

PHARMACEUTICAL
CONSULTANCY
SERVICES

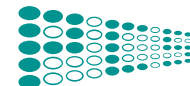
ENVIRONMENTAL MONITORING (VIABLES)

Jaap Koster

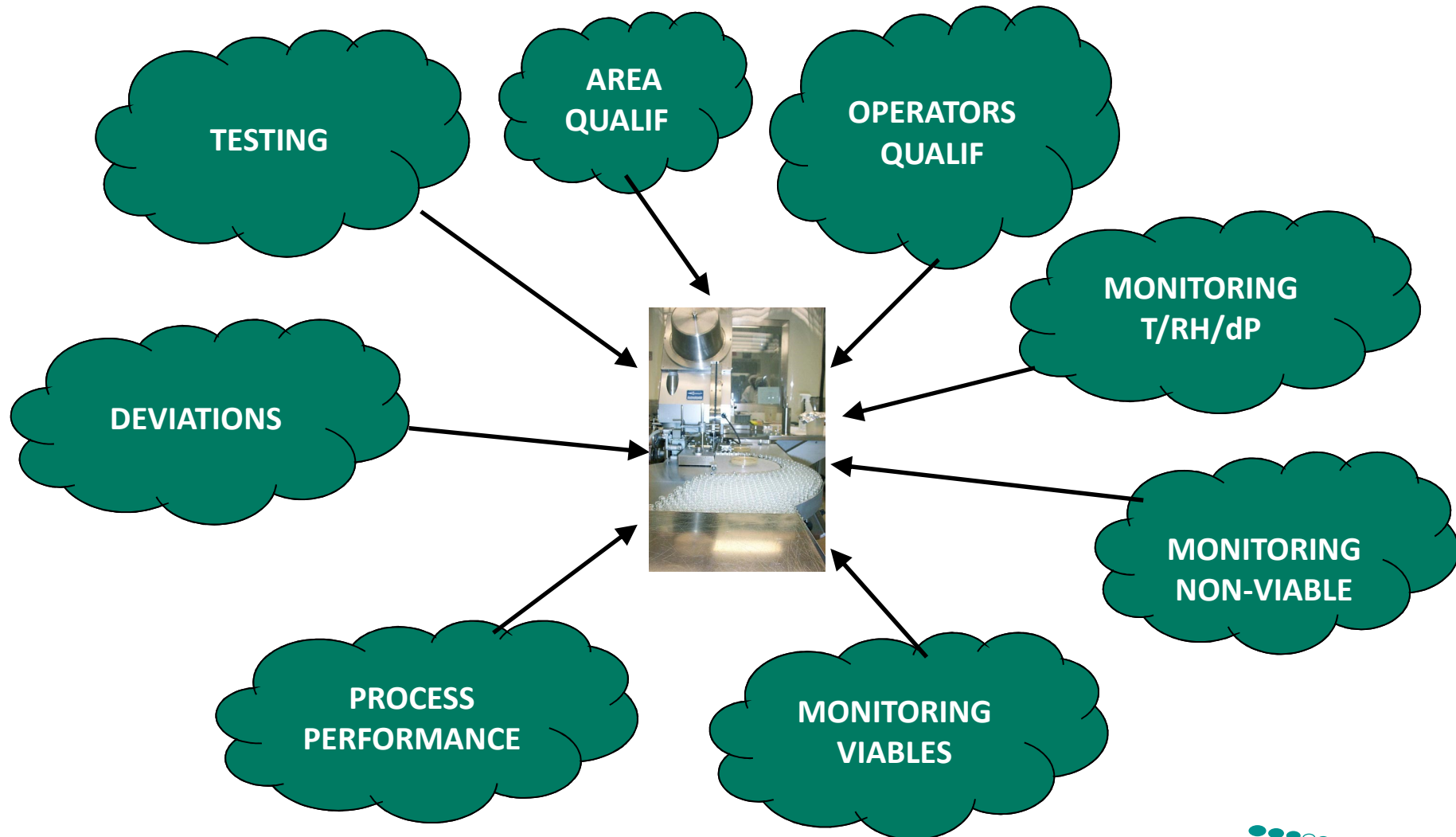
ENVIRONMENTAL MONITORING...

- Sterility testing and sampling for sterility testing is prone to “false negatives”.
- As a result: sterility testing is not the only activity to be considered before defining a batch “sterile”.

STERILITY TESTING IS NOT ENOUGH



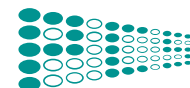
MINDMAPPING



ENVIRONMENTAL MONITORING...

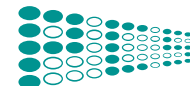
- To verify that clean/aseptic areas are routinely operating within their design specifications.
- To ensure that daily operations are not negatively influencing the required cleanliness level.
- To provide continuous data on the performance of clean/aseptic areas.
- Provide an integrated assessment of the performance of man, machine, process, practices etc.

**EM is an important feedback loop in the
Quality Management System**



ENVIRONMENTAL MONITORING INCLUDES...

- **Viability monitoring**
 - Active air sampling
 - Passive air sampling
 - Surfaces
 - Operators
- **Nonviable monitoring (particulates)**
 - Continuous
 - Discontinuous
- **Physical monitoring**
 - Temperature
 - Pressure
 - Humidity

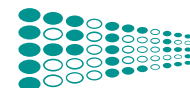


ROUTINE MONITORING ...

- **Critical areas (Class A)**

Locations where product, critical surfaces or primary packaging components are exposed to the environment,

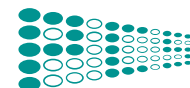
*e.g. personnel, ampoule filling sealing machines, stopper
hoppers, LAF units*



DEFINE ROUTINE MONITORING ...

- **Peripheral areas (Class B)**

These can be defined as filling rooms within the boundary of the aseptic process area, where product and containers are not exposed to the environment, *e.g. sealed equipment, surfaces or air, storage of autoclaved goods, closed containers*

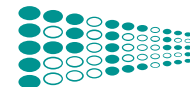



DEFINE ROUTINE MONITORING ...

- **Associated areas (Class C/D)**

Areas adjacent to the manufacturing and filling area:

- Access airlocks
- Changing room airlocks
- Changing rooms
- Material transfer airlocks
- Solution preparation areas
- Dispensing areas

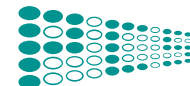


	Class A	Class B	Class C	Class D
Nonviable air counts	<ul style="list-style-type: none"> • Every batch • Continuous 	<ul style="list-style-type: none"> • Every batch critical areas only • All points frequently 	<ul style="list-style-type: none"> • No guidance recommend weekly, or as required by product need 	<ul style="list-style-type: none"> • No guidance recommend 3-monthly
Viable air counts (settle plates and/or volumetric samples)	<ul style="list-style-type: none"> • Every batch at critical points 	<ul style="list-style-type: none"> • Some points every batch • All points frequently 	<ul style="list-style-type: none"> • No guidance recommend weekly, or as required by product need 	<ul style="list-style-type: none"> • No guidance recommend monthly
Surface counts (contact plates)	<ul style="list-style-type: none"> • Every batch at critical points 	<ul style="list-style-type: none"> • Frequently (1-2 times per week) 	<ul style="list-style-type: none"> • No guidance recommend weekly, or as required by product need 	<ul style="list-style-type: none"> • No guidance recommend monthly
Gloves	<ul style="list-style-type: none"> • All operators working in Class A for each batch 	<ul style="list-style-type: none"> • All operators involved in critical operations for each batch • All operators on a regular basis 	<ul style="list-style-type: none"> • Not required • Company to set policy based on product need 	<ul style="list-style-type: none"> • Not required
Gown monitoring	<ul style="list-style-type: none"> • During gowning qualification only • Random (advise) 	<ul style="list-style-type: none"> • During gowning qualification only • Random (advise) 	<ul style="list-style-type: none"> • Not required • Company to set policy based on product need 	<ul style="list-style-type: none"> • Not required
Pressure differentials	<ul style="list-style-type: none"> • Continuously • Alarms 	<ul style="list-style-type: none"> • Continuously • Alarms 	<ul style="list-style-type: none"> • Continuously 	<ul style="list-style-type: none"> • Continuously
Temp/RH	<ul style="list-style-type: none"> • Continuously 	<ul style="list-style-type: none"> • Continuously 	No requirement (unless required by product need)	No requirement 

METHODS FOR ENVIRONMENTAL MONITORING

What is required?

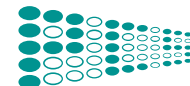
- Quantitative Air samples
- Qualitative Air samples (settle plates)
- Surface Samples
- Currently, all methods are growth based, although some progress is being made with rapid methods.



QUANTITATIVE AIR SAMPLING

Driven by a mechanical “ventilator” a known amount of air is led over a agar-plate, some examples given:

- Sieve impactors
- Slit-to agar (STA) Air Samplers
- Surface vacuum samplers
- Centrifugal impactors
- Filtration
- Liquid Impingement



QUANTITATIVE AIR SAMPLERS

CENTRIFUGAL IMPACTORS

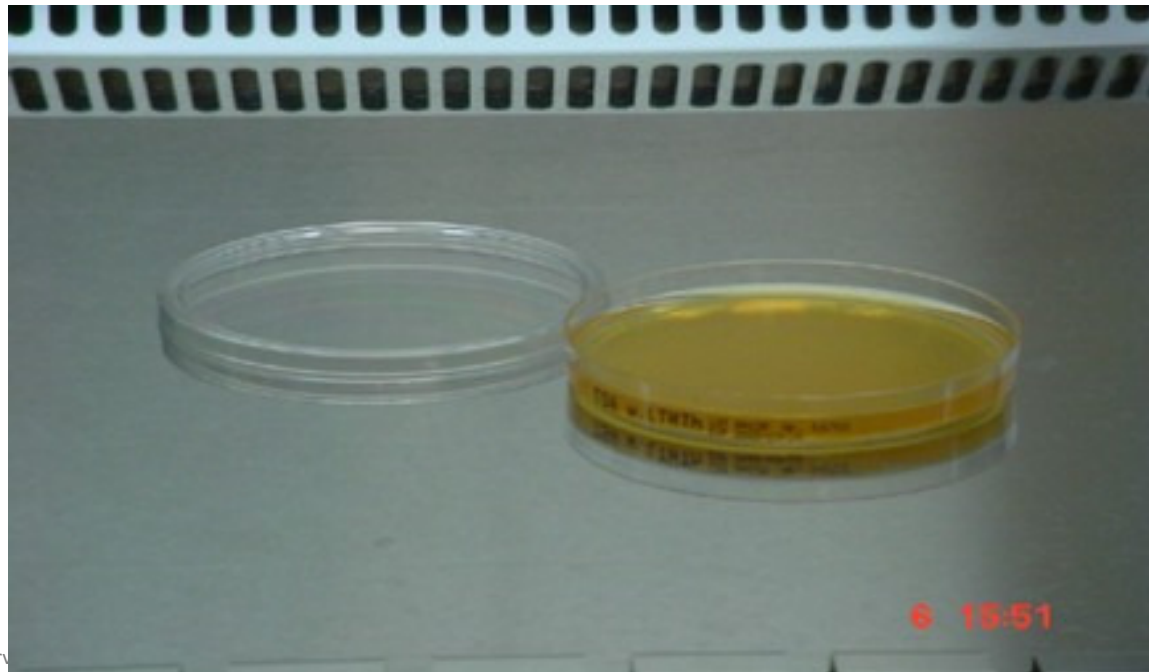


RCS High Flow (Biotest)



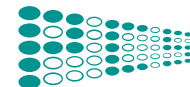
EM METHODS: SETTLE PLATES

- bioburden after exposure of a certain time (time must be validated)
- glove printing
- Possible issue: dry-out of media



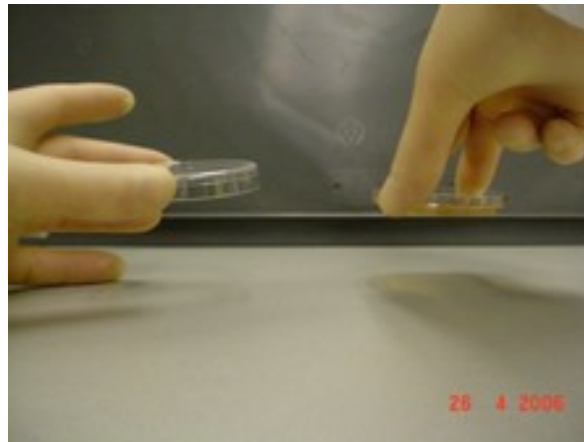
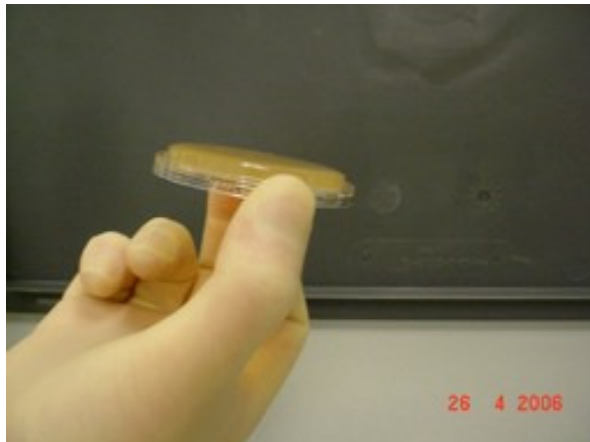
SURFACE SAMPLING METHODOLOGIES

- Contact plates or slides
- Flexible films (petri films)
- Swabs
- Surface rinse method



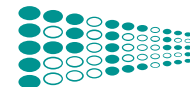
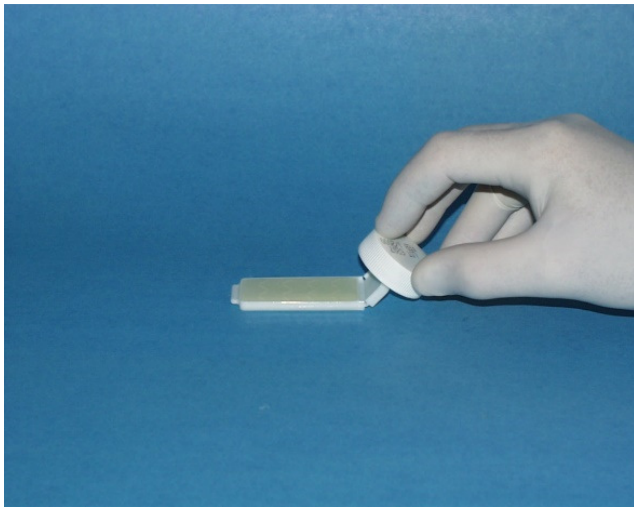
EM METHODS, CONTACT PLATE

- bioburden on a surface (55mm plate)
- cleanroom surface
- personnel contact print
- open plate, contact and clean



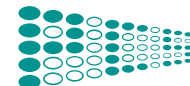
SURFACE MONITORING CONTACT PLATES OR SLIDES

- Easy to use
- Neutralising agents may be included in the media
- Strips have some flexibility
- Media residues need to be removed.



SURFACE MONITORING SWABS

- Useful for equipment and irregular areas
- From cotton swabs, at best recoveries are 20%
- Calcium alginate varieties can be dissolved and plated.



ENVIRONMENTAL MONITORING SPECIFICATION FOR VIABLE COUNTS

Recommended limits for microbiological monitoring of clean areas during operation.

Recommended limits for microbial contamination (a)

Notes

(a) These are average values.

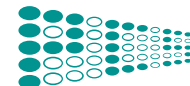
(b) Individual settle plates may be exposed for less than 4 hours

Grade	Air sample cfu/m ³	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
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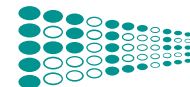
ENVIRONMENTAL MONITORING – IDENTIFICATION OF ISOLATES

- 90% of all clean room isolates will be identified as (in order of prevalence):
 - *Staphylococcus* (human)
 - *Micrococcus* (human, dust, air)
 - *Coryneforms* (human)
 - *Bacillus* (survivors of disinfection)
 - *Yeast and moulds* (human, dust, air)
 - *Streptococcus, propionibacterium* (human)



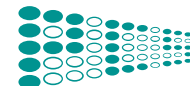
ENVIRONMENTAL MONITORING – IDENTIFICATION OF ISOLATES

- How far to go?
- Initially at start up, characterise all isolates to at least genus level
- However, be pragmatic – don't identify every colony; select and group on the basis of colonial morphology
- There should not be more than 10 or, at the most, 15 different types



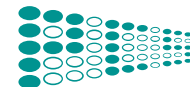
ENVIRONMENTAL MONITORING – IDENTIFICATION OF ISOLATES

- How far to go?
- Thereafter, use colony morphology to monitor changes in the cleanroom flora
- Identify any newcomers to at least genus level
- Evaluate the significance of the newcomer!
- Is it a transient or does it represent an issue?



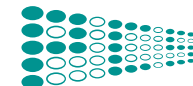
ENVIRONMENTAL MONITORING – SIGNIFICANCE OF NEW ISOLATES

- *Pseudomonas spp* : disinfection, water
- *Enterobacteriaceae spp* : water/training
- *Staphylococcus* : personnel
- *Micrococcus* : personnel
- *Corynebacterium* : personnel
- *Streptococcus* (human) : personnel training
- *Bacillus* : sterilisation/disinfection



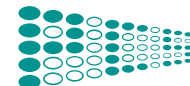
ENVIRONMENTAL MONITORING – IDENTIFICATION OF ISOLATES

- How far to go?
- Media fill failures establish a link with an operator
- Sterility failures to assure (most probable) cause of failure
 - Be aware that the likelihood to miss a bug with EM, is quite high. Meaning that it has happened quite often (in my work-experience) that EM is ok, while batch failed in sterility



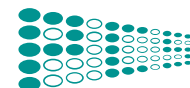
ENVIRONMENTAL MONITORING FOR PRODUCT RELEASE

- Annex 1 Guide to GMP
- FDA Aseptic Processing Guide
- EM data is reviewed prior to releasing the batch
- It is part of the Sterility Assurance Programme



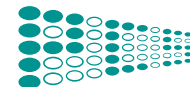
ENVIRONMENTAL MONITORING HOUSE FLORA...

- Determination of typical house flora is a requirement
- House flora profile continuously under review (annually!)
- House flora used to validate disinfectants, sterility test and medium fertility testing
- House flora should be based on the most typically recovered organisms from the site
- Representatives of each microbial type should be selected (e.g. Gram +ve, Gram –ve, spore former, mould, yeast)



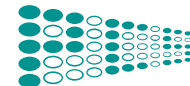
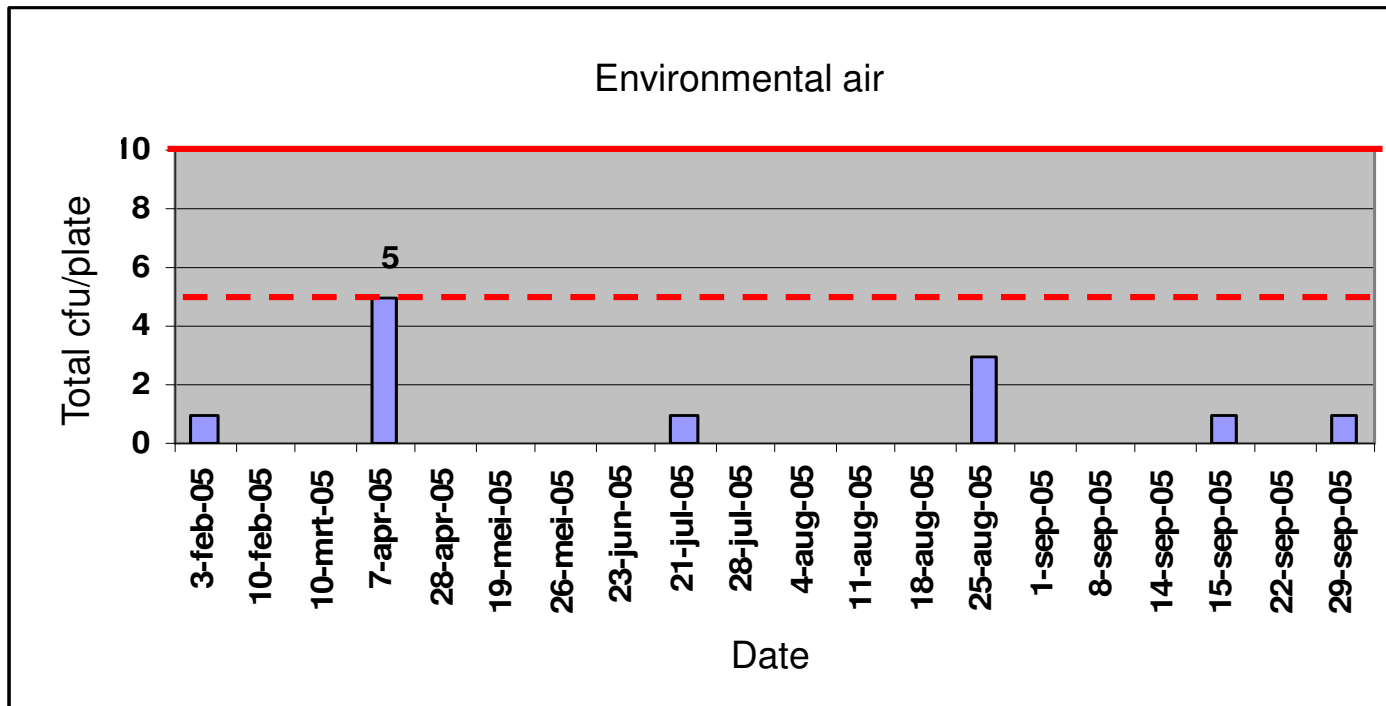
ENVIRONMENTAL MONITORING TREND REPORTING

- It is an essential control tool
- Ideally product contamination can be prevented by timely intervention
- OOT (Out of Trend) to be considered



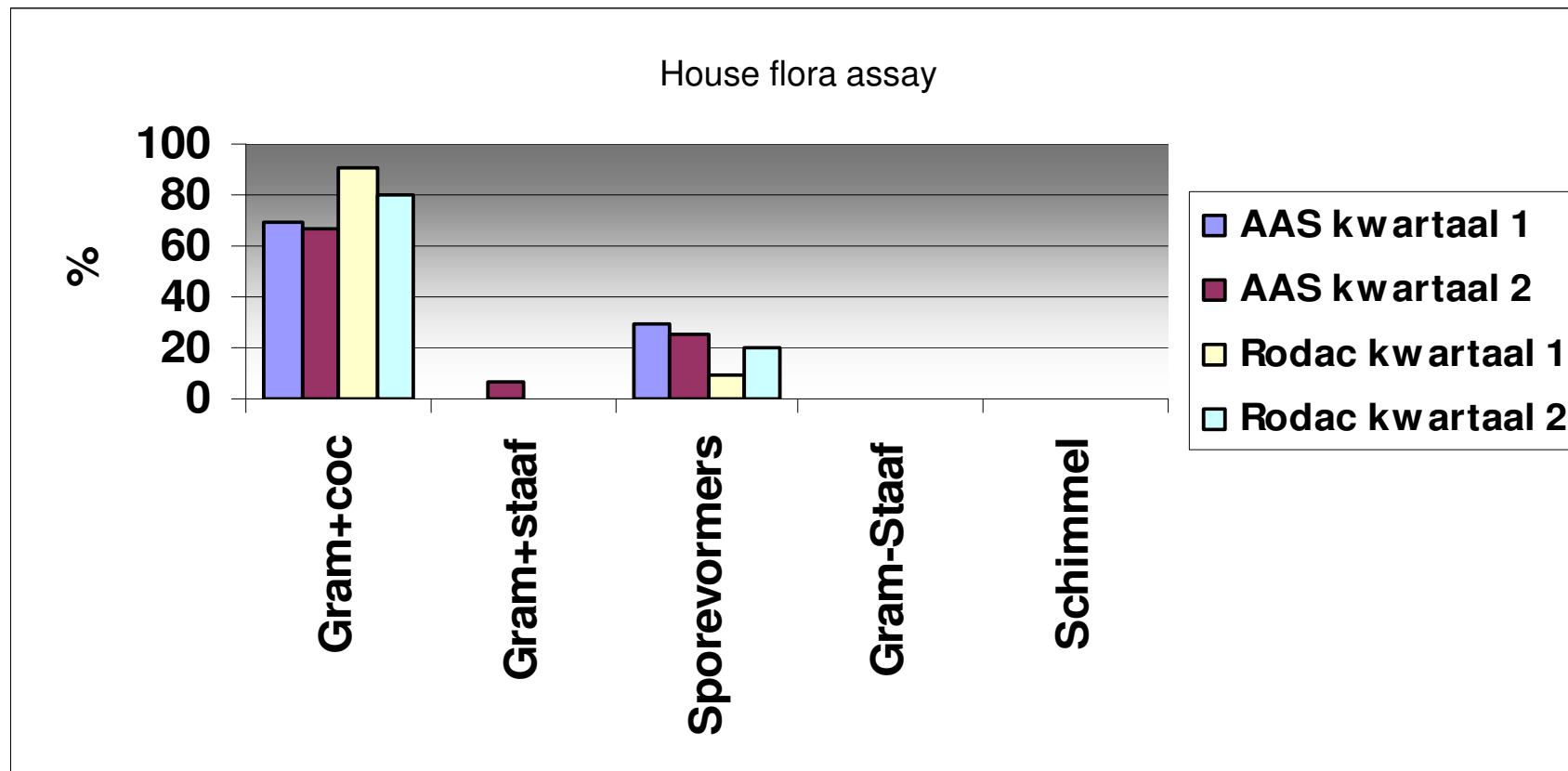
ROUTINE EM PROGRAMS

- Example trend graph class B area
 - 5 cfu/plate = alert limit
 - 10 cfu/plate = action limit



ROUTINE EM PROGRAM

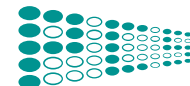
- Example trend graph house flora



ENVIRONMENTAL MONITORING

OOI INVESTIGATION/ACTIONS

- Evaluation of the impact on the product
- Typical scenarios:
 - Operator finger dabs 6 cfu left hand (Class B: 5 is Limit)
 - 6 cfu on settle plate at the point of fill (Class A: <1 is Limit)
 - 20 cfu on a contact plate from floor of Class B zone!
 - 1 cfu/m³ Class A zone



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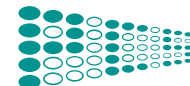
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ENVIRONMENTAL MONITORING OOL INVESTIGATION/ACTIONS

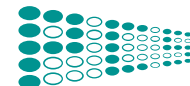
- Above the Evaluation on product impact:
 - The cause needs to be identified
 - A corrective action plan must be made and implemented to prevent re-occurrence



ENVIRONMENTAL MONITORING

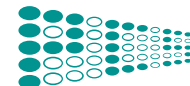
MANAGING OOL DATA

- Expectations for when an action limit is exceeded:
 - It does not necessarily mean you have to reject the batch!
 - It does mean that you will have to justify release on the basis of a thorough OOL investigation



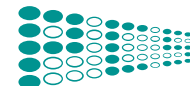
ENVIRONMENTAL MONITORING OOL INVESTIGATION/ACTIONS

- When an action limit is exceeded:
 - Do NOT perform additional cleaning and monitoring, without proper justification
 - Do review Room Air and HVAC system
 - Do review data for facility surfaces
 - Do review data for personnel gowning
 - Do (deep investigation)
 - Do evaluate the impact on the product

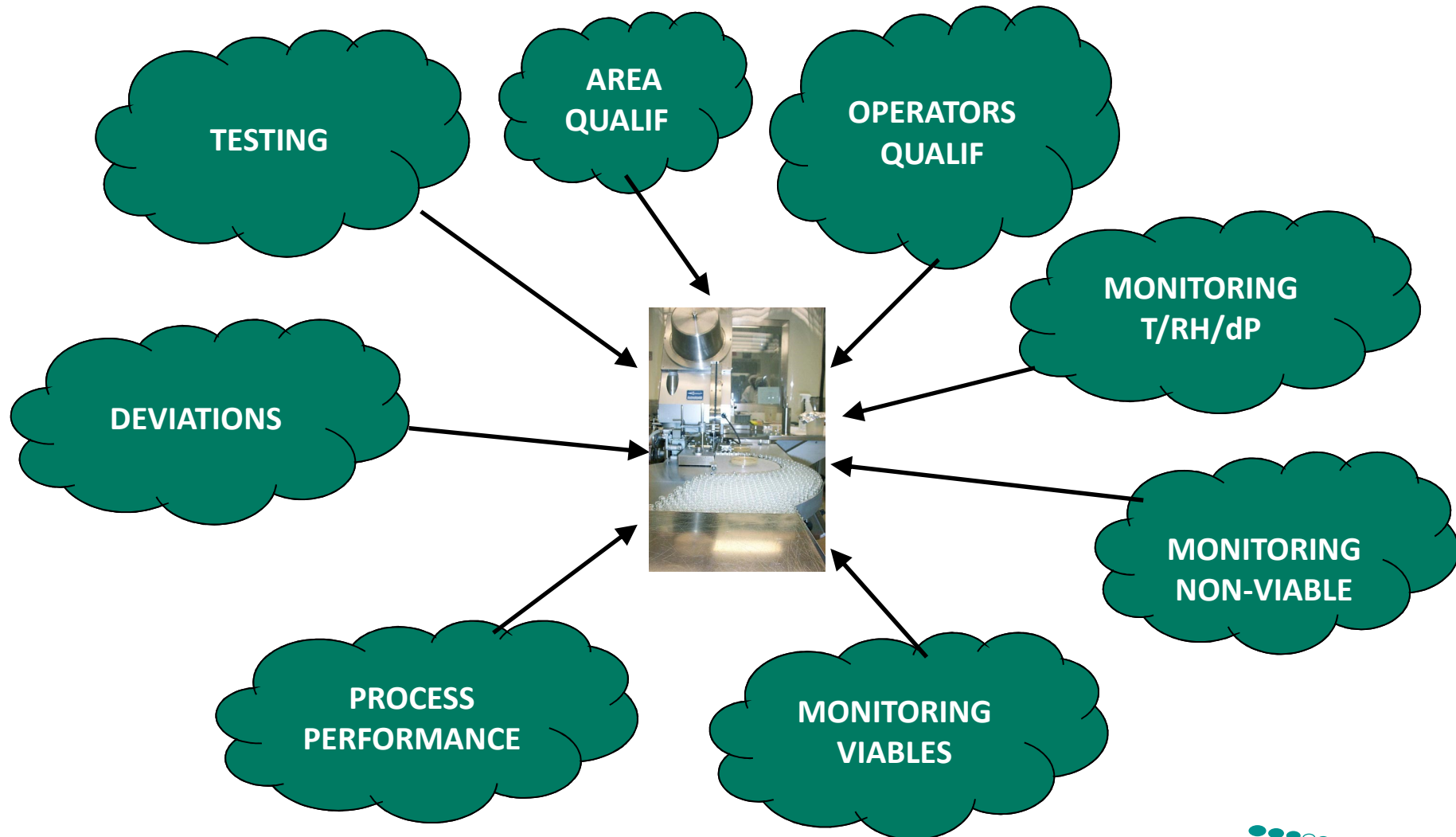


IN CONCLUSION

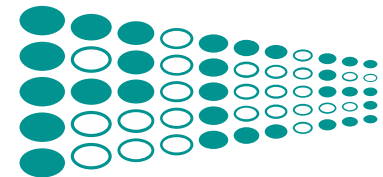
- EM positions and frequency to be determined by thorough analysis (SME's) of room/room-activity, position of HVAC in/outlets, doors, etc., as well as by guidelines.
- Consider at all time that EM is prone to “false negatives”
- EM is an important attribute for SAL, however many others are as well.



MINDMAPPING



**THANK YOU FOR
YOUR ATTENTION**



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