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# Environmental & Process Monitoring

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**2023 Annex 1 Workshop Series (Singapore)**



## Discussions on…

**Annex 1-Section 9.0**: Environmental & Process Monitoring

**Concepts & Critical Considerations**

# Annex 1-Section 9.0:
## Environmental & Process Monitoring

This section differs from guidance given in section 4(Premises) in that the guidance here applies to ***ongoing routine monitoring*** regarding the ***design of systems*** and ***setting of action limits, alert levels*** and reviewing trend data.

The section also gives guidance on the requirements of Aseptic Process Simulations (APS).





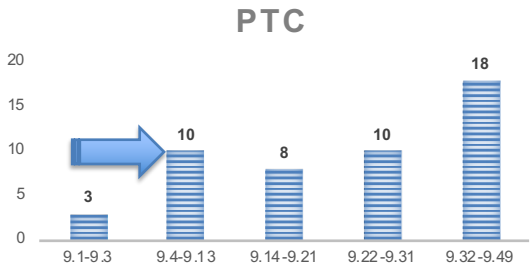
## Section 9: Environmental & process monitoring

**SUMMARY of SECTION**

| Sub-Section | Sub-topic | Theme |
|---|---|---|
| 9.1-9.3 | **General** | Overall **CCS-controls**; limitations of the reliability of viable, non-viable and APS (monitoring) systems when taken in isolation to be an indicator of asepsis, but to be together for the results to help confirm the **reliability of the design, validation and operation of the system that they are monitoring.** |
| 9.4-9.13 | **Environmental and process monitoring** | Assurance of **aptness of environment** and detection of **excursions** from **limits**, triggering investigations and risk assessment to product quality; Extensive details of **Risk Assessment** for unit operations, RA of EM Programs, **reliability**, justification of locations, justification of **levels** from the summation of data from area qualification data and regular trending, defines **approach to trends**, varying action limits based on activities and the associated risks for **Grades C and D**. |
| 9.14-9.21 | Environmental monitoring – **total particle** | Requirement of **continuous monitoring**, selection of the monitoring systems and its associated risks, justification of sample volumes |
| 9.22-9.31 | Environmental and personnel monitoring – **viable particle** | **Justification** for sampling methods, time of sampling, areas for sampling including non-operational areas, observations of aseptic operations, alternative monitoring systems, understanding technology, operation and interpretation of results, identification of microbes detected in all grades (**A + B to species level**) while those from Grades C + D based on what their appearance indicates (**loss of control, deterioration in cleanliness, or difficult to control-moulds/spore formers**) |
| 9.32-9.49 | Aseptic process simulation (**APS**) (also known as media fill) | The effectiveness of APS being determined through process design, adherence to the pharmaceutical quality system and process controls, training, and evaluation of monitoring data; "end of production or campaign APS" as additional assurance or for investigative purposes; all and more data of the APS process. |

## Section 9: Environmental & Process Monitoring

*Going Beyond monitoring using microbiological plates & testing?*




**Y=f(x)**

**Design:**

**Assurance:**

**Risks to Quality:**






**TOTAL PARTICLES** EMP

**VIABLE PARTICLES** EMP & PeMo

**TEMP, RH & SPECIFIC CHARACTERISTICS**

**APS**

- Facility & Area
- People – Numbers, Gowns, Gloves, Goggles
- Material handling & containment
- Accessories - storage, use and disposal
- Process of material transfer & manufacturing
- Aseptic Process Simulation

**Y=f**

**Design: Facility, Equipment, Process, People**

**Assurance: Qualified & Validated with ongoing verification**

**Risks to Quality: Microbial & Particle contamination**

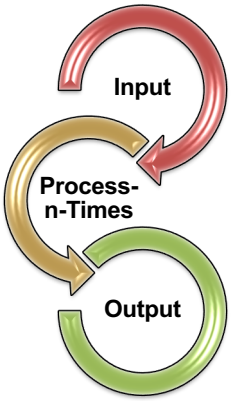
# RISK ASSESSMENT

PROCESS CONTROL/MONITORING CONSIDERATION

- Facility, Manufacturing process & Bioburden control
- **Facility**-Change Rooms & Airlocks
- **Quality of Utilities -** Air, Gas, Water
- **Material transfer & controls** (Airlocks, Containers, closures, product)
- **Equipment handling, material wrapping & sterilization**
- **People behaviour** to contain contamination
- **Cleaning, Disinfection of surfaces, Hold Times** (Facility, Equipment & People)
- **Gowning & De-gowning**
- **Environmental Monitoring & isolated Flora**
- **Testing and reporting Practices**
- **Maintenance Management**
- **Vendor Management Practices**

**Concept**

**Y=f(x)**








## Section 9.9 & 9.11: APPROACH TO TRENDING (1)

*Data collection-collation & trend analysis*

**Concept**

**Y=f(x)**

Environmental Monitoring Procedures should define the **approach to trending** (Grade A-B & Grades C-D). Trends should include but not limited to …

**4.31.** The microbial contamination level of the cleanrooms should be determined as part of the **cleanroom qualification**. The number of sampling locations should be based on a documented **risk assessment** and the **results obtained** from **room classification, air visualization studies** and **knowledge of the process** and **operations** to be performed in the area. The maximum limits for microbial contamination **during qualification** for each grade are given in Table 2. Qualification should include both "**at rest**" and "**in operation**" states.

Table 2: Maximum permitted microbial contamination level during qualification

| Grade | Air sample CFU/m3 | Settle plates (diameter 90 mm) CFU/4 hours (a) | Contact plates (diameter 55 mm) CFU/plate |
|---|---|---|---|
| A | No growth | | |
| B | 10 | 5 | 5 |
| C | 100 | 50 | 25 |
| D | 200 | 100 | 50 |

(a) Settle plates should be exposed for the duration of operations and changed as required after a maximum of 4 hours. **Exposure time should be based on recovery studies and should not allow desiccation of the media used.**

Note 1: All methods indicated for a specific grade in the table should be used for qualifying the area of that specific grade. If one of the methods tabulated is not used, or alternative methods are used, the approach taken should be appropriately justified.

Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.

Note 3: For the qualification of personnel gowning, the limits given for contact plates and glove prints in Table 6 should apply.

Note 4: Sampling methods should not pose a risk of contamination to the manufacturing operations.

## Section 9.11: APPROACH TO TRENDING (2)
*Data collection-collation & trend analysis*

**Concept**
**Y=f(x)**

9.11 (i) Increasing number of ***excursions*** from Action Limits or Alert Levels, ***per area***

9.11 (ii) ***Consecutive*** excursions from Alert levels

9.11 (iii) ***Regular but isolated*** excursions from action levels that have a ***common cause*** (example: excursions following **Planned PrMa**)

9.11 (iv) ***Changes in microbial flora*** (#, predominance of spore formers/molds)

9.26 Manual operations- ***Increased PeMo*** (specially gowns)

9.27 Where monitoring is routinely performed by manufacturing personnel, this should be subject to regular **oversight by the quality unit**

*(8.19- cross ref. Aseptic ops, including APS should be observed on a regular basis by personnel with specific expertise in AP to verify correctness of ops, incldg Op. behavior in the cleanroom and address inappropriate practices if detected)*

10.10 ***EM data*** and ***trend data*** generated for classified areas should be reviewed as part of product batch certification/release. A ***written procedure*** should be available that describes the actions to be taken when data from environmental monitoring are found ***out of trend*** or exceeding the established limits. For products with short shelf life, the environmental data for the time of manufacture ***may not be available***; in these cases, the compliance should include a review of the **most recent available data**. Manufacturers of these products should consider the use of **rapid/alternative methods**.





## APPROACH TO TRENDING (3)
*Data collection-collation & trend analysis*

**Examples**

**Concept**
**Y=f(x)**

Process Monitoring Procedures:

- Area qualification (*At rest vs In Operations-Regular operations*)
- Equipment qualification data - critical operation data *& alarms?*
- All Unit Operations & controls (Section 8)
- Operational area upkeep
- Non-operational area upkeep
- Effectiveness of the APS should be determined

1. *Define clean-up time* (at rest; in unmanned state and revert after completion of operations)
2. *Particle monitoring in Grade A*- Assembly to end of operations, for ≥ 0.5 and ≥ 5 $\mu$m with a flowrate of atleast 28.3 L/min
   - *so that all interventions, transient events and any system deterioration is captured.*
3. Each individual sample result – *correlated frequently* to alert-action levels
4. *Alarms, response to alarms and additional monitoring during excursions.*
5. *APS*- process design, adherence to the pharmaceutical quality system, process controls, training, and evaluation of monitoring data.

# Final Frontier

| Reference | Topic | Requirement |
|---|---|---|
| 8.7 | **Aseptic preparation and processing** | • The aseptic process should be **clearly** defined.<br>• The **risks** associated with the aseptic process, and any associated requirements, should be **identified**, **assessed** and appropriately **controlled**.<br>• The site's **CCS** should clearly define the **acceptance criteria** for these **controls**, requirements for **monitoring** and the **review** of their effectiveness.<br>• **Methods and procedures** to control these risks should be **described** and **implemented**.<br>• **Accepted residual risks** should be **formally** documented. |





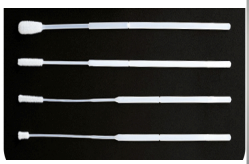

# Expectations of Annex 1: Section 9

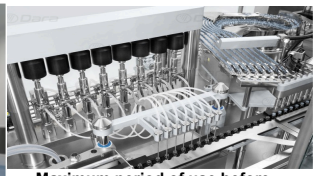
**CHECK**
**(DESIGN)**

**REVIEW**
**(ASSURANCE)**

**ASSESS**
**(RISK TO QUALITY)**

**Locations, reaction to cleaning/Disinfection practices, frequency, length of monitoring, sampling procedure, sample handling, incubation, data analysis, investigation-triggers, execution responsibilities.**





**Maximum period of use before replacement during a shift to be spelt in qualification and proven through validation.**

**Sufficient appropriate personnel, suitably qualified, trained and experienced**

**Trends and Review**

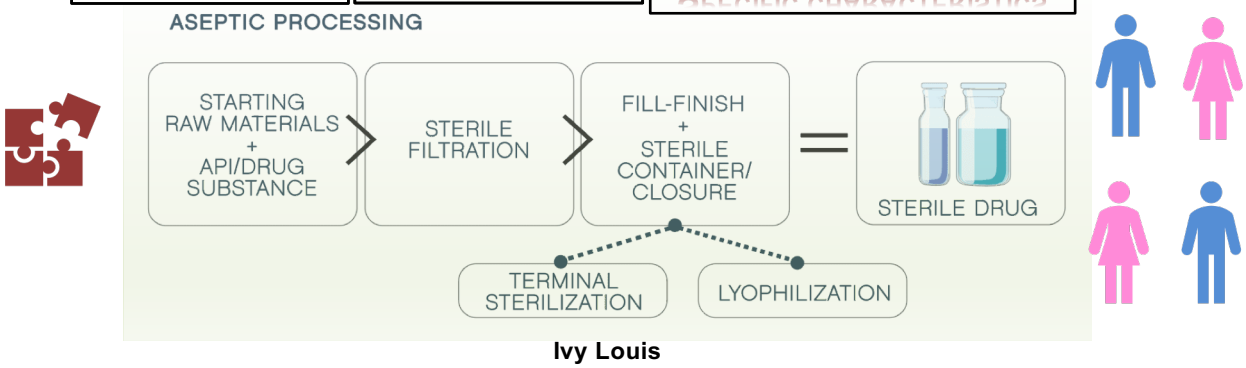
Summary:

**TOTAL PARTICLES** EMP

**VIABLE PARTICLES** EMP & PeMo

**TEMP, RH & SPECIFIC CHARACTERISTICS**

**APS**

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$Y = f(x)$