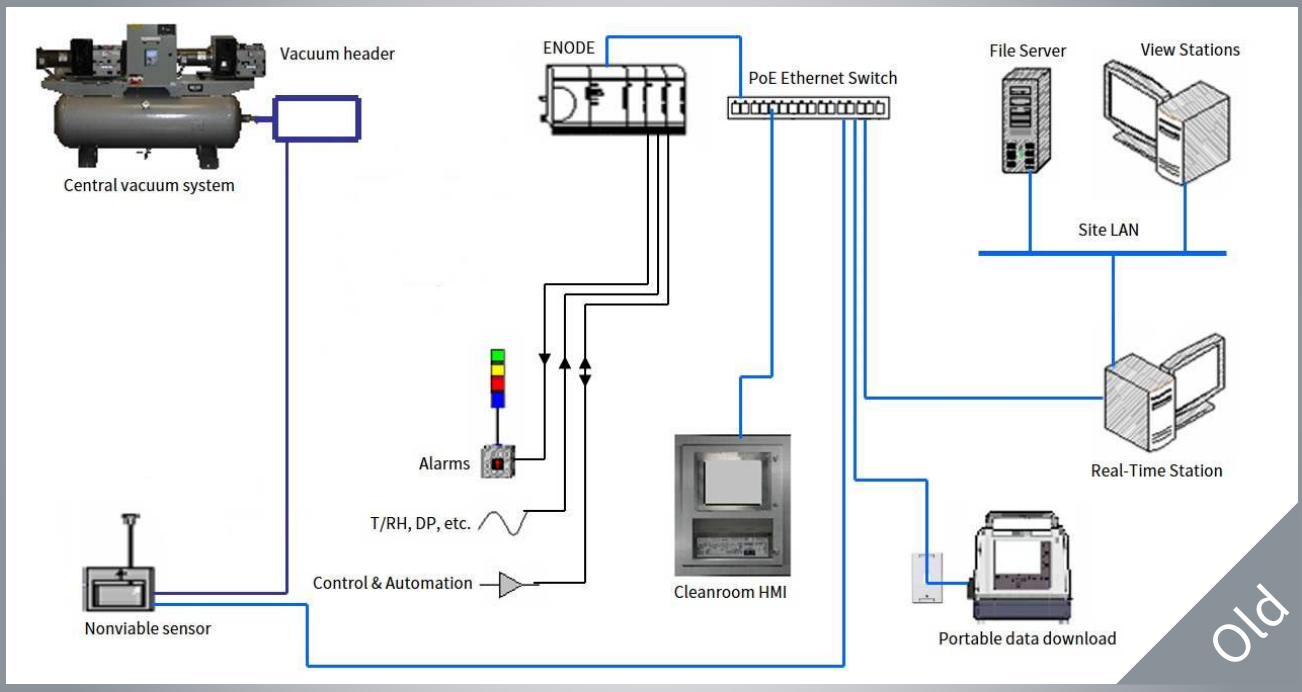

Figure 2. Computer-based implementation of automated system design

The following schematic demonstrates how ***industrial automation design*** is applied in the FacilityPro system.

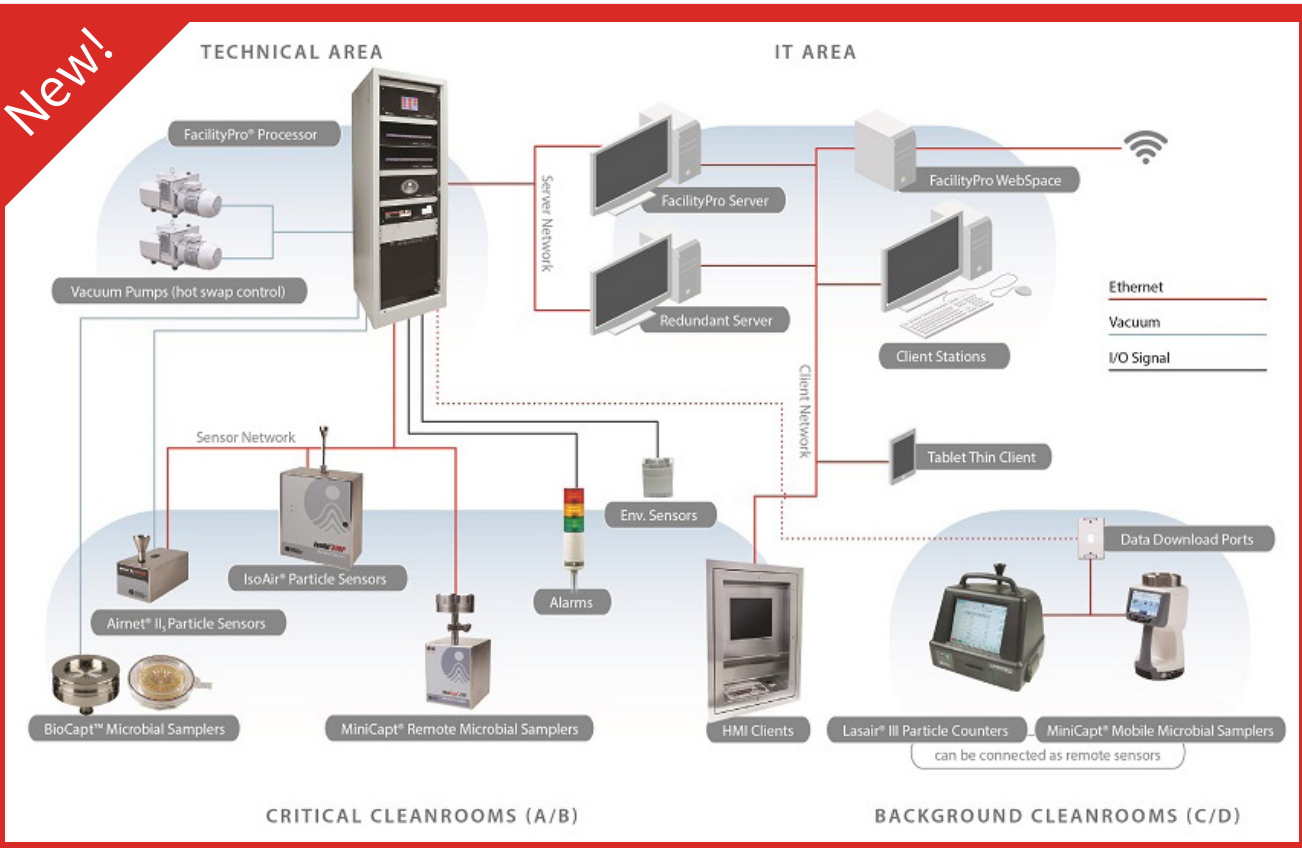

Figure 3. System architecture of applied industrial automation

In **Figure 3**, sensors are located in the cleanroom, a Programmable Logic Controller (PLC) in the technical area, Human Machine Interface (HMI) in the control room, with the HMI and database (DB) in a controlled area. Fixed stations or "thin" clients are used for data access. A risk analysis indicates the PC (HMI/DB) as the component with the highest possibility of failure. There are multiple ways to reduce this risk, with a more powerful PC being the standard response. A more effective solution to use in conjunction with the standard approach is a data buffer and system redundancy with twin DBs. This solution is possible due to sensor-driven time-stamping, a unique benefit of using PMS sensors versus a system integrator.

In comparison, **Figure 2** uses one server for which all data collection depends on. Rather than have the option of system interaction from multiple locations (including remotely via phone, tablet or PC), there is one real-time station with local viewing stations, and limited remote access. These old limitations have been removed with FacilityPro's system design.

Designing a system to work under normal conditions is straightforward, but becomes less-so when factoring in common problems such as vacuum failure (mitigated with vacuum pump redundancy), no communication between sensors and processors (reduced in impact with a data buffer in the sensor) and processor or PC failure (also reduced in impact with an data buffer with full system operation). All systems are managed with a turn-key approach, meaning setup is made easy and quick for installation, validation and upgrade. Components are modular, meaning selection of sensors and their associated modules is completely custom. The software is GAMP 5 Category 4 compliant, reducing validation time and validation complexity. The PMS system is an industrial platform and able to integrate with other industrial systems, such as filling lines, HVAC and others. It uses a standard method of communication via OPC drivers.

The industrial automation design is the key to ensuring reliability and data integrity. It is composed of 4 parts, with each layer having its own instrument and concept to apply. They are able to work alone if one of the other components has a problem.

- **Processor layer**, made by sensors (data conversion of multiple parameters to electronic/digital format), such as temperature (°C) into current (mA). PMS uses sensors like particle counters and/or viable samplers along with temperature, humidity and pressure sensors and switches.
- **Control layer**, made by PLC/DCS (Programmable Logic Controller/Distributed Control System), hardware designed for calculation and data acquisition, such as calculating CM and/or alarms. PMS uses its own type of PLC, the FacilityPro processor module. FacilityPro processors are closer to DCS, with the possibility to have a data buffer.

The difference between PLC and DCS:

- **PLC** is used when fast calculation is needed, not designed to store data (difficult for buffering).
- **DCS** is used when data needs more elaboration but without high speed (they have the memory to use for buffering).

The two types are converging into one (an ongoing trend).

- **HMI layer**, made by industrial software called SCADA (Supervisory and Control And Data Acquisition), it is specialized to provide the graphical interface for human management of the system. PMS uses the Proficy® iFix platform for this interface.
- **Data store layer**, made by industrial DB (Oracle, sql, Historian, PI, Register Marks, etc.)

Principle User Requirement Specifications (URSs) in FacilityPro's design include data integrity, automation, service and support, simplicity and integration. These requirements are important for:

- QA/QC: A system ensuring data consistency and essential for batch release and investigation. Preset reports are created using data algorithms and easily accessed.
- Production: For the ability to collect and review data despite system problems. They need a system to provide the necessary algorithms (cubic meters, cubic foot, N/m alarms, etc.) to meet QA/QC needs. A significant advantage is that production does not need to stop the system to acquire new data. Operators can also be easily trained to use the system.
- IT: Data recovery is under this group's responsibility, and a system with high integrity is required. With the system's automatic backup and secure database, data integrity is ensured.

Data integrity denotes robust system architecture which ensures data is always reliable and protected when needed for batch release and record retention. Supporting features of data integrity include the industrial approach and architecture design, sensor-driven time stamping, redundant iFix/Historian (SCADA) servers, data buffer, backup and recovery, redundant vacuum control (5010 series), and 21 CFR Part 11 compliance.

Automation makes it easier to collect, report and analyze data. In the FacilityPro system, automation is supported by viable, nonviable and environmental controls, sampling automation through recipes, batch identifiers and data filters, and configurable reports and data management. Recipes allow sampling to be performed on an automatic-basis, driven by the SOP. The system is designed to manage viable, nonviable and environmental sensors. Microbiological sensors require a start and stop to sampling, whereas particle and environmental sensors are usually sampling continuously. Logic needs to align in order to combine data. Reports can be filtered down for easier data management when dealing with a large volume of samples.

The simplicity of the design, which employs a standard modular concept, allows for expedited validation. PLC and SCADA programming are handled in advance, with ON/OFF switches for user accessibility and immediate application in an industrial setting. Standard industrial components make it possible for IT groups to manage the system without outside consultancy. Easy integration allows for FMS protocols to be written into cleanroom and process procedures.

The figure below illustrates the connectivity map of the FacilityPro system:

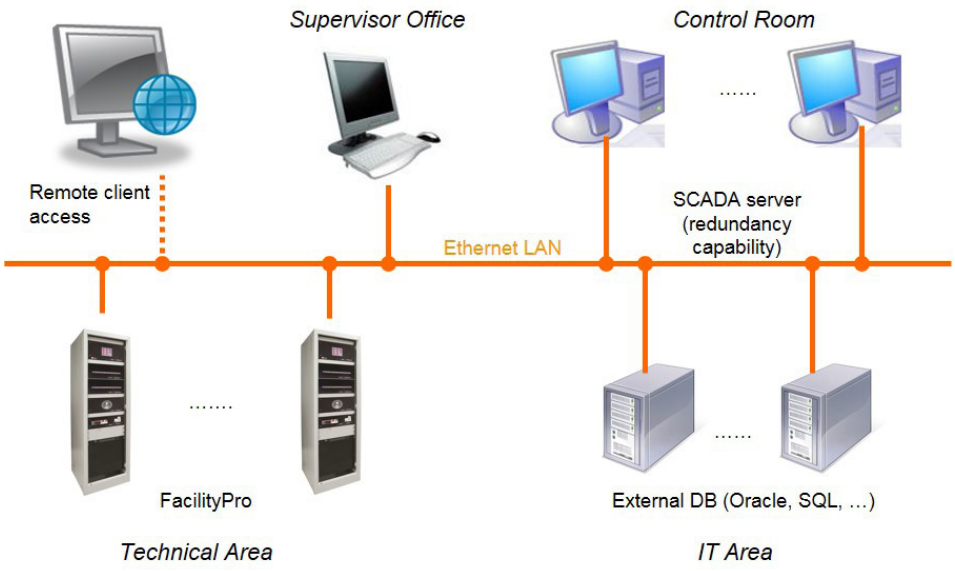

Figure 4. Connectivity and expandability of FacilityPro system

Risk Mitigation

For a risk of sensor data loss, PMS particle counters offer onboard data buffers that enable continued collection despite possible communication failure. To combat a risk to system data loss, FacilityPro processors also provide an onboard data buffer in case of communication failure with SCADA. The option to add a redundant SCADA server eliminates downtime if the primary SCADA becomes disconnected for whatever reason. In the case of vacuum pump failure, dual vacuum pumps can be installed to run with the FacilityPro processor in order to maintain sensor data collection.

The figure below shows the three layers of management for FacilityPro systems.

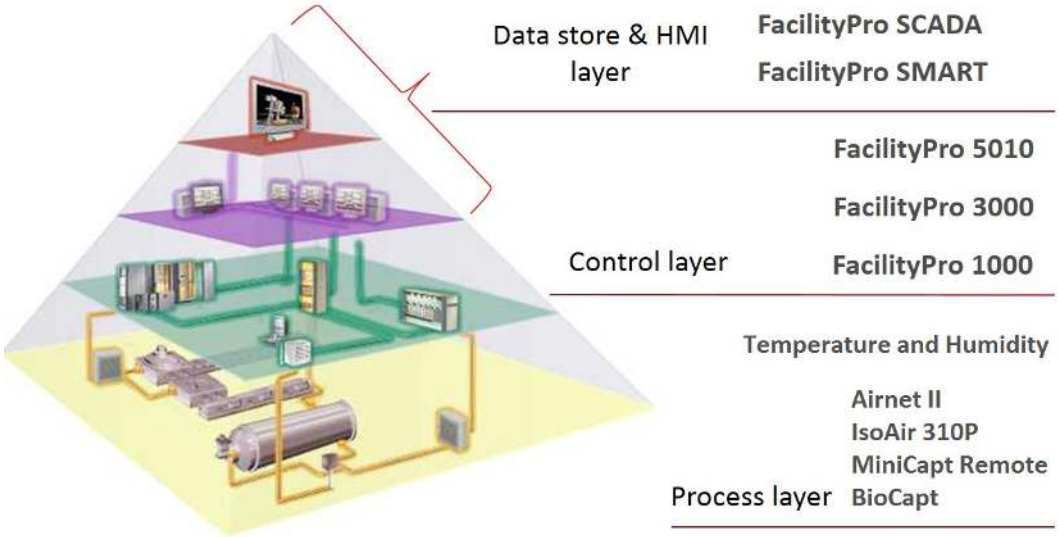

Figure 5. FacilityPro system: three layers of management

Upgrade to FacilityPro Procedure and Benefits

Switch-out of older systems that incorporate Pharmaceutical Net is a procedure involving three components:

- Replacement of current processor typically to a FacilityPro 1000 (three versions with 8, 16 and 32 monitoring points)
- Upgrade to the FacilityPro SCADA or SMART software interface
- Possible connection to the ENODE configuration (maximum: 96 A/I, 32 D/I, 72 D/O)

An addendum to the SW/HW IQ protocol, and performing a new SW/HW OQ will be required. Sensors may be reused or replaced (applies to Airnets and IsoAir Plus) based on age. With the use of FacilityPro, microbial data collection can be integrated to the system. User access connections can include SMART, SCADA, clients and HMI. Vacuum pumps can be reused or replaced depending on operation performance. Computers may also need an upgrade, with the option of physical or virtual machines.

The benefits to upgrading include the ability to add redundancy to your system, integrate microbial data collection, and improve report and audit trail functionality. With these essential features, your system will have an increased safeguard against shutdowns and data loss, improving process validation, productivity and data integrity.

Contact Particle Measuring Systems about upgrading from Pharmaceutical Net to FacilityPro.

Author

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Paul Hartigan has been involved in product management, engineering development and marketing for over 25 years. He has held a variety of product management positions covering most PMS products over his last 10 years with PMS. His background includes work for a variety of instrumentation companies serving pharmaceuticals, the oil and gas industry, industrial manufacturing, utilities, and municipal water industry. He has a Bachelor's Degree in Electrical Engineering Technology as well as a MBA in Marketing. He has published numerous application papers and presents at seminars around the world.

References

- ISO - International Organization for Standardization. *ISO 14644-1:2015 - Cleanrooms and Associated Controlled Environments* -- "Part 1: Classification of Air Cleanliness by Particle Concentration", 9 Dec. 2015.
- European Commission. *EU Guidelines to Good Manufacturing Practice*, *Annex 1: Manufacture of Sterile Medicinal Products*, 25 Nov. 2008.
- FDA - Food and Drug Administration. *Sterile Drug Products Produced by Aseptic Processing -- Current Good Manufacturing Practice*, Sep. 2004.