

A program can be established that will monitor (by observation or by measurement - physical or microbiological) these controls to assess the manufacturing process as operating properly and subsequently reducing the risk of microbial contamination.

There are specific circumstances or situations within the manufacturing process that may allow for a microbial hazard to occur. An assessment of the manufacturing process would include a review of the following:

- Raw materials (API and excipients)
- Manufacturing equipment
- Facility designs
- Cleaning & sanitization methods
- Water / utilities
- Processing conditions
- Pre/post manufacturing storage & transport conditions
- Personnel behaviors

The most common microbial hazards that can jeopardize product quality of solid oral dosage forms can often be attributed to contaminated raw materials. Microbial hazards may be introduced into a manufacturing process due to the improper sanitary design of the manufacturing equipment; especially equipment used for aqueous processing steps (i.e., wet granulation or tablet coating). For example, microbial contamination can arise from entrapped water or product residues that remain hidden from procedural cleaning processes due to threaded pipe fittings, non-sanitary valves, piping dead legs, non-sloping pipes, equipment crevices, recessed access ports, bottom discharge valves, and pocket flow meters. Inadequate equipment maintenance may also serve as a potential microbial hazard. For example, misaligned, damaged, or over torqued gaskets between piping connections may harbor a reservoir of trapped microorganisms.

Microbial hazards may also originate from improper facility design. Such hazards could include deficient control of humidity and temperature within the manufacturing area, improper air ventilation systems, or poor room construction design (e.g., porous walls, drop down ceilings, uncovered floor drains).

Inadequate cleaning and sanitization of the equipment and manufacturing areas can potentially serve as a major cause of microbial hazards. Other examples of potential microbial hazards could include the following:

- Cleaned equipment that is not properly dried after cleaning and stored water wet.
- Cleaned equipment that is not properly stored.
- Manufacturing areas that are not adequately or routinely cleaned before use (e.g., standing pools of water, construction materials, cardboard or other debris).
- Cleaning utensils such as mops, buckets, and brushes that are not stored dry or clean.
- For continuous manufacturing with no cleaning between batches, campaign lengths, with consideration of microbial growth, are not established.