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Review on ICH Guideline for Aseptic Laboratory

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Abstract: *ICH Guidelines were created by The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).ICH aims to provide uniform standards for technical requirements for pharmaceuticals for human use. They are developed by regulatory and pharma industry authorities. The purpose of ICH guidelines is to ensure safe, effective and high-quality medicines are developed and registered efficiently. ICH guidelines are a set of guidances to ensure safe, effective and high-quality medicines are developed and registered efficiently. These guidelines have been adopted by regulatory authorities throughout the world. Aseptic manufacturing is used in cases, where the drug substance is instable against heat, hence sterilisation in the final container closure system is not possible. Aseptic manufacturing means that the used drug substance and excipients were sterilised appropriately and all materials, equipment and container closure systems were used only after sterilisation. All working steps were performed in so called clean areas to avoid contamination. Therefore high standards have to be established concerning the manufacturing room, the personnel, the equipment and the supply systems (air system, water for injection, sterile gases used in the working process; for example compressed air, nitrogen etc.).*

Keywords: ICH Guideline, Aseptic Condition, Sterilization

I. INTRODUCTION

If the laboratory includes opinions and interpretations of test results in reports, this should be done by authorized personnel with suitable experience and relevant knowledge of the specific application including, for example, regulatory and technological requirements and acceptability criteria. The laboratory management should ensure that all personnel have received adequate training for the competent performance of tests and operation of equipment. This should include training in basic techniques, e.g. plate pouring, counting of colonies, aseptic technique, media preparation, serial dilutions, and basic techniques in identification, with acceptability determined using objective criteria where relevant. Personnel may only perform tests on samples if they are either recognized as competent to do so, or if they do so under adequate supervision. Competence should be monitored continuously with provision for retraining where necessary. Where a method or technique is not in regular use, the competency of the personnel to perform the test should be verified before testing is undertaken. In some cases it is acceptable to relate competence to a general technique or instrument being used rather than to particular methods. laboratories and certain support equipment should be dedicated and separated from other areas, especially from production areas. laboratories should be designed to suit the operations to be carried out in them. There should be sufficient space for all activities to avoid mix ups, contamination and cross-contamination. There should be adequate suitable space for samples, reference organisms, media (if necessary, with cooling), testing and records. Due to the nature of some materials (e.g. sterile media versus reference organisms or incubated cultures), separate storage locations may be necessary. Laboratories should be appropriately designed and should take into account the suitability of construction materials to enable appropriate cleaning, disinfection and minimize the risks of contamination. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions, including temperature and humidity controls where required, should be in place for microbiological laboratories. The air supplied to the laboratory should be of appropriate quality and should not be a source of contamination.

Access to the microbiological laboratory should be restricted to authorized personnel. Personnel should be made aware of:

- The appropriate entry and exit procedures including gowning.
- The intended use of a particular area.
- The restrictions imposed on working within such areas.

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- The reasons for imposing such restrictions.
- The appropriate containment levels.

Laboratory activities, such as sample preparation, media and equipment preparation and enumeration of microorganisms, should be segregated by space or at least in time, so as to minimize risks of cross contamination, false-positive results and false-negative results. Where non dedicated areas are used, risk management principles should be applied. Sterility testing should always be performed in a dedicated area.

1.1 Environmental Monitoring in the Laboratory

Where necessary and appropriate (e.g. in areas for sterility testing) an environmental monitoring programme should be in place which covers, for example, use of active air monitoring, air settling or contact plates, temperature and pressure differentials. Alert and action limits should be defi ned. Trending of environmental monitoring results should be carried out.

1.2 Cleaning, Disinfection and Hygiene

- There should be a documented cleaning and disinfection programme.
- Results of environmental monitoring should be considered where relevant.
- There should be a procedure for dealing with spillages.
- Adequate hand-washing and hand-disinfection facilities should be available.

1.3 Sterility Test Facilities

- Sterility test facilities have specific environmental requirements to ensure the integrity of tests carried out. WHO good manufacturing practices (GMP) for sterile pharmaceutical products (8) requires that sterility testing should be carried out and specifies requirements for sterility testing. This section details the clean-room requirements for a sterility test facility.
- Sterility testing should be performed under aseptic conditions, which should be equivalent to air quality standards required for the aseptic manufacture of pharmaceutical products. The premises, services and equipment should be subject to the appropriate qualification process.
- The sterility testing should be carried out within a Grade A unidirectional airflow protected zone or a biosafety cabinet (if warranted), which should be located within a clean room with a Grade B background. Alternatively, the testing can be carried out within a barrier isolator. Care should be taken with the design of the facility layout and room airflow patterns, to ensure that the unidirectional airflow patterns are not disrupted. The clean-room classification and air-handling equipment of the sterility test facilities should be requalified at least annually by a competent person or contractor. The environment should comply with the non-viable and viable limits, and verification of high efficiency particulate air (HEPA) filter integrity and room airflows should be performed. However, an alternative frequency of the monitoring may be justified based on quality risk management (QRM). Mapping locations for sample points for routine monitoring should be documented, as well as exposure duration, and frequency of all types of microbiological environmental monitoring should be specified in written procedures.

1.4 Personnel Hygiene

- Personnel should practice good sanitation and health habits.
- Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.
- Personnel should avoid direct contact with intermediates or APIs.
- Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.
- Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time

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(either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

1.5 Cleaning and Disinfection of Processing Areas for Sterile Pharmaceutical Product Manufacturing

Processing areas for manufacturing sterile pharmaceutical products should be cleaned and disinfected in accordance with relevant SOPs, and results of cleaning and disinfection should be recorded in writing and retained in an archive.

1.6 Cleaning Agents and Disinfectants

1. Cleaning agents and disinfectants should be validated for their appropriateness and reliability in removing contaminants prior to use. Cleaning and disinfection efficacy should be assessed and confirmed based on type and count of microorganisms characterized by periodic environmental monitoring.
2. Cleaning agents and disinfectants used in the APA should be pretreated with filtration or other appropriate sterilization procedures before use and controlled for the prevention of microbacterial contamination until use, unless commercial products certified to be sterile are used by breaking the envelope immediately before use.
3. When prepared in-house, the preparation of cleaning agents and disinfectants should be pursuant to applicable SOPs, and preparation records should be created in writing and retained in an archive. When commercial products are used after dilution, details of the dilution procedure such as diluents, dilution ratio, expiration date, storage conditions, and, if applicable, sterilization methods should be recorded in writing and approved by the quality department.
4. SOPs for the preparation and use of cleaning agents and disinfectants should address the following matters approved by the quality department: types or brands of cleaning agents and disinfectants, cleaning and disinfection schedules, directions for the use of disinfectants, necessity of cleaning following disinfection procedure where necessary, safety precautions for factory personnel, and procedures for management and storage of cleaning tools.
5. When cleaned or disinfected, the surfaces of facilities and equipment that may come into direct contact with pharmaceutical products should be verified by appropriate methods to be free of cleaning agents or disinfectants after the completion of cleaning or disinfection procedures.

1.7 Validation of Disinfection Procedures

1. The reliability and frequency of disinfection procedures should be established through an environmental monitoring program.
2. Disinfectants should be microbiologically assessed prior to use in each facility, and appropriate control procedures should also be instituted for each facility.
3. The efficacy of disinfectants should be assessed with respect to ensuring that microorganism counts remain below the count predetermined based on the type and count of isolates collected from various surfaces through the environmental monitoring program.

II. CONCLUSION

Harmonization achievements in the quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management. ICH mission is to achieve greater harmonization worldwide to ensure that safe, effective and high quality medicines are developed and registered in the most resource –efficient manner. Harmonization achievements in quality area include pivotal milestone such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more manufacturing practice (GMP) risk management.

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CONFLICT OF INTEREST

The author declared no conflict of interest.

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