Table 24-2 Examples of FDA 483 Observations on Stability Testing

- Stability failure not properly investigated, not conducted in a timely manner, conclusions questionable.
- Storage incubators not monitored; relative humidity not monitored
- Degradation products not identified
- Preservative efficacy test not done at end of stability period
- Reconstitution stability not evaluated at end of stability period
- No data on impurities
- No characterization, quantification, toxicology, clinical effects of degradation products
- Impurities found after assay was changed
- Unknown degradants discovered during stability testing, nothing done to study what degradant was and impact on product safety and quality.
- Change in upper-limit specification without QC unit appropriately justifying the change
- No data to correlate preservative efficacy test results to a HPLC assay for the preservative
- Very slow (>10 mo) investigation of unknown peaks in stability samples
- No data assuring sterility of product at end of shelf life
- Inadequate data supporting stability of reconstituted freeze-dried product, particularly at end of shelf life.

FDA INSPECTIONS AND 483 OBSERVATIONS RELATED TO STABILITY TESTING

Being a major quality system, stability testing and documentation are reviewed carefully by FDA and other government regulatory inspectors worldwide. Stability testing protocols can be complicated, especially for lyophilized products that must be tested both after reconstitution and after storage as solutions in potentially different diluents at different temperatures. Examples of 483 observations based on inspector concerns after reviewing stability testing protocols, data, and documentation supporting expiration dating are given in Table 24-2.

FDA STABILITY GUIDELINES APPLICABLE TO STERILE PRODUCTS

Storage requirements for drug products in semi-permeable and impermeable containers, and for drug products that require refrigeration or need to be frozen are as follows (2) (see also Table 24-3):

1. Storage requirements for drug products in semi-permeable containers
   (a) Accelerated: 40°C ± 2°C/NMT25% ± 5% relative humidity (RH)
   (b) Intermediate: 30°C ± 2°C/65% ± 5% RH
   (c) Long-term: 25°C ± 2°C/40% ± 5% RH
2. For drug products in impermeable containers, any controlled or ambient humidity condition
3. Storage requirements for refrigerated drug products
   (a) Accelerated: 25°C ± 2°C/60% ± 5% RH
   (b) Long-term: 5°C ± 3°C, monitor, not control, RH
4. Storage requirements for frozen drug products
   (a) Accelerated: 5°C ± 3°C/ambient humidity
   (b) Long-term: −20°C ± 5°C

BRACKETING AND MATRIXING (20)

Bracketing is allowed where stability data are obtained for the smallest and largest container and closure to be commercially marketed provided that intermediate packaging is of comparable composition and design. Storage must take place with the primary package both in the upright

Table 24-3 Storage Condition Requirements for ICH Stability Studies

Length of study	Storage conditions	Minimum time period covered by data at submission date
Long term	25°C ± 2°C/40% ± 5% RH or 30°C ± 2°C/65% ± 5% RH	12 months
Intermediate	30°C ± 2°C/65% ± 5% RH	6 months
Accelerated	40°C ± 2°C/NMT75% ± 5% RH	6 months