



Medial fills & Environmental monitoring

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The beginning

- Where do I start ?
- The regulations, guidelines and reference documents
- And there are many !!!
- Which one first?

References

- PE 009-8 Guide to good manufacturing practices
- PE 009-8 Annex 1 Manufacture of sterile medicinal products
- PI 007-6 Validation of Aseptic Practices
- ISO 14644 series Cleanrooms and associated controlled environments
- ISO 13408 Aseptic processing of healthcare products
- FDA guidance for industry Sterile drug products produced by Aseptic processing – Current Good Manufacturing practice

References

- <1116> Microbiological evaluation of clean rooms and other controlled environments
- PDA Technical report No.44 Quality risk management for aseptic process
- PDA Technical report No.13 (revised) Fundamentals of an Environmental monitoring program
- PDA Technical report No.35 A proposed Training Model for the Microbiological Function in the Pharmaceutical Industry
- PDA Technical report No.22 (Revised –draft) Process Simulation for Aseptically filled products

References

- PI 032-2 GMP ANNEX 1 REVISION 2008,
INTERPRETATION OF MOST IMPORTANT CHANGES FOR
THE MANUFACTURE OF STERILE MEDICINAL
PRODUCTS

• And lots more

Annex 1

PRINCIPLE

The manufacture of sterile products is subject to special requirements in order to minimise risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

Note: This guidance does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces, etc. Reference should be made to other documents such as the EN/ISO Standards.

Annex 1

Grade	Maximum permitted number of particles/m ³ equal to or greater than the tabulated size			
	At rest		In operation	
	0.5µm	5.0µm	0.5µm	5.0µm
A	3,520	20	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	not defined	not defined

Annex 1

	Recommended limits for microbial contamination ^(a)			
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
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Annex 1

18. Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitisation.

Annex 1

20. 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.

Annex 1

69. The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following should apply:
- When filling fewer than 5000 units, no contaminated units should be detected.
 - When filling 5,000 to 10,000 units:
 - a) One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill;
 - b) Two (2) contaminated units are considered cause for revalidation, following investigation.
 - When filling more than 10,000 units:
 - a) One (1) contaminated unit should result in an investigation;
 - b) Two (2) contaminated units are considered cause for revalidation, following investigation¹.

Annex 1

- 68. Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice a year per shift and process.
- 71. Care should be taken that any validation does not compromise the processes.

Other documents

- More details and facts to document
- And train
- And follow up
- And review
- And so on !

What next

So where to now ?

You have all the information !

(or do you ?)

What next

You have the start.

So what next ?

What next

Key elements

- New or existing facility the activity is the same (almost !)
- you have history with existing facility, and legacies (challenges)

Key information

- Understand your processes and facility.
- Map the process and understand how it works
- Map the process and understand the challenges to aseptic manufacture

Key information

Let's call the challenges:

RISKS !

Key information

- Understand your processes and facility.
- Map the process and understand how it works
- Map the process and understand the challenges to aseptic manufacture

(Just in case you missed it the first time)

Developing the knowledge

Knowledge will come from:

QC

QA

Validation

Manufacturing

Product development

Engineers

Other groups and importantly

OPERATORS AND LINE MANAGEMENT

Developing the knowledge

Only if you ask !

Now document it !

Information

- Validation/revalidation documentation
- Previous testing
- Data
- OOS's
- Deviations
- Investigations
- People
- Review

Developing the knowledge

- Environmental monitoring is not just about the single result
- Trending is the key
- Establishing limits: Reference & guidance documents
- Trending: driven by procedures
- People need to understand fundamentals
- Knowledge is the key

Understanding

Process

Performance:

facility,
personnel,
systems

Trends: Results and EM flora

Robust monitoring system

- Media fills: Designing and executing
- Environmental monitoring
- What needs to be monitored:
Environment, equipment, personnel
- When to monitor ?
- How to monitor? Viable and Non viable
- Understanding the risks points. (as well as compliance)

Documentation & Training

- Procedures
- Personnel training
- Understanding the limitations of the monitoring process
- Investigations/CAPA and Periodic reviews
- Change management: facility and process impact review

Target

- Control the facility and the people that run it
- Effective media fill and EM program
- Appropriate sampling points & frequency
- Appropriate monitoring techniques using suitable equipment and training personnel
- Ability to review, and improve
- **PRODUCT QUALITY ASSURED.**

Target

PI 007-6: VALIDATION OF ASEPTIC PROCESSES

- 2.3.7 It is the sum total of all validation data that provides the necessary level of assurance for aseptically produced products.

Nearly there

- QRM Environmental monitoring
- Be careful when using risk assessment to justify current locations.
- Risk assessment should be used to identify the most appropriate locations, (critical areas) what activities and when should it be undertaken

Key information

- Understand your processes and facility.
- Map the process and understand how it works
- Map the process and understand the challenges to aseptic manufacture

(Now you have seen it 3 times. Validated???)

Two to go

- Knowing what your neighbour is doing is nice but remember
- You have your own unique designs, age, practices, machines, people, products, etc.
- These need to be understood, assessed managed and appropriately monitored.

Last one & Last time

- Understand your processes and facility.
- Map the process and understand how it works
- Map the process and understand the challenges to aseptic manufacture
- AND then monitor the process, in the frequency and in the locations that you have assessed as being appropriate