Microbial Risk Management: Four Strategies to Protect Your Bottom Line

American Pharmaceutical Review™

SPONSORED BY ThermoFisher SCIENTIFIC

When it comes to microbial contamination, you can never be too safe. This is particularly true in the case of research and development for biological medicines, including biotherapeutics, which carry special considerations not applicable to other types of drugs. The World Health Organization outlines guidelines for performing risk assessment for biopharmaceuticals.[1] Performance of a quality risk management process will identify areas of concern and guide laboratory personnel in setting up a streamlined plan for monitoring and prevention of microbial contamination. For example, targeting processes such as cell line development, media prep, cell expansion, and cell culture for monitoring is advantageous as mycoplasma testing can be performed in 4 hours versus a 28-day culture test.

Adventitious Risk Assessment

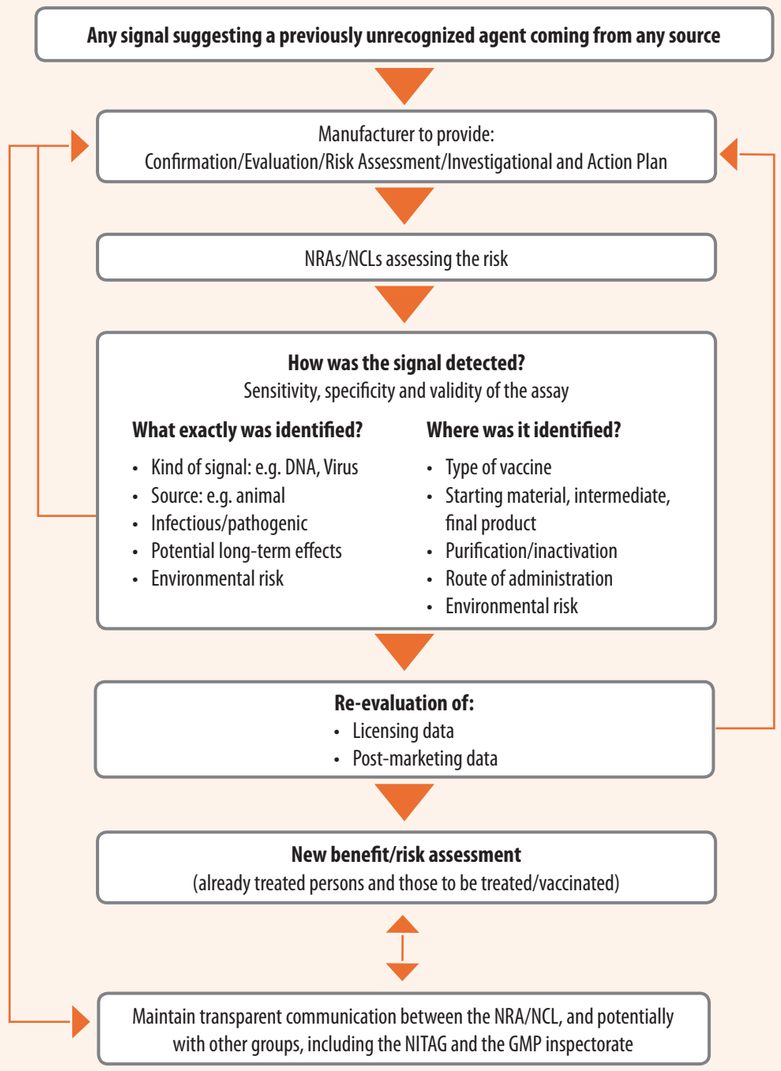
Description: Adventitious organisms are bacteria, yeast, mold, mycoplasma or viruses that can potentially contaminate prokaryote or eukaryote cells used in production. Potential sources of adventitious organisms include raw materials, serum used in cell culture media, persistently or latently infected cells, or the environment.

The goal is to have no adventitious organisms in the system during cell growth. Contaminating organisms in the bioreactor may adversely affect both the product yield and the ability of the downstream process to correctly separate and purify the desired protein. The presence or effects of contaminating organisms in the bioreactor can be detected in a number of ways -growth rate, culture purity, bacteriophage assay, and fatty acid profile.[2]

Points to consider:

1. Verify that there are written procedures to assure absence of adventitious agents and criteria established to reject contaminated runs.
2. Review cell growth records and verify that the production run parameters are consistent with the established pattern.
3. Review written procedures to determine what investigations and corrective actions will be performed in the event that growth parameters exceed established limits.
4. Assure proper aseptic techniques during cell inspection approach.
5. Determine that appropriate in-process controls are utilized prior to further processing.

Regulatory Oversight Flowchart



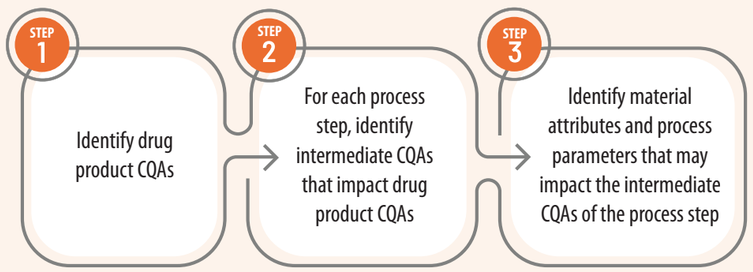
Critical Quality Attributes (CQA)

Description: A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8).

Points to consider:

1. Consider all drug product quality attributes; physical attributes, identification, assay, content uniformity, dissolution and drug release, degradation products, residual solvents, moisture, microbial limits, etc.[3]
2. Identify a CQA based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet that quality attribute.
   - Identified before taking into account risk control.
   - Does not change as a result of risk management.

Example Approach to Identify Material Attributes and Process Parameters



Aseptic Processing

Description: In aseptic processing, the drug product, container, and closure are separately subjected to sterilization methods, and then brought together. Aseptic processing presents significant challenges and risks not posed by terminal sterilization, but it is necessary in some cases, particularly in the development of biologics. To mitigate those risks, it is essential to follow current Good Manufacturing processes (CGMP) as outlined in parts 210 and 211.[4] The FDA offers detailed guidelines for following CGMP in a document titled Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice.

Points to consider:

CGMP recommendations cover the many variables involved in aseptic processing—including considerations for buildings and facilities, laboratory and personnel, and equipment. It also outlines methods for continual testing and maintenance of the aseptic process environment. Important testing controls include those for:

1. Environmental monitoring of the quality of the aseptic processing environment
2. Microbial media and identification for characterization of recovered microorganisms
3. Prefiltration bioburden to minimize the bioburden in the unfiltered product
4. Alternate microbiological test methods can be considered for environmental monitoring, in-process control testing, and finished product release testing after it is demonstrated that the methods are equivalent or better than traditional methods (e.g.,USP)
5. Routine particle monitoring for rapidly detecting significant deviations in air cleanliness from qualified processing norms (e.g., clean area classification)

FMEA: Risk Based Approach in Sterility Testing

Description: Sterility of each lot of a product should be demonstrated by performance of tests as described in 21 CFR Part 610.[5] This document outlines in-depth how bulk and final container material should be tested and the repeat tests to be performed should growth appear in any of the test media during testing of either bulk or final container material.

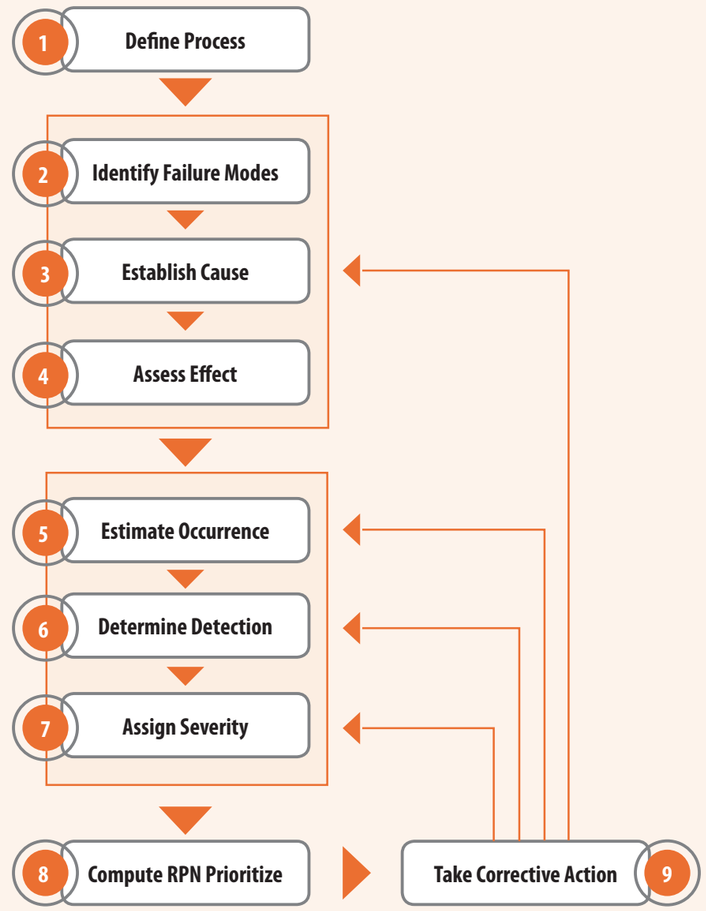
A failure modes and effects analysis (FMEA) can be used to examine potential failure modes within a system for classification by severity or determination of the effect of failures on the system. Failure modes are any errors or defects in a process, design, or equipment. Such modes can be potential or actual.

Points to consider:

FMEA involves the following:

1. Setting the scope.
2. Defining the problem.
3. Setting scales for factors of severity, occurrence and detection.
4. Process mapping.
5. Defining failure modes.
6. Listing the potential effects of each failure mode.
7. Assigning severity ratings to each process step.
8. Listing potential causes of each failure mode
9. Assigning and occurrence rating for each failure mode.
10. Examining current controls.
11. Examining mechanisms for detection.
12. Calculating the risk.
13. Examining outcomes and proposing actions to minimize risks.

FMEA Flow Diagram



References:

1. https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex2TRS-981.pdf WHO Guidelines on Quality Risk Management, WHO Technical Report Series No. 981, 2013
2. https://www.who.int/biologicals/RA_on_finding_adventitious_agent_marketed_vaccine.pdf Guidance on Scientific Principles for Regulatory Risk Evaluation on Finding an Adventitious Agent in a Marketed Vaccine, Expert Committee on Biological Standardization, Geneva, 13 to 17 October 2014
3. http://pqri.org/wp-content/uploads/2015/10/01-How-to-identify-CQA-CPP-CMA-Final.pdf How to Identify Critical Quality Attributes and Critical Process Parameters, FDA/PQRI 2nd Conference, North Bethesda, Maryland, October 6, 2015
4. https://www.fda.gov/media/71026/download Sterile Drug Products Produced by Aseptic Processing —Current Good Manufacturing Practice, FDA, September 2004 Pharmaceutical CGMPs
5. https://ntp.niehs.nih.gov/iccvam/methods/biologics/vaccine/2008-21cfrpart610.pdf Part 610—General Biological Products Standards, Food and Drug Administration, HHS, 21 CFR Ch. I, April 1, 2008 Edition