IRISH MEDICINES BOARD

Aseptic Process Validation

IMB GMP Information Seminar

27th September 2012

Gerard Sheridan,
Inspector

Overview

- Guidance
- Best Practices
- Common Deficiencies

IRISH MEDICINES BOARD

Aseptic Process Validation

=

Process Simulation (Media Fill)

?

IRISH MEDICINES BOARD

- A chain of linked activities

IRISH MEDICINES BOARD

Guidance

Annex 1

- Validation of aseptic processing should **include** a process simulation test using a nutrient medium (media fill)
- Imitate as closely as possible the routine aseptic manufacturing process
- Include all the critical subsequent manufacturing steps.
- Take into account various interventions known to occur during normal production as well as worst-case situations.

IRISH MEDICINES BOARD

Guidance

Annex 1

- Should be performed as initial validation with three consecutive satisfactory simulation tests per shift.
  - 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.

- The number of containers used for media fills should be sufficient to enable a valid evaluation. (Specific guidance given)

IRISH MEDICINES BOARD

Guidance

Annex 1

- For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated.

- Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

IRISH MEDICINES BOARD

Guidance

Annex 1

- No consolidated outline of sum total of validation of aseptic processing

  - Various sections include additional 'validation' requirements
  - E.g. It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle generating person, operation or machine to a zone of higher product risk.

IRISH MEDICINES BOARD

Guidance

PHARMACEUTICAL INSPECTION CONVENTION

PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 007-6
1 January 2011

RECOMMENDATION

ON THE

VALIDATION OF ASEPTIC PROCESSES

- Guidance beyond process simulations

IRISH MEDICINES BOARD

Guidance

PI 007

General Guidance

- Where filling takes place over extended periods, i.e. longer than 24 hours, the process simulation test should extend over the whole of the standard filling period. In order to prevent excessively high numbers of units being filled it is usually acceptable to just run the machine for a reasonable time, if the validity of the simulation is not diminished by this procedure.

- Inert gases will prevent the growth of aerobic microorganisms. Therefore for process simulations sterile filtered air should be used instead of inert gases, also for breaking vacuum

- General guidance on preparation of media

IRISH MEDICINES BOARD

Guidance

PI 007

Product Specific Guidance

- Liquid Products
  - Vial Products
  - Sterile Products in Plastic Containers
  - Ampoule Products
- Injectable Powder Products
- Suspension Products
- Freeze Dried (Lyophilised) Products

IRISH MEDICINES BOARD

Guidance

PI 007

Product Specific Guidance

Continued :

- Semi-Solid Products (e.g. sterile ointments)
- Clinical Trials Materials and Small Batch Size Products
- Biological and Biotechnology Products
- Sterile Bulk Pharmaceuticals

IRISH MEDICINES BOARD

Guidance

PI 007

Process Simulation Test Conditions

- Process simulation test should represent a "worst case" situation and include all manipulations and interventions likely to be represented during a shift.
  - Container size and line speed

- The fill volume of the containers should be sufficient to enable contact of all the container-closure seal surfaces when the container is inverted and also sufficient to allow the detection of microbial growth.

- Simulation tests should be performed on different days and hours during the week and not only at the beginning of a work day

IRISH MEDICINES BOARD

Guidance

PI 007

Other Requirements

- Selection of Growth Medium
- Incubation Conditions
- Reading of the Test
- Test Frequency
- Interpretation of Data

IRISH MEDICINES BOARD

Guidance

PI 007

Other Requirements

- Intervention Monitoring
  - Essential to include the various interventions known to occur during normal production runs, e.g. :
    - repair or replacement of needles / tubing,
    - replacement of on-line filters,
    - duration of stops on the line,
    - filling and manipulation of stoppers etc.

- The process simulation test should last long enough to accommodate all possible interventions and a "worst case scenario", which may include several unfavourable conditions which are occurring during routine processing.

IRISH MEDICINES BOARD

Guidance

PI 007

Beyond Process Simulation

IRISH MEDICINES BOARD

Guidance

PI 007

Beyond Process Simulation

Beside process simulation, validation of aseptic manufacturing includes, but is not limited to other important factors:

- Staff Training
- Container/Closure Integrity Testing
- Container/Closure Sterilisation
- Equipment Cleaning and Sterilisation

IRISH MEDICINES BOARD

Guidance

PI 007

Beyond Process Simulation

Continued :

- Disinfection
- Filter Validation
- Vent Filters
- Equipment Maintenance and Testing
- Sterility Test

IRISH MEDICINES BOARD

Guidance

PI 007

Beyond Process Simulation

- **Staff Training**
  - Special emphasis as people are potentially one of the main sources of microorganisms in the environment
  - Can't validate a person but can train them
  - Training encompasses:
    - basic microbiology,
    - good manufacturing practice principles,
    - hygiene (disinfection and sanitisation),
    - aseptic connections,
    - gowning procedures.

IRISH MEDICINES BOARD

Guidance

PI 007

Beyond Process Simulation

- **Container/Closure Integrity Testing**
  - Machine set-up is a critical factor
    - Relate to validated settings
- **Container/Closure Sterilisation**
- **Equipment Cleaning and Sterilisation**
  - Validation of sterilisation processes generally difficult
  - Focuses primarily on steam sterilisation

IRISH MEDICINES BOARD

Guidance

PI 007

Beyond Process Simulation

- **Disinfection**
  - Sporicidal agents should be used wherever possible but particularly for "spraying-in" components and equipment in aseptic areas.
  - The effectiveness of disinfectants and the minimum contact time on different surfaces should be validated.
- **Filter Validation**
  - Validation should include microbiological challenges to simulate "worst case" production conditions
  - Integrity test limits should be derived from the filter validation data

IRISH MEDICINES BOARD

Guidance

PI 007

Beyond Process Simulation

- **Vent Filters**
  - Less robust and more sensitive to pressure differentials during steam sterilisation
  - In practice fail the integrity test more frequently than product filters
- **Equipment Maintenance and Testing**
  - Aseptic holding and filling vessels should be subject to routine planned preventive maintenance
  - All vessels should be subject to regular leak testing (pressure hold or vacuum hold)

IRISH MEDICINES BOARD

Guidance

PI 007

Beyond Process Simulation

- Sterility Test

  - The sterility test can provide useful information on the validation status of aseptic process

    However;

Annex 1

  - The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned

IRISH MEDICINES BOARD

Best Practice

Sterility by Design ?

- Proactive approach
- Process mapping
  - All inputs with sterility impact
- Intervention mapping
  - Updated based on real experience
- Risk assessment / management

IRISH MEDICINES BOARD

An approach

Product Lifecycle Validation Sequence

Process mapping

Risk assessment

Identify, eliminate, reduce, mitigate, accept interventions

Procedures

Qualification of sanitisation and sterilisation

Filter validation

Smoke studies

Training

Monitoring

Parts, components hold studies

Gowning and personnel qualification

Facility and equipment qualification

Aseptic process simulations

Environmental monitoring

Sterility testing

Evaluation of interventions

Re-assessment

IRISH MEDICINES BOARD

Deficiencies

IRISH MEDICINES BOARD

Deficiencies

Media Fills / General

- Not all units filled during media fills were incubated.
- SOP 123 did not indicate that vials were to be re-inverted after the seven day incubation period.
- There was no reconciliation of the quantity of units inspected against the quantity incubated. Consequently, units which could not be accounted for could not be presumed to be positive for growth.
- SOP 123 did not define the circumstances under which media fills could be aborted or invalidated.

IRISH MEDICINES BOARD

Deficiencies

Media Fills / Process Simulation?

- Media fills did not proactively take into account the various interventions known to occur during normal production, as well as worst case situations.

- Interventions on filling nozzles were not simulated during media fills.

- Aseptic in process sampling for viscosity and water content was not simulated during media fills.

- Validation of aseptic processing was deficient in that media fills did not include a simulation of aseptic liquid manipulations relating to Component X, such as :
  - Aseptic addition to the homogenisation vessel,
  - Aseptic sampling from the vessel,
  - Aseptic transfer from the homogenisation vessel to stainless steel buckets,
  - Transfer of the filled buckets to the bulk vessel LAF,
  - Aseptic addition to the bulk vessel.

IRISH MEDICINES BOARD

Deficiencies

Media Fills / Personnel Qualification

- A list of personnel qualified through media fill participation, and the validity period of their qualification, was not maintained.
- The competence of individuals working in aseptic processing areas was not assessed through active participation in a media fill, prior to commencing routine work in the area.
- There was no requirement for individuals to be subject to routine requalification through active participation in media fills.
- There was no predefined minimum timeframe or predefined number and type of interventions which operators were required to perform, as part of qualification, during media fills.

IRISH MEDICINES BOARD

Deficiencies

Media Fills / Interventions

- There was no system of active control of the simulation of interventions by operators during media fills and further to this for those media fill records which were reviewed, simulation of interventions were observed to be primarily performed by a mechanic.

- The process simulation study for Process X was deficient in that interventions A and B had not been performed by all relevant personnel as required by the media fill protocol.

- The set-up connections, 0.2µm filtration and the aseptic addition of solids had not been observed/recorded and subject to critical assessment during media fill studies.

IRISH MEDICINES BOARD

Deficiencies

Media Fills / Failures

- In relation to the failure of Media Fill Batch 123, the assignable cause could not be substantiated in that:
  - There was no record of filled units being damaged prior to incubation.
  - The failure investigation report contained a statement with regard to an assignable cause for damage to units, which could not have been established retrospectively with regard to the detail in the associated batch manufacturing record.
  - A microbiology report, indicating that the number of positive units found and the nature of bacteria isolated could not be conclusively linked to leaking/damaged units, was not addressed in the overall failure investigation.

IRISH MEDICINES BOARD

Questions

IRISH MEDICINES BOARD