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Manufacture of Sterile Medicinal Products

Areas of Focus for GMP Inspections

GMP Information Day; 23rd October 2008.

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Inspector

Objectives

- Highlight areas frequently reviewed
- Examples of deficiencies
- Not a blueprint for next inspection!

Key:

- = General points
- = Areas of focus
- ❖ = Examples of deficiencies



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Objectives



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Deficiency Summary Report

Inspection Reference Number:	2008-000
Inspected Site:	GMP Compliant Sterile Manufacturer
Inspection Dates:	DD/MM/YYYY
References:	Manufacturer's Authorisation No. M00

I CRITICAL DEFICIENCIES

No critical deficiencies were identified during the course of this inspection.

II MAJOR DEFICIENCIES

No major deficiencies were identified during the course of this inspection.

III OTHER DEFICIENCIES

No other deficiencies were identified during the course of this inspection.

Quality Management

- **Deviations**
 - Adequacy of investigations
 - Appropriate conclusions?
 - Associated CAPA's
 - Timelines



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Quality Management

- **Change Control**
 - All changes captured?
 - Adequate assessment?
 - Impact on validated status
- ❖ The change control procedure did not apply to 'non-critical equipment'; however, 'non-critical equipment' was not defined within the procedure, and the method by which the criticality of equipment was assessed was not referenced.
- ❖ The significance of the modification on the equipment or process and the requirement / need to perform three media fills had not been formally assessed as part of the change control.



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Quality Management

- Risk Management
 - Annex 20 (ICH Q9)
 - Future Issue?
 - Objectivity
 - Inappropriate conclusions
- ❖ The Risk Analysis of the Sterility Assurance System at Company X was considered deficient in that:
 - Real data from the actual experiences (e.g. occurrence of certain failures) during the review period were not used to confirm or re-evaluate the hypothesis associated with various failure modes.
 - The hazards / failure modes associated with the visual inspection of units were not considered to have been sufficiently elaborated in that only the presence of leaking units was considered.
 - “Not following GMP” was considered too general as a reason for generation of a failure mode.



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Quality Management

- Deficiencies from a number of areas which have an overall impact on sterility assurance or have potential cumulative impact due to their systemic nature, in general, may be grouped together as a deficiency in relation to quality management.



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Personnel

- **Garbing**
 - Requirements for Inspectors
 - Selection of personnel to demonstrate garbing technique
- **Training**
 - Adequacy of training
 - Deficiencies against systems not against individuals



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Personnel

Garbing

- ❖ The method employed for garbing was considered to require excessive manipulation and touching of the outside of the garb.
- ❖ The controls in place for cleanroom garb and garbing for entry into the cleanrooms were inadequate in that:
 - During observation of a member of staff, who was garbing for entry into the cleanroom, the following issues which were considered to be inappropriate were identified:
 - The person touched the outside of the main body of the face mask, which was contrary to the training given.
 - The person touched the outside of the suit excessively.
 - The undergarment was observed touching the outside of the suit.
 - A person was observed reaching into the bin on the clean side of the changing area whilst fully garbed.



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Personnel

- ❖ The SOP for garbing did not specify that personnel inspect the garb for any obvious signs of holes or tears in the material.
- ❖ SOP 123 did not detail the procedure involved in transferring garb into the changing area.
- ❖ It was not specified in SOP 123, that personnel who had reached their expiry date for the requalification of garbing be removed from the authorized list and not be permitted entry into the cleanroom until satisfactory completion of a requalification.
- ❖ During the training of the inspectors, the garb was inspected. The level of holes and tears which were observed in the garb was considered to be inappropriate.
- ❖ The technical agreement with Contract Garb Company did not adequately detail the responsibilities of the vendor regarding inspection of the garb.



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Personnel

- ❖ Garbing for Grade A areas was non-compliant in that:
 - The final step involved selection and donning of elastic bands from a box of bands which were not monitored.
 - There was no disinfectant available during the garbing sequence.
 - The procedure did not refer to the step up box available for garbing.
 - The second step over bench was not disinfected prior to use.
 - The masks in use were not sterile.



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Personnel

- ❖ During observation of the garbing process the following was noted:
 - Excessive touching of the outside of the sterile garb with gloved hands as well as exposure of the outside surface of the garb to exposed skin surfaces
 - The procedure was not adequately detailed in its description of the garbing sequence
 - The garb was not considered to be appropriate for use within an aseptic process as it was not considered to be particulate retaining based on the type of stitch utilised on the seams.
 - The speed at which the garb was donned did not lend itself to good cleanroom or aseptic behaviour
 - Personnel were permitted to change the outer gloves and sleeves at or near the area where filling took place.



Personnel

Training / Adequacy

- ❖ The theoretical pressure (as derived from the steam tables) and actual pressure from the autoclave printout had been mixed up on the record for autoclave cycle number 1234. It was not clear if the person concerned fully understood the difference between the values.
- ❖ Training of manufacturing personnel only required the observation of aseptic powder additions and did not cover liquid manipulations.



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Personnel

- ❖ 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.
- ❖ Based on the observations arising from the review of the autoclave, ancillary equipment and service utilities, and discussion of relevant associated procedures, it was considered that the level of qualification, training and familiarity of relevant personnel relating to the scientific principles and practical application of terminal sterilisation was not adequate.



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Personnel

❖ Training was deficient in that:

- A cleanroom operative had been trained in 30 SOPs to the level of “read and understand” on DD/MM/YYYY. This was considered to be excessive.
- The training SOP did not specify requirements for training of personnel who may be off site for extended periods of time
- The training SOP did not specify the requirements for assessment evaluation by the trainer.
- The list of ‘Mandatory’ SOPs for a cleanroom operative, listed on appendix 2 of SOP 123, did not match the list of SOPs listed in the training matrix for a cleanroom operative.
- A cleanroom operative had not been trained in SOP 123 as required by SOP 234.



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Personnel

- ❖ Operators were not required to be trained in basic microbiology
- ❖ The training provided with respect to cleanroom behaviour and asepsis was not sufficiently detailed (did not provide sufficient detail to operators to understand the purpose behind the requirements).
- ❖ An employee with an eye infection was present in the Grade C area on DD/MM/YYYY.



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Personnel

Typical company response to a deficiency or assignable cause for a deviation often is:

“Human Error: The personnel involved have been retrained.”

- Missing the point?
- Fault within quality system?
- Adequacy of initial training?
- Work properly supervised or checked?



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Documentation

- High number of deficiencies
 - Access to procedures
 - Clear, concise and logical
 - ❖ SOP 123 was deficient in that it was not clear that.....
or did not detail that....
 - Follow through from validation documents
 - ❖ There was no documented procedure for the tracking of implementation of recommendations from validation reports.



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Premises and Equipment

- **Utilities**
 - Water Systems
 - Qualification
 - Requalification
 - Ongoing monitoring, control and maintenance
 - Air Handling Systems
 - Classification
 - EN ISO 14644-1 referenced in Annex 1
 - Requalification
 - Ongoing monitoring, control and maintenance



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Premises and Equipment

Utilities

Water Systems

- ❖ Qualification of the WFI system was considered deficient for the following reasons:
 - The qualification documentation for the system was not kept up to date, as the original IQ documentation referred to specific components, yet these were not in use on the system.
 - Certain supporting documents were not clearly legible e.g. Piping and Instrumentation Diagrams.
 - The slope of pipe work for the WFI system had not been assessed.

Premises and Equipment

- The timing of QC sampling of WFI relative to the use of the system had not been formalised to assess worst case scenarios and verify the hold period for WFI in the storage tank.
- ❖ In relation to the.....water system, it was observed that:
 - The feed line to the RO unit was leaking on DD/MM/YYYY.
 - The drainage of water during regeneration of the organic scavenger unit was inadequate in that it resulted in overflowing of the drain in the plant room.
- ❖ The in-house knowledge of the WFI system had not been maintained.



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Premises and Equipment

Utilities

Air Handling Systems

- ❖ HEPA filters in the sampling area were not checked for efficiency.
- ❖ Pressure differential limits were not established for HEPA filters.
- ❖ Airflow patterns and pressure differentials for the cleanroom areas were not adequately detailed.
- ❖ The methodology / protocols used for requalification of the air handling systems were not available at the site.



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Premises and Equipment

- **Steam Sterilisation**
 - Autoclaves
 - Acceptance criteria
 - Routine controls
 - Preventative maintenance
 - SIP
 - Validation
 - Acceptance criteria
 - Appropriate use



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Premises and Equipment

Autoclaves / Validation

- ❖ The terminology used during qualification was not adequately defined and used in a consistent manner e.g. hold time / exposure time.
- ❖ Appropriate thermometric acceptance criteria were not employed for the validation of autoclave cycles.
- ❖ Biological indicators were not subject to independent D value assessment or sub lethal cycle verification.
- ❖ A sixty second post equilibration settling down period was in place.
- ❖ The equilibration time was not part of the acceptance criteria.
- ❖ Temperature readings were only taken every 20 seconds.



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Premises and Equipment

- ❖ The sterilisation set point and associated tolerances for the production autoclave were such that the lower limit was below the sterilisation band and did not comply with the stated cycles of $\geq 121^{\circ}\text{C}$ for 15 minutes.
- ❖ A change to the orientation and location of three items within the load occurred during requalification. This was not changed in the production SOP nor was the load requalified.
- ❖ A deviation was identified during the validation relating to the fact that three items had been orientated incorrectly when compared to the manufacturing load. This deviation was not raised in a timely manner and the impact of the validity of processed loads was not adequately assessed.



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Premises and Equipment

- ❖ The validation and production departments had different understandings of “Non-routine loads” resulting in the situation that not all loads processed were validated.

Autoclaves / Routine Controls

- ❖ Control instrumentation for the autoclave was not independent of monitoring instrumentation and recording charts.
- ❖ Required testing not performed or not performed at appropriate frequency:
 - Steam Quality
 - Bowie Dick
 - Vacuum Leak
 - Air Detector Function



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Premises and Equipment

Autoclaves / Preventative Maintenance

- ❖ An autoclave maintenance checklist dated DD/MM/YYYY detailed that a fan bearing and the steam inlet gauge needed to be replaced; however, there was no documented evidence that replacement of the parts had been performed.
- ❖ The chart speed for the chart recorder was scheduled to be calibrated on a six monthly basis; however the last available calibration was observed to have been performed on DD/MM/2005. (Two years previously)
- ❖ Preventative maintenance procedures and associated checklists relating to the autoclave were not adequately detailed.



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Premises and Equipment

SIP / Validation

- ❖ Validation of the SIP system was inadequate in that:
 - Graphical results from the original qualification were restricted to the exposure phase only.
 - The above results indicated differences from cycle to cycle which had not been assessed.
 - The control and monitoring systems were not independent of each other.
 - Annual requalification results were not critically compared to original qualification results.
 - The assessment of the graphical result from the annual requalification was inadequate.



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Premises and Equipment

SIP / Routine Control

- ❖ A repeat SIP was permitted to be performed in cases where a failed cycle occurred; however, no deviation was required to be raised and the reason for failure was not documented.

SIP / Appropriate Use

- ❖ The company's approach to the validation of stopper processors was reviewed and was not considered satisfactory, in that the stopper processor was considered to be a SIP system rather than an autoclave.



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Premises and Equipment

- **Dry Heat Sterilisation**

- ❖ In relation to the control of dry heat cycles, there was no system in place to assure maintenance of appropriate differential pressure to the Grade D area during the cycles and during the holding of sterilised and depyrogenated loads in the oven.
- ❖ The fan speed was not assessed as part of the maintenance and calibration program for the dry heat oven.

- **Irradiation**

- ❖ Dose mapping studies were not available for a number of raw materials.
- ❖ Irradiation of Raw Material X was not reviewed or approved by the QP.



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Premises and Equipment

- **Sanitisation**

- Sterile disinfectants etc.
- Is cleaning verified?

- ❖ The sporocidal agent and the 6% peroxide solution utilised in Grade A/B areas were not sterile.
- ❖ Sterile 70% IPA Spray used in Grade A areas was not subject to microbiological monitoring and an in use shelf life had not been established.
- ❖ The method of sanitisation prior to transfer of equipment into the aseptic processing areas had not been appropriately validated and the risk of the storage of those items in the Grade A area had not been assessed.
- ❖ Equipment which was sanitised in place was not subject to routine environmental monitoring.

Premises and Equipment

- ❖ The cleaning of floors, as observed on DD/MM/YYYY, within the Filling Room and Lyo Load / Unload was not satisfactory in that:
 - The floors were recorded as having been cleaned on DD/MM/YYYY yet they did not appear clean in places and residues could be wiped off with a moistened wipe.
 - The cleaning process was said to include vacuum cleaning yet there were particles on the floor, including particles of glass and filling had been completed in this area on DD/MM/YYYY.
 - The floors in the Grade B area were not considered to be clean in that there were some particles visible on the floor.



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Premises and Equipment

- Preventative Maintenance & Calibration
 - Use of Contractors
 - Training
 - Use of Checklists
 - Alternatives
 - Items falling between the cracks?
 - Clearly defined responsibilities



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Premises and Equipment

- ❖ SOP 123 specified that planned maintenance was to be performed on a 12 monthly basis; however, according to the system manufacturer's schedule, a number of items of preventative maintenance were required to be performed on a twice yearly basis.

A plant lost a batch worth half a million after an uncontrolled filter change. Maintenance replaced the filter during scheduled maintenance. Due to poorly documented maintenance plans, it was not subsequently checked. Product was filtered and packed, and only later was it identified that the filter's pore size was 2 μm , not 0.2 μm .



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Production

- **Process Simulations**
 - General requirements (Annex 1)
 - Really a process simulation?
 - How close to actual process?
 - Routine and worst case
 - Interventions
 - Selection of interventions for media fills
 - Based on real experience?
 - Tracking interventions between media fills



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Production

Media Fills / General

- ❖ Not all units filled during media fills were incubated.
- ❖ It was not specified that units which could not be accounted for post incubation, were to be presumed positive.
- ❖ 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.



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Production

Media Fills / Process Simulation?

- ❖ 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.



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Production

Media Fills / Interventions

- ❖ 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.

A typical company statement:

Where an intervention has been performed in a media fill and is listed as a proceduralised intervention, there is no requirement to take additional sterility test samples on completion of these interventions.

- **Process Simulations**
 - Simulated does not mean validated!



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Production

- **Process Simulations**
 - Personnel Qualification
 - Appropriate level of participation
 - Handling of Failed Media Fills

Media Fills / Personnel Qualification

- ❖ 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.
- ❖ A list of personnel qualified through media fill participation, and the validity period of their qualification, was not maintained.



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Production

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.



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Production

- **Routine Production**
 - Aseptic Technique
 - Environmental Monitoring
 - Locations based on a formal risk analysis?
 - Identification of Isolates
 - Interventions
 - Defined?
 - Documented and Assessed?
 - Sterility Test Samples
 - Visual Inspection



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Production

Production / Aseptic Technique

- ❖ The manner in which the product was scooped 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
- ❖ The manner in which the product was sieved was not considered appropriate for an aseptic operation as it was considered to pose excessive risk to the product
- ❖ The final purification step required a breach to the sterile barrier. This was performed in a Grade D background
- ❖ The line was not required to be cleared during loading of the stopper bowl, which required an intervention across the filling line.



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Production

Production / Aseptic Technique

- ❖ Asepsis was not adequately assured in that during line set-up:
 - Unwrapped items were unnecessarily carried across the room.
 - The engineering technician unnecessarily leaned over the stopper bowls in order to fit them and other components.
 - IPA dripped from the technicians' gloves onto the equipment.
 - Some items were placed by touching the target housings.
 - A fitter had performed a significant intervention into the fill process on DD/MM/YYYY; however, no exit monitoring had been performed on this individual and no deviation had been raised



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Production

Production / Environmental Monitoring

- ❖ Records of environmental monitoring did not always indicate that they accurately covered the period of set-up and filling.
- ❖ Environmental monitoring was not performed in the compounding area during aseptic additions.
- ❖ The aseptic set up was not monitored for either viable or non-viable contaminants.
- ❖ There was no continuous non-viable monitoring during filling.
- ❖ There was no system in place for ongoing assessment of the adequacy of the environmental monitoring programme.



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Production

Production / Environmental Monitoring

- ❖ The alert and action limits set for viable monitoring of classified areas was outside those specified in Annex 1.
- ❖ The settle plates utilised in the grade A area were not irradiated and were labelled and wrapped in the microbiology lab in areas where viable organisms may be exposed.
- ❖ The critical zone where filling took place was not included as part of the viable monitoring programme.
- ❖ A settle plate was exposed only during connection of the product line and not during all the aseptic connections on the filling line.



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Production

Production / Interventions

- ❖ There was no procedure in place which described what constituted a significant intervention during the filling processes.
- ❖ Significant interventions were not defined and there was no requirement to take additional sterility test samples after significant interventions.
- ❖ The terminology applied to routine and non-routine interventions in SOP 123 was not consistent with that in the risk assessment on interventions.
- ❖ It was not clear that the company's policy regarding significant interventions would be to take samples for sterility testing regardless of whether these were interventions which had been proceduralised and covered in a media fill.



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Production

Production / Visual Inspection

- ❖ Visual inspection of vials was deficient in that:
 - The classification of particles/foreign matter in the cake and bung for both Product A and Product B as Major was considered to be inappropriate as this category had been classified as Critical for Product C.
 - The vial inspection personnel were permitted to adjust the lighting conditions used on the semi-automated VI equipment but the equipment had not necessarily been qualified under worst case conditions (e.g. lowest lux levels).
 - The background lighting had not been taken into consideration during qualification.
 - Qualification of personnel did not necessarily look at the ability of the person to identify and remove defects over a continuous working period.



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Quality Control

- **Microbiological Testing**
 - O.O.S Results
 - Identification of Isolates
- **Preparation of Media**
 - Manufacturers Recommendations
- **Sterility Test**
 - Failures
 - Invalidated Tests
 - Ph.Eur. criteria applied?
 - Sterility Test Suite
 - Reference Samples - UPDATE



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Quality Control

- ❖ Non-viable particulate monitoring was not alarmed at levels consistent with Annex 1 requirements.
- ❖ Media was not prepared and sterilised in accordance with the manufacturers recommendations.
- ❖ The use of media for viable monitoring, prior to completion of growth promotion testing was considered to be inappropriate.
- ❖ In relation to media used for environmental monitoring, the inhibitory effects of iso-propyl alcohol and cleaning agents had not been assessed.
- ❖ Media was not incubated as per the requirements of Ph.Eur.



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Quality Control

- ❖ The criteria for invalidation of a sterility test were not in line with the requirements of Ph.Eur.
- ❖ Additional sterility test samples taken post significant interventions during filling operations were not always included as part of the sterility tests.
- ❖ Procedures in relation to sterility testing were deficient in that:
 - In relation to four batches, the invalidation of positive sterility test results was not in accordance with the requirements of the European Pharmacopoeia or the company's own procedures.
 - Sterility test failure investigations did not include a documented critical review of relevant load sterilisation data.



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Quality Control

- ❖ In relation to the sterility test failures for two batches, the investigation reports retrospectively ascribed the failures to 'faults' during testing; however, contemporaneous documentation relating to each of the tests did not contain a record of any such faults.
- ❖ The premises and method of garbing used in relation to performance of the sterility test was not suitable for the aseptic manipulation of samples.



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Quality Control

- Reference Samples – UPDATE

Q. Is it necessary to retain sufficient number of samples of each batch of a sterile medicinal product in order to carry out a sterility test on two separate occasions?

A. For retention purposes, it is not necessary to keep the full number of samples required in table 2.6.1.3. of the European Pharmacopoeia sterility test monograph to repeat the sterility test performed for release purposes, but only a sufficient quantity to allow the carrying out, on two occasions, of a confirmative test using the minimum quantities described in table 2.6.1.2 of the monograph.



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Quality Control

- Additional samples to be held (Liquids)
 - $<1\text{ml} = 4$
 - $1\text{-}40\text{ml} = 2$
 - $100\text{ml} <> 40\text{ml} = 2$
 - $>100\text{ml} = 2$
- Incorporate into requirements for reference and retention samples!



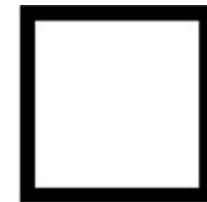
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Conclusion

- Awareness of issues



- Actions taken



Thank You For Listening!



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