There are many types of changes that require additional stability data:

- Manufacturing process of drug substance
- Manufacturing site(s)
- Formulation
- Addition of new strength for drug product
- Equipment
- Batch size
- Reprocessing step(s)
- Container closure
- Stability protocol.

It is beyond the scope of this chapter to discuss the types of changes that fall under each of the three filing requirements. However, in general, if any changed is viewed to affect the critical quality attributes of the drug product, stability data must be generated and reviewed by FDA before the change is approved.

Extra stability data also must be obtained if any manufacturing deviation occurs where the critical quality attributes of the product are in question. Examples of manufacturing deviations likely to necessitate the need for stability data generated on the affected product batch include:

- Time limits exceeded
- Administrative (release) limit not met despite data within regulatory limit
- Freeze dry cycle not met
- Finished product stored outside chill room for a period of time exceeding procedure
- Equipment breakdown, product remains in tank for extended period of time.

Distribution and Storage

Once unit dosage forms are filled into primary packaging and are stoppered, sealed, inspected, labeled, and placed in the appropriate secondary packaging, issues of distribution and storage come into play. Storage of finished dosage forms is of concern at the place of manufacture prior to distribution (shipping), the warehouse or distribution center as an intermediate storage place, and at the hospital or other final destination place (including the home). Distribution of finished products must be controlled with respect to temperature fluctuations and handling (i.e., stress, shear) during at least five transportation transfers (21,22):

- Preparing the products for transport
- Loading and unloading products into shipping equipment
- Loading and unloading products from one shipping equipment to another
- Receipt of products
- Handling of products between transportation (airport or harbor transit).

The need for good practices in storage and handling of parenteral drug products cannot be overemphasized. While all drug products must maintain strength and quality after manufacture until usage, parenteral drug products have the added requirement to remain sterile and maintain their high-purity characteristics. Difficulties encountered in the adequate storage and handling of parenteral drug products include temperature excursions, outdated shelf lives, and glass hairline cracks (not detectable) that may lead to microbial contamination.

The shipping process must be validated to assure product stability. Maps of the shipping process must be known to understand potential risk points to product stability. The product's susceptibilities to temperature excursions must be known and controlled. The packaging system must have the appropriate protective properties, e.g., light protection, insulation, cold storage compatibility. Actual temperature exposures during shipment must be monitored in order to assess any excursions and time exposure on product stability.

For temperature-sensitive products, as many biopharmaceutical products are temperature sensitive, cold chain distribution systems have become routine. Systems exist to assure that temperature-sensitive products are protected and remain at the proper temperatures