Aseptic Manufacturing
Recurring Deficiencies

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Inspections

• As of 2009
  - 85 Human MIAs
  - 25 Veterinary MIAs
  - 50 IMP Authorisations

• 2008 to 2009 – 209 GMP inspections
• 53 – Inspections of sterile manufacturers
Review of Critical & Major Deficiencies

- Investigation / deviation handling
- PQRs
- Autoclave Controls and Terminal sterilisation
- Asepsis / aseptic behaviour
- Garbing for Grade A / B
- Environmental Monitoring
- Visual Inspection
Areas with recurring Major Deficiencies:

- Asepsis / aseptic behaviour
- Garbing for Grade A / B
- Environmental Monitoring
Aseptic Manufacturing

Scope:

- IMB Expectations
- Best Practice
- Examples of Deficiencies
Garbing for Grade A/B areas

- **Main aim of procedure**
  - Minimise the potential impact to the Product / Area(s)

- **SOP**
  - Adequate detail
  - No outdoor clothing permitted – underwear acceptable!
  - Include use of Pictures / Video
  - System of disqualification
Garbing for Grade A/B areas

• Procedure
  - Initial pair of gloves
  - Hood – Integrity / obvious rips/tears
  - Face mask – securely fastened
  - Suit - Integrity / Obvious rips / tears
  - Boots - Integrity / Obvious rips / tears
  - Visor/Goggles
  - Final pair of gloves
  - Visual inspection
• Procedure
  - Avoid touching of the outside of the clean-room garb
  - Avoid touching floor with garb
  - Visually check garb for obvious rips or tears – Entry & Exit
  - Touch only extremities or inside of garb
  - Use Disinfectant during every step of the process
  - In case of error – Start Again
Garbing for Grade A/B areas

• Initial Qualification
  - SOP Training
  - Theory + Assessment
    e.g. Basic Microbiology
    Cleanroom Behaviour
  - Practical Training
Garbing for Grade A/B

Initial Qualification cont’d

• Practical Training
  - Practice
  - Practical assessment X 3
  - Observational Assessment
  - Microbiological assessment
Garbing for Grade A/B

- Requalification
  - Training
  - SOP
  - Theory
  - Practical demonstration
  - Hot topics e.g. Review of results / trends to date
Garbing for Grade A/B

• Requalification Cont’d

- Practical assessment
- Observational Assessment
- Microbiological assessment
Garbing for Grade A/B

Ongoing assessment:

- Microbiological monitoring
- Peer review
- Operator Vigilance
- Requalification / reassessment
Garbing - Inspection

- Training in garbing procedures
- Demonstration of garbing by qualified personnel
• Minimise company presence during this demonstration – Inspector, Operator and Trainer

• If visibility into aseptic areas poor – Inspector will enter, but not into filling suites during filling operations
Garbing – Key Deficiencies encountered

- Inadequate training
- Excessive handling of Garb
- Poor technique
- Incorrect garb material (not particulate retaining)
- Outdoor clothing permitted in changing areas
- Garb not examined for obvious rips / tears
Garbing – Key Deficiencies encountered

- Observational assessment not considered as part of the acceptance criteria for garbing qualification / requalification
Environmental Monitoring

- SOP
  - Adequate detail
  - Map of area indicating sites
  - Frequency
  - At rest monitoring
- Correct limits – Annex 1
- Counts should not be averaged
Environmental Monitoring

- Recovery studies – exposure time
- Use of inactivating agents within media
- Investigation into Action limits
- System for handling Alert limits
- SOP for trend evaluation
Environmental Monitoring

- Basis for approach and sites monitored
  - Initial Qualification
  - PQ
  - Ongoing assessment – Trend evaluation
    - Holistic approach
    - Critical assessment
    - Living document
    - Corrective Actions
      e.g. increased monitoring of area / personnel
Environmental Monitoring

- Consider:
  - Do zero counts in Grade A mean EM program is functioning satisfactorily?
  - Do we need additional sites monitored?
  - Has anything changed in the process?
  - Do we need to observe the process and reconsider EM sites?
Environmental Monitoring

- **Consider:**
  - Is sanitisation programme adequate?
  - Are plates located too close to areas where IPA is sprayed?
  - Do personnel spray hands immediately before monitoring?
EM Programme - Inspection

- SOP – EM Programme
  Adequate detail, Monitoring sites clearly indicated, map of area, frequency

- Trend reports and Evaluation – incl. evaluation of EM programme

- SOP for handling alert and action limit results. Detailed investigations

- SOP for identification of isolates
Examples of Deficiencies

Environmental monitoring of the cleanrooms was deficient in that:

- The aseptic set up was not monitored for either viable or non-viable contaminants
- There was no continuous non-viable monitoring during filling
- The alert and action limits set for viable monitoring of classified areas was outside those specified in Annex 1.
- The critical zone where filling took place was not included as part of the viable monitoring programme
- There was no system in place for ongoing assessment of the adequacy of the environmental monitoring programme
- Viable Monitoring did not take place during the initial cell culture stages and during the aseptic sampling
Examples of Deficiencies

**Environmental monitoring and controls of the sterility testing suite and ancillary areas were deficient in that:**

- The specification of 1 cfu/2 hours for grade A areas was not consistent with Annex 1 of the EU GMPs.
- Non-viable particulate monitoring was not carried out as part of routine environmental monitoring.
- Counts from passive monitoring were permitted to be averaged.
- The trend assessment did not consider an holistic review of the data.
- With regards to viable environmental monitoring, no alert limits had been set.
- No action limits had been set for the grade C gown up room.
- The set-up and preparation carried out for sterility testing had not been incorporated as part of the environmental monitoring programme.
Examples of Deficiencies

- The mechanism for personnel monitoring presented a risk of contamination in that it was observed that further work was permitted to continue after the finger dabs and contact plates for the garb had been taken.
- Detergents and disinfectants had not been routinely monitored for microbial contamination.
- There was no requirement to identify all organisms isolated from the Grade A area.
- The grade B background in the sterility test suite was not included as part of the routine environmental monitoring carried out during sterility testing.
- The inhibitory effect of disinfectants had not been considered in relation to viable monitoring.
Examples of Deficiencies

- Rodac and settle plates were permitted to be stored in an inappropriate manner in the microbiology incubators i.e. stacked too high, unstable and completely sealed with parafilm

- The location of the incubator used for the incubation of BI test samples next to the sterility test suite was not considered an appropriate location with respect to the potential for cross contamination
Aseptic Training and Assessment

• Personnel – greatest potential risk

• Extensive training is required

• Ongoing monitoring of effectiveness of training

• Successful completion of process simulation does not imply operator is qualified to perform aseptic operations
Aseptic Training and Assessment

- Asepsis can only be assessed

Ongoing assessment
- Training, EM, Garbing, Process Simulations, Behaviour, Practices
- Operator and microbiologist involvement
Aseptic Training and Assessment

• Training
  - Basic microbiology
  - Clean room practices / behaviour
  - Aseptic technique
  - Practical demonstration of aseptic manipulations
  - Off line training e.g. within the laboratory
• Training Cont’d
  - Critically Assess operators performance of most critical / intricate / difficult to perform aseptic manipulations.
    Include Observational assessment
    Practical assessment
  - Gowning
  - Ongoing Vigilance
  - System of disqualification
Aseptic Training - Inspection

- Detailed training modules
- Defined criteria to be met
- Ongoing assessment of effectiveness of training
- Process simulations – part of assessment of training effectiveness
Examples of Deficiencies

The aseptic set-up and filling operations were considered deficient in that the following was noted:

- The closure and sealing of the bottles containing the sterile product was performed by hand
- The operator was observed removing the sterile cover from the filling nozzle by hand
- Items were observed to be thrown into the bin from a distance which was not considered appropriate clean room behaviour
- The manner in which the stoppers were seated into the bottles required manual placement. This was not considered appropriate for an aseptic operation.
- The manner in which the product was transferred from one container to the product hopper was not considered to be an aseptic operation as there was intimate contact between the operator and product
- Operators were observed pushing items down into the bin to make additional room for waste. This bin contained gloves and sleeves which had been exposed to agar during personnel monitoring
Aspects of asepsis were considered deficient in that:

- The following was identified during the observation of the aseptic set up:
  - The filling needles were not considered to have been handled in a manner conducive to an aseptic process.
  - As part of the aseptic set up, operators were required to manually pass filling needles from one side of the critical zone to the other. This required the operators to lean into and over the critical zone.
  - An operator was permitted to remain within the area after viable monitoring of gloved hands had taken place. There was no requirement to don a new set of gloves following monitoring.

Additional aspects of this deficiency also related to issues concerning:

- Environmental monitoring programme
- Gowning
- Premises and equipment
Examples of Deficiencies

During observation of the filling simulation performed in LAF X on the XXX the following was noted:

- The location of the table in the Grade B area was considered to be in too close a proximity to the LAF.
- The movement in the area was considered to be excessively erratic for good clean-room behaviour.
- The technician was observed to be leaning against and into the LAF unit where aseptic filling took place.
- The method of sanitisation of gloved hands was not consistent and in some cases not sufficient.
Examples of Deficiencies

Sterility test samples were noted that had been stored for 14 days prior to testing, thus impacting the site's ability to continually assess the aseptic filling processes in a timely manner.

The Company appeared to use the media fill process to assess bad practice e.g. up to 10 people in a filling room at any one time.

Not all of the appropriate detail was present in the training material, for example the process used for hand washing was not included, neither was the checking nor reporting of suit and glove damage during gowning, whilst in the aseptic area or on exiting the aseptic area.

During the transfer of trays of vials from the cart to the turntable, the operator was observed to pull the tray of vials close to his body and also to partially lean over the open and exposed vials.
Summary

- Ongoing / continuous assessment
- Critic all information and effectiveness of training and systems
- Ensure operators are vigilant (peer review and assessment is key)
- Robust training including practical and observational aspects
Thank you

Questions??