

## The cGMP Final Rule for Dietary Supplements—Stability Testing

The Final Rule (21 CFR Part 111 in 2007) for current good manufacturing practices (cGMP) issued by the FDA has now become effective for all companies involved in manufacturing and distributing nutrition supplements. The rule states that all manufacturers of dietary supplements are not required to establish an expiration /shelf-life for their products; however, if they choose to use either an “Expiration Date” or “Best if Used By Date,” this claim must be supported and substantiated by scientific data (see 68 FR 12157 at 12204). The most relevant scientific data are from stability (shelf-life) studies. Although the FDA does not provide specific guidelines of methodology or procedures for such studies, it recommends that manufacturers have a written testing program designed to assess the stability characteristics of the dietary supplement, and to use the results of stability testing to determine appropriate storage conditions and expiration dates.

In general, USP <1150> pharmaceutical stability offers definitive stability guidance on how manufacturers can apply compendial procedures to monitor the stability of their product through product expiry. There are several important considerations when designing and conducting stability studies.

1. **Stability Protocols:** before each study, a stability protocol should be written. The protocol should address (1) sample size and test intervals based on statistical criteria for each attribute, (2) stability storage conditions, (3) reliable, meaningful, and specific test methods; and (4) testing of products in the enclosures of supplement in which the product is marketed. The method must be adequate in demonstrating the suitability for analyzing the active compounds as well as their degraded compounds. Also required in the protocol are the parameters and criteria not only of the active ingredients but also of physical appearance and characteristics.
2. **Design of the stability study:** an adequate number of batches (3 batches are usually recommended) of each product should be tested.
3. **Stability study conditions in environmentally-controlled chamber:**
  - a. **Accelerated stability:**  $45 \pm 2$  °C and  $75 \pm 5\%$  humidity. When this study shows the active ingredients and criteria set for the product are good for three months, the stability can be claimed for one year; if good for six months, it can be claimed for two years, and nine months for three years.
  - b. **Real time stability:**  $25 \pm 2$  °C and  $60 \pm 5\%$ . We can only claim the length of the actual study period. This is frequently used to back up the accelerated studies.
  - c. **Exceptional stability:** if the product is used in tropical and subtropical regions, the study conditions may require different temperature and humidity. (See USP <1150>)
4. **Testing:** each ingredient claimed on the label will be tested using a specific test method for a pre-determined interval. It is recommended that adequate data points (3 to 4 at the minimum) should be considered. For example, for a six month accelerated study, one can test the active ingredients at 0 (background or potency testing), 2, 4 and 6 months. For real time two-year-stability, the test intervals may be at 0, 3, 6, 12, 18 and 24 months. In addition to active ingredients, most samples should also be tested for physical characteristics such as color, odor, and microbial parameters. This is especially true for products without specific claims for active ingredients.
5. It is not recommended that we short-cut the testing program such as testing one batch, testing for only 2 to 3 data points, or testing a portion of selected active ingredients on the label. Each study is important due to the difficulty of repeating the testing program. Shortcuts lead to noncompliance with the cGMP, which will eventually cost more and delay the product’s introduction to market.

AAC Labs has 16 years of experience in stability studies on pharmaceutical and nutrition supplement products serving numerous customers worldwide. Please let us know if we can be of service to you.