Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion
What steps can be taken to prevent and control of fungal contamination in tablets?

The presence of water is the key element in the growth of fungal contamination. This document discusses the prevention and control of fungal contamination in tablets production to include: raw material and API testing, manufacturing processes, environmental monitoring, and final product testing.

Tablets are generally considered to be a self-preserved dosage form that possesses an inhospitable environment to most microorganisms because of the lack of available water. Still, many fungi (mold) populations, if introduced before or during manufacturing, can potentially survive (in a static state) or proliferate on or within the final tablet dosage form if the correct conditions are present. These conditions center on the presence of water, which is considered the key element in the proliferation of any fungal contamination. Fungal contamination is most commonly introduced into a tablet via the following:

1. Steps of the manufacturing process of the tablet where water is present (*e.g.*, wet granulation, coating solutions).
2. Contaminated raw materials, excipients or active pharmaceutical ingredients (API).
3. The lack of good manufacturing practices (*e.g.*, water quality, processing equipment sanitization).
4. Inappropriate storage, handling, and transport conditions where humidity may be problematic.

The primary concern of fungal contamination in a tablet is generally not the direct medical hazard it may cause the patient, but the possible spoilage of the product itself and non-compliance with contemporary regulatory expectations (cGMP) regarding microbiological quality of non-sterile dosage forms. It should also be noted that fungi are ubiquitous in nature and that their mere presence does not necessarily indicate that microbial control has been lost in the manufacturing process. The topics discussed below will provide more detailed information on the prevention and control of fungal contamination in tablets.

Raw Materials and Active Pharmaceutical Ingredient (API) Quality and Testing
The microbial quality of the raw materials and APIs directly impact the microbial quality of the final tablet product. Fungal populations that may be found in these raw materials can contaminate the final tablet product. This is because the manufacturing of most tablets does not include processing steps that can eliminate the indigenous bioburden found originally in the raw material. Based on the materials contribution to the final drug product and their ability to be validated for their microbial attributes, it may be necessary to test RMs and API on a routine or periodic basis. Therefore, it is recommended that raw materials and API's used in the manufacturing of the tablet be

Fungal growth has been noted on tablets in blister packs after packaging.
This is due the introduction of water from condensation produced during the blister packaging process, therefore, it is important to a.) Control the humidity and temperature in the packaging area and b.) Ensure that the fungal bioburden of the tablet be kept at a minimum, so that if some condensation occurs, there will be no subsequent fungal growth.

Storage, Handling and Transport:

It is recommended that the humidity and temperature of the environment are controlled during the storage, handling and transport of the final product tablet. This is because dry tablets (especially uncoated) may be hygroscopic and can potentially take up moisture quickly if the humidity is high in the surrounding environment. This can easily lead to the rapid growth of fungi on the stored tablets.

Final Product Testing

Tablets should be tested for Total Yeast and Mold. Skip-lot testing is appropriate for solid oral dosage forms when the lot history of the tablet demonstrates consistently low microbial counts. Typically the first 10 batches/lots of a new drug product should be tested before skip lot testing is considered. If all test results for the first 10 batches/lots are acceptable, reduced testing can be performed on every 10^{th} lot. The decision for skip lot testing should be not solely based upon lot product history. All at risk raw materials and APIs in the drug product should be tested as well.

If the final tablet test does not meet the prescribed fungal limits, an “Out of Specification” investigation should be conducted of the laboratory and the manufacturing environment to determine the source of the microbial contamination.

The Total Yeast and Mold Count tests for the final product tablets should be validated and assayed according to compendial methods and/or internal requirements. Specific limits for fungal levels in non-sterile drug products are used to ensure high microbial quality of the final dosage form.

