24 | Stability, storage, and distribution of sterile drug products

Consider the fact that the large majority of injectable and ophthalmic drugs are in the solution state, either "ready-to-use" or reconstituted. If not solutions, injectables or ophthalmics exist in a dispersed system state (e.g., suspensions, emulsions, gels) where the drug does not exist in a dry state environment. Therefore, sterile drugs are much more prone to chemical and physical degradation mechanisms than their oral solid dosage form counterparts. Major degradation mechanisms include hydrolysis, oxidation, and physical deterioration such as protein aggregation and visible particle formation. Other degradation mechanisms include photolysis and compatibility problems with packaging surfaces. Stability issues and stabilization have been covered in previous chapters (8–11). This chapter discusses good manufacturing practice (GMP) requirements for stability studies and submission of stability data for new drug applications or abbreviated new drug applications. Also, good practices for storage and distribution of sterile drug products will be covered.

GMP regulations (1) state two main requirements with respect to stability studies:

- (211.166) "There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates."
- (211.167) "An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained."

While these regulations provide the GMP basis for stability studies and establishment of expiration dates based on stability data, they do not provide details for specific requirements for submitting stability data for drug product approvals including stability requirements for bulk drugs (active pharmaceutical ingredients). Thus, the need for stability guidelines arose quickly and the first FDA stability guidelines were published in 1987 (2). Since then, the guidelines have been revised with respect to coverage within the guidelines and specific requirements for different dosage forms and different drug product submission categories (e.g., NDA, ANDA) (3–6). Requirements for bulk stability studies will not be covered.

Basic requirements for design and interpretation of stability studies for finished dosage forms are given in Table 24-1 and include the following (5):

- Full-term stability studies on at least three primary batches that represent the marketed formulation, package, and validated production process.
- Two of the three batches should be at least pilot scale, typically assumed to be at least 10% the size of the commercial batch. The third batch can be smaller if justified.
- Each batch should use a different lot of active pharmaceutical ingredient, where possible.
- Each active ingredient strength and container size must be stability tested unless the manufacturer can justify the bracket or matrix approach (discussed later).
- Photostability testing needs to be performed on one primary batch (6,7).

Stability testing should cover the following as a function of storage time and temperature:

- Physical, chemical, biological, and microbiological attributes
- Preservative (antimicrobial and/or antioxidant) content
- Functionality tests (breakloose and glide forces) for products packaged in syringe and cartridge containers.

The analytical procedures used to measure these attributes must be fully validated and stability indicating (8–12). Also differences between acceptance criteria for release of a batch and acceptance limits at the end of the expiration dating period must be justified. For example, if the potency at expiry be $\geq$95% of label claim and the acceptance limit for potency is 98% of