Particle Counting and Environmental Monitoring In Pharmaceutical / Life Sciences

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Introduction

- ★ The pharmaceutical and medical device industries are developing new technologies and new techniques at an ever increasing rate. Regulatory requirements are being defined, implemented and audited more frequently.

- ★ Certain aspects of manufacturing and R&D require the use of cleanrooms and controlled environments. In order to comply with the various cleanroom and regulatory requirements facilities must have environmental monitoring programs.

- ★ This presentation will cover the various cleanroom standards as they relate to environmental monitoring programs and highlight the use of particle counters and their use and implementation in the pharmaceutical industry. Additional information is provided on the use of FMS system for pharmaceutical monitoring, their validation and compliance with various regulations.

Outline

- ★ cGMP's and Regulations
- ★ Cleanroom Standards for Pharmaceutical and Medical Device Manufacturing and Explanation of Grades
- ★ The Purpose of an Environmental Monitoring Program
- ★ Regulatory Requirements
- ★ Recommendations for Microbial Contamination
- ★ What to Monitor

Current Good Manufacturing Practices

- ★ Umbrella GMPs, 21 CFR parts 210, 211
- ★ Biologics, 21 CFR part 600 series
- ★ Devices and Diagnostics, 21 CFR part 800 series
- ★ International GMPs
- ★ FDA Guidelines for Aseptic Processing
- ★ FDA Guidelines for Process Validation
- ★ FDA's "Points to Consider"
- ★ NIH Containment Guidelines
- ★ ISO 14644-1/FED-STD 209E

Application of Regulations

Pre-clinical Work

- ★ Material is Experimental with no GMPs applicable (Good Documentation Recommended)

Phase I Trails

- ★ Acute Toxicity to Animals and Then Very Preliminary testing of Healthy Volunteers: GMPs Apply for Raw Material Controls, Documentation, Analytical Methods etc.

Application of Regulations

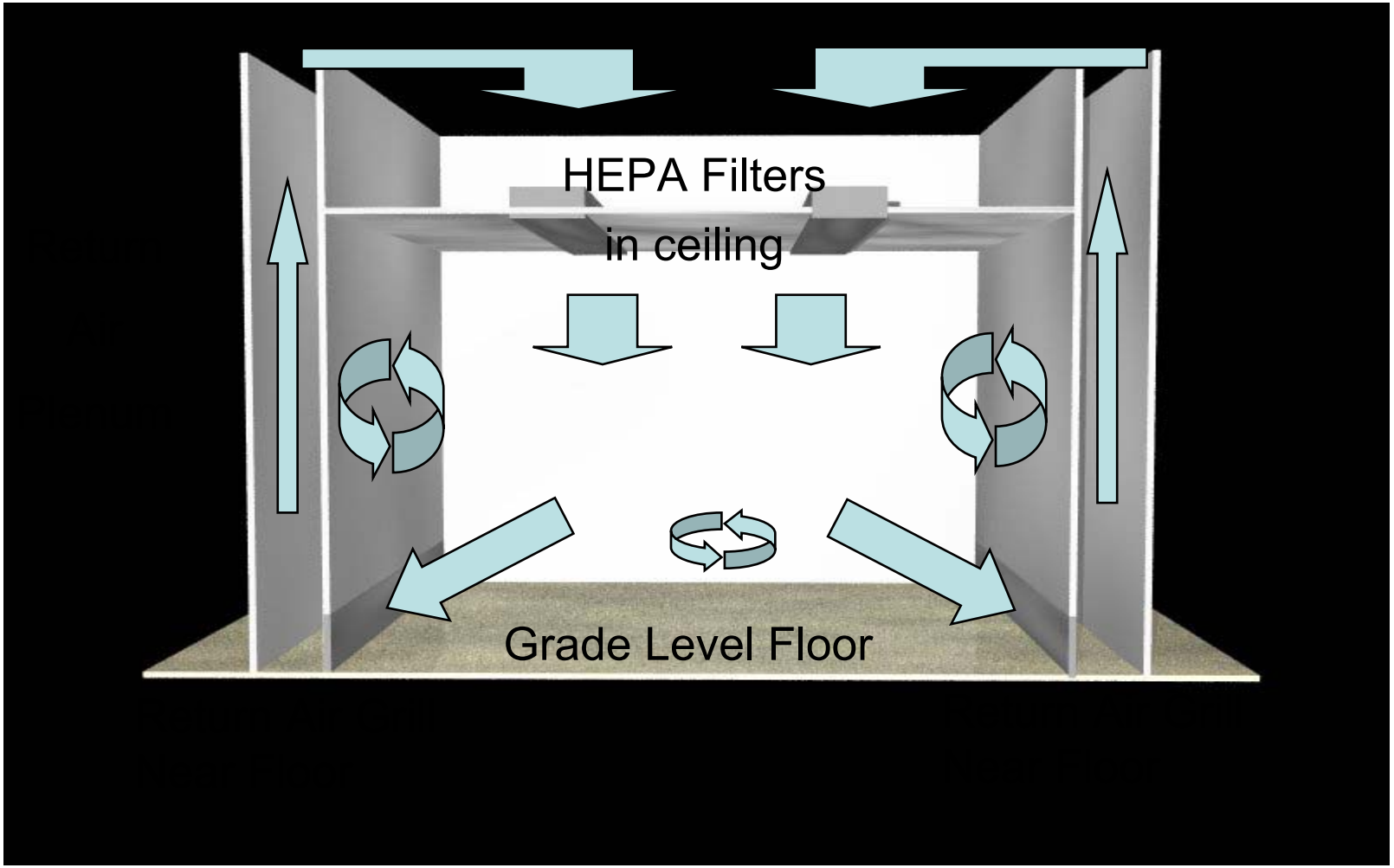
Phase II & III

- ★Compliance With Full GMPs and Validation

Production Phase

- ★Compliance With Full GMPs and Validation

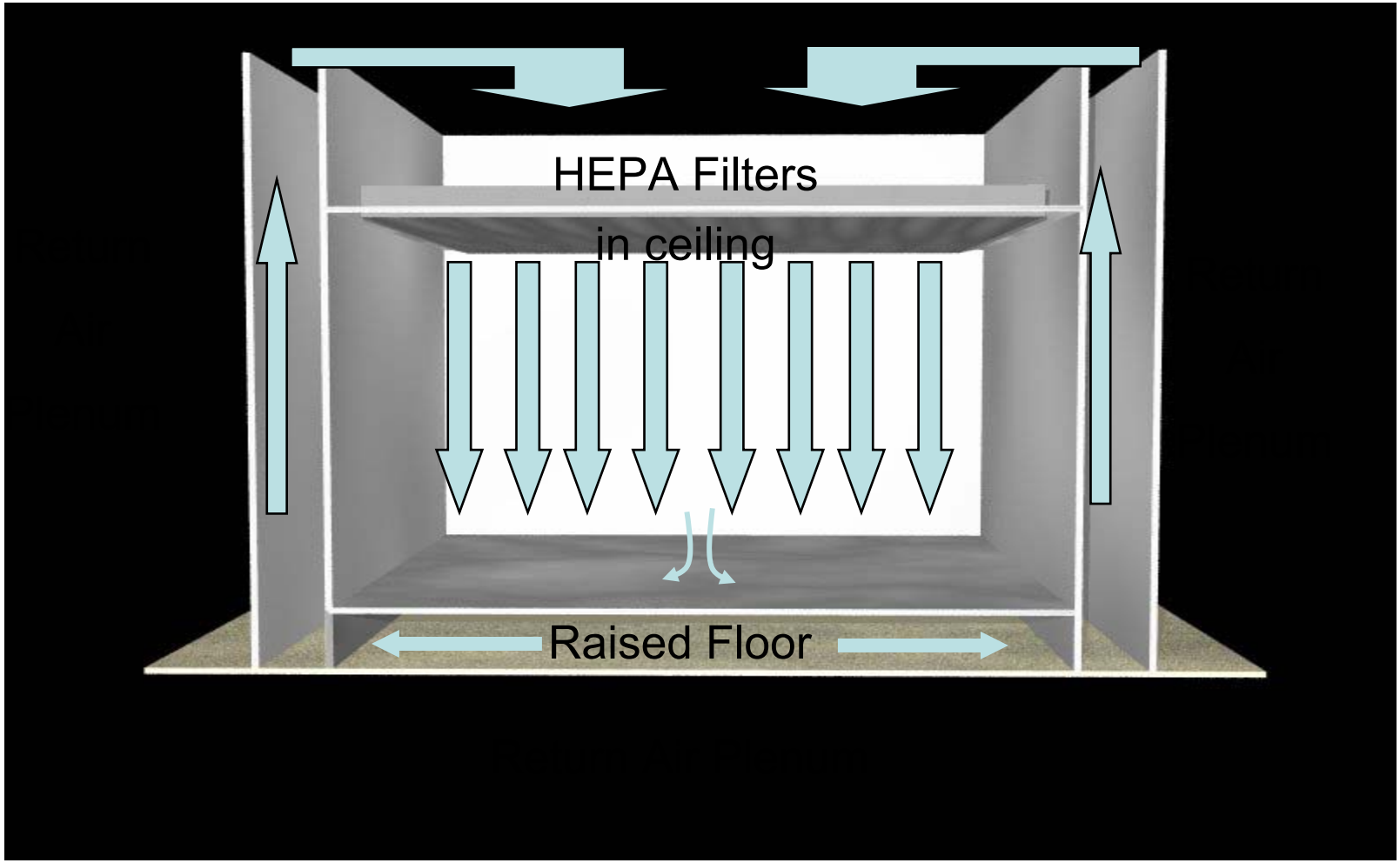
What Makes a Cleanroom Work? **Conventional Cleanroom**



1) Control Of Incoming Air Volume (Dilution)

2) Filtration

What Makes a Cleanroom Work? **Uni-Directional Cleanroom**



1) Control Of Air Flow and Direction

2) Filtration

Cleanroom Standards

- ~~FED-STD 209E~~
- ~~BS 5295~~
- ISO 14644-1
- EU GGMP

Fed-Std 209 E

FED-STD 209										
CLASS NAME		0.1µM		0.2µM		0.3µM		0.5µM		5.0µM
		VOLUME UNITS		VOLUME UNIT		VOLUME UNIT		VOLUME UNIT		VOLUME UNIT
S.I.	ENGLISH	(M^3)	(FT^3)	(M^3)	(FT^3)	(M^3)	(FT^3)	(M^3)	(FT^3)	(M^3)	(FT^3)
M1		350	9.91	75.7	2.14	30.9	0.875	10	0.283		
M1.5	1	1240	35	265	7.5	16	3	35.3	1		
M2		3500	99.1	757	21.4	309	8.75	100	2.83		
M2.5	10	12,400	350	2,650	75	1,060	30	353	10		
M3		35,000	991	7,570	214	3,090	87.5	1,000	28.3		
M3.5	100			26,500	750	10,600	300	3,530	100		
M4				75,000	2,140	30,900	875	10,000	283		
M4.5	1000							35,300	1,000	247	7
M5								100,000	2,830	618	17.5
M5.5	10000							353,000	10,000	2,470	70
M6								1,000,000	28,300	6,180	175
M6.5	100000							3,530,000	100,000	24,700	700
M7								10,000,000	283,300	61,800	17,500

Fed-Std 209 E

- ★ IEST WG 100 has recommended to the GSA (U.S. General Services Group) that they (GSA) "…discontinue the use and maintenance of FED-STD-209". The next step is for GSA to poll the U.S. Federal Agencies on the proposal that FED-STD-s09 be dropped and that the Federal Agencies use ISO 14644-1 and –2.

- ★ Many organizations refuse to change, stating the cost of document changes are too expensive to warrant replacement of the standard.

- ★ It is commonly accepted still in some facilites in the United States and in Asia.

BS 5295

Part 1 : 1989 Appendix 3 - Designation of Environmental Cleanliness

Table 2. Requirements for controlled environment installations

Class of environmental cleanliness	Maximum permitted number of particles/m3 (equal to, or greater than, started size)					Maximum floor area per sampling position for clean rooms	Minimum pressure difference*	
	0.3 µm	0.5 µm	5 µm	10 µm	25 µm	m2	Between classified area and unclassified area Pa	Between classified area and adjacent area of lower classification Pa
C	100	35	0	NS**	NS	10	15	10
D	1000	350	0	NS	NS	10	15	10
E	10000	3500	0	NS	NS	10	15	10
F	NS	3500	0	NS	NS			
G	100000	35000	200	0	NS	25	15	10
H	NS	35000	200	0	NS	25	15	10
J	NS	350000	2000	450	0	25	15	10
K	NS	3500000	20000	4500	500	50	15	10
L	NS	NS	200000	45000	5000	50	10	10
M	NS	NS	NS	450000	50000	50	10	NA***

* This applies only to clean rooms and totally enclosed devices
** NS: no specified limit
*** NA: not applicable as no limit specified

ISO 14644-1

Classification numbers numbers (N)	Maximum concentration limits (particles/m^3 of air) for particles equal to and larger than the considered sizes shown below					
	0.1μm	0.2μm	0.3μm	0.5μm	1μm	5.0μm
ISO 1	10	2				
ISO 2	100	24	10	4		
ISO 3	1 000	237	102	35	8	
ISO 4	10 000	2 370	1 020	352	83	
ISO 5	100 000	23 700	10 200	3 520	832	29
ISO 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO 7				352 000	83 200	2 930
ISO 8				3 520 000	832 000	29 300
ISO 9				35 200 000	8 320 000	293 000

ISO 14644-1

- ★ The most international of all cleanroom standards. Has effectively replaced FED-STD 209E and BS 5295 (in the UK)
- ★ Some organizations refuse to change, stating the cost of document changes are too expensive to warrant replacement of the standard.

EU Guide to Good Manufacturing Practice

Manufacture of Sterile Medicinal Products

Maximum permitted number of particles / m^3 equal to or above

	at rest		in operation	
Grade	**0.5µM**	**5µM**	**0.5µM**	**5µM**
A	3,500	0	3,500	0
B (a)	3,500	0	350,000	2,000
C (a)	350,000	2,000	3,500,000	20,000
D (a)	3,500,000	20,000	not definded (c)	not definded (c)

(c) Notes:
(a) In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate filters such as HEPA for grades A, B and C.

(b) The guidance given for the maximum permitted number of particles in the "at rest" condition corresponds approximately to the US Federal Standard 209E and the ISO classifications as follows: grades A and B correspond with class 100, M 3.5, ISO 5; grade C with class 10 000, M 5.5, ISO 7 and grade D with class 100 000, M 6.5, ISO 8.

(c) The requirement and limit for this area will depend on the nature of the operations carried out.

EU GGMP Explanation of the Grades

For the Manufacture of Sterile Medicinal Products Normally 4 Grades Can be Distinguished.

- ***Grade A: The Local Zone for High Risk Operations***
  - *Filling Zone*
  - *Stopper Bowls*
  - *Open Ampoules and Vials*
  - *Making Aseptic Connections*
  - *Normally Such Conditions are Provided by a Laminar Air Flow Work Station. Laminar Air Flow Systems Should Provide an Homogeneous Air Speed of 0.45 m/s +/- 20% (Guidance Value) at the Working Position.*

- ***Grade B: In Case of Aseptic Preparation and Filling***
  The background environment for grade A zone.

- ***Grades C and D:***
  Clean areas for carrying out less critical stages in the manufacture of sterile products.

Recommendations for Microbial Contamination

Recommended limits for microbial contamination (a)				
GRADE	*air sample cfu/m3*	*settle plates (diam. 90 mm), cfu/4 hours(b)*	*contact plates (diam.55 mm), cfu/plate*	*glove print. 5 fingers.cfu/glove*
A	*< 1*	*< 1*	*< 1*	*< 1*
B	*10*	*5*	*5*	*5*
C	*100*	*50*	*25*	*-*
D	*200*	*100*	*50*	*-*

Notes:

(a) These Are Average Values.

(b) Individual Settle Plates May Be Exposed For Less Than 4 Hours.

(c) Appropriate Alert And Action Limits Should Be Set For The Results Of Particulate And Microbiological Monitoring. If These Limits Are Exceeded Operating Procedures Should Prescribe Corrective Action.

Examples of operations to be carried out in the various grades

Grade	*Examples of operations for terminally sterilised products. (see par. 11)*
A	*Filling Of Products, When Unusually At Risk.*
C	*Preparation Of Solutions, When Unusually At Risk. Filling Of Products.*
D	*Preparation Of Solutions And Components For Subsequent Filling.*
Grade	*Examples Of Operations For Aseptic Preparations. (See Par. 12)*
A	*Aseptic Preparation And Filling.*
C	*Preparation Of Solutions To Be Filtered.*
D	*Handling Of Components After Washing.*

Order of Risk Based on Route of Administration

- ★ Parenteral & Ophthalmic Products
- ★ Inhalation Solutions
- ★ Aerosol Inhalants
- ★ Nasal Sprays
- ★ Vaginal And Rectal Suppositories
- ★ Topicals
- ★ Oral Liquids
- ★ Oral Tablets & Capsules

The Purpose of an Environmental Monitoring Program

Human Drug cGMP Notes, March, 1999 states that the purpose is to:

★ Provides crucial information on the quality of the aseptic processing environment during manufacturing

★ Prevents the release of potentially contaminated batch if appropriate standards are not fulfilled

★ Prevents future contamination by detecting adverse trends

Regulatory Requirements

What are the Regulatory Requirements for Microbial Monitoring in a Pharmaceutical Manufacturing Area?

Regulatory Requirements

- ★ 21 CFR 211.42 Design & Construction Features
- ★ 211.46 Ventilation, Air Filtration, Air Heating & Cooling
- ★ 211.113 Control of Microbiological Contamination
- ★ 211.22 Responsibilities of the quality control unit

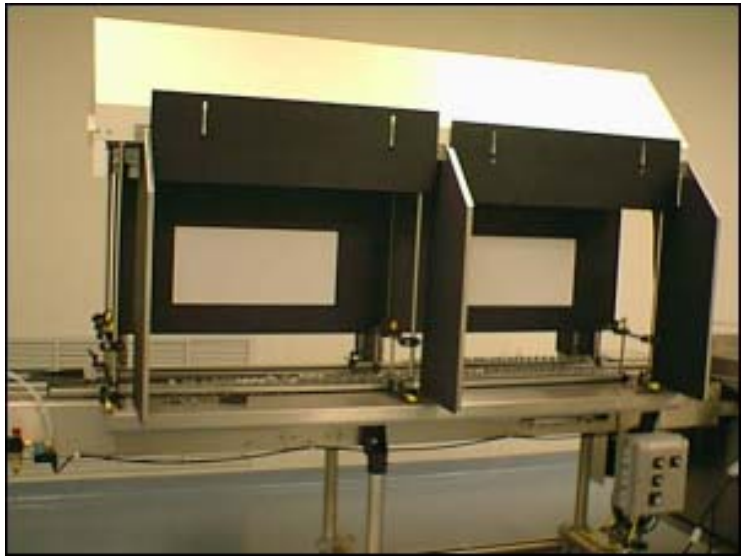
Regulatory Requirements

- ★ FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, June 1987
- ★ FDA Guide to Inspection of Sterile Drug Substance Manufacturers, July 1994
- ★ EU Guide to Good Manufacturing Practice. Annex on the Manufacture of Sterile Medicinal Products, June 1997

Regulatory Requirements: 21 CFR 211.42

21 CFR 211.42

Design & Construction Features highlights that buildings used to manufacture pharmaceutical products shall be of suitable size, construction & location to facilitate cleaning, maintenance and proper operation.



Regulatory Requirements: 21 CFR 211.42

21 CFR 211.42 (Cont)

Aseptic processing requires floors, walls & ceilings of smooth, hard surfaces that are easily cleaned, temperature & humidity controls, HEPA-filtered air, systems for environmental monitoring, cleaning & disinfecting, & maintaining the controlled environment.

Regulatory Requirements: 21 CFR 211.46

21 CFR 211.46

Ventilation, Air Filtration, Air Heating & Cooling (b) requires equipment for adequate control over microorganisms for the manufacture, processing, packaging or holding a drug product.

Regulatory Requirements: 21 CFR 211.113

21 CFR 211.113

Control of microbiological contamination. Requires that appropriate written procedures, designed to prevent the objectionable organisms in non-sterile drug products and microbiological contamination of sterile drug products, be established and followed. Such procedures shall include the validation of any sterilization process.

Regulatory Requirements: 21 CFR 211. 22

21 CFR 211. 22

Responsibilities of the Quality control unit.

Requires that the quality control unit monitor & ensure ongoing control of an aseptic process with the responsibility of approving or rejecting all drug products manufactured.

Regulatory Requirements

FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, June 1987

Guideline suggests that a clean room air quality of not more than 0.1 colony-forming unit (CFU) per cubic foot in a Class 100 aseptic process area is reasonable.

Regulatory Requirements

EU Guide to Good Manufacturing Practice. Annex 1 on the Manufacture of Sterile Medicinal Products, 1997

Recommends limits for environmental monitoring that differ from the USP

Industry Practice

- ★ PDA Technical Report No. 13 Fundamentals of a Microbiological Environmental Monitoring Program
- ★ *PhRMA Task Force Report on Environmental Monitoring in Non-Sterile Manufacturing Areas.
- ★ BS 5295 Classification, Design & Commissioning Cleanrooms
- ★ US Federal Standard 209E for Cleanrooms
- ★ ISO and BS 14644 for Cleanrooms

*Pharmaceutical Research and Manufacturers of America (PhRMA)

Difference between US and European Practices - Class 100

- US monitors during each operating shift
- For Grade A aseptic preparation & filling the EU recommended limits as average values are:
  - <1 cfu per m^3 of air
  - <1 cfu per 4 hour on a 90 mm settling plate
  - <1 cfu per 55 mm contact plate
  - <1 cfu for a 5 finger glove print

Setting Limits and Trend Analysis

- ★ Limits Would Be Consistent With Regulatory Guidelines
- ★ Alert Limits Should Be Set From Monitoring Histories At The 95% Percentile
- ★ With >98% Of The Samples Taken Containing No Microorganisms, Limit Setting & Trend Analysis Is More Difficult
- ★ Reaction Should Be To Consecutive Out-of-limit & Not Individual Results

Timing of Microbial Monitoring

The Air And Surface Monitoring Should Be Conducted Actively During The Aseptic Processing Operation With Personnel Monitoring When The Operator Leaves The Process Area. An Exception Would Be The Monitoring Of Product Contact Surfaces Which Would Be Monitored At The End Of The Filling Operation.

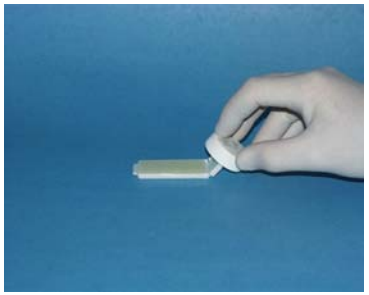
Environmental Monitoring Program

- ★ Surface Monitoring
- ★ Active Air Monitoring
- ★ Passive Air Monitoring
- ★ Microbiological Media and Identification
- ★ Particle Counting

Surface Monitoring

Testing Various Surfaces for Microbiological Quality:

- ★ Product Contact Surfaces
- ★ Floors
- ★ Walls
- ★ Ceilings



Testing Carries Out By Using:

- ★ Contact Plates
- ★ Touch Plates
- ★ Swabs
- ★ Surface Rinse Method

Active Air Monitoring

Method to Determine the Microbial Quality of the Air Using Active Devices Such as:

- ★ Slit to Agar
- ★ Membrane Filtration
- ★ Centrifugal Samplers

All Allow a Quantitative Testing of the Number of Organisms per Volume of Air Sampled

Passive Air Monitoring (Settling Plates)

- ★ Petri Dishes Containing Nutrient Growth Medium Exposed to the Environment
- ★ Lack Quantitative Value (Only What Settles On Plate)
- ★ Qualitative Value Important As Can Be Placed In Locations With The Greatest Risk

Microbiological Media and Identification

- ★ Routine Characterization of Recovered Microorganisms
- ★ Monitoring of Critical and Surrounding Areas
- ★ Monitoring of Personal
- ★ Should Require Identification of Species or Genus

The Goal Is To Reproducibly Detect Microorganisms For The Purpose Of Monitoring Environmental Control

Particle Counting

- ★ Useful in detecting significant deviations in air cleanliness from qualified processing classifications
- ★ Immediate understanding of air quality can be realized
- ★ Useful as a tool for qualification and monitoring before / during and after operations

Particle Counter Theory of Operation

There are three basic elements in all particle counting systems:

1) The Sensor

The Sensor Is The Device That Detects Particles Using A Light Scattering Techniques.

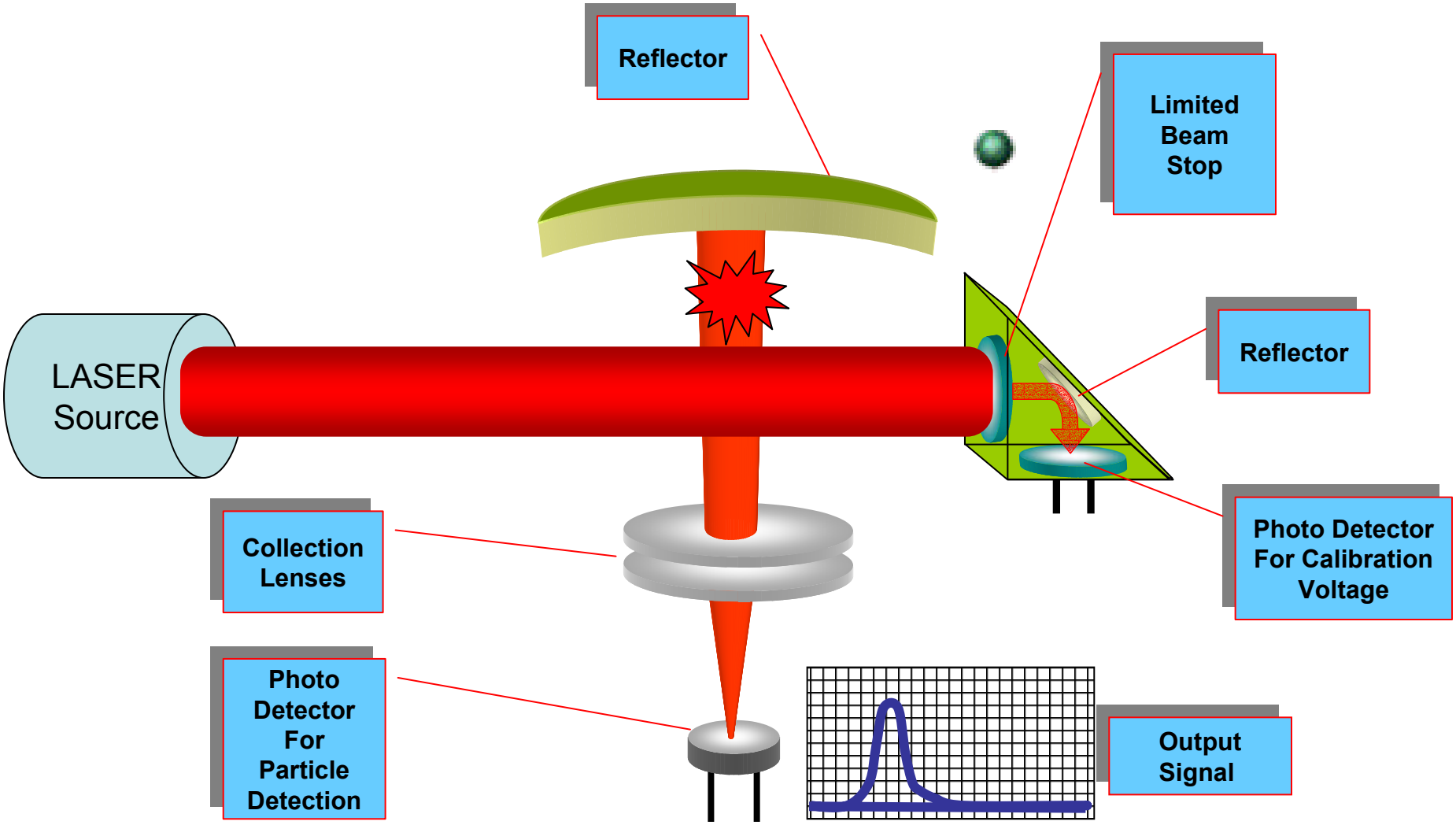
2) The Sample Delivery System

The Air Sample is Delivered the Sensor by Some Method.

3) The Counting Electronics

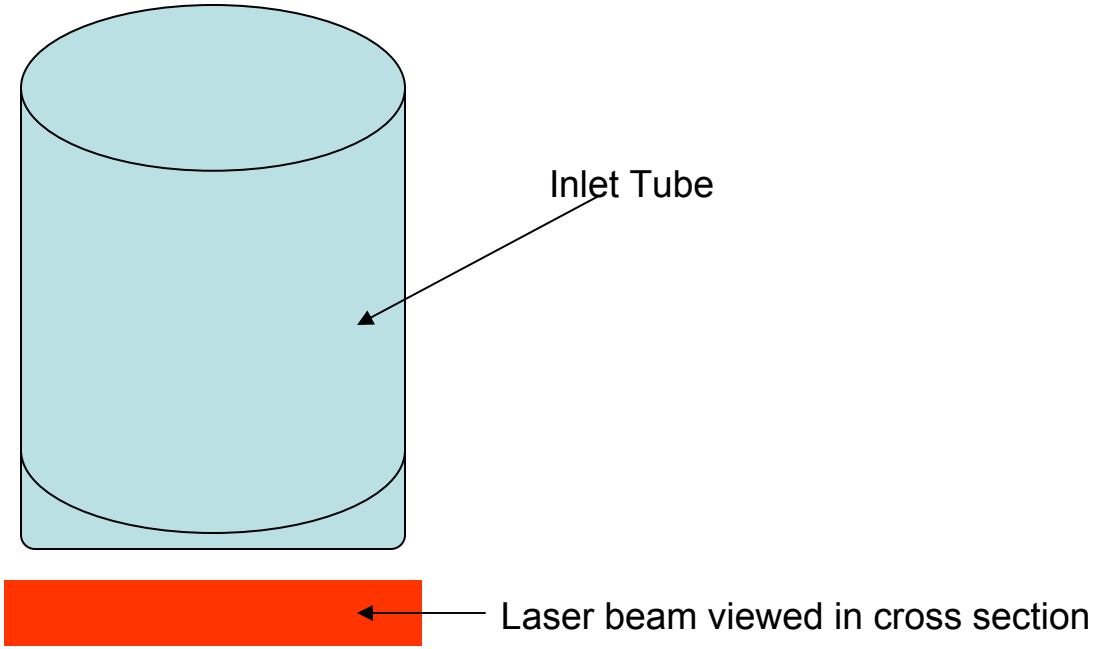
The Particle Counts Are Processed And Displayed By “On Board” Circuitry Or In Software In Facility Monitoring Systems (FMS).

Particle Counter Operation



Sensor View Volume

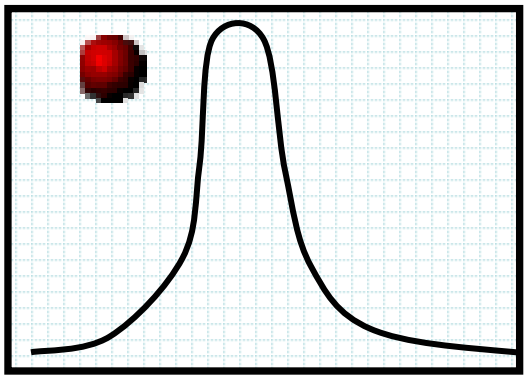
The View Volume is
The area where the
air stream and the
laser beam intersect.
The View Volume is
the width of the inlet tube
and ± 1mm high.



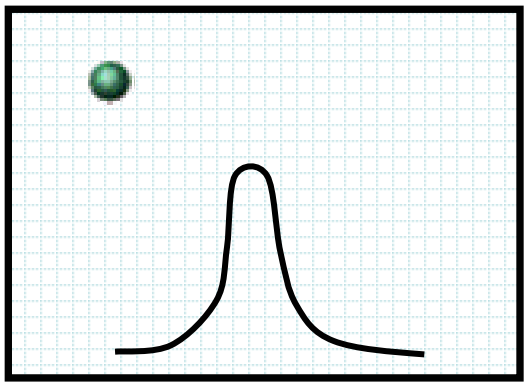
Particle Sizing

The larger the particle , the larger the corresponding output pulse from the sensor.

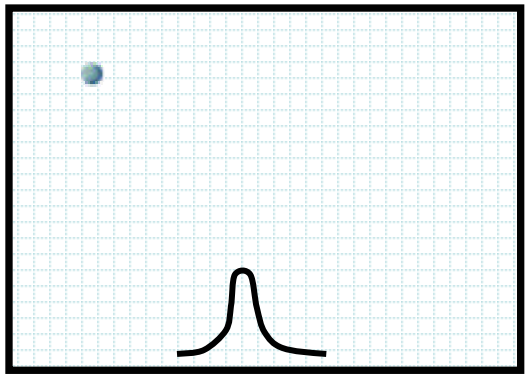
Largest



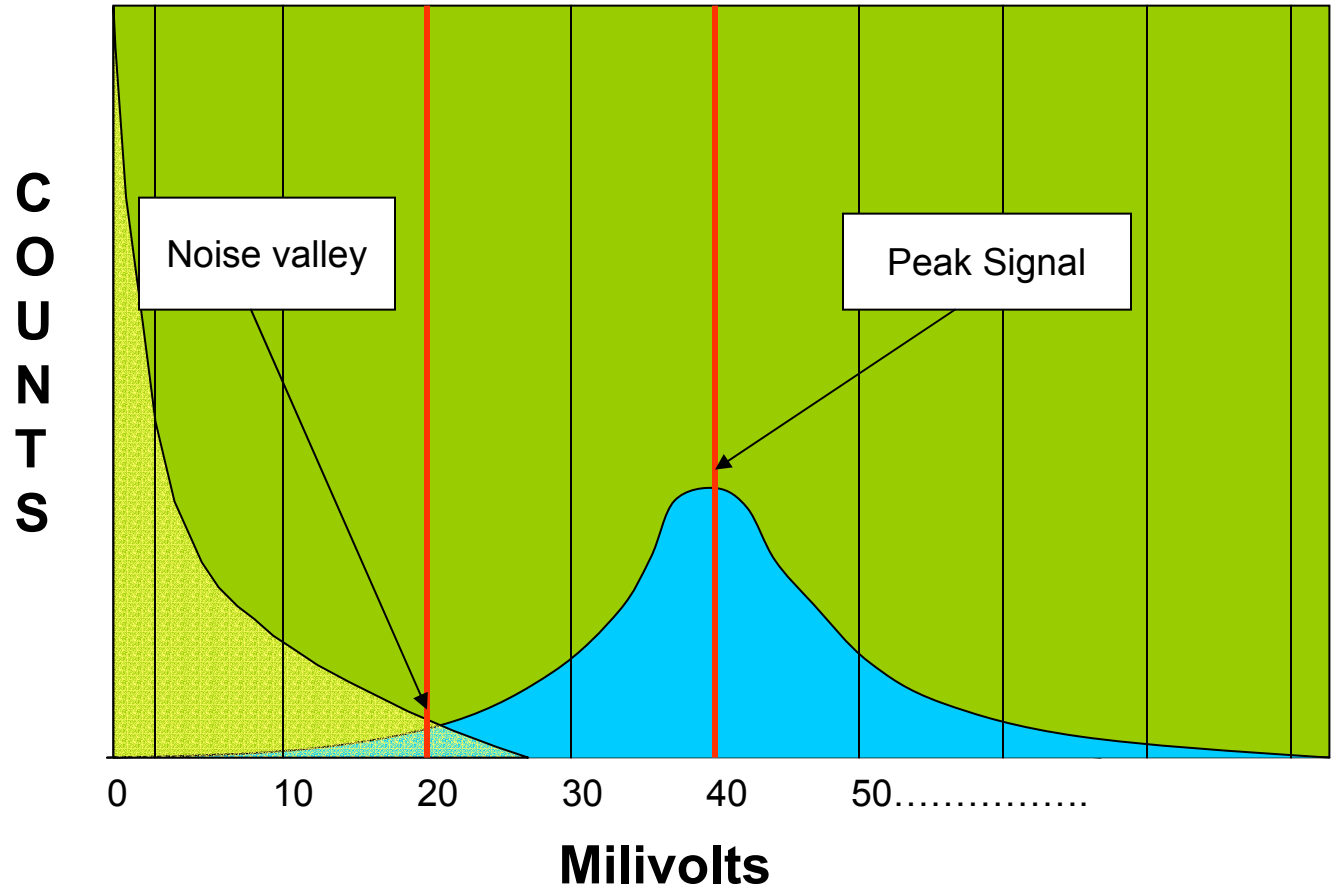
Larger



Smaller

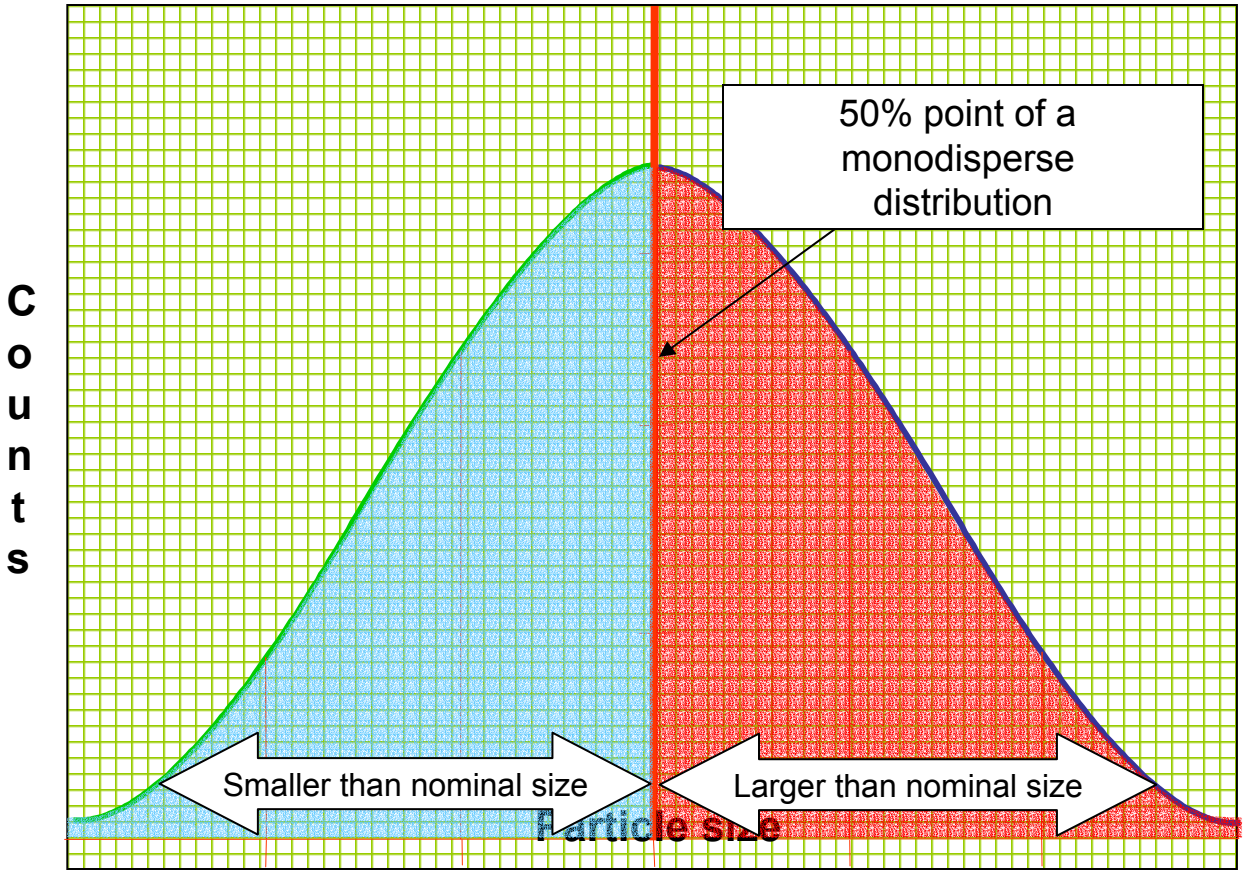


Signal To Noise Ration



In accordance with the Japanese Industrial Standard (JIS) the minimum Signal to Noise Ratio is 2 to 1.

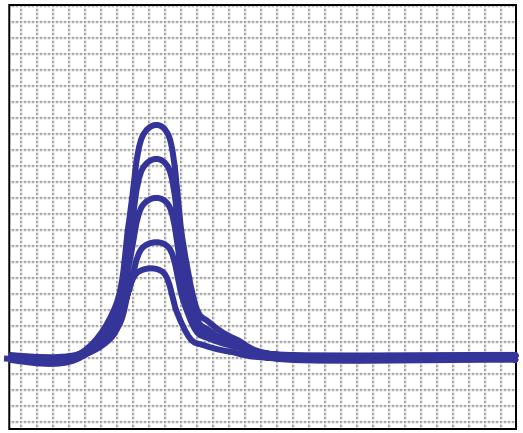
50% Counting Efficiency



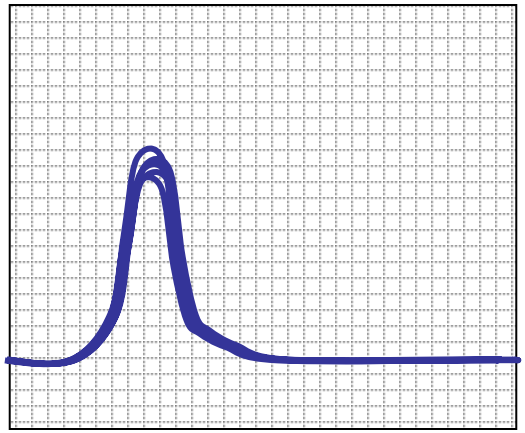
Definition: In a monodisperse distribution, the sensor detects all particles at the nominal size and larger.

JIS requires that the counting efficiency of the smallest detectable size of a sensor be between 30 and 70%.

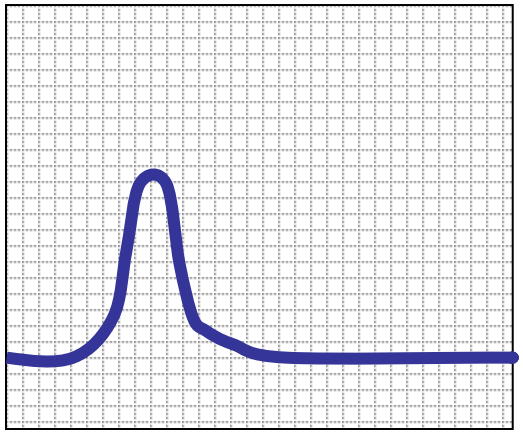
Sensor Resolution



Poor resolution



Good resolution



Perfect resolution

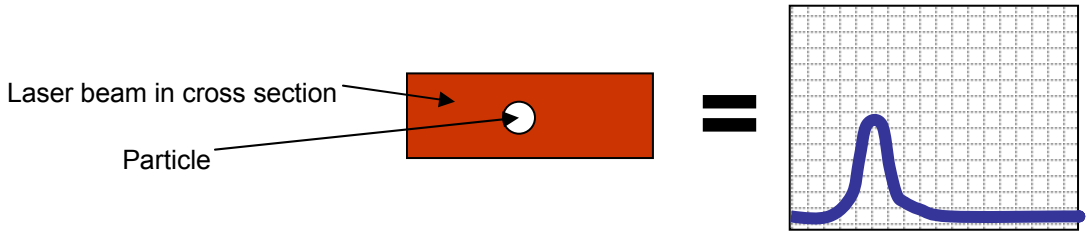
Causes of poor resolution:

Contamination. A buildup of particles in the sensor can disturb the light path.

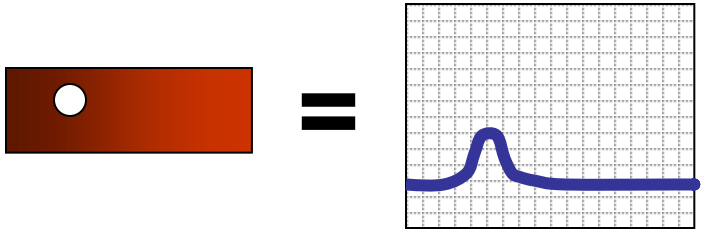
Misaligned sensor. A misaligned sensor must be returned to the factory for alignment.

Failing laser diode. This sensor must also be returned to the factory for diode replacement.

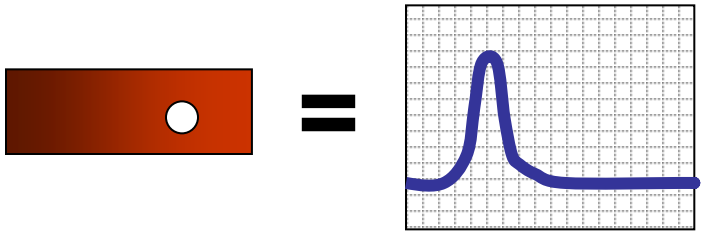
Why “perfect” resolution can not be achieved.



The above laser beam has uniform light intensity across the entire width.
Wherever a particle enters the beam the output pulse is the same.
This can not be achieved due to slight flaws in the optics and laser diode.



In this example a particle has entered the laser beam in an area of lower light intensity.
The resulting output pulse is low.

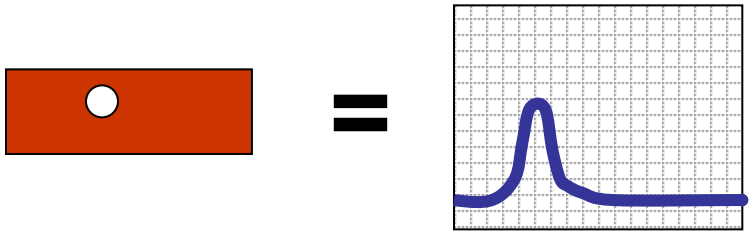


Note: These examples assume uniform sized particles

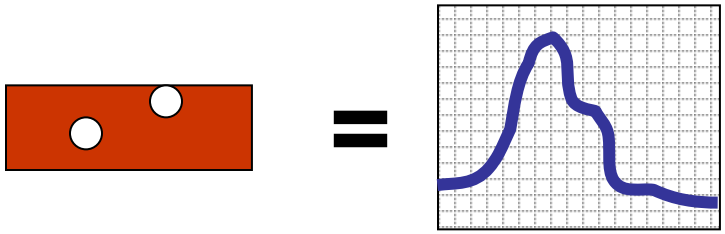
In this example the particle has entered the higher intensity area of the beam and the output pulse is higher in amplitude.

Coincidence Error

If particle counter is used in environments where the concentrations of particles are too high more than one particle at a time can enter the view volume. This results in coincidence errors.



In this example shows one 0.5µ particle in the view volume and it's output pulse.



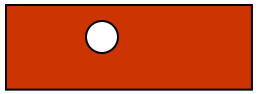
This example shows two 0.5µ particles in the view volume at the same time. The counter would report a size larger than 0.5µ and only one count.

Effects of Flow on Sizing

The amplitude of the sensor output is a function of the particle's residence time in the view volume.

1.0cfm flow rate

0.5µ particle



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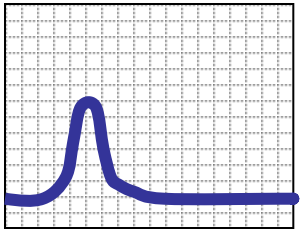
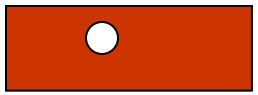


Optimum flow

1.2cfm flow rate

0.5µ particle



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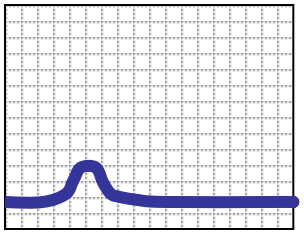
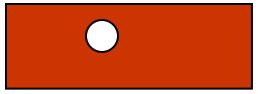


Flow is too high. The particle appears smaller than it actually is

0.8cfm flow rate

0.5µ particle



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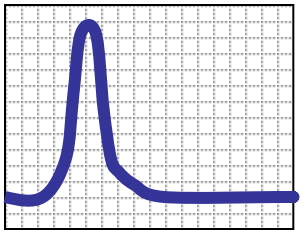
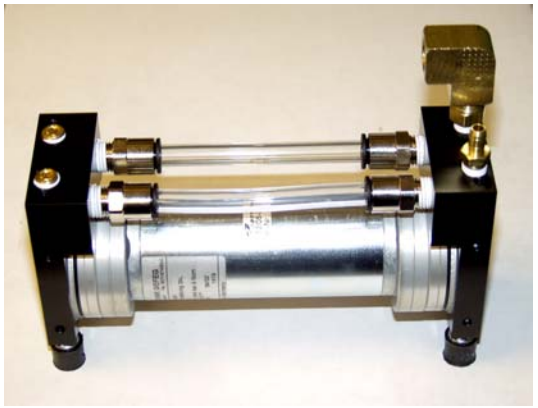


Flow is too low. The particle appears larger than it actually is.

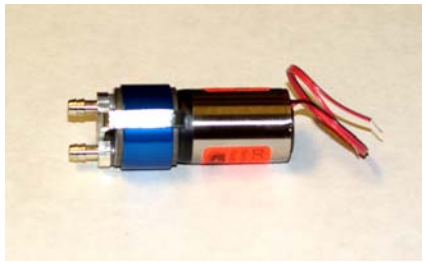
Sample Delivery

A vacuum pump is used to pull the sample air through the sensor. The flow is measured in cubic feet per minute (cfm). The use of some type of flow control is required to maintain the correct flow.

1.0 cfm pump

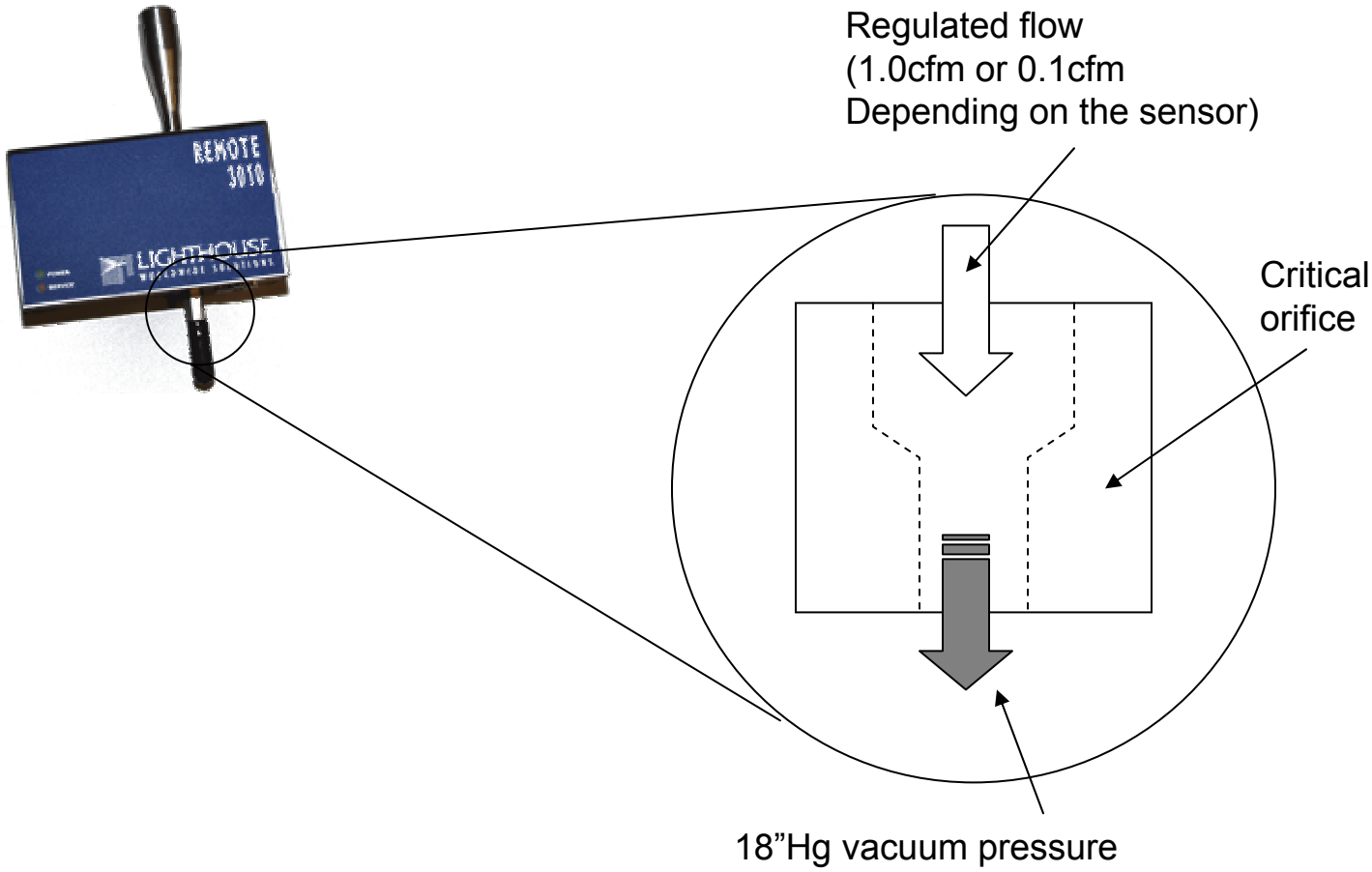


0.1 cfm pump



Critical Orifice

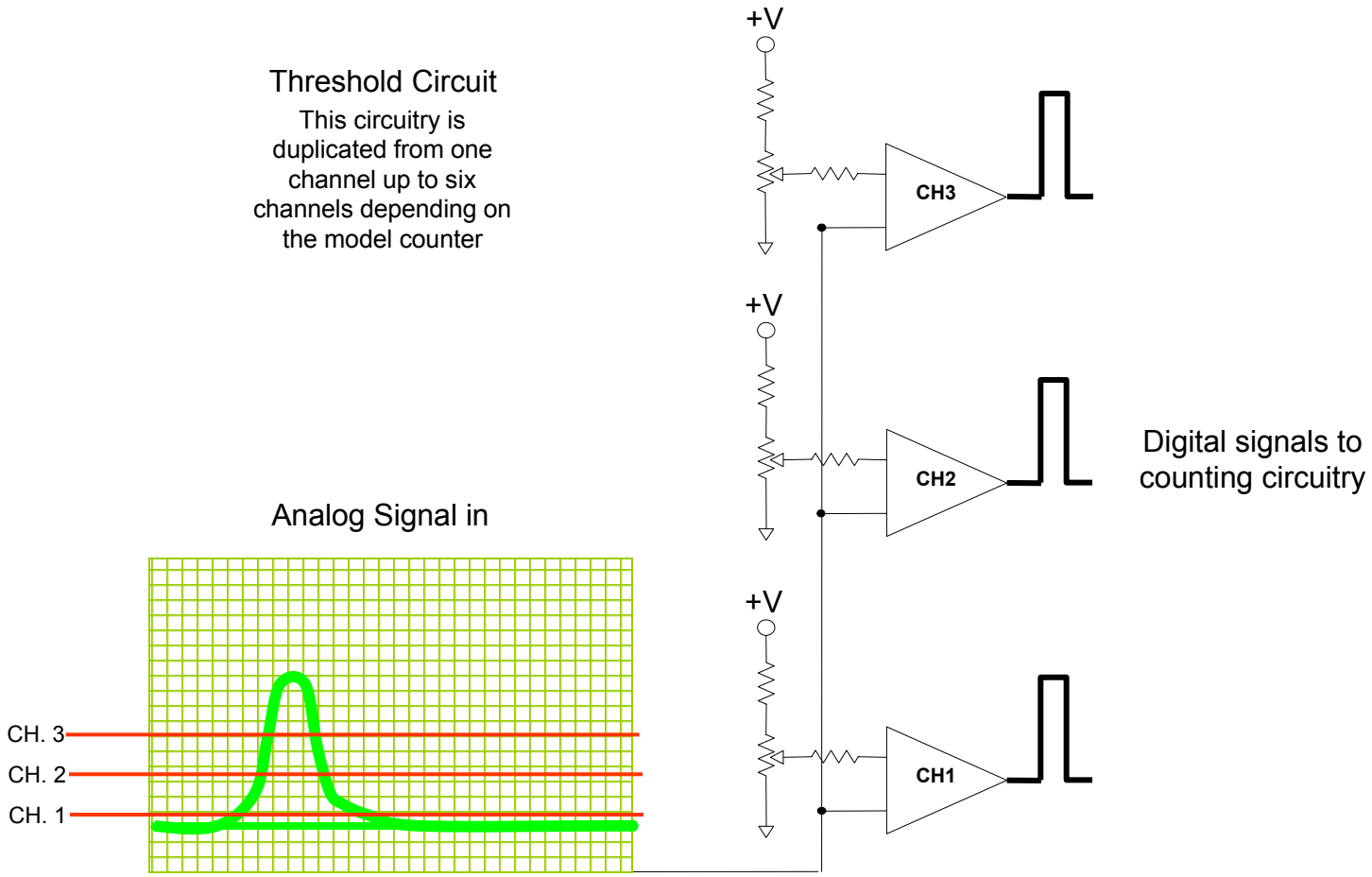
In remote counters a critical orifice is used to regulate the flow through the sensor.
A critical orifice is a precision opening that will only allow a certain amount of air flow once the critical vacuum pressure is applied.
In the case of Lighthouse counters the critical pressure is 18”Hg.



Counting Electronics

Threshold Circuit

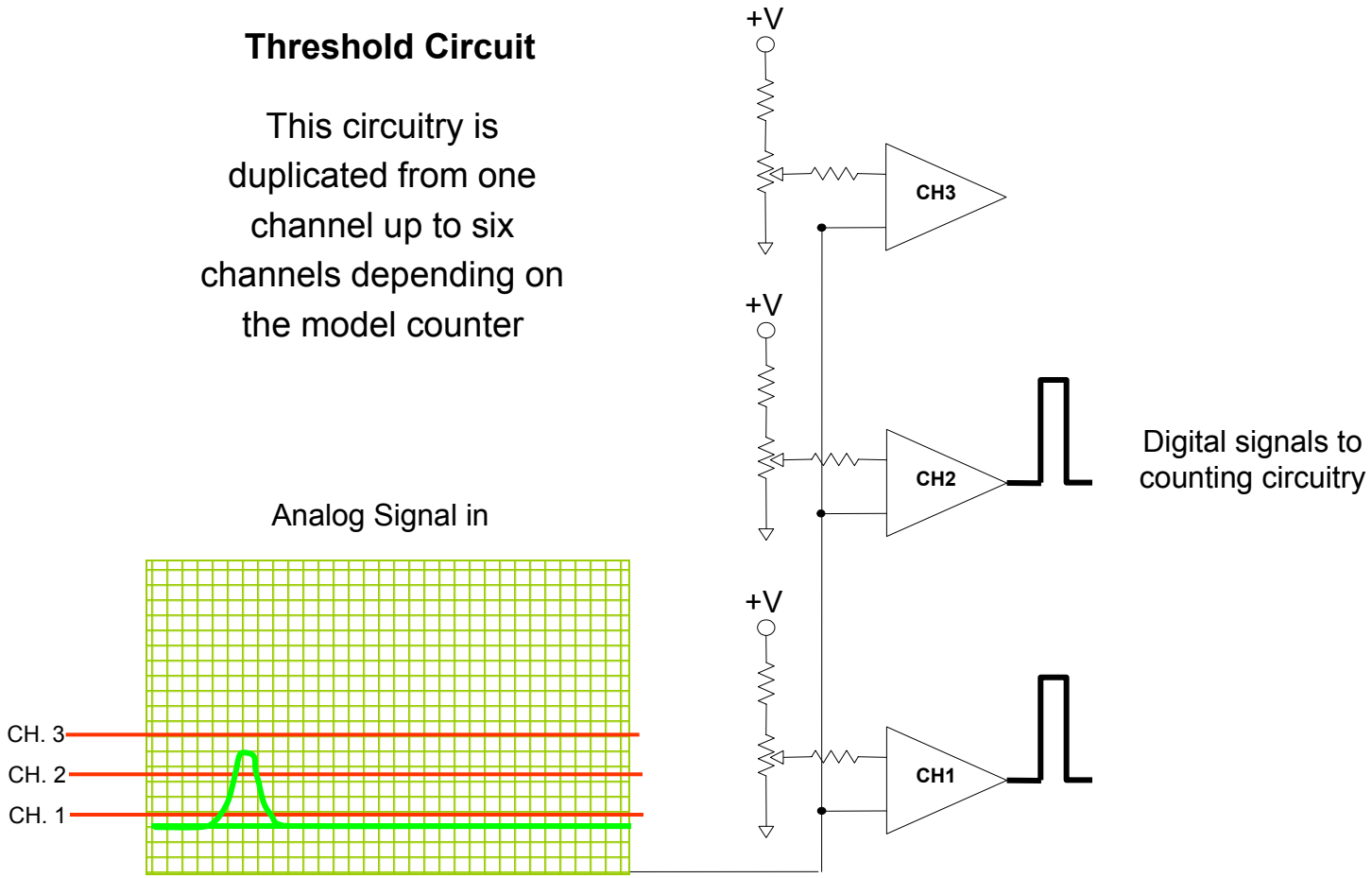
This circuitry is duplicated from one channel up to six channels depending on the model counter



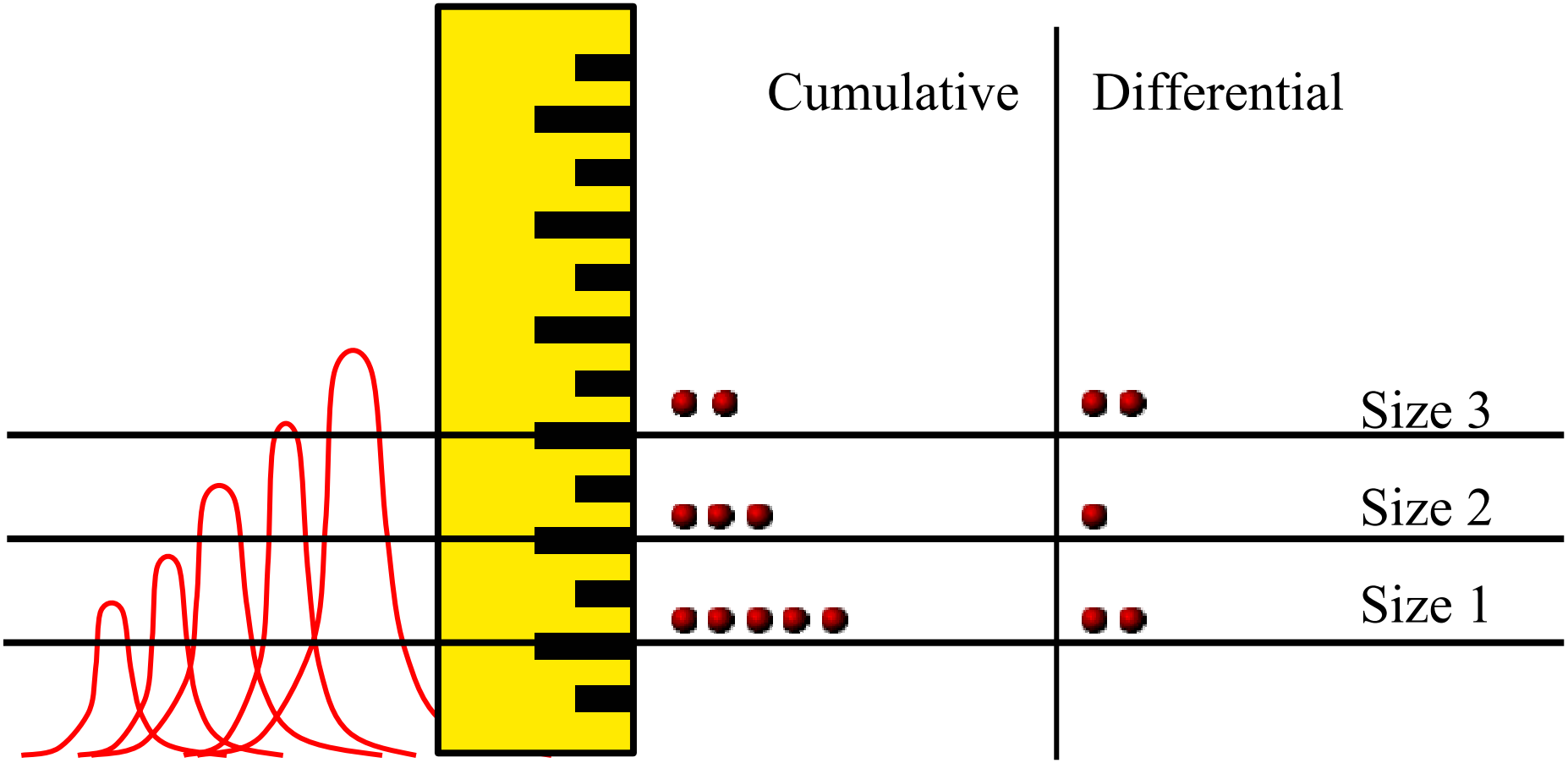
Counting Electronics cont.

Threshold Circuit

This circuitry is duplicated from one channel up to six channels depending on the model counter

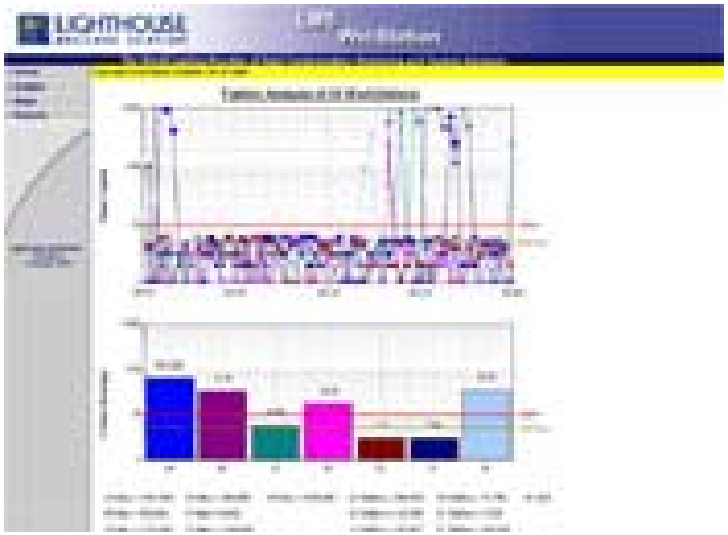


Counting Modes (Cumulative vs. Differential)

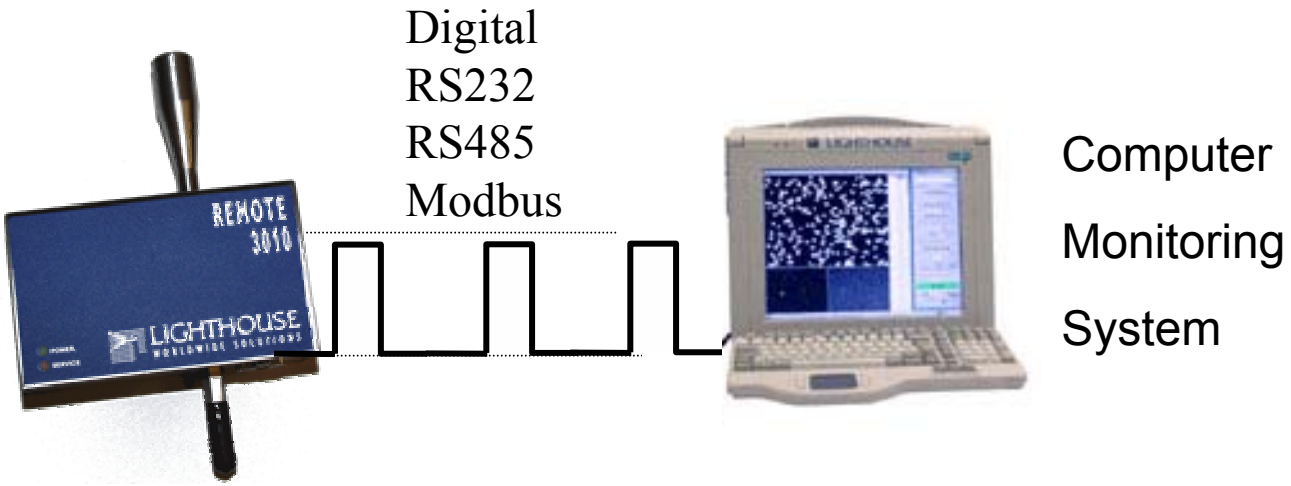


Data Display Modes (Printed vs. Electronic Records)

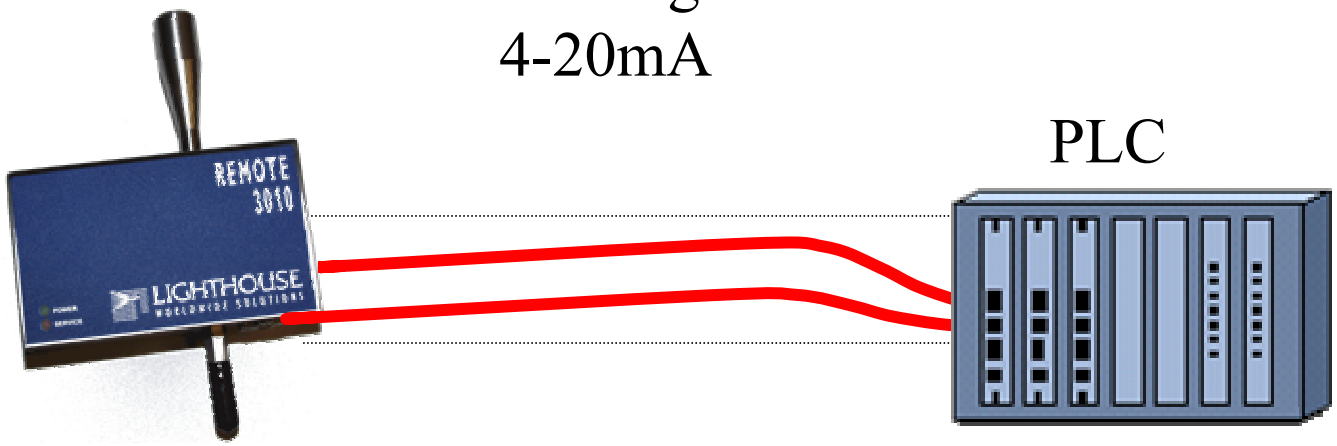
```
-------    SYSTEM STATUS    -------
TIME  =  08:30:53  AUGUST 12,1999

PARAMETER        STATUS      VALUE
---------        ------      -----
SENSOR CAL         PASS       1.01 V
Clock Battery      PASS       3.33 V
+5  Volt PS        PASS       4.95 V
+12 Volt PS        PASS      11.87 V
-12 Volt PS        PASS     -12.20 V
18v Battery        PASS      23.31 V
Flow               PASS       0.98 V
2084053-1A
```



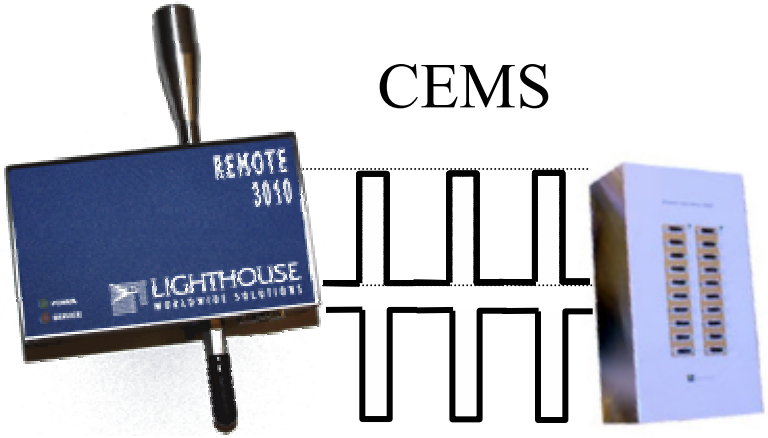
Remote Communication Modes



Remote Communication Modes



Remote Communication Modes



Sensor Interface Unit

SIU or SIU Lite

Particle Counting: Manual

Manual Particle Counting

- ★ Lowest Cost
  - Purchase
  - Service
  - Calibrate
- ★ Routine Tests For Compliance
- ★ Finding Contamination Sources
- ★ Used To Identify Sensitive Locations For Continuous Monitoring

Particle Counting: Extended Sampling

Manual Particle Counting

- ★ Program and “Forget”
- ★ Good for Long Term Testing
- ★ Flexible
- ★ Better Then Periodic Testing When Issues Arise

Portable Particle Counters

- Variety of Manufactures
- Tethered or Battery Operated Options
- Typically Higher Flow Rates (1 CFM)
- Built In Printers / Data Storage
- Some Units are “Manifold Ready”

Automated Sequential Particle Counting

A. Automated Tests For Compliance

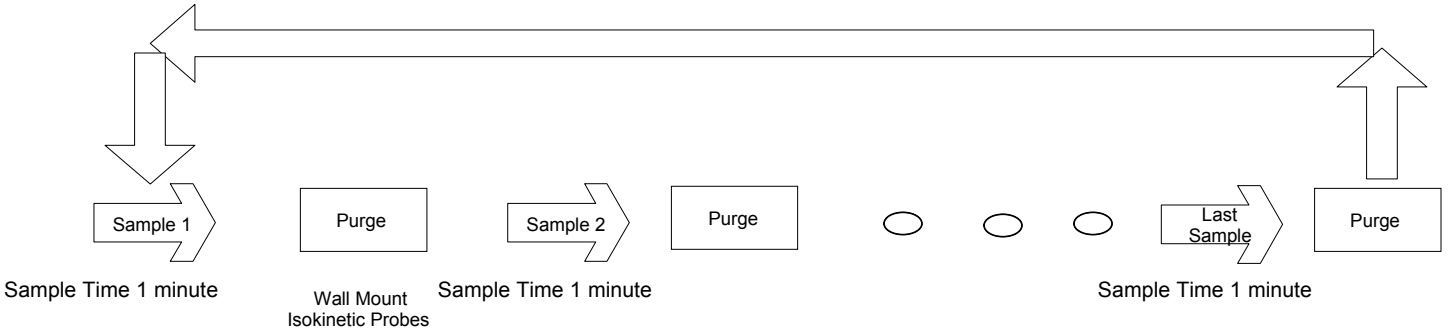
B. Up to 32 Points / Particle Counter (in sequence)

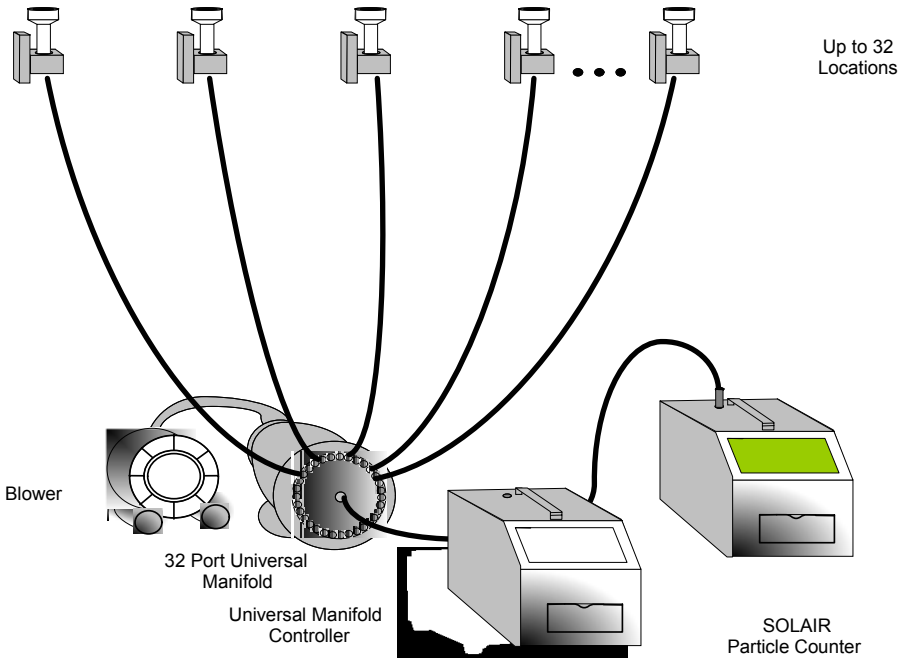
C. Sensitivity 0.1 micron

D. Time Between Particle Counts (same location) Based Upon The Number of Points Sampled by the Counter

E. Episodes Of Particle Excursions Can Be Missed

Sequential Particle Counting System Operation: (Manifold or Scanner)





Sequential Sampling Particle Counting Systems:

- ★ Variety of Manufactures
- ★ Lower Cost / Point (Higher Sensitivity Possible)
- ★ Monitor Up To *32 Points With A Single Counter
- ★ Maximum Time To Re-Sample Is Dependant On Number of Points
- ★ Connection To External System Easy
- ★ Lower Calibration Cost

* Manufacturer Dependant

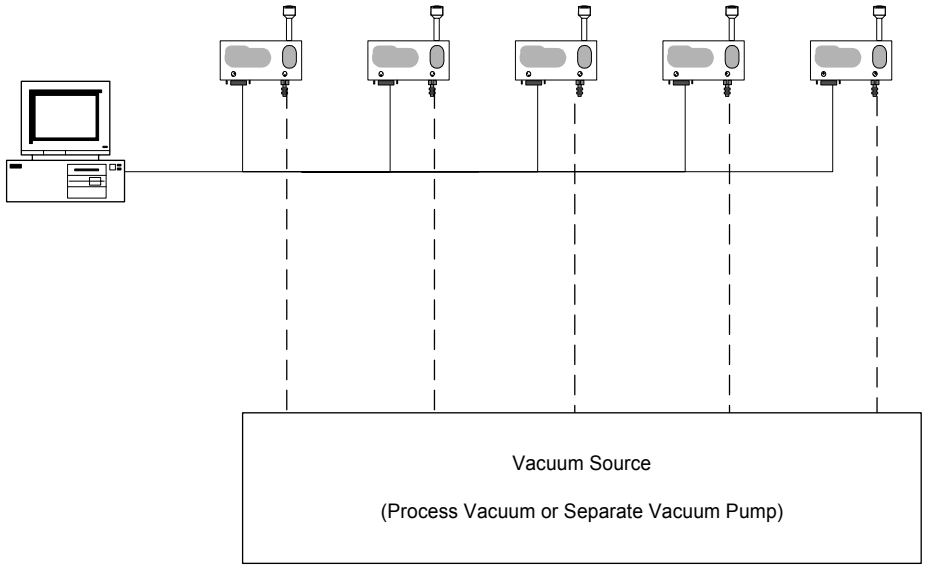
Manifold Points vs. Samples / Day

Number of Ports Samples	* Time between Samples at the same location	* Number of samples per day at same location
10 Ports	11 Minutes 40 Seconds	123 Samples
12 Ports	14 Minutes	103 Samples
16 Ports	18 Minutes 40 Seconds	77 Samples
24 Ports	28 Minutes	51 Samples
32 Ports	37 Minutes 20 Seconds	39 Samples
40 Ports	46 Minutes 40 Seconds	31 Samples

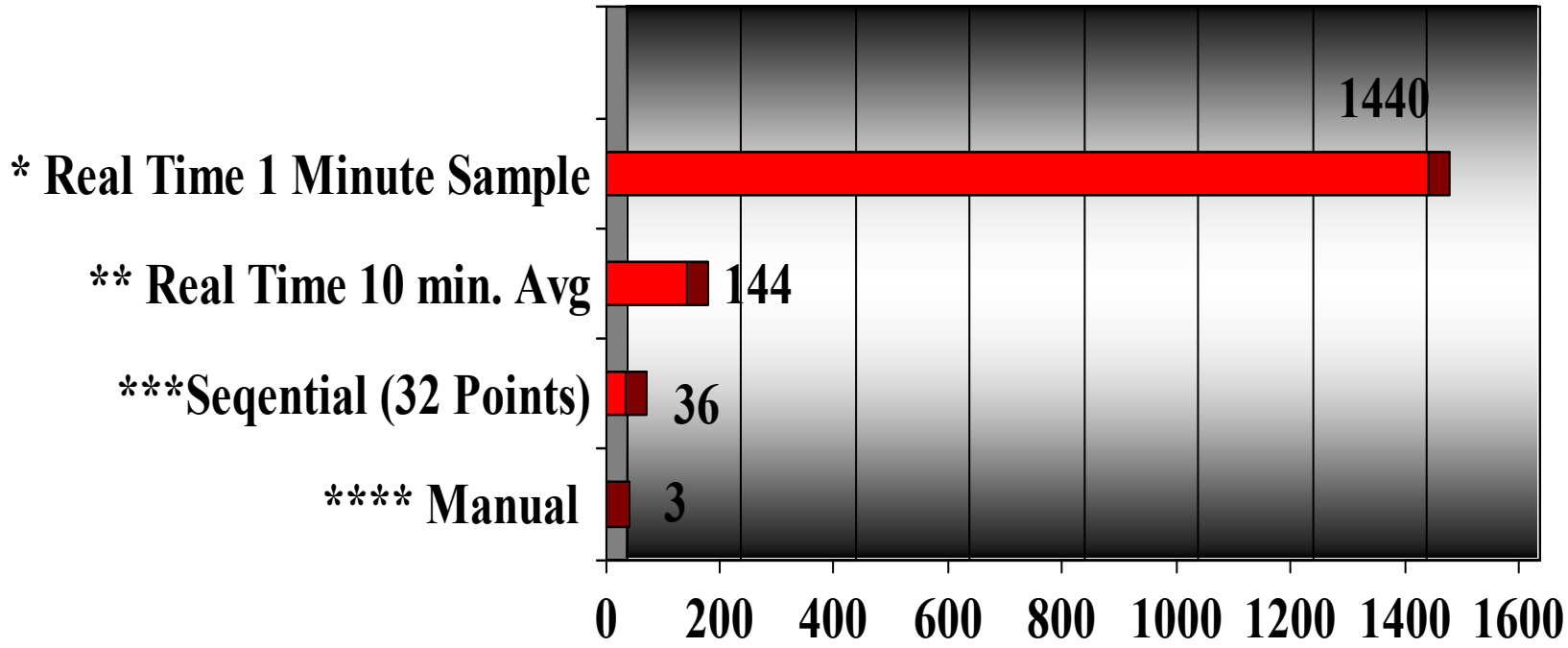
* Based on 1-minute sample, 10 second purge time

Dedicated Remote Particle Counters

A. Real-Time Monitoring and Alarming
B. Sensitivity 0.1 Micron
C. Catches Every Particle Event
D. Can Utilize Less Sensitive and Less Expensive Discrete Counters (0.3µm vs. 0.07 µm)



Comparison of Counting Techniques (Samples / Day Same Location)



* 1 Minute Sample Time

** Based On Continues Counting And Average Data For 10 minutes

*** Using 32 Port Sampling System, 1 Minute Sample / Point, 15 Second Purge Step

**** 1 Sample per Shift

Why Use an FMS System?

REGULATORY COMPLIANCE:

- ★ STATUTORY REQUIREMENTS
- ★ INDUSTRY STANDARDS
- ★ ISO COMPLIANCE

QUALITY CONTROL:

- ★ YIELD MANAGEMENT
- ★ RELIABILITY GROWTH
- ★ PROCESS CONTROL

Benefits of a Cleanroom Facility Monitoring System

Real Time Response – The monitoring system provides early warning when conditions exceed user defined limits. This minimizes environmentally induced yield losses by providing the operators and supervisors with the visibility they need to react to problems in real-time.

Benefits of a Cleanroom Facility Monitoring System

Process Improvement – By correlating cleanroom or process modifications against historical data from the system, better process improvement decisions can be made.

Yield Improvement – Early warning and correlation of events to yield losses helps in improving the manufacturing conditions. This correlation ability also facilitates the analysis of equipment maintenance cycles.

Benefits of a Cleanroom Facility Monitoring System

Proactive Contamination Control – Using an on-line system allows you to take a proactive roll in identifying potentially damaging contamination issues before they happen.

Customer Confidence – An on-line system gives your customer confidence that you are concerned about their products.

Benefits of a Cleanroom Facility Monitoring System

Data Correlation – The data from an on-line system allows you to correlate various events and tie them back to yield loss.

★ Shift change and particle counts

★ Particle counts and yield loss

★ Tool operation and particle, TRH and ESD

★ Differential pressure and particle

★ Humidity and ESD events

★ Product transport operations and particle counts

Air Quality in Cleanrooms

Many parameters affect the quality of the air in a clean room or minienvironment

A. Airborne particle concentration
B. Temperature and relative humidity
C. Room and minienvironment pressurization
D. Air velocity and direction
E. Airborne Molecular Contamination
F. Other Factors

Facility Monitoring System Parameters

Monitor Parameters:

Aerosol Particle Counts

Temperature

Relative Humidity

Differential Pressure

Air Velocity

TC, TOC

Conductivity

Electrostatic Discharge

Viable Particle Monitoring / Control

Liquid Particle Counts

WFI Particle / Conductivity

Considerations in System Design

PURPOSE OF THE SYSTEM

- ★ Watch Dog
- ★ Evaluation of Cleanroom Conditions
- ★ Tool For Facilities
- ★ Customer Satisfaction
- ★ Marketing Tool

Considerations in System Design

PARAMETERS TO BE MONITORED: Considerations

- ★ Sensor Sensitivity
- ★ Sensor Scale
- ★ Sensor Cost
- ★ Sensor Connectivity
- ★ Durability of Sensors for the Application
- ★ Service and Calibration Schedules of the Sensors
- ★ Sensor Location
- ★ Integration of Sensors Into the Cleanroom
- ★ Impact of Installation on Cleanroom

Factors To Consider When Choosing A System

System Management:

- ★ Who Will Be Using The System?
- ★ Who Will Be Managing The System?

Data Collection

- ★ How Will The System Respond To Catastrophic Events?
- ★ How Will The System Generate And Display Alarm Conditions?

Historical Records

- ★ How Will The System Record Incoming Information?
- ★ Will The System Generate Reports to Compare Different Areas at Different Times?

Factors To Consider When Choosing A System

Information Management:

- ★ How Will The System Record Data From The Installed Sensors?
- ★ Will The System Collect Data At A Higher Rate When The Sensor Is In An Alarm Condition And At A Lesser Rate When The Sensor Is In Normal Range?

Manipulation and Access

- ★ How Will The Interact With The User?
- ★ What Type Of Graphical User Interfaces Are Available With The System?
- ★ What Operating System Will The System Run On?
- ★ How Many Users Will Need To See The Data?

Factors To Consider When Choosing A System

Configuration And Expansion:

- ★ What Features Are Available To Assist Users In Configurations, Expanding and Managing The System?
- ★ How Will The System Be Expanded In The Future?
- ★ What Options Are Available to Connect Future Sensor Technology

What to Monitor? Cleanroom:

Cleanroom Conditions (Conditions Related to Cleanroom Operation)

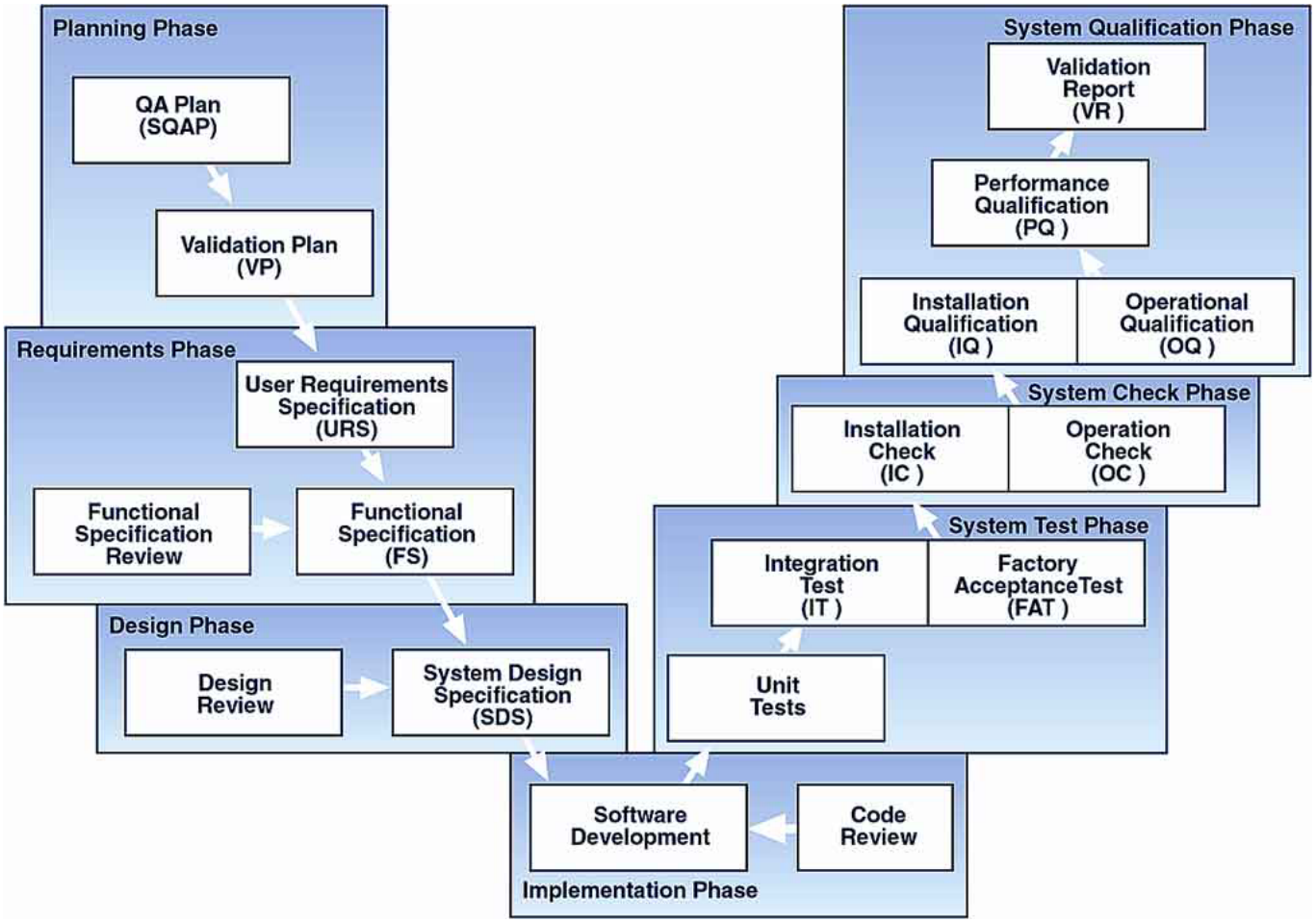
- ★ Aerosol Particle Counts
- ★ Differential Pressure
- ★ Temperature
- ★ Relative Humidity
- ★ Air Velocity
- ★ Air Changes / Per Hour
- ★ Air Handlers or Fan Filter Unit Status
- ★ Air Plenum Return Pressures

What to Monitor? Process:

Process Related Conditions (As Related To Products Produced)

- ★ Airborne Molecular Contamination Levels (AMC)
- ★ Electrostatic Charge (Environmental or on Product Surfaces)
- ★ Ionization System Status
- ★ Ground Status
- ★ EMI

SYSTEM DEVELOPMENT LIFE CYCLE • GAMP 4 V-MODEL



Electronic Records and Signatures

Audit Trails

- ★ Provide activity record as required by 21 CFR Part 11
- ★ Entries include
  - ➔ User ID
  - ➔ Date and Time
  - ➔ Type of Action or Event
  - ➔ Previous value
  - ➔ New Value
- ★ System can be set to require user to enter password and insert a comment when
  - ➔ making system changes
  - ➔ acknowledging alarms
- ★ Audit trail log can be printed
- ★ Logs of Alarm, Event or Audit Activities
  - ➔ each log can be separately printed

User Access Controls

- ★ Multi-level permissions
- ★ Unique User ID using Passwords
- ★ Password Aging
- ★ Auto Log out for User Inactivity
- ★ Lock Out of User after Failed Log-ins
- ★ Administrator can DISABLE access by a user
- ★ Separate public NAME used for listing on reports or comment fields

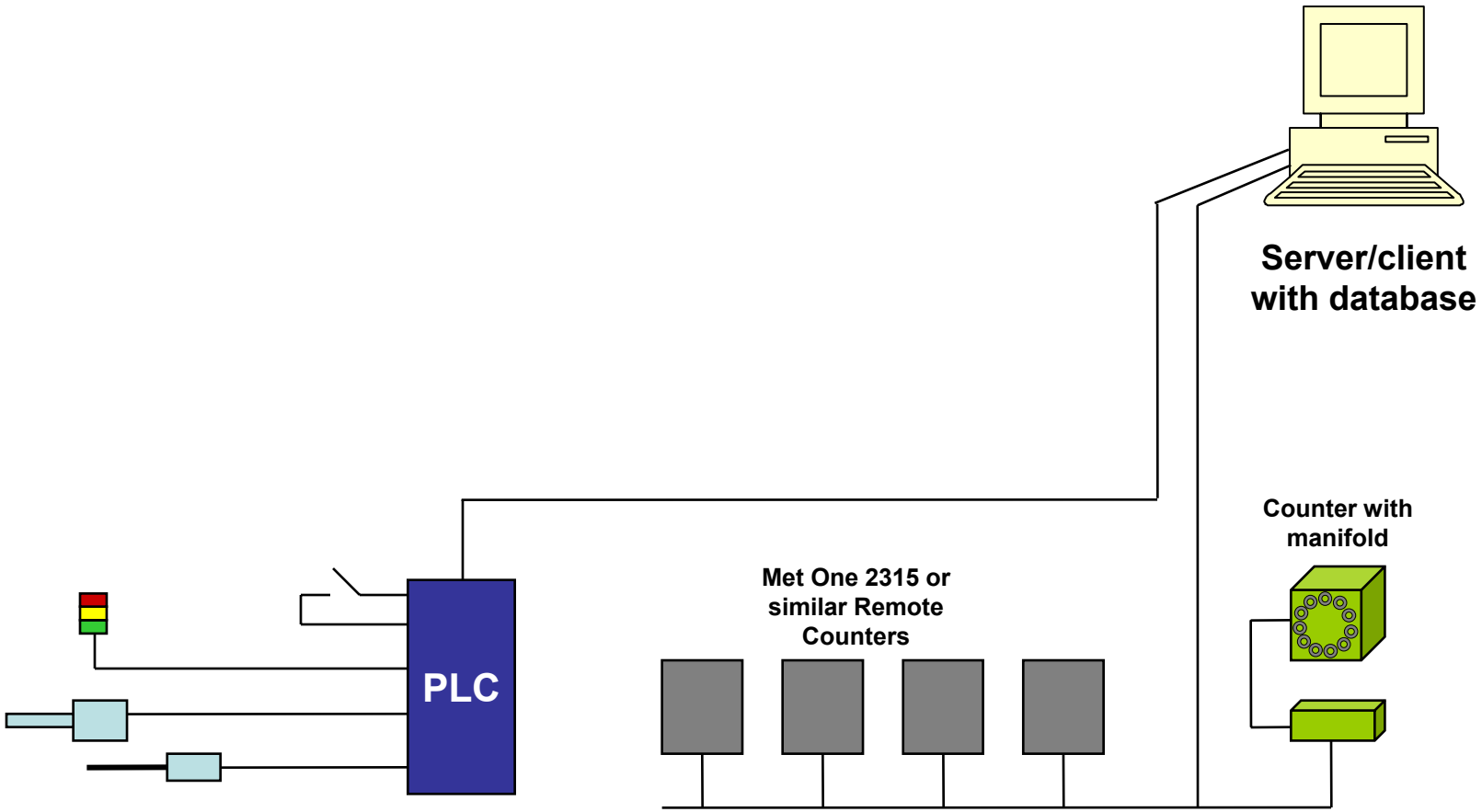
Hardware Supported

- ★ Room-to-room Pressure Differential
- ★ Humidity and Temperature
- ★ Air Velocity
- ★ PLC Inputs and Outputs
  - ➔ Contacts Closures (Doors, events)
  - ➔ Alarm signaling: Light stacks; audible alarms; relays
  - ➔ Analog inputs through PLC (0 to 5 v; 4 to 20 ma)
- ★ Liquid Parameters;
  - ➔ Liquid Particle Counts, TOC, Conductivity, pH, DO, and more
- ★ Airborne Particle Counters
  - ➔ Individual Counters
  - ➔ Manifold / Scanner Multi-point systems
  - ➔ Remote (Fixed) Counters
    - ➔ any combination of the above

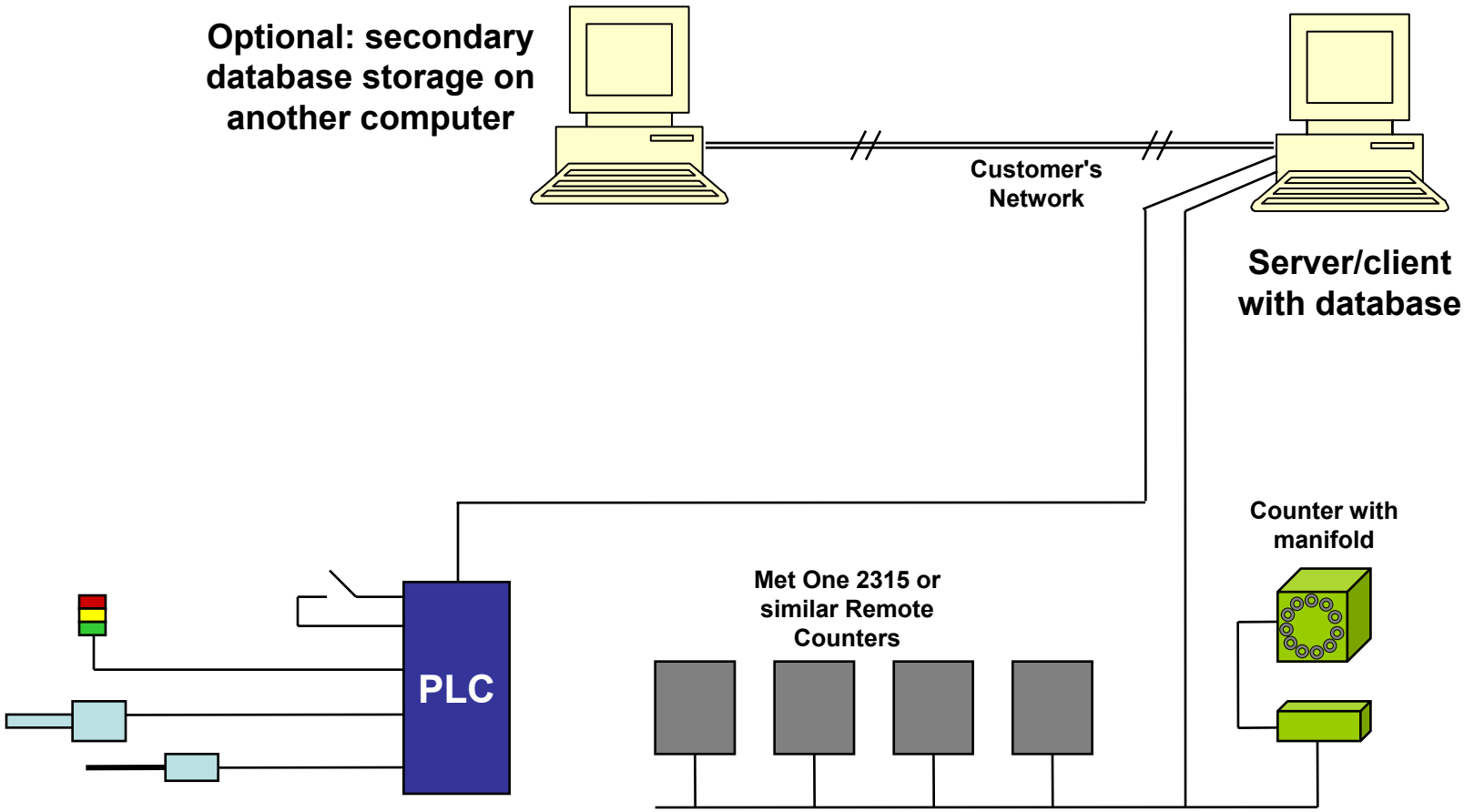
System Configuration Examples

- ★ Standalone system (server/client combined)
- ★ Standalone System with Network Mirror Site
- ★ Simple Networked system
  - ➔ Single server/database with multiple clients
- ★ Complex Networked System
  - ➔ Multiple servers and databases, multiple clients

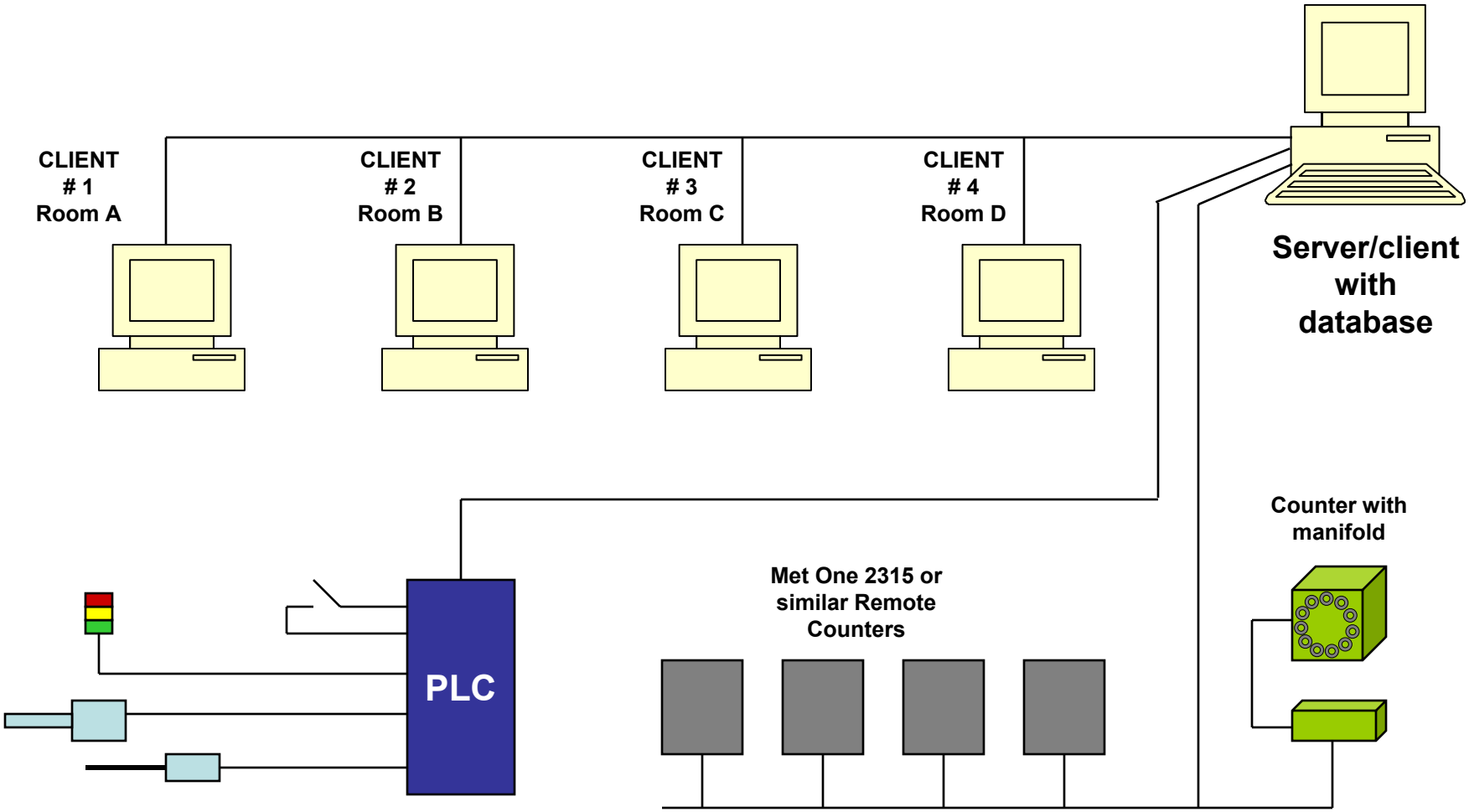
Standalone system (server/client combined)



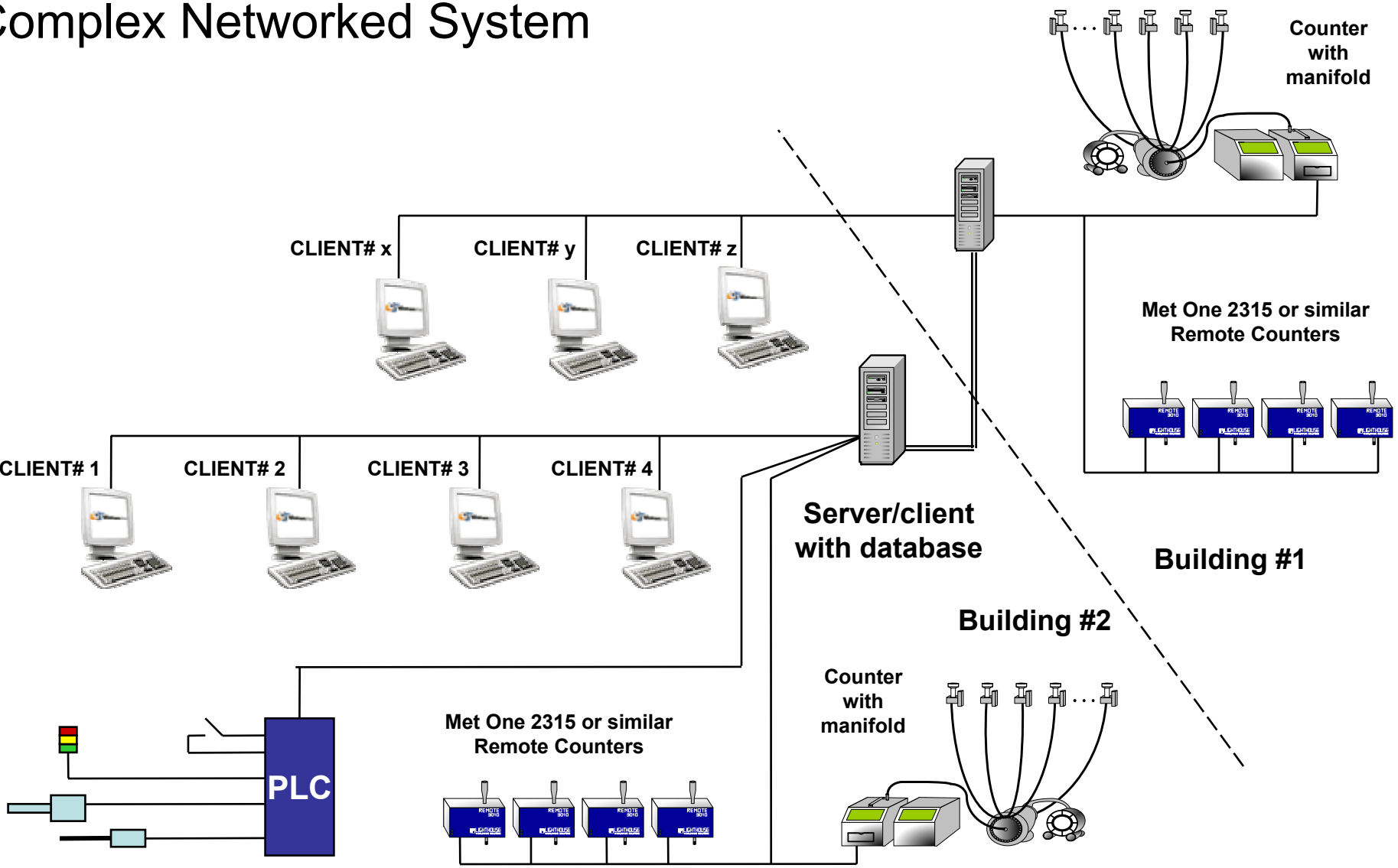
Standalone system with Database Mirror



Simple Networked System



Complex Networked System



Thank You

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