Requirements for Environmental Monitoring

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Requirements for Environmental Monitoring

- What are the GMP requirements?
  - GMP Basics and monitoring methods
  - Designing a monitoring programme
  - Incubation strategies
  - Excursion reporting/investigation
  - Trending
  - Weaknesses

- Find the right position in the isolator system
  - Know your machine and isolator!
  - Airflows; air visualization studies

What are the GMP requirements?

GMP Basics and monitoring methods

Designing a monitoring programme

Incubation strategies

Excursion reporting/investigation

Trending

Weaknesses

Environmental Monitoring GMP basics

- For the purposes of this training session current expectations will be presented but quotes from the Annex 1 (August 2023) will be used.

- Traditionally referred to as “viable and non-viable” particles
  - Viable = microbiological methods
  - Non-viable = particle counting equipment

Non-viable is often thought of as only ‘inert’ particles but could also include dead bacterial cells which wouldn’t be recovered by viable monitoring methods…

The term has been updated to ‘total particle count’ in the 2023 Annex 1

Environmental Monitoring GMP basics

- Section 9 of Annex 1 (August 2023)

- 'Environmental and process monitoring programme'
- part of the overall CCS
- used to monitor the controls designed to minimize the risk of microbial and particle contamination

i. Environmental monitoring – total particle.
ii. Environmental and personnel monitoring – viable particle
iii. Temperature, relative humidity and other specific characteristics.
iv. APS (aseptically manufactured product only)

Environmental Monitoring GMP basics

Annex 1; 9.3

- Information from these systems
  - for routine batch certification/release
  - for periodic assessment during process review or investigation

- Terminal sterilisation
- Aseptic processes

Environmental Monitoring GMP basics

Annex 1; 9.4

The purpose of the EM programme is….
i.

ii.

Environmental Monitoring GMP basics

Annex 1; 9.4

The purpose of the EM programme is….

i. Provide assurance that cleanrooms and clean air equipment continue to provide an environment of appropriate air cleanliness, in accordance with design and regulatory requirements.

ii. Effectively detect excursions from environmental limits triggering investigation and assessment of risk to product quality

Environmental Monitoring GMP basics

Annex 1; 9.4

Risk assessments performed to establish [Comprehensive],

- Sampling locations,
- Frequency of monitoring,
- Monitoring methods and
- Incubation conditions
  - (e.g. time, temperature(s), aerobic and/or anaerobic conditions)

Reviewed Regularly!

Techniques to assist:

- Touchpoint analysis (perform the process and tag items touched each time)
- Traffic flow analysis (aka heat maps)

Environmental Monitoring GMP basics

Annex 1; 9.4

Risk assessments based upon detailed knowledge of;

- The process inputs and final product,
- The facility,
- The equipment,
- The criticality of specific processes and steps,
- The operations involved,
- The routine monitoring data,
- The monitoring data obtained during qualification and
- The knowledge of typical microbial flora isolated from the environment.

Environmental Monitoring GMP basics

- Annex 1; 9.22
- Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods such as
  - settle plates,
  - volumetric air sampling,
  - glove,
  - gown and surface sampling (e.g. swabs and contact plates).

  The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on grade A and B airflow patterns.

  Cleanroom and equipment surfaces should be monitored at the end of an operation

Environmental Monitoring GMP basics

- Continuous monitoring – should be exposed during all processing activity in grade A (and often grade B) (or continuous active air sampling)

Continuous viable air monitoring in the grade A (e.g., air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and filling operations.

A similar approach should be considered for grade B cleanrooms based on the risk of impact on the aseptic processing.
The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be captured, and any risk caused by interventions of the monitoring operations is avoided - Annex 1; 9.24

Environmental Monitoring GMP basics

First Air Principles

- First air refers to filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone.

Environmental Monitoring methods - Viable

Table 7: Maximum action limits for viable particle contamination

Grade	Air sample Cfu /m^3	Settle plates (diam. 90 mm) Cfu /4 hours[(a)]	Contact plates (diam. 55mm), Cfu / plate[(b)]	Glove print, Including 5 fingers on both hands Cfu / glove
A	No growth[(c)]			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

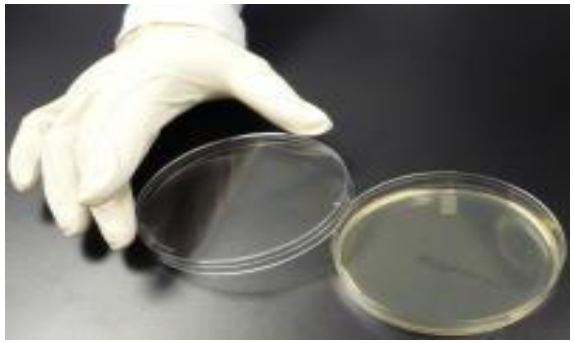
Environmental Monitoring methods - Viable

A1;9.23

Viable particle monitoring should also be performed within the cleanrooms when normal manufacturing operations are not occurring (e.g., post disinfection, prior to start of manufacturing, on completion of the batch and after a shutdown period), and in associated rooms that have not been used, in order to detect potential incidents of contamination which may affect the controls within the cleanrooms.

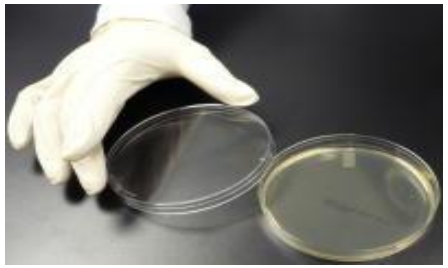
Environmental Monitoring methods

- Viable monitoring methods
  - Settle plates
  - Contact plates
  - Swabs
  - Active air sampling
  - Rapid methods



Settle plates

- Typically 90mm plates
- Tryptone Soya Agar (TSA) – general use, can recover both bacteria/moulds
- Sabaraud Dextrose Agar (SDA) – specifically for yeasts and moulds



Settle Plates

- May need to include neutralisers depending on application (e.g. monitoring of antibiotic powder-filling processes)
- Passive monitoring method
- Quantitative
- Exposure time four-hour maximum or duration of session if less than four hours (may need to be shorter time / more frequent changes to avoid drying out depending on location – but same limits still apply)

Contact plates

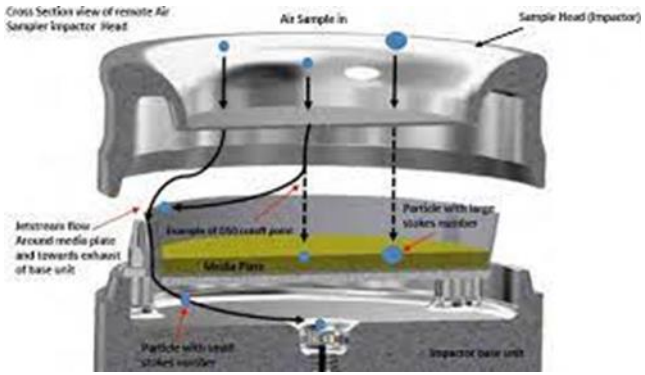
- Typically 55mm plates (~25cm^2)
- Typically need to include neutralisers (and validate – Annex 15, 9.3)
- Media is raised in the centre to allow full contact with the flat surface being monitored
- Quantitative
- Easy to use but only good for flat surfaces
- Residues need to be carefully removed
- NOT to be used for finger dabs…

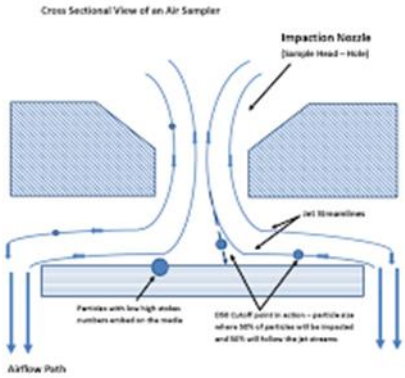
Swabs

- Good for uneven surfaces and nooks & crannies
- Need to be moistened prior to use (or pre-moistened)
- May or may not be quantitative
  - Can be placed directly in media (qualitative)
  - Can be plated out (quantitative – but need to validate recovery efficiency)

Active air sampling

- Sample a known volume of air (equipment needs routine calibration)
- Quantitative, but only a relatively small ‘snapshot’ of the overall volume
- Mobile samplers difficult to sanitise
- Need to sanitise (or sterilise for critical zones) the heads before use
- Variation in efficiency between different types (d50 value)





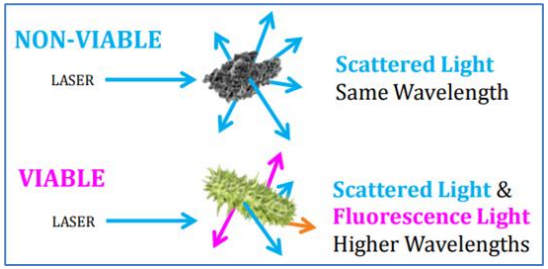
Personnel – finger dabs and gowns

- Finger dabs (all fingers plus thumb on each hand)
  - Should be taken after direct interventions to grade A zone (without spraying hands immediately before)
  - Also taken on exit from the cleanroom
  - Gloves should be changed if work session continues
  - Limits per glove (5 digits), not all 10 (no averages)

Personnel – finger dabs and gowns

- Gown monitoring
  - Routine monitoring of gowns should be performed
  - Typically on exit from the cleanroom – don't want residues of growth media left on gowns during a working session
  - Typically forearms, chest and head for routine monitoring

Rapid microbiological methods



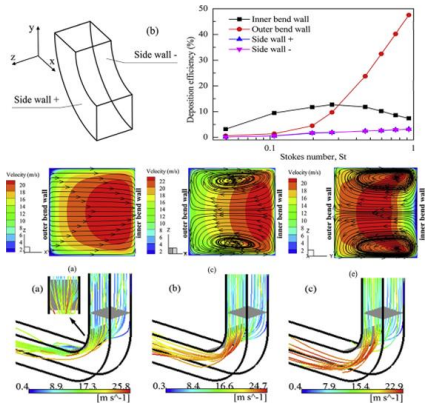
- Quicker time to a result but need robust validation
- Not widely adopted – fears of regulatory non-acceptance…
- Examples include:
  - ATP-bioluminescence
    - » Luciferin/luciferase reaction in growing cells
    - » Amount of light equates to the number of cells present
    - » Can also detect non-microbial ATP
  - Aurofluorescence detection
    - » All living cells fluoresce under blue light
    - » Regular scanning of plates during incubation for early colony detection
  - Colourimetric growth detection
    - » Limited range of organisms detected but good where specific absence is important

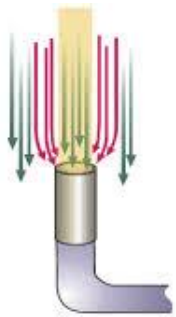
Methods – total particle monitoring

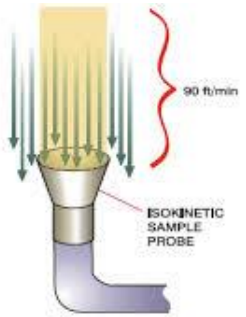
Grade	Maximum limits for total particle ≥ 0.5 µm/m³		Maximum limits for total particle ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not specified [a]	Not specified [a]
B	3 520	352 000	Not specified [a]	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined [b]	29 300	Not predetermined [b]

Methods – total particle monitoring

- Laser particle counters used for total particles
- Tubing length should typically be less than 1m
- No. bends minimised
- Bend radii per manufacturer's specifications
- Isokinetic sampling probes
- Continuous monitoring required in grade A
- Consider contamination risks from mobile counters

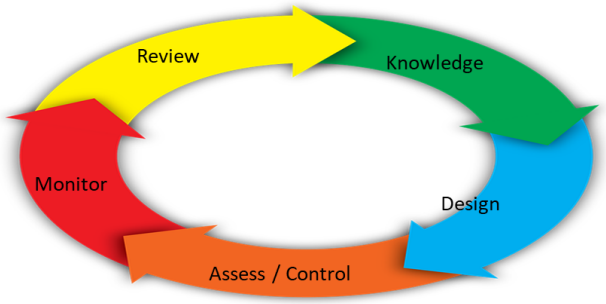






What are the GMP requirements?

- GMP Basics and monitoring methods
- Designing a monitoring programme
- Incubation strategies
- Excursion reporting/investigation
- Trending
- Weaknesses



Monitoring locations

- All EM and the associated locations should be based on an appropriate risk assessment:
  - Initial facility qualification
  - Ongoing monitoring, trending and knowledge development
- Assessment should include:
  - Knowledge of process and risks – e.g. review of number of manipulations in each zone, use of process heat maps etc.
  - Smoke studies
  - Historical review
  - Common sense (often missed!)

Monitoring locations

- Review of vectors that breach the ‘layers’ and other risks, and need to monitor accordingly:
  - Process flows
  - Equipment
  - Materials
  - People
- Important to remember that monitoring must however not compromise the process

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Incubation strategies

- Not a one size fits all
- Baseline expectation where only one media is used (TSA):
  - Aerobic
  - Incubate at 20-25°C (typically 3-5 days)
  - Followed by 30-35°C (typically 2-4 days)
- If not, needs to be a suitable scientific rationale, based on statistically valid data from the site's own facility

- If using separate media (not common) then respective incubation conditions apply – TSA 30-35°C; SDA 20-25°C

Incubation strategies

- But monitoring and incubation strategy needs to be based on process knowledge and risk
  - Anaerobes?
  - Psychrophiles or cryophiles?
  - Wet processes?
  - Specific organisms?
- Also remember the incubators should be qualified and subject to temperature mapping

Reading the plates

- Magnifying colony counters should be used – expecting low counts, so need the best opportunity to see them
- Manual process and potential for DI issues:
  - Has this been identified as a risk within the site's DI review?
  - e.g. are second checks performed on at least zero count plates?
  - How are the results recorded – paper / direct data entry?

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Excursion reporting / investigations

- Principles should be the same for all investigations:
  - Timely
  - Appropriate investigation to determine root cause
  - Documented
  - Commensurate to risk
  - Appropriate CAPA

Excursion reporting / investigations

- Common issues in general:
  - Risk assessment doesn't include an appropriate 'bracket'
  - Inspectors routinely see "*there was an excursion but all other data ok*"
  - "*EM the day before and day after OK so must be OK*" (but don't know root cause)
  - Initial risk assessment to understand the possible or actual risk to other products not done quickly
  - Not considering the wider picture and trends appropriately

Excursion reporting / investigations

- Common issues for smaller sites:
  - Contract labs – receipt of initial report can be slow
  - Generally not timely – time to sub culture for ID
  - IDs often also outsourced which adds to the timelines
  - Documented investigations weak
  - Risk assessments often based on literature (e.g. Bergey's Manual) with insufficient microbiology expertise in-house
  - All too often "*isolated excursion and all other data from that session were ok*"…

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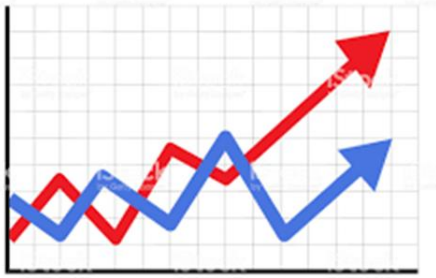

Limits and trending

- Limits for monitoring
  - Action limits
    - Annex 1 limits are used
    - Tighter action limits can be set for lower grades based on historical performance
  - Alert limits
    - Should be set based on historical data – science
    - Do not just set at 50% action limit
    - Limits should be regularly reviewed based on site data
  - If the trend review suggests the proposed alert limits are widened, this should trigger an investigation as it indicates a decline in performance

Trending

Should include….
i. Increasing numbers of excursions from action limits or alert levels.

ii. Consecutive excursions from alert levels.

iii. Regular but isolated excursion from action limits that may have a common cause, (e.g. single excursions that always follow planned preventative maintenance).

iv. Changes in microbial flora type and numbers and predominance of specific organisms.

- Particular attention should be given to organisms recovered that may indicate a loss of control, deterioration in cleanliness or organisms that may be difficult to control such as spore-forming microorganisms and moulds.

Trending

- Ideally data should be reviewed in different ways, appropriate to what is trying to be understood from the data
- Should include a microbiologist or appropriately experienced person
  - e.g. by area / workstation / activity / operator
- All provide different but meaningful data and sometimes issues may be missed by the way the data are presented
- e.g.:

  “0.1% of finger dab monitoring shows recovery so that’s a low level”

  If 90% of those recoveries were from one individual operator this would be missed without appropriate review

What are the GMP requirements?

GMP Basics and monitoring methods

Designing a monitoring programme

Incubation strategies

Excursion reporting/investigation

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Weaknesses

Weaknesses

- Microbiological monitoring is actually very inefficient…
  - Only a small fraction of air and surfaces that can impact product can be sampled
  - Monitoring techniques have low recovery efficiency
  - Limited range of organisms can be isolated using common media and incubation conditions

  - A positive recovery is therefore a significant event
  - A negative result may therefore be misleading…

Find the right position in the isolator system

Know your machine and isolator!!

Airflows; air visualization studies

Know your machine and isolator

- Location, Location, Location!!!

Know your machine and isolator

Annex 1;4.19

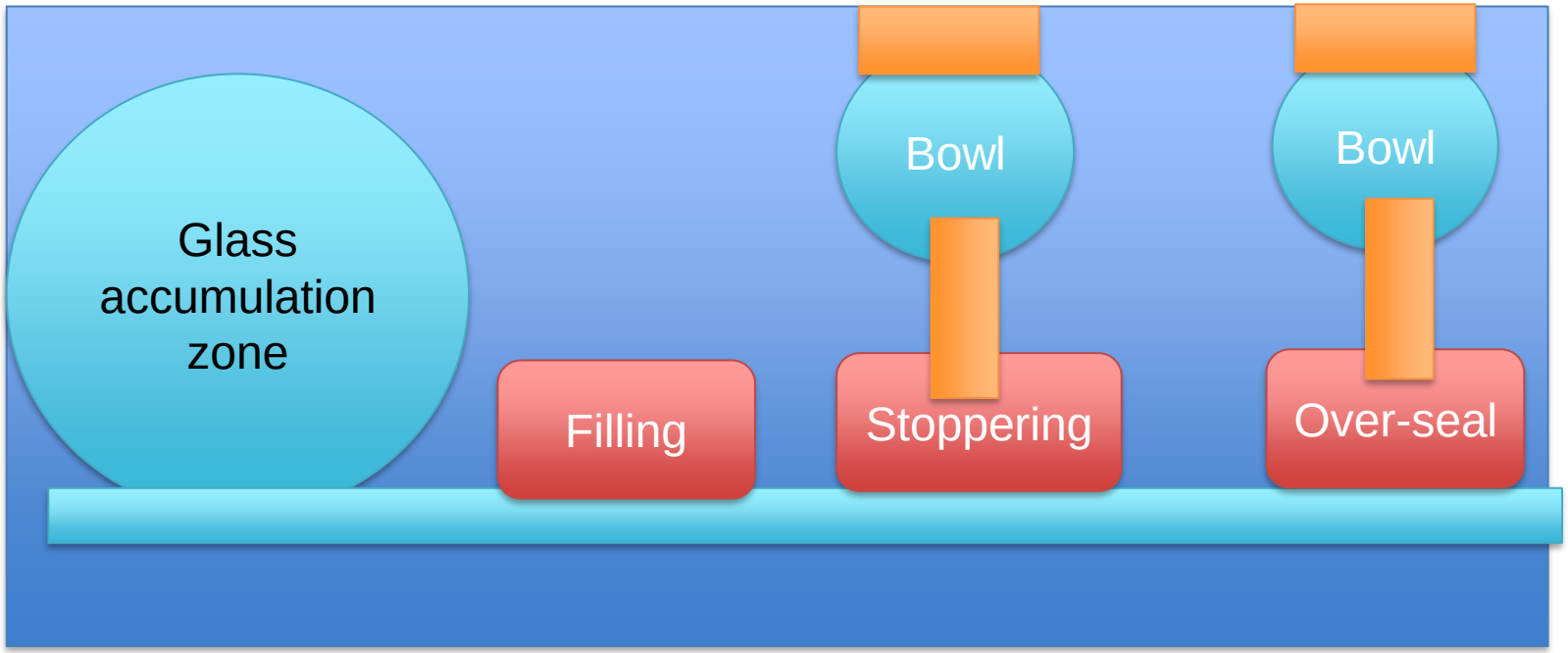
a. The design of open isolators should ensure grade A conditions with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing

b. The design of closed isolators should ensure grade A conditions with adequate protection for exposed products during processing.

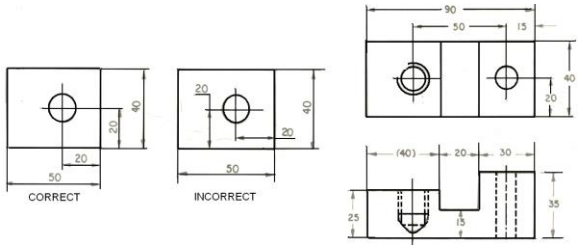
4.20 The background environment for isolators should ensure the risk of transfer of contamination is minimized.
open isolators - grade C
closed isolators - grade D
Based on RA & justified in CCS.

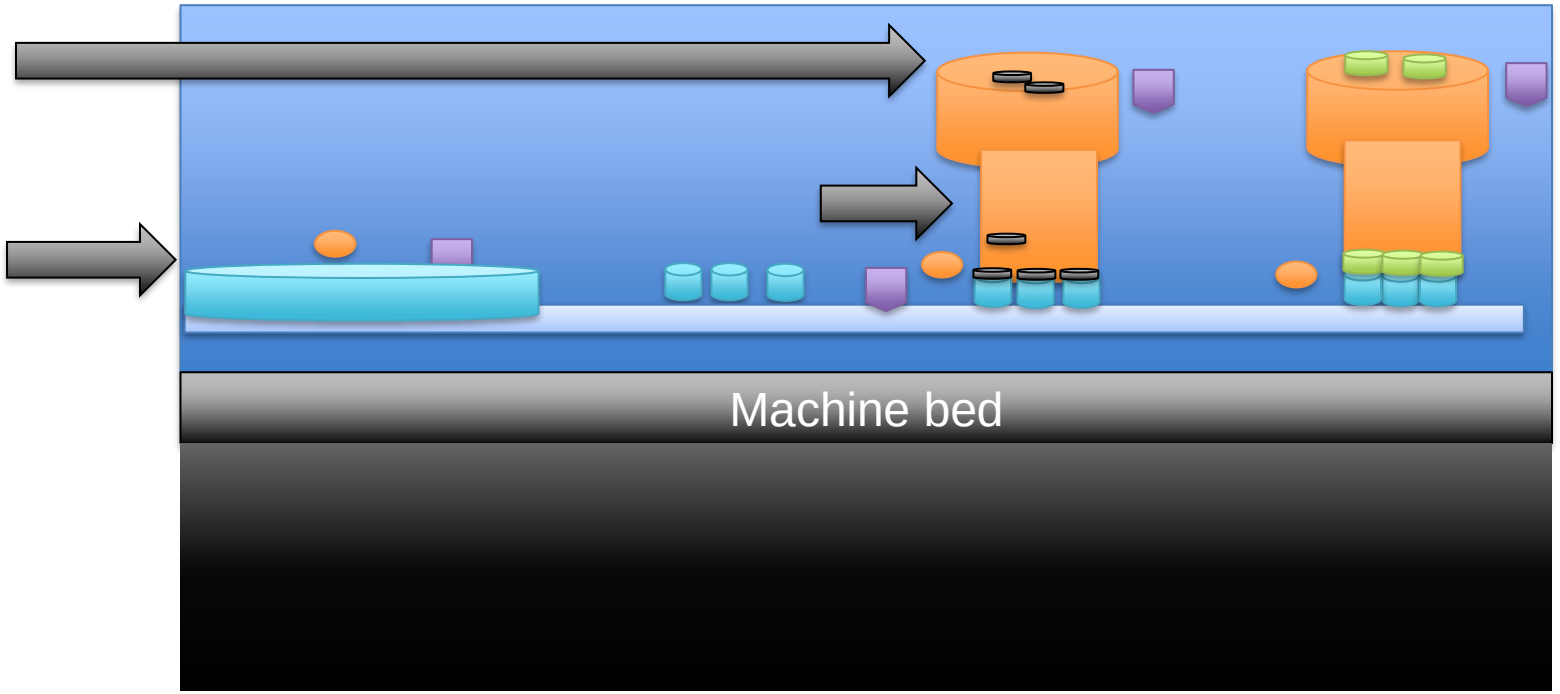
Know your machine and isolator

- Zones



Know your machine and isolator – 3D





Find the right position in the isolator system

Know your machine and isolator!!

Airflows; air visualisation studies

Air visualisation studies

- WFI generators
- Nozzles
  - Size
  - Shape
  - Direction
  - One size fits all?
- Not having a protocol!
  - Or a report!

Air visualisation studies

Smoke studies – air ingress and egress

Isolator door opened as part of set up to load indirect product contact parts. Open isolator in Grade C

Is the UDAF on when the door is open to Grade C?

'Mouse hole'

‘First Air’ and VHP considerations

Filtered air that has not been interrupted by items such as operators with the potential to add contamination to the air prior to reaching the critical zone

- *Hanging items in isolator for VHP considerations – fixed to avoid contact with each other but…*
  - *Is the item over open vials during filling activities?*
  - *Over the stopper bowl and stoppers?*

Summary

Summary

- Different monitoring methods form part of the overall tool kit
- EM should be based on good knowledge and understanding of both the process and the facility and the isolator!
- Any recovery, particularly from grade A should be unusual and investigated appropriately
- Monitoring methods are not very efficient so understanding the limitations is important
- Just because there was a zero count isn't the end of the sterility assurance story…
- Each zone should be monitored V + TP
- The location should be 3D and be capable of detecting risk to open units
- Air visualisation studies should be used in assessing location

Summary

What	How	When	Where	Batch related?
Facility; corridors, PAL, MAL	Active air, settle, rodacs	RA frequency (inc. 9.23 points)	Air, walls, floors	Not usually
Filling Room	All +TP	To cover the duration of the fill (inc. set-up) + RA frequency	Air, RA locations	Yes*
Filling Line	All +TP		Air, RA locations	Yes *
Operators	Contacts, finger dab plates	After critical intervention On each Exit	Gloves and gown	Yes*
Engineers				Yes*
Micro staff				Yes*
QA staff		On each Exit		Not usually