Process Analytical Technology (P.A.T.)

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GE Healthcare

Process Analytical Technology (P.A.T.)

Continuous, Cybernetic Remote Controls

Dr. Sandy Weinberg, Senior Director
Fast Trak, Vaccines

Introduction

The United States Food and Drug Administration has formed a working group to develop guidelines for encouraging or requiring the adoption of Process Analytical Technology (P.A.T.) to the biotechnology and pharmaceutical production industries. Ultimately, P.A.T. will be expanded to encompass applications in laboratory and clinical testing facilities as well.

P.A.T. has been extensively utilized in the petroleum and chemical industries for more than ten years. Simply stated, P.A.T. calls for continuous rather than end-stage testing and monitoring of a process, potentially from a remote location. Ideally, that monitoring is cybernetic. That is, the monitoring process is tied to a self-correcting mechanism to solve problems as they are encountered (or to discontinue the process if it is flawed or contaminated). A cybernetic, continuous remote monitoring system produces significant cost savings by minimizing quality related product discards and lost production time. More importantly, P.A.T. provides an added safety value by reducing the pressure placed on traditional end stage quality control testing and quarantine strategies.

Three characteristics of a P.A.T. system

A Process Analytical Control system is characterized by three inter-related factors: continuous, cybernetic, and remote monitoring. Continuous monitoring control provides an early warning mechanism. Cybernetic control provides a self-correcting mechanism. Thirdly, remote monitoring allows multiple and efficient quality assurance control mechanisms. Together, these three factors minimize

the cost of pharmaceutical production while maximizing the end-quality of those products. It is in the interaction of the three – continuous, cybernetic, remote monitoring – that the quality, safety and cost benefits accrue.

Continuous monitoring

Without attempting to solve Zeno's dilemma of the arrow in flight, a well- designed P.A.T. system makes measurement (albeit, discrete) with such a fluid rapidity as to be functionally continuous. Consider, for example, the difference between continuously measuring the particulate size of a powered pharmaceutical, assuring uniformity of mix and consistency, versus simply measuring the output at the end of an assembly process. In the "continuous" situation errors or problems can be near instantly corrected. This will result in potential cost savings (non-conforming batches need not be discarded or reworked) and improved safety (reducing reliance on the accuracy and statistical reliability of quarantine and quality assurance checks).

In more complex situations continuous monitoring can produce even more important results. In a fermentation environment, continuous monitoring of pressure and temperature can prevent dangerous production accidents and explosions. In multi-step biological processes, continuous monitoring can prevent the production of unwanted or dangerous impurities and mutations. In infectious disease vaccine production, continuous monitoring is a commonsense precaution against the unintended release of disease agents.

Continuous monitoring is a fundamental step in safety, cost control, and quality assurance as it provides an early warning mechanism rapidly identifying dangerous situations, production problems, errors and unintended consequences.

Cybernetic mechanism

The following are three examples of a cybernetic system:

As a colony of rabbits reaches a population exceeding its available food supply, the underfed animals begin consuming their own body fat. The change in fat content triggers a hormonal reaction that, among other effects, lowers the fertility rate in female rabbits, thus limiting and ultimately reducing the size of the colony.

A lever consisting of two fused metals with different expansion temperatures controls the thermostat in a home heating system. As the temperature in the house reaches the preset level, the differential characteristics of the two metals cause the lever to bend away from an electrical contact, breaking the circuit and turning off the furnace. When the house and the two metals have cooled, the lever returns to the previous position, completing the circuit and reactivating the furnace.

A water tank is equipped with a float arm connected to a shut-off valve. When the tank level is high enough to raise the float, the arm cuts off the water supply. If the tank level lowers though water use, evaporation, or leakage, the float drops and the fill-valve is reopened.

These three systems, controlling rabbit populations, home-heat and the water level in a tank, are cybernetic. They each have a self-regulating automated control mechanism that operates independently of intentional action (once the initial intervention levels are established). Of course, cybernetic systems are not perfect. There are massive rabbit overpopulations, overheated homes and overflowing water tanks. But, these problems are the result of external factors ("open" systems) or mechanical breakdowns. These "closed" systems operate consistently, accurately and reliably when mechanically sound and when not subject to externals (for example, rabbit migration). Perhaps most importantly, closed cybernetic systems operate independently of the foibles, flaws and errors of human intervention.

Consider a simple process where single unit dose containers are filled with an antibiotic liquid. Using a cybernetic system based upon the float in the water tank, the exact quantity indicated for each dose can be automatically injected into each container. While a final quality assurance inspection is appropriate to confirm the proper mechanical function of the fill-line, such a cybernetic system is a significant

improvement over a purely humanistic fill-process of estimation, measurement and pouring. In the cybernetic case, quality assurance problems would be unusual and hence high impact. In the humanistic fill situation, accuracy problems would be commonplace: hence less likely to attract significant attention. The cybernetic models of fill-lines, production processes, and controls make modern, cost effective, and safe pharmaceutical manufacture possible.

Remote monitoring

Perhaps because of a misunderstanding, the capability for remote monitoring of a process is the most controversial of the P.A.T. functions. While it is true that a remote capability makes it theoretically possible for an FDA investigator to monitor a process from a central (e.g., Rockville, Maryland) location, there is not intent to do so (and significant legal prohibitions preventing it).

But, with the remote capacity it would be possible to invite an FDA investigator to observe in order to discuss a problem or question, or for the FDA to, with advance notice and approval, observe from afar. However, these regulatory remote monitor capabilities are merely incidental. The real value of remote versus proximal monitoring lies in a very different direction.

If monitoring is only possible in direct proximity to a production line or facility there is little ability for a centralized quality assurance group to be involved on an on going basis. Even if measurements are continuous, they are likely to be reviewed only on a periodic (discrete) basis if the quality assurance team must physically travel (in some organizations, across the globe) to observe the data.

Remote monitoring provides the ability for a skilled and trained quality assurance professional to centrally review real time results in a variety of processing locations and systems.

The three dimensional graph

The three factors constituting a P.A.T. system – continuous, cybernetic, remote monitoring – can be represented on a three dimensional graph. Thus arbitrarily assigning the Y-axis to the ***continuous*** *versus* ***discrete*** *continuum*, the X-axis to the ***cybernetic*** *versus* ***non-self correcting*** *continuum* (for ease, "non-cybernetic") and the Z-axis to the ***remote*** *versus* ***proximal*** *continuum*.

Each continuum can be evaluated crudely on a "high – medium – low" scale:

1) Continuous:

Low: system makes a limited number of periodic, discrete measurements

Medium: system makes discrete measurements at all critical and/or significant periods

High: system makes ongoing measurements on a regular and frequent basis

2) Cybernetic:

Low: system monitors only, without any self-correcting mechanism

Medium: system monitors and provides limited self-correction

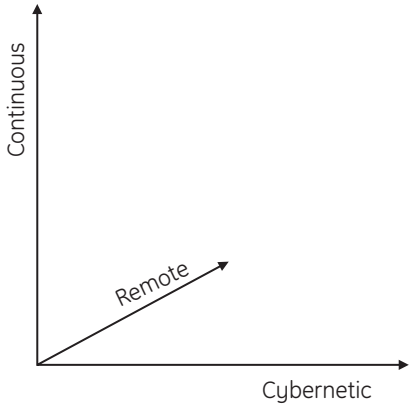
High: system is fully cybernetic, monitoring and self-correcting all variables

3) Remote:

Low: system offers only proximal monitoring: observer must be in direct proximity of the system

Medium: system offers limited remote monitoring through an accessible network or dial-in option

High: system offers full remote monitoring capability through a web-based or equivalent capability



In a three dimensional graphing situation as described the upper-right-raised quadrant (H-H-H) represents a system that has maximal P.A.T. capability. As P.A.T. standards evolve, a system that scores High on any two variables and at least Medium on third might arguably be considered "P.A.T. Compatible."

P.A.T. checklist

Evolving audit standards make a difficult moving target. Final FDA recommendations on the implementation of P.A.T. are not likely to emerge until 2007 (at the earliest). However, based upon current (circa 2005) thinking on the committee and advance plans for the eventual draft recommendations, it is possible to provide reasonable audit guidelines for P.A.T. compatibility.

I. System meet the requirements of 21 CFR Part 11 including:

A. System Validation including:
   1. Evidence of appropriate developmental documentation
   2. Evidence of appropriate management approved use procedures (SOPs)
   3. Evidence of documented testing against system requirements
   4. Evidence of appropriate system maintenance including change control
   5. Evidence of appropriate hardware and software Installation Qualification (IQ) and Operational Qualification (OQ)

B. Archiving of system output in both machine-readable and human readable formats

C. If electronic signatures are in use (optional):
   1. Signature provides unique identifier of signator
   2. Signature "locks" file content
   3. Signature attached to unambiguous time/date stamp
   4. System maintains a secure audit trail of data changes
   5. System users receive appropriate training and support

II. System analysis documents appropriate monitoring points including:

A. Process points in which the production process results in significant material modification of the end product

B. Process points that are subject to contamination or inadequate purification.

C. Other process points potentially impacting end-product safety or effectiveness

III. Monitoring points allow:

A. Trained users to appropriately respond to warning signals.

Or

B. A record of cybernetic corrective actions documented according to the table of appropriate interventions

IV. Output trail retained in both human-readable and machine-readable format for a time period appropriate to the production process (minimum: ten years):

A. Output trail includes records of both warning signals and cybernetic interventions

B. Output trail is tied to batch records, facility identifier and date

V. System users receive appropriate training and support

VI. Appropriate documentary support (Standard Operating Procedures) are available to users at all times. SOPs are:

A. Approved for procedural appropriateness by authorized Management

B. Version controlled

C. Reviewed periodically (generally annually) for accuracy and Appropriateness

VII. Periodic testing (generally every cycle) is conducted to assure the accuracy of the monitoring devices, software, and of the cybernetic controls

VIII. Continuation of end-stage Quality Assurance/ Quality Control testing with quarantine as appropriate:

A. Reconciliation, review and improvement procedure in place to analyze end-stage problems not identified in previous continuous monitoring

IX. Periodic (generally every two years) audit is conducted by a qualified and an independent person against emerging FDA guidelines for Process Analytical Technology.

Summary

Process Analytical Technology (P.A.T.) is an evolving guideline for improving the safety, cost effectiveness and control of biomedical manufacturing systems. Over time the P.A.T. guidelines will also apply to the laboratories that support those manufacturing processes, to other research and testing laboratories and to large scale clinical testing operations.The essence of P.A.T. is an interactive, three-fold method of monitoring processes:

- Monitoring that is continuous (rather than discrete) allows more rapid detection of problems, shorter periods of non-conformity (with resulting possible safety breeches and/or costly product destruction) and rapid identification of trends before those trends reach critical mass.
- Monitoring that is cybernetic allows automatic correction of identified problems without relying on human observation, interpretation, and intervention. The result is more certain, more rapid, and more direct elimination of or correction of deteriorating situations.
- Monitoring that is potentially remote (as well as proximal) allows observation and intervention by highly skilled quality assurance personnel not always available on the work floor. Remote monitoring also permits centralization of a secondary remote process overseeing proximal monitoring and theoretically allows direct (invited) consultation with regulatory investigators concerning emerging problems.

These three variables – continuous cybernetic, remote – can be graphically represented to identify a quadrant of current P.A.T. compatibility. As guidelines emerge over time the three variables can be more tightly quantified. This will define situations deficient in and proficient in the implementation of Process Analytical Controls.

This section shows how solutions from GE Healthcare meet the current demands for PROCESS ANALYTICAL TECHNOLOGY (P.A.T.)

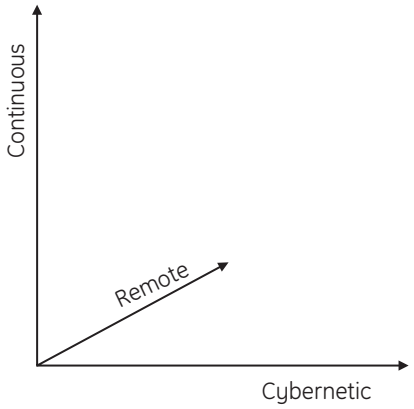
The information in this document is valid for the following software versions and systems:

- UNICORN™ version 5.01
- ÄKTAdesign™ systems
- BioProcess™
- OligoPilot™
- OligoProcess™

P.A.T. checklist compliance

Evolving audit standards make a difficult moving target. Based on current thinking about P.A.T. and advance plans for potential recommendations by the FDA, reasonable audit guidelines for P.A.T. compatibility can be provided.

Focus areas are continuous, cybernetic, and remote capabilities integrated into the manufacturing process.



I. System meets requirements of 21 CFR Part 11 including:

A. System Validation including:

1. Evidence of appropriate developmental documentation

✓ GE Healthcare is ISO 9001:2000 certified and manages the development documentation in a formal document management system. A summary of the development procedures and documentation routines used in software development is available in the Validation Support Package. GE Healthcare also regularly conducts and documents independent audits that are available for customer review.

2. Evidence of appropriate management of approved use procedures (SOPs)

✓ GE Healthcare provides different types of support for customer use of SOPs. Procedures managed by the software systems can be controlled through access restrictions and use is traced in the audit trail.

3. Evidence of documented testing against system requirements

✓ A summary of the development procedures and documentation routines used in software development is available in the Validation Support Package. GE Healthcare regularly conducts and documents an independent audit that is available for customer review.

4. Evidence of appropriate system maintenance including change control

✓ GE Healthcare provides products and services for change control procedures (CCP) through the regulatory business unit Fast Trak. Specific system solutions also support surveillance of maintenance needs of specific hardware parts in the system such as the monitors in the system.

5. Evidence of appropriate hardware and software Installation Qualification (IQ) and Operational Qualification (OQ)

✓ The regulatory business unit Fast Trak provides templates for performance of IQ/OQ to customers both for standard systems and for custom solutions. In addition, formal functional testing is performed on all produced system solutions before they leave the GE Healthcare manufacturing unit.

B. Archiving of system output in both machine-readable and human readable formats

✓ All produced data are stored in a "result file" that can be exported in many different formats, including a general text format. The customer can also choose to send generated data to an electronic batch record via the industry standard OPC.

C. If electronic signatures are in use (optional):

1. Signature provides unique identifier of signer

✓ The user authorization is made with a user name and password unique for the user of the system. The user access strategy is formally defined and approved by the customer.

2. Signature "locks" file content

✓ The software system supports this feature, which is fully documented and independently audited.

3. Signature attached to unambiguous time/date stamp

✓ The software system supports this feature, which is fully documented and independently audited.

D. System maintains a secure audit trail of data changes

✓ The software system provides extensive functions for tracing of changes to data. (Audit trail, System logbook)

E. System users receive appropriate training and support

✓ GE Healthcare offers different training programs to customers to support appropriate use of delivered equipment.

II. System analysis documents appropriate monitoring points including:

A. Process points in which the production process results in significant material modification of the end product

✓ The software and hardware solutions support logging of all types of monitor signals.

B. Process significant points subject to contamination or inadequate purification

✓ The software and hardware solutions support logging of all types of monitor signals.

C. Other process points potentially impacting end-product safety or effectiveness

✓ The software and hardware solutions support logging of all types of monitor signals.

III. Monitoring points allow:

A. Users to respond appropriately to warning signals.

✓ Preset alarms and messages are indicated in the system and manual actions are logged as they begin.

Or

B. A record of cybernetic corrective actions according to the documented table of appropriate interventions.

✓ Programmed cybernetic controls on monitored signals are logged as "method" interventions in the system logbook, part of the audit trail. (Watch instructions control on selected signals)

IV. Output trail retained in both human-readable and machine-readable format for a time period appropriate to the production process (minimum ten years):

A. Output trail includes records of both warning signals and cybernetic interventions

✓ The generated data (Result files) contain the audit trail record. Different export formats are available, including plain text.

B. Output trail is tied to batch records, facility identifier, and date

✓ The system provides multiple batch identities with date and other possible identities.

V. System users receive appropriate training and support

✓ GE Healthcare offers customers multiple training programs, such as installation training of customer staff.

VI. Appropriate documentary support (Standard Operating Procedures) is available to users at all times. SOPs are:

A. Approved for procedural appropriateness by authorized management

✓ The customer is responsible for defining SOPs. Procedures implemented in the design of the purification methods can be access controlled with the software system as well as logged when executed.

B. Version controlled

✓ The customer is fully responsible for document version control.

C. Reviewed periodically (generally annually) for accuracy and appropriateness

✓ The customer is fully responsible for periodical reviews of procedures.

VII. Periodic testing (generally every cycle) is conducted to assure the accuracy of the monitoring devices and software and of the cybernetic controls.

✓ GE Healthcare provides solutions that support online monitor surveillance. Calibrations have to be performed manually and instructions for the calibration procedures are submitted. There is also a preventive maintenance service available for customers.

VIII. Continuation of end-stage Quality Assurance/ Quality Control testing with quarantine as appropriate:

A. Reconciliation, review, and improvement procedures in place to analyze end-stage problems not identified in previous continuous monitoring

✓ The data evaluation solutions provide tools for trend data analysis on chromatographic and filtration data and support continuous improvement.

IX. Periodic (generally every two years) audit is conducted by a qualified and independent person based on emerging FDA guidelines for Process Analytical Technology.

✓ GE Healthcare provides independent audit reports from internal audits regarding compliance with FDA guidelines.

www.chromatography.amershambiosciences.com
www.gehealthcare.com

GE Healthcare
Amersham Biosciences AB
Björkgatan 30
751 84 Uppsala
Sweden

Asia Pacific Tel: +852 2811 8693 Fax: +852 2811 5251 • Australasia Tel: + 61 2 9899 0999 Fax: +61 2 9899 7511 • Austria Tel: 01/57606-1619 Fax: 01/57606-1627 • Belgium Tel: 0800 73 888 Fax: 03 272 1637 • Canada Tel: 800 463 5800 Fax: 800 567 1008 • Central, East, & South East Europe Tel: +43 1 982 3826 Fax: +43 1 985 8327 • Denmark Tel: 45 16 2400 Fax: 45 16 2424 • Finland & Baltics Tel: +358-(0)9-512 39 40 Fax: +358 (0)9 512 39 439 • France Tel: 01 69 35 67 00 Fax: 01 69 41 96 77 • Germany Tel: 0761/4903-490 Fax: 0761/4903-405 • Italy Tel: 02 27322 1 Fax: 02 27302 212 • Japan Tel: +81 3 5331 9336 Fax: +81 3 5331 9370 • Latin America Tel: +55 11 3933 7300 Fax: +55 11 3933 7304 • Middle East & Africa Tel: +30 210 9600 687 Fax: +30 210 9600 693 • Netherlands Tel: 0165 580 410 Fax: 0165 580 401 • Norway Tel: 815 65 555 Fax: 815 65 666 • Portugal Tel: 21 417 7035 Fax: 21 417 3184 • Russia & other C.I.S. & N.I.S Tel: +7 (095) 232 0250 Fax: +7 (095) 230 6377 • South East Asia Tel: 60 3 8024 2080 Fax: 60 3 8024 2090 • Spain Tel: 93 594 49 50 Fax: 93 594 49 55 • Sweden Tel: 018 612 1900 Fax: 018 612 1910 • Switzerland Tel: 0848 8028 12 Fax: 0848 8028 13 • UK Tel: 0800 616928 Fax: 0800 616927 • USA Tel: 800 526 3593 Fax: 877 295 8102

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