EMS

Environmental Monitoring Systems

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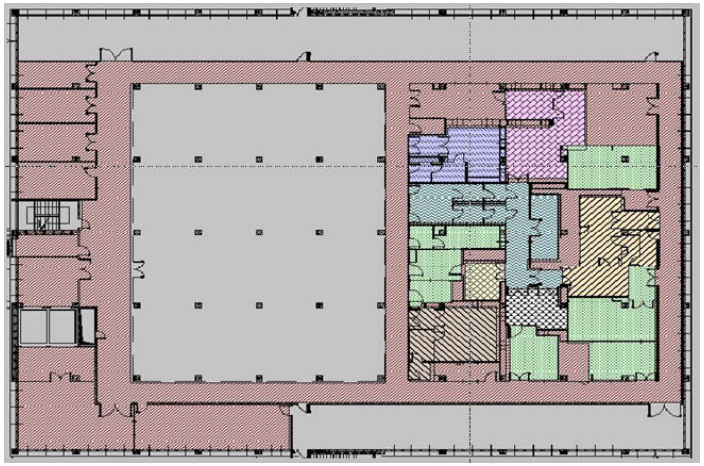
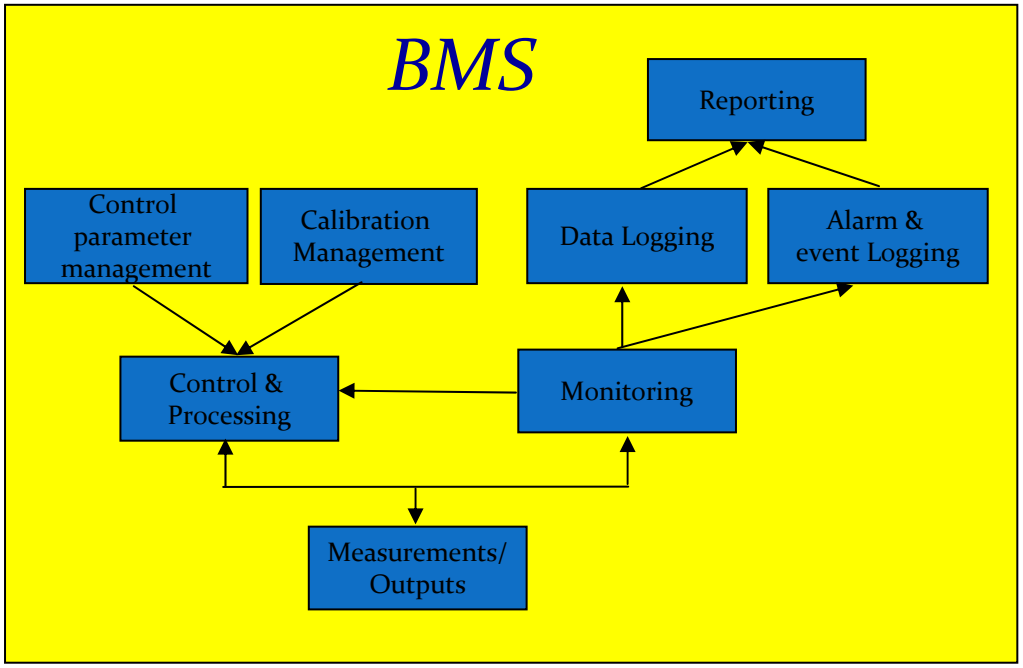
What is an EMS?

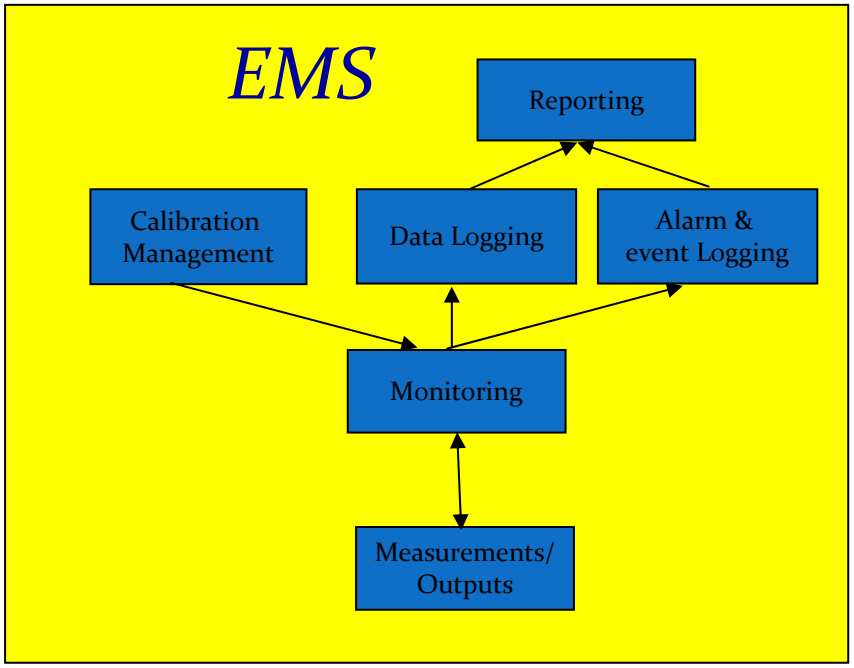
It is known by a number of names:

- Environmental Quality Monitoring System
- Environmental Monitoring System
- Independent Monitoring System
- Facilities Monitoring System



BMS VS EMS





- Provide control & monitoring of HVAC (AHUs
- May also include light control, energy monitoring
- BMS may cover both GMP and non-GMP area
- Generally doesn't require validation, GEP

- Provide monitoring of GMP areas: rooms, warehouse
- Normally independent from BMS to simplify validation
- Require validation following GAMP

Why EMS?

- Drugs are normally manufactured in clean rooms to avoid Contamination
- Rooms conditions may affect the product quality directly or indirectly
- Storage area temperature & humidity may effect product quality

Regulatory bodies (FDA, EMEA, etc) require monitoring and recording of environmental conditions

Why EMS?

GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS (August 2006)
CHAPTER 3
PREMISES AND EQUIPMENT
PREMISES - General
"Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment."

CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICAL (INCLUDES BLOOD AND BLOOD COMPONENTS)
211.46
(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.

Why EMS ?

FDA Warning Letter 2002-DAL-WL-04 (November 2001)
Extracted from FDA warning letter 2002-DAL-WL-04 USA
"2. Failure to provide equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature when appropriate for the manufacture, processing, packing or holding of a drug product [21 CFR 211.46(b)]. For example, the manufacturing and filling rooms of (a) **, ****, and **** are not equipped with differential pressure monitors; and (b) **** and **** are not equipped with temperature and humidity control monitors [FDA-483 Item 4]."**

Selected FDA 483 Observations (July 1999)
Product Manufacture
"Environmental monitoring systems (temperature and humidity) should be validated (IQ/OQ/PQ)."

Selected FDA 483 Observations (December 1999)
Sterile Product Manufacture
"Environmental monitoring results during dynamic and static conditions should be trended."

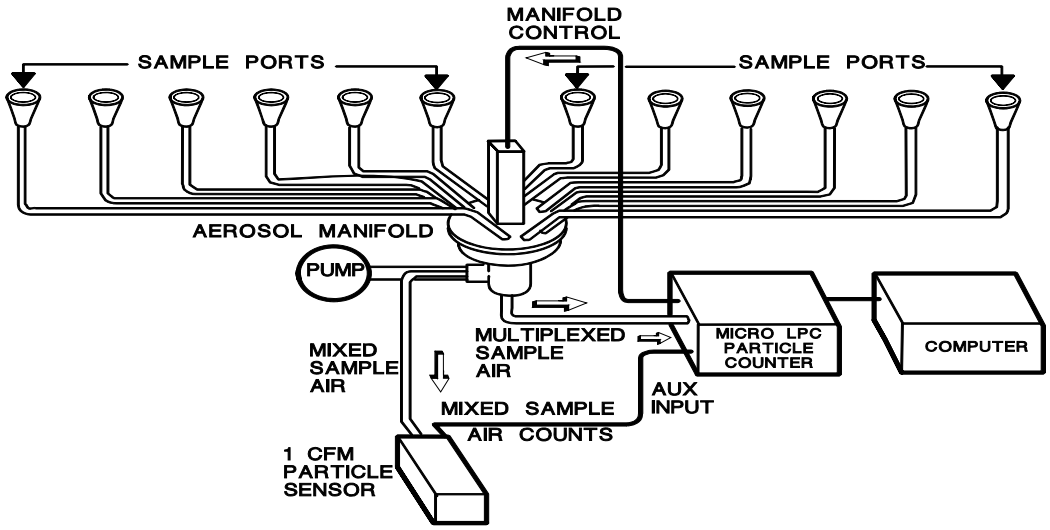
Environment Conditions Monitored

- Temperature
- Humidity
- Air Pressure
  - Rooms are kept at different pressure to outside to minimise exchange with outside air to stop cross contamination
  - Monitor the status of filters

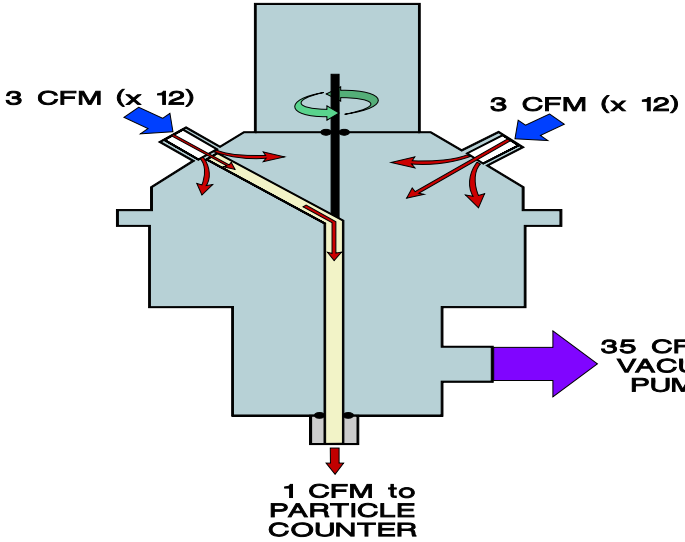
- Air Velocity
  - To ventilate and supply room with clean air regularly to stop contamination and bugs growing
- Airborne particles
  - Using particle monitoring units to monitor the classification of the room (Class A, B,C)
- Lighting

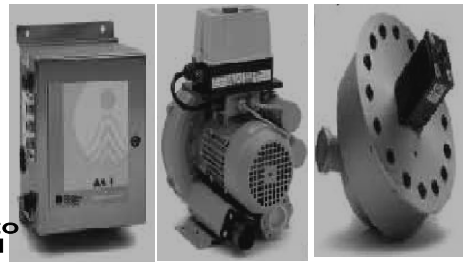
Particle Monitoring Units

- Measures Particle sizes and their concentration in the atmosphere
- Available as either portable or fixed
- Normally communicate using serial link e.g. Modbus



Continuous/Multiplexed Monitoring of a Facility using an Aerosol Manifold





Temperature & Humidity

FDA Warning Letter 02-BLT-13 (January 2002)
Extracted from FDA warning letter 02-BLT-13 USA 03/01/2002
"5. Failure to establish written procedures (21 CFR 211.22, 211.67, 211.80, 211.100, 211.122, 211.166, and 211.198) for the following: …
f. The monitoring of temperatures, humidity, and the air-handling system in the production area; …"

Extracted from FDA warning letter W/L 06-07 (February 2007)
Extracted from FDA warning letter W/L 06-07 USA
"Appropriate procedures have not been defined for controlling environmental conditions. Specifically your devices are labelled for room temperature or refrigerated storage. Your current manufacturing and warehousing facilities do not have temperature controlling equipment and you have no assurance that devices are maintained below the labelled 86ºF. [21 CFR 820.70]"

Differential Pressure

Selected FDA 483 Observations (April 2001)
Sterile Product Manufacture
"Differential pressures should be monitored continuously (not twice daily) in the aseptic fill controlled environment areas."

Selected FDA 483 Observations (December 2004)
Product Manufacture
"Pressure differentials between manufacturing rooms (encapsulation, granulation, tableting) should be continually monitored to determine that the pressure specification is maintained during production."

Selected FDA 483 Observations (January 1997)
Sterile Product Manufacture
"Air pressure differential data throughout the clean room monitoring locations should be trended, and there should be comparison or trending of environmental data from year to year."

Air Velocity

GUIDANCE FOR INDUSTRY
STERILE DRUG PRODUCTS PRODUCED BY ASEPTIC PROCESSING
- CURRENT GOOD MANUFACTURING PRACTICE (September 2004)
IV. Buildings and Facilities
C. Clean Area Separation
"Air change rate is another important clean room design parameter. For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable. Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas."

Selected FDA 483 Observations (December 2000)
Sterile Product Manufacture
"There should be specifications for the air velocity in an aseptic core."

Selected FDA 483 Observations (April 1997)
Sterile Product Manufacture
"There should be a routine air velocity monitoring program to assure the maintenance of a 90 foot/minute +/- 20% speed at critical filling sites during the filling operation."

Particle Monitoring

Selected FDA 483 Observations (January 2007)
Sterile Product Manufacture
"The airborne particulate monitoring program should adequately monitor locations in the aseptic processing zone that pose a contamination risk to the product, e.g. stopper hopper, filling heads and accumulating table (empty vials)."

Extracted from FDA Warning Letter 2006-NOL-04 (February 2006)
Extracted from FDA warning letter 2006-NOL-04
"2. You do not have control systems to prevent contamination, as required under 21 CFR 211.42(c)(10)(i). For example, you do not perform environmental monitoring for viable and non viable organisms in your aseptic areas."

FDA Warning Letter 2004-NOL-36 (September 2004)
Extracted from FDA warning letter 2004-NOL-36
"2. Your firm failed to establish a system for monitoring environmental conditions in the aseptic, processing area as required by 21 CFR 211.42(c)(10)(iv). Specifically, routine environmental monitoring of the aseptic filling area for viable and non-viable particulates is not done. Routine microbiological monitoring of the gowns and gloves of the employees working in the class 100 area is not done. [Reference: Form FDA 483, Observation 4]"

Calibration

Selected FDA 483 Observations (September 2000)
Product Manufacture
"There should be written procedures describing the calibration / certification methods and tolerance limits for all instruments used during production operations to include:

Selected FDA 483 Observations (December 1999)
Product Manufacture
"There should be calibration and maintenance procedures for HVAC equipment to include relative humidity and temperature sensors, and system sanitization."

FDA Warning Letter [Reference Obliterated] (July 2003)
Extracted from FDA warning letter
"10. Failure to establish and maintain adequate procedures to ensure that equipment is routinely calibrated, as required by 21 CFR 820.72(a). For example, the gauges used to measure the differential pressure across the clean room prefilter and HEPA filter are not subject to periodic calibrations."

Alerts & Alarms

CPGM-DB CHAPTER 56 - DRUG QUALITY ASSURANCE
7356.002M INSPECTIONS OF LICENSED BIOLOGICAL THERAPEUTIC DRUG PRODUCTS (October 2003), PART III – Inspectional, B. Inspection
9. GMP
b. Buildings (para 6)
"Review procedures for controlling and monitoring pressure differentials, humidity, and
temperature. Procedures should include actions to be taken when results are not within established limits. Ensure that the impact of out-of limit results on the product is adequately addressed."

GUIDANCE FOR INDUSTRY
STERILE DRUG PRODUCTS PRODUCED BY ASEPTIC PROCESSING - CURRENT GOOD MANUFACTURING PRACTICE (September 2004)
GLOSSARY
"Alert Level - An established microbial or airborne particle level giving early warning of potential drift from normal operating conditions and triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels
are always lower than action levels."
"Action Level - An established microbial or airborne particle level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation."

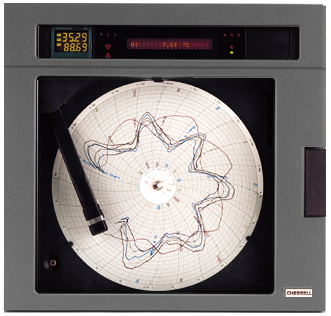
Alerts & Alarms

Selected FDA 483 Observations (March 1999)
Sterile Product Manufacture
"Environmental monitoring warning and action limits should be established through validation."

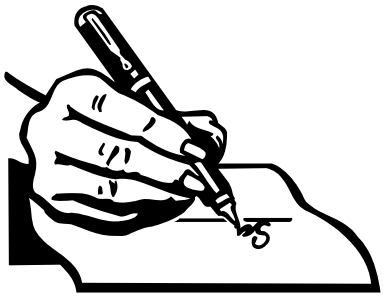
Selected FDA 483 Observations (December 2005)
Sterile Product Manufacture
"Environmental monitoring action and alert limits for clean rooms should be based on historical data and/or statistical rationale"

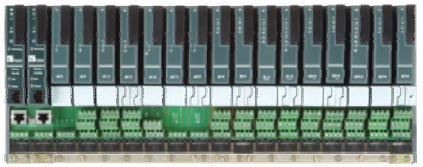
Selected FDA 483 Observations (November 2003)
Sterile Product Manufacture
"QA should review environmental monitoring data for excursions occurring during lot production to determine the potential impact on product quality."

EMS Solutions



Paper Recorder

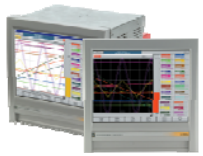
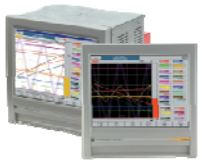




SCADA Solution

Electronic Recorder

EMS Solutions

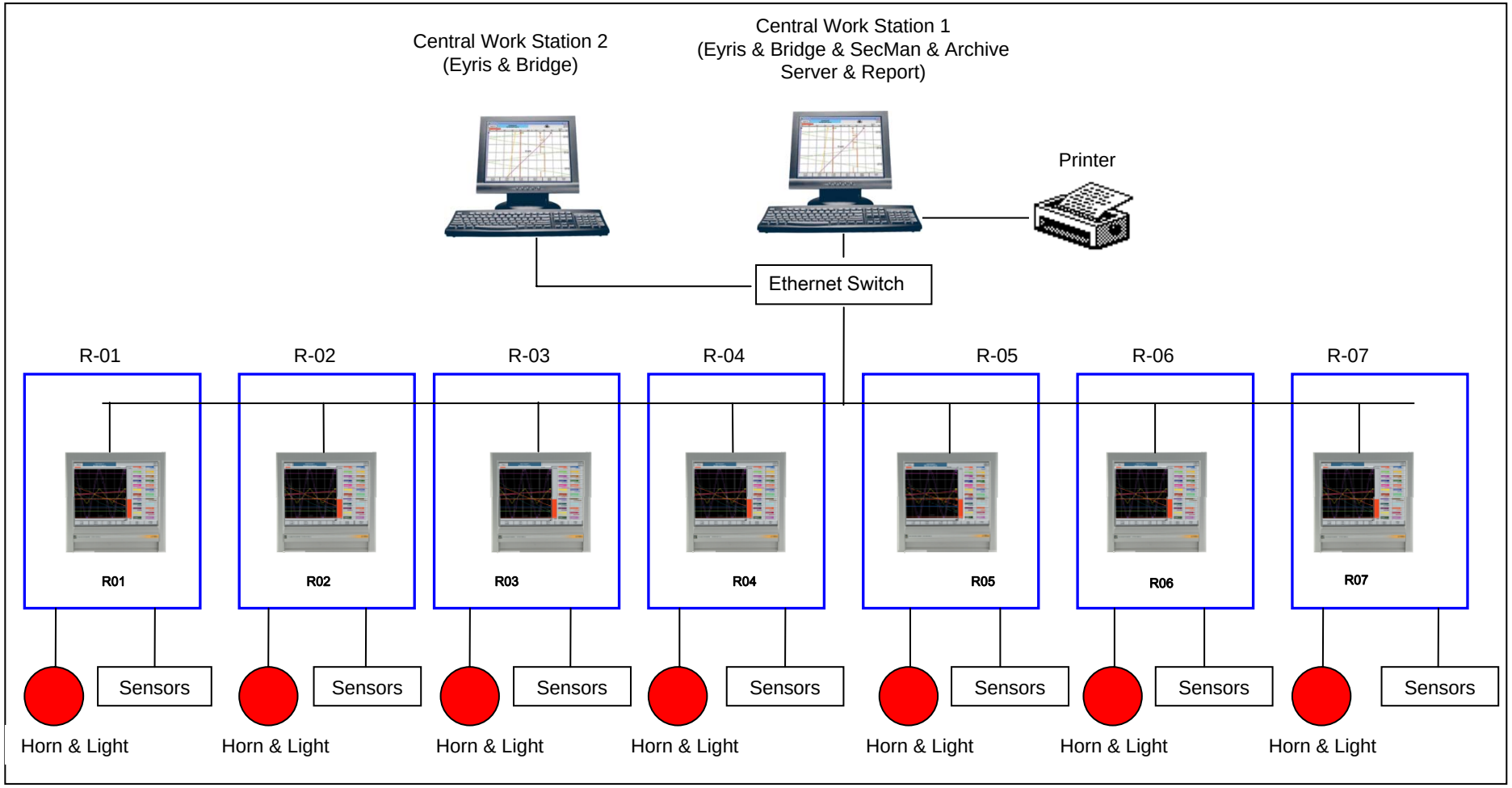
ROOM/Rooms	BUILDING	PLANT	ENTREPRISE
 Validation Doc	 Validation Doc	 Validation Doc	 Validation Docs
  Recorders	 Recorders	SCADA 	  OPEN ACCESS
	OR SCADA  	 	+ **Multiple Plant Solutions**
<48 I/O	50-200 I/O	> 200 I/O	Open Access to MES & ERP

Minimum Requirement of an EMS

- **Paper Recorders**
  - **Record data from the sensors with accurate Time & Date**
  - **Provide & Record Alarm with accurate Time & Date**
  - **Archive**

- **Electronics Data Recording**
  - **All above**
  - **Record Audit trail (events, operator actions, signatures) with accurate time & date**
  - **Store data securely**
  - **Create reports on demand**
  - **Ability to review and submit to inspectors on demand**
  - **Satisfy 21 CFR Part 11, Tamper proof log files & Electronics signature**

EMS Case Study



Software Categories

Recorder

6180A
(Standard fimware – CAT 3)
Parameterised elements include:
- network setup
- channel / alarm setup
- chart setup
- recording setup
- security setup

User Screens
(Configured Item – CAT 4)

Central Workstation

Central Workstation
(Windows XP operating system – CAT 1)

Eurotherm Security Manager Tool
(Standard package – CAT 3)
Parameterised elements include:
- network setup
- security setup

Eurotherm Eyris Viewing Tool
(Standard package – CAT 3)
Parameterised elements include:
- screens set-up

Eurotherm Review Tool
(Standard package – CAT 3)
Parameterised elements include:
- chart set-up
- data retrieval setup

Eurotherm Dream Report
(Standard package – CAT 3)

Report Configurations
(Configured Item – CAT 4)

Eurotherm Bridge Tool
(Standard package – CAT 3)
Parameterised elements include:
- network setup

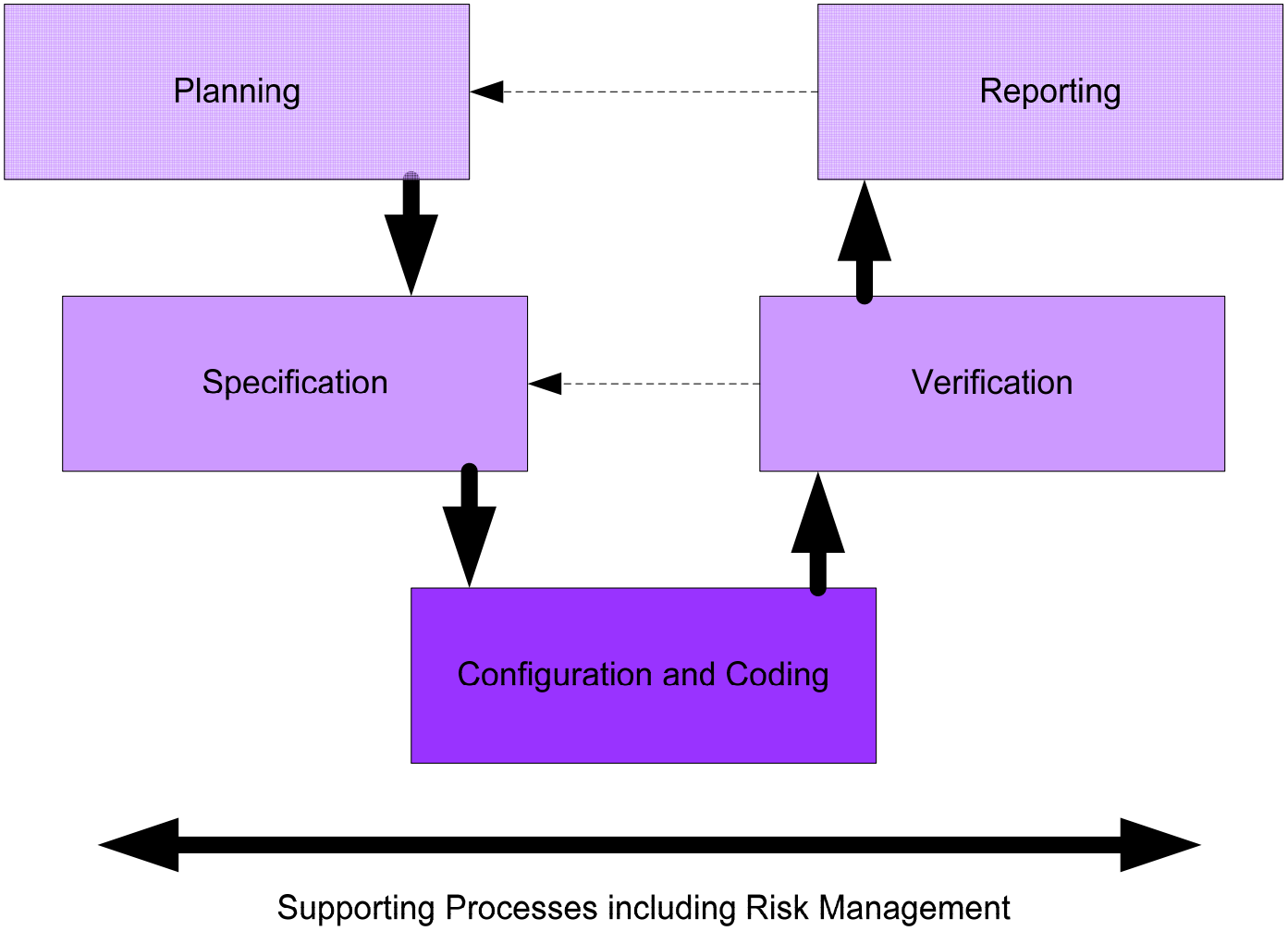
Security Guard Workstation

Security Guard Workstation
(Windows XP operating system – CAT 1)

Eurotherm Eyris Viewing Tool
(Standard package – CAT 3)
Parameterised elements include:
- screens set-up

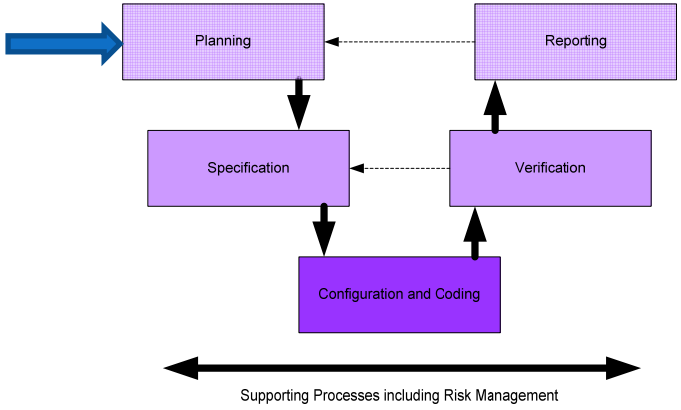
Eurotherm Bridge Tool
(Standard package – CAT 3)
Parameterised elements include:
- network setup

Life Cycle Model for an EMS



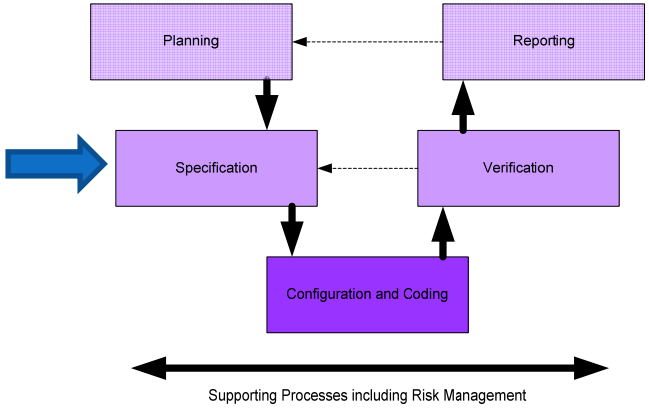
Planning Activities

Ref	Activity	Responsibility
A1	Review customers URS and initial risk assessment	PM
A2	Generate Project Plan (Gantt)	PM
A3.1	Generate Quality Plan	PM
A3.2	Review Quality Plan	QM
A3.3	Approve Quality Plan	(customer)



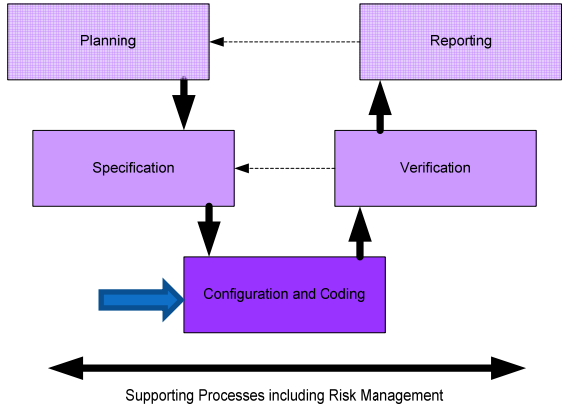
Specification Activities

Ref	Activity	Responsibility
B1.1	Generate Functional Specification (FS)	PM, LE
B1.2	Review FS	R
B1.3	Approve FS	(customer)
B2.1	Generate detailed design documentation for category 3 items	LE
B2.2	Review Definition Spreadsheets	R
B2.3	Approve Definition Spreadsheets	PM
B3.1	Generate detailed design documentation for category 4 items	LE
B3.2	Review Design Specifications	R
B3.3	Approve Design Specifications	PM
B4.1	Generate Hardware Design and Configuration Specification (HDS) for category including drawing package for enclosures	PM, LE, DO
B4.2	Review HDS	R
B4.3	Approve HDS	(customer)



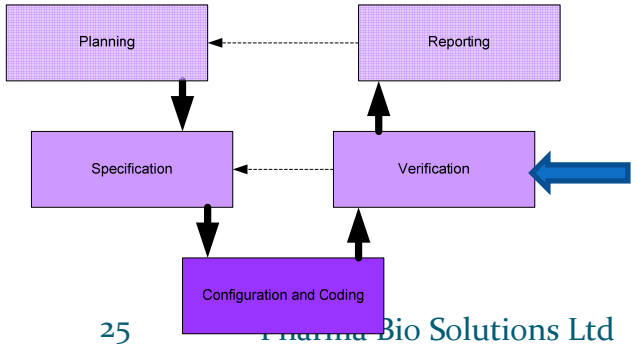
Configuration & Coding Activities

Ref	Activity	Responsibility
C1.1	Order hardware including calibration certificates	PM/LE
C1.2	Build Product	Production
C1.3	Receive bought-in product	LE
C1.4	Build Bespoke hardware: Enclosures	LE
C2.1	Produce configuration management schedules	LE/PE
C2.2	Produce Software	LE/PE



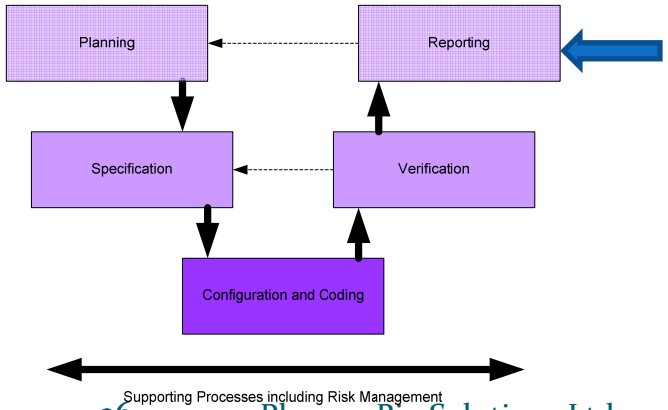
Validation Activities

Ref	Activity	Responsibility
D1.1	Generate test documentation for category 3 items	LE
D1.2	Generate test documentation for category 4 items	PM, LE
D1.3	Generate test protocol for hardware	PM, LE
D1.4	Review test documentation	R
D1.5	Approve test documentation	(customer)
D2	System Integration	PE
D3.1	Eurotherm Internal Test (unwitnessed)	PM/LE
D3.2	Review Integrated Test Results	R
D4.1	Factory Acceptance Test (witnessed by customer)	PM, LE, customer witness
D4.2	Review Factory Acceptance Test Results	Customer reviewer
D5	Ship to site	LE
D6	Cabling and Installation	PM, PE subcontractor
D7	Provide training	Training officer
D8.1	Site Acceptance Test (installation & functional tests)	PM, LE, customer witness
D8.2	Review Site Acceptance Test Results	Customer reviewer
D9	Loop Calibration & Sensors	(customer)

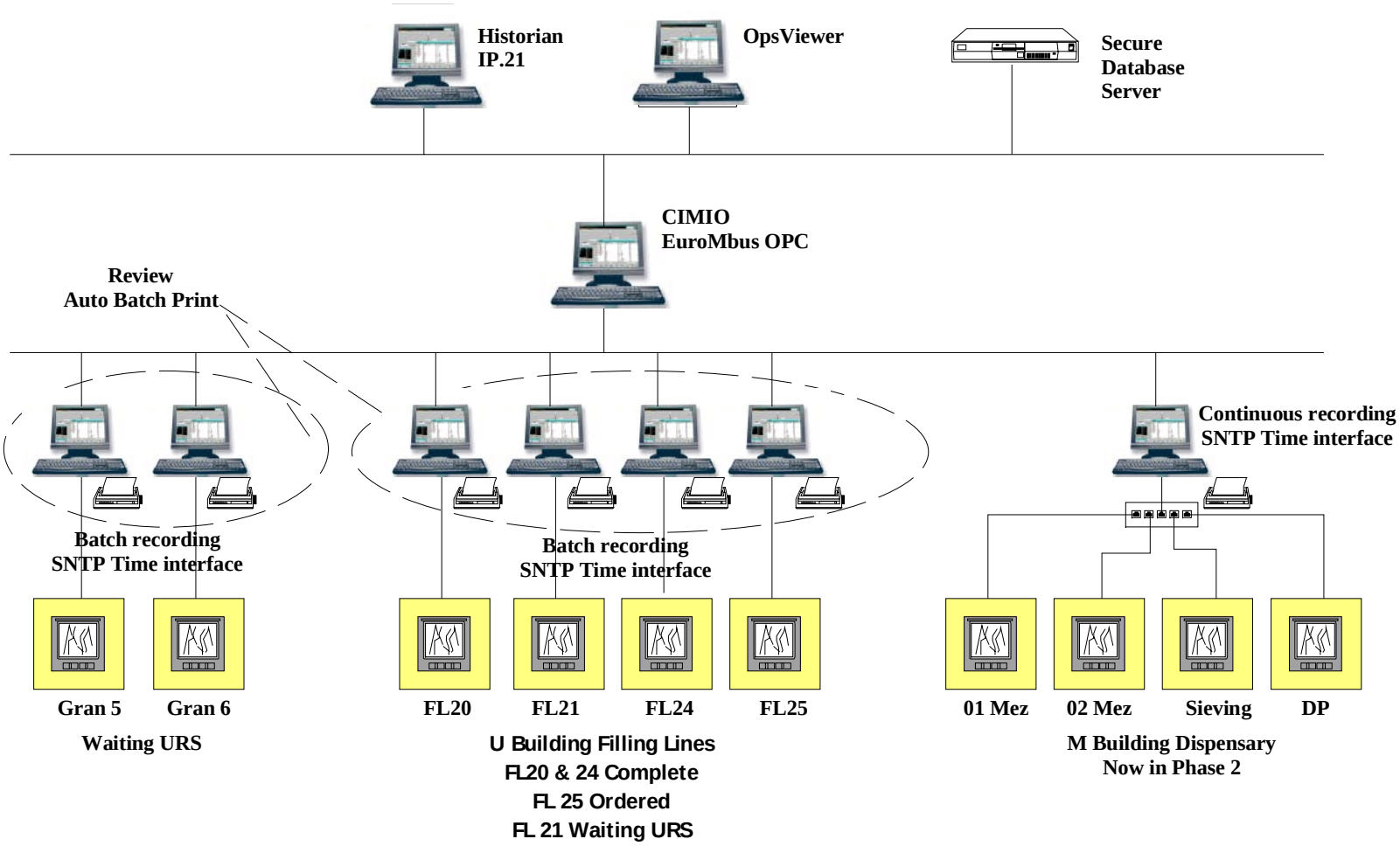


Reporting Activities

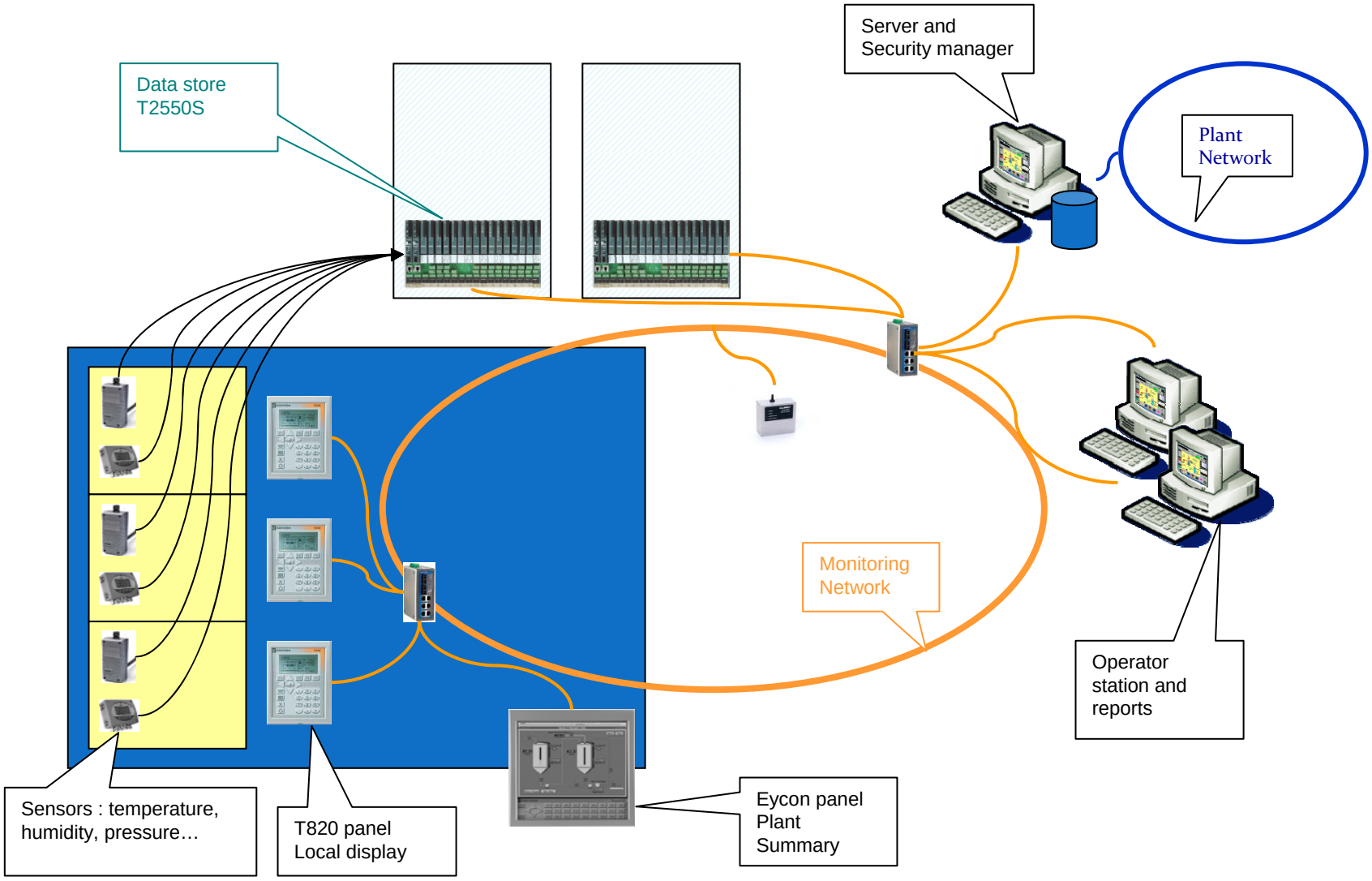
Ref	Activity	Responsibility
E1.1	Generate system final documentation	PM, LE
E1.2	Review ‘as built’ documentation	R
E1.3	Approve ‘as built’ documentation	(customer)
E3.1	Generate final quality report and handover checklist	PM
E3.2	Review final quality report handover checklist	QM
E3.3	Approve final quality report handover checklist	(customer)
E4	Assist customer with review of residual risks	PM/LE
E5	Archive documentation and configurations	LE



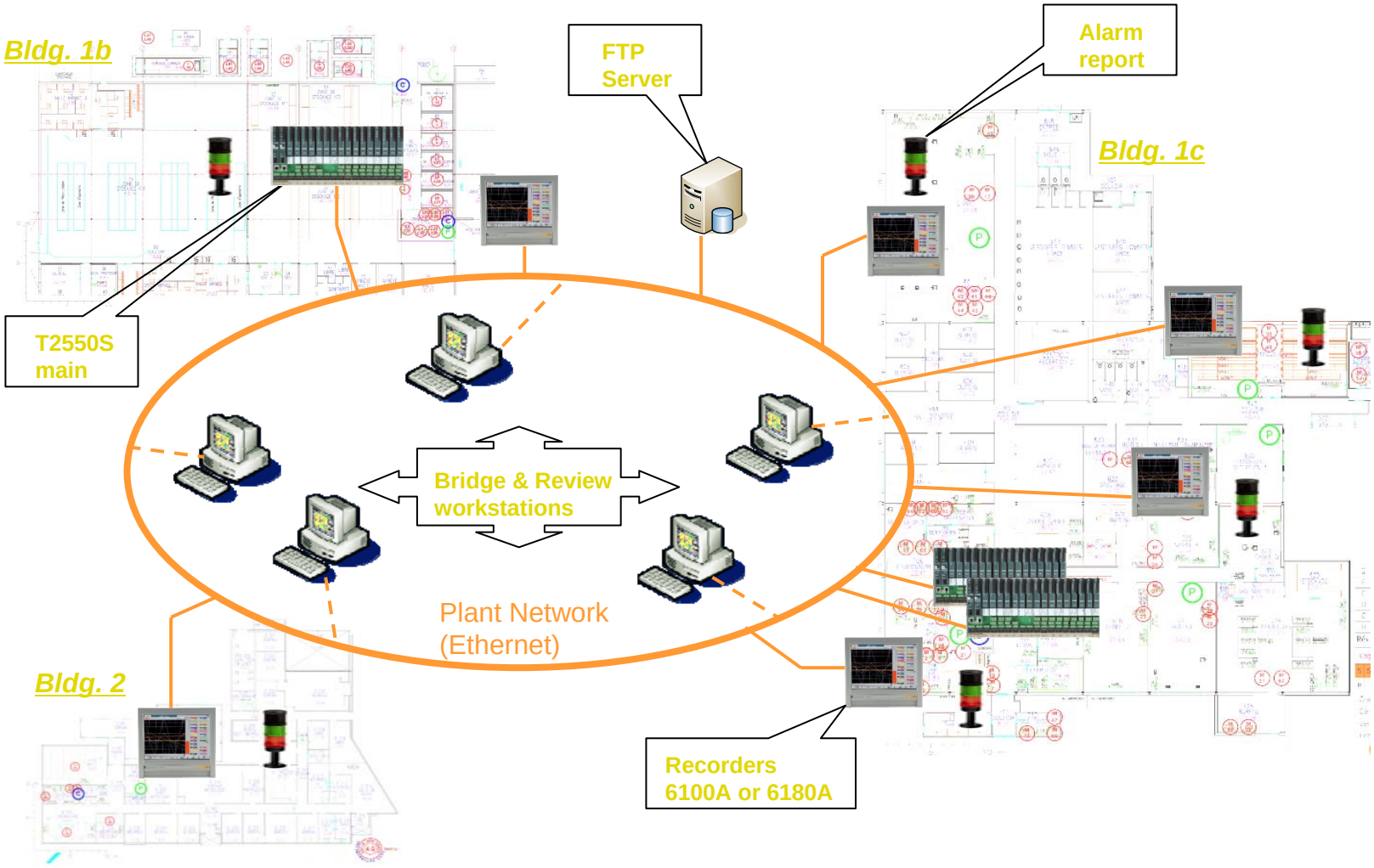
Typical Plant EMS



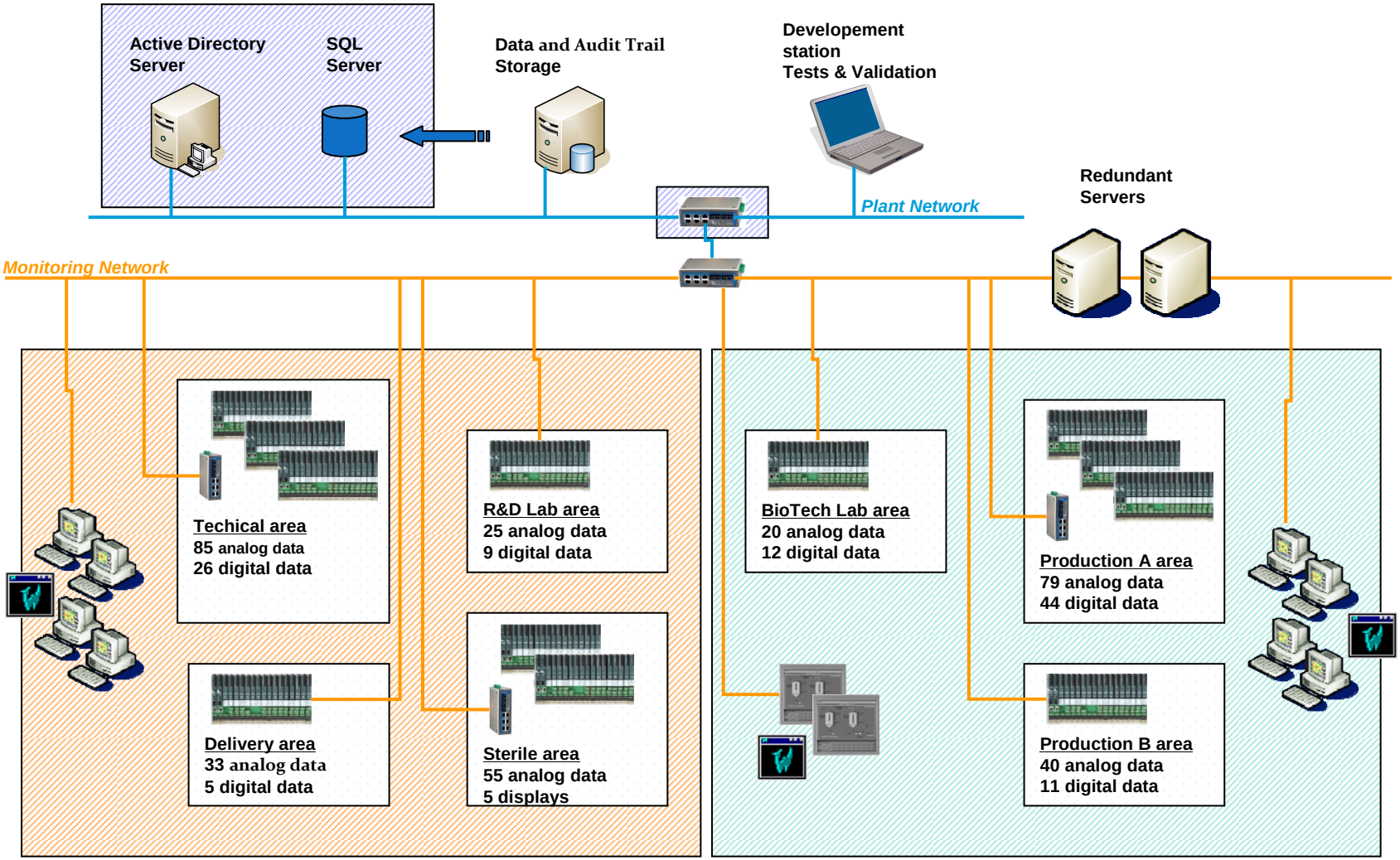
EMS for an R&D Building



EMS for an R&D Building



EMS for a Plant



EMS with Particle Monitoring