

# **Testing Automated Manufacturing Processes *(PLC based architecture)***

- ① Introduction.**
- ② Regulations.**
- ③ CSV Automated Manufacturing Systems.**
- ④ PLCs Validation Methodology / Approach.**
- ⑤ Testing.**
- ⑥ Controls during operation.**

# **Objective**

**This session outlines items to consider during the testing of PLC-based automated manufacturing processes.**

## References

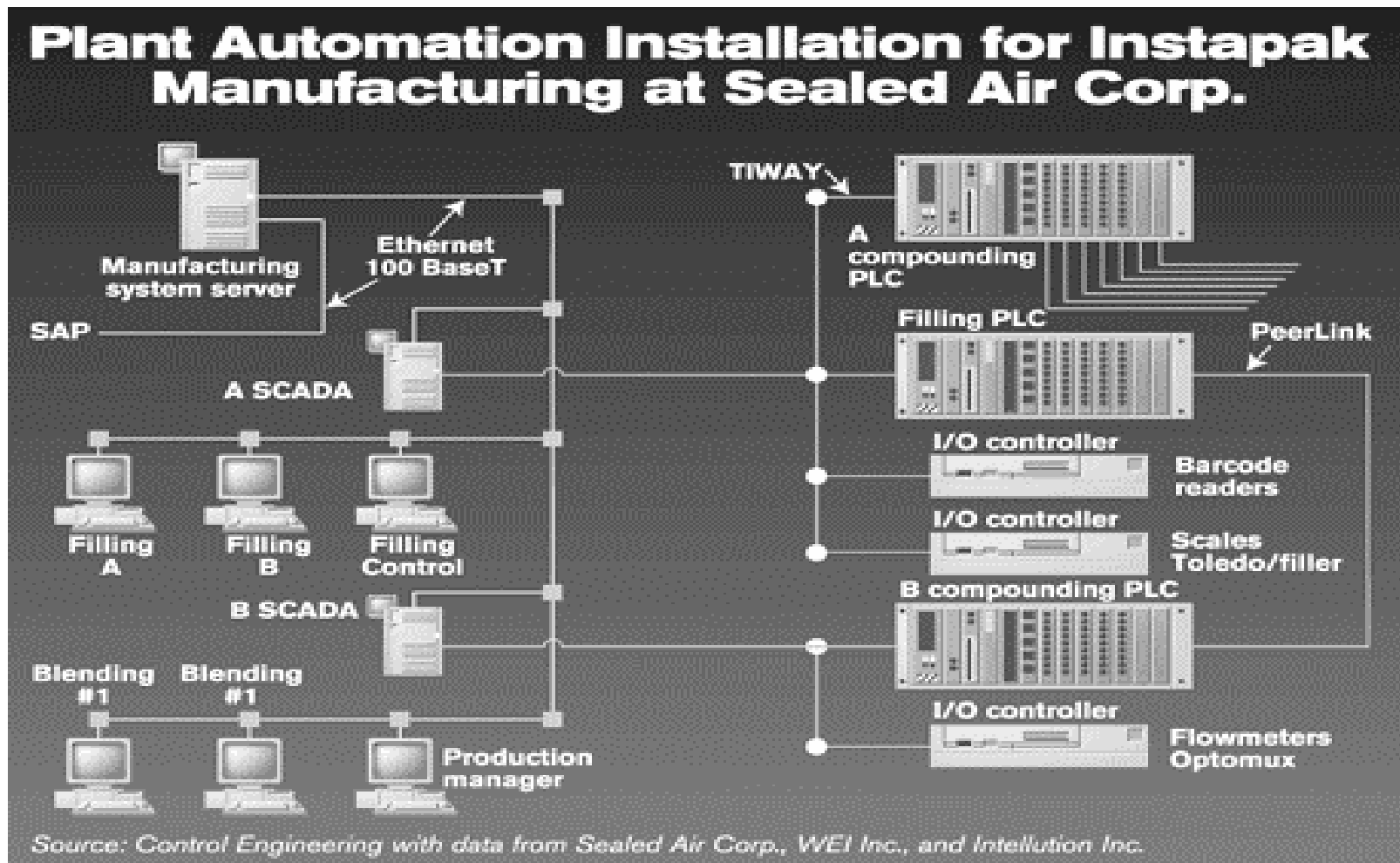
- **O. López, A Practical Guide to Regulatory Systems Hardware Qualification, Serentec Press, Inc., April 2000.**
- **O. López, Qualification of SCADA Systems, Serentec Press, Inc., March 2000.**
- **O. López, Automated Process Control Systems Verification and Validation, Pharmaceutical Technology, September 1997.**
- **GAMP Guide, Validation of Automated System in Pharmaceutical Manufacture, Version 3.0, April 1998.**

# **Introduction**

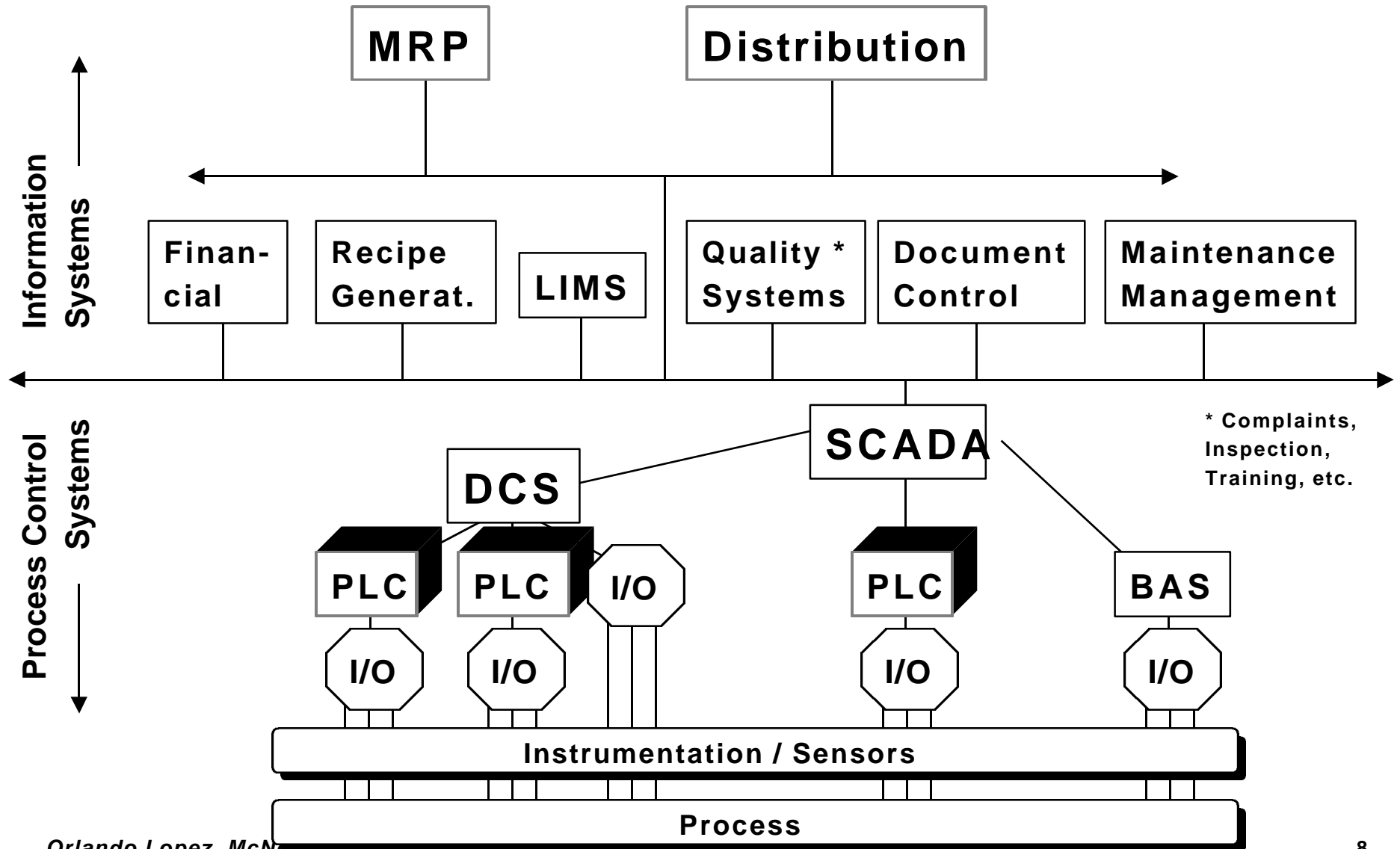
# **What is an automated manufacturing process?**

- **In simple terms, it is the use of computers to control or monitor one equipment or an entire manufacturing facility.**
- **The task may be as simple as turning off and on a motor (control) in response to a switch (instrument) or taking the temperature readings every one minute (data acquisition) and saving the data for future use.**
- **The task may be as complex as controlling an entire manufacturing facility and gathering and displaying data to facility personnel.**

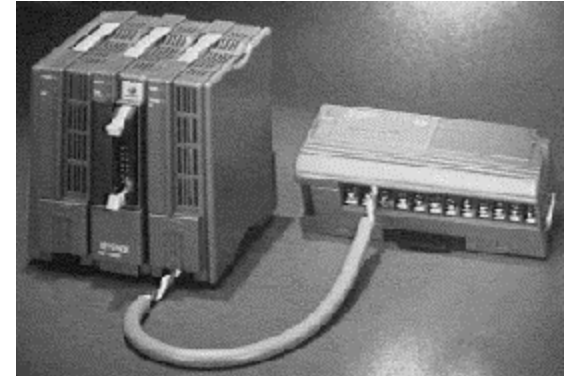
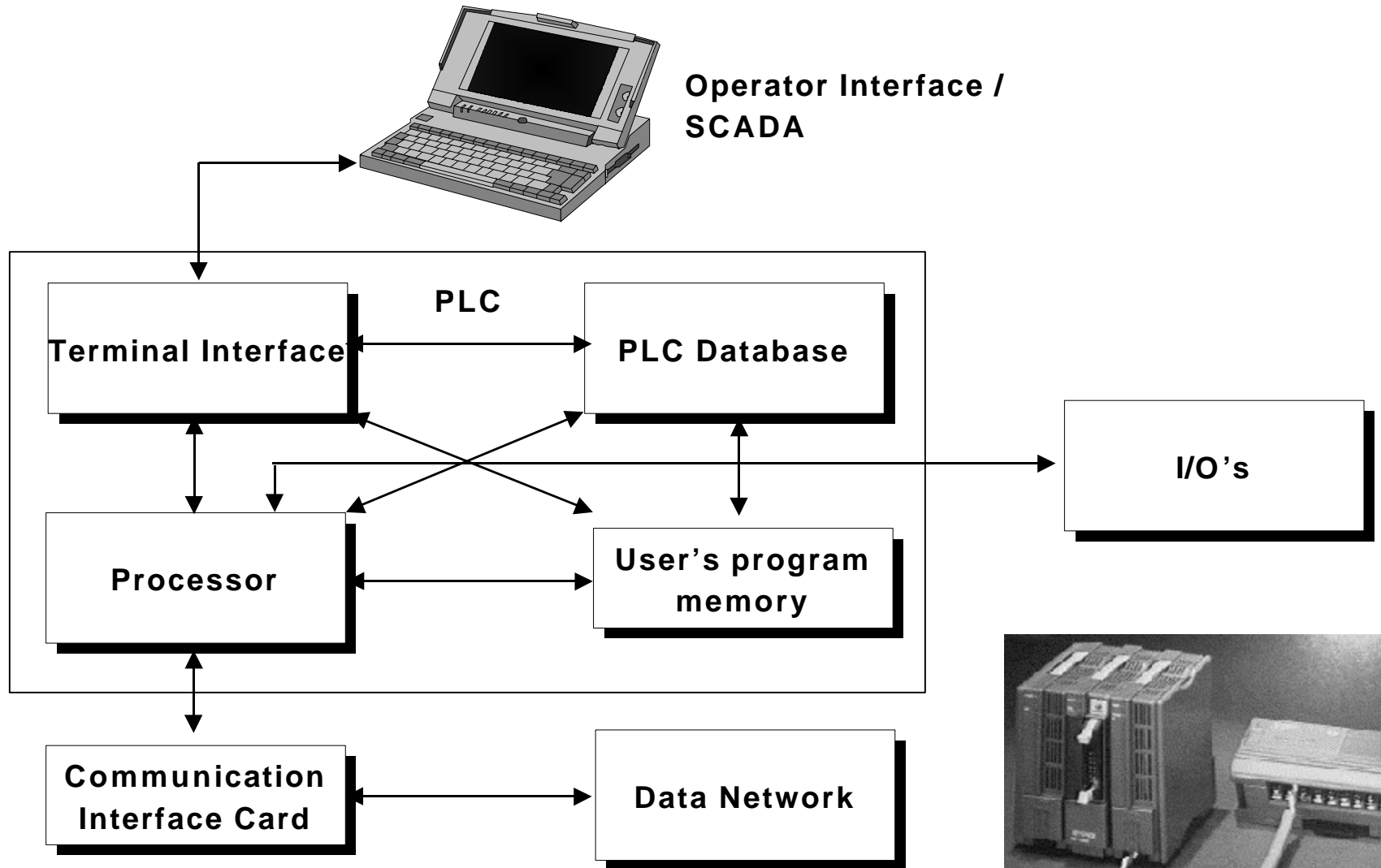
# An example of a simple automated manufacturing process



# Systems Architecture



# PLC Components



# **Software Components**

- **PLC software**, e.g., Ladder Logic.
- **HMI/SCADA** -- operator interface to the process, short term process data storage, supervisory control (e.g. recipe management and download) and alarm and event logging.
- **Batch application** -- batch automation solution.
- **Database**
- **Operating system** -- e.g., Windows NT.

# **PLC Basics -- Validation Issues**

- **I/O's.**
- **Part 11, Supervisory Control and Data Acquisition (SCADA).**
  - **Operator Interface.**
  - **Programming (Modularity).**

# **Pharmaceutical Manufacturing Regulations (summary) Automated Systems**

# **GxP Regulations**

- **GMP Regulations that apply to CS**

- ✓ **Computers.**

- **21 CFR 211.68**      **Automatic, Mechanical, and Electronic Equipment**
- **21 CFR 820.70 (i)**      **Automated processes**

- ✓ **Hardware, classified as equipment.**

- **21 CFR 211.63**      **suitable location of equipment**
- **21 CFR 211.67**      **maintenance programs**

# **GxP Regulations**

- **GMP Regulations that apply to CS**

- ✓ **Software, regarded as records.**

- 21 CFR 211.101(d) verification of records
- 21 CFR 211.180(a) record retention
- 21 CFR 211.180(c) record access
- 21 CFR 211.180(d) record media
- 21 CFR 211.180(e) record review
- 21 CFR 211.188(a) reproduction accuracy
- 21 CFR 211.188(b) (11) documentation
- 21 CFR 211.192 QC record review

# **GxP Regulations, cont.**

- **GLP Regulations that apply to CS**
  - ✓ **Hardware and data recording equipment**
    - **21 CFR 58.51**      **specimen and data storage**
    - **21 CFR 58.61**      **equipment design**
    - **21 CFR 58.63**      **maintenance and calibration of equipment**

# **GxP Regulations, cont.**

- **GLP Regulations that apply to CS**
  - ✓ **Software records and raw data.**
    - **21 CFR 58.33 study director responsible for raw data.**
    - **21 CFR 58.35 QA check that reports match raw data.**
    - **21 CFR 58.81 SOP for recording of deviations as raw data.**
    - **21 CFR 58.90 animal feed and water analyses as raw data.**
    - **21 CFR 58.185(a) report must define location of raw data.**
    - **21 CFR 58.190 raw data must be archived, retained and secured.**
    - **21 CFR 58.195 raw data retention period.**

## **GxP Regulations, cont.**

- **International Conference Harmonization (ICH) GCP Regulations that apply to CS**
  - ✓ **Electronic data systems**
    - ICH 5.5.3                      **data system validation**
  - ✓ **Electronic source data**
    - ICH 4.9.5                      **source data & document retention period**
    - ICH 5.5.3                      **data security and management**

## **Other Key Regulations / Guidelines**

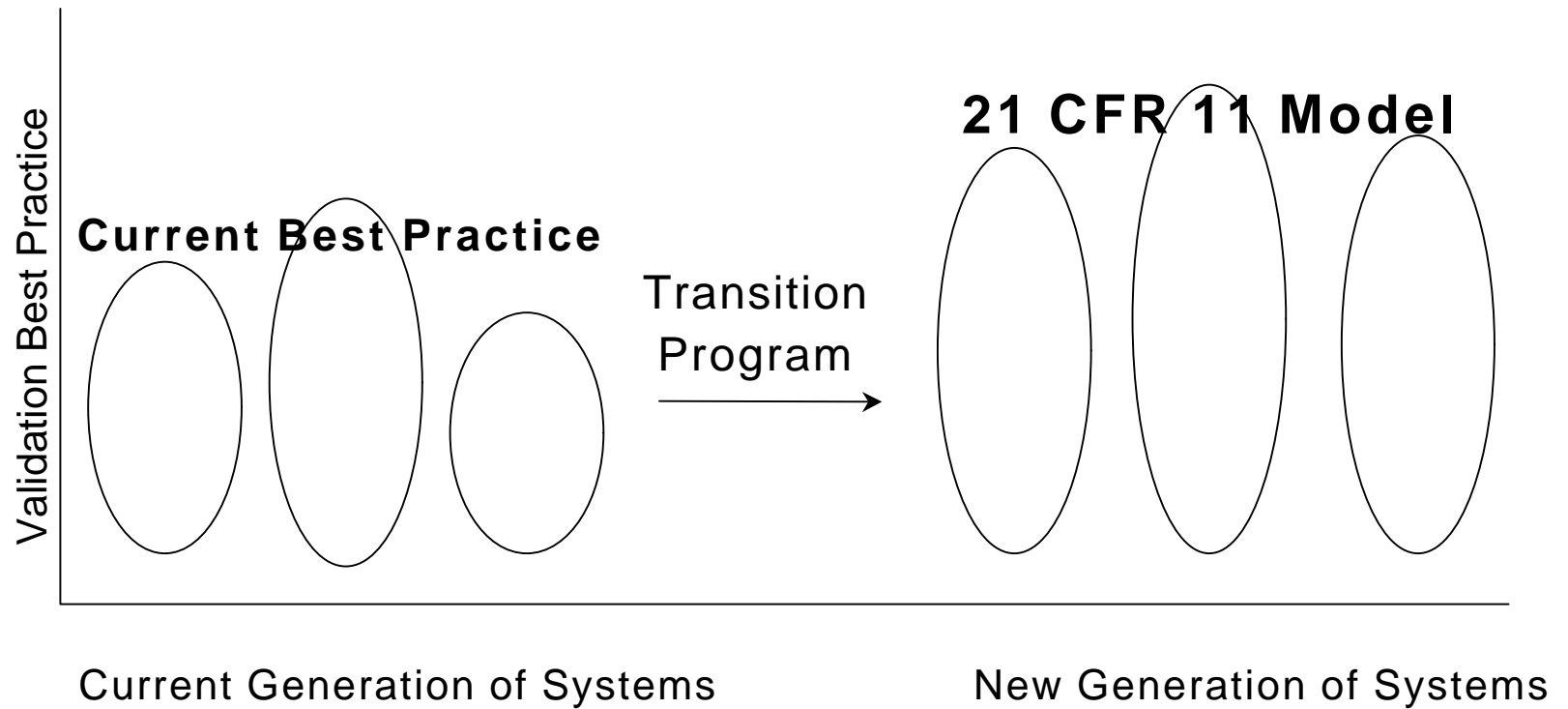
- **EU GMP, Annex 11 -- Computerized Systems.**
- **GAMP (Rev 3)**
- **CPGs**

# **Compliance Policy Guidelines**

- **I/O Checking (CPG 7132a.07).**
- **Identification of “Persons” on Batch Production and Control Records (CPG 7132a.08).**
- **Vendor Responsibility (CPG7132a.12).**
- **Source Code for Process Control Application Programs (CPG 7132a.15).**
- **CGMP Applicability to Hardware and Software (CPG 7132a.11).**
- **CGMP 21 CFR Part 11: Electronic Records, Electronic Signatures (CPG 7153.17).**

# Other Regulations

## 21 CFR 11 as a CSV model



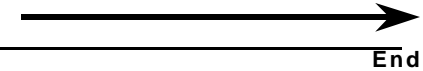
# **Automated Manufacturing Systems**

**CSV**

# **Automated Manufacturing Systems Validation Process**

- ❶ A systematic process to verify and test the implementation, installation, and testing for new computer systems or the modifications to an existing computer system.**
- ❷ Integrated with the system development methodology.**
- ❸ Life cycle methodology is recommended by worldwide regulatory authorities.**

# Computerized Systems Development Process



Start

End

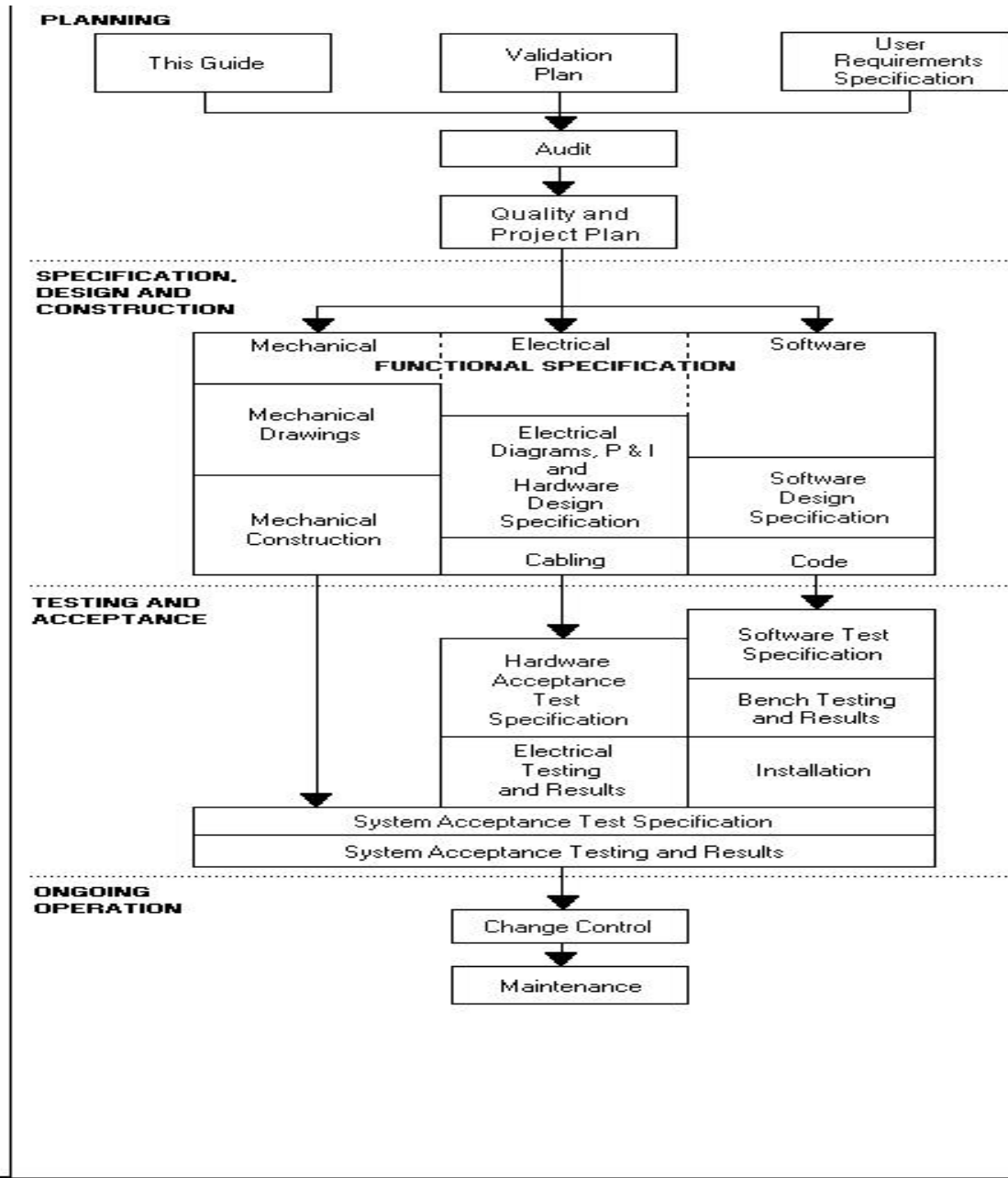
Phases →	System Development						Implementation and Acceptance	Operation / Maintenance	Retirement
	Initiation	Requirements	Design	Build	Test				
Responsibility	Users / IM / Eng	Users / IM / Eng	Developer	Developer	Developer		Users / IM / Eng	Users / IM / Eng	Users / IM / Eng
Deliverables	Justification Document (if applicable)	User Reqs. Val. Plan RFP RFP Response Vendor Audit (if applicable)  System Specification	Systems Design	Code	Unit and Integration Test Plans & Results  User Documentation System Documentation Training Documentation	FAT FAT Summary  Q Protocols and Sum. Docs.  SOPs  Transfer to production plan  VSR Release Memo  Support Log	Follow SOPs & Demonstrate Compliance	Retirement Plan	
Part 11 Considerations	Include Part 11 in Justification Document	Include Part 11 in: • Func. Reqs, • System Spec, • Val Plan, • RFP, • vendor audit • configuration	Build technical controls into system. Test technical controls.			Include procedural controls in SOPs.  Test technical controls in FAT  Include Part 11 in VSR	Periodic review for Part 11 requirements.	Include record retention requirements in Retirement Plan	

# **Critical Deliverables: Why, What, How and When**

- Business / Project Plan** → **Why the system was implemented.**
- User Requirements** → **What is needed to support the operations / operators.**
- Functional Specification** → **What the system is supposed “to do”.**
- Design Documents, Test Plans, IQ / OQ and PQ** → **Challenges How it was designed, specified, implemented and tested.**
- Requirements Matrix** → **What testing is required to confirm the user’s / system’s requirements and design.**
- Change Control** → **How / When it will be maintained in a validated state.**

**PLC**

**Design**



# **Control System Design**

- **Piping and Instrumentation Diagrams.**
- **Wiring Diagrams.**
- **Panel Drawings.**
- **Pneumatic Connection Diagrams.**
- **Instrumentation details diagrams.**
- **I/O List**
- **Instrument List**

## **Electrical and Instrumentation Design**

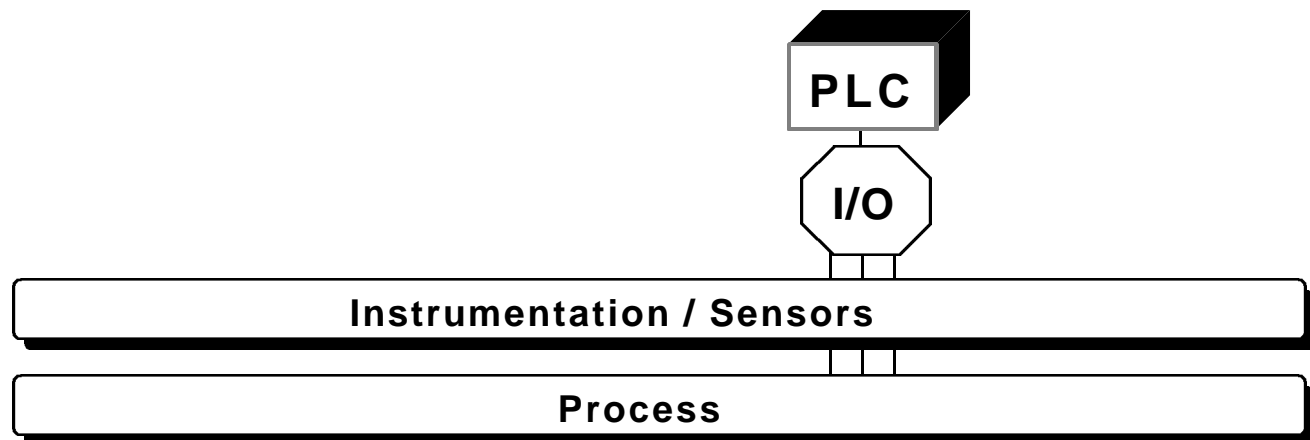
- **Code and Standards.**
- **Control Circuit Voltage.**
- **Grounding.**
- **Emergency Stop.**
- **Fault / Alarms Circuit.**
- **Operating Modes.**
- **Motor Starters.**
- **Enclosures.**
- **Motors.**
- **PLC.**
- **External Connectors.**
- **Electrical Control Devices.**
- **Rack Layouts.**
- **Recommended supply voltages.**

**PLC  
(stand alone)**

**CSV**

**PLCs -- the equipment / machine comes with a PLC and the PLC is stand alone**

- **GAMP type software 2 -- Microcontrollers.**
- **Electronic Raw Data.**



## **Summary of Part 11 Requirements Applicable PLC Systems (optional)**

**1 Validation**

**2 System Security**

**3 Operational Checks**

**4 Location Checks \***

**5 Document Control**

**6 Open/Closed Systems**

**7 Electronic Raw Data Protection**

**Note: Part 11 is applicable to electronic records and the computer system associated with the records.**

## Category 2

Category	Type of Software	Validation Approach
2	Controllers	Record configuration

- **Process / Instrumentation Design**
- **IQ**
- **Instrumentation Calibration**
- **OQ (Black Box)**

Examples: Tumbler controlled by a PLC  
(controller provided by equipment manufacturer).

# **Electronic Raw Data**

- Define the universe of data that will be collected, the procedures to collect it, and the means to verify its integrity, accuracy, reliability and consistency.

# Issues

- **Testing**

- **Demonstrate that the data acquisition functions:**

- ✓ accurately collecting and retrieving data;
    - ✓ “reading” data automatically after the prescribed period;
    - ✓ operational sequencing and security;
    - ✓ challenge data management, as appropriate;  
challenge under routine and heaviest load scenarios;
    - ✓ challenge the system response upon loss of communication.

# **GMP key elements**

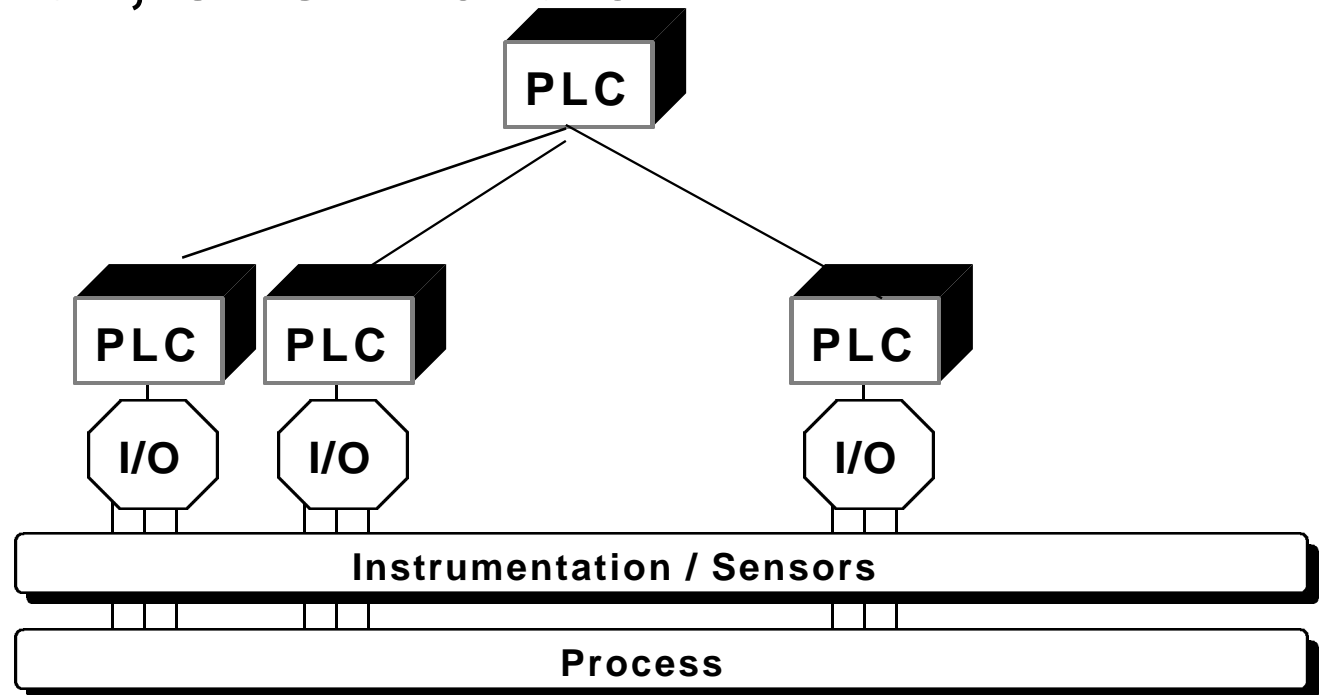
- **Qualification.**
- **Configuration Management.**
- **On-going monitoring.**
- **Periodic Reviews.**
- **Calibration.**

**PLC  
(connected to other equipment  
/ machines)**

**CSV**

## PLCs -- connected to other equipment / machines

- GAMP type software 5 -- Custom Built.
- Electronic Raw Data.
- Full validation, CPG 7132a.07.



## Category 5

Category	Type of Software	Validation Approach
5	Custom Systems	Audit supplier and validate complete system

- **SDLC and SQA Activities**
- **Supplier Audit**
- **Extensive Verifications**
- **The qualifications**

Examples: Packaging Lines.

(controller connected to other PLC / I/Os).

# Issues

- **System Design**
  - **Define the universe of data that will be collected, the procedures to collect it, and the means to verify its integrity, accuracy, reliability and consistency.**

# Issues

- **Testing**

- **Demonstrate that the data acquisition functions:**

- ✓ accurately collecting, storing and retrieving data;
    - ✓ “reading” data automatically after the prescribed period;
    - ✓ operational sequencing and security;
    - ✓ challenge data transmission to other plc network, as appropriate; challenge under routine and heaviest communication load scenarios;
    - ✓ challenge the system response upon loss of communication.

# **GMP key elements**

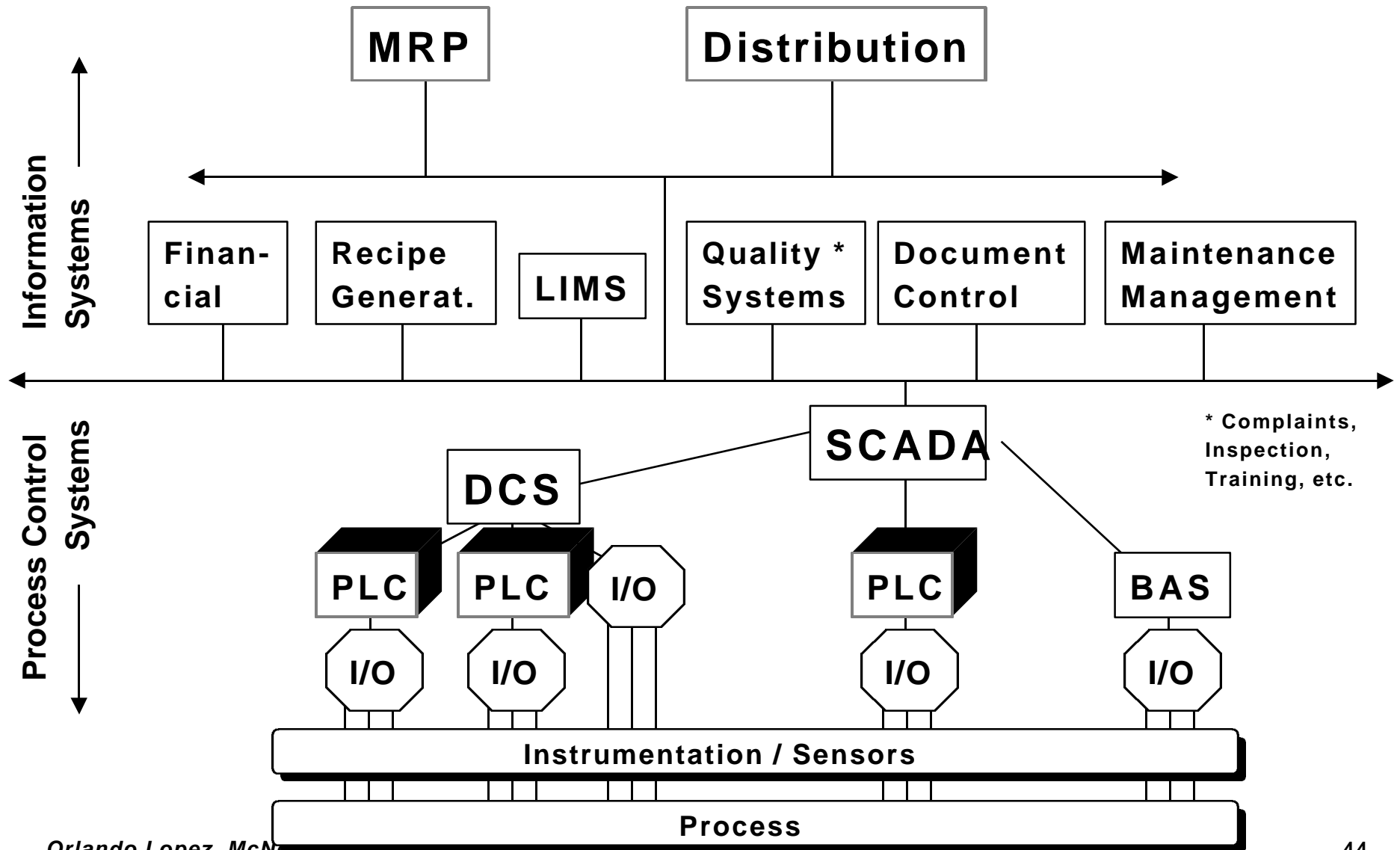
- **Validation.**
- **Configuration Management.**
- **On-going monitoring.**
- **Periodic Reviews.**
- **Calibration.**



# **PLC (linked with SCADA )**

## **CSV**

# PLCs -- connected to SCADA



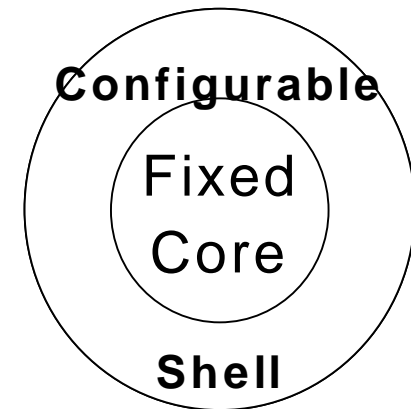
## **Summary of Part 11 Requirements SCADA Systems (required)**

- |  |                                   |
|--|-----------------------------------|
| <b>1 Validation</b>                                | <b>11 Operational Checks</b>      |
| <b>2 Audit Trails and Metadata</b>                 | <b>12 Authority Checks</b>        |
| <b>3 System Security</b>                           | <b>13 Location Checks</b>         |
| <b>4 Electronic Signature Security</b>             | <b>14 Document Control</b>        |
| <b>5 Code and Password Security</b>                | <b>15 Open/Closed Systems</b>     |
| <b>6 Code and Password Maintenance</b>             | <b>16 Signature Manifestation</b> |
| <b>7 Electronic Password Assignment</b>            | <b>17 Signature Purpose</b>       |
| <b>8 E-Sig <u>without</u> Biometric/Behavioral</b> | <b>18 Signature Binding</b>       |
| <b>9 E-Sig <u>with</u> Biometric/Behavioral</b>    | <b>19 Certification to FDA</b>    |
| <b>10 Record Retention/Protection</b>              |                                   |

# Category 4 and 5

Category	Type of Software	Validation Approach
4	Configurable Software Packages	Audit supplier, validate application and any custom code

- **SDLC and SQA Activities**
- **Supplier Audit**
- **Extensive Verifications**
- **The qualifications**



Examples: SCADA packages

# Category 4 and 5

Category	Type of Software	Validation Approach
5	Custom Systems	Audit supplier and validate complete system

- **SDLC and SQA Activities**
- **Supplier Audit**
- **Extensive Verifications**
- **The qualifications**

Examples: Ladder logic PLC based systems

# Issues

- **System Design**
  - **Define the universe of data that will be collected, the procedures to collect it, and the means to verify its integrity, accuracy, reliability and consistency.**

# Issues

- **Testing**

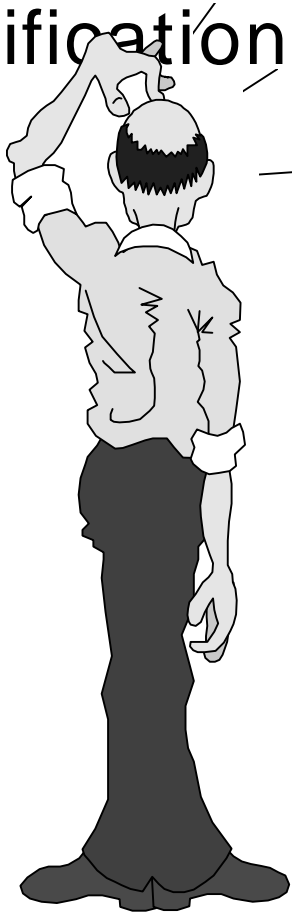
- **Demonstrate that the data acquisition functions:**

- ✓ accurately collecting, storing and retrieving data;
    - ✓ “reading” data automatically after the prescribed period;
    - ✓ operational sequencing and security;
    - ✓ challenge data transmission to other plc network, as appropriate; challenge under routine and heaviest communication load scenarios;
    - ✓ challenge the system response upon loss of communication.

# **GMP key elements**

- **Validation.**
- **Configuration Management.**
- **On-going monitoring.**
- **Periodic Reviews.**
- **Calibration.**

# What goes into a qualification protocol?



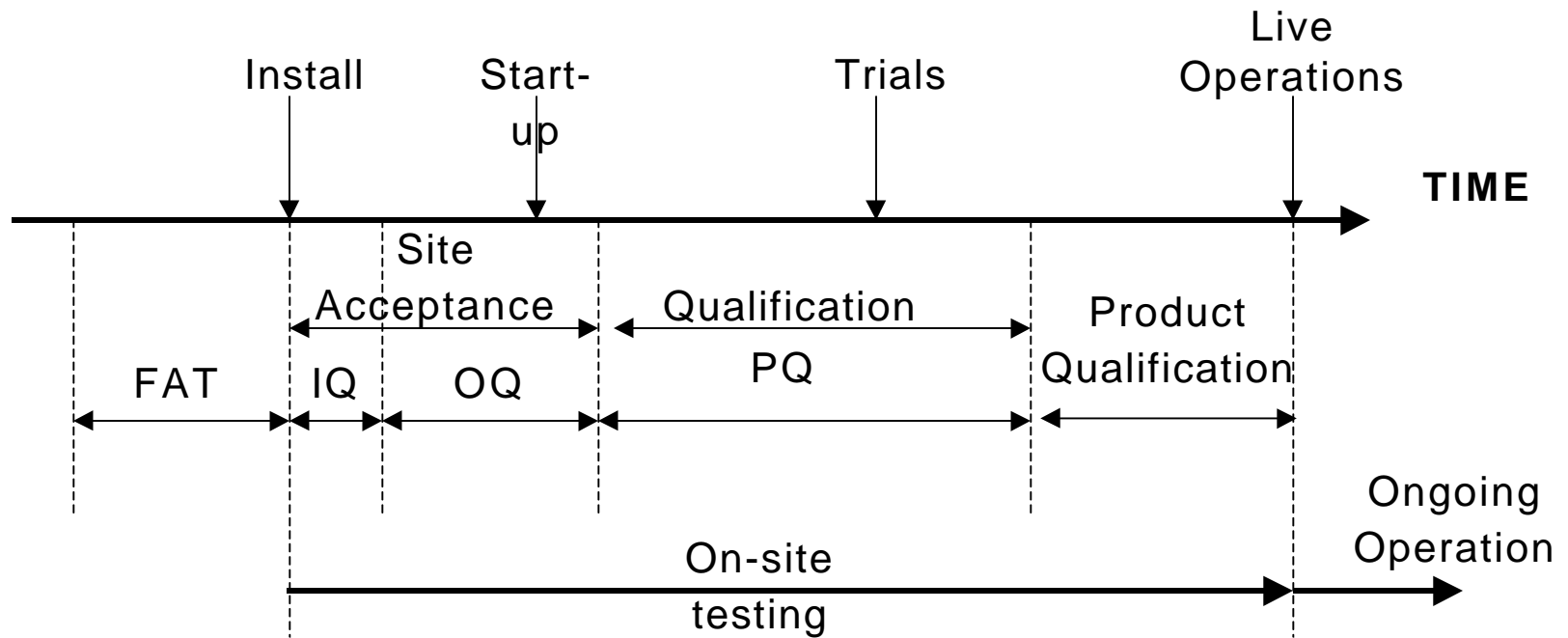
**Testing**

**Factory Acceptance  
Testing**

**Site Acceptance Testing**

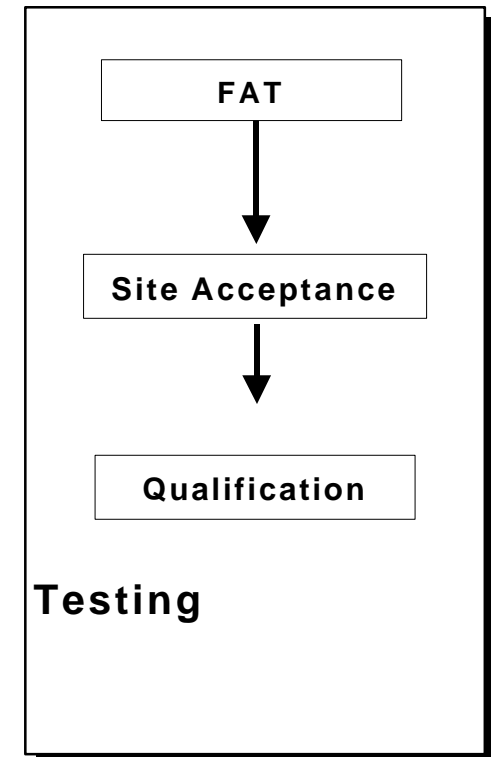
**Qualification**

# Testing Timeline



# FAT and Site Acceptance, and Qualification

- The focus of the FAT is the FS and the URS.
- The focus of the Site Acceptance is the requirements contained in the DS and FS. Don't repeat field independent User Acceptance test cases as part of Site Acceptance testing.
- A comprehensive Site Acceptance testing implies not to repeat during the Qualification the testing related with DS (IQ) and FS (OQ).
- The Qualification phase can concentrate only in testing the users requirements (PQ).



# **User and Site Acceptance, and Qualification**

## **. User Acceptance**

- **It is performed by the developer of the configurable elements at the developer's site.**
- **Test conditions are very similar to the hardware and software to be encountered in the operational conditions.**
- **Main tests, based on Functional Specification:**
  - ✓ Functional Testing.
  - ✓ Communication, including error detection protocol.
  - ✓ Screens Navigation/Verification.

# **User and Site Acceptance, and Qualification**

## **• User Acceptance**

### **➤ Main tests, cont:**

- ✓ Database structure, files tables and data archiving.
- ✓ Startup/Shutdown of the computer systems.
- ✓ Batch Control/Reports.
- ✓ Alarming.
- ✓ Timing.
- ✓ Sequencing.
- ✓ Loss of System Power.

# **User and Site Acceptance, and Qualification**

## **• User Acceptance**

### **➤ Main tests, cont:**

- ✓ Recipe Downloading and Saving.
- ✓ History Tracking, Data acquisition (e.g., scan I/Os from RTUs) and Database access controls.

# **User and Site Acceptance, and Qualification**

## **• Site Acceptance**

- **Set of activities comprised by the system installation, qualification of the installation, start-up, operational testing and turnover.**
- **Performed under operational conditions by the integrator.**
- **Main Tests: HW Qualification:**
  - ✓ Schematic drawings, P&ID, Instruments List, Loop Diagrams, I/Os List.
  - ✓ Calibration.
  - ✓ Wiring Checks.

# **User and Site Acceptance, and Qualification**

## **• Site Acceptance, cont.**

### **➤ Main Tests: HW Qualification, cont:**

- ✓ Hardware configuration and, interface verification and integration.
- ✓ Physical security.
- ✓ Built-in diagnostics (e.g., power supply, processor, peripheral equipment, communication)
- ✓ Interfaces.
- ✓ Control Panel Verification.

# **User and Site Acceptance, and Qualification**

- **Site Acceptance, cont.**

- **Main Tests: SW Installation Qualification:**

- ✓ Input / Output Module Test.
    - ✓ Man-machine interface installation verification.
    - ✓ Logical security.
    - ✓ Database installation and database configuration verification.
    - ✓ System start-up / shut-down.

# **User and Site Acceptance, and Qualification**

## **• Site Acceptance, cont.**

### **➤ Main Tests: SW Operational Qualification:**

- ✓ Recipe Downloading and Saving.
- ✓ Catastrophic recovery verification
- ✓ Man-machine-interface functional verification
  - Boundary values.
  - Invalid values.
  - Special values.
  - Decision point & branch conditions.
  - Control panel.

# User and Site Acceptance, and Qualification

## • Site Acceptance, cont.

### ➤ Main Tests: SW Operational Qualification, cont:

- ✓ Batch Control/Reports.
- ✓ Hardware redundancy verification.
- ✓ History Tracking, Data acquisition and Database access controls.
- ✓ Trending and alarms processing.
- ✓ Interface with other applications (e.g., SPC, EBR, Information Systems).
- ✓ Timing (if applicable).

# **User and Site Acceptance, and Qualification**

## **• Site Acceptance, cont.**

### **➤ Main Tests: SW Operational Qualification, cont:**

- ✓ Process Sequencing.
- ✓ PLC Security.
- ✓ User Interface Application / Operating System Security.
- ✓ Verification/evaluation of SOPs.
- ✓ Environmental Verification (\*).

# **User and Site Acceptance, and Qualification**

## **• Qualification**

- **Performance Qualification for the application.**
- **Occurs under operational conditions but not as part of the actual operational process.**
- **Final verification of the implementation of the URS.**

# **User and Site Acceptance, and Qualification**

## **. Qualification, cont.**

### **➤ Main Tests Performance Qualification.**

- ✓ Determination of the system accuracy in receiving, recording, storing, and processing electronically manufacturing information.
- ✓ Determination of the system accuracy in arriving at the appropriate disposition decision based upon the received data.
- ✓ Determination of the integration between all components.

# **User and Site Acceptance, and Qualification**

## **. Qualification, cont.**

### **➤ Main Tests Performance Qualification, cont.**

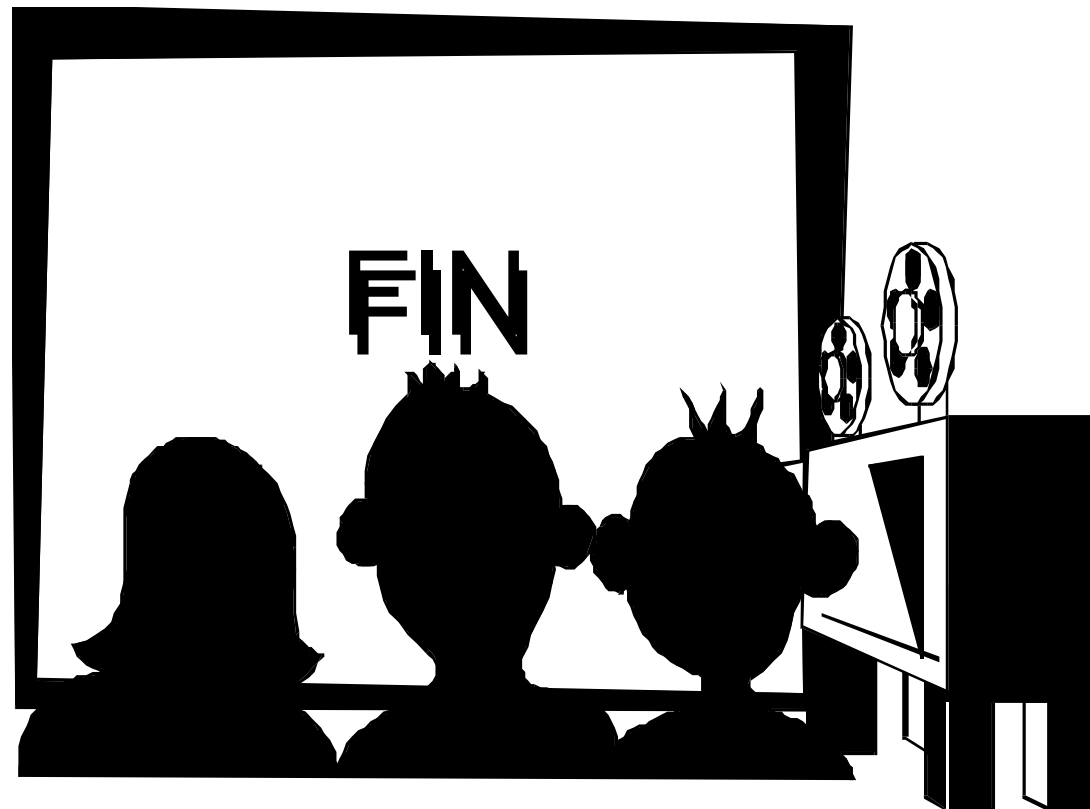
- ✓ Platform security.
- ✓ Audit trail reporting.
- ✓ Systems backup.
- ✓ System restoration.
- ✓ Database recovery.
- ✓ If database conversion, migration, or pre-loading with data is to occur prior to PQ testing, the verification of these activities and their associated data may be addressed in the PQ.
- ✓ Process Sequencing.

# **Controls during operation**

# Operation controls

- **Controls are required for the ongoing operation of the system.**
  - problem reporting
  - change control
  - user operating procedures
  - operating procedures such as back-up and recovery, database administration
  - disaster recovery
  - preventive maintenance
  - environmental control
  - training
  - security
  - periodic reviews

# Thank you for your attention!



**Questions?**

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