

Table 24-1 Basic Requirements of ICH Stability Guidelines

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- Three batches, two of which are pilot plant scale
 - Data on lab-scale batches not acceptable as primary information
 - Twelve-month stability data at the time of regulatory submission
 - $25 \pm 2^\circ\text{C}$, $60 \pm 5\%$ RH
 - Accelerated testing is defined as six months at $40 \pm 2^\circ\text{C}$, $75 \pm 5\%$ RH
 - If significant change occurs at accelerated conditions, then can use an intermediate condition:
 $30 \pm 2^\circ\text{C}$, $60 \pm 5\%$ RH
 - Different batches of drug substance
 - Three month testing frequency first year; six months second year
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label claim, there must be data to support the fact that <3% loss in potency will occur during the product's shelf life.

If significant change occurs at any time during six-month accelerated testing, additional testing at the intermediate storage condition should be conducted (unless $30^\circ\text{C} \pm 2^\circ\text{C}$ / 65% RH is the long-term condition, then there is no intermediate condition). Examples of significant changes include the following:

- Five percent change in assay from initial;
- Failure to meet potency criteria for biopharmaceuticals
- Degradation product exceeding acceptance criterion
- Failure to meet acceptance criteria for appearance, physical attributes, functionality
- Failure to meet acceptance criterion for pH
- Failure to meet acceptance criterion for dissolution for 12 dosage units.

Once determined by a manufacturer that the formulation, primary package, and process have been finalized (typically or ideally via a document signed off by all appropriate representatives from development, manufacturing, and quality), stability data must be generated on the first three production batches. Ideally, at time of regulatory submission, stability data cover the proposed shelf life from three production batches. Long-term stability studies will be conducted through the proposed product shelf life. Accelerated six-month stability data should be available, or if the drug is too unstable for six months at these stressful conditions, then shorter time periods might be acceptable with the appropriate label precautions regarding storage conditions for the relatively unstable product.

If, at the time of regulatory submission, there are no or incomplete data from at least production size batches of the product, then the commitment must be made to place the first three production batches on long-term (through proposed shelf life) stability testing as well as six-month accelerated stability testing.

The design and implementation of valid stability studies will include a justifiable sampling plan for assurance of unbiased selection of samples. At least two unit containers will be sampled at each sampling time. Assay of composites is allowable, although must be justified. Sampling intervals are usually standard (0, 1, 3, 6, 12, 18, and 24 months), although more frequent sampling pulls might be necessary. The number of sample replicates should be increased at the later sampling times.

Establishment of expiration dating period is typically computed by determining the best-fit linear regression analysis of real-time stability data and establishing the one-side lower 95% confidence time point (Figure 24-1). Expiration dating must use percent of label claim, not the percent of the average initial potency from the definite stability test lots. There are many sources of variability in stability testing, so the concern is to overestimate the expiration date. Equality of potency degradation slopes and intercepts from definitive stability test data must be compared to assure that the stability data are repeatable. Although rare, if there is little degradation and analytical variability (must be justified), then there is no need to apply formal statistical analyses.

For freeze-dried products after reconstitution, the standard stability period is 24 hours at room temperature and anywhere from 48 hours to two weeks at refrigeration, depending on chemical and physical stability. Long-term reconstituted stability may have more of a