PHARMSOL NEWS

CHALLENGES IN THE EUGMP INSPECTION OF STERILE FACILITIES

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Though there are many challenges in the preparation of a manufacturing facility going for the first time towards EU GMP inspection, this article brings up the key issues that are encountered.

Sterile Medicinal Products are administrated as injections through Intramuscular/Intravenous/ Intrathecal routes. Manufacturing of these sterile medicinal products are designed to ensure that they meet the basic GMP and pharmacopeial requirements for Quality, Sterility, Pyrogens, Particulate matter and other contaminants and where appropriate, contain inhibitors to stop the growth of microorganisms.

Parenteral preparations categorized based on the volume are:

- Small Volume Parenteral (less than 100 ml). Ex: Ampoules, Vials, Dry powder for injection, Suspension injections.
- Large Volume Parenteral (More than 100 ml). Ex: Multi-dose injectables.

Key Challenges during EUGMP Inspection

Qualified Person: The European Union (EU) has the specific requirement of release of batches through a Qualified Person (QP) while manufacturing and distribution of medicinal products within or importing into the EU. For many other countries, this concept is unfamiliar. Inspectors often observe during the GMP inspections outside the EU that the roles and responsibilities of Authorised Persons at the site and the EUQP are not defined throughout the Quality Management System.

Filtration: Sterile filtration is a critical step for aseptically filled products, where products are passed through a 0.22 µm filter, while controlling pressure and time parameters. Manufacturers lack to define and demonstrate the integrity of the sterilized filter assembly before use. Also, to verify the filter damage / failure of integrity during processing by online testing immediately after use (pre-use post-sterilization integrity testing- PUPSIT. These issues often categorized as Major Observations.

Equipment Design: All the aseptic connections and aseptic transfers shall be performed under Class A environment. The doors which are located inside Class A environment should not be opened in Class B area. The doors shall be opened under Class A zone only. Equipment design should not be disturbing the laminarity of the air. Air flow pattern should be visualized in grade A/B areas to evaluate and demonstrate the unidirectional air flow. The chances of contamination are always considered as a Major Observation and the CAPA is really complex as it involves the change in the equipment design or changing in the air zone.

Personnel: The maximum number of operators in critical areas should be determined based on process requirement and quality risk assessment. Inspections and other controls shall be conducted outside the clean areas as far as possible. Failure to establish the acceptable number of working personnel often noted as risk of contamination.

Sterilization: Inspectors focuses on the qualification of autoclaves and looks for the calibration of the temperature against a second independent calibrated temperature probe located at the same position. Further, the inspector looks at the validation parameters such as Equilibration time, Exposure time, and Correlation between pressure and temperature. The lack of comprehensive qualification of sterilizers often add to the risk of contamination and questions the Sterilization Assurance Level.

Application of Risk Assessment: As the risk-based approach evolved in the industry, the regulators often notice that the manufacturer's Quality Management System is deficient in the application of Quality Risk Management principles. The lack of Annual Risk Assessment Plan and Periodic Review of Risk Assessment, lack of scientific rationale to mitigate different categories of risk arising from risk assessments, failure to train employees to undertake risk assessments and inability of the team to define the actual root cause and implementation of pragmatic CAPA are always considered as potential failure of QMS.

Aseptic Processing: EU Inspectors looks at things scientifically and focuses on the lapses in the execution of Environmental Monitoring during machine setups/ assembly and critical operations. Failure to establish a defined Sample Frequency and Sample size impacts the monitoring of excursions as arises throughout the process. Not establishing the Pre-fill time, aseptic assembly, maximum exposure of sterilized articles as a part of media results in inadequate and unqualified practices and thereof comes to the attention of the inspectors during the inspection.

Non-Viable Particle Monitoring: Requirement to monitor clean rooms routinely 'In operation' has been expanded and requires justification of monitoring locations through risk assessment. Inspectors expect to see a formal risk assessment for the selection of all monitoring locations, including justification of critical locations. Use of classification and previous monitoring data shall be considered during the risk assessment. EU also insists the same system of monitoring of Grade A "continuous monitoring" in Grade B areas as well.

Stability Study: Execution of Stability Studies of vials at "Inverted Position" to demonstrate the compatibility and leachability of the drug product with rubber stopper is always expected as part of the inspection.

PharmSol, through its vast experience in providing solutions to the Pharmaceutical industry, envisages the issues through a systemic project handling and helps companies for a smooth and successful EUGMP inspection.

Compliance, post inspection is an expensive experience while Compliance before inspection is a great experience and reputation.

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