and inverted or on the side configurations unless there is clear validation that the container-closure system does not impact drug product quality. Typically, ongoing stability studies use inverted or on the side positions.

Matrixing reduces the number of stability samples and tests. The FDA must be consulted before implementing the study design. Matrixing applies typically for stable products with little variability in analytical methods. It is not required to have assay performed on all three lots at intermediate time points. Testing might only require two of three container-closure types within given strength of active ingredient. Matrixing does not apply to initial and final time points, test parameters, different formulations, and dosage forms.

EXTRACTABLES AND LEACHABLES AND STABILITY TESTING

Extensive extractable studies should be performed as part of the qualification of the container-closure components, including labels, adhesives, and ink. Use various solvents, elevated temps, and prolonged extraction times in conducting these studies. Adsorption or absorption of drug product components must be evaluated during stability studies.

Leachables have been covered in Chapter 7, but some reinforcement here. Leachables are potentially problematic with drugs stored in plastic syringes where components from the plastic or from the label migrate into the product. Leachables can occur from glass and rubber closures including tip caps of syringes and cartridges.

Stability studies must evaluate the sterility integrity of tip cap or needle, sterility integrity of the stopper, syringeability, and transportation fluctuations in temperature and pressure. For terminally sterilized products stability studies must evaluate and validate the terminal sterilization cycle with respect to minimization of stopper movement.

STABILITY STUDIES OF STERILE PRODUCTS CONTAINING ANTIMICROBIAL PRESERVATIVES

For products containing antimicrobial preservatives, acceptance criteria must be established for the chemical content of the preservative. Such criteria must assure that sufficient preservative activity will remain throughout the product shelf life as well as when the product is in use. Microbial challenge studies must be conducted using a preservative level less than the minimum amount specified as acceptable. The first three production batches should be tested with microbial challenge assay at start and end of stability period.

ASSURANCE OF STERILITY AND STABILITY TESTING

Stability studies of sterile products are unique from other dosage forms in that sterility must be monitored throughout the stability-testing period. A sterility test is performed at beginning of stability-test period and testing to assure integrity of the container-closure system must be conducted annually and at expiry. The container-closure test used must be a validated test, either microbiologically based or chemically based (see Chapter 30). There must be an established sensitivity to show the amount of leakage necessary to detect a failed barrier in the container-closure system.

Another unique characteristic of stability testing of sterile products is the need for pyrogens/bacterial endotoxins testing at the beginning and the end of the stability period. Sterile solid or ampoule products only need initial data.

STABILITY ASSAYS FOR DIFFERENT TYPES OF STERILE PRODUCTS

The FDA stability guidelines list various product characteristics that should be monitored during stability testing depending on the type of dosage form.

Solution Dosage Forms (Drug Injection Products)

Stability data should be generated for:

- The active ingredient
- If present, the antimicrobial preservative
- Appearance, especially any changes in color and clarity
- Degradation products