


Automation solutions with GAMP compliance

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Content

- Automation strategy for the regulated industry
- Intro Regulatory impact today  vision
- Validation Master Plan (VMP)
- Validation Plan (VP)
- V Model

Automation solutions with GMP compliance

What will you do when the FDA is at your door?

Two rules of thumb



...if you can imagine explaining your validation procedure with a straight face to an FDA inspector, you are probably okay. If the idea of explaining your procedure to a living, breathing FDA inspector makes you squirm, then you probably have some work to do!”...

“If it's not in writing it doesn't exist.”

Supplier Audits (General statement)

Preconditions to get projects in the regulated industries:

- **ISO9001/2000 certified**
 - Management system
 - Management handbook
- **Validation Master Plan (VMP)**
- Validation Plan (VP)
- **GAMP 4** (assessment)
- **GAMP 5** launch 8th and 9th April 2008 (Copenhagen)

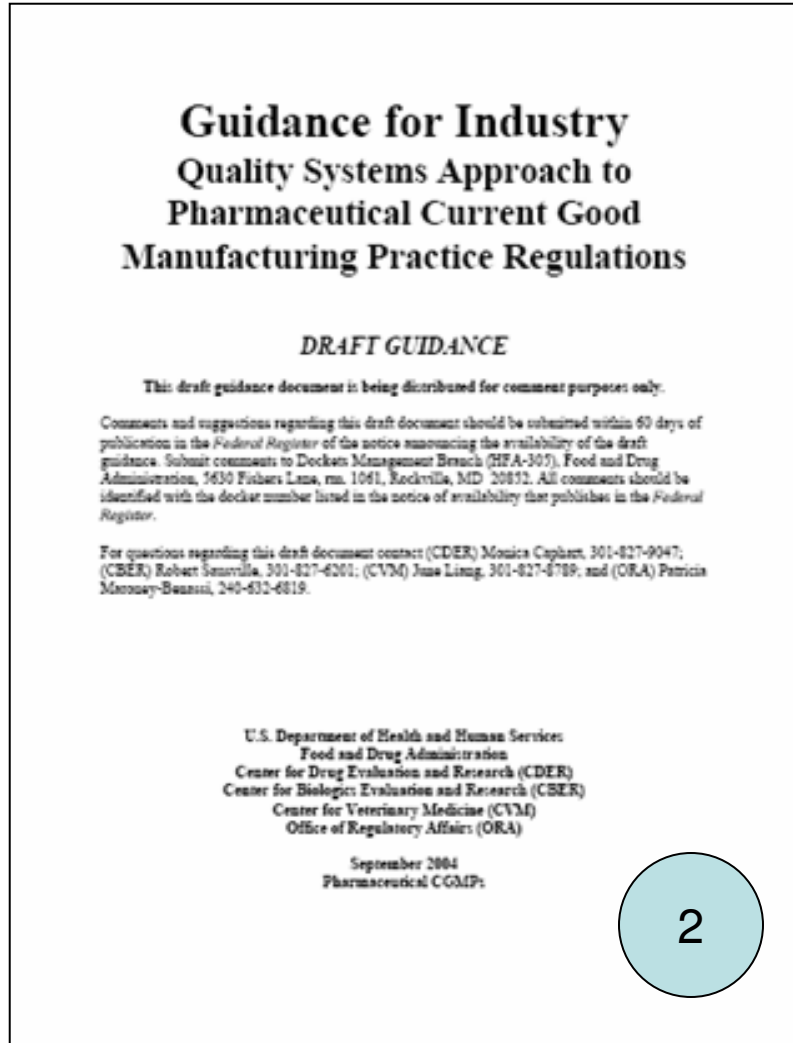
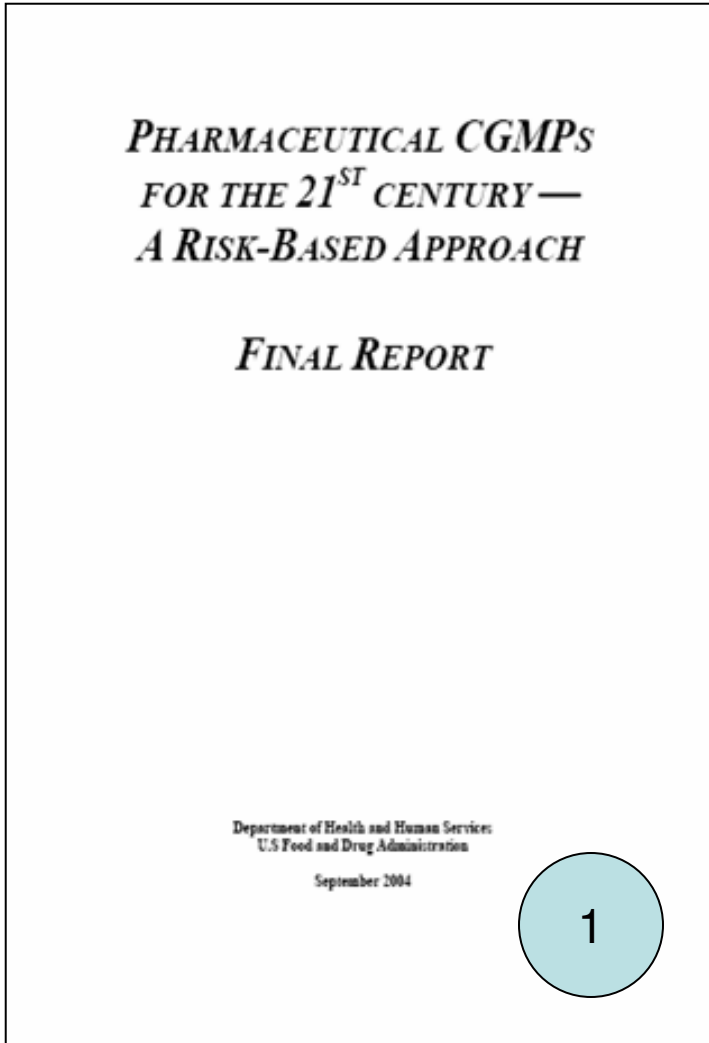
Supplier Audits (General statement)

Preconditions to get projects in the regulated industries:

- Trainings
 - Awareness GMP Training
 - GAMP Basic Training
 - GAMP Advanced Training
- Training planned, performed and documented

Trained and certified employees!

Intro Regulatory impact



Intro Regulatory impact

Guidance for Industry
PAT — A Framework for
Innovative Pharmaceutical
Development, Manufacturing,
and Quality Assurance

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

Pharmaceutical CGMPs
September 2004

3



Innovation

Stagnation

Challenge and Opportunity
on the Critical Path
to New Medical
Products

FDA
U.S. Department of Health and Human Services
Food and Drug Administration
March 2004

4


Regulatory impact

- Today:
 - **New initiatives to:**
 - ❑ Improve manufacturing quality
 - ❑ Accelerate development
 - ❑ Lower the regulatory burden
 - **FDA New principles:**
 - ❑ Quality by design & design space
 - ❑ Quality systems approach
 - ❑ Reflecting product & process understanding and knowledge
- **FDA's future focus:**

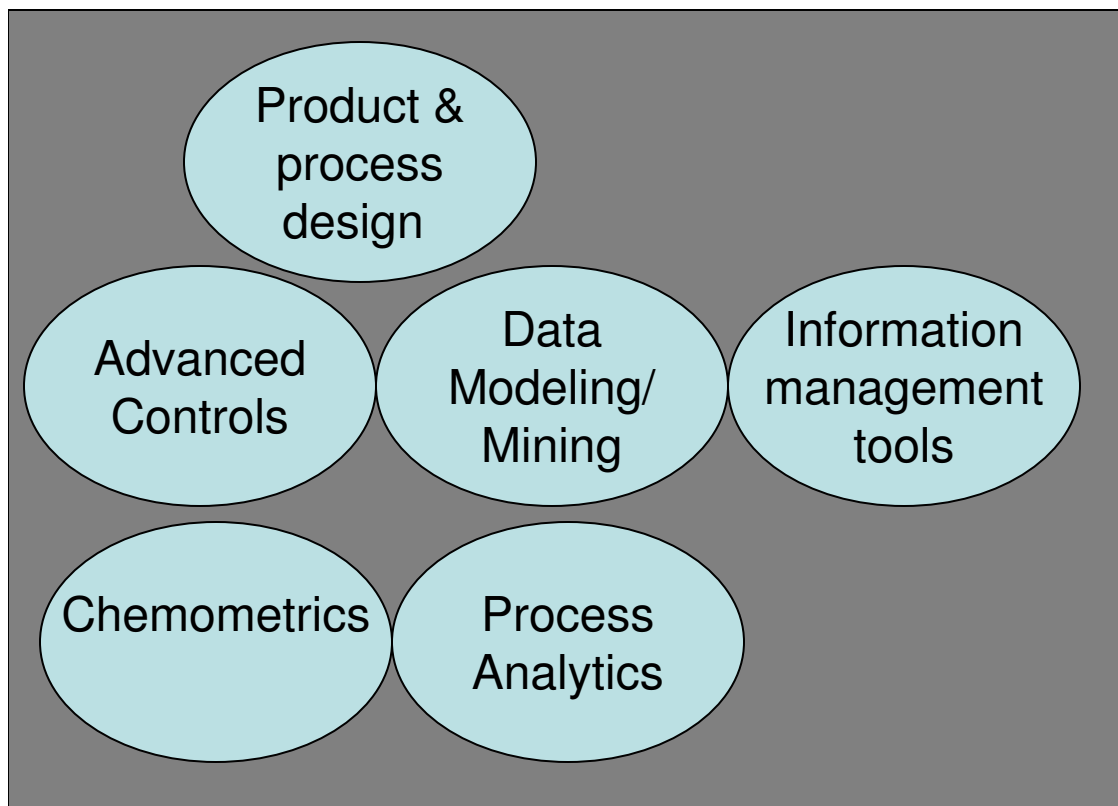
Keynote address at IFPAC February 2007, by FDA's Chief Medical Officer, Dr. Janet Woodcock, on

 - ❑ Development & manufacturing should be integrated
 - ❑ Development of quality surrogates for clinical performance (link critical product attributes to clinical outcomes)
 - ❑ Rigorous, mechanistically based and **statistically controlled processes**

Approach

- Top down
- Validation Master Plan (VMP) followed by
- Validation Plan (VP)
- The GAMP® 4 Guidance for Validation of Automated Systems is undergoing a comprehensive review, update, and enhancement  GAMP 5 risk-based approaches for the 21st century

Process Analytical Technology (PAT)



Process Analysers

Process Control tools

**Data analysis & mining tools
(Multivariate Data Analysis, ...)**

**Data collection, storage and
retrieval tools**

Reporting tools

**Continuous improvement &
knowledge management tools**

Many projects; easy to handle

More people can handle many projects



Project Managers, Project Leaders,

Engineering: special skills

- Engineering projects from site survey to maintenance
- Packaged and fully engineered solutions
- Harmonized engineering procedures



Engineered solutions

e. g. LifeScience Industry



Pharma & FDA requirements (21CFR Part11)

Qualification based on Memograph S PROFIBUS validation



Plant Asset Management

FieldCare, Compucal, W@M



Silo/Tank visualization and monitoring

Visualization based on P View, Fieldgate and Java Applets
Visualization for Inventory Control

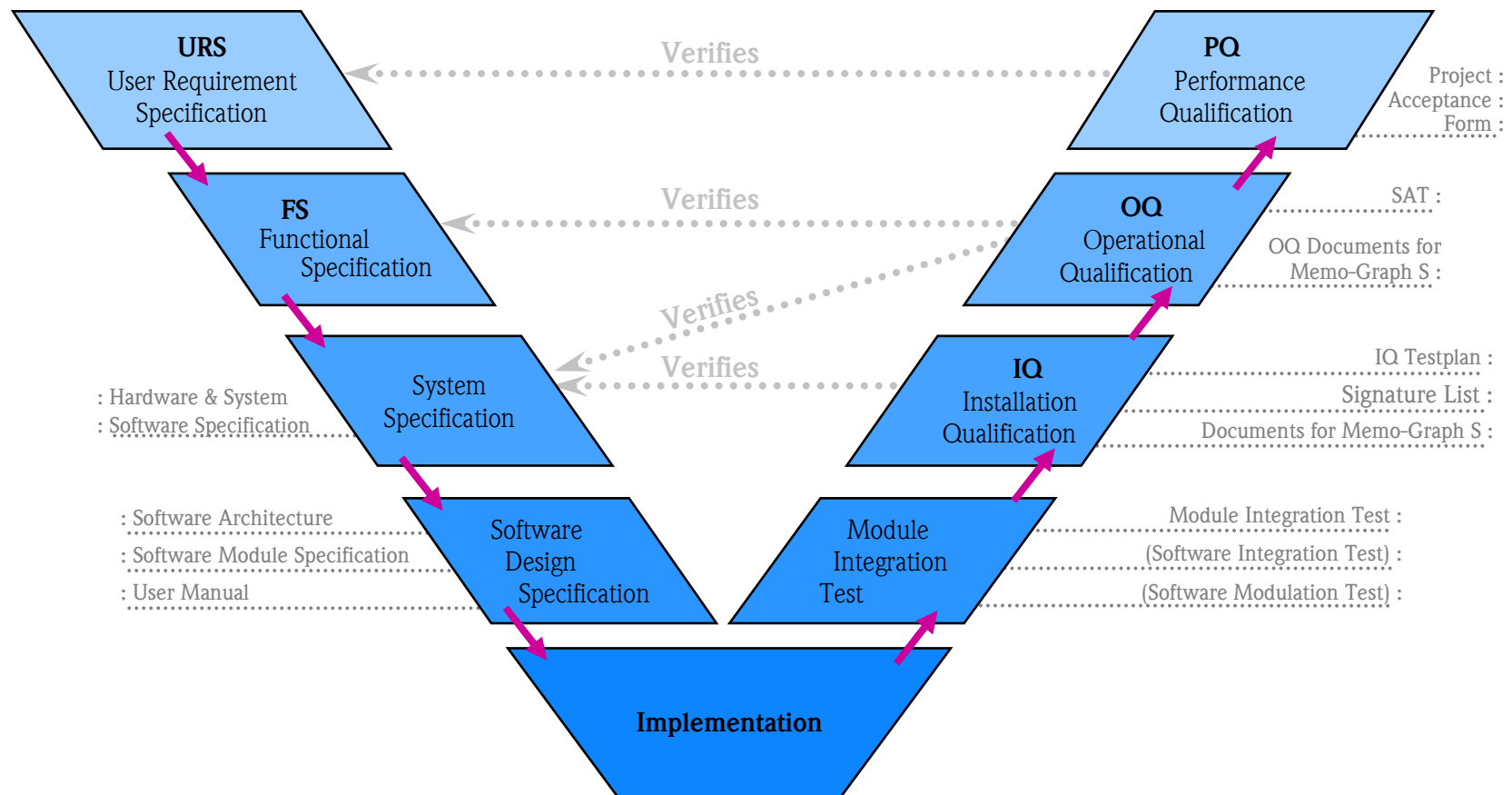


Fieldbus Engineering

Planning, calculation, optimization according to FISCO

Lifecycle V-Model

The V-Model is a common lifecycle model used in the Pharmaceutical Industry



GAMP principles

- Write procedures
- Follow the written procedures
- Document (record) the work
- Validate the work
- Design and build proper facilities and equipments
- Maintain the facilities and equipments
- Be competent (as a result of education, training & experience)
- Be clean
- Control for quality
- Audit for compliance.

Automation solutions (GMP compliant)

Clean Room Monitoring

Total automated pH inline measurement

Clean Room Monitoring



Operator

What is Clean Room Monitoring

Low Clean Room Requirements

- Functionality
- Clean Room > 10'000 (class 10'000)
Definition ISO 7:
rooms at rest; rooms in operation
- Basic criteria which have to be fulfilled
 - Walls, floors, ceilings, room overpressure, sealed window, door locked
 - Mixed ventilation, three steps filtered air, airflow change the existing room air
 - Number of air changes increase the air quality and the classification of the clean room

Clean Room Monitoring



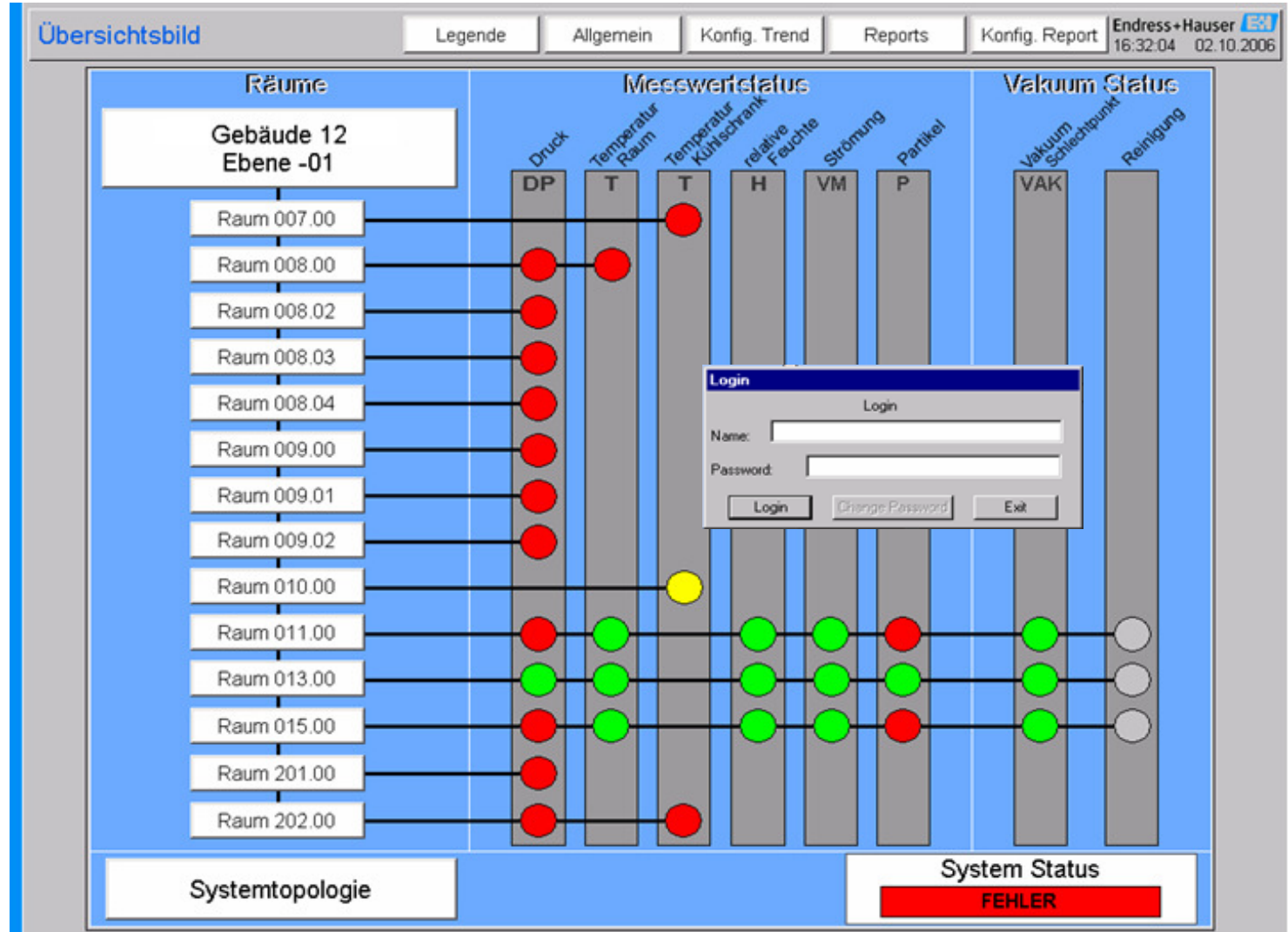
Panel PC



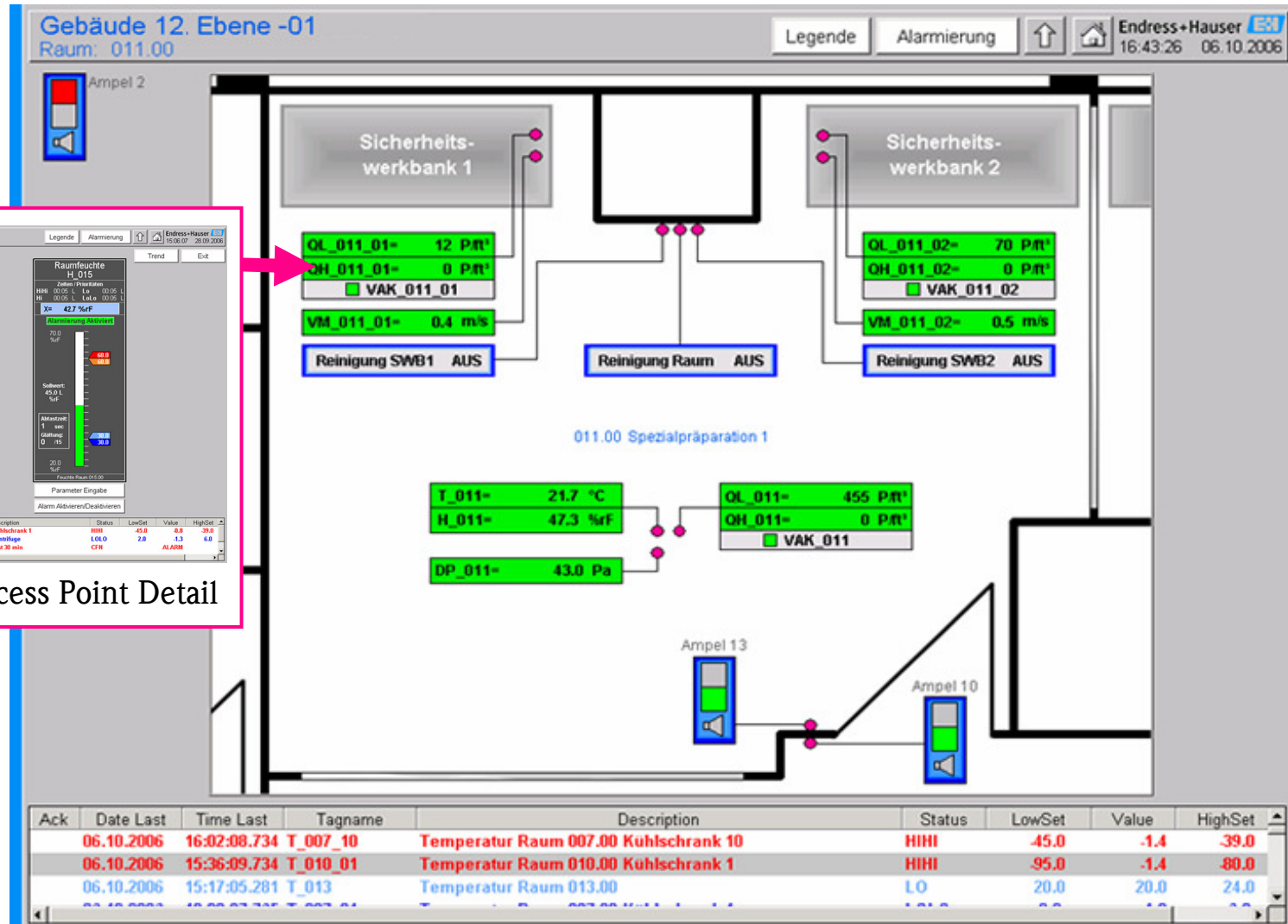
User Access Management

USER	ACCESS RIGHTS	DEPARTMENT
<ul style="list-style-type: none"> 1 Name 01 2 Name 02 3 Name 03 4 Name 04 5 Name 05 . . . n Name xx 	<ul style="list-style-type: none"> 1 View 2 Export Data 3 Trend Commenting 4 View Audit Trail 5 Change Set-limits + alarm functions 6 Reports Create 7 Data Administration 8 IT Administration 9 Alarm Acknowledge 10 Supervisor 11 Alarm Reset 12 Reports Check 13 Reports Approve 14 Historical Data Exchange 	<ul style="list-style-type: none"> GMP Area 1 GMP Area 2 GMP Area 3 Etc.

Visualization: (Start Screen with User Login Window)



Visualization: (Room Lay-Out)



Gebäude 12. Ebene -01
Raum: 011.00
Detail for Room No.: 011.00

Raumtemperatur T_015
Zuletzt (Prozentwert) 00:05 H 4.4 00:05 H
HI 00:05 H LoLe 00:05 H
KI 22.5 °C
Schwartz 22.0 L °C
Anzeige 1 sec
Gangung 0 ms
10.0 °C
Temperatur Raum 011.00
Parameter Eingabe
Alarm Aktivieren/Deaktivieren

Raumfeuchte H_015
Zuletzt (Prozentwert) 00:05 H 4.4 00:05 L
HI 00:05 L LoLe 00:05 L
KI 42.7 %rF
Schwartz 45.0 L %rF
Anzeige 1 sec
Gangung 0 ms
20.0 %rF
Feuchte Raum 011.00
Parameter Eingabe
Alarm Aktivieren/Deaktivieren

Click to see Process Point Detail

Visualization: (Set Point Parameters)

FDA Rule 21 Part 11 Compliance
 User must enter Comment for change and User Name/Password combination (electronic signature) to effect change

CFR21 Part 11 Check / User + Password Login

Username:

Password:

OK

	SOLLWERT:		VERZÖGERUNGSZEIT:		PRIORITÄT (L,M,H):	
	Aktuell:	Neu:	Aktuell:	Neu:	Aktuell:	Neu:
Eingriffsgrenze (HIHI):	50.0 Pa	50.0 Pa	00:05	00:05	L	L
Warngrenze (HI):	50.0 Pa	50.0 Pa	00:05	00:05	L	L
Sollwert :	45.0 Pa	45.0 Pa				
Warngrenze (LO):	40.0 Pa	40.0 Pa	00:05	00:05	L	L
Eingriffsgrenze (LOLO):	40.0 Pa	40.0 Pa	00:05	00:05	L	L

Abtastzeit: Aktuell: 1s Neu: 1s
 Glättung: Aktuell: 0 / 15 Neu: 0 / 15

Änderungsgrund: Letzter: 28.09.2006 14:37 BILL MOLONEY gwithu
 Neu: 28.09.2006 14:37 BILL MOLONEY gwithu

Ack	Date Last	Time Last	Tagname	Description	Status	LowSet	Value	HighSet
	28.09.2006	14:52:40.359	T_202_01	Temperatur Raum 202.00 Kuhlshrank 1	HIHI	45.0	-0.7	-39.0
	28.09.2006	14:52:31.203	T_202_02	Temperatur Raum 202.00 Zentrifuge	LOLO	2.0	-1.2	6.0

Safety Data Manager (Memo-Graph S Documentation)



- Operation Manual
- Technical Information
- System Information (soon)
- Transparencies
- TÜV Certificate (Technical Compliance Certificate)
- White paper
- Press release
- Professional article
- Accessory package Pharma

Engineering process

Step #	PROCESS SEQUENCE			Mile-stone	GxP PROJECT					
					Responsibility	Document Title	Template	SW-Tools		
Factory	Inquiry				SC Sales	Inquiry Summary Sheet ISS, all Input documents	ISS_DE_*.x.dot ISS_EN_*.x.dot	MS Word		
	Quotation				PCPS Sales & Engineering.	Engineering Quote (DE) Engineering Quote (EN)	Quote_ENG_DE_*.x.dot Quote_ENG_EN_*.x.dot	MS Word MS Excel		
	Order									
	Project Set-Up	Kick-off	Detail Engineering	Schematics created and approved	Typical system specific, electrical power & control cabinet layouts	PCPS BU Eng.	NA	NA	NA	
		Project		Software Design Specification (SDS)	Create if multiple modules are used.	PCPS BU Eng.	Software Design Specification (SDS)	MS500_1 SDS_ProjectNo_DE_V*.x.dot MS500_1 SDS_ProjectNo_EN_V*.x.dot	MS Word	
		Project		Software Module Specification (SMS)	Create for each module.	PCPS BU Eng.	Software Module Specification (SMS)	MS500_2 SMS_ProjectNo_01_ModuleName_DE_V*.x.dot MS500_2 SMS_ProjectNo_01_ModuleName_EN_V*.x.dot	MS Word	
		User F. Specif.		Installation Qualification Testplan	Testplans for Installation	PCPS BU Eng.	IQ Test Plan	MS500_4 IQ_ProjectNo_01	MS Word	
		Basic Engineering	Third	Operation Testplan						
		Qualif.	Integration Implementation	Set-up test	Commissioning / SAT Test	PCPS BU Eng.	Perform SAT - Site Acceptance Test	(conduct IQ/OQ according to IQ Test Plan and OQ Test Plan)	see above	MS Word
		Funci.		Factory /	Integration Test / FAT	PCPS BU Eng.	IQ/OQ Protocol	IQ/OQ Protocol	MS700_2 IQ/OQ_Protocol_*.x.dot MS700_2 IQ/OQ_Protocol_*.x.dot	MS Word
	Trace			Customer Training	PCPS BU Eng. & SC >Subcontractor	Perform customer training	Training Basic/Advanced Participant Lists; Training Basic/Advanced Training Certificates	MS700_3 TrainingBasic_ParticipantList_ProjectNo_EN_V*.x.dot MS700_4 TrainingCertificate_Basic_ProjectNo_EN_V*.x.do	MS Word MS PowerPoint	
	Device			Project Acceptance Form	PCPS BU Eng.	Project Acceptance Form signed by customer	Project Acceptance Form	MS700_6 Project_Acceptance_Form_ProjectNo_DE.dot MS700_6 Project_Acceptance_Form_ProjectNo_EN.dot	MS Word	
	Device			Documentation Handover	PCPS BU Eng.	Handover of project documentation	ALL	NA	Various	
				After Sales (Additional Services)	SC	Preventative Maintenance				
				Maintenance	SC					
				Recalibration	SC				CompuCal	
				Customer Support	SC Service & PCPS					

Qualification (documentation)

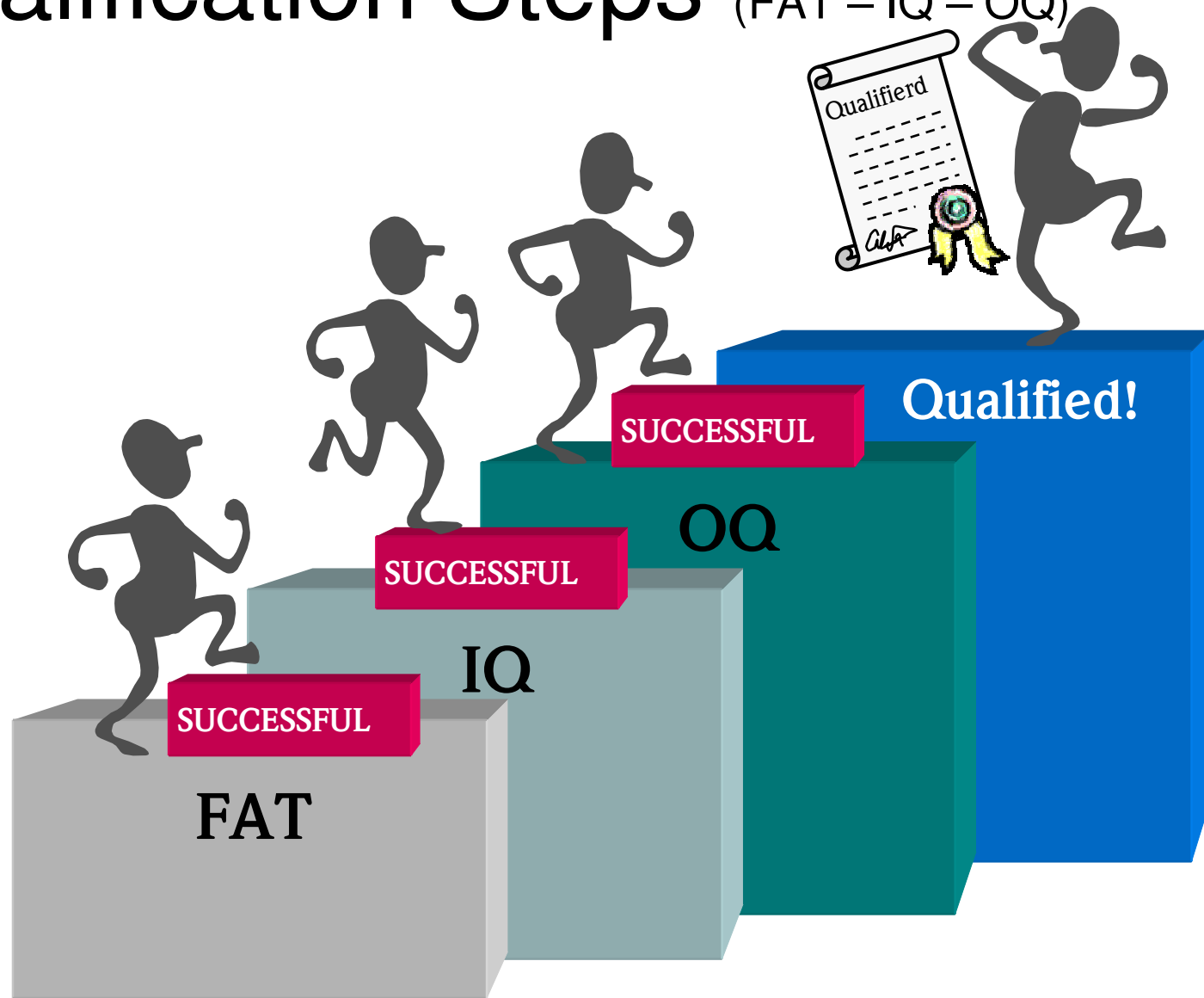
The collage displays several overlapping pages from qualification protocols. Key sections visible include:

- 6: Testing summary**: A table with columns for 'OO No.', 'OO DESCRIPTION', 'RESULT PASS/FAIL', 'SIGNATURE', and 'DATE'. It lists various tests like 'Power off verification', 'Serial interface verification', and 'Dust clock verification'.
- 7.8 Dust clock verification**: A table with columns for 'Specification', 'Actual Yes/No', 'Verified by', and 'Date'.
- 8: Testing summary**: A table with columns for 'OO No.', 'OO DESCRIPTION', 'RESULT PASS/FAIL', and 'INITIALS DATE'. It lists tests such as 'Documentation verification', 'Environmental / wiring verification', 'Voltage Supply', and 'Software verification'.
- 8.1 Documentation verification**: A table with columns for 'Version', 'Date', 'Author', and 'Description', showing a 'Version History' table.
- Installation Qualification Protocol**: A page with a title and a table for 'Unit serial number see title page'.
- Safety Data Manger**: A page titled 'Safety Data Manger memo-graph s PC Application readwin 2000' with a table for 'Operational Qualification Protocol / Control System'.
- Table of contents**: A page listing sections like 'Version History', 'Table of contents', and 'Introduction' with corresponding page numbers.

Original nameplate makes document valid (order code)

PharmaTech 7th March 2008, Hyderabad

Qualification Steps (FAT – IQ – OQ)

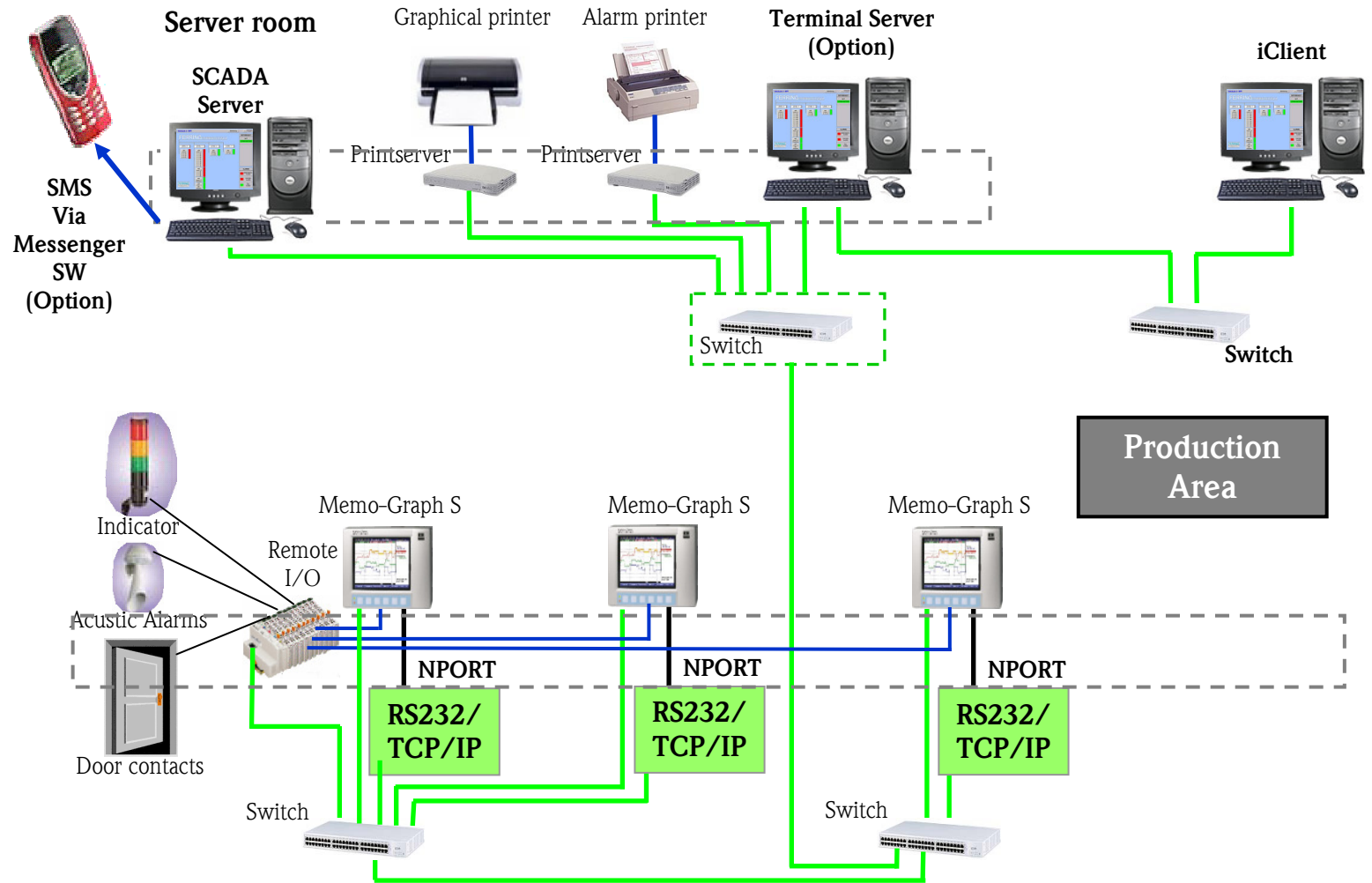


FERRING – the NFF project

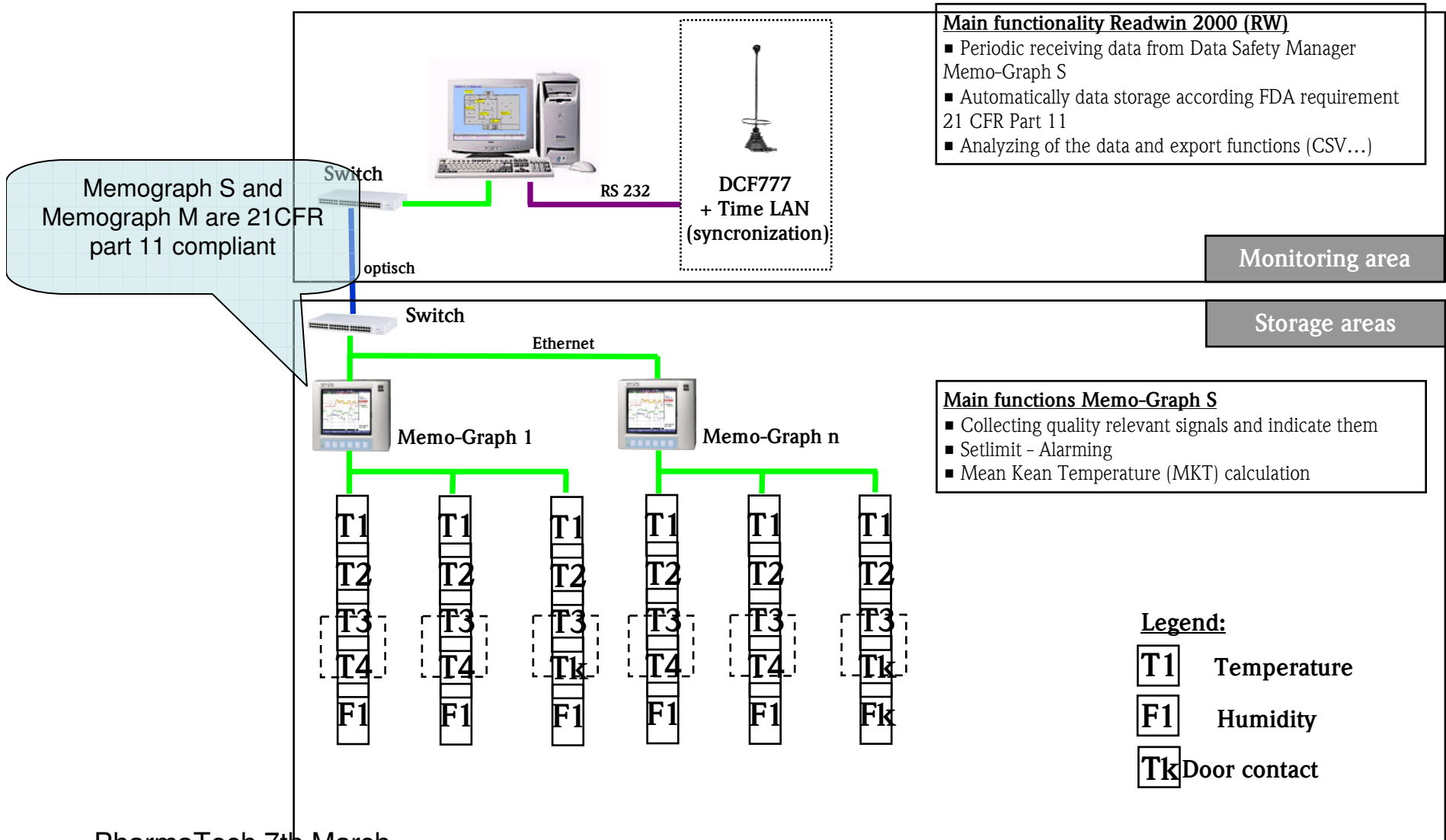
- In 2003, FERRING Pharmaceuticals in Kiel, Germany build a “New Freeze-drying Facility (NFF) for pharmaceutical nasal spray production.
- Complete supply of the Clean Room Monitoring System
- Our success was achieved by our ability to provide a complete total concept solution which could not be matched by other competitors.



Clean Room Monitoring (system overview)



Packaged Solution monitoring: (Storage areas)



Inline pH Measurement



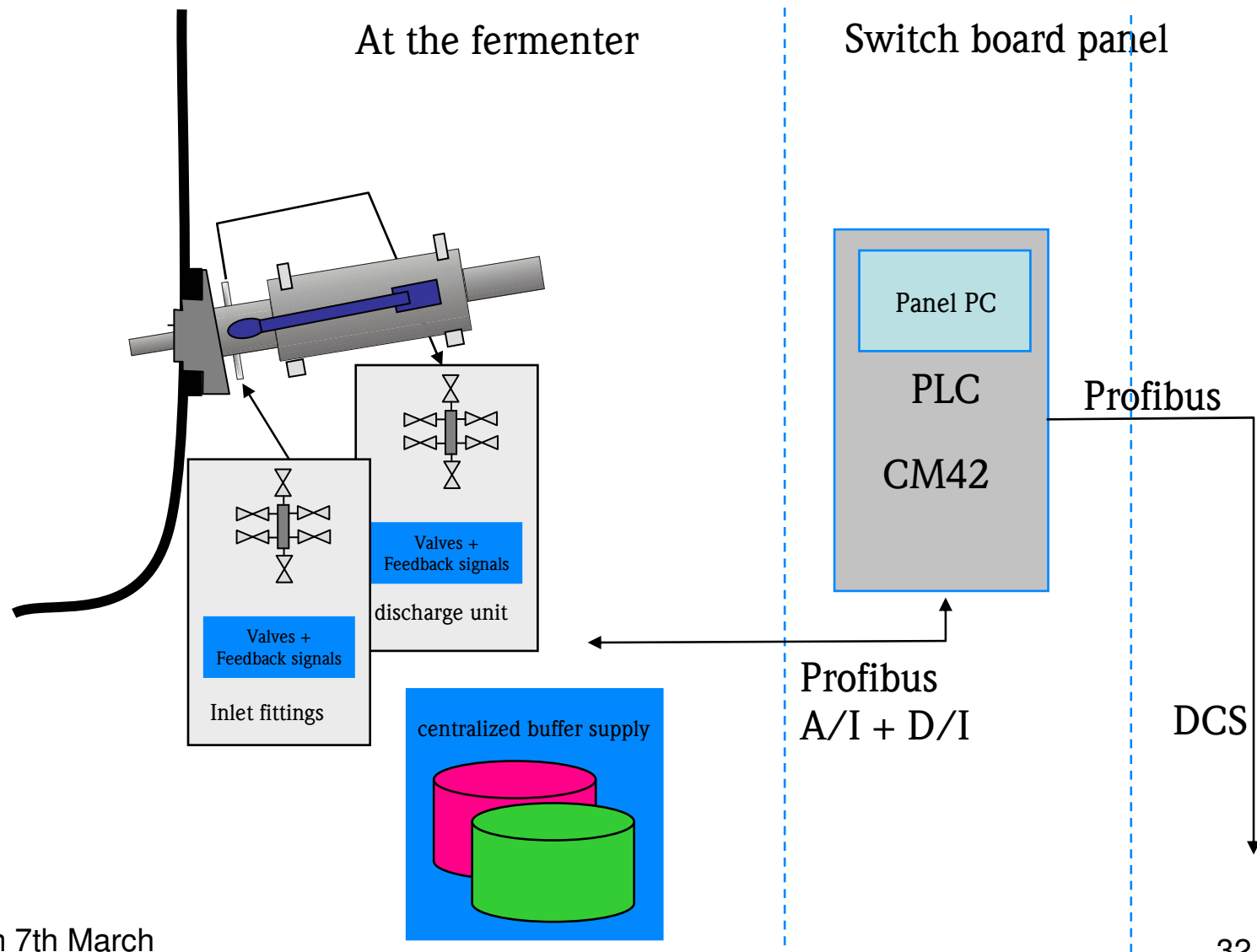
- completely automated
- reliable system
- integrated system based on open standards



Advantage:

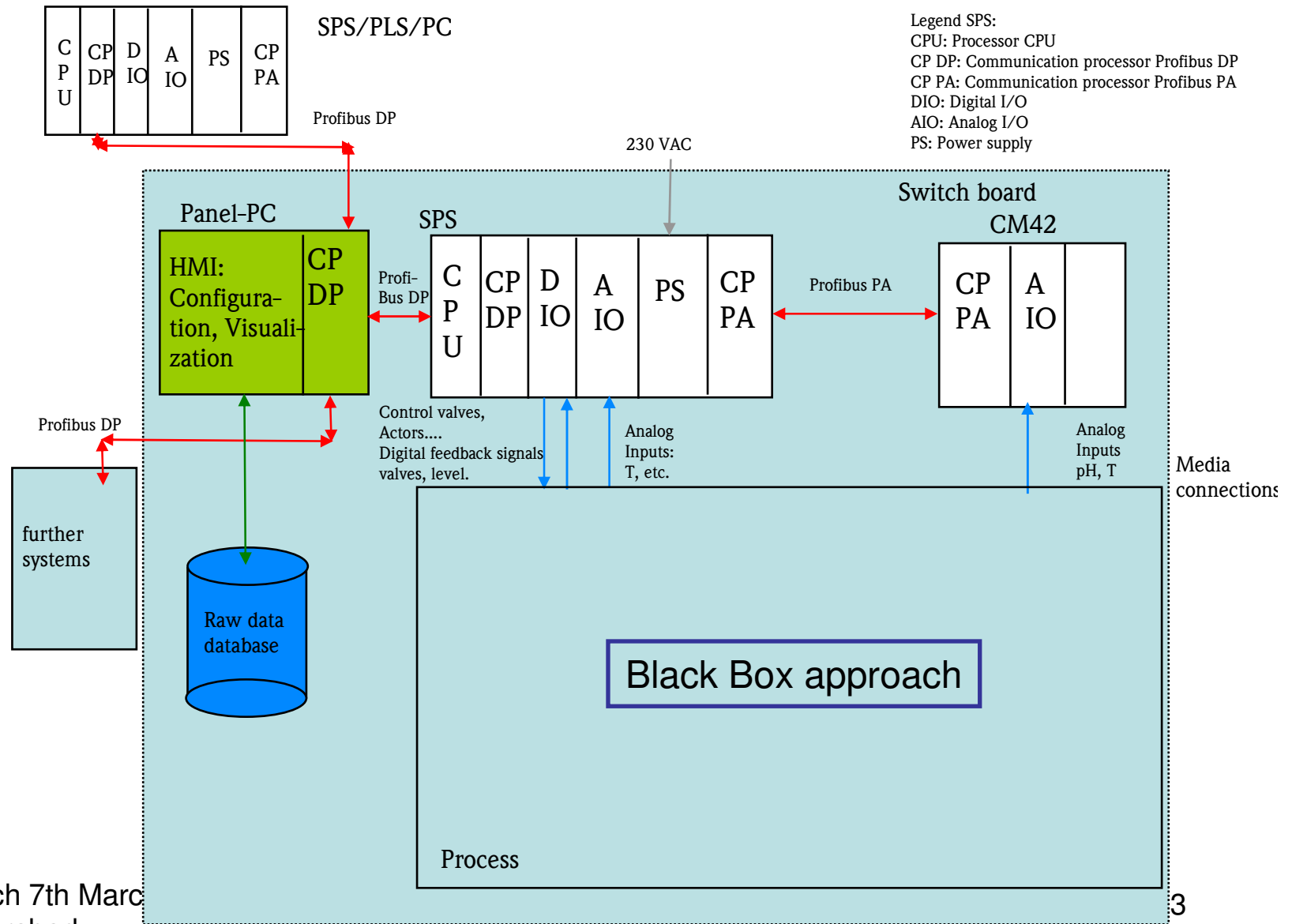
No waiting time receiving results from the lab
for the production

Basic version - schematic

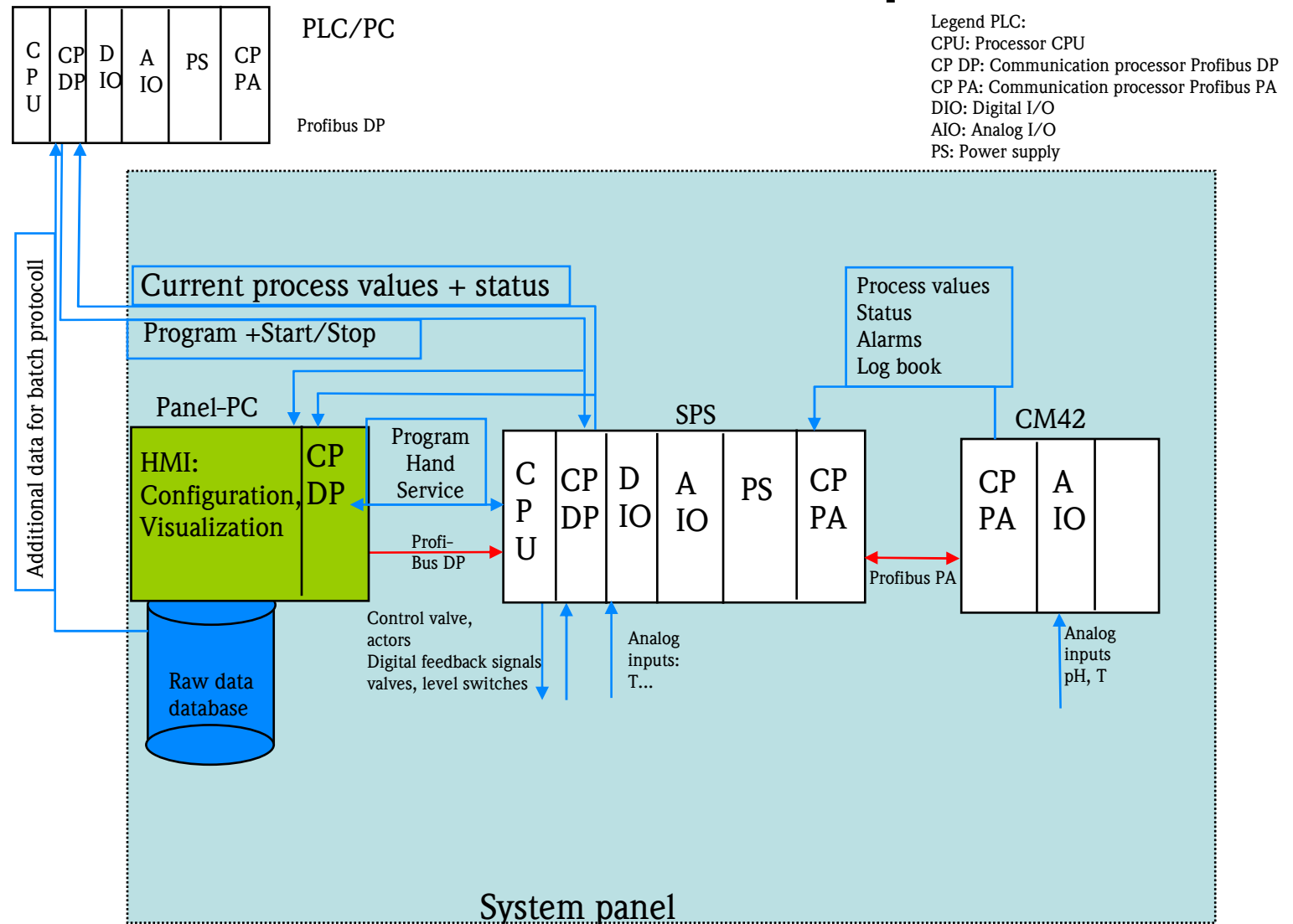


System overview

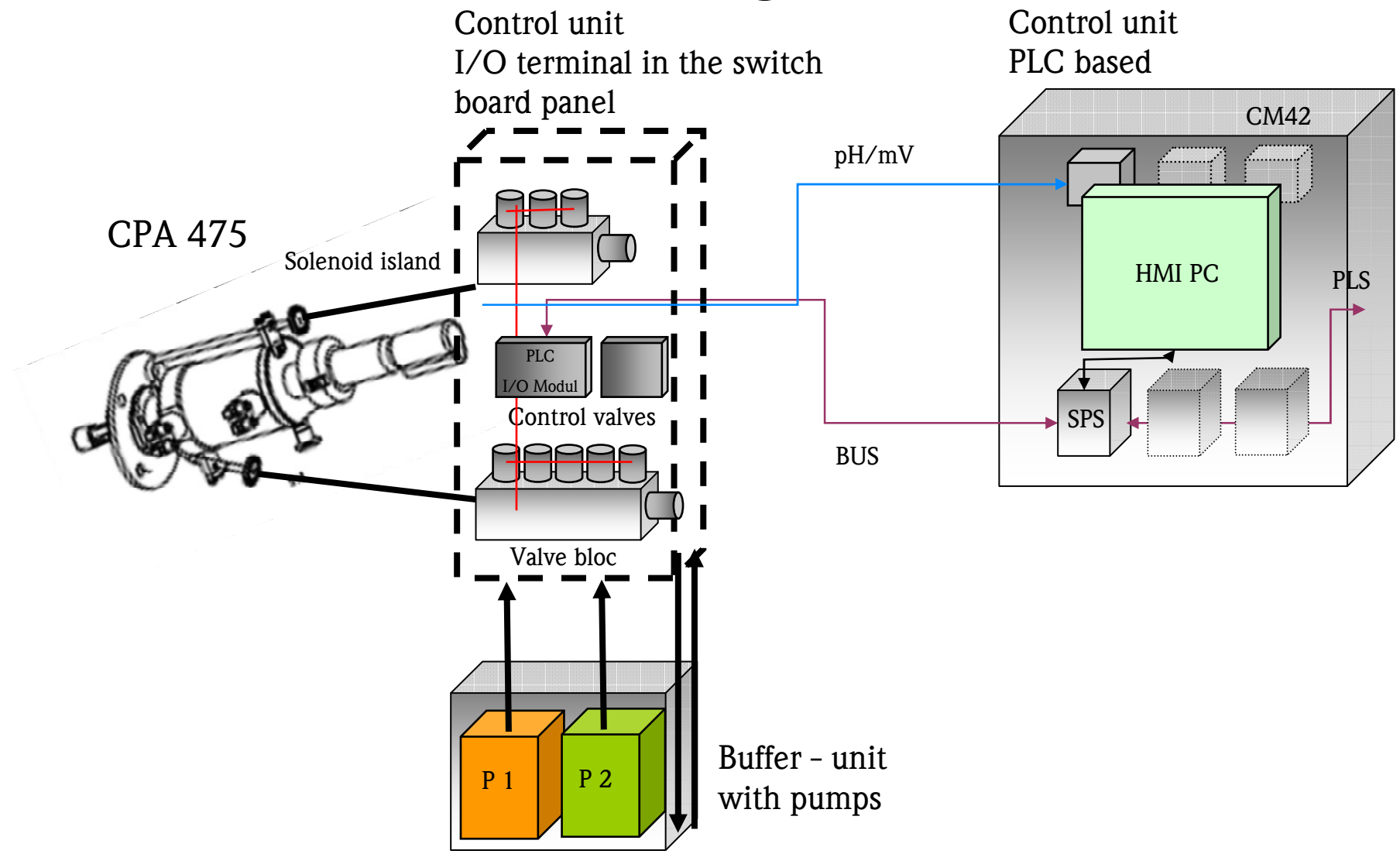
Automated pH inline measurement



Communication concept



Schematic Design — (Standard package)



Engineering services

(Control cabinet)

Packaged solution:

- Mycom
- Control cabinet
- Functional specification (FS)
- Qualification Plan (QP)
- Hardware Design Specification (HDS)
- Software Design Specification (SDS)
- Testplans for Factory Acceptance Test (FAT)
- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Support Performance Qualification (PQ)



Application notes (standard)

Cleanroom monitoring for the safe-guarding of quality

In the pharmaceutical industry, cleanrooms are the prerequisite for the manufacture of ultrapure active substances and modern, sterile presentation forms. A contamination of the processed substance must be prevented at all costs in order to avoid endangering the health of the patient during oral administration or other application modes. Therefore, particularly high standards of construction and equipment operation are necessary in cleanrooms. On the one hand, the contamination with foreign particles must be kept to an absolute minimum, on the other hand, purity and quality parameters such as temperature, humidity and the preservation of pressure levels must be regulated and, according to specifications, measured, identified and documented.

Klaus Köhler
Pharmaceutical Inertec Munster



Highest quality requirements from system supplier

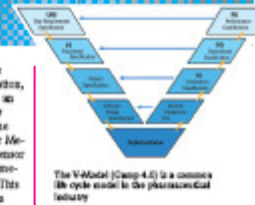
When setting up a cleanroom monitoring system, very high standards must be provided both by the supplier and the system itself. For many years now, Inertec+Hanser supply complete solutions for the monitoring of Cleanrooms. Here, a large number of successful projects, confirmed by audits, prove the high quality standard of the complete realization and the installed system. On the one hand, a clear project and system structure was important for all reference companies and on the other hand, obtaining everything from one reliable source was also given the highest priority. In cleanroom monitoring, as in most pharmaceutical processes, strict observation of GMP regulations and GAMP 4¹⁾ are standard work of software validation, as part of the fundamental working basis. A further basic requirement is the independence of the monitoring system from the building management system in order to comply with the FDA-Part 11 directive.

Top priority given to safety of file administration
The storage of measurement values (e.g. temperature, humidity, pressure levels) is carried out using a database system which reliably records the raw data and administers them according to the specifications of 21 CFR, Part 11. Each data record is

1) = Good Automated Manufacturing Practice

only present once and it is given a time stamp. All events as well as the preparation, checking and release of reports require an electronic signature and are completely documented in an audit trail. In case the data link is interrupted, a data manager Memorograph 5 is connected between the sensor and the database which provides intermediate data storage for a period of time. This temporary memory is read out and then the gap in the central raw data database is closed. The quality of this data is equally guaranteed by the Part 11 compatibility of Memorograph 5. Automatically, the system ensures that raw data are not present twice and are not overwritten.

With your peace in mind
Starting with the first concept consulting, via the engineering and the qualification of the system, Inertec+Hanser also look after the start-up of operations on site. A first quality control already takes place in the manufacturing plant within the scope of the Factory Acceptance Test (FAT). This date is also used to train the operating staff handling the system. After this, qualification takes place and finally the first operation begins in the actual working location. All measurement instruments are calibrated in their built-to condition. Recalibration and regular software updates preserve the availability and reliability of the system.

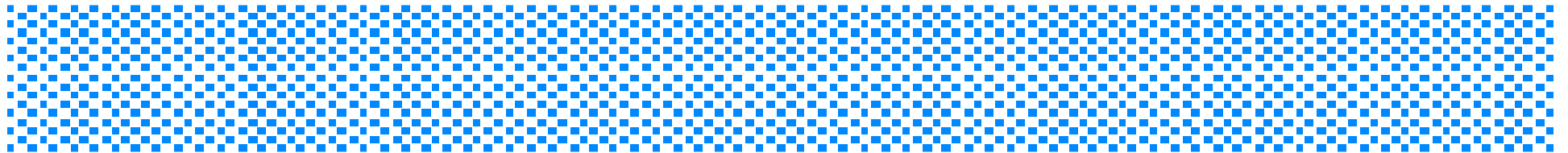


The V-model (Gamp 4.0) is a common life cycle model in the pharmaceutical industry

Project handling especially designed for pharmaceuticals according to GAMP 4
Inertec+Hanser projects cleanroom monitoring according to DIN EN ISO 14644, the FDA directives and GAMP 4. As well as compiling the Design Specification (DS) for the hard and software, this also involves the production of the qualification documentation for the Installation Qualification (IQ) and the Operation Qualification (OQ). A risk evaluation is also carried out within the preceding framework as the basis for the plan for monitoring air purity. After projecting has been completed, the customer is invited to a Factory Acceptance Test (FAT). Subsequently, the on-site start of operations is carried out with the Installation Qualification (IQ), the Operation Qualification (OQ) and the Site Acceptance Test (SAT). The calibration of the measurement instruments is carried out during and after the Installation Qualification.

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Any questions?



**... thanks
for your attention**