

immediately after combination, then 6 to 8 hours later and after 24 hours or longer storage. Evaluations should include

- Appearance
- Color
- Clarity
- Active ingredient potency
- Degradation products
- pH
- Particulate matter
- Interaction or compatibility data in container/closure system
- Sterility

Stability data must be obtained with the lowest and highest concentrations of the drug in each diluent including using three different lots of the drug product.

All Sterile Dosage Forms

There are other basic data related to stability throughout the shelf life of the product that should/must be known:

- Continued assurance of sterility, with emphasis on container/closure integrity
- For terminally sterilized products, stability following exposure to at least the maximum specified process lethality (i.e. the maximum sterilization equivalent time (F_0) exposure—see Chapter 17)
- Inclusion of testing for extractables/leachables if other qualification tests have not provided sufficient information or assurance from plastics and rubber
- Interaction of administration sets and dispensing devices.

Stability Data Requirements As a Function of Development Phase

Phase 1

A brief description is required of the stability study and test methods used to monitor stability of drug product during Phase 1 clinical studies. Stability data are considered preliminary in that there are neither requirements for detailed stability data nor stability protocols. Stability data must show that the drug will remain stable during the course of the trial.

Phase 2

It is expected that Phase 1 and 2 stability data will provide sufficient information to develop the final formulation and select the most appropriate container and closure system by end of Phase 2. Studies started for Phase 1 will continue, if possible, or new studies must be started to support shelf of the product used throughout Phase 2 studies.

Phase 3

Emphasis should be on testing final formulations in their proposed market packaging and manufacturing site. A final stability protocol must be well defined prior to initiation of Phase 3 studies. Scientists also must establish the appropriate linkage between preclinical and clinical batches of the drug substance and drug product, and the primary stability batches in support of the proposed expiration–dating period.

Need for Extra Stability Studies Following NDA/ANDA Approval

There are three possibilities for reporting changes (filing requirements) to an approved NDA or ANDA that typically required stability data to be generated to support the change (14):

1. Data provided in the product Annual Report—change does not require prior FDA approval.
2. Changes-being-effected (CBE) supplement—data reported to FDA, FDA has 30 days to provide any comments; otherwise manufacturer can proceed to implement the change.
3. Prior approval supplement—manufacturer must obtain FDA approval before implementing the change.