

In-Process and Bulk Drug Product Holding Times

Regulatory Basis:

FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion:

This Document sets out guidelines for the determination and validation of in-process and bulk product holding times.

Maximum allowable hold times should be established for bulk and in-process drug products (where applicable). Typically one lot can be used for validating hold times. Data to justify the hold time can be collected during development on pilot scale batches, during process validation, via a historical review of batch data, or as part of a deviation with proper testing.

Although there are no specific regulations or document documents on bulk product holding times, good manufacturing practice dictates that holding times should be validated to ensure that in-process and bulk product can be held, pending the next processing step, without any adverse effect to the quality of the material. This practice is supported by indirect references made to determining holding times in various FDA document documents, FDA regulations as follows:

- “if a firm plans to hold bulk drug products in storage.....stability data should be provided to demonstrate that extended storage in the described containers does not adversely affect the dosage form” .
- “stability data also may be necessary when the finished dosage form is stored in interim containers prior to filling into the marketed package. If the dosage form is stored in bulk containers for over 30 days, real-time stability data under specified conditions should be generated to demonstrate comparable stability to the dosage form in the marketed package. Interim storage of the dosage form in bulk containers should generally not exceed six months” .
- “when appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product.” .This regulation could be interpreted to include the time for holding bulk product as part of the production process. “holding times (includes storage times) studies may be conducted during development or carried out in conjunction with process validation lots and shall be representative of full scale holding conditions”. For purposes of clarification, refer to **Appendix A** for definitions relating to bulk holding time. Holding time data may be generated in the following situations:
 - Bulk holding studies may be conducted on product developmental pilot scale batches to demonstrate comparable stability to the dosage form in the marketed package.
 - Holding data may be generated as part of a process validation study. Data can be collected on the bulk product itself after holding or collected after the held product has been packaged.

In-Process and Bulk Drug Product Holding Times

Typically, if these in-process products are used within 24 hours of manufacturing, no bulk holding time studies are deemed necessary. An in-process product that is held for longer than 24 hours should be monitored for physical characteristics and microbial contamination. A solution/suspension should be held for the defined hold period. At the test points, a sample should be taken from the storage container and tested. Results obtained should be compared with the initial baseline data of the solution/suspension control sample results.

Typical tests include the following: Microbial count; Yeast/Mould count; Specific Gravity; and Viscosity.

3) ***Holding time considerations for Tablet Cores, Extended-Release Beads or Pellets.***

Typically, in-process products such as cores, extended-release beads or pellets may be held for up to 30 days from their date of production without being retested prior to use. An in-process product that is held for longer than 30 days should be monitored for stability under controlled, long-term storage conditions for the length of the holding period. A representative portion of the core/bead/pellet should be held for the defined hold period. At the test points, a sample should be taken from the storage container and tested. Results obtained should be compared with the initial baseline data of the core/bead/pellet control sample results.

Typical tests include the following: Hardness; Friability; Appearance; Dissolution/Disintegration; Assay; Degradation Products (where applicable); and Moisture Content.

4) ***Holding time considerations for Bulk Tablets and Capsules.***

Typically, bulk tablets and capsules may be held for up to 30 days from their date of production without being retested prior to use. A bulk product that is held for longer than 30 days should be monitored for stability under controlled, long-term storage conditions for the length of the holding period. Interim storage of the dosage form in bulk containers should generally not exceed six months. At the test points, a sample should be taken from the storage container and tested. Results obtained should be compared with the initial baseline data of the tablet/capsule control sample results.

Typical tests include the following: Hardness; Friability; Appearance; Dissolution (in the case of controlled and extended release products, the establishment of a dissolution profile is recommended); Disintegration; Assay; Degradation Products (where applicable); Moisture Content, and microcount (where applicable).

5) ***Holding time considerations for Oral Liquids and Semi-Solids (Suspensions, Creams, and Ointments).***

Typically, liquid and semi-solid dosage form products should be held for no more than 5 days without a hold time study. Full scale batches should be used for these studies. Samples should be taken from the holding vessel after transfer from the manufacturing vessel, and again at the completion of the holding period. Multiple samples should be taken at each time point if holding can impact product uniformity. Samples would be taken to prove that product uniformity of actives and preservatives