Data Evaluation for Classified Environments

Frederic B Ayers
Research Scientist
Eli Lilly and Company

DISCLAIMER

This presentation and the content expressed within are those of the speaker only and do not necessarily represent the position or policy of the speaker's company.

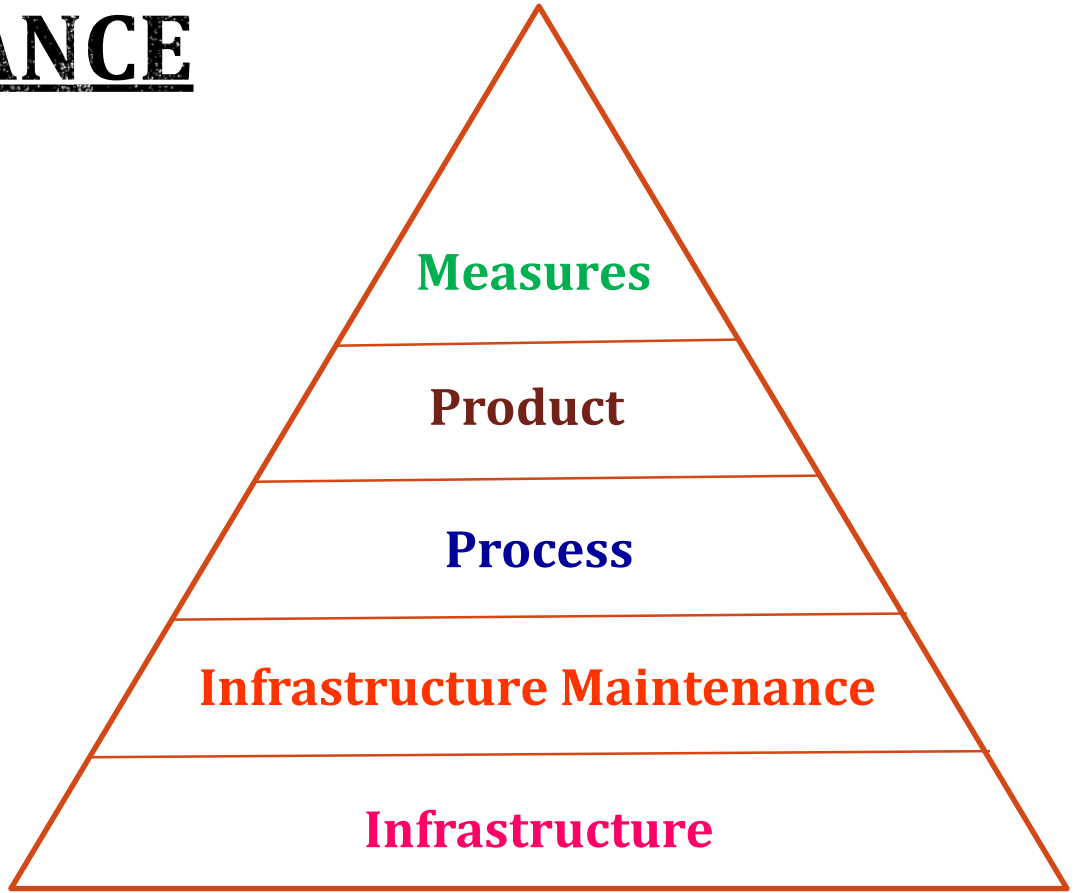
AGENDA

Sterility Assurance Strategy
Environmental Monitoring
Data Evaluation
- Action Limits
- Alert Limits
- Percent with Regulatory

STERILITY ASSURANCE STRATEGY

STERILITY ASSURANCE STRATEGY

Sterility assurance is the sum of all process controls, practices to ensure a high degree of confidence that products are free of microbial contamination



SA MEASURES

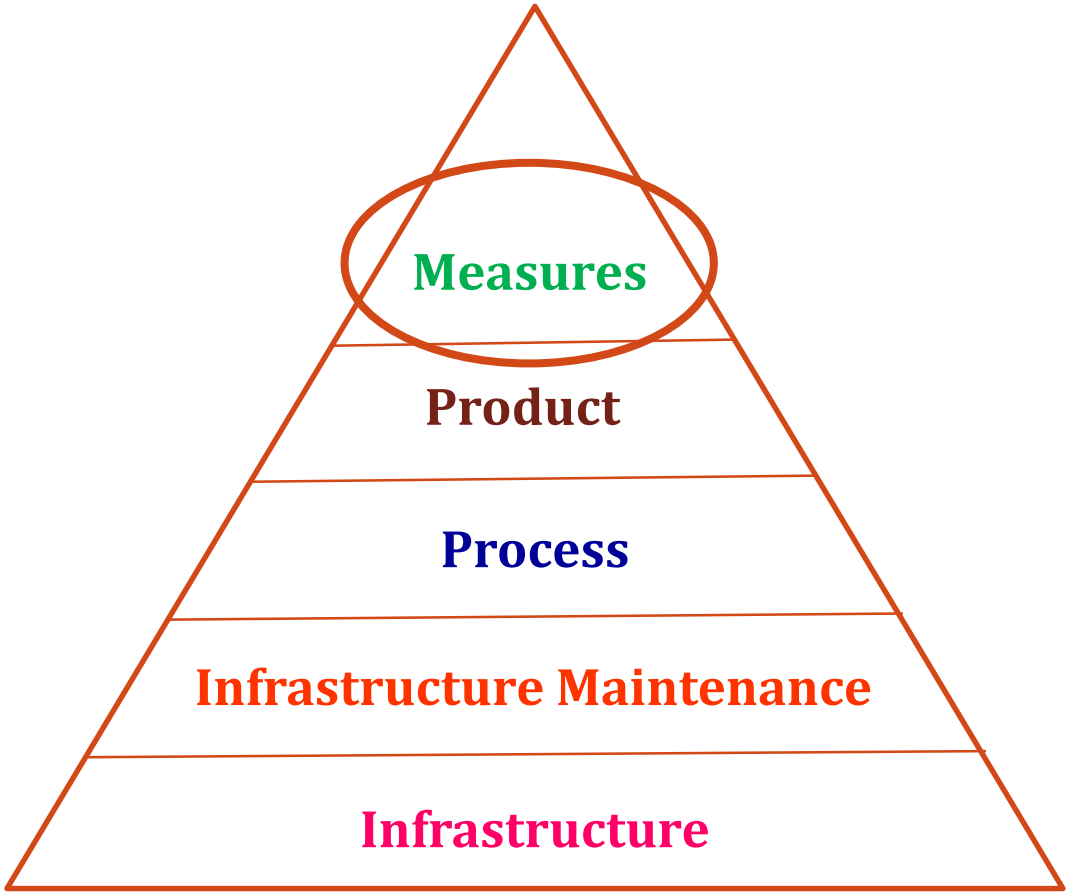
Aseptic Process Simulation

Bioburden

Endotoxin

Environmental Monitoring

Particulates



ENVIRONMENTAL MONITORING

ENVIRONMENTAL MONITORING

It is key that personnel understand the Environmental Monitoring (EM) is providing a measure of the environmental conditions, but it is not a direct measure of product quality. Product quality related measures may be, but not limited to, the following:

1) Clean Utilities (e.g., Water for Injection) Bioburden / Endotoxin / Particulates
2) Excipient Bioburden / Endotoxin / Particulates
3) In-Process Product Bioburden / Endotoxin / Particulates

ENVIRONMENTAL MONITORING

A robust EM program required when manufacturing medicinal products. To develop this program an individual must understand the following:

1) Regulatory Requirements
2) Facility Design
3) Aseptic Behavior / Technique
4) Process Knowledge
5) Airflow Visualization
6) Importance of Risk Anlaysis

ENVIRONMENTAL MONITORING

A robust EM program measures indirectly multiple parts of a facilities Contamination Control Strategy (CCS). These include, but are not limited to, the following:

1) Facility HVAC
2) Facility Cleaning
3) Facility Sanitization / Disinfection
4) Facility Personnel Flow
5) Personnel Gowning and Hygiene

DATA EVALUATION

ENVIRONMENTAL MONITORING – ACTION LIMITS

Globally it is typical that facilities utilize EU Annex 1 Limits for facility EM. These limits are the allowable microbiological recovery associated with the specific type of testing for identified classified areas.

	Passive Air	Active Air	Surface	Personnel
Grade A	0	0	0	0
Grade B	5	10	5	5
Grade C	50	100	25	N/A
Grade D	100	200	50	N/A

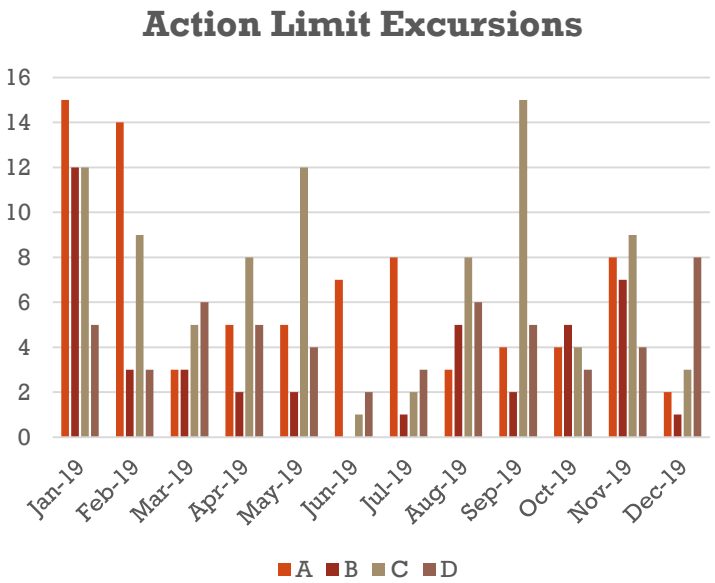
ENVIRONMENTAL MONITORING – ACTION LIMITS

Limit excursions can easily be tracked, typically within a LIMS or general spreadsheet to evaluate overall performance.

Tracking these types of excursions will allow the microbiologist to evaluate overall facility performance or classified area performance

Site Month-Year	A	B	C	D	Total
Jan-19	15	12	12	5	44
Feb-19	14	3	9	3	29
Mar-19	3	3	5	6	17
Apr-19	5	2	8	5	20
May-19	5	2	12	4	23
Jun-19	7	0	1	2	10
Jul-19	8	1	2	3	14
Aug-19	3	5	8	6	22
Sep-19	4	2	15	5	26
Oct-19	4	5	4	3	16
Nov-19	8	7	9	4	28
Dec-19	2	1	3	8	14

ENVIRONMENTAL MONITORING – ACTION LIMITS



Limit excursions can easily be visualized by most LIMS or in a spreadsheet to evaluate overall performance.

Visualizing the data is key to understanding overall performance of the facility performance

ENVIRONMENTAL MONITORING – ALERT LIMITS

Typically the microbiologist / sterility assurance subject matter expert will work with statistics to develop alert limits, which would be based upon historical data gathered from the facility. This data will be analyzed to generate alert limits that will provide an escalated notification of an atypical or non-routine recovery or contamination event. Due to this type of limit being derived from historical data, no facility will have the same alert limits. Grade A does not have alert limits as the expectation is that zero samples demonstrate recovery.

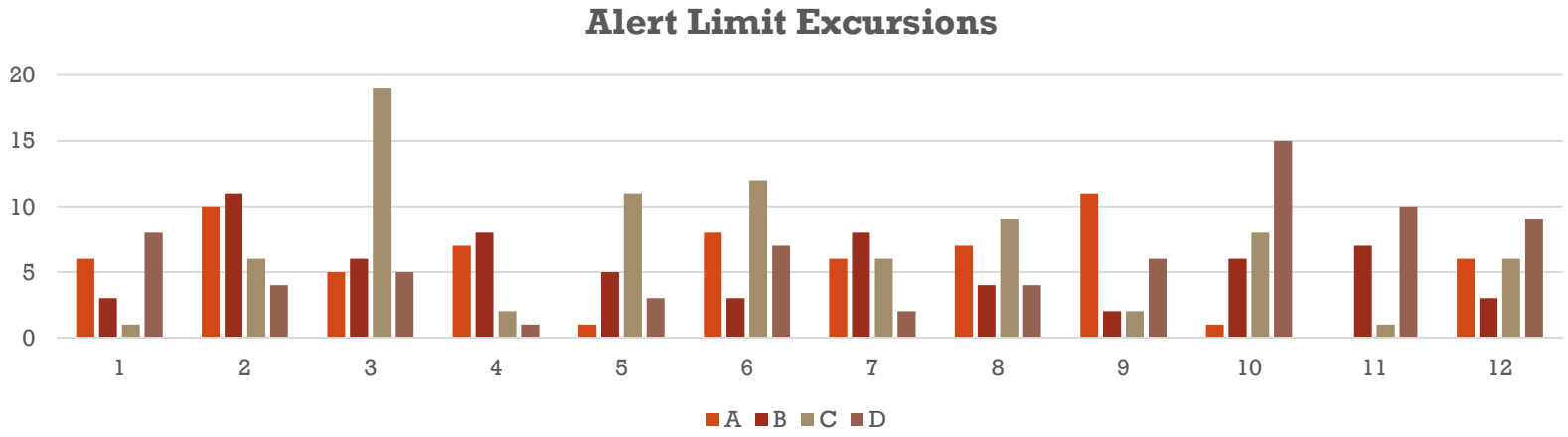
ENVIRONMENTAL MONITORING – ALERT LIMITS

Site Month-Year	A	B	C	D	Total
Jan-19	6	3	1	8	18
Feb-19	10	11	6	4	31
Mar-19	5	6	19	5	35
Apr-19	7	8	2	1	18
May-19	1	5	11	3	20
Jun-19	8	3	12	7	30
Jul-19	6	8	6	2	22
Aug-19	7	4	9	4	24
Sep-19	11	2	2	6	21
Oct-19	1	6	8	15	30
Nov-19	0	7	1	10	18
Dec-19	6	3	6	9	24

Alert limit excursions can should also be tracked (typically within a LIMS or general spreadsheet) to determine if there are any classified areas that are performing different than expected, based upon historical performance.

Tracking alerts will allow the microbiologist to evaluate overall facility performance to identify those areas for further evaluation, prior to becoming deviations.

Typically alert excursions can be trended by area, site, room, etc.



ENVIRONMENTAL MONITORING – ACTION LIMITS

It is important to visualize alert limit excursions to better understand overall performance.

Visualizing the data also allows performance communication to key stakeholders

ENVIRONMENTAL MONITORING – PERCENT WITHIN REGULATORY

It is critically important to identify and investigate excursion that exceed action limits, as this could demonstrate the area(s) did not remain in a state of control during the manufacturing process. If an area is observing multiple action limit excursions this can cause a drain on resource utilization at a facility that will result in more reactive solutions (i.e., CAPA) versus proactive solutions (i.e., Continuous Improvement). Additionally, higher level of deviation rates will be identified through regulatory personnel when evaluating Quality Metrics for facilities. areas.

Therefore, a system must be established to determine the effectiveness of **all** facility and personnel environmental controls of the Contamination Control Strategy. As stated in a prior slide, Environmental Monitoring, by itself is not a direct measure of control, but should be used along with other facility engineering controls to determine if a facility or portion of a facility remains in a state of control.

USP<1116> discusses the use of recovery rate (number of positive[1] sample / total number of samples) to further evaluate a pharmaceutical manufacturing environment.

[1]sample with ≥1 Colony Forming Unit (CFU)

ENVIRONMENTAL MONITORING – PERCENT WITHIN REGULATORY

- Recovery Rates can be tracked within a LIMS or spreadsheet to evaluate overall performance.
- The difficulty is that the number it provides is not readily understood by leadership or personnel not working with this type of data on a day-to-day basis.
- This data overtime can easily be used to develop statistically based control limits to assist the microbiologist's evaluation of facility control

Site Month-Year	Action Total	Sample Total	Recovery Rate
Jan-19	44	22568	0.1950
Feb-19	29	29378	0.0987
Mar-19	17	29435	0.0578
Apr-19	20	31254	0.0640
May-19	23	24879	0.0924
Jun-19	10	31005	0.0323
Jul-19	14	18394	0.0761
Aug-19	22	31258	0.0704
Sep-19	26	30456	0.0854
Oct-19	16	34587	0.0463
Nov-19	28	36294	0.0771
Dec-19	14	32497	0.0431

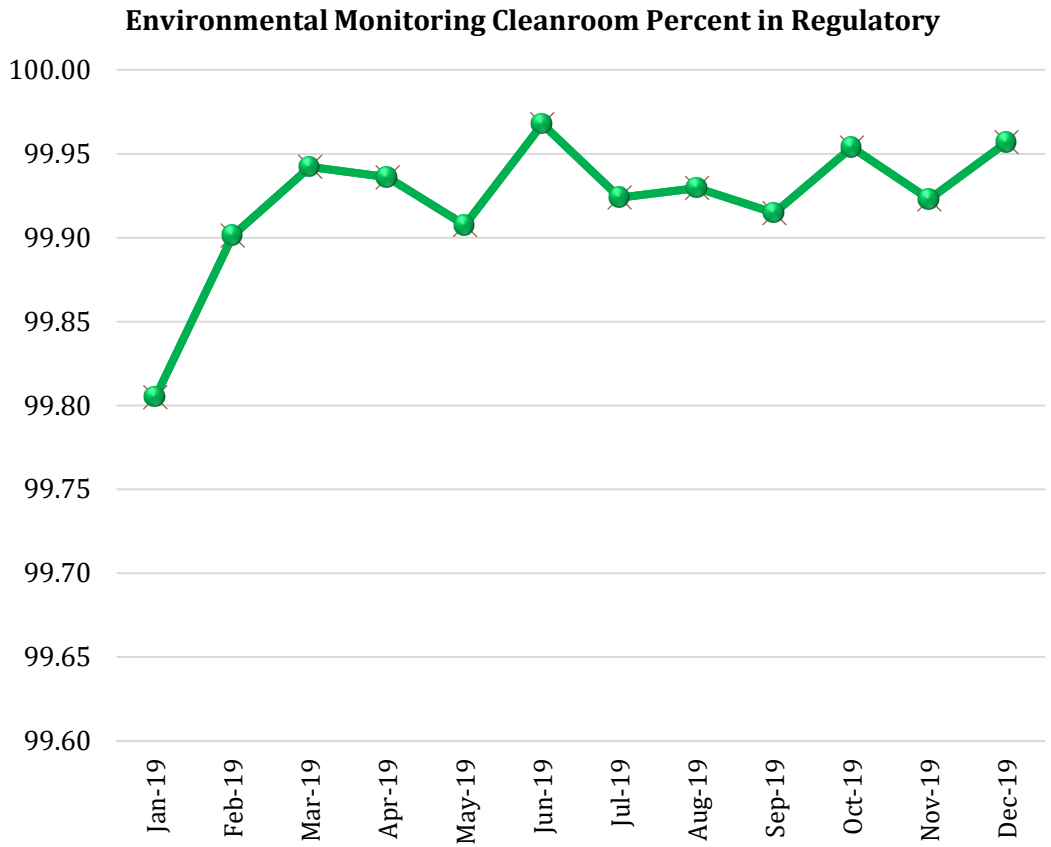
Identify an easy way to demonstrate overall facility control & effectiveness of programs

Quickly communicate to key stakeholders the rate of resource utilization related to EM deviations

Site Month-Year	Action Total	Sample Total	Recovery Rate	Percent in Regulatory
Jan-19	44	22568	0.1950	99.8050
Feb-19	29	29378	0.0987	99.9013
Mar-19	17	29435	0.0578	99.9422
Apr-19	20	31254	0.0640	99.9360
May-19	23	24879	0.0924	99.9076
Jun-19	10	31005	0.0323	99.9677
Jul-19	14	18394	0.0761	99.9239
Aug-19	22	31258	0.0704	99.9296
Sep-19	26	30456	0.0854	99.9146
Oct-19	16	34587	0.0463	99.9537
Nov-19	28	36294	0.0771	99.9229
Dec-19	14	32497	0.0431	99.9569

Tabulation of the recovery rates has already been demonstrated, which is used to create Percent within Regulatory (PwiR).

100% - Recovery Rate = Percent within Regulatory



PERCENT WITHIN REGULATORY

Visualization of PwiR allows for quick and easy communication of overall facility performance over time and resource utilization.

This will allow key stakeholders to better utilize resources to investigate excursions and portions of the site / facility to focus on for improvements.

SUMMARY

1) Environmental Monitoring along with other facility engineering control monitoring is a realistic measure of a facilities ability to remain in a state of control.

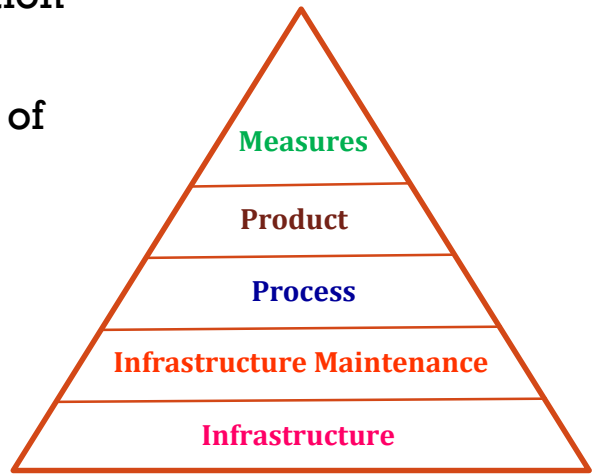
2) Multiple ways to evaluate Environmental Monitoring Data for a facility

3) Action limit excursions must be investigated to determine impact

4) Alert limit excursions should be trended for proactive evaluation of facility performance

5) USP <1116> provides guidance around development and use of recovery rates

6) Percent within Regulatory utilizes recovery rates to quickly visualize overall environmental performance and resource utilization



THANK YOU for your attention

Thank you to the PDA Midwest and the sponsors of this event