Microbial Attributes Testing of Non-Sterile Solid Oral Dosage Forms and Materials

Introduction
The intention of this document is to provide guidance to determine the need for performing microbial attributes testing of drug product raw materials, non-sterile excipients, active pharmaceutical ingredients (APIs), and finished drug products. This guidance is recommended in order to ensure the microbiological quality of any non-sterile solid oral dosage form.

It is not mandatory to examine the microbial quality of drug product raw materials, non-sterile excipients, APIs, and finished solid oral drug products unless required by the compendia or a regulatory filing. However, a microbial assessment should be performed on all raw materials, non-sterile excipients, APIs, and finished drug products that are not required to be tested by compendia or regulatory filing. This assessment will determine if microbial attributes testing is warranted.

Microbial attribute testing estimates the number of and/or types of microorganisms present in a sample of material or product by utilizing the total aerobic bacterial count test, the total yeast and mold count test, or the presence of specified microorganisms test. Because of the wide diversity of materials and finished solid oral drug products, not all products are equally susceptible to microbial contamination, and therefore, microbial attributes testing may not be the same for all products. This guidance has been developed to help determine the need for microbiological testing.

Recommendations
Materials:
The raw materials, non-sterile excipients, and APIs of a solid oral dosage form are considered a potential major source of microbiological contamination in pharmaceutical products. Consequently, a risk assessment of each material is recommended to determine if microbial testing is appropriate. In order to assess each material used in the manufacture of non-sterile solid oral dosage forms, a decision tree has been appended to this guidance (see figure 1).

This decision tree is based upon such factors as regulatory requirements, material source, water activity, inherent inhibitory or antimicrobial properties, nutrients available for growth, historical bioburden data, and the manufacturing process of the material. A rationale for the decision to test or not to test can be generated based upon this decision tree. If it has been determined that testing of a raw material is needed,
Figure 1. Testing rational for excipients and non-sterile APIs used in the manufacture of non-sterile solid oral dosage forms

1. Is there a registered or compendial requirement to test the material?
   - NO

2. Is the material used in a solid oral drug product that requires routine microbiological testing of the final dosage form?
   - YES
   - NO

3. Is the material microbicidal? (e.g., aqueous solution or suspension)
   - NO
   - YES

4. Are the final stages in the manufacturing process of this material microbicidal? (e.g., aqueous solution or suspension)
   - NO
   - YES

5. Is the material water wet?
   - NO
   - YES

6. Is the water activity of this material ≥ 0.6?
   - NO
   - YES

7. Establish test frequency and implement testing as required.
   - YES
   - NO

8. Is the material of natural origin? Is there a history of high bioburden, or is the material a substrate for microbial growth?
   - NO
   - YES

9. Microbiological testing is not required.

1. Microbicidal is defined as being an organic solvent or strong acid base (pH ≤ 3 or ≥ 10) or exposed to these materials or high temperature conditions (>121°C for ≥ 15 min.).
2. Natural origin is defined as not chemically modified (e.g., extraction or purification). APIs are not considered of a natural origin.