Bioburden Control of Non-Sterile Drug Substances and Products

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- No well defined regulatory standards or guidance exists for the microbiological / bioburden control of non-sterile pharmaceutical manufacturing environments
- Environmental control and monitoring of non-sterile processes either range from non-existent to parallel programs to aseptic processing
- Data generated from some programs may be of little value for the control of the microbiological quality of non-sterile environments in which the product is manufactured
So, how do we effectively apply microbial control in the manufacture of non-sterile products?

- Microbial contamination in non-sterile products is controlled to a level consistent with patient safety, but excessive controls that would add complexity/cost without a commensurate safety benefit are not advantageous to either the end user or the manufacturer.

- Therefore, a scientifically pragmatic approach to management of the microbial bioburden in non-sterile products requires consideration of patient risk and the contamination control objectives required to achieve a practical level of risk management.
Approach

– Use HACCP to understand the process

➢ Hazard Analysis & Critical Control Points (HACCP) is a safety management system that relies on process controls to minimize risks

– Define where microbial contamination could occur
– Effectively determine the best control and monitoring methods
A hierarchy of non-sterile drug dosage forms with potential risk (high to low) to end users from a microbial contamination perspective is:
- Metered-dose and dry powder inhalants
- Nasal sprays
- Otics
- Vaginal suppositories
- Topicals
- Oral liquids (aqueous)
- Oral liquids (non-aqueous)
- Rectal suppositories
- Liquid-filled capsules
- Compressed tablets and powder-filled capsules
Non-Sterile Product Microbial Influences

- Facility Design & Maintenance
- Personnel Flow
- Equipment Design
- HVAC
- Storage Conditions
- Personnel Practices & Training
- Equipment Cleaning & Maintenance
- Manufacturing & Filling Processes
- Tools & Utensils
- Influences From Adjacent Areas
- Seasonal Effects
- Process & Cleaning Water
- Facility Housekeeping / Sanitization
- Non-Product Contact Equipment
- Validation
- Product & Material Flow
- Personnel Gowns & Hygiene
- Primary Packaging Components

In-Process Materials

Products
While there are many factors that can result in the introduction of microorganisms, recent data on product failures and recalls indicate that the following factors are the most likely to result in product recalls due to higher than acceptable levels of microbiological content. These manufacturing risk factors are, in descending order: (1) ingredient water, (2) pharmaceutical ingredients, (3) process equipment, and (4) manufacturing personnel and (5) manufacturing environment.
Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed (21 CFR 211.113 Control of microbiological contamination).
Points to be considered by pharmaceutical microbiologists and product development teams when assessing the potential risk associated are:

- Synthesis, isolation, and final purification of the drug substance
- Microbial attributes of the drug substance
- Microbial attributes of the pharmaceutical excipients
- Formulation and microbial, chemical and physical attributes of the drug product
Points to consider:

• Water activity of the drug product
• Manufacturing process for the drug product
• Delivery system for the drug product
• Packaging of the drug product
• Storage conditions for the finished dosage form
• Route of administration of the drug product
• Expected treatment procedure and dosage regime
• Age and medical status of the intended recipients of the drug product
Process water is the single most important risk element contributing to the contamination of nonsterile products. The quality or type of water used for nonsterile product formulation and final rinse of clean equipment should be chosen based on product risk. Purified waters used in pharmaceutical manufacturing are deionized and thus do not contain chlorine to control microbial growth.
Water

- Substantial populations of Gram negative rod-shaped bacteria and many molds are able to grow in such purified dechlorinated water. Therefore, purified water should not be allowed to stand in pools or puddles for extended periods of time. Standing purified water should be drained or physically removed quickly and efficiently from both production vessels and equipment, as well as work surfaces and floors.
Water

- Process waters used for manufacturing of excipients, and, in some cases, active ingredients for nonsterile products present a substantial risk for microbial colonization and proliferation, particularly for ingredients of natural origin that have received minimal processing to reduce bioburden or to control microbial proliferation.
Pharmaceutical Ingredients

- Ingredients and excipients utilized in process formulation can be a significant source of microbial contaminants and are in fact the second leading cause of product recalls for microbial contamination.

- Vendor audits, specifications, testing, package selection, shipping, storage conditions and expiry dates are all critical in the reduction of microbial risk associated with these materials.
Pharmaceutical Ingredients

- When manufacturers cannot conduct extensive vendor audits, they should select vendors who have submitted a Drug Master File to a competent regulatory authority and have satisfactorily passed GMP inspections conducted by regulators. Of particular concern are unprocessed materials of natural origin and those that have a high level of water activity.

- Supplier audits should be conducted to establish that the supplier has a well-designed and validated microbiological control program for its manufacturing and packaging facilities. Depending on the microbial characteristics of an ingredient, manufacturers should consider periodic monitoring of the supplier’s facility to assess microbiological contamination.
Pharmaceutical Ingredients

- Materials that have low water activity, possess high or low pH, are not of natural origin, are inherently antimicrobial, or contain an antimicrobial preservative have a low risk for microbial colonization or proliferation. Risk assessments should consider ingredient characteristics regarding microbial survival, support of microbial growth, or frank antagonism to microbial survival.
• The introduction of moisture into stored materials notably increases the risk of microbial contamination. Condensation in storage tank headspace or impermeable storage containers can result in contamination of materials with water-borne organisms even when the product under storage is expected to preclude microbial colonization or proliferation.
Manufacturers also should consider the suitability of methods for detecting relevant noncompendial organisms.

Primary packaging and intermediate containers (e.g., drum liners, plastic bags, and so on) can be a source of microbial contamination, and manufacturers should consider their initial quality, storage conditions, preparation, and handling procedures.
Equipment Design and Use

- Formulating and manufacturing equipment can be a source of contamination, and risks are higher when water and ingredients that are susceptible to microbial survival or growth are used.
Therefore, cleaning, drying, and, where appropriate, sanitization of manufacturing equipment can be beneficial, but disinfectant residues should be limited in the operating environment and should be removed from product-contact surfaces. The isolation of water-borne organisms, particularly Gram negative rods, is a likely indicator of failure to remove standing water on equipment and environmental surfaces.
Equipment Design and Use

• Equipment specifications for the selection of equipment to be used in the manufacture of non-sterile products should include sanitary design; clean ability of equipment to allow removal of contaminants.

• Equipment should use sanitary fittings and be designed for easy use of cleaning and sanitizing agents and complete rinse water drainage.
• Residual water in tanks, piping, or on equipment surfaces introduces the risk of colonization by water-borne organisms. Manufacturing equipment that cannot be cleaned in place should be readily accessible for manual cleaning, and parts that must be cleaned out of place should be not only easily accessible but also readily or easily removable.
A further consideration is the compatibility of equipment with the typical range of disinfectants, including sporicidies, used in cleaning procedures to sanitize equipment.
• Cleaning and sanitization processes should include the evaluation of microbial content both after sanitization and before use. Properly designed storage protection should mitigate the possibility of microbial growth before use, so after proper storage conditions are validated ongoing monitoring of equipment and utensils should not be required.
Surface microbial sampling either immediately after cleaning or immediately before use must be done with caution; media residues and residual moisture must be carefully eliminated if sampling is performed.
In-Process Control

• It is important to evaluate whether products that are manufactured using a piece of processing equipment may, under some processing circumstances, promote the growth of microorganisms.

• This evaluation is necessary to properly establish processing hold times and to define equipment use conditions post-cleaning. Intermediates that require hold times include granulation solution, wet granulations, film coating solution and aqueous material prior to the addition of antimicrobial preservatives.
Personnel

• In addition to emphasis on personal hygiene, operators should be trained and dressed appropriately for the function they are performing

• Attention should be given to when product is exposed to manufacturing personnel in open systems
Design elements to control microbial contamination

• Common design elements to control microbial contamination may include the following:

• Walls, ceilings, and floors are constructed of nonporous materials that are readily cleanable and are resistant to cleaning agents and disinfectants.
Design elements to control microbial contamination

- Floor drains are permitted in nonsterile product manufacturing areas provided that they can be closed during processing or fitted with a suitable air break if they are open during area and equipment cleaning.
- Access should be limited to essential personnel.
- Material, equipment, and personnel flows should avoid contamination.
Design elements to control microbial contamination

- Ventilation and air filtration should be adequate to maintain the specified cleanliness, space pressurization (if required), temperature, and relative humidity.
- Good housekeeping and good general hygiene should be applied at all times.
Design elements to control microbial contamination

• Cleaning and use status of all tools and implements used in production and all process equipment should be known at all times.

• Product-contact or water-supply tubing, valves, and fittings should be cleaned and sanitized according to a defined schedule, should be stored dry, and should be labeled with respect to status.
Design elements to control microbial contamination

- Manufacturers should implement a formal housekeeping and sanitization program for operating areas, corridors, equipment storage, material staging, and other common areas.

- Classified environments are generally not required for nonsterile product manufacturing, e.g., those specified in ISO 14644-1.
Microbial Monitoring

- A monitoring program, commensurate with the risk, may be of value confirming the effectiveness of microbiological controls and in early detection of potential problems within the manufacturing areas.

- The microbial methods and practices utilized for aseptic facilities may be utilized; however the contamination recovery rates defined in <1116> Microbiological Control and Monitoring of Aseptic Processing Environments are NOT intended for non-sterile environments.
Unlike aseptic processing for which facility requirements are generally uniform in specification and performance, nonsterile product manufacturing environments typically involve diverse products and microbial contamination control requirements. In general, liquid, cream, or ointment products require a greater level of contamination risk mitigation than do solid dosage forms.
Microbial Monitoring

• The frequency of monitoring should reflect the potential risk associated with the dosage form

• Products that are resistant to microbial colonization or have microbiocidal or microbiostatic characteristics require little or no microbiological monitoring.

• In general, environments for tablet and powder- and liquid-filled capsule manufacturing should require no monitoring or infrequent monitoring.
Microbial Monitoring

- Monitoring programs should be risk based, and the intensity and number of sampling sites should reflect the risk level. Manufacturing areas for higher-risk dosage forms such as inhalant products require more frequent monitoring and typically are manufactured in rooms classified to a particulate air quality level, e.g., ISO 8.
Microbial Monitoring

• For most nonsterile product manufacturing environments, because of their limited environmental controls and comparatively low product risk, the establishment of alert and action levels may not be required. Environmental monitoring is considered an informational survey of the general hygienic conditions of the environment and should not be used in product-release decisions.
Overall Program

• The management of a successful microbiological control program includes the following: identification of suitable suppliers of pharmaceutical ingredients and excipients that have good microbiological quality; conducting a microbial risk assessment of the manufacturing process and packaging system; and the establishment of an appropriate monitoring and control system.
Overall Program

• Although environmental contamination is by no means the most significant cause of nonsterile product recalls or contamination events, environmental monitoring may be a useful component in the overall microbiological control program.
Overall Program

- The microbiological contamination control program should be developed for identifying and controlling product risk-based on a formal assessment of risk modalities. The risk analysis should result in the identification of critical control points and should facilitate proper equipment selection, process layout and design, and facility requirements.
Overall Program

- Critical factors for the prevention of microbiological contamination during nonsterile product manufacturing are control of the microbiological quality of ingredients and water, along with the development of proper cleaning and sanitation procedures. Microbiological monitoring does not mitigate risk, but it can serve as a sentinel.
Overall Program

- No monitoring program can provide the assurance of contamination control like a proper proactive analysis of potential sources of contamination followed by the adoption of sound preventive measures. Consistent control of contamination can be achieved mainly by process evaluation via risk assessment and studies to ensure that measures are in place to prevent conditions conducive to contamination.
Questions
Thank You