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# ANNEX 1 REVISION

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IMB Information Day. 23<sup>rd</sup> October 2008

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Acting Executive Inspector

# CHANGES TO ANNEX 1

- Review Period – Nov. 05 - Dec. 2007
- Published 14<sup>th</sup> Feb 2008
- Date for coming into operation  
01<sup>st</sup> March 2009

Provision for capping  
01<sup>st</sup> March 2010



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# 4 – 7 'Cleanroom and Clean Air Device Classification'

- Classification – EN ISO 14644-1
- Grade A  $\geq 5\mu\text{m}$  particle size – 20 (at rest & in operation)
- Sample volume  $1\text{m}^3$  / Location
- Classification
  - Grade A - ISO 4.8
  - Grade B - ISO 5
  - Grade C - ISO 7 & 8
  - Grade D - ISO 8



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# 4 – 7 'Cleanroom and Clean Air Device Classification'

- Use of portable particle counters with short length sample tubing
- Isokinetic Sample heads - unidirectional airflow units
- In operation classification



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# 'Cleanroom and Clean Air Device Classification' - Expectations

- Classification in accordance with ISO EN 14644-1 – vendor certification
- Correct sample volume?  
1m<sup>3</sup> / location
- Number of locations?  
Based on criteria specified in ISO standard



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# 'Cleanroom and Clean Air Device Classification' - Expectations

- Certification of portable particle counters utilised for classification.
- Length of sample tubing appropriate
- For unidirectional airflow – use of Isokinetic sample head
- Demonstration of In Operation Classification



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# 8 – 13 & 15 'Cleanroom and Clean Air Device Monitoring'

- Risk based approach to identify locations for monitoring
- Frequency & sample size:
  - Grade A  
Full duration of the critical process  
Including the set-up
  - Grade B  
Similar system recommended as grade A. Frequency may be decreased
  - Grades C & D  
Quality risk management approach



# 8 – 13 & 15 'Cleanroom and Clean Air Device Monitoring'

- Types of particle monitoring systems
  - Independent Particle counters
  - Network of sampling points
  - Combination of the above
- Remote systems  
Length of tubing and radii of bends
- Sample size – Function of sample rate of system used  
Need not be same as that for classification
- Significance -  $\geq 5\mu\text{m}$  particle



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# 'Cleanroom and Clean Air Device Monitoring' - Expectations

- Locations for routine monitoring  
Documented Risk assessment.

Consider for example:

- Results from classification / requalification
  - Trend data – viable and non-viable
  - Changes to process / personnel flow
  - Micro & Production involvement in review
- Alarms set for counts  $\geq$  alert limits for Grade A & B
  - Monitoring Grade A – capture all interventions, transient events and any deterioration of the air handling system



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# 'Cleanroom and Clean Air Device Monitoring' - Expectations

- Type of Particle Monitoring system – Take account of risk presented by materials used in operation
- Length / Orientation sample tubing – prove ability to detect particulates
- Handling of Alerts / Actions
- Investigation - Comprehensive
  - E.g. Previous requalification, HEPA integrity test results, trend data – viable / non-viable, personnel monitoring trends, Equipment PM, Asepsis – during set up and operation



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# 'Cleanroom and Clean Air Device Monitoring' - Expectations

- 'At Rest' monitoring  
Appropriate justification for frequency.  
Compliance with limits.
- Monitoring Grade B  
Justification for approach
- Monitoring C & D  
Dependant on operations. Justification.



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# 69 – 'Processing'

- Process Simulation test limits amended
  - <5,000 units filled – no contaminated units
  - 5,000 – 10,000
    - 1 contaminated unit  
(Investigate, consider repeat)
    - 2 contaminated units  
(Investigate, revalidate)
  - >10,000 (as per 5,000 – 10,000)
  - Gross failures



# 80 – 'Processing'

- Bioburden Testing
  - Aseptically filled – Each batch
  - Terminally Sterilised products
    - Each batch
    - Overkill parameters – scheduled intervals – appropriate justification
    - Parametric Release – In-process test performed on each batch
- Endotoxin monitoring



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- Partially stoppered freeze dried vials in Grade A until stopper fully inserted
- Vial Capping
  - Relates to units not terminally sterilised
  - Container closure not integral till aluminium cap is crimped
  - Separate location for capping station
  - Aseptic process - Grade A /B
  - Clean process - Grade A air supply
  - Reject vials with missing or displaced stoppers
  - Technology used to prevent direct contact
  - Use of RABs or Isolators



# Finishing of Sterile Products - Expectations

- Scenario A - Aseptic process
  - Grade A with B background
  - Capping station location separate to critical zone
    - minimise potential for contamination
    - Adequate air extraction
  - Component hoppers and equipment sterile. Aluminium seals sterile.



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# 'Finishing of Sterile Products - Expectations

- Scenario B - 'Clean' Process
  - Grade A air supply – Qualification / monitoring
  - System for detection of displaced stoppers  
Min. acceptance criteria? Appropriate justification?  
Use of raised stopper detectors? Qualification?
  - Technology utilised to minimise direct contact with vials and the potential for microbial contamination



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THANK YOU

