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Typical Microbiology Concerns in a FDA Inspection – Part 1

By **Jeanne Moldenhauer Jul 26, 2018 1:34 pm PDT**

Abstract

The announcement of a FDA inspection can trigger fear emotions to many in the company. If you have not been through an inspection, it can be difficult to know how to prepare for the inspection. This paper discusses some of the inspectional concerns of FDA and expands on the guidance to describe how it may be interpreted. It also describes some of the areas where FDA will request information or want to observe activities. This paper is limited to microbiological concerns that are identified as part of the six systems under inspection by FDA. Incorporated into this six-system review are the inspectional items suggested for the facility and the laboratory. They are broken down into the appropriate control system for review.

Background

Since the advent of CMPG 7356.002, "Drug Manufacturing Inspections" in 2002 and updated in 2017, the methodology used by FDA in inspections has changed (FDA, 2017). This policy guidance (CMPG 7356.002) divides the typical pharmaceutical site into six systems: quality system, facilities and equipment system, materials system, production system, laboratory system and labeling and packaging system. It would be easy to assume that all the concerns for microbiology in the inspection would be limited to the laboratory system. While a nice thought, it isn't the truth. FDA has microbiology concerns in other aspects of the production systems. The only system that is not identified as having microbiology concerns is the packaging and labeling system. Some of these concerns have been identified in the Pharmaceutical Microbiology Manual (FDA, 2014). Another source of identifying FDA concerns in inspections is information provided in FDA Warning Letters, which are available on the FDA's Website, in the Electronic Reading Room.

The Quality System

When you have notice of a FDA inspection in advance, e.g., you are an international drug manufacturer, it is common to ask for some documents to be available at the time the inspection is initiated. Some of those documents that are asked for, in advance (relative to microbiology) include:

- A listing of the discrepancy and failure investigations related to manufacturing and testing (both microbiology and chemistry). This expectation includes evaluation of how the investigations were documented, investigated, and evaluated. This includes verification that the investigations were completed in a timely manner. Unfortunately for microbiologists, timely manner is frequently discussed as within thirty days. It can be difficult to complete an investigation that requires resampling and retesting of microbiology methods. Depending upon the methodology used, the testing alone can take a week or more of time to complete. Unless your site has implemented all rapid methods, it can be difficult to complete this investigation within thirty days. While common to request an extension, it is important to work and keep the time of the evaluation down to the real time needed. It is common to also look at how the product disposition analysis was performed.
- A listing of the validation/revalidation status of all equipment, computer systems, processes, and laboratory methods. It is important to ensure that all required validation/revalidations are performed on time.
- A listing of training/qualification of personnel in the quality control unit (including the laboratories).

These documents would all affect microbiology as described in the FDA's Pharmaceutical Microbiology Manual (PMM) (FDA, 2014).

Facilities and Equipment System

There are various aspects of these systems of interest relative to microbiology, e.g., (FDA, 2014 and FDA, 2017):

- A properly designed facility and air-handling systems which prevents cross-contamination and mix-ups.
- The room and equipment design should be such that is it accessible for cleaning and disinfection. Aseptic areas and associated equipment and utilities are appropriately designed, certified and within validation. Testing of these areas was performed under dynamic conditions including: maximum number of personnel in place, normal personnel and equipment traffic, room differential pressures and temperatures, and adequacy of the primary and secondary barriers.
- Cleaning and maintenance of the facilities, including equipment cleaning procedures and cleaning validation
- The disinfection and sanitization agents used should include periodic use of a sporicidal agent. Concerns may also arise from how the solutions are prepared (are dilutions correct), how they are applied (e.g., mop, spray, aerosol), exposure time, contact areas, whether supervision takes place during use, what types of residues are left behind, are ultra-violet lights used, and the like.
- Identification and use of the disinfectants and sanitizing agents used in/on water systems, filling equipment, work surfaces, process columns and how were they validated.
- Properly and adequately designed equipment of the appropriate size and location. This should include surfaces that are non-reactive, additive or absorptive.
- Controls to prevent contamination, including pesticides, toxic materials other toxic materials, drugs or drug chemicals on the equipment.
- Sanitation of the building including the use of rodenticides, fungicides, insecticides, cleaning and sanitizing agents.
- Appropriate air-handling units, lighting, potable water, washing and toilet facilities (including hot water), sewage and refuse disposal for the facility.
- Qualification, calibration, and maintenance of storage equipment, like refrigerators and freezers, ensuring standards for raw materials, reagents, and the like are stored at the correct conditions.

It is important to remember that validation in the facilities and equipment system include the installation and operational qualifications. Performance qualifications (validations) are part of the production system.

While it may not be abundantly clear how all these aspects affect microbiology, it is FDA's interpretation. Some regulatory observations have been issued for improper validation/qualification of equipment like incubators, refrigerators, and freezers. Similar observations have been issued for stability chambers. Often these units are not properly cleaned and disinfected as shown by contamination being present in the units.

The Materials System

The materials system also can lead to inspectional observations in microbiology. Some of the concerns stated in the PMM include (FDA, 2014 and FDA, 2017):

- Components, containers and closures are either tested for conformance or the supplier's test results have been validated (including microbiology tests like bioburden and endotoxin)
- Components, containers, and closures that do not meet the stated acceptance criteria are rejected. The site should have procedures to verify the source of the components.
- Appropriate retesting/reexamination of components, containers, and closures is conducted, if allowed.
- Containers and closures should not be additive, reactive, or absorptive to the drug product.
- The water and process gas supply are appropriately designed, maintained, validated, and operated.
- The water purification and delivery system have significant risks of contamination, e.g. the vulnerability of distillation, reverse osmosis, cartridge filters and the like. Concerns also exist for UV lights, dead legs, biofilm, corrosion (heat exchangers). There are a variety of water-borne microorganisms (nanobacteria) and endotoxin production.
- Potential disinfectant issues with cold water systems.
- All discrepancies are appropriately investigated, and the investigation is documented.

One may question why water is part of the materials system however, water is used as a main ingredient in various pharmaceutical preparations.

The Production System

The production system includes production activities as well as the performance qualification aspects of the equipment used in the process. Microbiology concerns exist for the following: (FDA, 2014 and FDA, 2017)

- Training and qualification of personnel, e.g., gowning qualification of personnel entering aseptic areas. There should be training for aseptic technique, gowning procedures, cleaning and maintenance personnel that enter Class 100, ISO5, and Grade A/B areas. The personnel should also be qualified and monitored using glove and garment monitoring procedures.
- Validation and verification of cleaning, sterilization, and depyrogenation of containers and closures.
- Dry heat ovens used for depyrogenation of glass containers, washing and rinsing for stoppers should be validated for depyrogenation using spiked endotoxin indicators. Recovery studies should be performed prior to depyrogenation. Studies used to depyrogenate filtration and column applications should also be a concern
- Product sterilization and bioburden reduction stages and the associated validation are microbiology concerns. This includes aseptic processing, filtration, moist heat, Ethylene oxide, radiation, and other chemical processes. Note: A listing of sterilization processes is identified in USP <1229> and its associated sub-sections.
- Established time limits for completion of phases of production (i.e., which prevent or limit the microbial growth potential of product)
- Implementation and documentation of in-process controls, test, and examinations (e.g., bioburden determination pH, adequacy of mix)
- Justification and documentation of in-process specifications and drug product final specifications
- Prevention of objectionable microorganisms in no-sterile drug products
- FDA also considers Burkholderia cepacia complex (BCC) organisms as objectionable for non-sterile, aqueous products although it is not listed in USP. (FDA, 2017a)
- Equipment cleaning and use logs are available for all equipment.
- Maintenance records should be reviewed. It is important to determine the dates and location of equipment failure or out-of-service that may have an impact on microbial ingress. The investigator should look for signs of roof leaks and water stains on ceiling panels. The degree of dirt and dust accumulation on the supply and exhaust vents is also a concern. The investigator should query the firm on new construction, plumbing or air handling systems, and why the changes are being made or have been made.
- Compressed air systems should be reviewed to ensure that sterile process air is used appropriately, that a 0.2 µm, hydrophobic filter to filer microbial particulates. Condensate in the filters is a concern as it causes blockage and microbial growth. There should be routine point-of-use sampling, maintenance, and filter integrity testing.
- Process validation, including validation and security of computerized or automated processes (i.e., simulation studies)
- Documented investigation into any unexpected discrepancy.

The Laboratory Control System

As expected, these requirements apply to microbiology as well as chemistry. Where lists or information are cited for review by the inspector, it is important to be sure that you have the data available, ready, and have reviewed it for any issues you can resolve before the inspection. The concerns include: (FDA, 2014 and FDA, 2017):

- Training and qualification of personnel had been conducted and documented.
- Personnel are qualified and trained to conduct each step of the analysis.
- Qualification and training of management to critically review data and interpret its significance, i.e., risk assessment is conducted.
- Adequacy of staffing for laboratory operations. A common way to determine this is to evaluate whether all testing and reporting is being conducted on time, e.g., are stability tests conducted when they should be.
- Adequacy of equipment and the facility for its intended use.
- Calibration and maintenance programs for analytical instruments and equipment are implemented, followed and maintained.
- Equipment and instruments, e.g., Steritest, manifold, automated/molecular identification equipment, Vitek, isolators, bio-decontamination systems, should be calibrated, maintained, and validated (IQ, OQ, and PQ)

- Validation and security of computerized or automated processes (data integrity and compliance with 21CFR§11) is conducted.
- Reference Standards: source, purity, and assay. Tests to establish equivalency to the current official reference standards have been performed as appropriate. Note: Endotoxin standards are reference standards.
- Microbiological standards are established for raw materials, finished product, water bioburden and environmental monitoring for analytical areas.
- System suitability tests have been performed on chromatographic systems (e.g., gas chromatography or high-performance liquid chromatography). You may ask why this is a microbiology concern. Keep in mind that chromatography equipment is used for several kinds of microbial identification systems. You also need to worry about contamination using some of these systems.
- The method description, modifications, and verifications along with recording of sample results and appropriate reviews and evaluations are conducted by management.
- Specifications, standards, and representative sampling plans are established and used.
- Product sampling plans are representative of the lot required minimum values in USP <71> for quantity per container and units per batch. Additionally, they look at whether the sample storage (time and temperature), sampling port sanitization or sterilization problems are handled appropriately. There can be problems with skip lot testing of raw materials.
- An appropriate environmental monitoring program is established for the laboratory and production areas. It should include the types of equipment used and require that it be calibrated, operated and maintained in good condition. Sampling should include: surfaces, air, personnel and water.
- Media fills (process simulation studies) should be conducted for process validation. It should include evaluation of growth promotion, reading turbidity, adequacy of the testing volume of media, ensuring that the entire surface is contacted during the incubation period, using a sanitizer neutralizing media as appropriate, e.g., TSA w/ lecithin and polysorbate 80, use of appropriate aseptic technique during sampling should be observed, samples collected should represent dynamic/operational conditions.
- Data from the environmental monitoring program should be trended.
- Finished product testing should be using USP or non-compendial methods. For tests like: sterility, bacterial endotoxins, microbial limits, antimicrobial effectiveness testing, bioburden determination, and water quality control testing should have all original test results reviewed.
- Validation/verification of analytical methods. Note: Non-compendial methods should be validated, and compendial methods should be verified to show that they can be performed correctly at your site with your equipment and personnel.
- Method suitability testing should be performed for sterility test methods.
- Preparatory test methods should be followed for all bacterial endotoxin tests.
- Validation should be conducted for all bioburden and water analysis methods.
- Adherence to the written methods of analysis
- Reagents and media should be properly stored. The items used should be within the expiration date. Growth promotion studies should be conducted for media.
- A control system should be established and followed for implementing changes in the laboratory operations
- The required testing is performed on the correct samples.
- Documented investigations are conducted into any unexpected discrepancy
- Complete analytical records are available for all tests and summaries of results
- The integrity and accuracy of the laboratory information management system (LIMS) for microbiology data entry, review and approval selection should be reviewed. Also reviewed are the selection, handling and storage of biological indicators (BIs).
- Quality and retention of raw data, e.g., chromatograms and spectra
- Correction of result summaries to raw data; presence of unused data
- Risk assessment should be conducted for microbiological results for non-sterile products.
- Adherence to an adequate out-of-specification (OOS) procedure which includes timely completion of the investigation
- A list of the entire laboratory's Microbial Data Deviations (e.g., OOS, OOT, OOL results) and Corrective Action Preventative Action (CAPA) since the last FDA inspection should be requested and reviewed.
- Adequate reserve samples; documentation of reserve sample examination
- Stability testing program, including demonstration of stability indicating capability of the test methods, i.e., container/closure testing, antimicrobial effectiveness testing.

- In-vitro diagnostic test kits should be properly used and controlled. This includes positive and negative controls, interpretation and reliability of results.
- If Contract Laboratories are used, review the quality agreements, data review, and associated problems. Look at whether there have been any changes in contract labs. If so, why were the changes made?

Conclusion

Review of the items in this paper can help you prepare for potential FDA inspections and provide you with information regarding the types of information that will be requested/reviewed at your site. As a microbiologist, it is important to ensure that you understand the risks associated with your portion of the inspection.

Literature Cited

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