# Best Practice for Continuous Particle Monitoring in Pharmaceutical Clean Rooms

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Jörg Dressler
PMT GmbH
j.dressler@pmt.eu

# Abstract

Presentation touches the most common user questions regarding interpretation of Annex 1:

- Monitoring frequencies
- Sample volumes for monitoring
- Clean up period
- Particle loss in tubing
- Sample points via risk analysis
- How to define limits

# Documents to be discussed

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods
Pharmaceuticals

Brussels, 14 February 2008

**EudraLex**
**The Rules Governing Medicinal Products in the European Union**

**Volume 4**
**EU Guidelines to**
**Good Manufacturing Practice**
**Medicinal Products for Human and Veterinary Use**

**Annex 1**
**Manufacture of Sterile Medicinal Products**

| Document History | |
|---|---|
| Previous version dated 30 May 2003, in operation since | September 2003 |
| Revision to align classification table of clean rooms, to include guidance on media simultations, bioburden monitoring and capping of freeze-dried vials | November 2005 to December 2007 |
| Date for coming into operation and superseding | 01 March 2009[1] |

[1] Note: Provisions on capping of freeze-dried vials should be implemented by 01 March 2010.

PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 032-2
8 January 2010

**RECOMMENDATION**

**GMP ANNEX 1 REVISION 2008, INTERPRETATION OF MOST IMPORTANT CHANGES FOR THE MANUFACTURE OF STERILE MEDICINAL PRODUCTS**

# CLEAN ROOM AND CLEAN AIR DEVICE CLASSIFICATION

"The maximum permitted airborne concentration for each grade is given in the following table:"

| | **Max. Particle Concentration (per $m^3$)** | | | |
|---|---|---|---|---|
| | AT REST | | IN OPERATION | |
| Grades | ≥ 0,5 µm | ≥ 5,0 µm | ≥ 0,5 µm | ≥ 5,0 µm |
| A | 3.520 | 20 (ISO 4,8) | 3.520 | 20 |
| B | 3.520 | 29 | 352.000 | 2.900 |
| C | 352.000 | 2.900 | 3.520.000 | 29.000 |
| D | 3.520.000 | 29.000 | nA | nA |

These limits apply for clean room classification.

They do not automatically apply for monitoring sample points.

Monitoring "limits" will be discussed later.

# MICROBIAL MONITORING

| | limits for microbial contamination (a) | | |
|---|---|---|---|
| | Volumetric sampling ($cfu/m^3$) | Settling plates (D= 90 mm) cfu / 4 hr (b) | Contact plates (D= 55 mm) cfu / plate |
| Grades | | | |
| A | < 1 | < 1 | < 1 |
| B | 10 | 5 | 5 |
| C | 100 | 10 | 25 |
| D | 200 | 100 | 50 |

(a) Average values

(b) Individual settling plates < 4 hrs

# CLEAN ROOM …… MONITORING

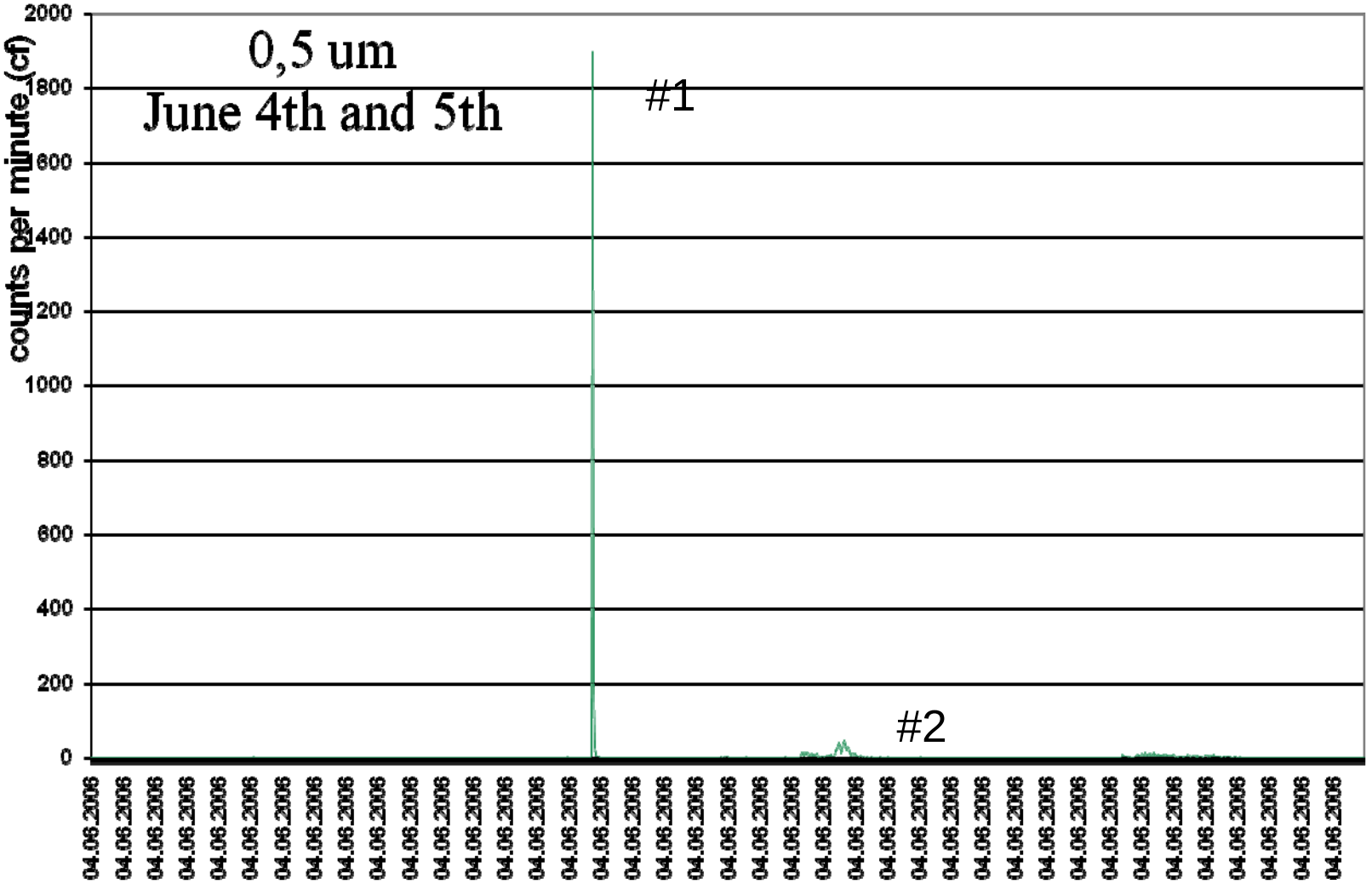
In Grade A areas monitoring is mandatory

"For grade A zones, particle monitoring should be undertaken for the full duration of critical processing ……"

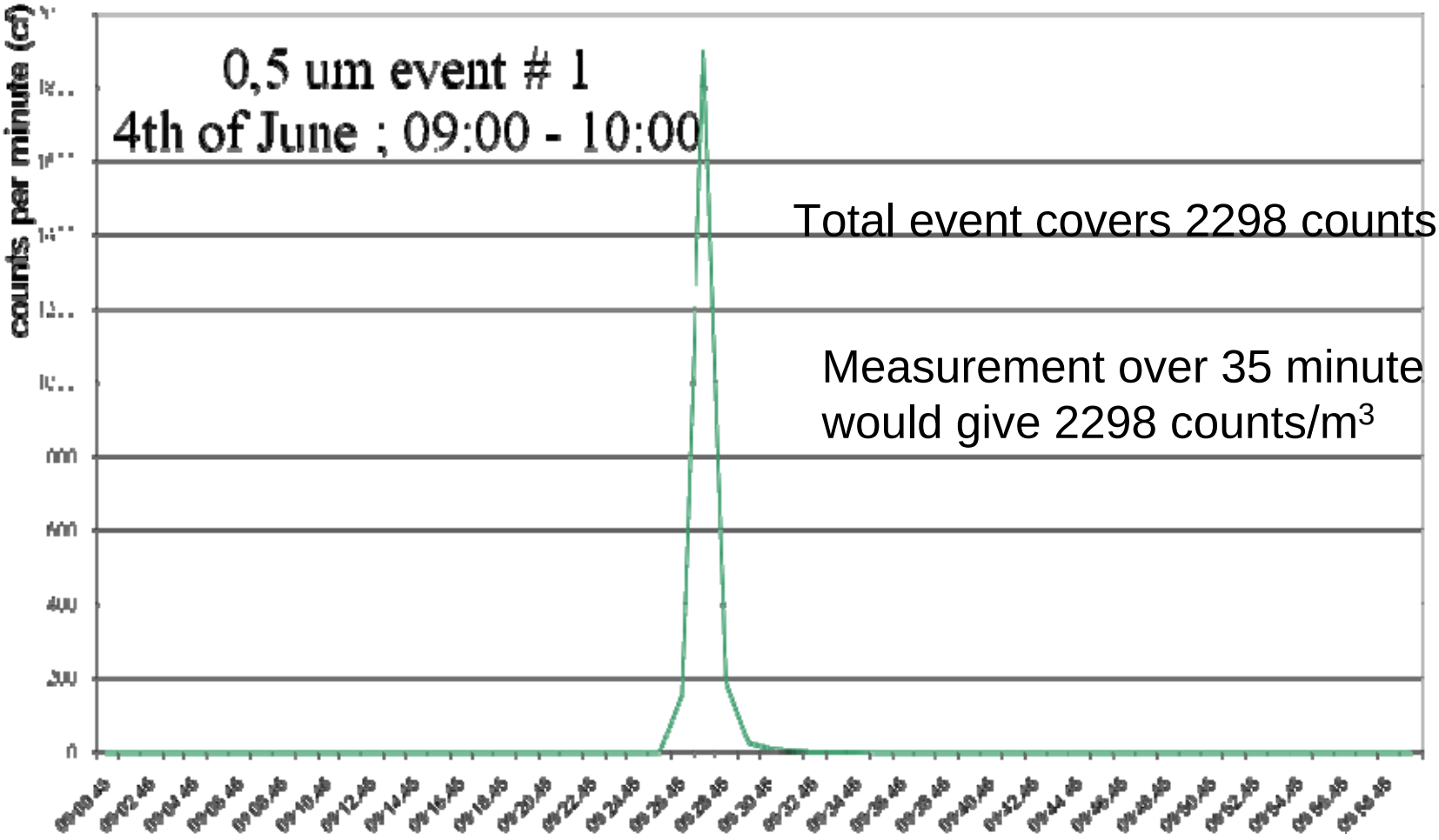
Getting a complete picture is mandatory too

"Grade A zones should be monitored at a frequency and with suitable sample size that all interventions, transient events, and any system deterioration can be captured"

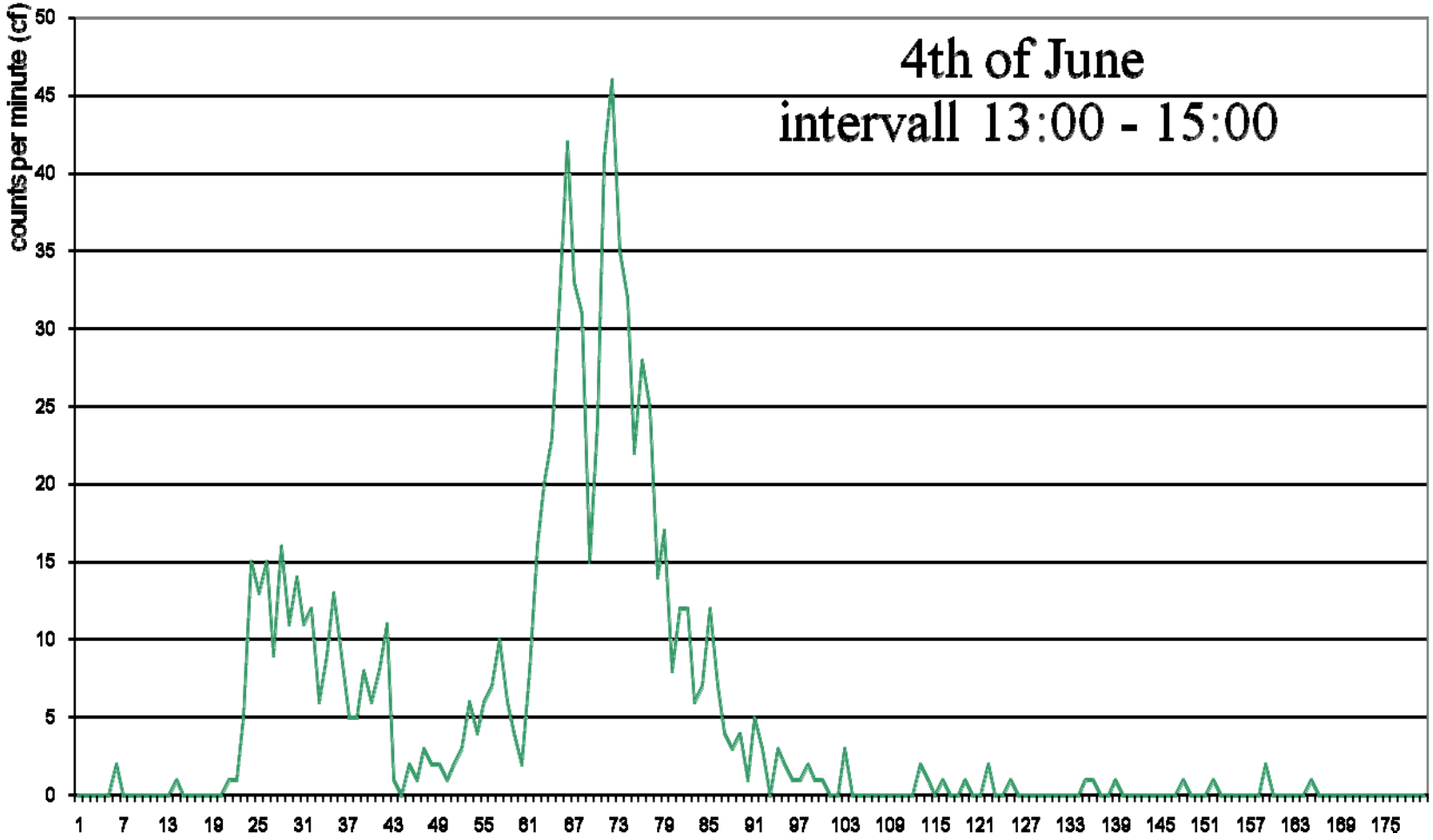
# Example - 48 hrs ≥ 0,5 um data - A area



# Catching the transient events – example # 1



# Analysing the ≥ 0,5 um events – example # 2



# CLEAN ROOM …… MONITORING

It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones.

The Grade B zone should be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded

The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management

# CLEAN ROOM …… MONITORING

1 $m^3$ sampling is NOT suitable for monitoring

"The sample size .....using automated system will be a function of the sampling rate of the instrument used.
It is not necessary for the sample volume to be same as that used for formal classification of cleanroom and clean air devices"

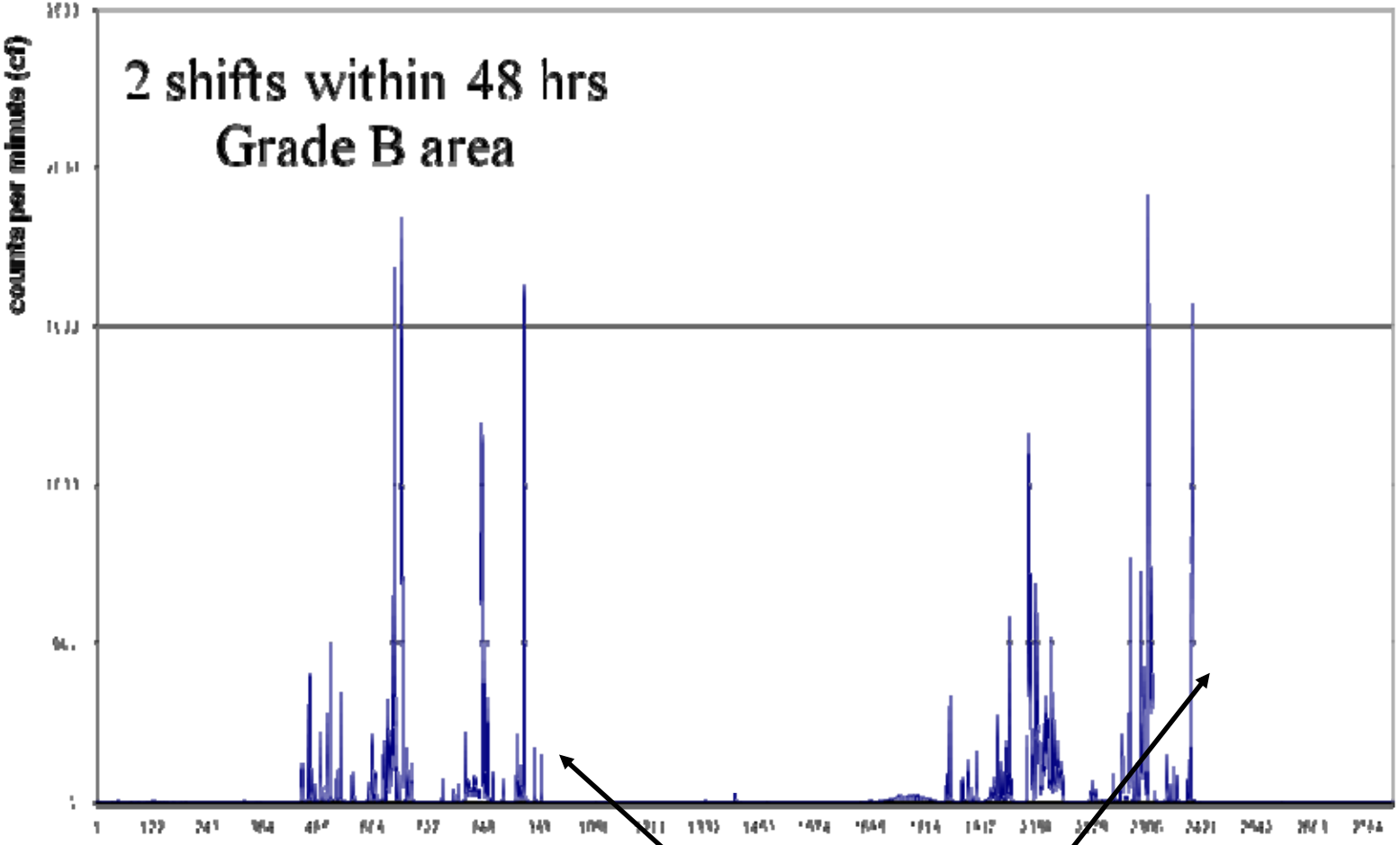
# CLEAN ROOM …… MONITORING

"In Grade A and B zones, the monitoring of the ≥5.0 µm particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure"

Comment lecturer:
Even moresoe the ≥ 0,5 um data – due to the better statistical significance

"The particle limits given in the table for the at rest state should be achieved after a short clean up period of 15-20 minutes (guidance value) in an unmanned state after completion of operations"

# Clean up period ≥ 0,5 um events



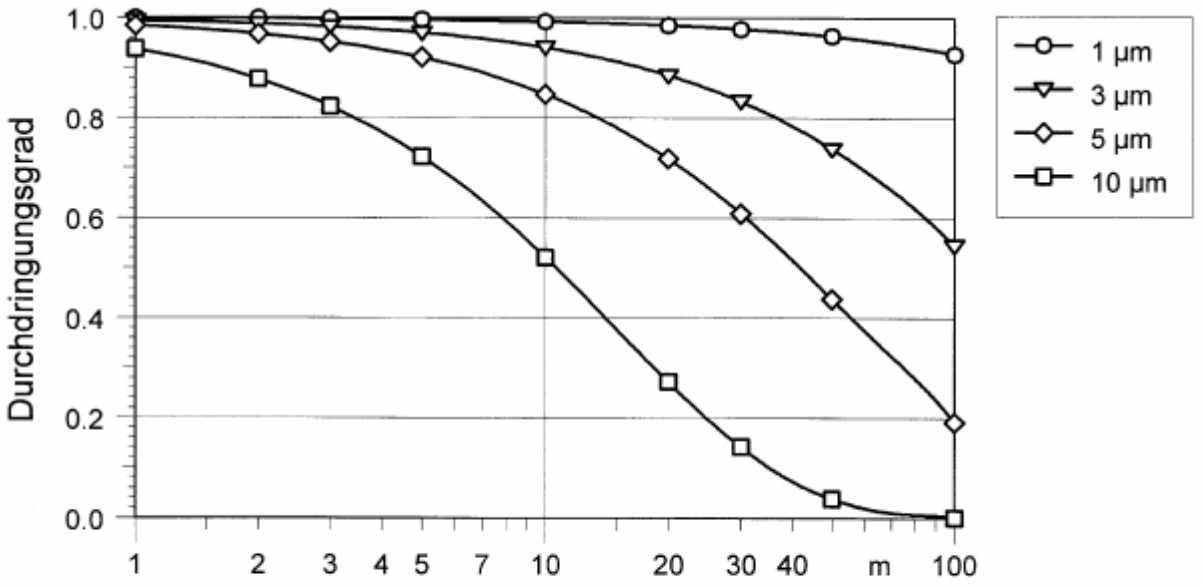

At rest values after
20 Min clean up phase

# Bad practice

!

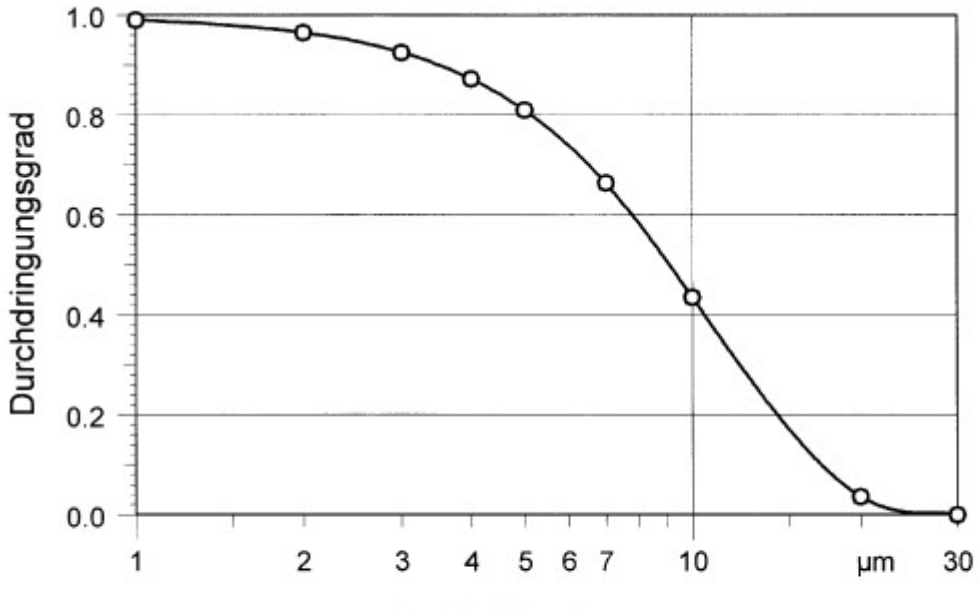
"Portable particle counters with a short length of sample tubing should be used….because of the relatively higher rate of precipitation of particles ≥ 5 um in remote sampling systems with long lengths of tubing"

# Particle losses – theoretical data



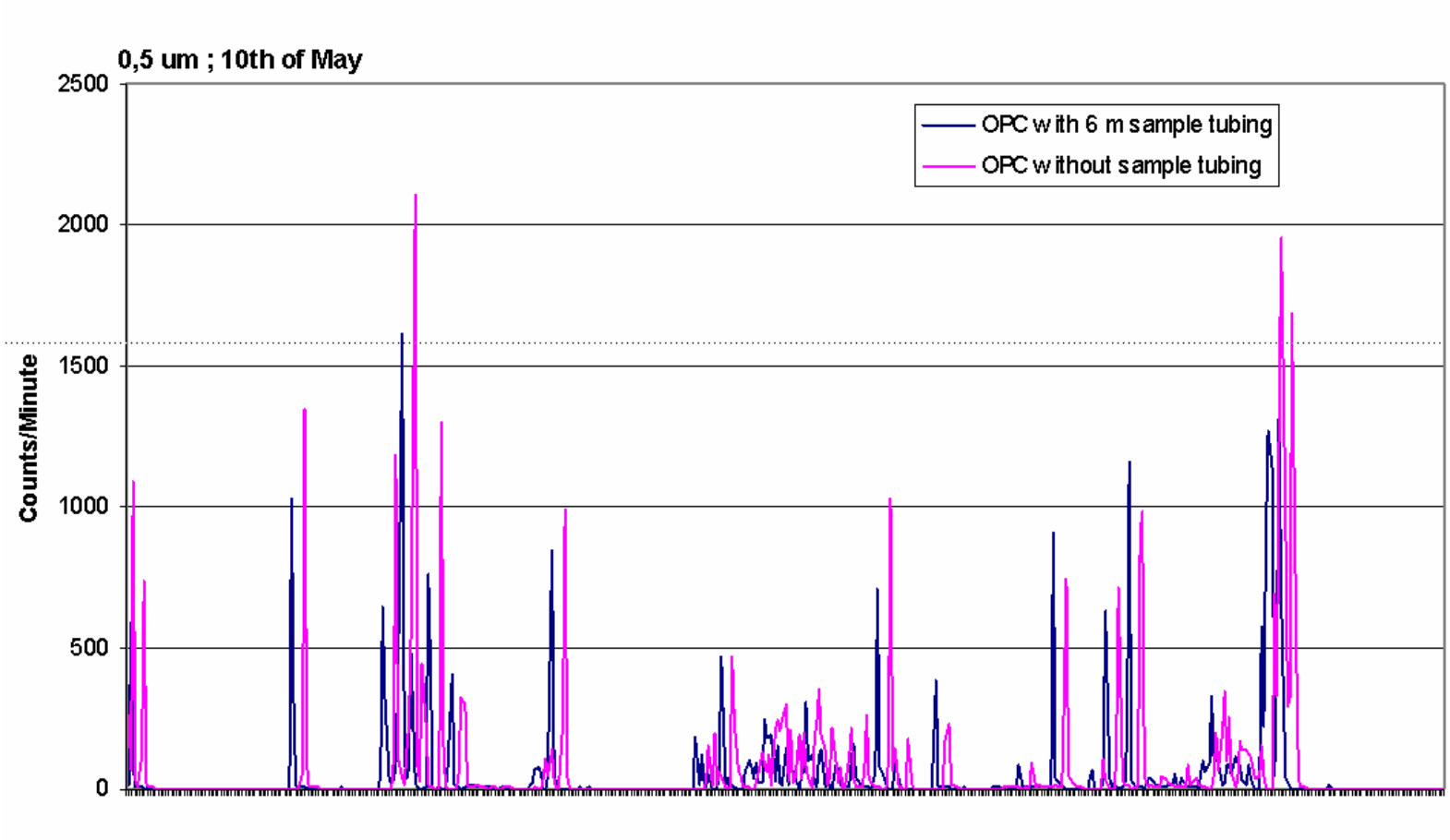

Horizontal tube
1cm inner diameter // 28,3 l/min flow

# Particle losses – theoretical data

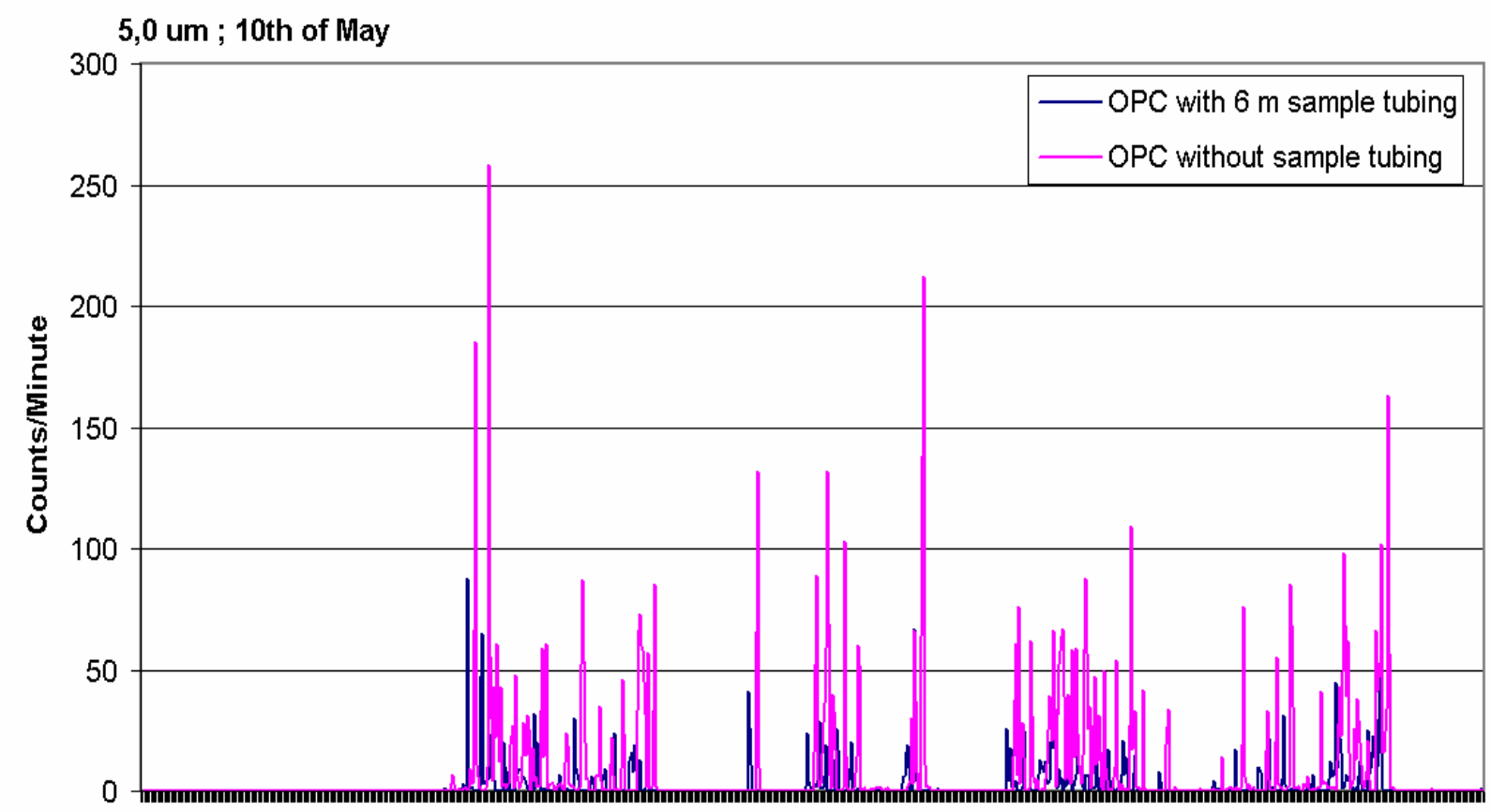



Loss per $90^0$ elbow
1cm inner diameter // 28,3 l/min flow // density 1 $g/cm^3$

# Loss of ≥ 0,5 um particles - real data - D area



# Loss of ≥ 5,0 um particles - real data - D area



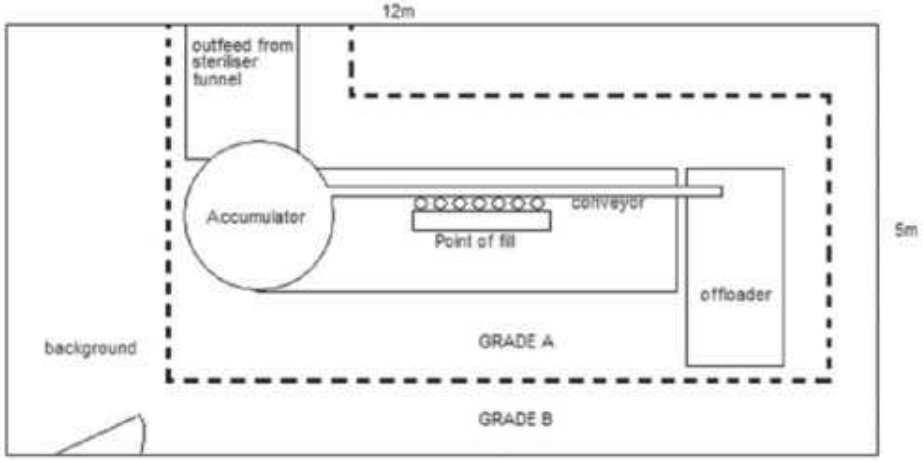
# CLEAN ROOM…….MONITORING

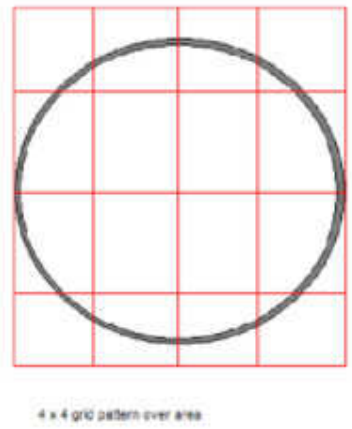
"Clean rooms and clean air devices should be routinely monitored in operation"

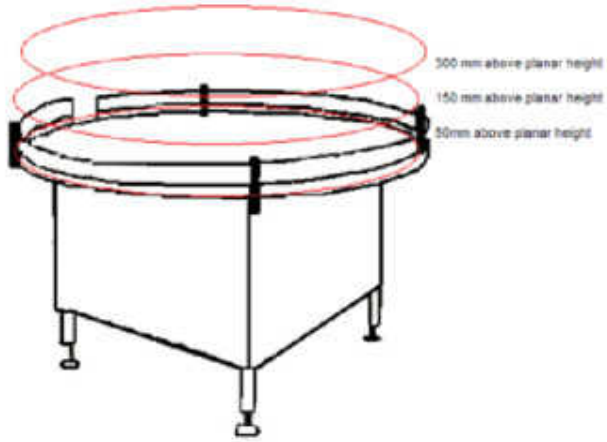
and

"the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices"

# Risk analysis

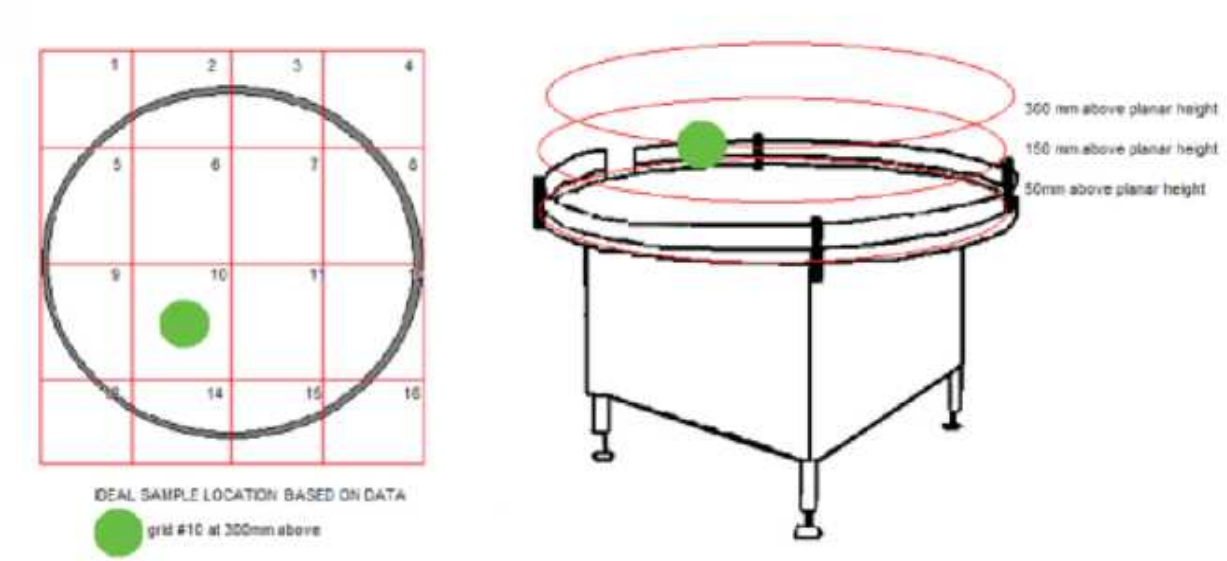



Drawings in chapter “risk analysis“ provided by
M. Hallworth/ Particle Measuring Systems Inc

# Risk analysis – step 1




**Results of particle survey**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.5 | *125* | *156* | *222* | *134* | *144* | *245* | *111* | *134* | … | … | … | … | … |
| 5.0 | *1* | *0* | *0* | *0* | *1* | *1* | *0* | *0* | … | … | … | … | … |
| | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** |
| 0.5 | … | … | … | | | | | | | | | | |
| 5.0 | … | … | … | | | | | | | | | | |

# Risk analysis – step 2

**Assessment of critical nature**

1= not critical; 2 = low critical; 3 = moderate critical; 4 = very critical

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RANK | 2 | 3 | 3 | 4 | 3 | 4 | 2 | 2 | 2 | 3 | 4 | 4 | 3 |
| | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** |
| RANK | 4 | 2 | 3 | 2 | 2 | 2 | 3 | 3 | 4 | 3 | 4 | 2 | 3 |

*You will notice where the sample is close to an operator it gets more critical – this is just guidance and each exercise may have other factors – doors, access, restriction to operators, activities etc…*

**Results of particle survey**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.5 | 125 | 156 | 222 | 134 | 144 | 245 | 111 | 134 | … | … | … | … | … |
| 5.0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | … | … | … | … | … |
| | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** |
| 0.5 | … | … | … | | | | | | | | | | |
| 5.0 | … | … | … | | | | | | | | | | |

**Results x Risk Factor**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.5 | 250 | 468 | 666 | 536 | 432 | 980 | 222 | 268 | … | … | … | … | … |
| 5.0 | 2 | 0 | 0 | 0 | 3 | 4 | 0 | 0 | … | … | … | … | … |
| | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** |
| 0.5 | … | … | … | | | | | | | | | | |
| 5.0 | … | … | … | | | | | | | | | | |

# CLEAN ROOM …… MONITORING

"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, e.g. live organisms and radiological hazards. In such cases monitoring during routine equipment set up operations should be undertaken prior to exposure to the risk."

# CLEAN ROOM …… MONITORING

"It is accepted that it may not always be possible to demonstrate low levels of ≥ 5,0 µm particles during filling operations due to the generation of particles or droplets from the product itself"

# Sample points as result of risk analysis

# Sample points as result of risk analysis

# Sample points as result of risk analysis

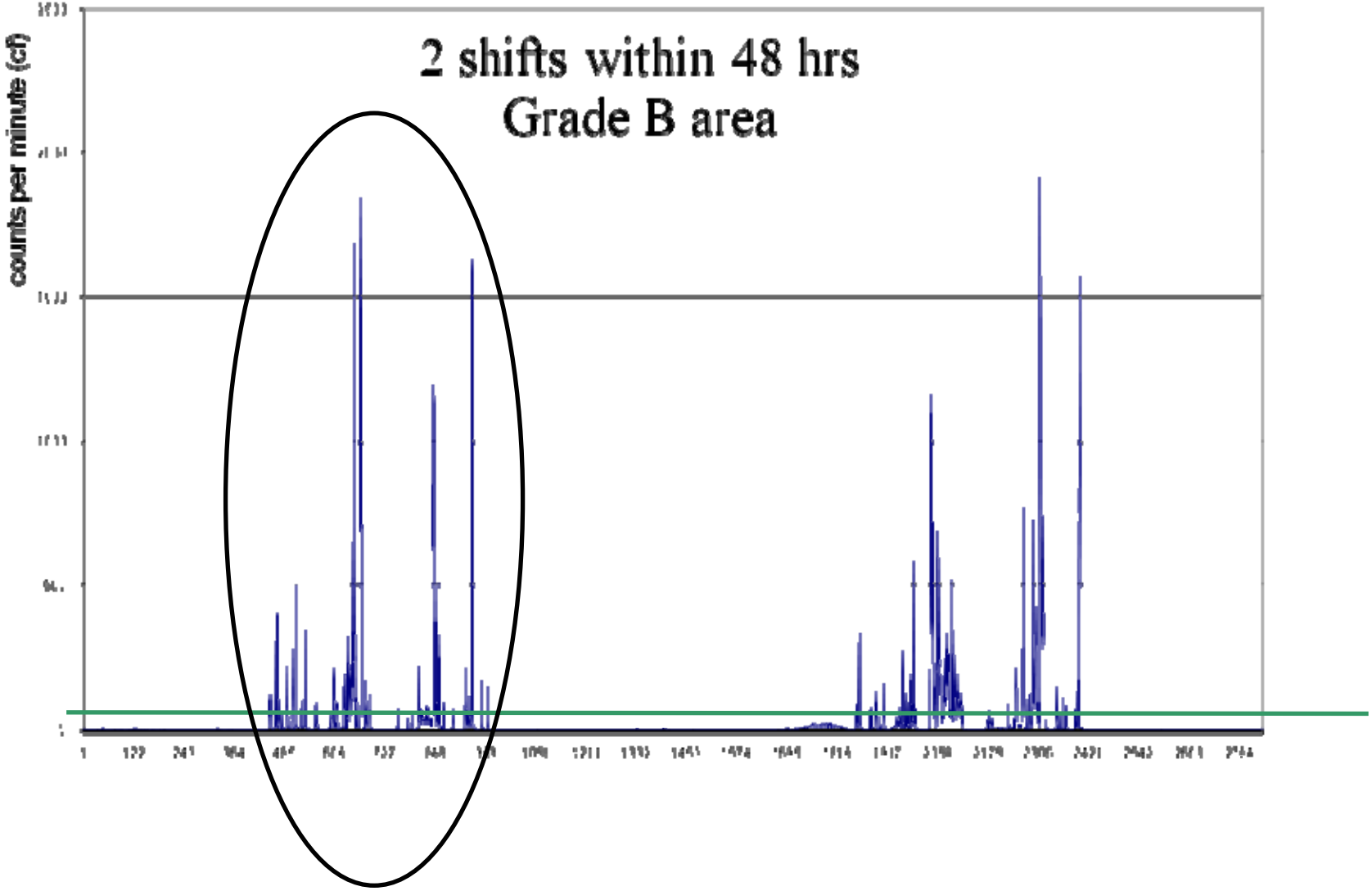
# Sample points as result of risk analysis

# Sample points as result of risk analysis

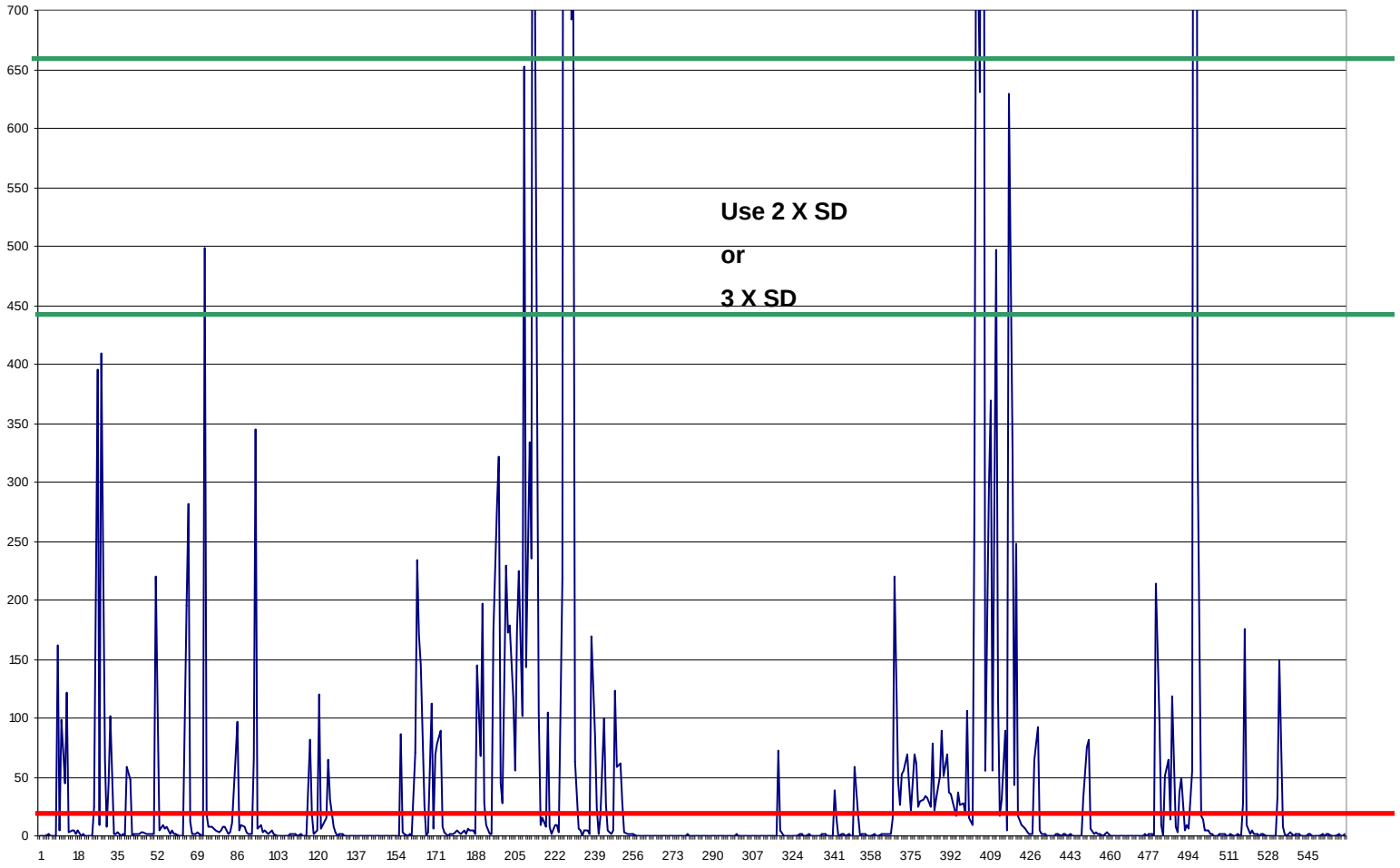
# Alert and action limits

"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"

# Alert and action limits ≥ 0,5 um



# Alert and action limits ≥ 0,5 um



# Alert and action limits

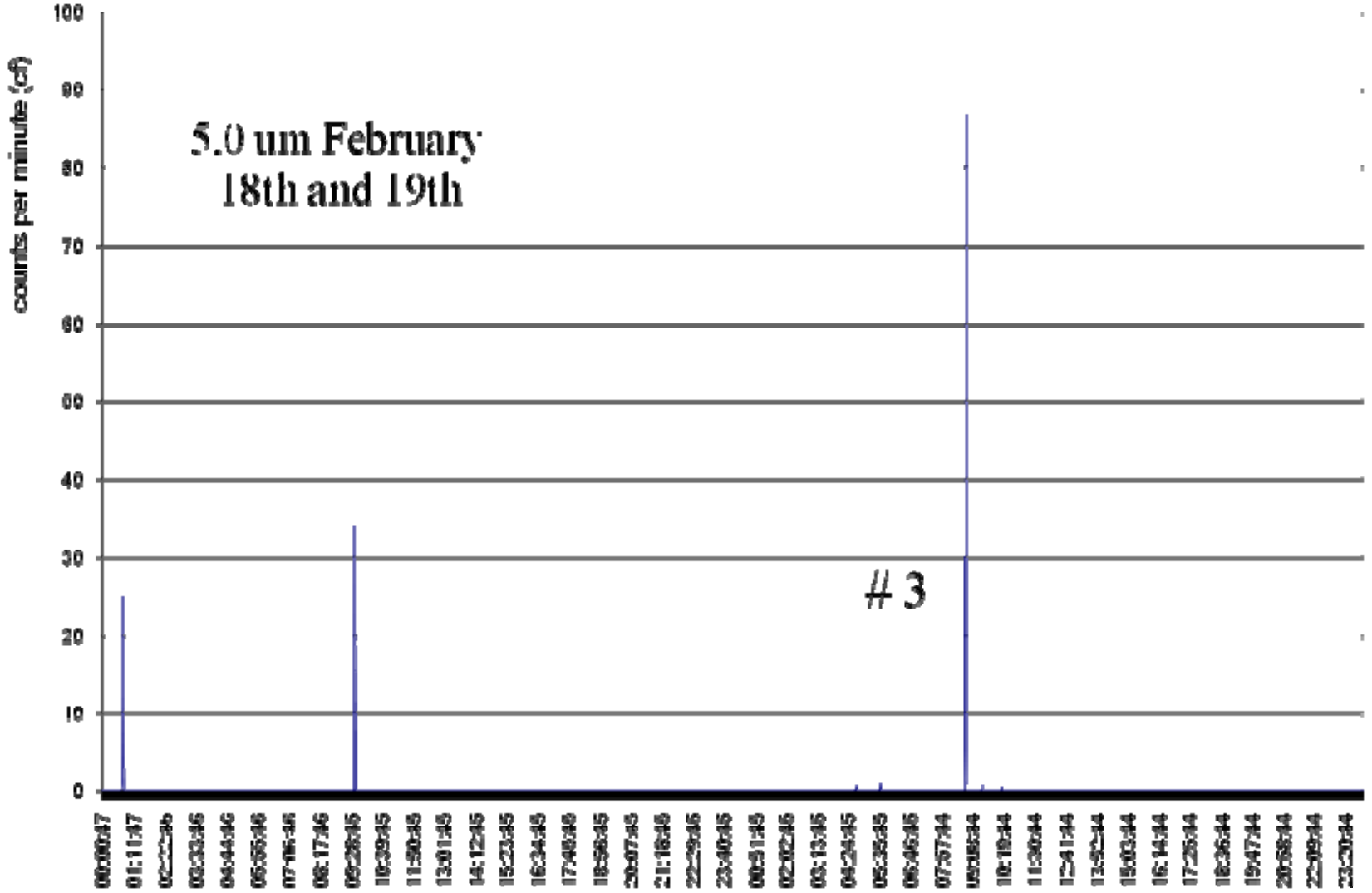
For ≥ 0,5 um  particle data (with good statistical significance):

A 95% confidence limit should be established for the actual events during production.

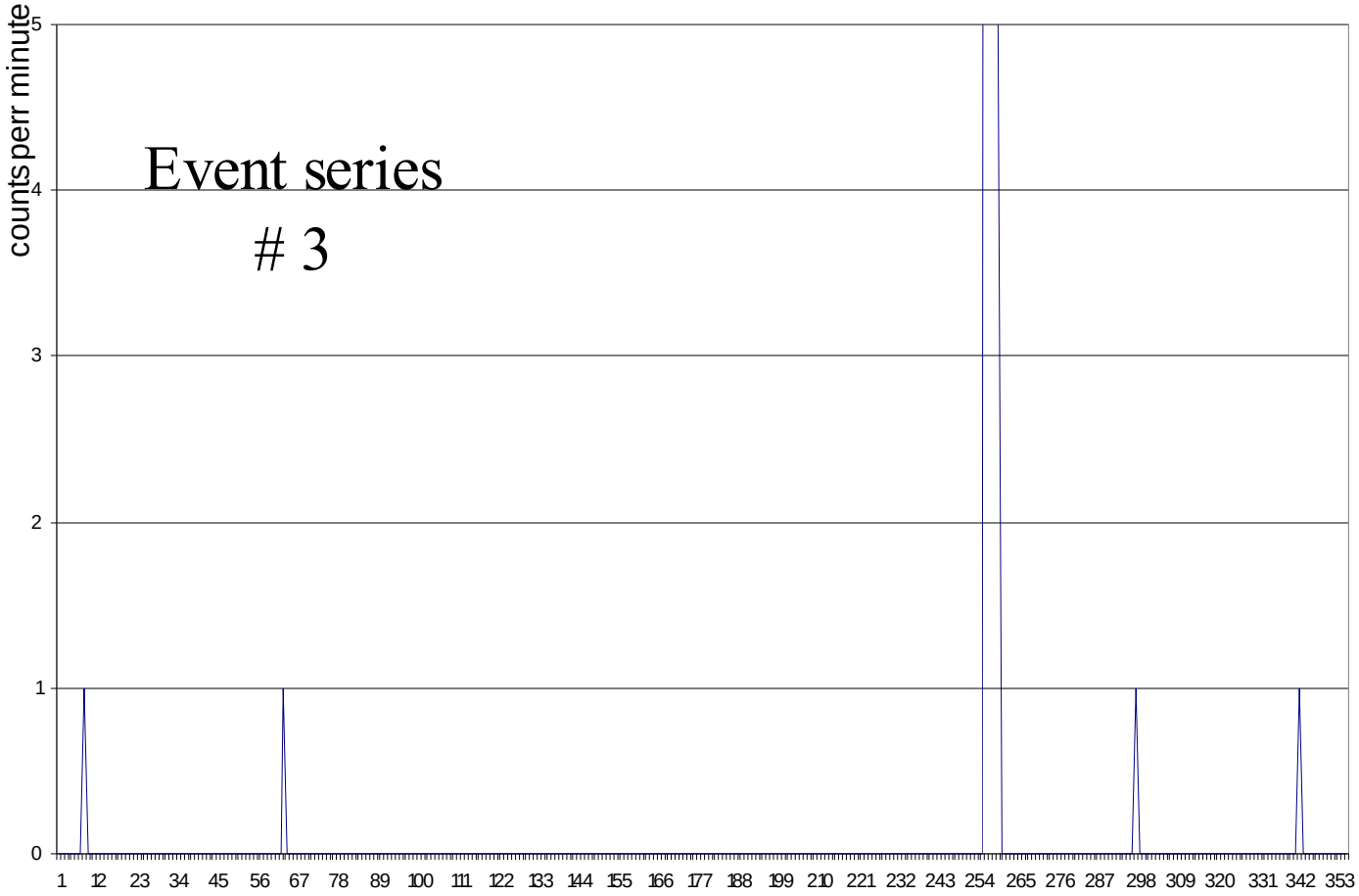
Data can be achieved during media fills while operators are following SOPs in ‘normal’ operations.

The limits found may be less than the class limits

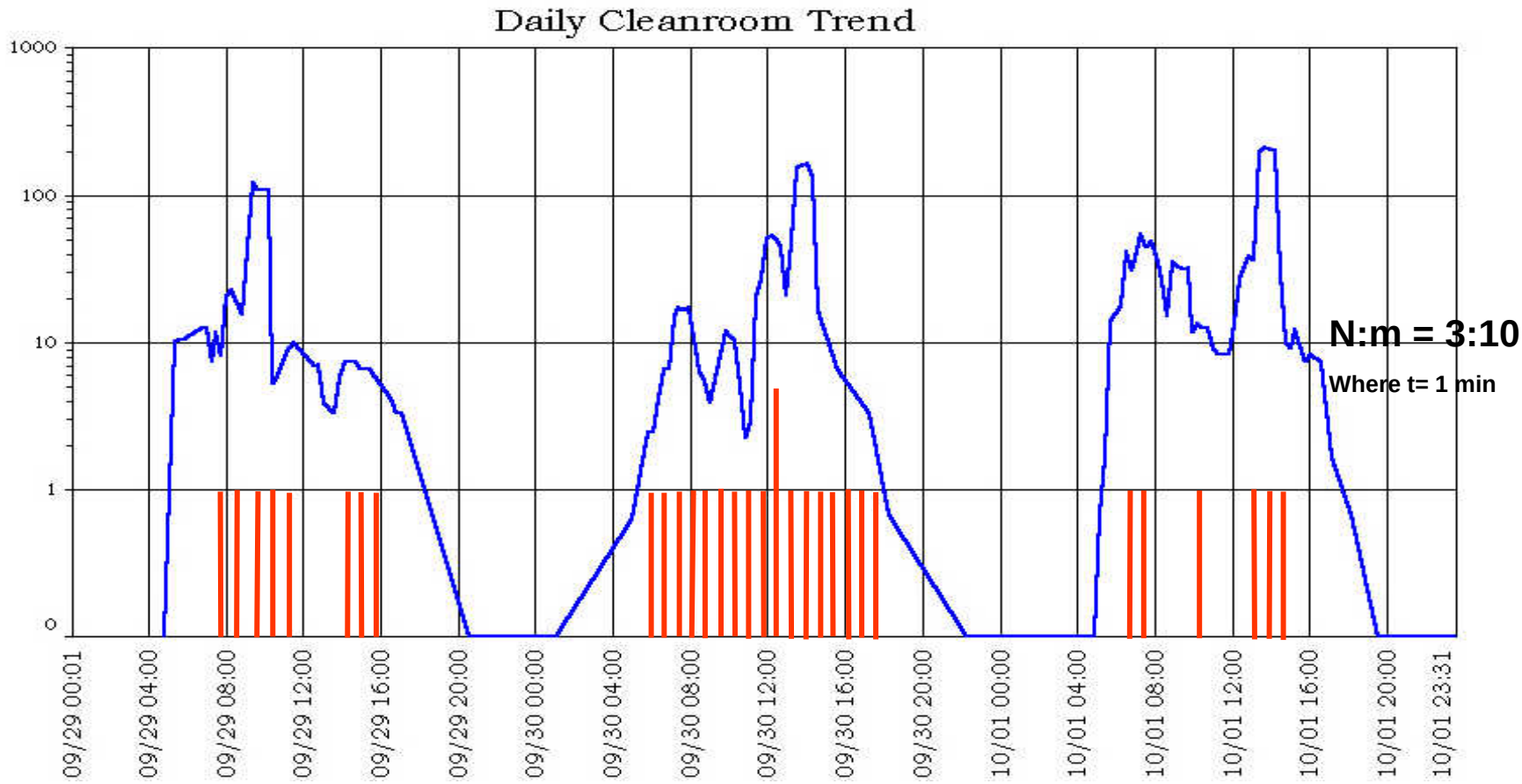
# Alert and action limits ≥ 5,0 um



# Alert and action limits ≥ 5,0 um



# Alert and action limits




Drawing provided by M. Hallworth/ Particle Measuring Systems Inc

# Alert and action limits

For ≥ 5.0 µm particle data (with poor statistical significance):

A number of events per unit time should be used.
Frequency has been estimated to be no more than 3 events in any 10 minutes to create an action (n:m = 3:10; 3rd event rule) and potentially 2:10 events for an alert.

Values are 0 or 1 and (even though it is unusual statistics) "standard deviation" is 1

One event with 3 counts will lead into an alert; one event with 4 counts causes actions