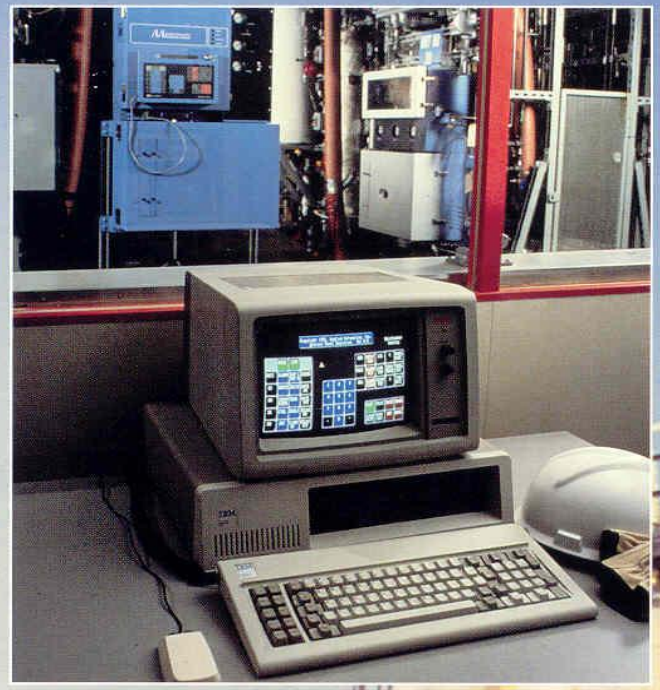
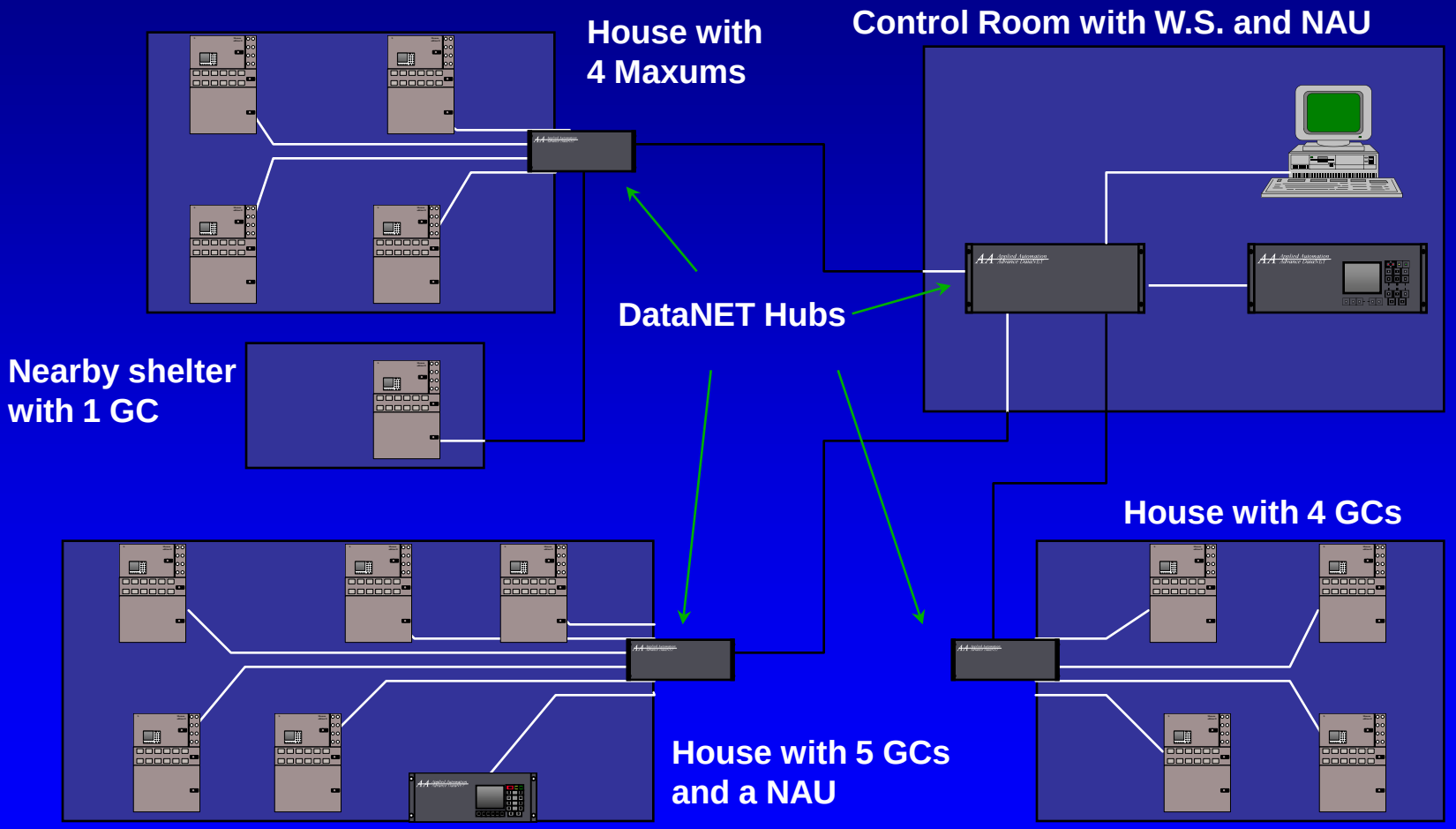


PAT for Continuous Processes

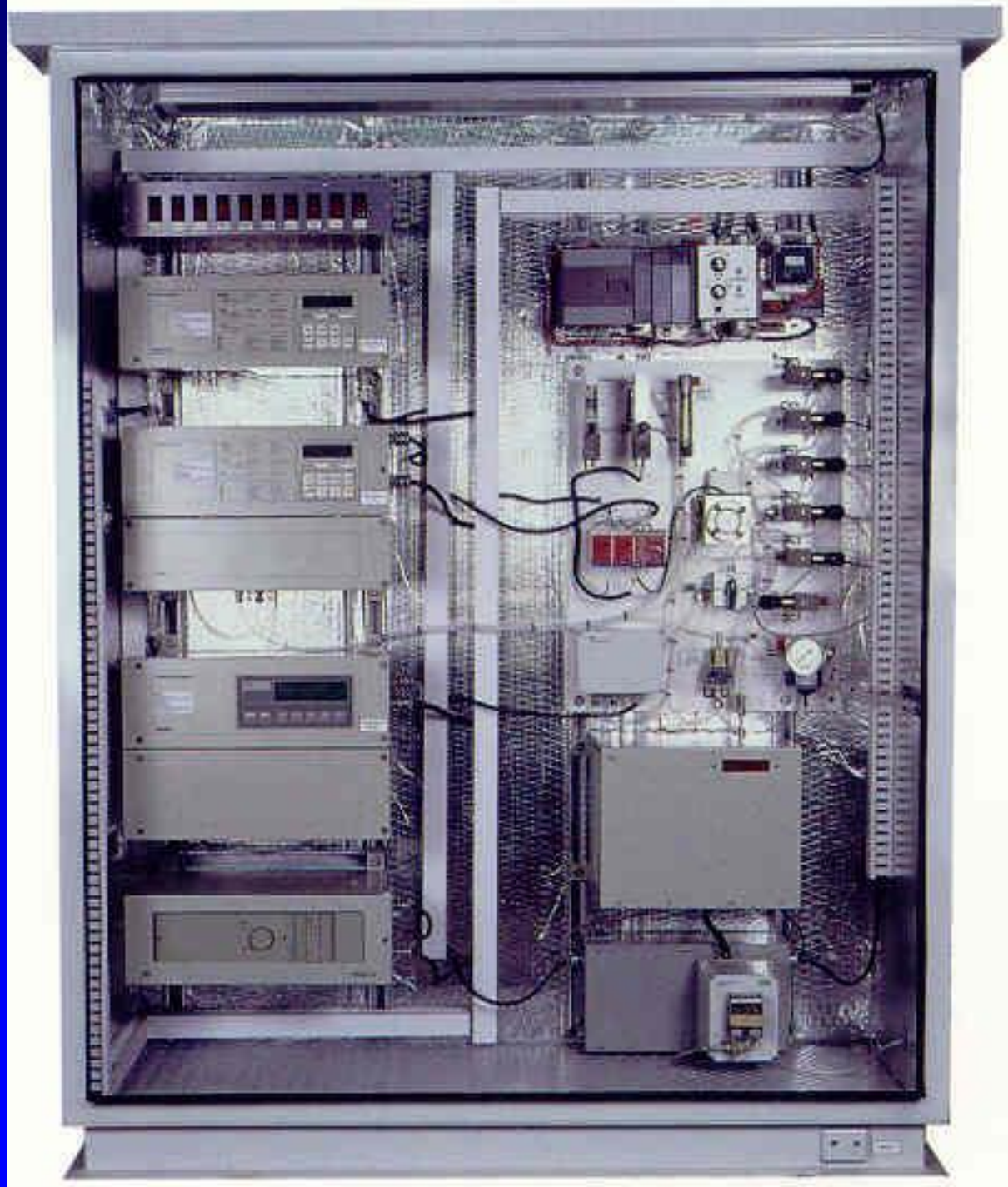
Network Installation



CONTINUOUS GAS ANALYZERS

UV, IR, paramagnetic for O2, and Thermal Conductivity.

Manufactured in Germany at Hartmann and Braun, packaged by daughter company Applied Automation. These instruments are now produced by ABB because of a merger.



PROCESS GC

Produced by Applied Automation prior to merger with Siemens.

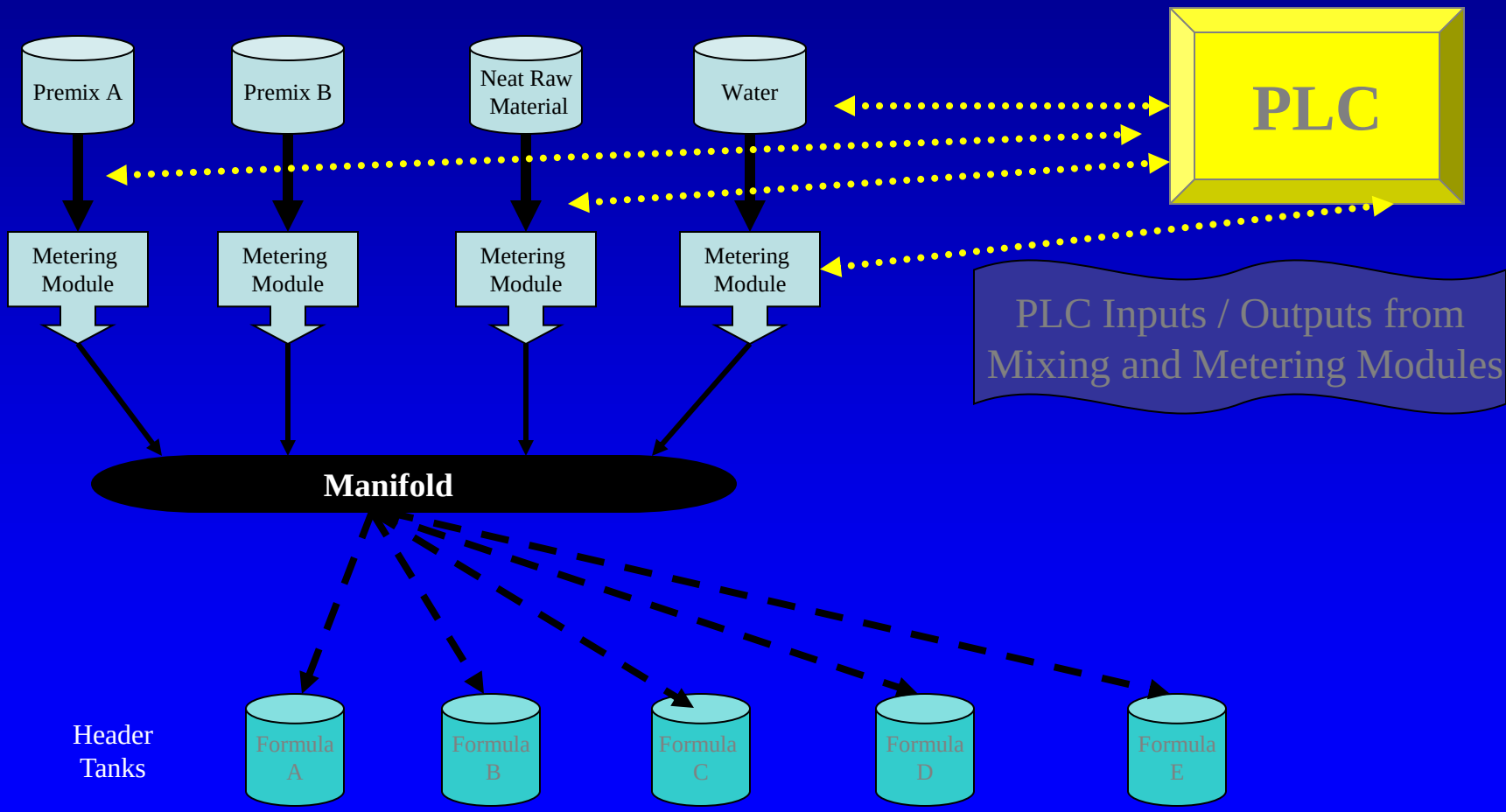
Typical Constraints for On-line Process Analyzers

- Operate 24 hours a day
- Must require little maintenance
- Short analysis time e.g. 8 minutes
- Must be reliably repeatable
- Temperature design to limit sample phase change (vapor and liquid)
- Must be suitable for hazardous environment
- Suitable for ambient temperature changes e.g. 0 - 50 C.

Quality by Design
Right First Time Manufacturing

- Automated processes designed with numerous critical feedback measurements to PLC (Programmable Logic Controller) for control
- On-line Gas Chromatographic measurement of active ingredients and alcohol for monitoring of quality attributes

ILLUSTRATION OF CONTINUOUS AUTOMATED MANUFACTURING

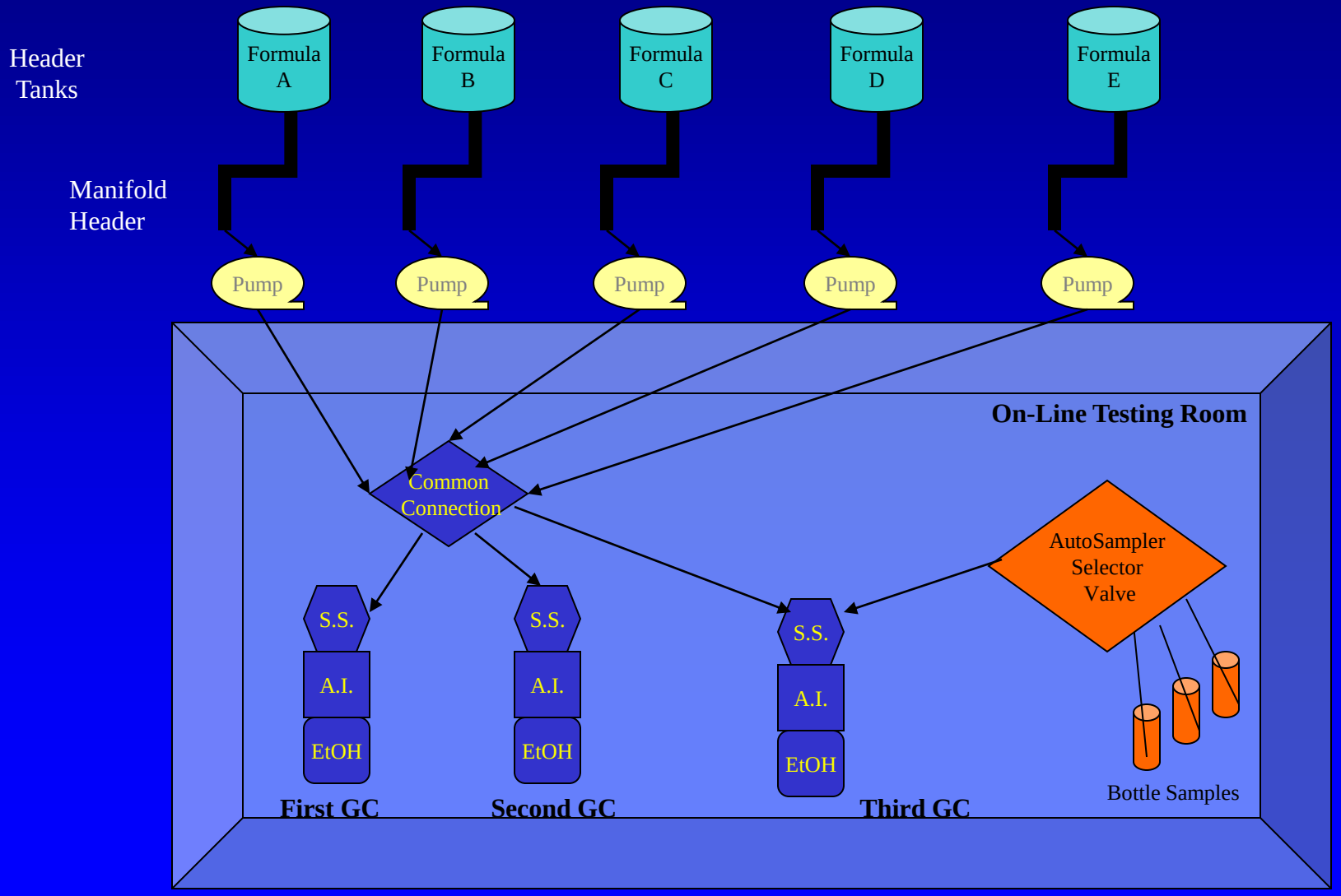


Measurements and Controls

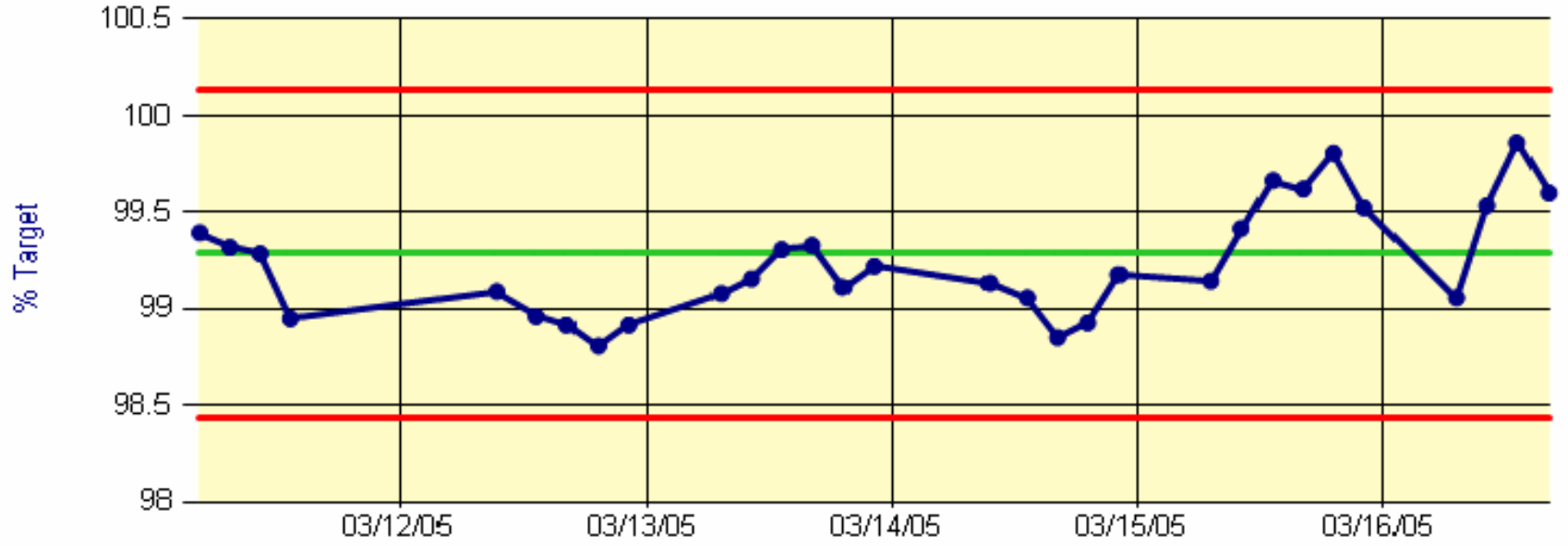
Examples:

- Temperature and pressure
- RPM sensor
- Mass flowmeters
- Specific gravity determination
- Check weighers
- Mass balance algorithms
- Alarming and diversion mechanisms

ILLUSTRATION OF ON-LINE MEASUREMENTS

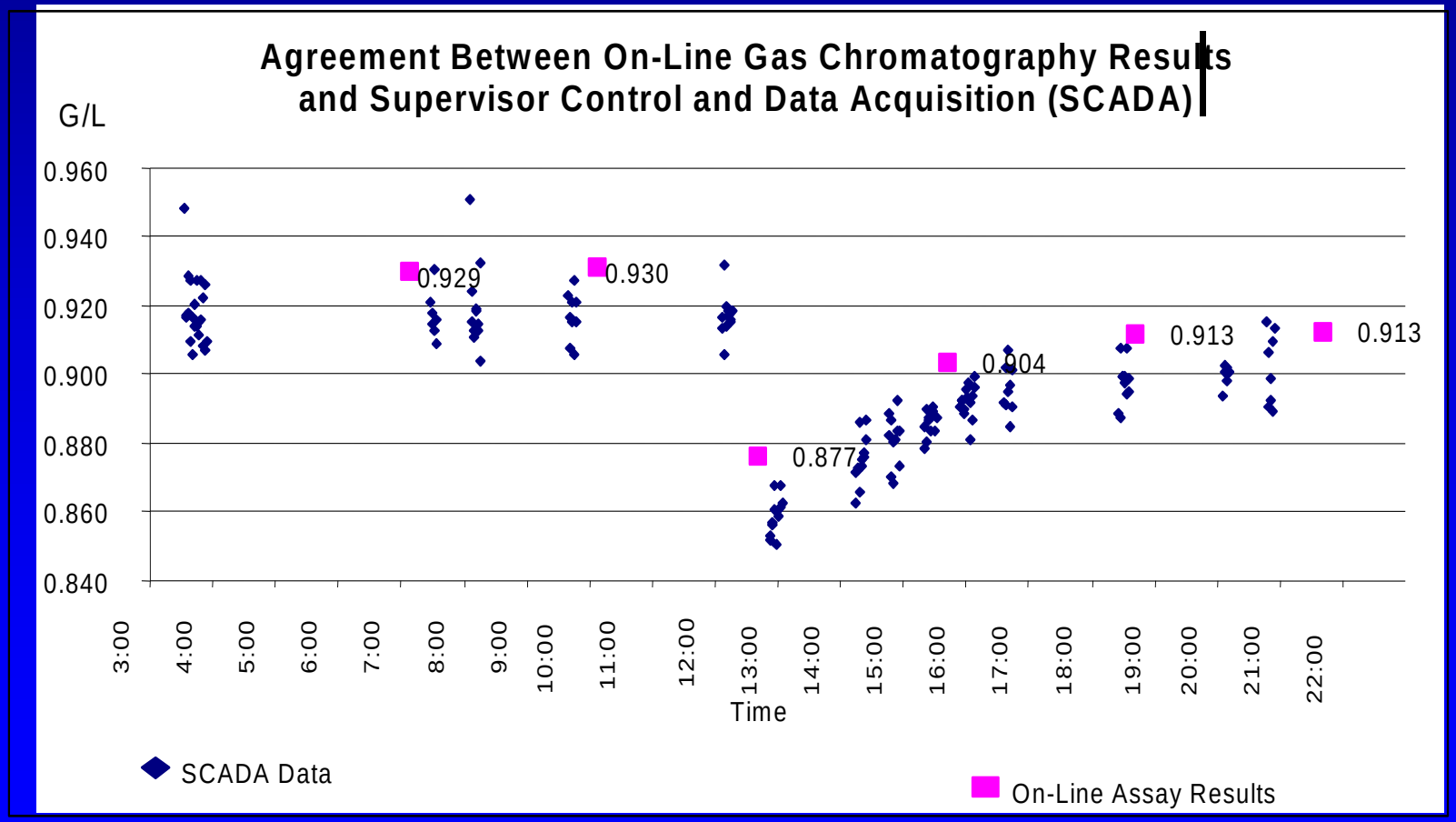


Process Monitoring Graphs

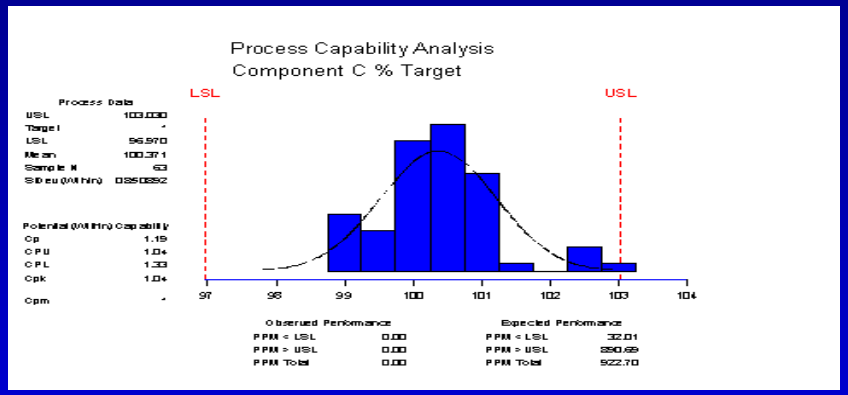


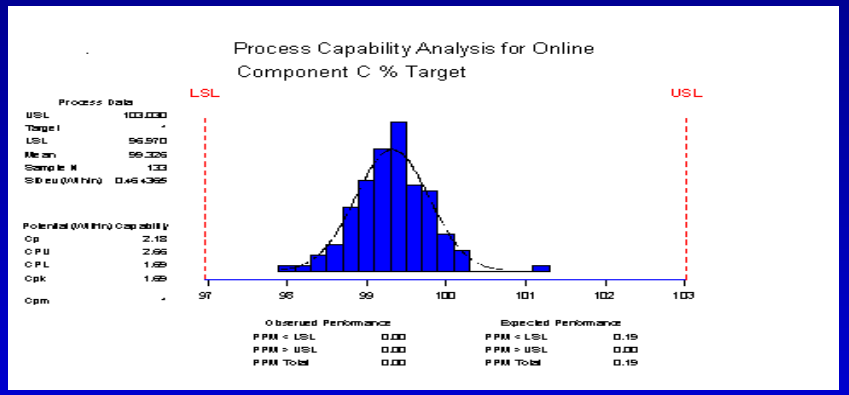
Summary Data for	Date	# of Samples	Mean % Target	Std Dev % Target	RSD of Standard
Last Run Date	03/16/2005	4	99.5	0.3	0.1

On-Line Agreement with SCADA



Demonstration of Process Capability and Precision of On-line GCs





	Laboratory (Cpk)	On-Line (Cpk)
Component A	1.12	1.74
Component B	1.30	2.92
Component C	1.04	1.69
Component D	1.08	2.77

CpKs were calculated using data from the same time period to compare calculations using each of the methodologies.

Questions???

PAT for Continuous Processes

- Is anyone else working on PAT for Continuous Processes?
  - API?
  - Drug Product?
  - Fermentation?
  - Biologics packaging?
- Instruments
  - NIR?
  - Other spectroscopic?
  - Chromatographic?
  - Other?

PAT for Continuous vs. Batch???

- How fast is fast enough?
  - Monitor vs. control? --- CQA vs. CPP?
  - Time constant of process?
  - Drug Substance (API) or Drug Product process?
  - Form of material: Liquid, powder, tablet, media broth, lyophilized cake, sterile liquid?
- What sample size?
  - Dose level
  - NIR of blends

PAT for Continuous vs. Batch???

- How to deal with large number (N) of data points?
  - Release from filed spec or statistically equivalent?
  - Primary method vs. alternative method?

PAT for Continuous vs. Batch???

- What happens if have a problem?
- Example of consumer:
  - Spare instrument for hot back up
  - Questionable result caused notification to whole teamd with a Page and e-mail
  - Statistical tracking available via internet
  - PC anywhere could access the instrument
  - SOPs with flow chart for problem shooting

Instrument Questions???

- Speed of acquisition and results?
- Baseline drift issues?
- How do you build a model for NIR?
- Calibration stability?
- Model maintenance?