Where "significant change" occurs under accelerated testing, additional testing at an intermediate condition, 30 ± 2°C/60 ± 5% RH, should be conducted. "Significant change" at the accelerated condition is defined as follows [5,6]:

- A 5% potency loss from the initial assay value of a batch
- Any specified degradant exceeding its specification limit
- The product exceeding its pH limits
- Dissolution results exceeding the specification limits for 12 capsules or tablets
- Failure to meet specifications for appearance and physical properties, e.g., color, caking, and hardness

Should significant change occur at 40°C/75% RH, the ANDA applications should include a minimum of 6 months' stability data at 30°C/60% RH; the same significant change criteria will then apply. The long-term testing should be continued beyond 12 months to derive shelf-life data.

### Postapproval Changes

21 CFR Part 314.70(a) requires applicants to notify the FDA when there are any changes to an approved ANDA application. To facilitate less burdensome post-approval changes within the meaning of this regulation, the FDA has published three guidances [25–27] on postapproval changes, including two separate scale-up and postapproval change (SUPAC) guidances on IR and MR products. These guidances provide recommendations on the following categories of postapproval changes:

- Changes in the components and composition
- Changes in the site of manufacture
- Changes in batch size (scale-up/scale-down)
- Changes in manufacturing equipment and manufacturing process

The guidances have defined levels of changes and, for each level of change, specified the requirements for stability data in support of the change. Because of the increasing necessity for site transfers in the pharmaceutical industry, stability documentation requirements for site changes are discussed below. The stability documentation requirements outlined in SUPAC-IR and SUPAC-MR for the other categories of changes are not included in this discussion.

### Site Transfer

Site transfer usually consists of relocating manufacturing, packaging, and/or laboratory testing operations to a different site or to an alternate site. With increasing competition and consolidation in the generic pharmaceutical industry, site transfer of products has become popular to increase operational flexibility and speed and, at the same time, decrease cost of marketing products.