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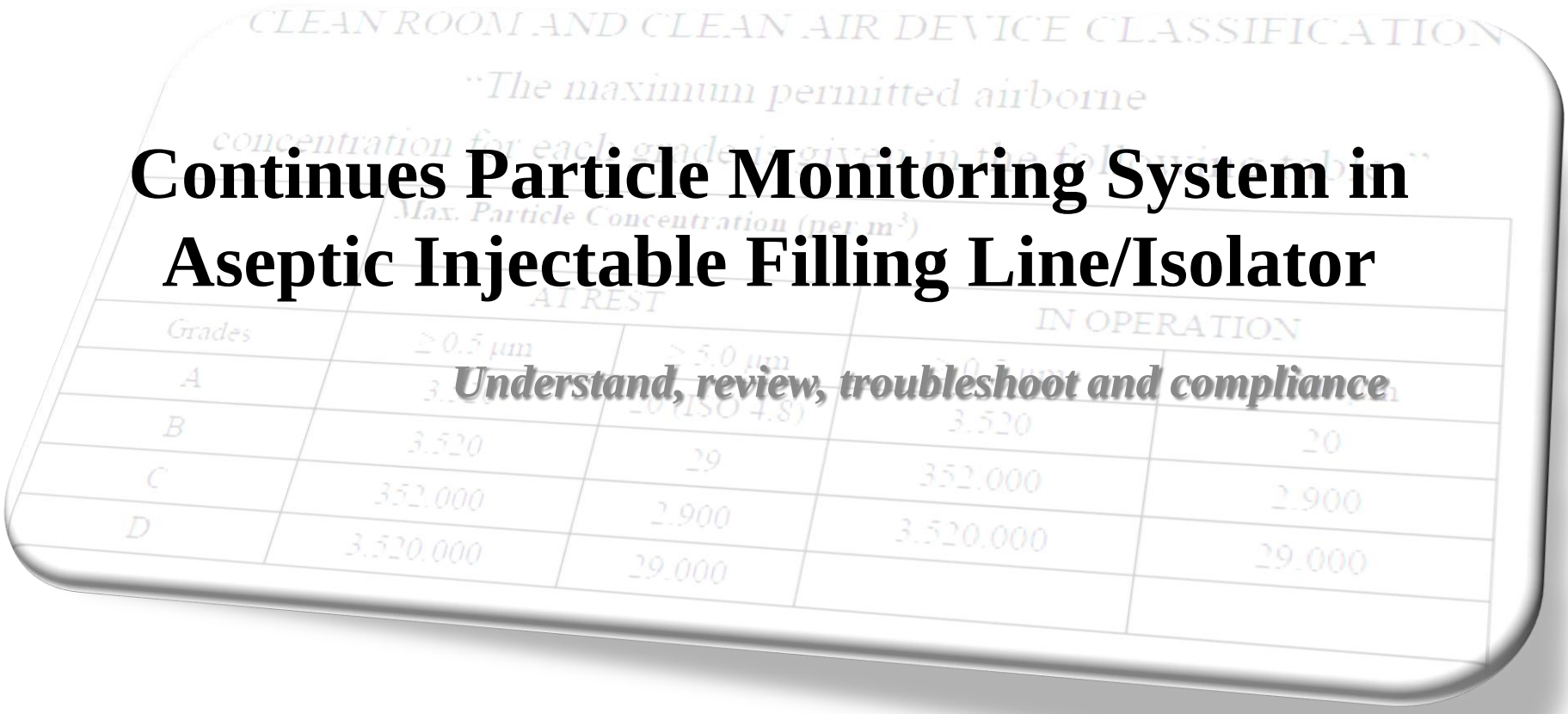

Continues Particle Monitoring System in Aseptic Injectable Filling Line/Isolator

Understand, review, troubleshoot and compliance

By : Palash Chandra Das, M.Pharma

Why do we care about Particle Count?

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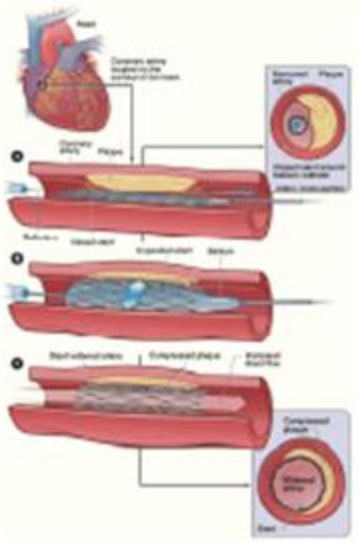
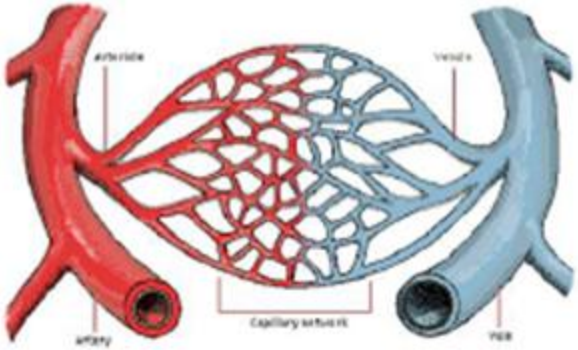
Pharmaceutical, Biotechnology

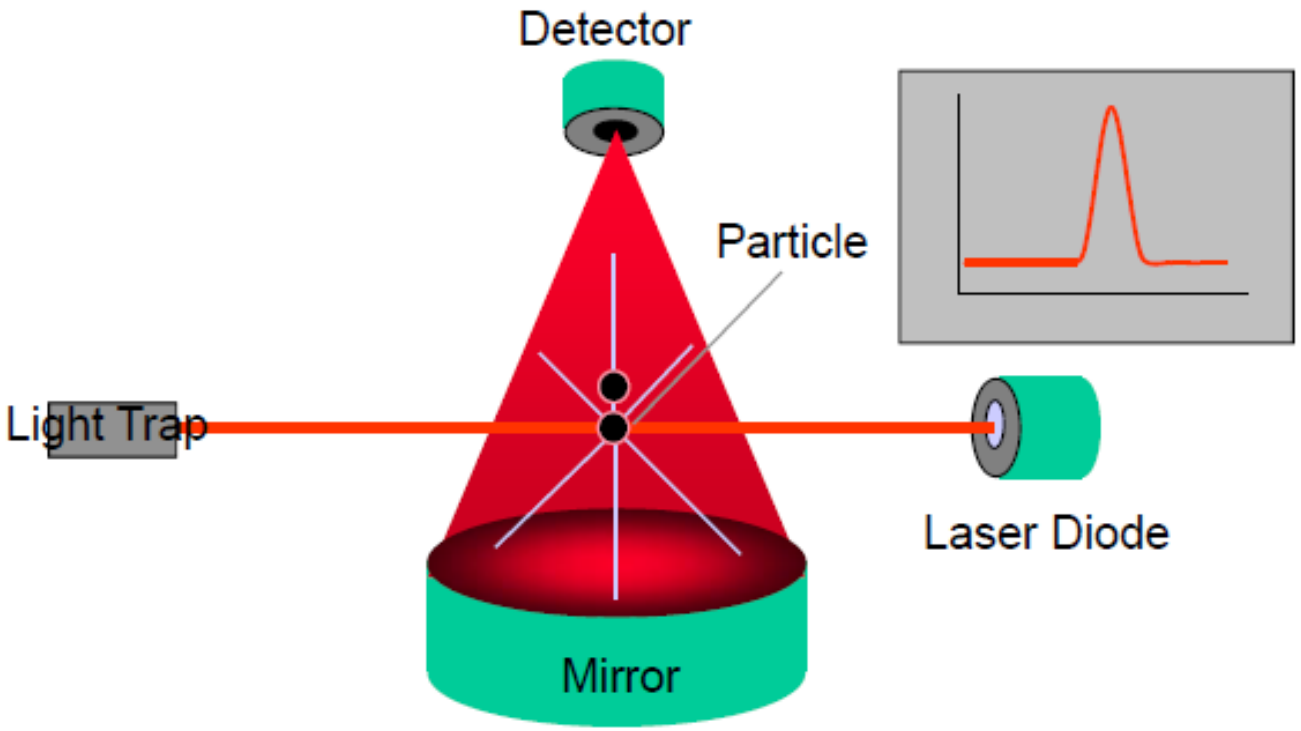
- Particles in injection could cause occlusion of blood vessels
  - Red Blood cells are about 5 µm
  - Capillary (5 to 10 µm)
  - Large veins (10 to 50 µm)
- Viables in injection can trigger infection
- Possibility of reaction to foreign substances (RES/allergic reaction)





- **Medical Devices**
  - Poor adhesion of medicated coating in stent creates embolisms
- **Medical and photographic films**
  - Contamination prevents complete image recovery

How an airborne particle counter works..



Principle: Light Scattering

What need to check in Calibration certificate of CPMS

ISO 21501-4

- Size calibration
- Verification of size setting
- Counting efficiency
- Size resolution
- False count rate
- Concentration limit
- Sampling flow rate
- Sampling time
- Sampling volume

Calibration program should meet the requirement of ISO 21501

ISO 21501-4 Parameters	Limit
Sampling Flow Rate (volumetric)	± 5%
Counting Efficiency at channel 1.	50% ± 20%
Counting Efficiency at particle size 1.5 to 2 times channel 1.	100% ± 10%
Particle Size Setting Error	≤ 10%
Instrument Resolution (at manufacturers specified size)	≤ 15%
Zero count test	≤ 1 count / 5 minutes
Maximum particle number concentration (manufacturer specified)	≤ 10%
Sampling Time	± 1%
Response Rate	≤ 0.5%
Calibration Interval	≤ 1 year

ZERO COUNT TEST (THE PURGE TEST)

- Before you begin your daily round of sampling, it is good practice to install a purge filter onto the inlet, and perform a one-minute False Count Test (also known as a Zero Count Test) to ensure the particle counter does not have a fundamental or catastrophic failure.
- Performing a Zero Count Test for a longer period of time serves no additional benefit. To the contrary, the cumulative hours spent performing excessive Zero Count Testing will result in the laser diode being operated unnecessarily, thus reducing the monitoring life of the instrument.

VHP SANITATION

- It is an excellent practice to VHP all microbial samplers and particle counters at most every six months to ensure no bio-contamination growth occurs within the equipment.
- But frequency based on the Vendor only.

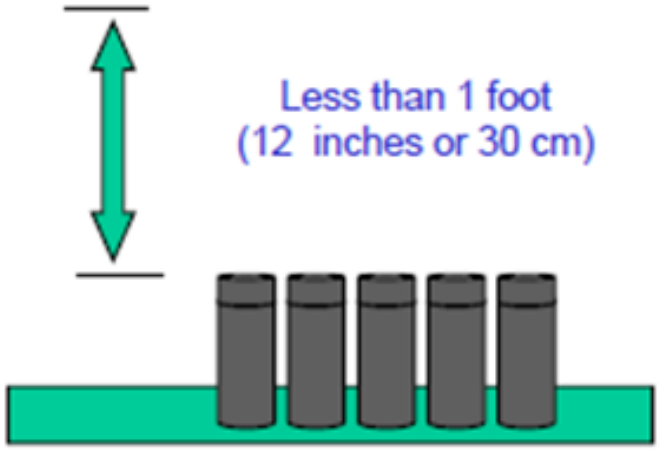
Placement of Sample Probes

- Annex 1: No guidance
- FDA: Sample near to exposed product
  - Generally near work height and exposed product
  - If liquid sterile fill, guidance is to sample air approaching the product within 12" (30 cm) of exposed

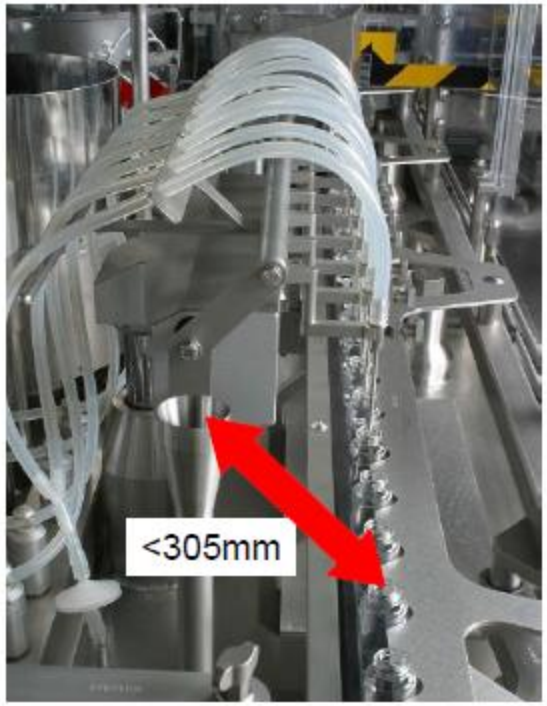
Sample near to points of intervention by operators

Examples:

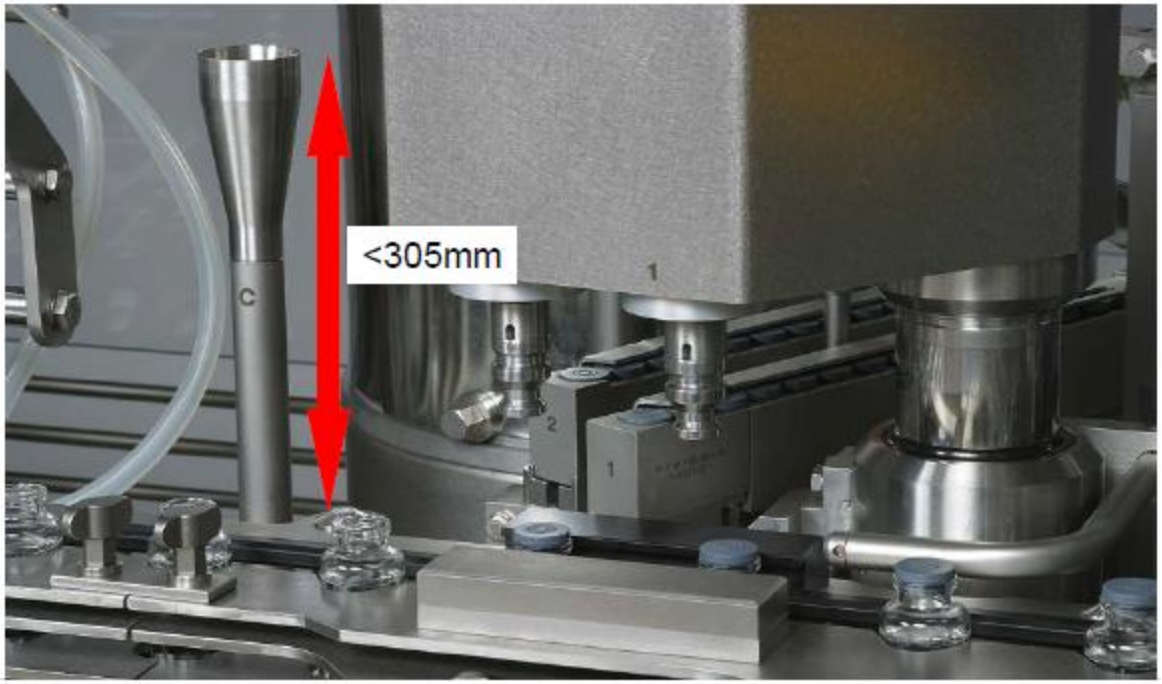
- Descrambler table
- Filling needles
- Stoppering process



Probe Positioning



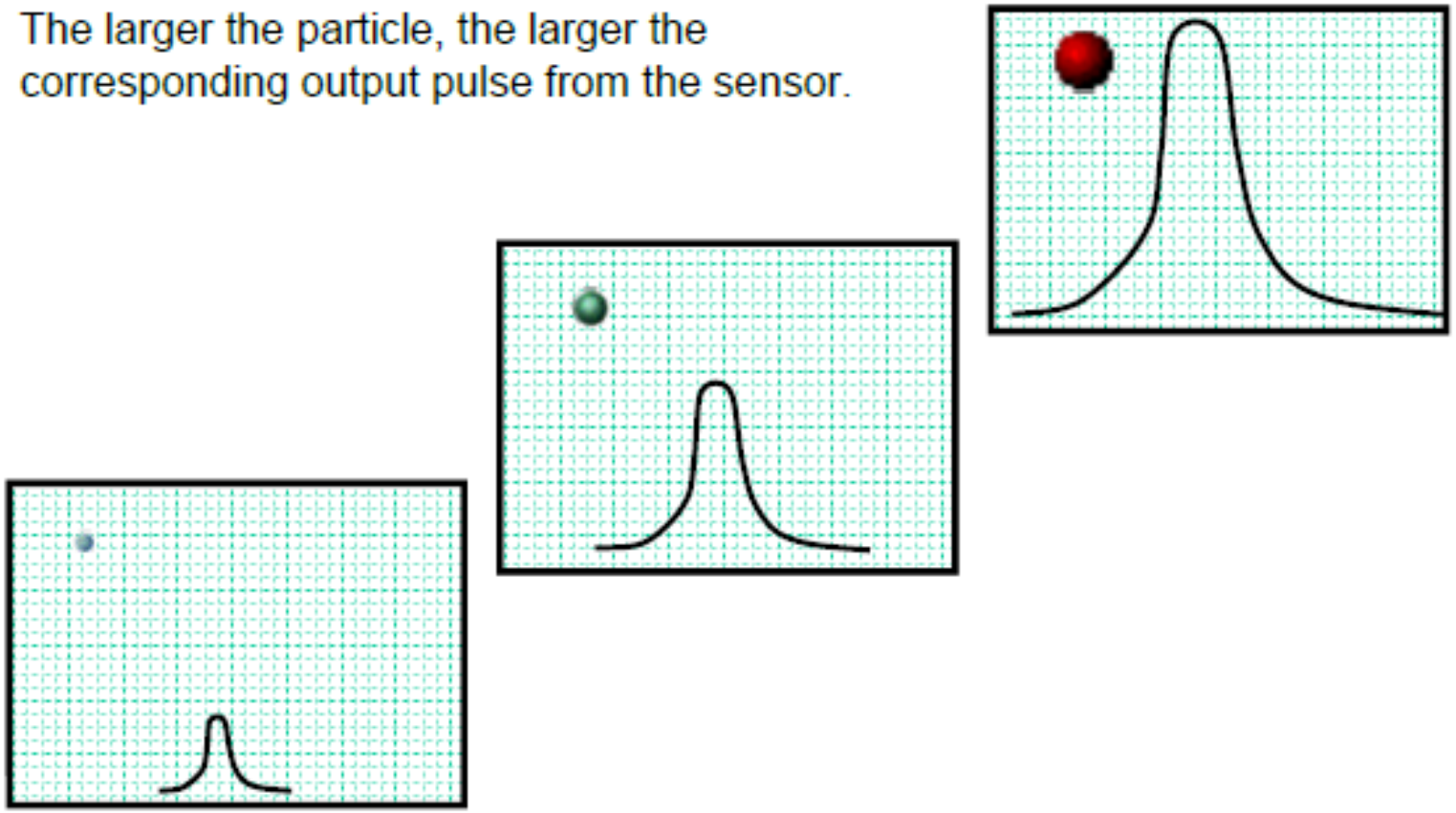
Positioning the Probes Filling Line



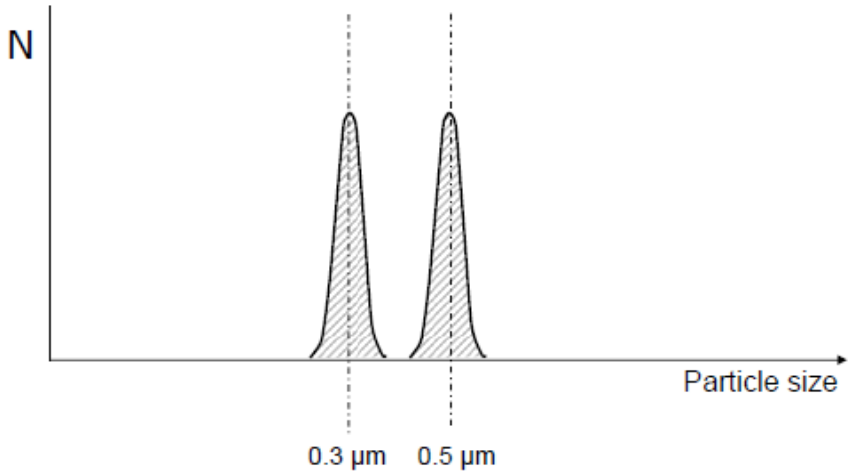
Positioning the Probes Stoppering Station

Output pulse based on Particle size

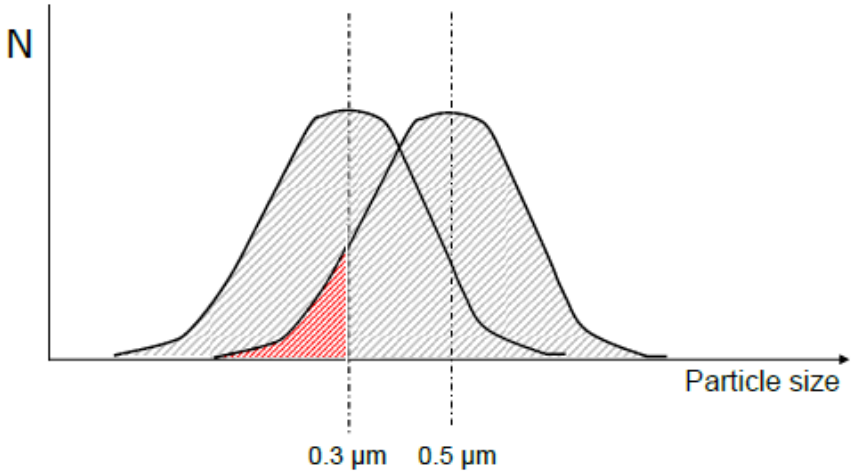
The larger the particle, the larger the corresponding output pulse from the sensor.



Resolution and counting accuracy

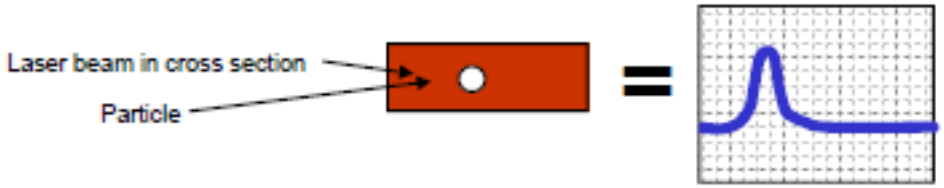


Good Resolution

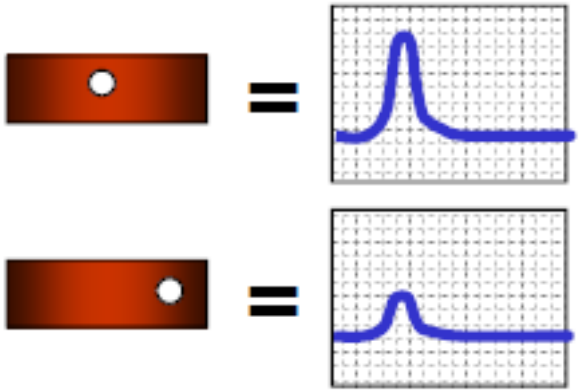


Poor Resolution

Illumination Uniformity affect resolution



Ideal: Even illumination in the view volume provides the same pulse height regardless of where the particle passes through the beam

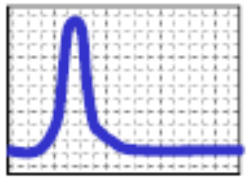


Not ideal: Uneven illumination causes pulse height variance. High illumination intensity leads to high intensity peak, and low intensity illumination leads to low peak height

Effects of Flow Rate on pulse

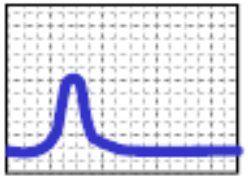
The amplitude of the sensor output is a function of the particle's residence time in the view volume.

28.3 lpm flow rate



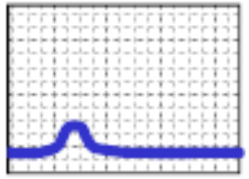
At 28.3 LPM, residence time yields a strong response from 0.5µ particle

50 lpm flow rate



As flow rate is increased, residence time decreases and response decreases

100 lpm flow rate



At very high flow rates, performance can be challenging as the particles pass through the view volume very quickly and calibration is based on a weaker signal

Preliminary assessment on the excursion of CPMS:

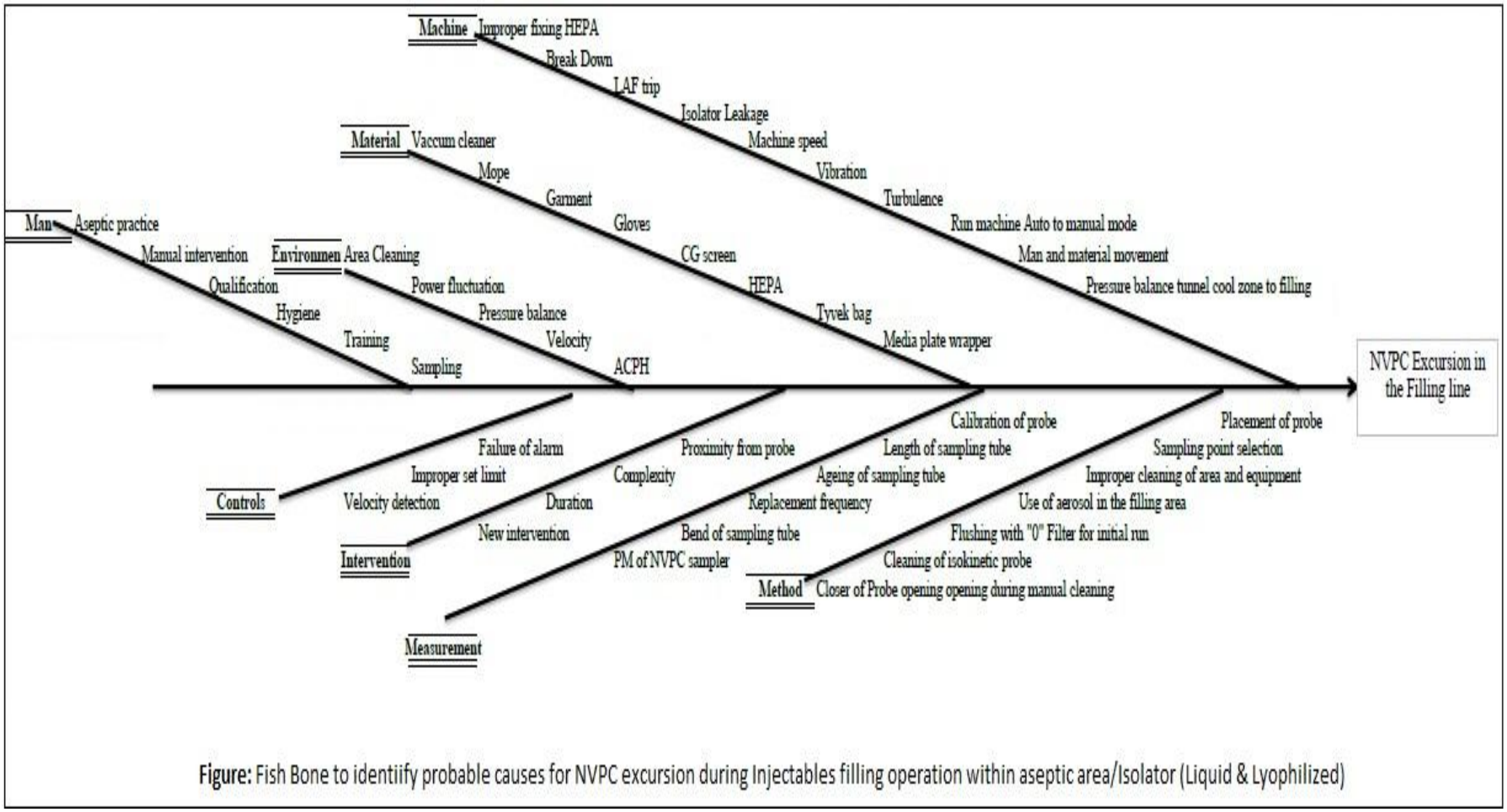


Figure: Fish Bone to identiify probable causes for NVPC excursion during Injectables filling operation within aseptic area/Isolator (Liquid & Lyophilized)

Root Cause Identification 1/2

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Sr. No.	Category	Root Cause	Sr. No.	Category	Root Cause
1	Man	Training	41	Machine	Leakage from Glove/sleeve system
2	Man	Hygiene	42	Machine	Turbulence
3	Man	Qualification	43	Machine	Pressure balance tunnel cool zone to filling
4	Man	Intervention	44	Machine	Turbulence as return riser obstruct with material
5	Man	Aseptic practice	45	Machine	Sharp ages of machine
6	Man	Sampling	46	Machine	Concealed base of Isolator
7	Man	Stress/ Work load	47	Machine	Isokinatic probe near isolator exhaust create turbulence in air flow
8	Man	Cross contamination	48	Machine	Filling and bunging machine
9	Man	Sampling/EM activity	49	Machine	Machine speed variation
10	Man	Improper Tyvek bag tear off	50	Machine	Vibration
11	Machine	Air Handling Unit	51	Machine	Run machine Auto to manual mode
12	Machine	Improper fixing HEPA to ceiling	52	Machine	Post PM, improper assembling
13	Machine	HEPA filter damage/leakage/Age	53	Machine	Sharp ages of machine
14	Machine	Door Interlock	54	Machine	Other
15	Machine	Vial Washing	55	Machine	Use of sharp item within filling activity
16	Machine	Improper cleaning of vials due to,	56	Machine	Vacuum Cleaner efficiency
17	Machine	Low pressure in utility	57	Machine	vacuum cleaner filter bag damage
18	Machine	Filter quality used for utility	58	Material	Mope quality
19	Machine	improper handling of vials	59	Material	Garment quality
20	Machine	Dismantled machine guard	60	Material	Gloves quality
21	Machine	Depyrogenation tunnel	61	Material	CG screen aging
22	Machine	Final washer to tunnel in feed GAP	62	Material	Tyvek bag
23	Machine	HEPA filter damage/leakage/Age	63	Material	Media plate wrapper
24	Machine	Dirt chaired in 350 temperature	64	Material	Non GMP tooling used
25	Machine	Mope lint in tunnel track	65	Material	Damage bag of Vacuum Cleaner
26	Machine	DP disturbed	66	Material	CA/Nitrogen purging
27	Machine	Entry and exit flap setting	67	Material	Integrity Air Filters use for CA/Nitrogen
28	Machine	Gloves integrity Tester	68	Material	Drug product crystal formation from spillage
29	Machine	Calibration	69	Material	Media spillage
30	Machine	Gloves integrity Failed	70	Method	Placement of isokinetic probe
31	Machine	Online particle counter	71	Method	Sampling point selection
32	Machine	Amplitude of the sensor output function	72	Method	Flushing with "0" Filter for initial run
33	Machine	Effect of flow on sizing in counter/Pulse Height	73	Method	Cleaning of isokinetic probe
34	Machine	Isokinetic sample heads shall be used in unidirectional airflow systems	74	Method	Tube length and distance
35	Machine	VHP tolerant flow path and optics	75	Method	Lid of Probe opening during manual cleaning
36	Machine	Illumination Uniformity Affects Resolution	76	Method	Setting of warning level
37	Machine	Isolator	77	Method	Alert/Action level and Trending
38	Machine	Improper fixing HEPA/integrity	78	Method	Cleaning of area and equipment
39	Machine	LAF trip/Interruption in power supply	79	Method	Use/ generation aerosol/powder in the filling area
40	Machine	Isolator Leakage	80	Method	Man and material movement

Root Cause Identification 2/2

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Sr. No.	Category	Root Cause
81	Method	Machine stoppage reporting procedure
82	Method	Post brake start up procedure
83	Method	Qualification of area and equipment
84	Method	Break Down maintenance
85	Method	HEPA replacement frequency
86	Measurement	Online particle counter
87	Measurement	Calibration of probe
88	Measurement	Air velocity or flow rate of the particle counter
89	Measurement	Tubing length
90	Measurement	Number of tubing bends
91	Measurement	The radius of these bends
92	Measurement	Tubing diameter
93	Measurement	Tubing material.
94	Measurement	Ageing of sampling tube
95	Measurement	Distance of installed probe
96	Measurement	Replacement frequency
97	Measurement	Bend in sampling tube
98	Measurement	PM of NVPC sampler
99	Environment	ACPH
100	Environment	Velocity
101	Environment	Pressure balance/drop
102	Environment	Power fluctuation
103	Environment	Inadequate cleaning
104	Environment	Laminar air flow
105	Environment	Unidirectional Air flow
106	Controls	Failure of alarm
107	Controls	Improper set limit
108	Controls	Velocity detection sensor
109	Controls	Pressure low alarm
110	Controls	Door position sensor
111	Controls	Disable machine controls & sensor
112	Intervention	Proximity from probe
113	Intervention	Complexity
114	Intervention	Duration
115	Intervention	New intervention
116	Intervention	Unidentified intervention
117	Intervention	Corrective
118	Intervention	Inherent

Identify the root cause of CPMS excursion ….

WHO 961, Annex 6 Requirements

- For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, for example, live organisms and radiological hazards. In such cases monitoring during routine equipment set-up operations should be undertaken before exposure to the risk.
- Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at a frequency and sample size such that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. **It is accepted that it may not always be possible to demonstrate low levels of ≥ 5.0 µm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.**
- Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or multiple small particle counters located near monitoring points and networked to a data acquisition system. Combinations of systems can also be used. The system selected should be appropriate for the particle size considered.
- Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing should be considered in the context of particle losses in the tubing. The selection of the monitoring system should take account of any risk presented by the materials used in the manufacturing operation, for example, those involving live organisms or radiopharmaceuticals.
- The sizes of samples taken for monitoring purposes using automated systems will usually be a function of the sampling rate of the system used.

EU Annex 1 Requirements

- For grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly. The grade A zone should be monitored continuously and with a suitable sample size (at least 28 litres (a cubic foot) per minute) so that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded.
- The occasional indication of macro particle counts, especially ≧ 5.0 μm, may be considered false counts due to electronic noise, stray light, coincidence, etc. However, consecutive or regular counting of low levels may be indicative of a possible contamination event and should be investigated.
- Such events may indicate early failure of the room air supply filtration (HVAC) system, filling equipment failure, or may also be diagnostic of poor practices during machine set-up and routine operation. Monitoring conditions such as frequency, sampling volume or duration, alert and action limits and corrective action including investigation should be established in each manufacturing area based on risk assessment.

FDA Audit check point

- What type of instrument is used to check non-viable particle counts in the classified areas?
- Is the air sampled continuously? If continuous, is there an alarm when counts exceed pre-set limits or detects clean room doors open for an extended time?
- What is done in response to the alarms?
- Is there an alarm log?
- Are permanently installed sensors used or portable units that are taken into and out of the critical areas? What is done if counts meet or exceed alert and action limits?

PMDA Requirements

- The occasional indication of ≥5.0 μm particle counts may be false counts due to electronic noise, stray light, coincidence, etc.
- However consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated.
- Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation.
- Crimping of the cap should take place as soon as possible after the stopper has been inserted. As the crimping process can generate large numbers of non-viable particles, it should be done at a different station.

Standard Definition

- **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 and are established based on historical and qualification trend data and periodically reviewed.
- **Action Level** - An established microbial or airborne particle level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.
- **Isokinetic sampling head** – A sampling head designed to disturb the air as little as possible so that the same particles go into the nozzle as would have passed the area of the nozzle had it not been there.
- **Unidirectional flow** - An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed, to reproducibly sweep particles away from the critical processing or testing area

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Mr. Palash Chandra Das is recognized as an expert in the field of aseptic manufacturing of parenteral products, and is a frequent presenter at several web conferences and technical training for Sterile Drug Manufacturing.

He earned his Master's for Pharmaceutical chemistry from the University of West Bengal University of technology in India.

Since 2011 Palash has associated with installation, qualification and operation several production-lines in standard Clean room Technology as well as in Isolator Technology at major regulatory facility across India.

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