Specifications

Separate specifications are required to verify the quality of the intermediates used in the production of the finished product. Usually, the analytical methods for the finished product are also utilized in testing of intermediates.

Holding Time

21CFR Part 211.111 requires, where appropriate, time limits for the completion of each phase of production to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation must be justified and documented.

A draft guidance [5], though subsequently withdrawn by the FDA, represented the agency's approach at the time in favor of an intermediate to be held for a maximum period of 30 days from the date of production without being retested before its use in manufacturing. A holding time period of 1 month, instead of 30 days, would also be acceptable, if that is necessary for scheduling convenience. In the guidance, the date of production is defined as the initial date that an API has been added to the inactive ingredients during manufacturing. An intermediate that is held longer than 30 days (or 1 month) should be retested before use. The first production batch of the corresponding finished product should be monitored through long-term stability studies. For blends, the purpose of retesting is to ensure that they have remained stable and that no degradation or demixing took place during prolonged storage. For intermediate pellets, retesting ensures that the dissolution quality has not been affected. Retesting of cores assures that the assay, degradation, and dissolution results are acceptable.

If a longer holding time, for example, 3 months, is necessary to facilitate routine production planning, the quality of an intermediate batch stored in the warehouse under the controlled room temperature condition should be checked for the duration of the holding time. The guidance suggests that at least three test points beyond the initial release should be selected for stability testing. The first finished product batch produced from an intermediate held for the desired duration in the warehouse should be tested. If the test results are found to be satisfactory upon completion of the stability testing of the finished product batch, the holding time of 3 months is deemed to have been qualified and can be routinely used without further stability testing of future batches of the intermediate and the corresponding IR or MR drug products if these intermediate batches are held for not more than 3 months. Because the expiration date of the finished product is assigned from the date of production as defined above, its shelf-life is essentially shortened by the length of a holding time greater than 30 days (or 1 month). Therefore, it is advisable to limit the qualification of the holding time to 3 months or shorter. It should be noted that, if an intermediate is not stable for 30 days (or 1 month), its holding time should be appropriately decreased after review of its short-term stability profile.

DRUG PRODUCT STABILITY

Stability testing plays a crucial role in the development of generic drug products. It provides valuable information regarding the behavior of drugs when exposed to